Corticospinal responses to patellar tendon pain and the effects of externally paced strength training

Thesis in progress submitted for the degree of

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General Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two original papers published in peer reviewed journals, one publication conditionally accepted with minor revisions to be made and two publications in submission. The core theme of the thesis is quantifying the corticospinal responses of people with patellar tendon pain and the effect of strength training. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Physiotherapy, Faculty of Medicine, Nursing and Health Sciences under the primary supervision of Professor Jill Cook.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. The studies in this thesis were granted ethics approval from the Monash University Human Ethics Committee (CF12/0230-2012000067, Appendix A) and the Deakin University Ethics Committee (2012-090, Appendix B).

In the case of Chapters 2-6 my contribution to the work involved the following:

Thesis Chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
2	The pain of tendinopathy: Physiological or Pathophysiological?	Published	Literature search and critical evaluation, preparation of the manuscript as guarantor of the manuscript.
3	Elevated corticospinal excitability in patellar tendinopathy compared to other anterior knee pain or no pain.	Published	Developed study design, performed data collection, statistical analysis and preparation of the manuscript as guarantor of the manuscript.
4	Isometric exercise induces analgesia and reduces inhibition in patellar tendinopathy.	Published	Developed study design, performed data collection, statistical analysis and preparation of the manuscript as guarantor of the manuscript.
5	Isometric contractions are more analgesic than isotonic contractions for patellar tendon pain: an inseason	Submitted	Developed study design, performed data collection, statistical analysis and preparation of the

	randomised clinical trial.		manuscript as guarantor of the manuscript.
6	Tendon neuroplastic training: changing the way we think about tendon rehabilitation.	Published	Developed study design, performed data collection and statistical analysis, preparation of the manuscript as guarantor of the manuscript.

Signed: ....

Date: .………………………………

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Oli.

List of publications, conference presentations, awards and invited chapters arising during PhD candidature

Publications in this thesis by chapter

Rio E, Moseley GL, Purdam C, Samiric T, Kidgell D, Pearce AJ, Jaberzadeh S & Cook J. (2013) The pain of tendinopathy: physiological or pathophysiological? *Sports Med*. Jan; 44(1):9-23. doi: 10.1007/s40279-013-0096-z. **Impact Factor: 5.237 (Chapter 2, typeset journal article as published appears in Appendix C)**

Rio E, Kidgell D, Moseley GL & Cook, J. (2015) Elevated corticospinal excitability in patellar tendinopathy compared to other anterior knee pain or no pain. *Scand J Sport Med*. first published online Sep 2015. doi: 10.1111/sms.12538. **Impact factor: 2.868 (Chapter 3)**

Rio E, Kidgell D, Purdam C, Gaida J, Moseley GL, Pearce, AJ & Cook, J. (2015) Isometric exercise induces analgesia and reduces inhibition in patellar tendinopathy. *Br J Sport Med.* doi: 10.1136/bjsports-2014-094386. **Impact factor: 5.025 (Chapter 4)**

Rio E, van Ark M, Kidgell D, Docking S, Gaida J, Moseley GL, Akker-Scheek I, Zwerver J & Cook J. (2015) Isometric contractions are more analgesic than isotonic contractions for patellar tendon pain: an inseason randomised clinical trial. *Under review at Clin J Sport Med.* **(Chapter 5)**

Rio E, Kidgell D, Moseley GL, Docking SI, Gaida J, Purdam C & Cook J. (2015) Tendon neuroplastic training: changing the way we think about tendon rehabilitation. *Br J Sport Med.* doi:10.1136/bjsports-2015-095215 **Impact factor: 5.025 (Chapter 6)**

Additional peer reviewed publications within this candidature

van Ark M, Cook J, Docking SI, Zwerver J, Gaida J, Akker-Scheek I & **Rio E.** (2015) Do isometric and isotonic exercise programs reduce pain in athletes with patellar tendinopathy inseason? A randomised clinical trial. *Accepted with minor revisions by the J Sci Med Sport.* **(Appendix D)**

Rio E, Mayes S & Cook J. (2015) Heel pain: a practical approach. *Aust Fam Physician.* 2015; 44(3):96-101. **Impact factor: 0.67 (Appendix E)**

van Ark M, Docking SI, van den Akker-Scheek I, Rudavsky A, **Rio E**, Zwerver J, Cook J. (2015) Does the adolescent patellar tendon respond to 5 days of cumulative load during a volleyball tournament? *Scand J Med Sci Sports.* Feb 18. doi: 10.1111/sms.12426. **Impact factor: 3.174 (Appendix F)**

Ganderton C, Docking SI, **Rio E,** van Ark M, Gaida J & Cook J. (2014) Achilles tendinopathy: understanding the key concepts to improve clinical management. *Sportphysio (in German)* 2(3) pg.112-7

Docking S, Samiric T, **Scase E,** Purdam C & Cook J. (2013) Relationship between compressive loading and ECM changes in tendons. *Muscles ligaments and tendon J.* May 21;3(1):7-11. doi: 10.11138/mltj/2013.3.1.007. **(Appendix G)**

Chalmers S, Magarey ME & **Scase E.** (2013) Junior Australian football injury research: are we moving forward? *Phys Ther Sport.* Aug;14(3):175-82. doi: 10.1016/j.ptsp.2013.06.001. **Impact factor: 1.830 (Appendix H)**

Scase E, Magarey ME, Chalmers S, Heynen M, Petkov J & Bailey S. (2012) The epidemiology of injury for an elite junior Australian Football cohort. *J Sci Med Sport.*

May;15(3):207-12 doi: 10.1016/j.jsams.2011.12.002. Epub 2012 Jan 4. **Impact factor: 3.493 (Appendix I)**

Chalmers S, Magarey ME, Esterman A, Speechley M, **Scase E** & Heynen M. (2012) The relationship between pre-season fitness testing and injury in elite junior Australian football players. *J Sci Med in Sport*. Jul;16(4):307-11. doi: 10.1016/j.jsams.2012.09.005. Epub 2012 Oct 23. **Impact factor: 3.493 (Appendix J)**

Opar D & **Rio E.** (2015) The juxtaposition of medicine and science in sport. Can we all play nicely together? *Br J Sports Med. (Ed.)* Published online first doi: 10.1136/bjsports-2015-094719. **Impact factor: 5.025 (Appendix K)**

Opar D & **Rio E.** (2015) Research at the coal face of clinical sports medicine. *Br J Sports Med. (Ed.)* doi: 10.1136/bjsports-2015-094819. **Impact factor: 5.025 (Appendix K)**

Additional peer reviewed publications in submission

Malliaras P, Purdam C, Cook J & **Rio E.** (2015) Patellar Tendinopathy: Clinical Diagnosis, Load Management, and Advice for Challenging Case Presentations. *JOSPT.* doi:10.2519/jospt.2015.5987. **Impact factor: 3.627 (Appendix L)**

Simpson M, **Rio E** & Cook J. (2015) At what age do children and adolescents develop lower limb tendon pathology or tendinopathy? A systematic review and meta-analysis. *Submitted to Sports Medicine Journal.* **(Appendix M)**

Invited reviews (non-peer reviewed)

Rio E & Opar D. (2015) Lower limb injury: improving our translation of research into clinical practice for acute injuries and long term sequelae *Br J Sports Med* doi: 10.1136/bjsports 2015-094820. **Impact factor: 5.025 (Appendix N)**

Cook J, Docking SI & **Rio E.** (2014) Patellar tendinopathy and its diagnosis. *Sport Health* Vol 32. Issue 1. **(Appendix O)**

Rio E & Cook, J. (2013) Tendinopathy: what about the pain? *Terra Rossa emagazine (13).* **(Appendix P)**

Scase E, Cook J & Purdam, C. (2011). Explaining ultrasound images of tendon pathology; A pathology model of load–induced tendinopathy. *Sound Effects: The Quarterly Publication of the Australian Sonography Association* (2): 16-20. **(Appendix Q)**

Scase E, Cook J & Purdam C. (2011) Matching tendinopathy stage with efficacious intervention. *Sound Effects: The Quarterly Publication of the Australian Sonography Association* (4): 14-18. **(Appendix R)**

Invited book chapters

Rio E, Docking SI, Cook J & Jones M. (2015) 'To hell and back: Achilles insertional tendinopathy' *in Clinical Reasoning for Manual Therapists* 2nd Ed. **(Appendix S)**

Cook J, **Rio E** & Lewis J. (2015) Managing Tendinopathies *in Grieves MMPT.* **(Appendix T)**

Invited journal contributions

Invited guest editor with Dr. David Opar for the lower limb issue of BJSM (2015) with associated podcast recorded "The juxtaposition of medicine and science in the elite sporting environment, can we all play nicely together."

Promoted to Senior Associate Editor of British Journal of Sports Medicine

Conference Presentations

Rio E, Docking SI & Cook J. (2015) How can we change tendon pain in rehabilitation and inseason? (within symposium) accepted presentation (funded as part of ASICS Sports Medicine Australia award 2014) *4th Congress of the European Congress of the Sports and Exercise Physicians "Muscle and tendon – Inspiring clinical excellence"* Barcelona, Spain

Rio E, Kidgell D, van Ark M, Docking SI, Zwerver J, Gaida J, Akker-Scheek I, Moseley GL & Cook J. (2015) Tendon neuroplastic training reduces tendon pain and muscle inhibition inseason: changing the way we think about exercise. Accepted for a podium presentation at *ASICS Sports Medicine Australia*, Sanctuary Cove, Australia

Rio E, Kidgell D & Cook, J. (2014) Exercise affects cortical inhibition & reduces pain in patellar tendinopathy: a randomised cross over trial. *International Scientific Tendon Symposium,* Oxford, United Kingdom

Rio E, Kidgell D, Moseley GL & Cook, J. (2014) Tendon neuroplastic training: its dynamite. *ASICS Sports Medicine Australia,* Canberra, Australia

Rio E & Cook, J. (2014) Isometric exercise for patellar tendon pain: is it effective on the road? *ASICS Sports Medicine Australia,* Canberra, Australia

Rio E, Kidgell D & Cook J. (2013) Exercise affects cortical inhibition & reduces pain in patellar tendinopathy: a randomised cross over trial. *ASICS Sports Medicine Australia*, Phuket, Thailand

Rio E & Cook J. (2013) Isometric exercise: clinical and cutting edge. *ASICS Sports Medicine Australia,* Phuket, Thailand

Rio E, Kidgell D, Pearce AJ, Moseley GL, Gaida J & Cook J. (2013) Investigating corticospinal changes associated with patellar tendon pain. *11th Motor Control and Human Skills Conference,* Melbourne, Australia

Rio E, Kidgell D, Moseley GL, Gaida J & Cook, J. (2013) Corticospinal differences associated with patellar tendinopathy and effects of rehabilitation. *HDR student conference,* Monash University, Clayton, Australia

Rio E, Kidgell D, Moseley GL, Gaida J & Cook J. (2014) Corticospinal differences associated with patellar tendinopathy and effects of rehabilitation. *3MT School and Faculty presentations,* Peninsula and Clayton, Monash University, Australia

Keynote speaker invitations

Rio E, Purdam C & Cook J. (2015) Isometrics and tendinopathy. *St. George Shoulder conference,* Sydney, Australia

Rio E, Docking SI, Purdam C & Cook J. (2015) Management of the difficult tendon in the AFL. *Australian Football League Physiotherapy Association Professional Development Symposium,* Melbourne, Australia

Rio E & Cook J. (2014) Achilles Tendinopathy: risk factors and management. *Sports Podiatry New Zealand,* Dunedin, New Zealand

Rio E, Purdam C & Cook J**.** (2015) Lower limb tendinopathy and isometric exercise. *Australian Sports Medicine Physician Registrars Conference,* Melbourne, Australia

Rio E & Cook J. (2013) Tendinopathy: Beyond Eccentrics. *Soft tissue therapy Conference,* Sydney, Australia

Conference Poster Presentations

Rio E, Kidgell D, Moseley GL & Cook, J. (2015) Why is differential diagnosis of the anterior knee important? Because the brain thinks it is! Accepted at *ASICS Sports Medicine Australia Conference 2015,* Sanctuary Cove, Australia

Rio E, Kidgell D & Cook, J. (2014) Exercise affects cortical inhibition & reduces pain in patellar tendinopathy: a randomised cross over trial. Accepted at the *American College of Sports Medicine Conference* for a poster session and special invitation clinical session, Orlando, USA

Scase E, Kidgell D, Pearce AJ, Jaberzadeh S & Cook J. (2014) Tendon pain: is it all in my head? The clinical implications of cortical changes associated with patellar tendinopathy. *PainAdelaide,* South Australia: Post Graduate Poster Session

Scase E, Kidgell D, Pearce AJ, Jaberzadeh S & Cook J. (2012) Tendon pain: is it all in my head? The clinical implications of cortical changes associated with patellar tendinopathy. *ASICS Sports Medicine Australia,* Sydney, Australia

Awards during candidature

ASICS Ken Maguire Award for Best New Investigator (2013) Clinical sports medicine at *ASICS Conference of Science and Medicine in Sport,* Phuket, Thailand ($3000 travel prize)

PainAdelaide Conference (2014) **Best presentation: Clinical Science** ($300 prize)

3 Minute Thesis Competition (2014) **School of Physiotherapy winner** ($50 gift voucher)

3 Minute thesis competition (2014) **3rd place in Faculty of Health Sciences final** ($300 prize)

ASICS Ken Maguire Award for Best New Investigator (2014) Clinical sports medicine at *ASICS Conference of Science and Medicine in Sport,* Sydney, Australia ($3000 travel prize)

Finalist for Best of the Best (top five podium presentations of the conference) (2014) at *ASICS Conference of Science and Medicine in Sport,* Sydney, Australia

BJSM Best Clinical Paper (2014) at *International Scientific Tendon Symposium,* Oxford, United Kingdom ($1500 British Pounds - prize to go towards research)

External grants obtained during candidature

Australian Postgraduate Award (full time)

Australian Institute of Sport Clinical Research Fund: Chief Investigator, $22,000

Abbreviations and terminology

AKP: anterior knee pain

AMT: active motor threshold

ASIS: anterior inferior iliac crest

BMI: body mass index

CNS: central nervous system

Corticospinal tract / pathway: descending motor pathway controlling voluntary movement

CPM: conditioned pain modulation. CPM is based upon the 'pain-inhibits-pain' paradigm. It is investigated by applying a tonic painful conditioning stimulus and observing the effect it has on a phasic test stimulus. It is now the preferred term replacing diffuse noxious inhibitory control (DNIC).

DNIC: diffuse noxious inhibitory control, sometimes used interchangeably in the literature with CPM

ECM: extracellular matrix

EIH: exercise induced hyperalgesia

EPI: endogenous pain inhibition

GABA$_A$: γ-aminobutyric acid type A

GABA$_B$: γ-aminobutyric acid type B

GAG: glycosaminoglycan

H-reflex: represents the excitability of spinal alpha motor neurons

LMN: lower motor neurons

LTP: long term potentiation

M1: primary motor cortex

MEP: motor evoked potential

MCID: minimum clinically important difference

MSK: musculoskeletal

M_{WAVE} / M_{MAX}: maximum compound action potential (M-wave)

MRI: magnetic resonance imaging

NMDA: *N*-methyl-D-aspartate

NRS: numerical rating scale

PFJ: patellofemoral joint

PFP: patellofemoral pain

PT: patellar tendinopathy

RC: rotator cuff

RFD: rate of force development

RM: repetition maximum

***rms*EMG:** root mean squared electromyography

sEMG: surface electromyography

SLDS: single leg decline squat

SICI: short-interval intra-cortical inhibition

SP: silent period

TMS: transcranial magnetic stimulation

US: ultrasound

_µ_V: microvolts

VISA-P: Victorian Institute of Sport Assessment tool (patellar tendon)

v-wave: volitional wave, represents the level of efferent neural drive from spinal α-motorneurons during maximal muscle contraction

Abstract

Patellar tendinopathy (PT) is most commonly characterised by localised, load-dependent pain at the proximal attachment of the tendon to the patella. The quadriceps is the muscle group that loads the patellar tendon, and the corticospinal control of the quadriceps, including corticospinal excitability (CSE) and short-interval intra-cortical inhibition (SICI) was quantified in this work using transcranial magnetic stimulation. An understanding of the corticospinal control of the quadriceps and the effects of strength training in people with PT was important because:

1) the mechanisms by which tendons become painful remain poorly understood as no local nociceptive driver has been identified;

2) other musculoskeletal pain conditions are associated with changes to motor control;

3) there may be primary motor cortex (M1) changes that contribute to chronicity and recalcitrance to treatment and

4) exercise, known to be a powerful modulator of the M1, is the mainstay of treatment for PT, yet the analgesic and corticospinal responses to exercise, in particular the modes of strength training in PT is unknown and may influence rehabilitation of people with PT.

A comprehensive literature review highlighted that the clinical presentation of tendon pain exhibits features of both physiological and pathophysiological pain and that possible changes to the M1 in people with tendon pain warranted investigation (Chapter 2). Chapter 3 investigated the CSE in jumping athletes with, (separated into those with PT or other anterior knee pain [AKP]), and without AKP. Athletes with PT displayed greater

CSE than controls and those with other AKP, however no differences were detected between the control group and other AKP group. This study improved our understanding of the CSE relating to different sources of knee pain (with similar, but different clinical presentations) and may direct better treatment approaches.

There are few non-invasive interventions that reduce tendon pain. Chapter 4 demonstrated that externally paced isometric contractions of the quadriceps muscle group had a greater analgesic effect than externally paced isotonic quadriceps muscle contractions. Importantly, pain reduction was paralleled by a reduction in cortical inhibition, and therefore that muscle performance (evidenced by increased quadriceps torque) was improved following isometric muscle contractions. The clinical implications of these findings are important as the findings show that isometric muscle contractions may be used to reduce pain in people with PT without a reduction in muscle performance.

In Chapter 5, two strength training programs, isometric and isotonic quadriceps muscle contractions that used external pacing to control the timing of the movement, were compared for their immediate analgesic effect in a 4-week withinseason randomised clinical trial. Both protocols were efficacious for inseason athletes to reduce pain; however, the isometric intervention demonstrated significantly greater immediate analgesia throughout the trial, which may increase the ability to load the patellar tendon.

Chapter 6 reviewed knowledge about changes to the M1 and motor control in tendinopathy, identified parameters shown to induce neuroplasticity in strength training such as the use of external pacing, aligned these principles with current tendon loading protocols and proposed future direction for tendon rehabilitation.

These studies demonstrated that PT was associated with substantial differences in the corticospinal control of the quadriceps. Externally paced strength training was capable of not only modifying tendon pain, but excitability and inhibitory control of the quadriceps. Changes to corticospinal control would logically alter tendon load and therefore may be important in reducing recalcitrance or symptom recurrence. An improved understanding of the methods that optimise neuroplasticity of the M1 may be an important progression in how the clinical prescription of exercise based rehabilitation in tendinopathy for pain modulation and potentially restoration of the corticospinal control of the muscle-tendon complex.

Chapter 1. Introduction

This chapter details the terminology associated with tendinopathy, transcranial magnetic simulation (TMS) and corticospinal responses and how the terms are used throughout this thesis.

1.1 Terminology associated with tendon pain and pathology

The clinical features of tendon pain are unique; the pain is well localised and occurs with tendon loading (Kountouris and Cook, 2007). However, pain is not definitively correlated with tendon pathology on clinical imaging (Malliaras and Cook, 2006, Malliaras et al., 2006a) and the driver of nociception in tendons remains unclear (Chapter 2). Tendon pain that is associated with tendon pathology that is usually evidenced by imaging abnormality, without investigation of the histopathology is termed tendinopathy (Khan et al., 1999). Tendon pathology can occur without pain but it is then not termed tendinopathy. Tendinosis describes a degenerative pathology without clinical or histopathological signs of inflammation (Khan et al., 1999). The term tendinitis is controversial, most histopathology studies do not show evidence of inflammatory processes (Khan et al., 1999, Alfredson et al., 2001, Alfredson, 2005), and the role of inflammatory mediators in pain or pathology remains unknown (Rees et al., 2014). Clinical use of the term tendinitis may cause coaches and athletes to underestimate the importance and impact of the condition (Khan et al., 1999). The terms tendinopathy and tendon pain will be used throughout this thesis interchangeably. Where there is no pain, but tendon abnormality on ultrasound (US) imaging, 'tendon pathology' will be used.

This thesis investigated patellar tendinopathy (PT), which is pain and dysfunction in the patellar tendon, and most commonly occurs at its proximal insertion (Ferretti et al., 1983,

Kountouris and Cook, 2007) (Figure 1.1). It is common in athletes whose tendons are exposed to repeated high tendon load during jumping and landing activities and change of direction (Cook et al., 2000a, Ferretti, 1986, Zwerver et al., 2011a). The term 'jumpers' knee', though commonly used interchangeably with the term PT, is not preferred as it often encompasses proximal insertion patellar tendon pain that was investigated in this thesis, but also encompasses quadriceps tendon injury and injury at the distal insertion at the tibial tuberosity (not covered in this thesis) (Ferretti et al., 1983). Furthermore, jumping athletes may be vulnerable to other types of anterior knee pain (AKP) associated with nociceptive drivers other than the quadriceps muscle-tendon complex, for example patellofemoral pain (PFP) (Barber Foss et al., 2012), so the term 'jumpers knee' can be misleading.
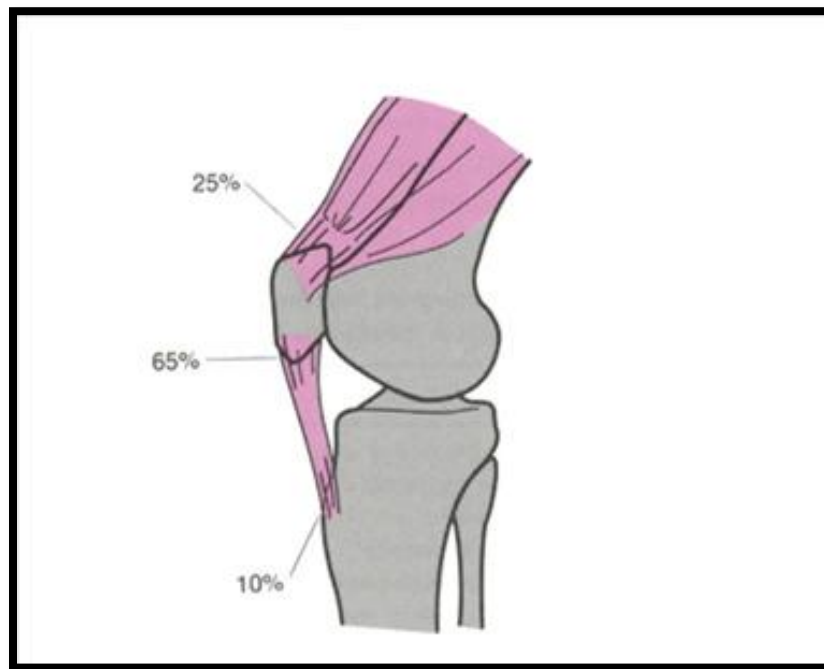
Figure 1.1 Patellar tendon pain occurs most commonly at the attachment at the inferior pole ((Ferretti et al., 1983) with permission)

The distinct clinical presentation of tendinopathy (local load-based pain) does not vary with duration of symptoms (Kountouris and Cook, 2007), unlike other pain conditions where chronicity can result in spreading of symptoms and an increased size of the region where a stimulus may provoke symptoms (Giesecke et al., 2004, O'Neill et al., 2011). However, despite the persistence of tendon pain and the tendency to recur, there has been little investigation of the involvement of the central nervous system (CNS) and in particular, corticospinal control of muscle in people with tendon pain.

1.2 Terminology associated with corticospinal responses

Transcranial magnetic stimulation was used throughout all studies to quantify corticospinal responses of the quadriceps muscle (represented by rectus femoris). The theory that underpins TMS is detailed in section 2.13.2. The TMS method(s) used are contained in each chapter and further detail is also provided (Appendix U). This section briefly describes TMS to enable an explanation of how the terms corticospinal excitability (CSE), short-interval intra-cortical inhibition (SICI) and corticospinal control of muscle will be used in this thesis.

Transcranial magnetic stimulation was used to deliver a magnetic stimulus over the M1 via a coil held over the skull in the region of the M1 that corresponds to the contralateral quadriceps muscle group based on human topography (Penfield and Boldery, 1937). This induced an electrical current, which at sufficient intensity activated the lateral corticospinal pathway. This in turn caused a muscle twitch in the target muscle, the rectus femoris in this thesis – and this twitch was recorded via surface electromyography (sEMG).

Activation of the M1 and the descending spinal pathway was quantified using single-pulse TMS. The active motor threshold (AMT) is the minimum stimulus required to obtain a response in the muscle detectable by sEMG (Groppa et al., 2012), and the muscle response is termed a motor evoked potential (MEP). Direct electrical stimulation of the femoral nerve that innervates the rectus femoris muscle produces a maximal compound wave (M_{WAVE}) and the plateau in muscle response at maximal stimulation is termed M_{MAX} (Lentz and Nielsen, 2002). The amplitude of the mean MEPs recorded during increasing M1 stimulus intensities were divided by M_{MAX} to create a stimulus response curve (Pearce et al., 2013a). The AMT and the slope of the curve are two representations of CSE (Kidgell and Pearce, 2011).

Cortical inhibition was tested in this work using paired-pulse TMS with a technique that enabled SICI to be measured (Ziemann, 2003). Short-interval intra-cortical inhibition provides information about the cortical inhibitory circuits, which measures the synaptic efficacy of the inhibitory neurons that synapse onto corticospinal cells located in the M1. When discussing the overall neural activation, the term *corticospinal control* will be used in this thesis to refer to the balance between the excitability (CSE) and inhibitory modulation (SICI). This controls the activation of the quadriceps muscle through the motorneuron pool that incorporates both spinal and supraspinal modulation (Gandevia, 2001). Corticospinal control is an important determinant of muscle function (Kidgell and Pearce, 2011).

Changes to corticospinal control – evidenced by changes to CSE and SICI – have been reported in other musculoskeletal (MSK) conditions (Chapter 2) but have been minimally investigated in tendinopathy with two studies investigating upper limb tendinopathy

(Ngomo et al., 2014, Schabrun et al., 2015). Although exercise based treatments are the cornerstone of rehabilitation for tendinopathy, the mechanisms behind the clinical improvement are largely unknown and clinical improvement is not reflected by improvements on imaging such as ultrasound (US) or Magnetic resonance imaging (MRI) (Drew et al., 2014). There is strong evidence that certain types of exercise, such as muscle strength training, can modify the CNS and in particular CSE and SICI (Goodwill et al., 2012, Kidgell and Pearce, 2010, Weier et al., 2012a). However, no studies have investigated the corticospinal response to strength training in tendinopathy, nor the potential for strength training interventions to induce analgesia within tendinopathy management.

1.3 Thesis aims

Patellar tendinopathy is a persistent pain state, yet the pain remains localised and temporally linked with tendon loading regardless of chronicity. This presents a quandary to physiologists, pain scientists, clinicians and patients alike. There has been little investigation of non-invasive interventions that may offer immediate analgesia for athletes with PT. While exercise-based interventions are the cornerstone of rehabilitation of tendinopathy, little is known about how different types of strength training may modulate the CNS and which type may be the most efficacious. The primary aim of this thesis was to quantify the corticospinal control of the quadriceps muscle in people with PT using transcranial magnetic stimulation, to provide novel information regarding the corticospinal inputs and direct future rehabilitation. The specific aims of this thesis by chapter were;

1.   To describe the current understanding of possible contributors to the pain of tendinopathy (Chapter 2).

2.   To compare the CSE of the quadriceps in jumping athletes with PT, other AKP and healthy activity matched controls (Chapter 3).

3.   To compare the effect of an acute bout of externally paced isometric and isotonic quadriceps muscle contractions on CSE, SICI and tendon pain (Chapter 4).

4.   To compare the effect of externally paced isometric with isotonic strength training on immediate tendon pain changes, CSE and SICI among jumping athletes during the competitive season (Chapter 5).

5.   To review the changes to the M1 in tendinopathy and parameters in strength training that optimise neuroplasticity of the M1 (Chapter 6).

Individual aims and hypotheses are provided in each chapter.

1.4 Outline of chapters

This thesis contains seven chapters consisting of:

Chapter 2 reviews the literature on the potential local nociceptive drivers of tendon pain and the associated motor and sensory changes. The CNS contribution to the clinical presentation of pain and dysfunction was explored. Chapter 2 also reviews quantification of corticospinal responses; and the effect of strength training on tendon and muscle function; and the corticospinal control of the quadriceps muscle.

Chapter 3 reports a cross sectional study that investigated CSE in jumping athletes with and without AKP. Anterior knee pain was sub-grouped into PT and other AKP for analysis.

Chapter 4 presents a single blinded randomised cross over study that compared an acute bout of externally paced strength training that involved either isometric or isotonic muscle contractions for their effect on CSE, SICI, maximal voluntary isometric contraction (MVIC) quadriceps torque and tendon pain immediately and 45 minutes after intervention.

Chapter 5 reports a randomised clinical trial (RCT) with two externally paced strength training intervention arms, which compared isometric and isotonic strength training for immediate analgesic effect over a 4-week inseason intervention.

Chapter 6 presents a concept paper regarding the potential use of heavy externally paced strength training in tendinopathy to address pain and corticospinal control of muscle.

Chapter 7 summarises the main findings of the studies and compares with other MSK pain presentations that have been reported in the literature, highlights the strengths and limitations of studies in this thesis, as well as discusses potential future research directions.

This thesis is submitted by publication with two chapters published in peer-reviewed journals, one chapter accepted with major changes, one paper under peer review and one in submission. For this reason, there is a degree of repetition across the chapters, particularly in the methods. Due to the large number of abbreviations associated with the work, the full term is used at the start of each chapter or if the term has not been recently used, for the benefit of the reader. Each chapter contains an introduction prior to the manuscript and the publication commences with the abstract. A single reference list is provided and figures and tables are listed in numerical order within the thesis.

Chapter 2. Literature review.

A comprehensive search of the literature on local nociceptive drivers and potential central nervous system (CNS) changes in tendinopathy was undertaken and published (section 2.2-2.8). For cohesion of the thesis, the manuscript is embedded within this chapter including updated references; the original typeset version is provided (Appendix C). Section 2.9-2.13 provides an overview of the patellar tendon, patellar tendinopathy (PT), the neuroplasticity of the M1 and the corticospinal responses to strength training.

2.1 Declaration of thesis for Chapter 2

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
The pain of tendinopathy: physiological or pathophysiological? An overview of patellar tendon, PT, neuroplasticity and corticospinal responses to strength training.	70

The following co-authors contributed to this work:

Name	Nature of contribution
Moseley GL	Preparation of the manuscript
Purdam C	Preparation of the manuscript
Samiric T	Preparation of the manuscript

Kidgell D	Preparation of the manuscript
Pearce AJ	Preparation of the manuscript
Jaberzadeh S	Preparation of the manuscript
Cook J	Senior supervision and preparation of the manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidates and co-authors contributions to this work.

Candidate's signature (and date)

Main supervisor's signature (and date)

The pain of tendinopathy: physiological or pathophysiological?

2.2 Abstract

Tendon pain remains an enigma. Many clinical features are consistent with tissue disruption - the pain is localised, persistent and specifically associated with tendon loading, whereas others are not - investigations do not always match symptoms and painless tendons can be catastrophically degenerated. As such, the question "what causes a tendon to be painful?" remains unanswered. Without a proper understanding of the mechanism behind tendon pain, it is no surprise that treatments are often ineffective.

Tendon pain certainly serves to protect the area - this is a defining characteristic of pain - and there is often a plausible nociceptive contributor. However, the problem of tendon pain is that the relation between pain and evidence of tissue disruption is variable. The investigation into mechanisms for tendon pain should extend beyond local tissue changes and include peripheral and central mechanisms of nociception modulation.

This review integrates recent discoveries in diverse fields such as histology, physiology and neuroscience with clinical insight to present a current state of the art in tendon pain. New hypotheses for this condition are proposed, which focus on the potential role of tenocytes, mechanosensitive and chemosensitive receptors, the role of ion channels in nociception and pain and central mechanisms associated with load and threat monitoring.

2.3 Introduction

Tendon pain is baffling for clinicians and scientists alike. It is difficult to understand why it is so persistent and why it comes and goes with little reason. Scientifically this translates to the absence of a clear mechanism that can explain the clinical features of

tendon pain. It is therefore no surprise that treatments for tendon pain are often

ineffective (Cumpston et al., 2009, Buchbinder et al., 2011, Buchbinder et al., 2006,

Kingma et al., 2007).

Tendinopathy, the clinical syndrome of pain and dysfunction in a tendon, is often a

chronic condition (Kettunen et al., 2002). Like other chronic pain conditions, in

tendinopathy there is disconnect between tissue damage seen on clinical imaging and

clinical presentation, which creates confusion for both patients and clinicians. However,

key features of tendon pain are different from other chronic pain conditions. The purpose

of this chapter is to: i) explore the clinical questions surrounding tendon pain, ii)

summarise what is known about tendon pain iii) examine evidence from relevant fields to

provide direction for future research and iv) review the evidence for strength training and

neural adaptation for the management of tendon pain.

2.3.1 Clinical features of tendon pain

The clinical presentation of tendinopathy includes localised tendon pain with loading

(Cook and Khan, 2003, Cook and Purdam, 2003, Kountouris and Cook, 2007), tenderness

to palpation (Ramos et al., 2009) and impaired function (Khan et al., 2002, Maffulli et al.,

1998, Silbernagel et al., 2007c). Pain defines the clinical presentation (Maffulli et al.,

1998), regardless of the degree of tendon pathology (Cook et al., 2004a). Tendinopathy,

despite being an umbrella term, is usually limited to intra-tendinous presentations, with

more specific terminology being applied to pathology in surrounding tissue with different

disease processes, such as paratendinitis (Maffulli et al., 1998).

Microscopic examination of tissue biopsies from painful tendon reveals variable features

of tendon pathology including collagen disorientation, disorganisation and fibre

separation, increased proteoglycans and water, increased prominence of cells, and areas with or without neovascularisation, which collectively is termed tendinosis (Khan et al., 2000). Many imaging studies (i.e. ultrasound [US], magnetic resonance imaging [MRI]) indicate that these changes can exist in the tendon without pain, and people without symptoms rarely present clinically. Therefore, tendinosis may be an incidental examination finding and does not in itself constitute the diagnosis of tendinopathy, which requires clinical symptoms (Maffulli et al., 1998).

Tendon pain has a transient on/off nature closely linked to loading, and excessive energy storage and release in the tendon most commonly precedes symptoms (Lichtwark and Wilson, 2005, Bagge et al., 2011, Cook et al., 2002, Ferretti, 1986). Pain is rarely experienced at rest or during low load tendon activities; for example, a person with PT will describe jumping as exquisitely painful yet not experience pain with cycling due to the different demands on the musculotendinous unit. A further characteristic pain pattern is that the tendon "warms up", becoming less painful over the course of an activity, only to become very painful at variable times after exercise (Kountouris and Cook, 2007).

2.3.2 Defining pain concepts

Clinicians and researchers distinguish between physiological and pathophysiological pain. Physiological or 'nociceptive' pain is considered to reflect activation of primary nociceptors following actual or impending tissue damage or in association with inflammation. This type of pain is a helpful warning sign and is considered to be of evolutionary importance. Pathophysiological pain is associated with functional changes within the nervous system such as ectopic generation of action potentials and stimulus independent pain (Amir et al., 2005), facilitation of synaptic transmission (Takasusuki et

al., 2007), loss of synaptic connectivity (Costigan and Woolf, 2000), formation of new synaptic circuits (Fitzgerald, 2005), and neuroimmune interactions as well as cortical topographical changes (Costigan and Woolf, 2000), making it resistant to tissue-based treatments and it appears to provide no evolutionary advantage or helpful warning. Some aspects of tendinopathy fit more clearly into pathophysiological pain. Painful tendons can have little pathology (Cook et al., 2004a, Malliaras and Cook, 2006) and pain can persist for years (Cook et al., 1997). Furthermore, pain during tendon rehabilitation exercises has been encouraged (Jonsson and Alfredson, 2005b, Young et al., 2005a, Ohberg et al., 2004, Fahlstrom et al., 2003) and may not be deleterious (Silbernagel et al., 2007a), providing evidence that tendon pain does not necessarily equate with tissue damage. Overuse tendon injury does not involve an inflammatory process with a clear end point that underpins most physiological pain (see section 2.4 for more detail). However, other aspects of tendinopathy fit more clearly into physiological pain - pain remains confined to the tendon (Ramos et al., 2009) and is closely linked temporally to tissue loading (Wilson and Best, 2005). A clinical presentation that fails to be explained by either pain state classification is the rupture of a pathological yet pain free tendon, where nociceptive input would have been advantageous.

In order to explore the cause of tendon pain, it is helpful to briefly review newer concepts of pain. Modern understanding of pain suggests that nociception is neither sufficient nor necessary for pain (Butler, 2009). Nociception refers to activity in primary afferent nociceptors – unmyelinated C fibres and thinly myelinated Aδ fibres – and their projections to the cortex via the lateral spinothalamic tract (Figure 2.1). The projections terminate in multiple regions but predominantly the thalamus, which transmits impulses

to the somatosensory cortex. Primary nociceptors respond to thermal, mechanical or chemical stimuli. In contrast, neuralgia describes pain in association with demonstrable nerve damage and is often felt, along with other sensory symptoms, along the length of the nerve or its peripheral distribution.

Pain, on the other hand, is an emergent property of the brain of the person in pain (Thacker and Moseley, 2012). A useful conceptualisation is that pain emerges into consciousness in association with an individually-specific pattern of activity across cortical and subcortical brain cells (Tracey and Mantyh, 2007). Innumerable experiments and common every-day experiences show that pain is most often triggered by nociceptive input. However, carefully designed experiments in healthy volunteers show that pain can be evoked without activating nociceptors (Bayer et al., 1991) and that pain is readily modulated by a range of contextual and cognitive factors (Moseley and Arntz, 2007).
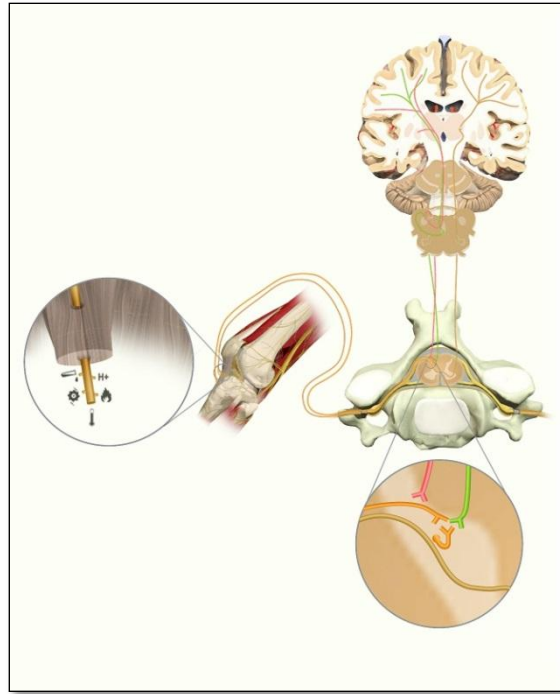
Figure 2.1 Schematic representation of the basic physiology of tendon pain (adapted

from (Kuner, 2010, Alberts et al., 2008) and used with permission)

The peripheral end of nociceptors, or free nerve endings, on thin unmyelinated (type C fibres) or thinly myelinated

(type A delta fibres) situated in the peritendon and the peripheral portions of tendon tissue contain thermal, heat and

mechanically activated ion channels. Changes in the chemical thermal or mechanical environment are transformed

here to elicit signals or action potentials in the nociceptor. The signal travels to the dorsal horn of the spinal cord (in

the superficial laminae I and II), where the nociceptor synapses with second order or spinal nociceptor. The spinal

nociceptor sends a signal to the thalamus via the lateral spinothalamic tract and thence the brain. The medial aspect of

the spinothalamic tract and the spinoparabrachial tract project to medial thalamus and limbic structures and are believed

to mediate the emotional component of pain. A complex evaluative process occurs across multiple brain areas and

protective outputs are activated. One such output is pain. Others include motor output, autonomic, endocrine and

immune activation. In addition, descending projections (shown here in red and green) modulate nuclei in the

brainstem, which in turn send signals down the spinal cord to modulate the same synapse in the dorsal horn. These

neurones are activated to either facilitate or inhibit the spinal synapse, thereby either turning nociception up, or turning

it down. The manner of modulation here depends on the brain's evaluation of the need for pain and protection. As

such, the spinal cord represents the first stage of integration and processing of the nociceptive signal.

The relationship between nociception and pain becomes more tenuous as pain persists, and research has uncovered profound changes in the response profile of neurons within the nociceptive neuroaxis (Moseley and Flor, 2012). The mechanisms that underlie these changes have been extensively reviewed (Wand et al., 2011, Moseley and Flor, 2012, Woolf and Salter, 2006). The clinical manifestations of these changes -- sensitisation and disinhibition (or 'imprecision') -- are important because they can be compared and contrasted with the clinical presentation of tendinopathy. Sensitisation refers to an upregulation of the relationship between stimulus and response where pain is evoked by stimuli that do not normally evoke pain – allodynia – and stimuli that normally evoke pain evoke more pain than normal – hyperalgesia. Allodynia and primary hyperalgesia are attributed to sensitisation of the primary nociceptor and relate to the area of usual pain. In tendinopathy, if normally pain-free movements, for example jumping, evoke tendon pain, this can be termed allodynia. If palpation of the Achilles tendon evokes more pain than usual, this can be termed primary hyperalgesia. In both scenarios, the tendon pain mechanism is over-sensitive. Notably, tendon palpation is only a moderately sensitive clinical test (Cook et al., 2001b) and tenderness, or primary hyperalgesia does not correlate with tendon function.

Secondary hyperalgesia and allodynia are attributed to sensitisation of nociceptive neurons within the CNS, collectively called central sensitisation, and relate clinically to areas away from the primary 'zone'. Tenderness and evoked pain that spread, in a non-dermatomal, non-peripheral nerve distribution is best explained by central sensitisation (Woolf, 2000).

The astute clinician will observe that, in the clinical presentation of tendinopathy, there is clear evidence of allodynia and primary, but not secondary, hyperalgesia (Kettunen et al., 2002). This observation strongly implies the tendon tissue or the primary nociceptors that innervate it, are the nociceptive driver of tendon pain. We must look then more closely for potential local sources of nociception. However, tendinopathy is a chronic and persistent pain state and thus a scientist will ponder whether tendinopathy exhibits subclinical signs of central sensitisation and disinhibition identified in other chronic painful conditions (Leis et al., 2004, Schwenkreis et al., 2003, Stanton et al., 2012). We must then also look for potential central contributions to tendinopathy that may promote chronicity but not manifest in secondary hyperalgesia. To do this it is important to understand normal and pathological tendon structure.

2.4 Tendon histology and pathology

2.4.1 Normal tendon

Normal tendons are mainly composed of fibroblastic tendon cells, called tenocytes, surrounded by extensive extracellular matrix (ECM). The ECM is predominantly made up of tightly packed collagen fibres (mainly Type I) that are orientated along the primary loading direction (Donnelly et al., 2010). Also present are several proteoglycans (PG) (mainly small molecular weight decorin) and other non-collagenous proteins. Connective tissue both surrounds the tendon (peritendon) and infiltrates the tendon (endotendon).

Tenocytes manufacture all of the components of the ECM (Kjaer et al., 2009). Tenocytes lie end to end in channels between collagen fibres, with cell processes linking the cells within and between rows allowing communication (McNeilly et al., 1996). Gap

junctions that link cell processes are capable of being remodelled in hours (Maeda et al., 2012), and appear to couple cells metabolically, chemically and electrically (McNeilly et al., 1996, Alberts et al., 2008, Maeda et al., 2012). They allow rapid exchange of ions and small metabolites between cells and different types have shown to be stimulatory and inhibitory in response to load (Waggett et al., 2006). Gap junction channels are gated open more often than closed, therefore it is the selectivity of the channel that dictates what passes from cell to cell (Goldberg et al., 2004). The probability of gap junction channels being open or closed is influenced by pH, calcium concentration, the voltage across the gap junction and mechanical load (Maeda et al., 2012, Maeda and Tsukihara, 2011).

Whilst tenocytes have important roles in manufacturing ECM and load sensing, there are other cell types in tendon whose role is currently unclear, including a multi-potent population capable of differentiation (Roufosse et al., 2004, Bi et al., 2007). Mast cells, associated with immune function and found near blood vessels in tendon (Scott et al., 2008) are bone marrow derived and capable of phagocytosis, cytokine production, vasoactive substance release and immune receptor expression. Glial cells, not yet investigated in tendon but evident in other connective tissues (Kasantikul and Shuangshoti, 1989), share a bone marrow lineage (Bossolasco et al., 2005) and an immune role. Glial cells, which are capable of neurotransmission in chronic injury (Wieseler-Frank et al., 2004), communicate information between the peripheral nervous system (PNS) and CNS (Neumann, 2001, Jessen and Mirsky, 2005) and when activated are implicated in ongoing pain (Cao and Zhang, 2008) and may be another cell type potentially involved in tendon pain. Classic inflammatory cell types have been

associated with rupture (Cetti et al., 2003) but have been infrequently shown in chronic tendinopathy (Alfredson et al., 1999).

2.4.1.1 What is the neural supply to the tendon?

Tendon pain is well localised (implying small receptive fields) (Feindel et al., 1948), occurs instantly with loading (implicating the involvement of myelinated/fast fibres) yet 'warms up' (implying a gating mechanism or exercise-induced inhibition). However, few studies have investigated these neural pathways.

Innervation studies in human tendon show scant innervation in the tendon proper, however tendon connective tissue and blood vessels are well innervated (Bjur et al., 2005, Danielson et al., 2006b) with three neuronal signalling pathways; autonomic, sensory and glutamatergic (Bjur et al., 2008, Danielson et al., 2006a, Danielson et al., 2006b). Autonomic nerves, particularly sympathetic nerve endings in blood vessel walls (Lian et al., 2006), have been reported in the tendon, peritendon and endotendon of the patellar tendon (Danielson et al., 2007a, Danielson et al., 2008). Sensory and sympathetic perivascular innervation of the walls of large and small blood vessels occur in peritendinous loose connective tissue, and there are some sensory nerve endings in the superficial endotendon (Bjur et al., 2005). Sparse sensory nerves have been identified in the body of the patellar tendon (Danielson et al., 2006a, Lian et al., 2006), in contrast surrounding structures such as retinaculum and fat pad are richly innervated (Goucke, 2003, Shaw et al., 2007, Benjamin et al., 2004). Mechanoreceptors are concentrated at myotendinous junctions and tendon insertions.

2.4.2 Tendon pathology

Tendon pathology results in cell activation and proliferation, matrix change (collagen disorganisation and increased large PG) and neovascularisation, in various combinations and severity (Jozsa et al., 1990, Cook et al., 2005, Alfredson, 2003). Tendon pathology is not always painful (Gisslen et al., 2005) but clinical presentation of tendinopathy is almost always associated with pain (tendon rupture may have been previously pain free). Change in collagen structure is the most obvious candidate for nociception because it is the load bearing structure in tendon, but loss of collagen integrity does not correlate with tendon pain (Cook et al., 2004a). In fact, pain-free tendons can have sufficient structural disorganisation that they rupture (Kannus and Jozsa, 1991).

2.4.2.1 Does the innervation pattern change with pathology?

There are few afferent nerves within tendon, and innervation patterns do not change with pathology (Bjur et al., 2005, Ackermann et al., 2001). New vessels primarily bring autonomic vasomotor nerves (and some sensory nerves) but neovascularisation is not present in every painful tendon. Tendon pain may be associated with nerve ending sprouting, or changes to nerve function rather than type, for example Aβ fibre activation can cause pain when there is production of nociceptive substances and/or central sensitisation (Butler, 2009, Woolf and Salter, 2006, Woolf, 2000).

Innervation may not be uniform throughout a pathological tendon. The area dorsal to the proximal patellar tendon, which is targeted in some injectable and surgical interventions because of the neovascularity in this area, has mainly sympathetic nerves and few sensory nerves (Danielson et al., 2008). The vessels display marked perivascular innervations and adrenoreceptor immunoreactions (Danielson et al., 2008).

These changes to innervation do not appear to explain the clinical features of tendon pain. To reflect all the clinical features, the local nociceptor must have a threshold for activation, be responsive to mechanical stimuli and exhibit saturation. Tendon pain may result from non-nociceptive pathways playing nociceptive roles.

2.5 Potential contributors to pain

If local nociception drives tendon pain then the nociceptive signal needs to be relayed to the CNS. One way to interrogate the nociceptive capability of tissue is via experimentally induced pain. Hypertonic saline activates nociceptors via chemically-driven ion channels. Hypertonic saline injected into healthy tendon induces pain and mechanical sensitivity but no pain referral – a pain pattern similar to that of load induced tendinopathy (Slater et al., 2011). In contrast, hypertonic saline injected intramuscularly evokes referred pain (Graven-Nielsen et al., 1997), which clearly implicates convergence within the CNS. However, chemically induced experimental pain studies do not mimic the characteristic load-dependent nature of tendinopathy pain (Gibson et al., 2006). A complementary approach is to look more closely at the tendon itself. As classical (i.e. cell-mediated/prostaglandin-driven) inflammation has not been associated with tendinopathy and as the innervation pattern does not differ greatly for normal and pathological tendon, potential sources of nociception in tendon include changes in the matrix, vascular supply, cell function, bioactive substance production, ion channel expression, cytokine and neurotransmitter expression, metabolism and mechanotransduction) or a combination of these.

2.5.1 Matrix changes

The increased production of large PGs seen with tendon pathology, most notably aggrecan, may compromise cell adhesion, migration and proliferation and interfere with cell-matrix interaction (Wight et al., 1992). Large PGs, particularly aggrecan, attract and bind water causing the tendon to swell, which will stimulate local C fibres (Fu et al., 2007) and increase interstitial potassium (K+) and hydrogen (H+) concentrations. This in turn can stimulate nociceptors and influence ion channel expression and/or activation. Kubo et al (2012) reported that nociceptive neurons were sensitised by low pH through augmenting the mechanical response of thin fibre afferents, and that this sensitisation was attenuated by versican, but not by blocking intracellular signalling pathways.

Larger PGs may also disrupt mechanotransduction, reducing communication between cells and between the cells and the ECM (Waggett et al., 2006). This may result in a loss of gap junctions between parallel rows of tenocytes (mediated by connexin 43) and even between longitudinal cells. It is feasible that disruption of gap junctions alters tendon homeostasis sufficiently to activate nociceptors. Cell and consequent matrix changes may also compromise gap junction permeability and ion channels that regulate neuronal excitability (Grillner, 2003). Conversely, the disruption of communication in a disordered matrix may protect the tendon by isolating the cell and preventing toxic communication of substances to healthy neighbours.

2.5.2 Vascular change

Increased vascularity has been reported to be a source of nociception in tendinopathy (Cook et al., 2005, Ohberg et al., 2001). Nerves, and receptors such as adrenoreceptors, are found in vessel walls in tendinosis and are likely to be associated with angiogenesis

and blood flow rather than having any role in nociception. As the tenocyte is responsible for producing the components of the ECM, stimulation of tenocyte receptors may drive structural change rather than be involved in nociception (Danielson, 2009).

Neovascularisation has been associated with degenerative tendinopathy but is not a feature of early pathology (Cook et al., 2004a). Not all painful tendons have increased vascularity (Cook et al., 2005, Cook et al., 1998) and vice versa (Cook et al., 2005), therefore the vessels or the nerves and receptors on vessel walls fail to explain tendon pain across all pathological presentations. Sclerosing treatment of neovascularity has resulted in variable improvements in pain and vascularity (Alfredson et al., 2006, Alfredson and Ohberg, 2005, Hoksrud and Bahr, 2011, van Sterkenburg et al., 2010). Sclerosants may work by changing the biochemical environment or disrupting neural pathways. If local nociceptors are critical to tendon pain, then they must be present across all stages of pathological change, in which case the tenocyte may be the key.

2.5.3 Tenocyte changes in structure and function

Tenocytes respond to changes in their mechanical, ionic and osmotic environment (Backman and Danielson, 2011, Andersson et al., 2008, Danielson et al., 2007c). In tendinopathy, tenocytes proliferate, become more rounded, and contain a higher proportion of protein-producing organelles (Cook et al., 2004a). These changes appear to increase production of substances and receptors involved in nociception (section 2.3.4). Cell changes may also alter gap junction function and affect cell communication, nociception transmission or mechanotransduction, affecting tendon homeostasis and possibly nociceptive communication (Waggett et al., 2006). In addition to changes in cell

structure and communication, the biochemical environment in tendinopathy has a myriad of substances that may be involved in nociception and further alter cell function.

2.5.4 Biochemical changes: cytokines, neuropeptides and neurotransmitters

There are many biochemical changes in tendinopathy, none of which can fully explain tendon pain. Bioactive substances and their receptors may be important in pain behaviour. Neuropeptides and neurotransmitters, formerly attributed only to neurons, are now known to also be produced by tenocytes.

Autocrine signalling occurs when a signalling molecule binds to a receptor on the same cell type. Paracrine cell signalling functions by signalling to another cell type. Signalling agents can have very short half-lives (for example nitric oxide (NO) is less than 0.1s) and be influenced by the presence of concurrent substances such as glutamate and calcium ions (Ca^{2+})(Zhao et al., 1999). It is not clear whether autocrine or paracrine signalling has a role in tendon pain.

Tendon pain is likely mediated by substances that have pro- and anti-inflammatory effects, for example cytokines (tumour necrosis factor-alpha (TNFα) and interleukin 1β (IL-1β),signalling molecules (Ca^{2+}, adenosine triphosphate [ATP]), neuropeptides (substance P [SP], neuropeptide Y) and neurotransmitters such as glutamate. These substances have been studied in other chronic pain conditions (Parkitny et al., 2012) and may be important contributors to tendinopathy (both pain and pathology). Cytokines are involved in intercellular communication and modulation of gene expression. The TNFα system, implicated in tendinopathy and possibly activated by mechanotransduction, seems to be involved in matrix structure change and is capable of inducing apoptosis

(Hosaka et al., 2005, Millar et al., 2009, Gaida et al., 2012, John et al., 2010, Uchida et al., 2005). TNFα also causes a dose-dependent increase in afferent Aδ and C firing and may have a role in tendinopathy nociception (Sorkin et al., 1997). IL- 1β, upregulated in a human tendon cell culture model, is capable of causing cell proliferation and apoptosis (Tsuzaki et al., 2003). These cytokines do not show rapid on/off response profiles, but that does not exclude them from being important in tendinopathy. Substances such as TNFα and interleukin-6 (IL-6) are among those that have thus far been studied in tendinopathy, yet there are many other cytokines that might play a role. Glial cells, a primary expressor of such cytokines, are critical for synaptic transmission (Guo et al., 2007) in spinal or supraspinal communication (Wei et al., 2008), and may be a feasible mechanism by which nociception could be upregulated at the level of the CNS.

Neuropeptides such as SP and calcitonin gene-related peptide (CGRP) transmit signals across a synapse. Both SP and CGRP are released by the terminals of nociceptors and SP has been shown to be released by tenocytes. SP afferent immunoreactivity has been demonstrated at the enthesis (Ljung et al., 2004) and in tendon tissue (Danielson et al., 2006a, Bjur et al., 2005), which indicates thin fibre sensory innervation, most likely serving a nociceptive function. Substance P (and its receptor, neurokinin-1 receptor [NK-1 R]) and CGRP have also been identified in nerve fascicles in large and small blood vessels in tendinopathy (Alfredson and Lorentzon, 2007). Binding of SP to its receptor has been associated with the transmission of nociception (Levine et al., 1993).

Substance P can cause vasodilation and protein extravasation in surrounding tissue – a process termed neurogenic or peptidergic inflammation. Substance P increases cell metabolism, cell viability and cell proliferation in tenocytes (Backman et al., 2011). The

peptidergic inflammatory mechanism of nociceptors is initiated by nociceptor activation. However, antidromic mechanisms driven within the CNS can lead to peptidergic inflammation and this raises the possibility that central mechanisms influence tendon pain.

Acetylcholine (ACh), a neurotransmitter in the CNS and PNS that is also produced by activated tenocytes (Danielson et al., 2007c), is capable of modulating nociceptive input, influencing collagen production, inducing cell proliferation, and regulating vessel tone (Vogelsang et al., 1995, Danielson et al., 2007b). Muscarinic ACh receptors of subtype M2 (M2Rs) have been found on tenocytes (in tendons with hypercellularity), nerve fascicles and the local blood vessel walls (Danielson et al., 2007b). Upregulation in the cholinergic patterning also correlated with recalcitrance to treatment (Danielson et al., 2007c).

Immunoreactions for adrenergic receptors have been found in blood vessel walls, tenocytes and in some of the nerve fascicles in the patellar tendon (Danielson et al., 2007b). Increases in nerve fibres showing neuropeptide Y immunoreactions as well as those involved in synthesis pathway of norepinephrine and epinephrine and their receptors have been observed in vessels in pathological tendon (Danielson et al., 2008, Danielson et al., 2007b).

Adenosine triphosphate can be released by neurons and has been implicated in both central and peripheral pain mechanisms as it functions as a signalling molecule (Newman, 2003). Adenosine triphosphate facilitates nociceptive behaviour and electrolyte transmission, elicits glutamate release (Burnstock and Sneddon, 1985,

Burnstock, 2006), acts directly on the dorsal horn, regulates cell death and vascular tone, degranulates mast cells and induces prostaglandin synthesis. Adenosine triphosphate is released from damaged cells (Cook and McCleskey, 2002) and could activate primary afferent nociceptors.

High intratendinous levels of glutamate and its receptor, the N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDA) receptor, have been demonstrated in tendinopathy (Scott et al., 2008, Schizas et al., 2012). Glutamate, also produced by the tenocyte, is involved in nociceptive modulation in other persistent pain states, is involved in vasomodulation, is capable of inducing oxidative stress has a role in ECM metabolism and is associated with tenocyte proliferation and apoptosis (Molloy et al., 2006, Takeuchi et al., 2006). Glutamate receptors can be activated by SP and it is the major neurotransmitter mediating fast excitatory transmission in the CNS. These factors seem to implicate glutamate in tendinopathy, however, resolution of tendon pain with rehabilitation does not change glutamate levels (Alfredson and Lorentzon, 2003). However, NMDA receptors require glutamate and glycine (also a neurotransmitter) interaction (Petrenko et al., 2003) so perhaps it is glycine levels that change (or another substance not examined). Notably, prolonged firing of C fibres is thought to increase glutamate release, which seems inconsistent with the on/off non-spreading nature of tendinopathy pain.

2.5.5 Biochemical changes: metabolites

All cells and tissues require the maintenance of intracellular and tissue pH, as many processes and proteins only function within specific pH ranges (Alberts et al., 2008). Cell membrane potential, which is the difference in voltage between the inside and outside of the cell, determines the excitability of the cell and is influenced by tissue pH.

Lactate can decrease pH, and microdialysis of tendinopathic tissue showed lactate levels at rest were double that shown in healthy control tendon (Alfredson et al., 2002). Increased lactate, due to a predominant anaerobic metabolism, occurs in tendons of older people as well as tendinopathy (Tuite et al., 1997, Floridi et al., 1981), and is compounded by the high metabolic rate in tendon pathology (25 times that of normal tendon) (Parkinson et al., 2010).

At physiological pH, lactic acid almost completely dissociates to lactate and hydrogen ions, the latter are known to modulate nociceptor activity and alter ion channel expression (Uchiyama et al., 2007). Lactate is not just a waste product; it is an active metabolite, capable of moving between cells, tissues and organs. Lactate can stimulate collagen production and deposition, activate tenocytes (Klein et al., 2001) and increase vascular endothelial growth factor (VEGF) and neovascularisation (Trabold et al., 2003). Lactate also closes the inhibitory gap junctions between rows of tenocytes, which may exaggerate response to loading (Ek-Vitorin et al., 1996).

Accumulated lactate has been associated with pain in other tissues such as cardiac and skeletal muscle and the intervertebral disc (IVD) (Uchiyama et al., 2007), but it has not been fully investigated for tendons. It is notable that tendon pain has some features that are consistent with accumulated lactate: rapid easing in symptoms after a change of posture (sustained positions are painful in tendinopathy), poor response to anti-inflammatory medication (true in tendons for most anti-inflammatory medications, those that alter pain and function appear to do so by tenocyte down regulation and PG inhibition (Christensen et al., 2011, Riley et al., 2001) and sometimes no evidence of clear pathology (Butler, 2009). However, other features require further explanation –

transient load-dependent pain (requires gating) and decreasing pain with ongoing activity (implies saturation).

2.5.6 Cell changes: ion channels

Ion channels, present in cell membranes, alter the flow of ions in and out of a cell and respond to voltage, movement or chemicals. Ion channels in tenocytes may perform a number of roles including mediation of calcium signalling, osmoregulation and cell volume control, control of resting membrane potential levels and the detection of mechanical stimuli (Magra et al., 2007). Ion channels are important in tendon pain; they may be involved in sensing the nociceptive stimuli, communicating with the afferent nerves and neuronal transmission to and within the cortex.

Ion channels are often linked to the cytoskeleton and to an extracellular structure, allowing them to be directly gated by mechanical deformation and almost certainly altered with a change to tenocyte shape with tendinopathy. On nerve cells they enable neuronal communication (in both the PNS and CNS), communication between different tissue types, and the conversion of a force or load into an action potential in a nerve.

2.5.6.1 Ion channels: sensing the stimulus

Ion channel expression is likely to change in tendinopathy because of a more acidic environment due to excess lactate. A decrease of the extracellular pH influences the expression of acid sensing ion channels (ASIC) (Kellenberger and Schild, 2002). The magnitude of currents in ASICs is sufficient to initiate action potentials in neurons (Kellenberger and Schild, 2002), ASICs are activated quickly by hydrogen ions and inactivate rapidly despite continued presence of low pH, exhibiting features of saturation.

Acid sensing ion channels have been associated with painful conditions that have accompanying tissue acidosis and ischemia, and they were therefore originally thought to only be expressed by neurons. However, connective tissue cells of the IVD (Uchiyama et al., 2008, Uchiyama et al., 2007), bone cells (Jahr et al., 2005), chondrocytes and synoviocytes (Rong et al., 2012, Yuan et al., 2010, Kolker et al., 2010) have been shown to express ASICs. These connective tissues share similarities with tendon; low blood supply, few nerves, subject to compression and tension and pain that is not always correlated with tissue damage (Jensen et al., 1994). In IVDs and articular cartilage, cell metabolism is almost entirely anaerobic (Risbud et al., 2006, Agrawal et al., 2007) and the tissues have high lactate levels and low pH, similar to tendinopathy. In bone, an acidic environment directly impedes osteocyte activity (Arnett, 2008), thus ASICs have a role not only in nociception but also cell activity.

Other ion channels in tendons may be important in nociception. The transient receptor potential cation channel subfamily V member 1 ion channel (TrpV1) is believed to function as a molecular integrator of noxious stimuli including heat, acid and endogenous pro-inflammatory substances (Cortright and Szallasi, 2004). Stretch-activated ion channels (SAC), voltage-operated ion channels (Wall and Banes, 2005, Banes et al., 1995) or other mechanically gated channels may be implicated in nociception sensing and transmission (Sachs, 2010). Activation of SACs would fit the load based on/off nature of tendon pain and the clinical observation that pain gets stronger with increased loading (which would correlate with increased channel activation) and the "warming up" phenomenon as ion channels become saturated. Mechanosensitivity (membrane stretch, fluid flow etc.) is phenotypic (Sachs, 2010) and therefore SACs are likely to be selective

to other stimuli such as voltage or acid. SACs have been shown to be blocked by gadolinium and more specifically by mechanotoxin 4 (GsMTx4); a peptide that modulates ionic currents across calcium, sodium or potassium ion channels and blocks capsaicin receptor channels. Investigation of these blockers may lead to identification of potential treatment options for tendinopathy that may address both pain and the pathological process.

Voltage operated calcium channels (VOCC) have been demonstrated in human tenocytes, as well as the mechanosensitive tandem pore domain potassium channel (2PK (+)) TREK-1, which is sensitive to membrane stretch, intracellular pH and temperature (Magra et al., 2007). Importantly, these channels are known to be associated with electrically excitable cells (Catterall, 1998) so tenocytes may be capable of conducting an electrical potential as they open and close in response to voltage across the membrane.

2.5.6.2 Ion channels: communicating with nerves

To activate neuronal pathways, receptors and ion channels are required. Ion channel expression in tenocytes may change, but ion channel expression in the afferent nerve may also change in response to repeated activation (Woolf and Salter, 2000). This sensitises the primary neuron to the very stimulus that evoked the adjustment. Ion channels transduce noxious stimuli into neuron membrane depolarisations that trigger and conduct action potentials from the peripheral site to the synapse in the CNS (McCleskey and Gold, 1999). As there is a limited relationship between pain and the presence of neural ingrowth in humans (Cook et al., 2005), additional mechanisms may be performing a nociceptive function. Intercellular signalling via non-synaptic mechanisms are important in the nervous system and between tissues and the nervous system but are not as clearly

understood as synaptic communication (Barres, 1989). In fact, cells may communicate with glial cells (Charles et al., 1991) via neurotransmitters through neurotransmitter-gated ion channels (Usowicz et al., 1989, Barres et al., 1990) and voltage gated ion channels (Barres et al., 1990); glial cells may also communicate among themselves. Cell-cell communication within a tendon and with the nearest sensory nerve may well occur via this form of signalling. Alternatively, perhaps load-sensing mechanisms within, or separate from, the tendon play a nociceptive function. If so, they would utilise complex threat-evaluation systems within the CNS.

2.6 How might these changes relate to tendon pain?

The presence of stretch and ion activated channels in either neurons or tenocytes would fit many features of tendon pain. Ion channels are normally closed in the absence of a stimulus, but open for a few milliseconds to allow equalisation along an electrical gradient (Johnson and Ascher, 1990). With prolonged (chemical or electrical) stimulation, many of these channels close and desensitise, leaving them refractory to further opening unless the stimulus is removed.

Although ASICs have not been studied in normal, pathological or painful tendons, the tendon environment can become acidic (Alfredson et al., 2002) to levels that would open ASIC channels if they were expressed by tenocytes or neurons. Desensitisation occurs with persistent stimulation of ASICs after approximately three minutes (Jones et al., 2004), which may explain the clinical feature of tendons being initially painful during activity then warming up. Recovery from desensitisation occurs slowly, over many hours, which may fit with later pain and stiffness. Acid sensing ion channels are rapidly activating and inactivating (< 5ms to activate, 400 ms to deactivate) (de Weille et al.,

1998) which may also fit with the on/off nature of tendon pain. Further investigation of the presence and role of ion channels in tendon pain is warranted.

To be a practical theory, tendon pain must be explained across the range of clinical presentations. These presentations may be a combined result of changes in structure, biochemical levels and cell function that interact to cause pain. Theoretically, in reactive tendinopathy (as described by Cook and Purdam 2009) there may be increased expression of nociceptive substances because of cell activation and proliferation, but no change in innervation. In degenerative tendinopathy there may be little expression of nociceptive substances due to cell inactivation or death but greater innervation. At both ends of the spectrum pain is possible. The painfree tendon may have substantial matrix disorganisation and cell compromise, but insufficient production of nociceptive substances and /or the neural network to reach a threshold to cause pain. An example is tendon rupture in asymptomatic people, where tissue threatening loads are not communicated to the CNS as pain prior to tendon rupture.

2.7 Central mechanisms – the spinal cord and brain

Primary nociceptors have their proximal synapse in the dorsal horn of the spinal cord where they communicate with spinal nociceptors, using glutamate or SP. The spinal nociceptor projects to the thalamus and then onward to access the network of cortical and subcortical areas associated with pain (Apkarian et al., 2005). Experimental pain studies reveal that the contralateral insular cortex, the anterior cingulate cortex, cerebellum, the contralateral thalamus, the putamen, primary and secondary somatosensory cortex, prefrontal cortex and premotor cortex are involved in the pain experience, although much variability exists (Minoshima and Casey, 1999, Casey, 1999b, Casey, 1999a, Crofford

and Casey, 1999, Coghill et al., 1999) and recent discoveries suggest this network of brain areas more accurately reflects a 'salience matrix' than a pain-dedicated matrix (Henry et al., 2011, Lee et al., 2009).

There is no theoretical or clinical reason to conclude that tendon pain serves an alternative purpose to other types of pain – to protect the painful part. This rather pragmatic view requires acceptance that the entire evaluation of whether or not a tendon is in danger occurs outside of consciousness, and that the spinal nociceptor is just one contributor to this evaluation. Theoretical models that attempt to integrate the research on pain all emphasise the multifactorial nature of pain and the complex and bidirectional interactions that occur between the state of the body and pain. This brings challenges because it raises the possibility that higher centres can target local tissues, if the brain concludes that they are in danger.

The tendon, attached bone and muscle, and overlying skin are all represented within the brain. All bodily representation (including motor, sensory, visual and auditory) is plastic and is influenced by use, injury, pain and disease (Henry et al., 2011, Chen et al., 2006, Schieber, 2001, Nudo et al., 2001, Bara-Jimenez et al., 1998, Rossini et al., 1994). Although motor and sensory representations, cortical excitability (or descending inhibition) and cognitive modulation of pain have all been well studied in other pain states, little research has been undertaken on tendon pain.

2.7.1 Does tendon pain centralise?

The PNS and CNS neural networks that mediate nociception demonstrate plasticity in pathological states (Kuner, 2010). The regions that are most likely upregulated are the

tendon itself, the nociceptor, the dorsal horn, or in the brain. Sustained peripheral nociceptive activity may lead to the development of central sensitisation (Butler, 2009). Although central sensitisation accounts for widespread pain and hyperalgesia/allodynia in chronic pain patients, excessive pain response is not a clinical feature of tendon pain regardless of symptom chronicity. This may be explained by the on/off nature of tendon pain, reducing the likelihood of long-term potentiation or depression, or local saturation of the receptor that would then fail to stimulate the afferent nerve.

Few studies have examined if upregulated central nociceptive processes are involved in tendon pain states (Slater et al., 2011, van Wilgen et al., 2013). Tendinopathy pain would seem a unique chronic pain because pain generally occurs during loading, and although there is more pain with increasing load it disappears once the load is removed. Spreading of pain (for example secondary hyperalgesia) is not a common clinical feature of tendinopathy, especially in the lower limb. However, developing symptoms on the other side is common (Paavola et al., 2000) and this mirroring is often attributed to bilateral loading patterns, although CNS neuroimmune mechanisms offer an equally feasible explanation (Guo et al., 2007). The odds ratio of rupturing the other Achilles tendon after a unilateral rupture is 176, when compared to the general population (6% of the participants ruptured the contralateral tendon) (Aroen et al., 2004). This may be due to high bilateral loads, but may also indicate central drivers to pathology and /or pain or systemic or genetic factors. Bilateral tendinopathy in both the loaded and unloaded limb of baseball pitchers would support this (Miniaci et al., 2002). This view is further strengthened by data from an animal model where bilateral cell changes were observed in

unilaterally loaded rabbits (Andersson et al., 2011) and a unilateral chemically induced model of tendinopathy in horses (Williams et al., 1984).

There are several features of tendon pain that suggest cortical changes. High frequency train of input (e.g. repetitive high tendon load) strengthens synaptic transmission, and makes the next cell within the CNS more excitable for several days (Woolf and Salter, 2000). In tendinopathy, substantial time between high loads is important to control pain (Kountouris and Cook, 2007). It is possible that this may be not only related to local tendon adaptation such as collagen production and local cellular responses, but also to the sensitivity of the pathway.

Tendon pain has been associated with local sensory change such as increased mechanical sensitivity (pain with activity and tendon pressure) (Maffulli et al., 2003, Almekinders et al., 2003). Individuals with unilateral lateral epicondylalgia (LE) demonstrated hyperalgesia and bilateral changes to pressure pain thresholds (Fernandez-Carnero et al., 2009). The affected side was worse than the unaffected side, and both sides were worse than controls. Individuals also showed bilateral changes to thermal sensitivity (Ruiz-Ruiz et al., 2011). These differences in mechanical and thermal hyperalgesia may indicate central sensitisation (or at least potentially secondary hyperalgesia). However, another study in tendons demonstrated no differences in cold and heat pain, cold and warm detection thresholds (van Wilgen et al., 2013). Furthermore, secondary hyperalgesia may simply reflect persistent nociceptive input as it has been demonstrated even in acute pain such as inversion ankle injury (Ramiro-Gonzalez et al., 2012).

Van Wigen et al (2013) completed quantitative sensory testing in people with and without patellar tendinopathy to assess central sensitisation. The pressure pain thresholds

of asymptomatic athletes differed significantly from athletes with a diagnosis of patellar tendinopathy (van Wilgen et al., 2013). Mechanical pain threshold and vibration threshold were found to be significantly lower in people with patellar tendinopathy. Reduced mechanical pain thresholds or pinprick allodynia may reflect the involvement of central sensitization (myelinated Aδ-fibres).

No study has investigated corticospinal responses of muscle in lower limb tendinopathies, there are two studies in the upper limb including one that investigated corticospinal excitability (CSE) of the infraspinatus in people with rotator cuff (RC) tendinopathy (Ngomo et al., 2014) and reported decreased CSE compared to the unaffected side (no control group). The second study reported increased CSE of affected muscles in people with persistent lateral elbow pain compared with a control group (Schabrun et al., 2015). Data appear conflicting and the measure used to represent CSE were different between studies. Furthermore, use-dependent plasticity may affect results, especially in upper limb studies. It is unclear if these findings may be translated to lower limb tendinopathy.

If there are minimal cortical changes in tendinopathy, it is important to know if a tendon transmits nociception in a way that protects the brain from central change. First, long term cortical plasticity changes involve long term potentiation (LTP) (repetitive increase in the strength of synaptic transmission that lasts for more than a few minutes) (Butler, 2009) or long term depression (LTD) (involving gamma-aminobutyric acid [GABAergic] pathways). The nature of tendon pain, being on/off, may prevent LTP or LTD. Second, local inflammation, which is not a feature of tendinopathy, is an important event in the onset of many chronic pain states (Skaper et al., 2012, Weng et al., 2012, Guillot et al., 2012, Latremoliere and Woolf, 2009, Padi and Kulkarni, 2008, Wu et al., 2008). During

inflammatory processes, pro-inflammatory mediators (e.g. prostaglandins etc.) that are released from damaged tissues activate receptors, stimulate mast cells to release further pro-inflammatory cytokines, which lowers nociceptive threshold firing and increases the rate of firing. Third, the activation of intracellular second messengers is required and subsequent alterations to gene and ion channel expression may be a more transient change with expression changing with the removal of the painful load.

2.7.2 Central mechanisms – future directions

There may be non-nociceptive mechanisms that play a nociceptive role in tendon pain. One such mechanism may be related to an internal calculation of tendon load. This idea is consistent with the modern idea of pain being about protection and not dependent on nociception, and shares characteristics with the central governor theory of fatigue (Noakes et al., 2004). Alternatively, tendon pain may reflect an error in the internal calculation of tendon load. Several of the local dysregulations discussed here could contribute to erroneous load-information. These ideas are speculative but not outrageous – that central evaluation of danger to body tissue modulates pain is well accepted (see (Butler and Moseley, 2003) for review), and that internal comparators evaluate predicted and actual motor responses has been established for some time (von Holst, 1954, Gandevia, 1996, Gandevia et al., 1996).

2.8 Summary of the current understanding of tendon pain

The molecular biology of tendon in pathological and healthy states highlights many potential contributors to pain and the search for these needs to extend beyond the tendon. Nociception could occur from cell–cell signalling via ion channels that communicate with an afferent neuron that could transmit, suppress or amplify the nociceptive signal.

Nociception may be modulated spinally or above and descending mechanisms may exert nociceptive pressure that manifest locally. Finally, pain could be evoked via non-nociceptive mechanisms through a load-detection system, which itself could be disrupted via local or central dysfunction. The question of the pain of tendinopathy, physiological or pathophysiological, remains unanswered; however there is evidence for both; tendon based nociceptive contributions and extensive mechanisms within the periphery and the CNS. Importantly for clinicians, tendon pain is complex and requires thorough assessment of both musculoskeletal and neural contributors as well as excellent clinical reasoning to account for nociceptive input from local tendon pathology as well as potential central mechanisms.

Although many tendons succumb to tendinopathy, few are suitable for studies on pain. Several tendons have complex surrounding structures that can contribute to nociception, some, such as the Achilles affect a diverse group of people, and yet others are difficult to access, diagnose and image. On the other hand, the patellar tendon provides the best model to investigate tendon pain, it occurs in a relatively homogeneous population (primarily young athletes that play jumping sports), it is a superficial tendon and the motor area in the cortex is accessible for investigation. Therefore the patellar tendon will be used in the studies in this thesis; the next section will review its clinical presentation.

2.9 Overview of the patellar tendon

The patellar tendon attaches the quadriceps muscle group (rectus femoris, vastus medialis, vastus lateralis and vastus intermedialis) to the tibial tuberosity and is an extension of the quadriceps tendon where the patellar is embedded as a sesamoid bone (Figure 2.2). A critical role of the patellar tendon in athletic activities is to store and

release energy during jumping and change of direction activities, making movements

faster and more metabolically efficient (Anderson and Pandy, 1993).
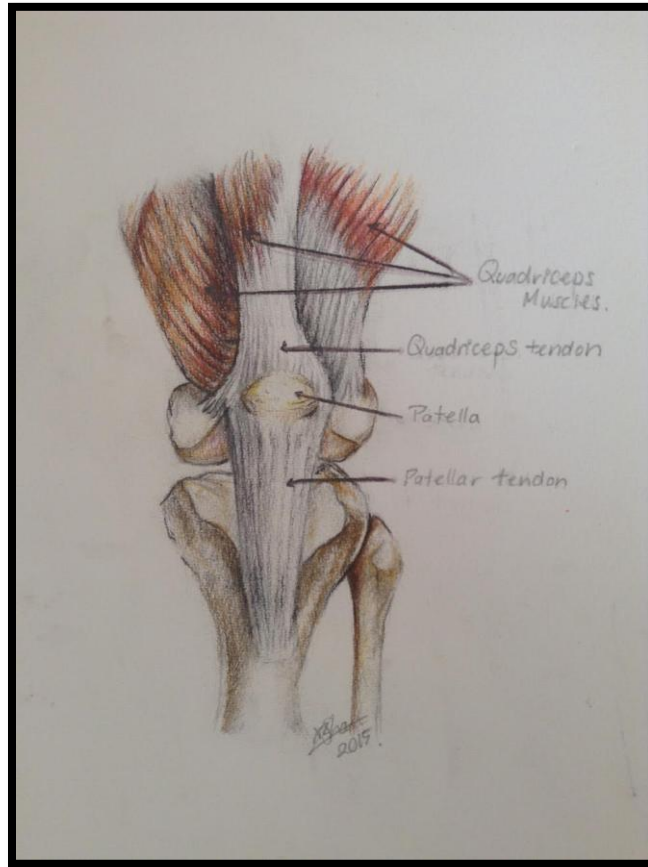
Figure 2.2 The patellar tendon in relation to quadriceps musculature and bony

landmarks (used with permission – artwork by Shan Shan Zhang).

Tendinopathy is most commonly related to the extrinsic factor of overload (Cook and

Purdam, 2009, Ferretti, 1986) though it is the result of a complex interaction between

intrinsic (person related) and extrinsic (environment related) risk factors.

2.10 Factors affecting tendon health

There are a number of intrinsic risk factors including medical conditions and anthromorphology (van der Worp et al., 2011) that are linked with tendinopathy including; rheumatologic conditions (example see (Mobasheri and Shakibaei, 2013, Filippucci et al., 2009, Burner and Rosenthal, 2009, Nalebuff and Potter, 1968)), diabetes (Sasaki et al., 2007, D'Ambrogi et al., 2005, Ramirez and Raskin, 1998, Machtey, 1986, Campbell and Feldman, 1975) and genetic based conditions that affect connective tissue such as Marfan syndrome and Ehlers–Danlos syndrome (Callewaert et al., 2008), physical attributes include increased waist to hip ratio (Rechardt et al., 2010, Gaida et al., 2010, Gaida et al., 2004, Cook et al., 2004b) and decreased ankle dorsiflexion lunge range (Backman and Danielson, 2011, Whitting et al., 2011, Malliaras et al., 2006b). These associated factors may reduce tendon capacity to repetitively transmit high tensile load during jumping and landing, leaving it vulnerable to overload and pain.

2.11 Patellar tendinopathy

Patellar tendinopathy (PT) is a common and debilitating injury that affects athletes in sports such as volleyball and basketball (Gisslen et al., 2005, Cook et al., 1997, Cook et al., 1998, Lian et al., 2005). Patellar tendinopathy is recalcitrant to treatment (Danielson et al., 2007c), impairs function (especially power based movements) and can cause a decline in performance or even withdrawal from health promoting physical activity (Cook et al., 1997). The seriousness of this condition was demonstrated by studies that showed 50% of athletes with patellar tendon injury were forced to retire from sport, and continued to have pain with stairs when surveyed 15-years later (Kettunen et al., 2002)

and more than a third of patients presenting to a sports medicine clinic with PT were unable to return to sport within six months (Cook et al., 1997).

The prolonged recovery may be partly attributed to the clinical features. A 'warm-up phenomenon' is well described where pain is diminished as exercise continues, only to be very painful the next day (Kountouris and Cook, 2007). Clinically, it is noted that this warm-up pattern is often confusing for people with PT and can result in fluctuations between overload (as the tendon warms up during activity so athletes continue) and rest / underload (as the tendon is very painful the next day thus athletes often feel the need to remove all load). Both underload and overload can be detrimental for tendon (Cook and Purdam, 2009). The attempt to control symptoms with fluctuation between loading and periods of rest may also delay consultation with a medical practitioner, diagnosis and rehabilitation (Khan and Maffulli, 1998).

2.11.1 Diagnosis of patellar tendinopathy

Patellar tendinopathy is a clinical diagnosis based on the presence of localised pain at the proximal attachment of the tendon to the patella (Ferretti et al., 1983, Khan et al., 1998, Cook et al., 2000a). Importantly, pain remains confined to the proximal attachment and temporally linked with loading regardless of the length of time of symptoms (Khan et al., 1998) and this feature of localised pain is used clinically to differentiate it from other potential diagnoses of anterior knee pain. Despite the localised nature of tendon pain, tendon palpation is only a moderately sensitive but not specific test, and mild tenderness is frequently present in asymptomatic jumping athletes (Cook et al., 2001b).

Patellar tendon pain is aggravated by tendon load that requires energy storage and release within the tendon, for example when jumping and landing (Cook and Purdam, 2003, Wilson and Best, 2005, Cook and Khan, 2003). In addition to a history of pain at the inferior pole of the patella with jumping and landing, the best clinical pain provocation test is the single leg decline squat (SLDS) (typical error measurement = 0.50, 95% CI 0.41-0.62, n = 50 knees) (Purdam et al., 2003) (Figure 2.3). This squat is completed on a board set at 25 degrees, which preferentially loads the patellar tendon (Zwerver et al., 2007, Kongsgaard et al., 2006). Pain at the inferior pole is recorded by the participant providing a numerical rating score between zero and ten with zero meaning no pain and ten denotes maximal pain. Importantly, while the SLDS may be provocative for other anterior knee pain conditions, the pain remains localised to the inferior pole in PT.

Figure 2.3 The single leg decline squat used to assess patellar tendon pain (Zwerver et al., 2007) used with permission

There is a poor correlation between pathology visualised on imaging and pain (Cook et al., 1998), therefore US or MRI are not considered essential to make a diagnosis. While abnormality on US itself does not constitute a diagnosis of tendinopathy, it can be used to establish the presence or absence of pathological tendon (Khan et al., 2002) and is considered superior to MRI for tendon imaging (Campbell and Grainger, 2001, Warden et al., 2007). The pathology is most commonly located in the posterior region (deepest portion) of the proximal patellar tendon as this area is most likely subjected to greater tensile strains especially during jumping and deep squatting (Dillon et al., 2008). There are various imaging appearances considered to represent pathological tendon, including

thickening and hypoechogenic areas within the tendon (Appendix V). More recent

advances in US technology such as ultrasound tissue characterisation (UTC) provide a

more sensitive assessment of tendon pathology than traditional greyscale US as the image

is standardised relative to a bony landmark (the patella) and the probe is fixed in a tracker

that eliminates errors associated with transducer tilt (Docking et al., 2012, van Schie et

al., 2010b).

2.11.2 Quantifying patellar tendon function

The Victorian Institute of Sport Assessment tool for the patellar tendon (VISA-P) is used

to quantify patellar tendon pain and function (Visentini et al., 1998) (Appendix W). The

VISA-P is scored out of 100 points, with 100 representing pain-free full function and

normal healthy individuals score 95-100 points (Visentini et al., 1998). The VISA-P has

high test-retest (r = .99, n = 54 knees) and inter-tester (r =. 99, n = 47 knees) reliability

(Khan et al., 1996) and a change in score of greater than 13 points (or >15.4% change

from original score) has been shown to be the minimum clinically important difference

(MCID) (Hernandez-Sanchez et al., 2014). The VISA-P is used both clinically and in

research to provide a measure of severity (lower scores indicate high levels of pain and

dysfunction) and quantify the effectiveness of interventions.

2.12 Current rehabilitation concepts in tendinopathy

2.12.1 Exercise stimulates tendon

Experimental pain studies in healthy people demonstrate that strength training has the

capacity to induce analgesia (Koltyn, 2000), and therefore warrants investigation in

tendon pain. Tendon load through exercise is the only stimulus used in rehabilitation of

tendinopathy that has been shown to positively affect the tendon matrix (Kjaer et al., 2009), reduce pain over time and improve function (Ingber, 2003a, Ingber, 2003b, Silbernagel et al., 2007a).

Loading induces tenocytes to produce structural proteins used in the extracellular matrix (ECM), and in vitro studies have shown that different loading stimuli alter tenocyte responses and ultimately tissue composition and tissue mechanics. For example, cyclical strain of around 10% of equine extensor tendons caused proliferation of tenocytes (Goodman et al., 2004), but at 5% strain no cell proliferation or increases in glycosaminoglycan (GAG) content were observed, only upregulation of collagen synthesis (Screen et al., 2005). Conversely, a lack of loading can negatively affect the ECM (Lavagnino and Arnoczky, 2005).

Reduction of load achieved through the release of loaded cell matrix gels resulted in increased breakdown of collagen and a reduction in type I collagen production at 24 hours (Lavagnino and Arnoczky, 2005). Similarly, removal of strain or inactivity causes tissue to become disorganised (Kjaer et al., 2005) thus altering the mechanical properties of the tendon. These laboratory based studies support the concept of optimisation of load in tendon rehabilitation.

In vivo studies have demonstrated that loading increased collagen turnover (Langberg et al., 2001) and tendon stiffness in trained athletes compared with controls (Couppe et al., 2008, Rosager et al., 2002) and in the elderly following strength training (Reeves et al., 2003). Increased collagen turnover has also been reported in tendinopathic tendons after eccentric training (Langberg et al., 2007) and heavy slow strength (concentric / eccentric)

training (Kongsgaard et al., 2009). Different types of training may have varied effects; strength training but not plyometric training, has been shown to increase Achilles tendon stiffness (Kubo et al., 2007). Long duration protocols, but not short duration, using isometric contractions increased tendon stiffness (Kubo et al., 2001). The increase in collagen turnover and increases in stiffness may contribute to more effective force transmission from the contractile elements to bone (Bojsen-Moller et al., 2005).

The adaptation of tendon to load contributes to the mechanical and structural properties of tendon (Kjaer et al., 2009, Kjaer et al., 2005, Kjaer et al., 2006). Load is also important in modifying the rate of force development and efficiency of the muscle (Bojsen-Moller et al., 2004). Loading, in particular strength training, has a number of benefits for the muscle architecture including; hypertrophy (increase in cross sectional area), strength and changes to the substrates that improve efficiency (Gonyea et al., 1986, O'Shea, 1966, Chui, 1964). Strength training alters tendon and muscle characteristics and these changes may be part of the mechanism behind functional improvement in people with tendinopathy.

2.12.2 Evidence for loading in tendinopathy

There is evidence that eccentric exercise reduces pain and allows return to function in recalcitrant tendinopathy (Woodley et al., 2007, Jonsson and Alfredson, 2005a, Young et al., 2005b, Ohberg et al., 2004). It has been shown to be more effective than passive treatments such as ultrasound, frictions, 'wait and see', stretching, splinting and also concentric only exercise (Woodley et al., 2007). However, eccentric exercise, the most commonly researched muscle contraction type in tendinopathy, increased pain in the first two to four weeks of a 12-week program (Alfredson et al., 1998).

Many studies investigating eccentric exercise have investigated Achilles tendinopathy and have recruited older people (mean age > 40 years) who are aiming to return to recreational level activity (for example, (Mafi et al., 2001b, Norregaard et al., 2007, Alfredson et al., 1998)). The results of these studies with older less active people are frequently, and possibly inappropriately, applied to athletes in the clinical setting with other tendinopathies, such as PT. When athletes have been studied, it has been shown that eccentric exercise can induce patellar tendon pain in those with asymptomatic tendon pathology when used prophylactically in the pre-season (Fredberg et al., 2008a). Eccentric exercise in season is provocative (Visnes et al., 2005), or there is a risk of poor adherence (Woodley et al., 2007) suggesting that athletes should rehabilitate their tendinopathy while not actively training and playing their sport.

Despite the widespread clinical use of eccentric exercise in PT rehabilitation, there are limited data that demonstrate a positive effect on clinical outcome measures (Visnes and Bahr, 2007). No study that has a positive result has been conducted inseason. In fact, there are no data about suitable rehabilitation for athletes with PT during the competitive season.

The eccentric protocol provokes pain and traditionally progression is made based upon inducing certain levels of pain (Alfredson et al., 1998, Young et al., 2005b). It is possible that painful exercise may have negative effects along the neuroaxis (such as long term potentiation) that may predispose people to recurrence. It is important to consider that exercises that do not evoke pain may have benefits beyond athlete adherence, such as reducing the strength of synapses associated with nociception. Investigation into other, non-provocative muscle contraction types is warranted.

There are few investigations into other muscle contraction types such as isometric exercise or isotonic (concentric / eccentric) for people with tendinopathy. No published studies have investigated the use of isometric exercise in the rehabilitation of tendinopathy. Heavy slow strength training (isotonic) has been compared to eccentric exercise (Kongsgaard et al., 2010). The 12-week study compared eccentric exercise, isotonic exercise and a glucocorticoid injection and all groups improved in tendon pain and function significantly at twelve weeks. No data were reported on pain provocation during or immediately after exercise when completing isotonic exercise. At the 6 month follow up, treatment satisfaction was highest in the isotonic group. The activity in any group was not significantly different to baseline (nor was the amount reported), thus it is possible that participants had not returned to their chosen level of activity. It is unclear from these data whether isotonic strength training is suitable for inseason athletes, when patellar tendon pain is at its highest (Cook and Purdam, 2014).

Of the studies that have demonstrated improvement in tendon pain and function with exercise over time (for example, (Silbernagel et al., 2007b, Dimitrios et al., 2012)) the mechanism behind clinical improvement is unknown and symptomatic improvement does not appear to correlate with changes on imaging of tendon pathology (Drew et al., 2014). Therefore, it is pertinent to review the neuromuscular adaptations to exercise and potential mechanisms behind pain reduction (both immediately and over time) at a corticospinal level.

2.13 Strength training: implications for the CNS

Neuromuscular adaptations to strength training require an understanding of the neural control of skeletal muscle as well as an appreciation of the neuroplasticity that may occur

with pain or strength training. An overview of the neural control of skeletal muscle is

provided (Appendix X).

2.13.1 Concepts of neuroplasticity in the M1

Neuroplasticity is the ability of the nervous system to undergo structural and functional

changes in response to activity (Pascual-Leone et al., 2011, Munte et al., 2002). It can be

a positive adaptive change in response to frequent stimuli or after injury or illness when

the changes enable function, but maladaptive changes can occur that offer no functional

advantage (Henry et al., 2011). Repeated muscle activation manifests as use-dependent

neuroplasticity of the M1 and its projections (Butefisch et al., 2000).

Muscle activation is modulated by a balance between excitatory and inhibitory control of

neurons that synapse on the motor neuron pool (Farina et al., 2014); excitatory synapses

transmit action potentials from a pre-synaptic neuron that causes an action potential in a

post-synaptic neuron due to depolarisation and the reverse is true for inhibitory synapses

as action potential generation is depressed due to hyperpolarisation. Excitatory synapses

use glutamate as their neurotransmitter, whereas, inhibitory synapses use γ-Aminobutyric

acid (GABA). There are two types of GABA receptors that respond to the

neurotransmitter, $GABA_A$ and $GABA_B$.

$GABA_B$ receptors mediate long interval cortical inhibition and the silent period

(McDonnell et al., 2006), which were not examined in this thesis. $GABA_A$ receptors are

ligand gated ion channels and are located on the inhibitory neurons that synapse onto

corticospinal cells in the M1 to mediate short-interval intra-cortical inhibition (SICI) (Ilic

et al., 2002, Ziemann, 2003) and influence motor unit activation. The TMS paired-pulse

design delivers a sub-threshold conditioning stimulus that activates inhibitory circuits that

use GABA as their neurotransmitter causing synaptic inhibition of neurons that are

activated by the supra-threshold test stimulus.

Changes to SICI have been proposed as a primary mechanism behind neuroplasticity

(Wolff et al., 1993). It is not known whether patellar tendon pain is associated with

changes to CSE and/or SICI of the quadriceps, thus these corticospinal responses needed

to be investigated.

2.13.2 Quantifying neuroplasticity of the Primary motor cortex

An overview of the theory that underpins TMS and the relevant terms are provided, as

this technique was used in Chapters 3-6. The method(s) for each study appears in

Chapters 3-6 and given the importance of standardising TMS technique including,

electrode placement and participant set up, in obtaining reliable TMS responses

(Thickbroom et al., 1999a, Carroll et al., 2001b) additional information pertaining to the

TMS methods used is provided in Appendix U.

Transcranial magnetic stimulation is a non-invasive method of investigating the function

of the corticospinal pathway, membrane excitability and synaptic efficacy by using a

magnetic field to induce electrical currents in conductive neural tissue of the M1 (Carroll

et al., 2001b). This enables quantification of corticospinal excitability (CSE), cortical

inhibition (in this thesis, SICI) and topographical representation. The stimulus evokes

multiple descending waves via action potentials in corticospinal neurons. The first direct

wave is thought to arise from excitation of the corticospinal cell itself and it is followed

by indirect waves, which are thought to stem from transynaptic excitation of corticospinal

cells by different sets of intracortical neurons (Aimonetti and Nielsen, 2001, Boroojerdi

et al., 2001). The magnetic stimulation evokes a motor response (twitch) in the muscle

that is recorded using sEMG on a target muscle; the response is known as a motor evoked

potential (MEP) (Figure 2.4). The amplitude of the MEP is influenced by inhibitory and

excitatory connections descending onto the motor neuron pool at the time of stimulation

(Carroll et al., 2001a). Transcranial magnetic stimulation can be applied as a single or a

paired-pulse paradigm.

Single-pulse TMS can be delivered at different stimulus intensities that correspond with

an MEP of increasing amplitude until plateau, which represents MEP_{MAX}. Paired-pulse

TMS, with an inter-stimulus interval of three milliseconds, can explore SICI (Trompetto

et al., 2001). The inter-stimulus interval is the time between the sub-threshold

conditioning stimulus and the supra-threshold test stimulus. It is the ratio between the

amplitudes of the conditioning and test stimuli that represents SICI and can be used as an

indicator of intracortical neuronal processing.

The following terms that relate to TMS testing are summarised (Figure 2.4);

MEP: if the current applied is of sufficient amplitude and duration, it will depolarise

neural tissue and be recorded as an MEP. From the MEP a number of measures can be

derived to probe both the corticospinal responses.

Latency: a measure of the corticospinal conduction time is measured from the time of

stimulation to the onset of the MEP and reflects both peripheral and central pathways.

Silent period (SP): provides an indication of the strength of inhibition in the

corticospinal pathway and is a combination of subcortical (spinal cord) and cortical

inhibition (Carroll et al., 2001a). It is measured as the time from onset of MEP until the

return of sEMG activity. Latency and SP were not calculated in this work because other

measures of CSE and cortical inhibition (SICI) were used, therefore definitions are

provided for completeness.
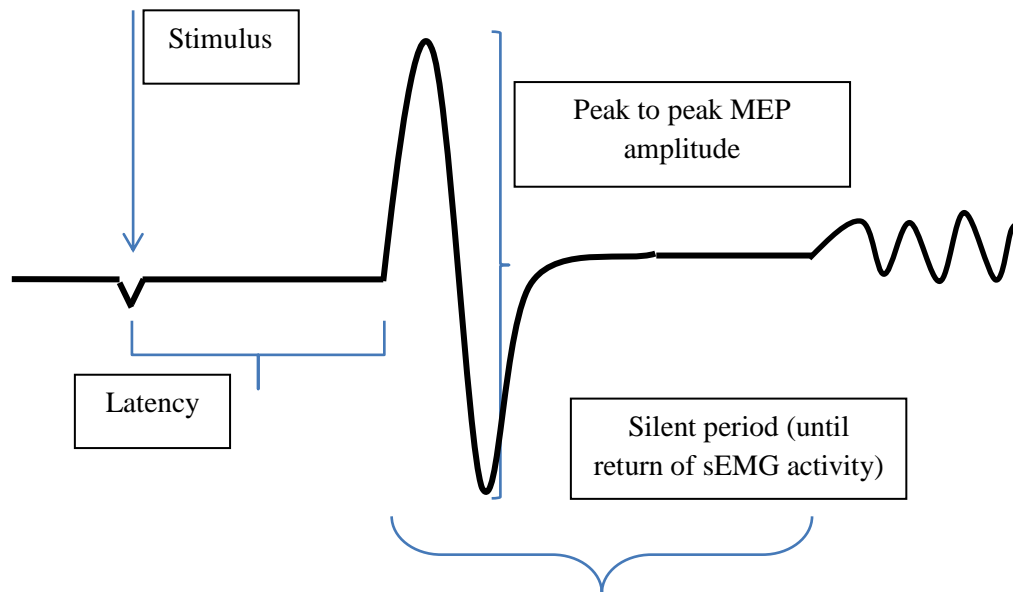
Figure 2.4 Terms associated with the motor evoked potential

MEP, motor evoked potential. sEMG, surface electromyography

Motor threshold (MT): the minimum stimulator intensity where at least three out of five stimuli produced an MEP with amplitude ≥ 200 microvolts (μV). Due to the location of the quadriceps muscle group representation on the M1 (near the vertex), the active motor threshold (AMT) rather than resting motor threshold is traditionally used, as AMT requires lower stimulation intensity and also reduces variability of MEP responses (Wassermann et al., 1996). Therefore AMT was used throughout this work and all TMS testing was completed during 10% maximal voluntary isometric contraction (MVIC). Reliable MEPs can be obtained from the quadriceps muscle (Goodwill et al., 2012, Latella et al., 2012b) (Figure 2.5).
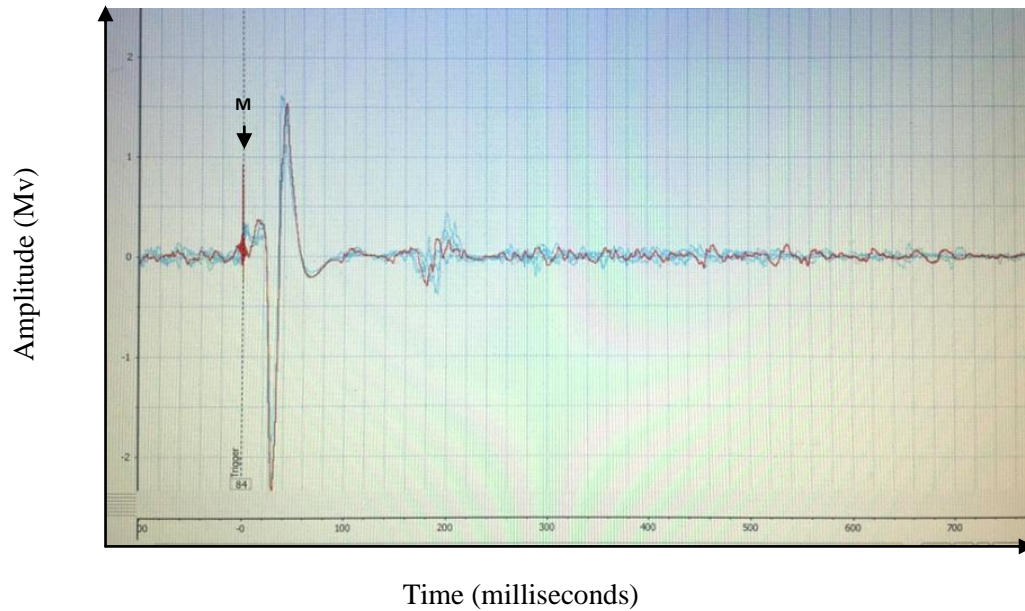
Figure 2.5 Example of overlays of motor evoked potentials from the quadriceps of one participant

Motor evoked potentials are recorded from the rectus femoris using surface electrodes whilst delivering stimuli via transcranial magnetic stimulation. M, denotes the stimulus.

Stimulus response curve: a stimulus response curve was constructed by obtaining a series of MEPs at different stimulus intensities until plateau. The studies in this thesis used a ramped protocol (Pearce et al., 2013a). The stimulus response curve was constructed by, dividing the mean MEP amplitude corresponding to a stimulus intensity, by the maximal compound wave (M_{MAX}) for that participant.

Stimulus response curves provide information about the strength of the corticospinal projection to the muscle by correlating TMS stimulus intensity and output in the muscle (Kidgell and Pearce, 2011). The curve is reported to be a sigmoid shape (Kidgell and Pearce, 2011) and the slope of the curve is believed to reflect the size of the cortical

representation and the distribution of excitability within the corticospinal projection (Smith et al., 2011). The area under the curve is an overall measure of corticospinal output and projection strength (Pitcher et al., 2003).

2.13.3 Maximising neuroplasticity induced by strength training and rationale for training

The specific neural changes that occur in strength training reportedly account for as much as 60% of the strength increases observed (Narici et al., 1989). The contribution of the neurophysiological adaptations to strength gains are demonstrated by, the significant strength improvements shown to occur prior to muscle hypertrophy (Yue and Cole, 1992, Enoka, 1988), increases in strength following motor imagery (Leung et al., 2013) and in the contralateral untrained limb in cross-education strength studies (Fimland et al., 2009, Goodwill et al., 2012, Hendy et al., 2012a, Kidgell et al., 2011).

The specific neural and cortical changes that can occur with strength training include the number of neurotransmitter receptors on a synapse and an optimisation of the biochemical environment for synaptic efficacy (Abraham, 2008). Strength training can influence both supraspinal and spinal mechanisms, such as increased motor unit discharge rate (Christie and Kamen, 2010), increased central motor drive, elevated motor neuron excitability and reduced presynaptic inhibition (Aagaard et al., 2002a, Aagaard et al., 2002b, Kidgell and Pearce, 2011, Kidgell et al., 2010, Kidgell et al., 2011, Pearce et al., 2013b).

However, strength training designed to facilitate neuroplasticity of the M1 incorporates a number of elements aside from the applied load. Externally paced strength training, which increases the complexity of the task (Carroll et al., 2011), has been shown to

induce changes to CSE and SICI in healthy people (Kidgell and Pearce, 2011, Weier et al., 2012a). External pacing constrains the movement enforcing control and attention and can be achieved with simple addition of auditory cueing with a metronome. This makes the muscle contraction similar to a skilled task, thus when external auditory pacing cues have been used in heavy strength training, use-dependent plasticity has been comparable to skill training (Leung, *in press*). Importantly, self paced strength training, even when using heavy loads that would challenge neuromuscular control, has not been shown to produce changes in CSE and SICI (for example, (Leung, *in press;* Carroll, 2002; Ackerley, 2011)). Earlier studies proposed that strength and skill training induced different adaptive changes (Jensen et al., 2005, Adkins et al., 2006) however more recent data have consistently shown similar changes to skill training in CSE and SICI are observed when strength training is externally paced (Kidgell and Pearce, 2011, Weier et al., 2012a, Goodwill et al., 2012, Kidgell et al., 2010).

Interestingly, motor imagery that requires participants to focus attention and imagine muscle contractions have also been shown to induce changes in CSE (Clark et al., 2004, Fadiga et al., 1999) and increases in CSE were augmented with a more complex task (Roosink and Zijdewind, 2010). This poses the question whether actual load is important for modulation of CSE or if imagined load may be sufficient. In fact, heavy imagined and heavy active contractions have demonstrated similar neural processes, (Leung et al., 2013) except that there appear to be differences in the locus of motor inhibition. In preparation for actual contractions, impulses are inhibited at the spinal cord level to prevent premature firing of motor neurons. In contrast, during imagined contractions, the inhibition that prevents movement is controlled at a cortical level (Stinear et al., 2006)

indicating that differences in the locus of inhibition are present between imagined and actual contractions. Furthermore, strength gains are greater during actual compared with imagined contractions, reinforcing the fact that adaptations resulting from strength training are not purely confined to the M1 (Leung et al., 2013).

Evidence suggests contracting with load (rather than imagined contractions) may be important in rehabilitation interventions. First, motor imagery ability strongly influences an individual's corticospinal response to imagery training (Williams et al., 2012) indicating there is variability in the general population in response to such training. This may limit its effectiveness as an intervention. Furthermore, imagery is unlikely to provide the necessary stimulus for tendon and muscle (section 2.12). Second, increases in strength following motor imagery of heavy muscle contractions have been demonstrated (16% increase in maximal voluntary isometric contraction in a 3-week training intervention, 4 sets of 6-8 imagined repetitions at 80% 1 repetition maximum [RM]) (Leung et al., 2013). However, the group that performed actual repetitions demonstrated a 39% increase in strength ($p = 0.027$) indicating that actual muscle contractions are more effective (for strength). It is worth noting that the motor imagery group were cued to imagine lifting heavy loads and this was also the case in another study demonstrating strength increases with motor imagery where they were shown videos of peoples completing calf raises with a heavy barbell (Zijdewind et al., 2003) and muscles of the hand during imagined maximal isometric contractions (Yue and Cole, 1992).

These studies also suggest *heavy* load may be important as studies that used loads of 80% 1RM (active or imagined) were identified to produce strength changes, thus load would

appear to be an important consideration in optimising neuroplasticity of the M1. Heavy

load isolated for the quadriceps muscle group can be provided using a leg extension

machine with external weights and furthermore, open kinetic chain exercise, for example

seated leg extension for the quadriceps muscle group, have been shown to produce higher

neuromuscular activation than closed kinetic chain exercise (for example, squat)

(Andersen et al., 2006) thus this may provide a stronger training stimulus.

2.13.4 Summary of load protocols that may optimise stimulation for tendon, neuromuscular and corticospinal adaptation

There are a number of factors that appear important in designing a rehabilitation

intervention in tendinopathy to address each potential level of dysfunction. First, heavy

load has shown to be successful in tendon rehabilitation and matrix stimulation

(Kongsgaard et al., 2009, Kongsgaard et al., 2010), muscle architecture, hypertrophy and

neuromuscular adaptations (Mitchell et al., 2012, Aagaard et al., 2002a, Andersen et al.,

2006) as well as modulation of corticospinal responses (Goodwill et al., 2012, Kidgell et

al., 2010, Latella et al., 2012b). Second, open chain leg extension exercises may optimise

neuromuscular activation (Andersen et al., 2006). Lastly, and potentially of critical

clinical importance, is the additional of external pacing to optimise neuroplasticity of the

M1.

The type of muscle contraction that may be most efficacious is unknown as there are a

lack of studies that have investigated isometric and isotonic muscle contractions in

tendinopathy. Eccentric, isometric and isotonic muscle contractions have been shown to

improve the strength and efficacy of the neural circuits that control muscle in normal

participants (Carroll et al., 2009, Carroll et al., 2002a, Kidgell and Pearce, 2011, Aagaard

et al., 2002a). However, no studies have investigated excitability and inhibition of neural circuits in people with tendon pain. Studies have demonstrated poorer/lower muscle function is exquisitely linked to pain, both experimentally and in a range of musculoskeletal conditions (Ingber, 2003a, Ingber, 2003b, Ingber, 1993, Hodges and Richardson, 1996, Hodges and Richardson, 1999).

2.13.5 Pain models

Experimentally induced pain is capable of changing motor control and thus provide opportunity to study transient responses to nociceptive input. There are multiple models constructed from experimentally induced pain that attempt to describe motor control changes and the relationship with pain including the pain-adaptation and the pain-spasm-pain model. The theories present somewhat conflicting predictions on how pain affects motor output and both are equivocally supported by the literature.

The pain-spasm-pain model proposes that pain results in increased muscle activity that will in turn cause pain (Roland, 1986). In contrast, the pain adaptation model postulates that pain actually reduces activation of agonist muscles and increases activation of antagonist muscles (Lund et al., 1991) to reduce movement velocity and the range of motion to avoid further mechanical provocation of pain and damage to tissues. Several studies have investigated changes in motor control (usually the agonist muscle) using either experimentally induced pain or different MSK conditions.

2.13.5.1 Evaluating cortical output during pain

Whilst, nociception is the neural process of encoding noxious stimuli and is the most common trigger for pain, pain is an output of the CNS that is modulated by a range of contextual and cognitive factors (Moseley and Arntz, 2007). The experience of pain

from transient, noxious stimuli, where participants are advised it will subside, may be different to the experience of musculoskeletal (MSK) pain, particularly as it becomes more longstanding, thus corticospinal measures and changes to biomechanics or motor patterning reported for these two scenarios will be discussed separately.

Studies that have investigated the effect of acute noxious stimuli in normal participants, most commonly use intra-muscular hypertonic saline or capsaicin injections that result in immediate, dose dependent pain (Scanlon et al., 2006). Pain is associated with a loss of contraction force (Graven-Nielsen et al., 1997, Henriksen et al., 2011b) and muscle endurance (Graven-Nielsen et al., 1997) and reduced sEMG activity of the painful muscle and increased antagonist muscle activity (Graven-Nielsen et al., 1997), which is consistent with the pain adaptation model (Lund et al., 1991). However, as previously outlined this may not be representative of people with MSK pain.

A recent systematic review by Heales et al., (2013) on the sensory and motor deficits of the non-injured side of patients with unilateral tendon pain included one study in the patellar tendon and one study in the Achilles tendon and 18 in the upper limb tendons reflecting the paucity of literature in lower limb changes. The two included lower limb studies investigated arch height in PT (Crossley et al., 2007) and an imaging paper of the Achilles tendon (Grigg et al., 2012). It is not clear how arch height and imaging changes may relate to sensory or motor control changes, thus the sensory or motor control changes in lower limb tendinopathy require further investigation. Interestingly, a recent systematic review in chronic regional pain syndrome only identified data from upper-extremity studies (Di Pietro et al., 2013). It is possible that differences in functional reorganisation in the primary somatosensory (and/or M1) cortices following upper limb

versus lower limb injury may exist that limit the extrapolation of upper limb findings to the lower limb. Given that the predominant role of the upper limb musculature is to position and control the hand in space, and the fact the hand is well represented on the somatosensory cortex and M1, injury to upper limb regions may have different manifestations associated with chronicity to the lower limb. There appears to be a bias towards investigations of upper limb conditions.

There are several studies in lower limb tendinopathy demonstrating motor control changes. People with chronic unilateral Achilles tendinopathy have showed an increase in the volitional wave (v-wave), which measures the magnitude of motor output from alpha motorneurons (α-motorneurons), relative to their other side (Wang et al., 2011). They also had reduced normalised rate of force development (RFD) and higher antagonist (tibialis anterior) to agonist (soleus) sEMG ratios during explosive contractions, which somewhat supports the pain-adaptation model. This is in contrast to an experimental Achilles tendon pain model (injection of intratendinous hypertonic saline) where pain was associated with reduced sEMG activity in the agonist, synergistic and antagonist muscles (Henriksen et al., 2011a). Thus, it appears that experimental tendon pain models may not reflect load induced tendinopathy. The conclusions that can be drawn from these studies are that, (1) there appear to be changes to motor control but there are few studies and (2) experimentally induced tendon pain may not represent changes to motor control present in load induced tendinopathy.

Given the limited studies of motor control or corticospinal responses using techniques that may enable inference of the locus of adaptation, it is pertinent to review some of the more global biomechanical studies that have been conducted in tendinopathy.

Tendinopathy can be provoked during the stretch shortening cycle (SSC). The SSC is where an eccentric contraction immediately precedes a concentric contraction. This manoeuvre produces greater force output than an isolated concentric contraction. In jumping, horizontal landing places the highest load on the patellar tendon compared with a vertical landing, despite the latter having higher ground reaction forces (Edwards et al., 2010) and quickly moving out of this position after landing demonstrates the SSC in volleyball. The SSC is taxing for skeletal muscles and is enabled by the viscoelastic properties of the tendon (Kubo et al., 2005). Changes to jumping biomechanics can infer changes to motor control even if not explicitly studied.

2.13.5.2 Differences in biomechanics and motor output: pain versus pathology

Data has shown that people with PT jumped higher than controls (termed the 'jumpers knee paradox') and that better jumping ability was a risk factor for developing PT (Visnes et al., 2013). The odds ratio of developing jumper's knee (sic) (either at the proximal insertion or quadriceps insertion) among young active volleyball players in an elite training environment, when corrected for previous training was 1.79 (95% CI 0.96 to 3.35). However, talented jumpers may be more likely to play in positions that require more jumping such as outside hitters and blockers compared with setters, therefore they may actually jump more with trainings and games. However, it may not be simply volume of load (defined as jumping repetition multiplied by the amount of training over the course of a period), but changes within the jumping and landing pattern that leads to symptoms.

Van de Worp et al., (2014) systematically reviewed studies that investigated jumping biomechanics in people with PT and included six studies (n = 49 controls, n = 18

symptomatic PT, n = 13 asymptomatic PT and n = seven tendon pathology). There were

no significant differences between controls and participants with PT in kinematics,

however the meta-analysis only included two of the six studies (n = six athletes with

symptomatic PT). There were no differences between controls and those with a past

history of PT (currently asymptomatic). The only significant differences were in those

participants with tendon pathology compared with controls. The presence of tendon

pathology was associated with a different landing strategy compared with controls in

horizontal landing resulting in more hip flexion, higher hip extension velocity, more knee

flexion and higher knee extension velocity than controls (Edwards et al., 2010). It would

be interesting to prospectively follow these athletes, as it is known that tendon pathology

is a risk factor for developing symptoms (Malliaras and Cook, 2006). The differences in

their landing strategy may be protective due to the presence of pathology or might

potentially place them at increased risk of symptoms. Conversely, they may have tendon

pathology as a result of this landing strategy. While jumping is provocative for PT,

strength training appears beneficial in rehabilitation. There is also evidence muscle

activation may be analgesic.

2.13.6 Evidence that loading reduces pain

Eccentric exercise, which is the most commonly prescribed (and researched) exercise for

the treatment of tendinopathy (for example, (Frohm et al., 2007b, Jonsson et al., 2008,

Kongsgaard et al., 2006, Maffulli et al., 2008, Purdam et al., 2004, Shalabi et al., 2004,

Visnes and Bahr, 2007, Woodley et al., 2007)) is painful to complete (Alfredson et al.,

1998). Management of tendinopathy is especially problematic during the competitive

season, during which there are constant time and performance pressures (Cook and

Purdam, 2014). When eccentric exercise has been completed in the competitive season, there has been poor adherence due to pain, and either no benefit (Visnes et al., 2005) or poorer outcomes (Fredberg et al., 2008b). Athletes are reluctant to cease sporting activity to complete eccentric exercise programs (Jonsson and Alfredson, 2005b), and they may be more adherent with exercise strategies that reduce pain to enable ongoing sports participation.

Exercise-induced pain relief would have several clinical benefits. First, athletes may be able to manage their pain with exercises either immediately prior to, or following, activity. Second, exercise is non-invasive and without potential pharmacological side effects or sequelae of long-term use that are associated with some interventions. Third, exercises that reduce pain are likely to have greater adherence. Therefore, alternative muscle contraction types other than eccentric exercises warrant investigation.

Isotonic exercise (heavy slow concentric and eccentric strength training) has been shown to be as effective as eccentric only exercise in PT for pain and participation (Kongsgaard et al., 2009, Frohm et al., 2007b), however the immediate effect of isotonic exercise on pain has not been studied. A single bout of strength training that used isometric muscle contractions have been shown to reduce pressure pain thresholds in normal participants (Kosek and Ekholm, 1995, Koltyn and Umeda, 2007) but have not been investigated in people with tendon pain. The analgesia following a local isometric contraction demonstrated in previous studies of normal participants is widespread (Hoeger Bement et al., 2011), which implicates CNS involvement and warrants investigation.

2.13.7 Summary of muscle contraction parameters with regards to tendinopathy

It appears that the use of both isometric and isotonic strength training require investigation for their utility in tendinopathy management. Isometric strength training has been shown to be analgesic in experimental studies of healthy people and this warrants investigation in those with PT. Heavy isotonic load is beneficial for strength (Bird et al., 2005) and parameters may be matched for comparison to isometric contractions including length of time under tension and rating of perceived exertion (RPE). As there were no protocols for tendon loading that may induce analgesia, protocols were developed with pilot testing (Appendix Y).

2.13.8 Summary of clinical outcome measures and interventions used based upon review of the literature

Patellar tendinopathy was diagnosed using clinical testing and UTC imaging in a cohort of jumping athletes (basketball, volleyball, Australian football and martial arts). Pain at the inferior pole of the patella during the SLDS that did not radiate or refer was required for the clinical diagnosis of PT in all studies. The VISA-P was used to quantify tendon pain and function. With the exception of Chapter 3 that classified athletes into PT or other AKP, athletes with pain other than PT were excluded. As tendon pathology on imaging and pain do not correlate, the combination of clinical and imaging tests allowed for separation of people with unilateral or bilateral symptoms and /or pathology (as it is not known how the ipsilateral M1 is affected in tendinopathy) and to ensure that control participants neither had patellar tendon pain nor ultrasound abnormality that may affect their corticospinal responses.

Corticospinal responses were quantified using single-pulse (to evaluate CSE) and paired-pulse (to evaluate SICI) TMS. Strength training, specifically isometric muscle contractions have been shown to induce immediate and widespread analgesia in studies of healthy people (evidenced by increased PPTs) thus warranted investigation in PT (Chapter 4). Evidence supports strength training in the rehabilitation of tendinopathy and it is known to have positive effects on tendon matrix and muscle architecture. There is evidence for heavy, externally paced strength training being capable of modifying corticospinal control of muscle in healthy people. Based upon the evidence for strength training in tendon rehabilitation, muscle adaptation and neurophysiological mechanisms, a number of parameters were considered in study design and the process of piloting two protocols was provided (Appendix Y). Therefore, the strength training interventions used in this thesis (Chapters 4-6) utilised a leg extension machine, heavy load with intervention protocols matched for rating of perceived exertion (RPE), time under tension and rest to ensure the only difference in groups was muscle contraction type (isometric or isotonic) and importantly, used external pacing to maximise the opportunity for neuroplasticity. Furthermore, the inseason RCT intervention study (Chapter 5) was chosen to be 4-weeks in duration as the primary area of interest was the neuromuscular changes, in the absence of changes in muscle morphology.

Chapter 3. Is corticospinal excitability differentially modulated in jumping athletes with and without anterior knee pain?

3.1 Declaration for thesis Chapter 3

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Elevated corticospinal excitability in patellar tendinopathy compared to other anterior knee pain or no pain.	70

The following co-authors contributed to this work:

Name	Nature of contribution
Kidgell D	Assistance with study design, input into methodology used and preparation of the manuscript
Moseley GL	Preparation of the manuscript
Cook J	Senior supervision and preparation of the manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidates and co-authors contributions to this work.

Candidate's signature (and date)

Main supervisor's signature (and date)

3.2 Chapter introduction, aim and hypothesis

As discussed in Chapter 2, patellar tendinopathy (PT) is a highly prevalent and debilitating injury in athletes who play sports that require stretch shortening of the quadriceps musculotendinous unit such as jumping or change of direction (Gisslen et al., 2005, Cook et al., 1997, Cook et al., 1998). Therefore, it is important to understand the corticospinal excitability (CSE) of the quadriceps muscle in people with and without anterior knee pain (AKP). For this study, athletes with knee pain were further sub-grouped into PT and other AKP.

First, pilot testing was undertaken to establish the specific effect of regular jumping, and not just habitual physical activity, on the CSE of the quadriceps (Appendix Y). Based on these data, jumping athletes displayed significantly greater CSE than non-jumping athletes (p=0.002) and there was no effect of gender (p=0.26) therefore, male and female jumping athletes were included in all studies of this thesis. The inclusion of jumping athletes with other AKP enabled investigation of the potential for nociceptive specificity influencing the corticospinal control of the quadriceps. Therefore, the aims of this chapter were;

Aim: To compare the CSE via a stimulus response curve in jumping athletes that have PT with activity matched athletes that have no pain and those with other AKP.

Hypothesis: It was hypothesised that jumping athletes with PT and other AKP pain would have greater CSE, evidenced by an increase in the slope of the stimulus response curve, than those with no pain but there would be no differences between PT and other AKP in CSE.

Null hypothesis: There will be no differences in CSE between the three groups.

This chapter presents a cross sectional study that used single-pulse TMS to obtain stimulus response curves. A full equipment list is provided (Appendix Z). The manuscript has been accepted with major changes by the Scandinavian Journal of Sports Medicine .

3.3 Participants

Participants in this study were aged over 18 years of age. Those below 18 years were excluded for two reasons. First, athletes under this age may have adolescent injuries that mimic patellar tendinopathy pain including Sinding-Larsen—Johansson syndrome (Barber Foss et al., 2012, Barber Foss et al., 2014, Barbuti et al., 1995, Medlar and Lyne, 1978). Second, the guidelines for the safe application of TMS recommends participants are aged over 18 years (Chipchase et al., 2012). Participants over 60 were excluded due to the potential for age related changes to CSE (Sale and Semmler, 2005).

Further exclusion criteria for transcranial magnetic stimulation (TMS) included a past history of epilepsy or seizure activity, heat convulsion, head injury or history of epilepsy and seizure in first degree relatives, psychiatric or neurological illnesses (including brain injury or cranial surgery), metal implants in the head (outside the mouth) any metallic particles in the eye, implanted electrical biomedical device (defibrillator, acoustic device), pregnancy, use of medications that affect arousal level, excessive use of caffeine or energy drinks, sleep deprivation and the inability to speak, read and write English (Rossi et al., 2009).

Elevated corticospinal excitability in patellar tendinopathy compared to other anterior knee pain or no pain.

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Running title: Source of knee pain alters CSE

Key Words: Corticospinal excitability, patellar tendinopathy, knee pain, quadriceps

3.4 Abstract

Introduction Anterior knee pain (AKP) is a frequent clinical presentation in jumping athletes and may be aggravated by sustained sitting, stair use and loading of the quadriceps. Corticospinal activation of the quadriceps in athletes with AKP has not yet been investigated, but is important in guiding efficacious treatment. **Method** This cross-sectional study assessed corticospinal excitability (CSE) of the quadriceps in jumping athletes using transcranial magnetic stimulation (TMS). Groups consisted of Control (no knee pain); PT (localised inferior pole pain on single leg decline-squat [SLDS]); and other AKP (non-localised pain around the patella). SLDS (numerical score of pain 0-10), VISA-P, maximal voluntary isometric contraction (MVIC), active motor threshold (AMT), CSE and M_{max} were tested. **Results** 29 athletes participated; control n = 8, PT n = 11, AKP n = 10. There were no group differences in age ($p = 0.23$), body mass index ($p = 0.16$) or MVIC ($p = 0.38$). PT had elevated CSE compared to controls and other AKP ($p < 0.001$), but no differences were detected between AKP and controls ($p = 0.47$). **Discussion** CSE appears to be greater in PT than controls and other AKP. An improved understanding of the corticospinal responses in different sources of knee pain may direct better treatment approaches.

3.5 Introduction

It can be difficult for the clinician to establish and identify the key nociceptive contribution to anterior knee pain (AKP) as many structures contain nociceptors. The most commonly involved structures in non-traumatic presentations of knee pain are thought to be the patellofemoral joint (PFJ) and patellar tendon (Cook et al., 2000b, Wood et al., 2011, Baquie and Brukner, 1997) however the contribution of the fat pad to nociception is unknown. Anterior knee pain can have similarities in clinical presentation where wasting of the quadriceps is observed (Ferretti et al., 1985, Young et al., 1982) but it is not known if clinically similar conditions have comparable corticospinal control of the quadriceps. Understanding how the corticospinal pathway modulates muscle activation across conditions may provide new and important information that will enable the development of targeted and effective guidelines for rehabilitation.

Anterior knee pain may be aggravated by jumping and landing and change of direction activities and frequently has an insidious onset that may be due to overload, where clinicians may find it difficult to pinpoint the cumulative or relative overload. There are no consistent findings on imaging to confirm involvement of particular tissue in the clinical presentation, with tendon or PFJ pathology present on imaging in asymptomatic individuals (Cook et al., 2001a, Witvrouw et al., 2005). Palpation is of limited clinical utility as tendon palpation may induce pain in athletes for whom PT is not the cause of their AKP (Cook et al., 2001b). Patellar tendinopathy pain can be provoked on the single leg decline squat test (Purdam et al., 2004) but is likely to be painful for other types of AKP, thus it is not diagnostic but a pain provocation test with diagnosis relying on clinician judgment.

While there are clinical similarities between different presentations of AKP, there are also differences including pain behaviours and specific aggravating factors. PT at the proximal insertion is not common in running athletes, presumably because patellar tendon load is low during running (Scott and Winter, 1990), yet other AKP can be very painful during running (Besier et al., 2009). PT rarely causes pain at rest and does not result in global joint swelling, whereas other AKP, for example PFP can ache diffusely following activity and can be associated with joint swelling (Malek and Mangine, 1981). PT is associated with a warm-up phenomenon in which pain reduces during activity, but is painful the next day (Kountouris and Cook, 2007), whereas people with other AKP often report increasing pain during activity. Whilst the term 'jumpers knee' is used interchangeably with PT, athletes involved in jumping sports also spend a significant amount of time in knee flexion (i.e. volleyball), resulting in retropatellar compression (Wallace et al., 2002). Similarly, these athletes may also frequently land on their knees irritating other anterior knee structures.

Of the common AKP conditions, PT has two distinguishing clinical features that assist with diagnosis; (1) localised, non-radiating pain, and (2) dose-dependent load-related pain (Ferretti et al., 1990, Kountouris and Cook, 2007). All other presentations may be clinically grouped as AKP due to the clinical difficulty in ascertaining the exact nociceptive structure (e.g. fat pad). The similarities in non-traumatic AKP presentations make it vital to understand if the corticospinal control over the associated quadriceps muscle is differentially modulated in PT compared with other AKP as this may influence rehabilitation.

Muscle and therefore tendon loading is driven by the corticospinal control of the muscle. Several musculoskeletal conditions have been shown to result in persistent changes in the control of the affected area and can alter the topography of the primary motor cortex (M1) (Tsao et al., 2008, Schwenkreis et al., 2010, Nijs et al., 2012) . These changes may be positive and protective, or may be negative and even contribute to symptoms or resistance to rehabilitation. Nociceptive input from local tissue may result in differences in corticospinal control that can be addressed for optimal rehabilitation.

A review by Heales (2014) reported bilateral sensory and motor deficits in people with unilateral tendon pain, providing rationale that corticospinal deficits might exist. Of the 20 papers included in that systematic review, 18 investigated upper limb conditions (17 lateral elbow tendinopathy and one rotator cuff), indicating a paucity of literature investigating CNS involvement in lower limb tendinopathies. Furthermore, it has yet to be determined if different clinical conditions at the same anatomical location impacts the corticospinal pathways.

Current approaches for managing AKP are likely to be improved with a better understanding of the contributors to pain and dysfunction. Whilst these pain conditions have local nociceptive drivers, treatment directed solely at these local contributors have had variable results in, for example PFP (Crossley et al., 2001) and PT (Larsson et al., 2012), with the most effective rehabilitation strategies focussing on exercise based therapy. Exercise therapy is usually directed towards the quadriceps and an improved understanding of the corticospinal control of the quadriceps may improve the understanding of the similarities or differences in various AKP presentations and treatment approaches. Therefore, the aim of this study was to determine if individuals

with PT possess altered corticospinal excitability of the quadriceps muscles compared to 'undefined anterior knee pain' or asymptomatic individuals.

3.6 Method

Active, healthy men and women aged over 18 years were recruited to participate in this cross-sectional study. Participants were recruited from sub-elite volleyball and basketball competitions and by word of mouth. Athletes that participated in jumping activities three times per week (for example two training sessions and one game) were invited to participate by using stands at basketball and volleyball events and flyers. Standard transcranial magnetic stimulation (TMS) exclusion criteria were applied that includes past history of epilepsy or seizure activity, heat convulsion, head injury or history of epilepsy and seizure in first degree relatives, psychiatric or neurological illnesses (including brain injury or cranial surgery), metal implants in the head (outside the mouth) any metallic particles in the eye, implanted electrical biomedical device (defibrillator, acoustic device), pregnancy, use of medications that affect arousal level, excessive use of caffeine or energy drinks, sleep deprivation and the inability to speak, read and write English (Rossi et al., 2009, Chipchase et al., 2012), and anyone with lower limb injury (other than knee pain) within the past twelve months were also excluded. This study was approved by university ethics committees, conformed to the declaration of Helsinki and all athletes provided written informed consent.

3.6.1 Surface electromyography and transcranial magnetic stimulation

The area of electrode placement was shaved, abraded and cleaned with 70% isopropyl alcohol. Bipolar gel Ag-AgCl electrodes were placed over the mid belly of the rectus femoris muscle and the grounding electrode was placed over the patella and subsequently

used as a common reference for all electrodes. The exact area of placement was three fifths of the distance between the anterior superior iliac spine (ASIS) and the upper border of the patella. sEMG signals were amplified (1000x), bandpass filtered (high pass at 13 Hz, low pass at 1000 Hz), digitized online at 2 kHz for 500 ms, recorded and analysed using PowerLab 4/35 (ADInstruments, Bella Vista, Australia).

Familiarisation with TMS and the maximal voluntary isometric contraction (MVIC) torque were conducted prior to the experimental testing session. The MVIC torque for the quadriceps on the tested side was recorded in N·m using an isokinetic dynamometer (Biodex system 4 Pro, 1 Biodex Medical 2 Systems, Shirley USA). The participant was seated in 90 degrees hip flexion and quadriceps were tested at 60 degrees knee extension with three efforts completed with identical instructions, vocal encouragement and set-up for each trial, with two minutes rest between efforts. MVIC torque was defined as the maximum torque recorded during these three efforts. This was also used to establish the 10% MVIC for TMS testing.

Measures of CSE were obtained using single-pulse TMS. The accuracy of TMS was optimised by aligning the coil with reference markers on a tight fitting cap worn by participants and marked with a latitude-longitude matrix, positioned with reference to the nasion-inion and interaural lines (Wilson et al., 1993).

Single-pulse stimulus-response (SR) curves were obtained during low-level isometric contractions of the quadriceps muscle group. Low level contractions were performed by maintaining the knee joint at 60º flexion, while performing a 10% MVIC, which equated to $10 \pm 2\%$ of root mean square EMG (rmsEMG) during MVIC. The 10% isometric

contraction was reported to be a pain free task for all participants. Consistent muscle

activation was confirmed by recording pre-stimulus rmsEMG throughout the session

(Goodwill et al., 2012). For a single SR curve, 10 stimuli were delivered at each intensity

from 90% of the participant's active motor threshold (AMT) until plateau (in 5%

increments to achieve a SR curve). The stimuli were delivered using a ramped protocol

(Pearce et al., 2013a). The amplitude of the motor evoked potential (MEP), slope and

V50 of the SR curve represents corticospinal excitability (Carroll et al., 2001b) and the

top represents MEP maximum.

TMS was delivered using a Magstim 200^2 stimulator connected via a BiStim unit

(Magstim Co, Dyfed, UK) and a 110-mm concave double-cone coil (maximum output of

1.4 T) was used. The motor hotspot for the rectus femoris muscle (with posterior-to-

anterior induced current flow in the M1) was determined. Sites were explored in the

estimated motor region of the quadriceps to ascertain the optimal site or 'hot spot': the

site at which the largest MEP response was recorded.

3.6.2 Maximal compound muscle action potential

Direct muscle responses were obtained from the rectus femoris muscle by supramaximal

electrical stimulation (pulse width 2000 µs; DS7A, Digitimer, UK) of the femoral nerve

under resting conditions. The site of stimulation that produced the largest M-wave was

located by positioning the bipolar electrodes in the femoral triangle. An increase in

current strength was applied to the femoral nerve until there was no further increase

observed in the amplitude of the sEMG response (M_{MAX}) (Goodwill et al., 2012, Weier

et al., 2012a). To ensure maximal responses, the current was increased an additional

20% and the average M_{MAX} was obtained from five stimuli, with a period of 6-9 s separating each stimulus.

3.6.3 Grouping by knee pain status

Participants were separated into one of three clinical groups by the same experienced sports physiotherapist (but a different researcher to the one conducting TMS testing) on clinical presentation. Patellar tendinopathy was defined as pain localised to the inferior pole of the patella reported during jumping and landing activities and during testing on the single leg decline squat (SLDS). Participants provided a numerical pain rating score for the decline squat on an 11-point numerical rating scale (NRS), anchored at left with '0, no pain' and at right with '10, worst possible pain.' Athletes with bilateral symptoms were asked to nominate their most painful knee on the SLDS and this was the testing leg (measures of quadriceps torque were taken from this side only and the contralateral hemisphere was stimulated with TMS.) The clinical diagnosis of PT was supported by the presence of characteristic features on ultrasound (US) imaging (e.g. hypoechoic area). Imaging abnormality in isolation without the clinical presentation of PT did not constitute a diagnosis of PT as jumping athletes can have tendon imaging abnormality without tendon pain (Cook et al., 2001b). Diagnosis of other AKP was made by the same physiotherapist based upon clinical presentation – radiating / non-localised AKP during jumping and landing activities and during testing on the SLDS (Figure 3.1). This term was chosen because the specific structure is difficult to ascertain clinically when the pain is vague and no definitive clinical or imaging test exists. The SLDS was used for all participants as it elicits AKP in many conditions (however, pain only remains localised in

PT). Control participants had neither pain on testing, nor tendon abnormality on ultrasound.

Figure 3.1 Difference in the clinical presentations of patellar tendinopathy (far left) and other variations of anterior knee pain

3.6.4 Blinding

The TMS tester remained blinded to knee pain status throughout testing. Grouping into control, PT and other AKP was conducted by a different researcher to the one that performed the TMS testing. All data were analysed blind to knee pain status.

3.6.5 Demographics

Athletes were asked to complete a VISA-P, which is a questionnaire about patellar tendon pain and function that is scored between 0 and 100 with 100 being maximal pain-free function (Visentini et al., 1998). Participant age and body mass index (BMI) were also recorded.

3.6.6 Data analyses

Each stimulus was automatically flagged with a cursor. The peak-to-peak amplitude of MEPs evoked in the period 10-50 ms after stimulation was analysed using LabChart 8 software (ADInstruments, Bella Vista, NSW, Australia). Peak-to-peak values (µV) were averaged, normalised to M_{max} and multiplied by 100. To construct SR curves, stimulus intensity was plotted against MEP amplitude, then fitted with a non-linear Boltzmann equation using Prism 6 (Graphpad software Inc., California, USA) (Weier et al., 2012b). The slope is given in arbitrary units. V50 represents the stimulus intensity at which the MEP amplitude is 50% of the MEP_{max} (half peak slope).

3.6.7 Statistical analyses

Tests of normality were applied (Shapiro-Wilk normality test). Where data were normally distributed, mean and standard deviation (SD) were calculated and data were analysed using a one way ANOVA and post hoc t-test. Where data were not normally distributed, or failed other assumptions of parametric statistics, median and range were obtained and data were analysed using the equivalent non-parametric test (Kruskal-Wallis or Mann Whitney U) and post hoc analysis (Dunns multiple comparison test or Kolmogorov-Smirnov test). Significance was set at $\alpha=0.05$.

3.7 Results

Thirty two athletes were recruited and three athletes without AKP were found to have patellar tendon abnormality and were excluded from the control group. Therefore, twenty nine jumping athletes were included: eight controls, 11 participants with PT and ten with AKP (Table 3.1). The PT group included three athletes with bilateral symptoms. There were no differences between the groups for age ($p = 0.23$), BMI ($p = 0.16$), MVIC

($p = 0.38$) or duration of symptoms between the AKP and PT groups ($p = 0.81$). The

mean VISA-P score in the control group was significantly higher than the PT and AKP

group ($p < 0.001$) but there were no differences between PT and AKP groups ($p = 0.40$).

The SLDS NRS scores differed between control group and the PT and AKP pain groups

($p < 0.001$) but there were no differences between PT and AKP ($p = 0.71$).

Table 3.1 Participant characteristics

	Controls	PT	AKP
Number	8 (n = 7 men, 1 woman)	11 (n = 10 men, 1 woman)	10 (n = 6 men, 4 women)
Age (median + range)	26 years (18-37)	26 years (18-37)	26.5 years (18-37)
BMI (median + range)	24.44 (21.84-27.68)	25.49 (22.95-34.91)	25.02 (19.71-29.48)
Length of time of symptoms (median months + range)	N/A	90 (5-192)	90 (12-264)
Activity details	Volleyball n=5	Volleyball n=7	Volleyball n=7

	Martial arts n=1	Australian football n=1	Australian football n=1
	Basketball n=2	Basketball n = 3	Basketball n=2
VISA-P (mean±SD)	97.5 ± 2.66	56 ± 18.18*	64 ± 18.85*
Pain during SLDS (mean ± SD)	0	5.36 ± 2.01*	5 ± 2.40*
MVIC torque (N∘m)	172.50	194.82	160.50
(median+range)	(134-284)	(113-294)	(115-303)

BMI: body mass index. MVIC: maximal voluntary isometric contraction torque. *denotes significantly different from control group, no difference between PT and AKP p<0.05

There were no differences between groups in active motor threshold ($p = 0.06$, Cohens d 1.07, r = 0.47), V50 ($p = 0.58$) or the top of the curve ($p = 0.51$, Table 3.2). The PT group demonstrated significantly higher CSE (a steeper slope of the SR curve) than the other groups did (Table 3.2; $p < 0.001$; Figure.3.2) however there were no differences between groups for V50 ($p = 0.58$) or the top of the curve ($p = 0.51$).

Table 3.2 Corticospinal responses

	AMT (mean±SD)	Slope (AU) (mean±SD)	V50 (AU) (median+range)	Top (AU) (mean±SD)
Control	42 ± 7.90	6.02 ± 1.54	19.06 (13.35-29.87)	57.26 ± 18.56
PT	34.5 ± 5.93	2.75 ± 0.84*	17.70 (1.44-35.92)	48.39 ± 20.03
AKP	37.1 ± 5.09	6.67 ± 2.00	18.94 (6.85-39.35)	48.73 ± 14.34

AMT: Active motor threshold. *denotes significantly different from control and AKP $p < 0.001$ AU:

Arbitrary units
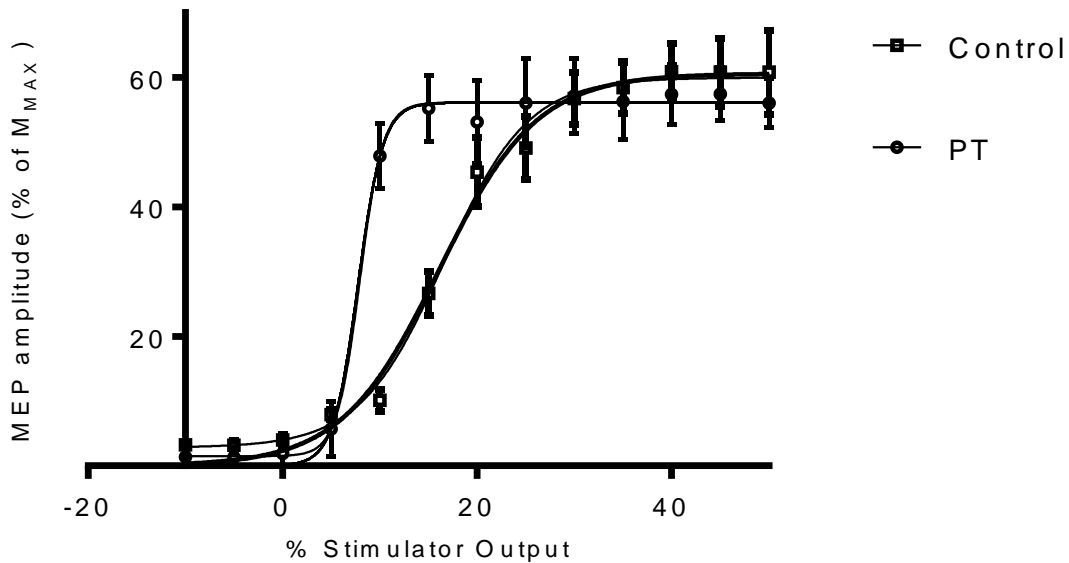
Figure 3.2 Stimulus response curve data (group mean ± SEM) for the control group and the patellar tendinopathy group

PT, patellar tendinopathy

3.8 Discussion

This study demonstrated for the first time that jumping athletes with PT experienced elevated CSE for the rectus femoris muscle compared to healthy activity matched controls and people with other AKP. This is a novel finding that may help to inform rehabilitative practices for PT, with a focus on restoring normal corticospinal control to the knee extensors.

Patellar tendinopathy appears to evoke excitatory abnormalities, evidenced by a sharp rise in the slope and immediate plateau of the SR, rather than a traditional and expected sigmoid curve (Mathias et al., 2014) observed in controls and AKP. The slope reflects the physiological strength of corticospinal projections onto the motorneuron pool, membrane excitability and corticospinal cell recruitment (Smith et al., 2011). Therefore, the increase in peak slope observed for the rectus femoris of people with PT indicate hyper excitability and an altered ability to modulate corticospinal control of the rectus femoris muscle. The reasons for these physiological phenomena may be protective to reduce activation or tendon load; however the lack of difference in force producing capabilities (MVIC torque) between groups does not support this explanation. The similar MVIC torque in all groups may reflect the knee joint angle that testing was completed in, that is there may be deficits in other ranges that were not observed. Interestingly, the lack of strength deficit observed supports previous research where those with PT are better jumpers, termed the jumpers knee paradox (Visnes et al., 2013).

The lack of difference between groups in V50 or top indicates that there are other factors relating to PT that contribute to the different corticospinal responses. Other factors may include stage of pathology, potential changes to control of antagonist muscles and

inhibitory mechanisms. Inhibitory mechanisms (not measured in this study) also influence the slope of the SR curve due to synaptic inputs altering descending drive to the muscle. The use of single-pulse TMS provides a response that is reflective of the net excitatory drive to the muscle, but does not provide any information as to the site of contributing synaptic activities. Therefore, the slope of the SR curve is influenced by the balance between excitatory and inhibitory mechanisms so despite large forces still possible (evidenced by MVIC torque and no difference in the top), the ability to recruit the quadriceps in a smooth graded pattern may be impossible resulting in an "on or off" pattern though the net drive to the muscle is maintained. To put in a clinical context, people with PT may have difficulty grading activation of their rectus femoris muscle in functional tasks and may overshoot or undershoot recruitment compared with task demands.

It is difficult to explain the lack of differences in the CSE with pain from varied structures of AKP. Activity has been shown to influence the motor cortex (Nudo, 2003). However, activity does not appear to sufficiently explain the difference in CSE in people with PT as participants were all involved in jumping activities three times per week. Clearly, enhanced CSE is not simply a consequence of having pain, because the AKP group had pain of comparable intensity and duration. It is possible however, that the differential results are due to the differing clinical presentations and reflect the more precise functional relevance of the patellar tendon to rectus femoris activation. A change in corticospinal drive reflects the predicted need for protection as hypothesised on the basis of modern models of pain and motor control (Moseley et al., 2003, Hodges and Moseley, 2003). Moreover, the testing procedure did not provoke pain, but did provoke

differential corticospinal effects which would also be predicted on the basis of widespread central nervous system adaptations that are considered part of chronic pain states excitability and inhibitory mechanisms (see (Wand et al., 2011{Moseley, 2012 #98) for reviews). The current finding suggests that real time noxious input does not mediate the effect as testing was painfree. This study showed clear abnormalities in corticospinal function in a condition that is characterised by strictly load-dependent and localised pain, both of which are inconsistent with other chronic pain states (see (Rio et al., 2014) for review).

Another consideration is that corticospinal abnormalities in people with non-PT anterior knee pain affect other quadriceps muscles such as the vastis medialis oblique (VMO). One study has reported changes in corticospinal control in the quadriceps in people with PFP (On et al., 2004). That study recorded from the VMO and vastus lateralis, rather than rectus femoris and also used the size of MEP response as an indicator of CSE rather than a SR curve (so data were not normalised to the individuals M_{MAX}). Although the contrasting results of that study and ours might simply reflect different methods and analysis, it is also possible that they reflect condition-specific and nuanced alterations in cortical function, a possibility that would have potentially important implications for our understanding of knee function in both health and disease.

The active motor threshold is another representation of CSE. We did not find any differences in AMT in people with PT and controls, which contrasts with Ngomo et al., (2015) and Strutton et a., (2005) findings in rotator cuff tendinopathy and people with low back pain respectively. However, there were differences in study design; the Ngomo et al (2015) study compared affected and unaffected side, which, with upper limbs, would

presumably involve marked use profiles due to handedness. The current study compared symptomatic PT with active, healthy age matched controls and only collected unilateral data. It is possible due to bilateral changes reported in tendon pathology (Docking et al., 2014) that the contralateral side may not be an ideal control. Certainly, there are other persistent pain states that are characterised by bilateral abnormalities of motor cortical excitability, even when symptoms are unilateral (Di Pietro et al., 2015). It is not known if bilateral changes in CSE exist in unilateral lower limb tendon presentations.

It is also possible that there may be differences in the corticospinal responses associated with tendinopathy depending upon the location and contextual factors around the injury. For example, the upper and lower limbs have different sensory representation and the upper limb is often involved in activities of daily living and self care. This frequency of nociceptive input may drive long term potentiation and be a point of difference between, for example, someone with PT who experiences pain during volleyball (a presumably enjoyable activity) in which they participate three times per week and someone with lateral epicondylalgia who experiences pain during manual labour (work they may not enjoy) and during simple daily tasks (lifting the kettle) that they perform frequently. Modern pain theories remind us of the potential of real time and persistent modulatory effects of a wide range of variables on cortical protective function, not least pain and motor control. We recognise that though PT is predominantly an 'athlete's condition', it remains vulnerable to such effects (Moseley et al., 2003).

There may be important clinical implications from these data. It is possible that aberrant neural control of the muscle may cause abnormal tendon loads and represent a disruption of their internal load sensing (Rio et al., 2014). Furthermore, these corticospinal changes

associated with tendon pain may contribute to recalcitrance as quadriceps activation may indeed be irritating the tendon. As this was a cross-sectional study, causality cannot be established as it is unknown if these changes may precede the onset of tendon pain. Examining corticospinal changes in people with tendon pathology and no pain may contribute to our understanding of the "chicken or the egg" in pathology and pain. Whether the abnormalities we have discovered reflect an enhanced protective strategy or a risk for further pain or pathology is unknown.

There are limitations of this study. We chose the rectus femoris muscle because it is the only one of the quadriceps muscle group where the fibres continue to become the patellar tendon (the others blend with the retinaculum), and the concept that there is preferential wasting of certain quadriceps muscles is unsupported in PFP (Giles et al., 2013) and there are no data for other AKP (such as fat pad) and quadriceps wasting. It is likely a range of knee conditions were included in the AKP pain sample and future larger studies should aim to sub-group these, though it is likely to be difficult as no agreed criteria exist for PFP or fat pad involvement. This study utilised clinical assessment and may be strengthened by further imaging, however the link between imaging changes in many musculoskeletal conditions and pain remains somewhat tenuous (Rio et al., 2014). Future studies should examine other muscles including antagonists and other tendinopathies and compare with musculoskeletal conditions that cause similar pain at the same anatomical location.

3.9 Perspective

We contend that this study reinforces that it is important to look outside the tendon to improve our understanding of tendon pain and patient outcomes. The finding that CSE

was abnormal in people with PT but not other AKP, may lead us to develop alternative approaches to management and prevention of PT. However, future larger studies should aim to sub-group AKP if possible. It is possible that rehabilitation may need to utilise principles of neuroplasticity to address corticospinal response (as well as tendon-based concepts) to try to improve outcomes. Future studies should determine if these responses precede pain, are reversible with successful rehabilitation or may be a predictor of recalcitrance.

Chapter 4. Acute neural and pain responses to a single bout of loading

4.1 Declaration for thesis Chapter 4

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Isometric exercise induces analgesia and reduces inhibition in patellar tendinopathy.	70

The following co-authors contributed to this work:

Name	Nature of contribution
Kidgell D	Assistance with study design, input into methodology used and preparation of the manuscript
Moseley GL	Preparation of the manuscript
Purdam C	Assistance with protocol design and preparation of the manuscript
Gaida J	Preparation of the manuscript
Cook J	Senior supervision, assistance with protocol design and preparation of the manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidates and co-authors contributions to this work.

Candidate's signature (and date)

Main supervisor's signature (and date)

4.2 Chapter introduction, aims and hypotheses

The previous study identified that people with patellar tendinopathy (PT) displayed greater corticospinal excitability (CSE) than healthy controls however cortical inhibition, which also contributes to the net drive to the quadriceps muscle, was not examined. Paired-pulse transcranial magnetic stimulation (TMS) allows short-interval intra-cortical inhibition (SICI) to be quantified. In addition to recording the corticospinal responses (CSE and SICI), this study also investigated the immediate and sustained analgesic effect of an acute bout of loading on tendon pain and muscle torque, by comparing two types of quadriceps muscle contractions — either isometric or isotonic. This single blinded cross over study aimed to answer an important clinical question: what type of muscle contraction could be used to reduce tendon pain immediately and what are the effects on muscle performance? The aims and hypotheses of this study were:

Aim one: To investigate the immediate and sustained analgesic effect of isometric and isotonic muscle contractions pain during the single leg decline squat (SLDS) in people with PT.

Hypothesis one: Isometric muscle contractions will induce greater immediate analgesic effects than isotonic muscle contractions.

Null hypothesis one: There will be no differences in analgesic effects between isometric and isotonic muscle contractions.

Aim two: To quantify SICI following isometric and isotonic muscle contractions in people with PT.

Hypothesis two: Isometric but not isotonic muscle contractions will cause a release of SICI (reduced cortical inhibition).

Null hypothesis two: There will be no differences between isometric and isotonic muscle contractions for their effect on SICI.

Aim three: To measure quadriceps muscle isometric torque following isometric and isotonic muscle contractions.

Hypothesis three: Isometric muscle contractions will cause an increase in muscle torque that will not be observed following isotonic muscle contractions.

Null hypothesis three: There will be no differences between muscle contraction types on muscle torque.

The equipment and personnel used for this study were the same as those used for Chapter 3 (Appendix Z). Additional equipment specific to this study included the use of paired-pulse TMS, a metronome, stop watch, and a leg extension machine (Figure 4.1) to conduct the isotonic intervention. The Biodex Pro described in Chapter 3 was used for the isometric condition so that maximal voluntary isometric contraction (MVIC) torque of the quadriceps could be tested (Appendix U, Figure U2). This set up also provided visual feedback of torque to ensure that 70% MVIC was maintained throughout the intervention.

Pilot testing was undertaken to match the isometric and isotonic protocols for RPE and to ensure that they could be completed in full. Pilot testing was also used prior to data

collection to check that there were no interactions from testing or repeated testing within

the session (Appendix Y).

Figure 4.1 The leg extension machine used for the intervention in Chapter 4

(Deakin University Laboratory)

4.3 Correlation

In addition to the published data, a correlation was conducted to examine the relationship

between a reduction in pain and the release of SICI. The greater the decrease in pain,

evidenced by a reduction in pain on the SLDS, the greater the percentage change in

inhibition ($r = 0.75$, $r^2 = 0.6$, Figure 4.2). This study has been published in the British

Journal of Sports Medicine.
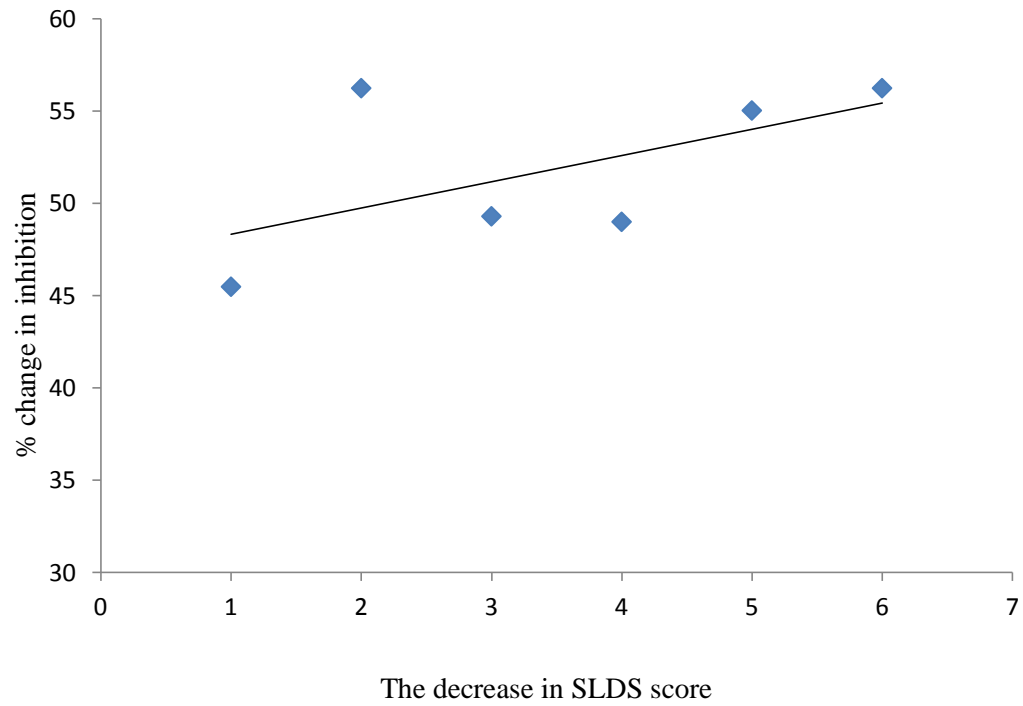
Figure 4.2 Correlation between change in motor inhibition and change in pain with a single bout of isometric strength training

SLDS: single leg decline squat

Isometric exercise induces analgesia and reduces inhibition in patellar tendinopathy

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4.4 Abstract

Few interventions reduce patellar tendinopathy (PT) pain in the short term. Eccentric exercises are painful and have limited effectiveness during the competitive season. Isometric and isotonic muscle contractions may have an immediate effect on PT pain. **Methods** This single blinded, randomised cross-over study compared immediate and 45-minute effects following a bout of isometric or isotonic contractions. Outcome measures were PT pain during the single leg decline squat (SLDS, 0-10), quadriceps strength on maximum voluntary isometric contraction (MVIC) and measures of corticospinal excitability and inhibition. Data were analysed using a split-plot in time repeated measures ANOVA. **Results** Six volleyball players with PT participated. Condition effects were detected with greater pain relief immediately from isometric contractions: isometric contractions reduced SLDS (mean ± SD) from 7.0 ± 2.04 to 0.17 ± 0.41 and isotonic contractions reduced SLDS (mean ± SD) from 6.33 ± 2.80 to 3.75±3.28 ($p < 0.001$). Isometric contractions released cortical inhibition (ratio mean ± SD) from 27.53 ± 8.30 to 54.95% ± 5.47 but isotonic contractions had no significant effect on inhibition (pre 30.26 ± 3.89, post 31.92 ± 4.67) ($p = 0.004$). Condition by time analysis showed pain reduction was sustained at 45-min post isometric but not isotonic condition ($p < 0.001$). The mean reduction in pain scores post isometric was 6.8/10 compared with 2.6/10 post isotonic. MVIC increased significantly following the isometric condition by 18.7 ± 7.8%, and was significantly higher than baseline ($p < 0.001$) and isotonic condition ($p < 0.001$) and at 45 minutes ($p < 0.001$). **Conclusion:** A single strength training bout of isometric contractions reduced tendon pain immediately and for at least 45 minutes post intervention and increased MVIC. The reduction in pain was paralleled

by a reduction in cortical inhibition, providing insight into potential mechanisms. Isometric contractions can be completed without pain for people with PT. The clinical implications are that isometric muscle contractions may be used to reduce pain in people with PT without a reduction in muscle strength.

Key words: tendon pain, isometric, patellar tendinopathy, exercise, isotonic, corticospinal

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What are the new findings?

- Heavy isometric exercise immediately reduced patellar tendon pain that was sustained for at least 45 minutes

- People with patellar tendinopathy have higher amounts of cortical muscle inhibition for their quadriceps than normative values from healthy controls

- Heavy isometric exercise reduced cortical muscle inhibition and may be a factor in the mechanism of pain reduction

- Isotonic exercise did not result in sustained pain relief or any changes to muscle inhibition

How might it impact on clinical practice in the near future?

- Isometric exercise may be used as analgesia - to reduce pain immediately in patellar tendinopathy

- Isometric exercise may be useful inseason, pre or post activity when alternate loading such as eccentric exercise has not shown to be beneficial

- Patellar tendon pain affects muscle inhibition – isometric exercise may be used to reduce pain and change muscle inhibition without a reduction in muscle strength

4.5 Introduction

Tendinopathy (tendon pain and dysfunction) in athletes is difficult to manage. Eccentric exercise, which is the most commonly prescribed exercise for the treatment of tendinopathy (Frohm et al., 2007b, Maffulli et al., 2008, Visnes and Bahr, 2007, Woodley et al., 2007), is often painful to complete (Alfredson et al., 1998). Tendinopathy is especially problematic in the competitive season, where there are constant time and performance pressures (Cook and Purdam, 2014). Where eccentric exercise has been completed in the competitive season, there has been poor adherence due to increased pain, and either no benefit (Visnes et al., 2005) or worse outcomes (Fredberg et al., 2008a). Athletes are reluctant to cease sporting activity to complete eccentric exercise programs (Jonsson and Alfredson, 2005b), and they may be more compliant with exercise strategies that reduce pain to enable ongoing sports participation.

Exercise-induced pain relief would have several clinical benefits. First, athletes may be able to manage their pain with exercises either immediately prior to, or following, activity. Second, exercise is non-invasive and without potential pharmacological side effects or sequelae of long-term use that are associated with some interventions. Third, exercises that reduce pain are likely to have greater adherence. Therefore, alternative muscle contraction types other than eccentric exercises warrant investigation.

Isotonic exercise (heavy slow concentric and eccentric strength training) has been shown to be as effective as eccentric only exercise in patellar tendinopathy for tendon pain and activity participation (Kongsgaard et al., 2009, Frohm et al., 2007b) however, the immediate effect of isotonic exercise on pain has not been studied. Isometric muscle contractions have been shown to reduce pressure pain thresholds in

normal participants (Kosek and Ekholm, 1995, Koltyn and Umeda, 2007) but have not been investigated in tendon pain. The pain inhibition following a local isometric contraction demonstrated in previous studies of normal participants is widespread (Koltyn and Umeda, 2007), implicates central nervous system (CNS) involvement and warrants investigation.

The effect of exercise on the motor cortex may be modulated in the presence of pain. Exercises that are painful to complete may change motor control and cause cortical reorganisation, as pain itself is known to alter cortical representation (Tsao et al., 2011).

This may contribute to persistence of tendon pain through the continuation of aberrant motor patterns. In the CNS, the primary regions involved in motor control are the primary motor cortex and corticospinal tract, which activate the motorneuron pool and control motor function. Changes in motor output however, are a combination of changes in the excitatory and inhibitory neural pathways. This motor neuroaxis can be investigated using single-pulse transcranial magnetic stimulation (TMS). Paired-pulse TMS can measure short-interval intra-cortical inhibition (SICI), which is thought to be mediated at a cortical level via $GABA_A$ receptors (Ziemann, 2003), rather than at the spinal cord and quantifies the effect of the inhibitory neurons that synapse onto pyramidal cells in the primary motor cortex (Kobayashi et al., 2008).

Exercise, the cornerstone of tendon rehabilitation, is capable of changing both excitatory and inhibitory measures (Goodwill et al., 2012, Pitman and Semmler, 2012). No study has examined if exercise can immediately reduce tendon pain and if exercise changes the motor neuroaxis. This may clarify the mechanism behind clinical improvement following exercise based rehabilitation (Drew et al., 2014).

The primary aim of this study was to determine if either isotonic or isometric exercise would induce immediate pain relief in PT. The secondary aim was to explore the mechanisms and investigate changes to cortical motor function. Therefore, this study compared an acute bout of isometric and isotonic quadriceps loading on patellar tendon pain, maximal voluntary isometric strength and measures of corticospinal excitability and inhibition.

4.6 Method

This was a within subjects, single blinded, randomised cross over trial with two intervention arms (Figure 4.3). Six male volleyball athletes (median age 26.9 years, range 18-40yrs) who were taking no medication were recruited for the study. Three had unilateral pain and three had bilateral patellar tendon pain. This study was approved by university ethics committees and all athletes provided written informed consent. Diagnosis of PT was made by the same experienced sports physiotherapist on clinical presentation – pain localised to the inferior pole of the patella during jumping and landing activities and during testing on the single leg decline squat (SLDS). The diagnosis was confirmed by the presence of characteristic features on ultrasound imaging (e.g. hypoechoic area). All athletes were playing once per week and training twice per week. The TMS tester was blind to intervention status during testing and all data were analysed blind to intervention status. All testing was completed exactly one week apart to ensure stability of loading prior to testing (training and game days were consistent). The order of intervention was randomised by asking the athlete to draw an opaque sealed envelope with no external markings (concealed randomisation) (Schulz and Grimes, 2002b).

Figure 4.3 Testing protocol of week two and three
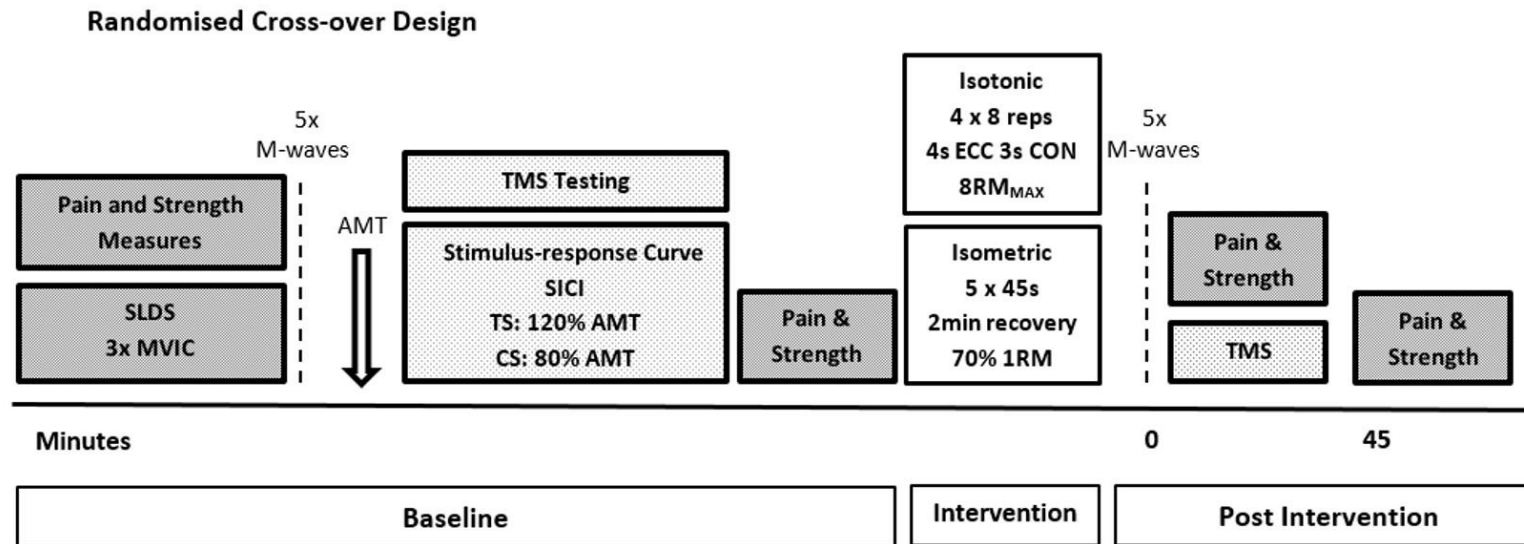
SLDS: single leg decline squat; MVIC: maximal voluntary isometric contraction; AMT: active motor threshold; SICI: short-interval intra-cortical inhibition; RM: repetition maximum

4.6.1 Baseline testing

At week one, baseline testing was completed without any intervention to ensure that the strength and pain testing measures and TMS measures themselves did not affect the primary outcome measures and to familiarise participants with the equipment and protocol. Athletes with bilateral symptoms were asked to nominate their most painful knee on the single leg decline squat and measures of quadriceps torque were taken from this side only and the contralateral hemisphere was tested with TMS. Athletes were asked to complete a VISA-P, a questionnaire about patellar tendon pain and function that is scored between 0 and 100 with 100 being maximal pain free function (Visentini et al., 1998). At week two and three, baseline measures were repeated (to enable comparison to week one baseline as well as the baseline of that intervention session).

4.6.2 Pain and strength testing

Tendon pain and quadriceps strength were tested at baseline. The single leg decline squat, a reliable patellar tendon pain provocation test (Purdam et al., 2003), was completed on each leg. Participants provided a numerical pain rating score for the decline squat on an 11-point numerical rating scale (NRS), anchored at left with '0, no pain' and at right with '10, worst possible pain'. Maximal voluntary isometric contraction (MVIC) torque for the quadriceps on the tested side was recorded in N∘m using isokinetic equipment (Biodex system 4 Pro, 1 Biodex Medical 2 Systems, Shirley USA) with three efforts completed with identical instructions, vocal encouragement and set up for each trial at 60 degrees of knee flexion. The outcome was the maximum peak torque recorded during these three efforts.

4.6.3 Transcranial magnetic stimulation and electromyography

Baseline measures of corticospinal excitability and short-interval intra-cortical inhibition (SICI) were obtained using single and paired-pulse TMS respectively. We optimised the accuracy of TMS by aligning the coil with references markers on a tight fitting cap worn by participants and marked with a latitude-longitude matrix, positioned with reference to the nasion-inion and interaural lines (Wilson et al., 1993).

Single-pulse stimulus-response curves were obtained during low-level isometric contractions of the quadriceps muscle group. Low level contractions were performed by maintaining the knee joint at 60º of flexion, while performing a 10% MVIC, which equated to $10 \pm 2\%$ of root mean square EMG (rmsEMG) during MVIC (Table 1). A 10% isometric contraction is a non-painful task for someone with PT. Consistent muscle activation was confirmed by recording pre-stimulus rmsEMG throughout the session. For a single modified stimulus-response curve, 10 stimuli were delivered in 20% increments from 90% of the participant's active motor threshold (AMT) up to 170% of their AMT. The stimuli were delivered using a ramped protocol (Pearce et al., 2013a). The amplitude of the motor evoked potential (MEP) or slope of the stimulus-response curve represents corticospinal excitability (Carroll et al., 2001a).

SICI is a subthreshold stimulus that activates inhibitory interneurons that synapse onto pyramidal neurons in the M1 and results in reduced number of action potentials by the subsequent suprathreshold stimulus (Reis et al., 2008). To quantify SICI, 10 single-pulse stimuli and 10 short-interval paired-pulse stimuli were delivered in random counterbalanced order. Intensity was set at 120% of AMT, which was determined during familiarisation and adjusted if there was a change in AMT. The conditioning stimulus for paired-pulse stimulation was set at 80% of AMT, the inter-

stimulus interval was 3 milliseconds, and posterior to anterior current flow was used to induce I3 waves (Garry and Thomson, 2009, Ilic et al., 2002). Muscle activation during testing does not affect SICI (Ilic et al., 2002). SICI is represented as a percentage ratio where high levels of inhibition are indicated by a low SICI ratio. Therefore an increase in the SICI percentage represents a reduction in inhibition.

Participants were tested at the same time of day and the same day of the week (Chipchase et al., 2012). TMS was delivered using two Magstim 200^2 stimulators connected via a Bistim unit (Magstim Co, Dyfed, UK) and a 110-mm concave double-cone coil (maximum output of 1.4 T). The motor hotspot for the rectus femoris muscle (with posterior-to anterior-induced current flow in the cortex) was determined and AMT were established as the intensity at which at least five of 10 stimuli produced MEP amplitudes of greater than 200µV recorded from the rectus femoris (RF) muscle. The RF muscle was selected as the tendon fibres of the RF muscle are the only tendon fibres of the quadriceps muscle group that continue over the anterior surface of the patellar to form the patellar tendon (Reider et al., 1981), which was the tendon of interest. Valid EMG data for RF can be captured with surface electrodes.

The area of electrode placement was shaved to remove fine hair, rubbed with an abrasive skin rasp to remove dead skin, and then cleaned with 70% isopropyl alcohol. Bipolar gel Ag-AgCl electrodes (8 mm diameter, model E258S; Biopac, Goleta, CA, USA) were placed over the RF muscle (centre-centre inter-electrode distance = 2 cm). A grounding electrode was placed over the patella and subsequently used as a common reference for all electrodes. All cables were fastened with tape to prevent movement artefact. The exact area of placement was three fifths of the distance between the anterior superior iliac spine (ASIS) and the upper border of the patella.

An impedance meter was used to check impedance did not exceed 10 kΩ prior to testing. sEMG signals were amplified (1000x), bandpass filtered (high pass at 13 Hz, low pass at 1000 Hz), digitized online at 2 kHz for 500 ms, recorded and analysed using PowerLab 4/35 (ADInstruments, Bella Vista, Australia).

Table 4.1 Mean (± SEM) Root mean square EMG: condition average as a percentage of EMG recorded during maximal isometric contraction

Exercise	SP 130% AMT		SP 120% AMT		PP	
	Pre	Post	Pre	Post	Pre	Post
Isotonic Trials	10.80 ± 0.15	10.69 ± 0.16	10.34 ± 0.18	10.25 ± 0.17	10.77 ± 0.16	10.69 ± 0.16
Isometric Trials	10.42 ± 0.11	10.67 ± 0.10	10.63 ± 0.16	10.69 ± 0.12	10.47 ± 0.13	10.25 ± 0.15

PP denotes paired-pulse. SP denotes single-pulse.

Pre-stimulus rmsEMG activity was determined in the rectus femoris muscle 100 ms prior to each TMS stimulus during pre and post testing. Any trial in which pre-stimulus rmsEMG exceeded $10 \pm 2\%$ of maximal rmsEMG were discarded and the trial repeated. The surface rmsEMG was calculated from a 500 ms segment that occurred during the asymptote of each MVC and was calculated as the amplitude of the RMS value.

4.6.4 Maximal compound muscle action potential

Direct muscle responses were obtained from the rectus femoris muscle by supramaximal electrical stimulation (pulse width 2000 μs; DS7A, Digitimer, UK) of the femoral nerve under resting conditions. The site of stimulation that produced the largest M-wave was located by positioning the bipolar electrodes in the femoral triangle. An increase in current strength was applied to the femoral nerve until there was no further increase observed in the amplitude of the sEMG response (M_{MAX}). To

ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} was obtained from five stimuli, with a period of 6-9 s separating each stimulus. M_{MAX} was recorded at baseline and following the intervention, to ensure that there were no changes in peripheral muscle excitability that could influence MEP amplitude (Carroll et al., 2002a).

4.6.5 Intervention protocols

Protocols were matched for time under load and rest between sets (set at two minutes to allow muscle recovery) (Ahtiainen et al., 2003b) (Table 4.2). Repetition maximum and MVIC were determined in the familiarisation session. As muscle work during isometric exercise and isotonic exercise cannot be directly measured, protocols were matched for perceived exertion on the basis of pilot studies. Isotonic repetitions were paced by a metronome. The metronome was also used for isometric contractions, so as to control for any potential confounding effect. Furthermore, auditory cues have been shown to be beneficial on the induction of neuroplasticity (Goodwill et al., 2012, Hendy et al., 2012a, Kidgell and Pearce, 2010, Kidgell et al., 2011, Latella et al., 2012b, Weier et al., 2012a).

Table 4.2 Loading protocols in the study

Exercise Protocol Parameters

	Apparatus	Prescription	Recovery	Loading Bolus
Isometric	Biodex Pro	5 x 45 sec at 60°	2 min	70% MVC
Isotonic	Leg Extension Machine	4 x 8 Reps *4 sec eccentric phase* *3 sec concentric phase*	2 min	100% 8RM

MVC, maximal voluntary contraction. Sec, seconds. Reps, repetitions. RM, repetition maximal

4.6.6 Follow-up testing and time course

Testing immediately after the intervention consisted of pain and strength testing measures (SLDS and MVIC), M_{MAX}, and TMS measures (stimulus-response curve and SICI). Testing for M_{MAX} was timed so that it was tested a minimum of 4-5 minutes after training (Selvanayagam et al., 2012, Lentz and Nielsen, 2002). Single leg decline squat and MVIC were also tested 45 minutes post-intervention (Figure 4.3).

4.6.7 Data analyses

The peak-to-peak amplitude of MEPs evoked in the period 10-50 ms after stimulation were analysed using LabChart 8 software (ADInstruments, Bella Vista, NSW, Australia) after each stimulus was automatically flagged with a cursor, providing peak-to-peak values in μV, averaged and normalised to the M_{MAX} and multiplied by 100. To construct stimulus-response curves, stimulus intensity was plotted against

MEP amplitude, then fitted with a non-linear Boltzmann equation using Prism 6 (GraphPad software Inc., California, USA) (Weier et al., 2012a).

The conditioning MEP amplitude was expressed as a percentage of the unconditioned test MEP amplitude to calculate the level of intracortical inhibition.

4.6.8 Statistical analysis

All data were screened with the Brown–Forsythe test and found to be normally distributed (all $p > 0.05$) and thus the assumptions of the ANOVA were not violated. A split-plot in time, repeated measures ANOVA was used to compare the effect of each condition (isometric and isotonic) on pain, strength, and corticospinal excitability and inhibition. When appropriate, univariate and post-hoc t-tests (with Bonferoni correction) analyses for pairwise comparisons of means for each dependent measure were used when significant interactions were found. For all tests, if the assumption of sphericity was violated the Huynh-Feldt correction was applied. Alpha was set at $p < 0.05$, and all results are displayed as means±SD and CI where appropriate within the text. Where mean ± SEM are reported, this has been indicated.

4.7 Results

Participants had substantial tendon pain, the mean VISA-P was 52.8 (47.5-66.5). There were no systematic differences detected in baseline SLDS pain, stimulus response slope, SICI or MVIC at the first or each subsequent testing session indicating sufficient wash-out between sessions. Therefore, only pre and post intervention data (week two and three) are reported. There were no differences detected in M_{MAX} at any time point ($p = 0.88$). The 10% muscle contraction maintained during TMS testing was a painfree activity for participants.

Baseline SLDS pain did not differ significantly prior to either intervention. Pre-isometric intervention pain (mean ± SD) was 7/10 ± 2.04 and pre-isotonic intervention pain was 6.33/10 ± 2.80 (p > 0.99). Isometric exercise reduced pain on the SLDS (mean ± SD) immediately from 7/10 ± 2.04 to 0.17/10 ± 0.41 ($p = 0.004$); the reduction was sustained at 45 minutes ($p < 0.001$) (Figure 4.4). Isotonic exercise resulted in immediate pain relief on SLDS (mean ± SD) from 6.33/10 ± 2.80 to 3.75/10 ± 4.67 ($p = 0.04$) but this was not sustained at 45 min. This corresponds to an immediate mean reduction in pain following isometric exercise of 6.8/10 compared with 2.6/10 post isotonic exercise. Individual data are shown in Figure 4.5.
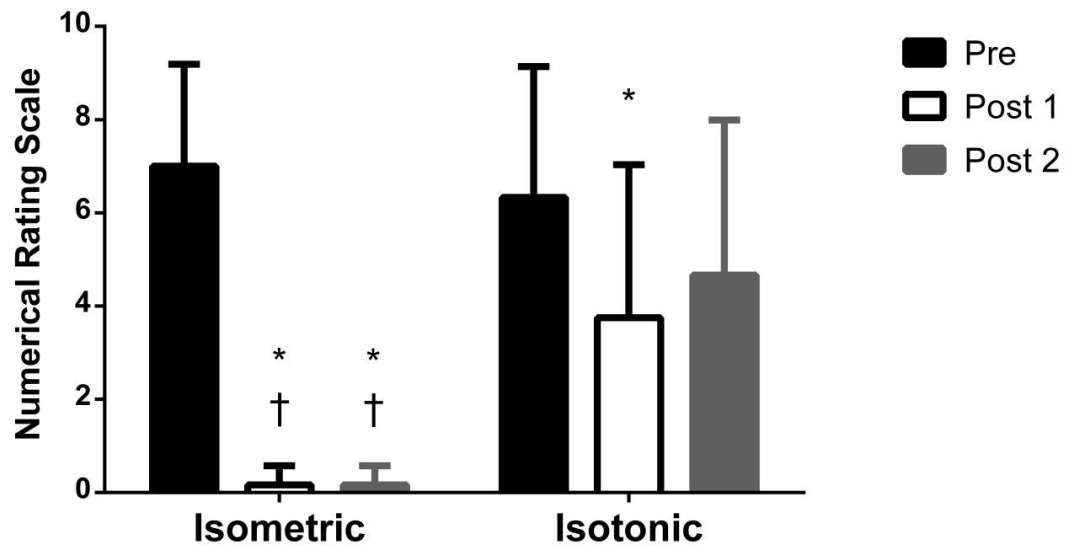
Figure 4.4 Single leg decline squat (tendon pain) pre & post intervention: Mean (± SD) changes in single leg decline squat pre and post isometric and isotonic strength training

Immediately following an acute bout of isometric strength training, SLDS numerical pain rating scale improved by 87% and was sustained at 45 minutes post compared to isotonic. Immediately following an acute bout of isotonic strength training, SLDS numerical pain rating scale improved by 42%, however by 45 minutes post the intervention, it was not significantly different to baseline. * denotes different to pre-intervention ($p < 0.05$); † denotes different to same time point for the isotonic intervention ($p < 0.05$.)
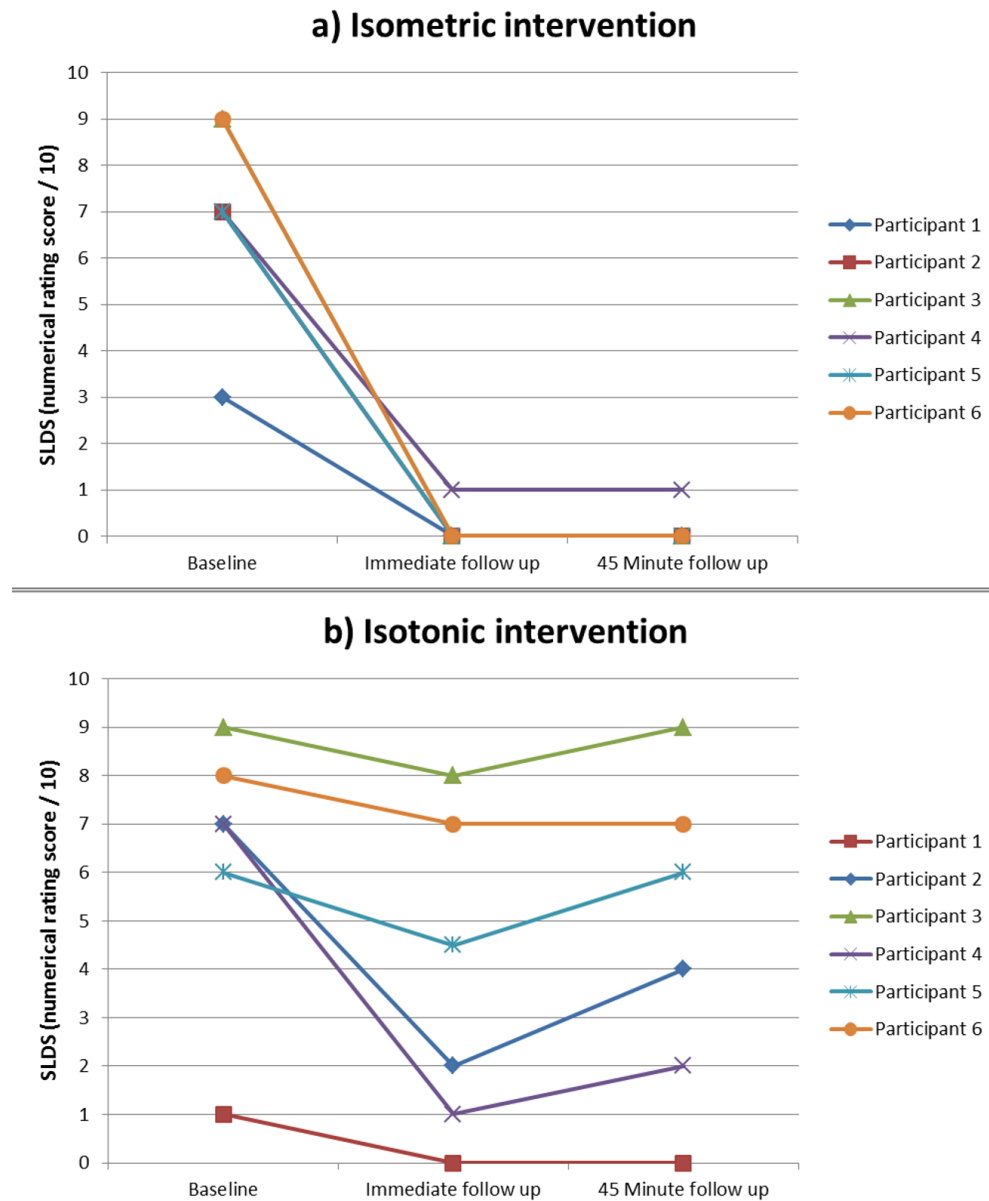
Figure 4.5 Individual participant data for SLDS pre, post and at forty-five minutes: SLDS pain scores at each interval for individual participants. (a) isometric intervention (b) isotonic intervention

Note due to the same pain scores reported for different participants, lines in the isometric intervention graph overlap.

An increased MVIC torque was observed immediately after the isometric intervention (mean increase of 18.7% compared with baseline isometric, mean difference between

isometric and isotonic 27 N∘m, 95% CI 12.96 to 41.04, $p < 0.001$) that was sustained for at least 45 minutes post-intervention (mean increase from isometric baseline 17.4%, mean difference between isometric and isotonic 30.5 N∘m, 95% CI 16.46 to 44.54, $p < 0.001$). This increase was significantly different to the isotonic exercise that resulted in a small but non-significant reduction in MVIC immediately following the intervention and at 45 minutes after (Figure 4.6).
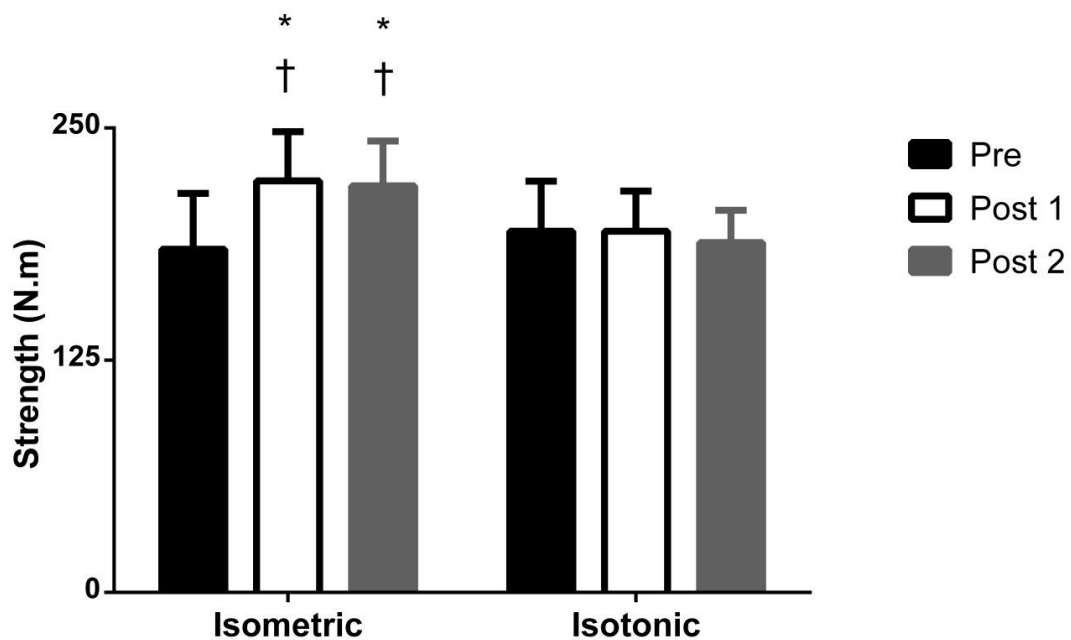
Figure 4.6 Maximal voluntary isometric strength: Mean (± SD) Maximal voluntary isometric contraction torque pre and post isometric and isotonic strength training

Immediately following an acute bout of isometric strength training, isometric strength increased by 19% and was sustained at 45 minutes post compared to no change following a single bout of isotonic strength training. * denotes different to pre-intervention (p < 0.05); † denotes different to the same time point for the isotonic intervention (p < 0.05.)

The mean SICI ratio prior to the isometric intervention was 27.53 ± 8.30% (Figure

4.7) and prior to the isotonic condition was 30.26 ± 3.89 (p = 0.31). There was a

significant condition by time effect immediately post; isometric exercise significantly

released this inhibition to 54.95% ± 5.47% (an increase in SICI ratio) (mean

difference compared with isotonic 23.66, 95% CI 12.28 to 35.05, p = 0.004) (Figure

4.7). Inhibition was not measured at 45 minutes.
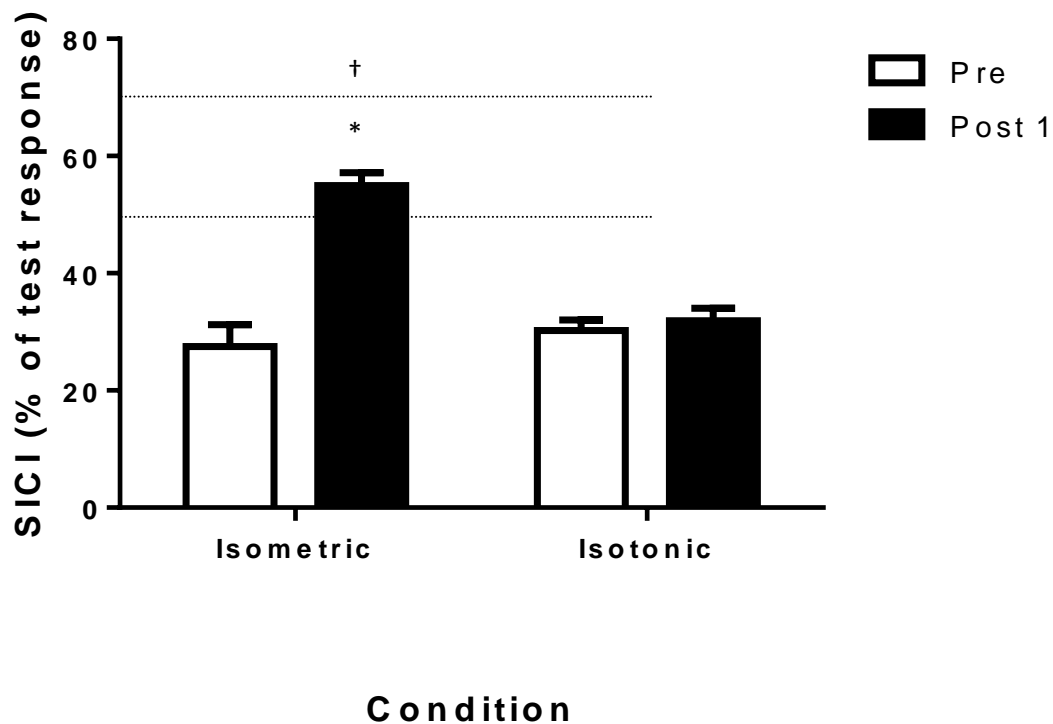
Figure 4.7 Effect of intervention types on SICI

There were no differences at baseline in SICI. Short-interval intra-cortical inhibition (SICI) before and

after isometric and isotonic interventions. *denotes significant to pre ($p < 0.05$); † denotes significant

to isotonic group ($p < 0.05$.) --- denotes range of normal SICI ratio reported in the literature for the

quadriceps.

There was no difference in SLDS pain scores in the contralateral leg after a unilateral exercise intervention in people with bilateral PT, however there were only three participants. There were no systematic differences detected between isometric and isotonic exercise in corticospinal excitability as represented by the slope of the modified stimulus-response curve ($p = 0.81$).

4.8 Discussion

Isometric exercise immediately reduced patellar tendon pain with the effect sustained for at least 45 minutes. There was a smaller magnitude immediate effect for isotonic exercise that was not sustained. Release of intracortical inhibition was associated with pain reduction and may be implicated as an underlying mechanism for the changes in pain. There was an increase in MVIC post isometric exercise that may be attributed to a decrease in intracortical inhibition. Time course testing of SLDS and the inclusion of a purely baseline measure (no intervention) one week prior to the first intervention session demonstrated that changes were due to the intervention and not TMS or MVIC testing.

The pain reduction observed following isometric exercise may be due to the cortical changes observed and motorneuron pool recruitment, and/or driven by changes at a tissue level. Spinal and supraspinal activation strategies and signals may be different depending upon the type of contraction (Duchateau and Enoka, 2008). The percentage of motor unit activation during an isometric contraction is significantly higher than during either eccentric or concentric contractions (Babault et al., 2001). These differences may be due to the signal discharged from the spinal cord and/or the central activation of the α (cells bodies located in the ventral horn of the spinal cord that innervate extrafusal muscle fibres) or γ (innervate intrafusal muscle fibres found

within the muscle spindle) motorneuron pools (Tax et al., 1990). The distinction between isometric contraction and an isotonic contraction is simply whether there is fibre length or whole muscle length change (Ishikawa et al., 2005). During a concentric/eccentric action there must be constant modulation of motor unit activity as less is required in the eccentric phase. There is also greater feedback from muscle spindles during eccentric contractions (Hulliger et al., 1985). It has been hypothesised that there may be unique activation patterns rather than simply a scaled down version of the activation signal used during the concentric movement related to torque requirements (Enoka, 1996, Nardone and Schieppati, 1988) and that there is more cognitive attention required during eccentric actions especially in planning and movement execution (Duchateau and Enoka, 2008). However, this is quite complex as different studies report different size motor evoked potentials (representing cortical) and H-reflexes (representing peripheral) depending upon contraction type (Abbruzzese et al., 1994).

Local tissue effects may include changes to cell metabolism, receptor expression and the biochemical environment during isometric exercise, which are then transmitted to the CNS. For example, the balance of ion channel and receptor operated channel function may change in milliseconds (Hudspith et al., 2006). This would implicate a different local tissue effect when completing an isometric compared with an isotonic muscle contraction. A potentially important finding in this unilateral protocol was that there was no effect on the contralateral leg pain in those with bilateral PT (n=3) however this warrants further investigation with greater numbers. The changes to intracortical inhibition indicate no widespread CNS pain inhibition (a feature following isometric exercise that has been reported in populations without musculoskeletal pain using pressure pain thresholds). The lack of any detectable

effect on the contralateral knee pain of those with bilateral pain demonstrates that the analgesia observed on the exercised leg is not simply a consequence of systemic inhibitory control, although it does not rule out this consideration.

Cortical reorganisation reflects changes in the response profile of brain cells. Reorganization of the M1 can be detected by changes in both the magnitude of the muscle response and the cortical topographical motor maps that are evoked by stimulation. Although the changes might occur anywhere along the motor neuroaxis, they are generally attributed to changes in cortical excitability. We did not observe an effect of a single bout of isometric or isotonic contractions on cortical excitability however this protocol employed modified stimulus response curves. Therefore, it cannot be ruled out that changes were simply not observed using this method. Furthermore, neuroplastic changes to the M1 could require repeated and targeted strategies to address them.

Unlike cortical excitability, SICI appears to be mediated through low threshold $GABA_A$ receptor dependent inhibitory pathways (Ziemann, 2003) and was altered with a single bout of isometric exercise. Strength training is known to modulate inhibition in normal controls (Aagaard et al., 2000) however few studies have examined intracortical inhibition in other musculoskeletal conditions. In osteoarthritis-related pain, inhibition did not significantly differ from the control group whereas in chronic neuropathic pain following peripheral nerve lesion, there was a significant reduction in inhibition (Schwenkreis et al., 2010). When normal volunteers are subjected to experimental muscle pain SICI levels are increased (Chipchase et al., 2012), however the intervention protocol of the current study was non-painful. Despite the limited literature available for comparison, the high levels of

inhibition present in people with PT, (mean of 27% whereas data reported for the quadriceps in normal participants ranges between 50-70%) (Goodwill et al., 2012) appears to be a novel finding. Further, this was altered following a single bout of isometric exercise.

Inhibition affects motor patterning by altering the number of action potentials that reach the corticospinal pathway to activate the motorneuron pool. People with PT appear to be using large amounts of inhibition to moderate their motor output, which may be an aberrant control mechanism compared with normal motor control. This strategy may contribute to the recalcitrance of PT and may be a new and important consideration in effective rehabilitation. Furthermore, isometric exercise but not isotonic exercise modulated inhibition in those with PT, which improves the net corticospinal drive to the motorneuron pool. This change occurred without evidence of a systematic decline in muscle performance (fatigue), as muscle performance (MVIC) was actually improved by the isometric protocol. This difference between the protocols indicates the effect is not simply the result of load or exercise based analgesia but is task specific and only observed during isometric contractions. The clinical implications are that isometric exercise using 70% of MVC may be a useful protocol prior to activity to reduce pain without inducing muscle fatigue. Increased inhibition may be a method of reducing motor recruitment in PT and could be an important finding to address in rehabilitation.

Motor evoked potentials are reduced during experimental pain conditions (Le Pera et al., 2001). The testing and intervention protocols here were not painful and this excludes the possibility that the observed effect reflects competitive inhibition or diffuse noxious inhibition.

There are a number of limitations of the study. First, it is acknowledged that the sample size was small. The robustness of the study was improved by the cross over design and three week protocol where sessions were completed on the same day at the same time of day with consistent loading prior (and therefore tendon pain). However, it is unknown if the results are generalisable given the small numbers. Second, these results are not applicable to people with anterior knee pain and may be specific to PT. The diagnosis of PT is important, it is not expected that positive results would be observed if other presentations of anterior knee pain were included, for example heavy quadriceps loading may aggravate someone with patellofemoral pain, due to the compression in this position. Third, this study only included men but did include both unilateral and bilateral pain presentations. Lastly, the inclusion of a non-intervention control group would provide greater quantification of the changes observed.

This study has several clinical implications. Despite the small sample size, participants reported a broad pain severity at baseline reflecting the variability of clinical presentations. Furthermore, there were no non-responders to isometric exercise regardless of pain severity or length of time of symptoms. In contrast, there was variation in the amount of pain reduction following isotonic exercise (and significantly less than isometric) and the effect was not retained at forty five minutes thus it may be a less attractive pain relief option. The clinical implications are that isometric exercise may be used to reduce pain and motor inhibition in the early stages of rehabilitation and provide an important option for clinicians to offer in painful tendons that are difficult to load. There may be a role for using isometric exercise to reduce motor inhibition and improve responses to strength training as it is currently known that deficits persist despite rehabilitation (Harno et al., 2000). Tendon

rehabilitation needs to be progressed beyond isometric exercise to enable a resilient tendon to return to sport, however this may provide an important option for clinicians to offer in painful tendons that are difficult to load without aggravating symptoms or potentially pre-strength training sessions in latter stages.

As a further consideration, the optimum prescription of isometric exercise for pain reduction is not yet known. Whilst this study extensively piloted different protocols prior to data collection, further studies should identify optimal load, length of time under tension, rest and sets. In summary, this is the first study to demonstrate immediate pain reduction using strength training in people with tendinopathy. Future research should continue to investigate exercise for pain relief in other tendons and also provide optimal guidelines around dosage.

Chapter 5. What type of contraction has a greater immediate analgesic effect over 4 weeks inseason?

5.1 Declaration for thesis Chapter 5

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Isometric contractions are more analgesic than isotonic contractions for patellar tendon pain: an inseason randomised clinical trial	70

The following co-authors contributed to this work:

Name	Nature of contribution
Kidgell D	Assistance with study design, input into methodology used and preparation of the manuscript
Moseley GL	Preparation of the manuscript
van Ark M	Assistance with data collection during RCT, analysis of the US images and preparation of the RCT manuscript
Zwerver J	Preparation of the RCT manuscript
Akker-Scheek I	Preparation of the RCT manuscript

Purdam C	Assistance with protocol design and preparation of the manuscript
Gaida J	Preparation of the manuscript
Docking, SI	Data collection and analysis of the US images, preparation of the manuscript
Cook J	Senior supervision, assistance with protocol design and preparation of the manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidates and co-authors contributions to this work.

Candidate's signature (and date)

Main supervisor's signature (and date)

5.2 Chapter introduction, aim and hypothesis

Chapter 4 demonstrated the analgesic effect of an acute bout of quadriceps loading and that it is possible to modulate both pain and short-interval intra-cortical inhibition (SICI) with isometric load, however it is important to evaluate the cumulative effect inseason to determine its clinical utility. This chapter presents a randomised clinical trial (RCT) that investigated the clinical effect of externally paced isometric and isotonic muscle contractions in producing an immediate reduction in pain during the single leg decline squat (SLDS) and this has been submitted to the Clinical Journal of Sports Medicine.

Based upon the differences observed in motor drive in Chapter 3-4 the intervention used in the RCT was specifically designed to optimise corticospinal response. Several decisions were made based upon this goal.

First, four weeks was selected as strength training studies of short duration (<4-weeks) have demonstrated significant improvements in strength in the absence of muscular hypertrophy, which implicated corticospinal changes as the mode of effect (Deschenes et al., 2002). Secondly, strength training has been shown to improve corticospinal excitability (CSE) when elements of skill are included, such as attention to the task and requiring co-ordination of the timing of the movement with a metronome, to induce long term potentiation (LTP) (Nudo et al., 2001) (Chapter 2). The inclusion of constraints around the movement pattern is important, self paced strength is insufficient to produce a corticospinal change (Carroll et al., 2002b). The protocols used in this trial were similar to Chapter 4 in that it used external pacing to control the movement pattern including time under load and these auditory cues have been shown to be important for cortical change (Goodwill, 2012; Rothman, 2001;

Thomas, 2001; Lan, 2001; Kidgell, 2011; Kidgell, 2011). Changes were made to the protocol to prevent muscle soreness in the athletes who were in the competitive season (Appendix Y).

A sham intervention was not included as these are athletes with pain who are looking for symptom relief. Isotonic contractions, which were shown to be well tolerated in Chapter 4, were used rather than eccentric contractions as this was an in season intervention and painful exercise via eccentric loading was likely to result in study dropouts (Woodley et al., 2007).

The aim of this study was;

Aim: To investigate the immediate analgesic effect of strength training that uses either isometric or isotonic muscle contractions over a 4-week inseason period.

Hypothesis: Strength training that uses isometric muscle contractions will provide greater immediate analgesia than strength training that uses isotonic muscle contractions.

Null hypothesis: There will be no differences between the isometric and isotonic groups in immediate analgesia.

The transcranial magnetic stimulation (TMS) testing equipment was the same as for Chapter 4. Additionally, athletes were provided with access to a leg extension machine. If they were not a member of a gymnasium with a leg extension machine, a 4-week membership was arranged at a convenient gymnasium. All athletes were also provided with a SLDS board to enable pre and post numerical rating scale (NRS) of pain testing. This study received funding from the Australian Institute of Sport Clinical Research Fund (CRSCAS).

5.3 Participants

The ethics approval obtained for the previous chapters was amended to include athletes aged over 16 years of age to maximise the number of athletes eligible for inclusion in the RCT.

Isometric contractions are more analgesic than isotonic contractions for patellar tendon pain: an inseason randomised clinical trial

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5.4 Abstract

Objective This study aimed to compare the immediate analgesic effects of two strength programs in inseason athletes with patellar tendinopathy (PT). Strength training is non-invasive, a principle stimulus for corticospinal and neuromuscular adaptation, and may be analgesic.

Design: Within season randomised clinical trial. Data analysis was conducted blinded to group.

Setting: Sub-elite volleyball and basketball competitions.

Participants: 20 jumping athletes aged over 16 years, participating in games/trainings three times per week with clinically diagnosed PT.

Interventions: Two quadriceps strength protocols were compared; (1) isometric leg extension holds at 60 degrees knee extension (80% of their maximal voluntary isometric contraction) or (2) isotonic leg extension (at 80% of their eight repetition maximum) four times per week for 4-weeks. Time under load and rest between sets was matched between groups.

Outcome measures: (1) Pain $(0 - 10$ numerical rating score) during single leg decline squat (SLDS), measured pre and post intervention sessions. (2) VISA-P, a questionnaire about tendon pain and function, completed at baseline and after four weeks.

Results: 20 athletes with PT (18 men, mean 22.5 ± 4.7 years) participated (isotonic n = 10, isometric n = 10). Baseline median SLDS pain was 5/10 for both groups (isotonic range 1-8, isometric range 2-8). Isometric contractions produced significantly greater immediate analgesia $(p < 0.002)$. Week one analgesic response positively correlated with improvements in VISA-P at four weeks $(r^2 = 0.64)$.

Conclusions: Both protocols appear efficacious for inseason athletes to reduce pain, however isometric contractions demonstrated significantly greater immediate analgesia throughout the 4-week trial. Greater analgesia may increase the ability to load or perform.

Key words: isometric, isotonic, strength training, analgesia, inseason, patellar tendinopathy, exercise

5.5 Introduction

Patellar tendon pain can be debilitating and cause attrition from physical activity (Cook et al., 1998). However, athletes can often continue to play with tendon pain yet at reduced training volumes or frequency to prioritise participation in games/competition. Performance might be compromised in people with chronic or recurrent pain due to physical deficits associated with tendinopathy (Coombes et al., 2009, Rio et al.), excessive cognitive demand associated with pain (Eccleston and Crombez, 1999), decreased cognitive resources (Berryman et al., 2013), or disrupted spatial and motor representations associated with evaluation of ongoing threat (see (Moseley and Flor, 2012, Rio et al., 2014) for relevant reviews). Thus, it is important to investigate methods of reducing tendon pain inseason that allow the athlete to fulfil their playing and training commitments.

Exercise-based treatments are but one type of the many available treatments for tendinopathy. Other options include injection therapies (Gosens et al., 2012, Muneta et al., 2012), extracorporeal shockwave therapy (Standaert, 2012, Zwerver et al., 2011b), surgery (Maffulli et al., 2011, Alfredson, 2011) and many other treatments that are not without risk and often come at great expense. Furthermore, invasive interventions are frequently based on animal models of induced tendon injury that

may not replicate the pathoaetiology of human load-based tendinopathy (i.e. collagenase injections (Lui et al., 2011)) nor do they have long term data on their efficacy. Finally, and importantly, athletes are often reluctant to follow advice to have downtime after such interventions, which means they either have the treatment but not the downtime, or decline the treatment altogether.

Tendon load through exercise is the only stimulus that positively affects the tendon matrix (Kjaer et al., 2009) and has been shown to reduce pain perception and improve function over time (Silbernagel et al., 2007a). There are a number of variably efficacious exercise programs for tendinopathy (Morrissey et al., 2011, Woodley et al., 2007); however, few studies have compared the effect of different exercise regimes on immediate analgesia. Immediate improvement in symptoms throughout an exercise-based rehabilitation program may lead to better adherence or improved performance.

Several studies have evaluated eccentric exercise in patellar tendinopathy (PT) with clinical outcomes. It has been shown that eccentric exercise increased pain in the first two to four weeks (Alfredson et al., 1998). Investigations of eccentric exercise inseason have either shown no benefit (Visnes et al., 2005) or worse outcomes (Fredberg et al., 2008a). Given that eccentric exercise is poorly tolerated by the inseason athlete, other muscle contraction protocols warrant investigation.

One study has directly compared isotonic contractions (heavy slow strength) with isolated eccentric exercise. Isotonic contractions were as effective as eccentric only exercise in PT and with higher patient satisfaction over time (Kongsgaard et al., 2009). The immediate effect (either increase or decrease in tendon pain) was not reported. Athletes in that study remained active if their pain was less than 3/10 on a

numerical rating scale (NRS) and activity levels were not significantly different to baseline thus findings may not be applicable to the inseason environment. Rio et al., (2015) reported that isometric contractions demonstrated superior pain relief in terms of immediate effect on single leg decline squat pain (SLDS) lasting at least 45 minutes and without a decline in muscle performance. However, this was a single intervention and the cumulative effect in the intervention inseason is unknown. Neither isometric nor isotonic contractions resulted in an increase in pain in the Rio et al., (2015) study, thus these contraction types may be better tolerated than eccentric contractions in an inseason trial.

There are clear benefits to inducing immediate analgesia without muscle fatigue in a sporting environment. Athletes may choose to complete the protocol immediately prior to training or competition, which could result in continued and/or greater participation in competitive sport. Therefore, the primary aim of this study was to compare the immediate effect of strength training that involved either isometric or isotonic muscle contractions on patellar tendon pain during a 4-week competitive season in jumping athletes. It was hypothesised that isometric muscle contractions would provide greater immediate analgesia than isotonic contractions. The secondary aim of the study was to compare the effect of isometric and isotonic contractions on pain and function as measured by the VISA-P after four weeks. It was hypothesised that both groups would improve more than the minimum clinically important difference (MCID) after 4-weeks.

5.6 Method

This randomised clinical trial over 4-weeks had two intervention arms, either isometric or isotonic quadriceps muscle contractions. Male and female volleyball and

basketball athletes aged over 16 years were recruited from sub-elite and elite competitions. The study was approved by the Monash University Human Research Ethics Committee (MUHREC), Australia (CF12/0230 – 2012000067). This trial was registered in the Australian New Zealand Clinical Trial Registry (ACTRN12613000871741) and all athletes provided written informed consent. These data formed part of larger trial (van Ark et al, unpublished data).

Clinical diagnosis of PT was defined as pain localised to the inferior pole of the patella during jumping and landing activities and during testing on the SLDS, a reliable patellar tendon pain provocation test (Purdam et al., 2004, Zwerver et al.). The diagnosis was confirmed by the presence of characteristic features on ultrasound imaging (e.g. hypoechoic area and/or tendon thickening). Exclusion criteria were the existence of other knee pathology, previous patellar tendon rupture, previous patellar tendon surgery, inflammatory disorders, metabolic bone diseases, and type II diabetes, use of fluroquinolones or corticosteroids in the last 12 months, known familial hypercholesterolemia and fibromyalgia.

5.6.1 Baseline testing

Participant height (cm) (Seca 213) and weight (kg) was recorded (Omron HN283) without footwear. Measurements were recorded three times and the mean was recorded if there was any variability. VISA-P, a questionnaire about patellar tendon pain and athletic function were completed where a score of 100 represents full pain free function (Visentini et al., 1998). Baseline maximal voluntary isometric contraction (MVIC) of the quadriceps was tested and recorded for participants randomised to the isometric group. Eight repetition maximum (8RM) was tested for isotonic group. This provided the starting weight for week one. All testing was

completed on the same leg extension machine that each individual participant used for the duration of the trial.

5.6.2 Randomisation procedure

Randomisation was completed using the random number generator function (Excel 2007©) and concealed inside an unmarked, individual opaque envelope (Schulz et al., 2002). Participants selected a small envelope from a larger opaque, unmarked envelope that contained the code for the groups.

5.6.3 Intervention

Investigators determined the starting weights in the first session as described above. This session also demonstrated the intervention and the exercise diary. The exercise diary recorded the weight completed for each session and the pre- and post-exercise pain scores. This was a numerical rating score (NRS) from zero to ten whilst completing one single repetition on the single leg decline squat (SLDS) for each leg.

Both protocols were completed on a leg extension machine (Table 5.1). The leg extension machine was chosen as a way of isolating the quadriceps muscle group without pain (Rio et al., *in press*). As muscle work during isometric and isotonic muscle contractions cannot be directly measured, protocols were matched for ratings of perceived exertion during pilot studies. All participants were provided with an auditory recording, which also served to pace participants and match time under tension and rest periods. The recovery length of one minute was chosen to allow muscle recovery (Ahtiainen et al., 2003b). Athletes were requested to avoid other quadriceps exercises during the 4-weeks but were free to complete all other gym, training and competition.

Table 5.1 Isometric and isotonic muscle contraction protocols used in the study

	Isotonic	Isometric
Parameters	4 x 8 @ 80% 8RM Seven seconds per repetition: Four -second eccentric phase immediately followed by a three second concentric phase.	5 x 45 second holds @ 80%MVIC
Recovery	One minute between sets	One minute between sets
Knee joint angle	Through a chosen, comfortable range of motion between 10-90 degrees	60 degrees flexion
External pacing	Audible recording with metronome set at 1hz and verbal instructions to retain attention to task	Audible recording including metronome set at 1Hz and verbal instructions to retain attention to task
Progression	2.5% progressive overload weekly if able	2.5% progressive overload weekly if able

Key - MVC: maximal voluntary contraction, 8 RM: Eight repetitions maximum, MVIC: maximal voluntary isometric contraction. Note: the protocol was modified Chapter 4 to prevent delayed onset muscle soreness.

Each participant was contacted weekly by a researcher and weight was increased by 2.5% if all sessions were completed at the previous weight and if the athlete felt they could increase the weight on their leg extension machine exercise. Otherwise the weight was maintained for a further week. If participants were not able to complete their repetitions (for example due to

fatigue induced muscle shaking), they were instructed to lower the weight on the machine for the next repetition and still complete the entire session so that there was equal time under tension.

5.6.4 Follow-up

At the end of four weeks, participants completed a VISA-P and returned their completed exercise diaries.

5.6.5 Outcome measures

The primary outcome measure for the study was the difference in pain during a SLDS before and after every intervention session. The secondary outcome measure was the VISA-P completed at baseline and 4-weeks, a change in score of more than 13 has been shown to be the minimum clinically important difference (MCID) for the VISA-P (Hernandez-Sanchez et al., 2014).

5.6.6 Data and statistical analysis

For those athletes with bilateral symptoms, the side that they reported the highest NRS on the SLDS at baseline training was chosen for analysis. If this was equal, the limb was chosen at random. Change in pre and post NRS pain scores were calculated by subtracting the pre from the post score for every session. If the data did not satisfy assumptions of parametric statistical tests, then the equivalent non-parametric analysis was used. Starting weights were recorded and mean and standard deviation is presented. For those participants who returned their diaries but missed sessions, the last observation carried forward (LOCF) method was applied. Athletes who were randomised but did not complete any sessions were excluded from analysis (Heyting et al., 1992). Intention to treat analysis was performed for athletes who failed to return their booklets but were known to complete at least one session; they were allocated a pre NRS score of five and a post NRS score of five so that the change score was zero. This conservative option was

selected to avoid overestimating the effect by using the group median (Heyting et al., 1992). Area under the curve was used to measure exposure, in this case analgesia from the intervention training. A correlation was performed between the response in week one and the final VISA-P change score to identify potential responders to inseason training. Significance was set at α=0.05.

5.7 Results

Twenty nine athletes were randomised to the study, seven athletes did not complete any of the intervention sessions as they were unable to be contacted by the researchers after randomisation. Two athletes dropped out during the intervention period, one for personal reasons and the other for an unrelated injury (both prevented basketball participation). Both were excluded from analysis as they were no longer playing/training three times per week. Twenty athletes were included in the analysis, ten in each group. One athlete in the isotonic group and two athletes in the isometric group did not return their booklet and were therefore allocated a change score of zero for the duration of the intervention period. The groups did not differ at baseline for measures of tendon pain and function (SLDS and VISA-P) and starting load (Table 5.2). Athletes in both groups continued to play and train three times per week, with no athlete missing any games or team training sessions due to tendon pain. Data were not normally distributed and non-parametric analysis was used.

Table 5.2 Baseline comparison of the intervention groups

	Isotonic N=10	Isometric N=10
Bilateral symptoms	N=5	N=3
Gender	N=9 men	N=9 men
SLDS (median + range)	5/10 (1-8)	5/10 (2-8)
VISA-P (0-100) median+range	69.5 (46-83)	72.5 (13-88)
Starting weight (mean±SD)	29.5kg±9.88	29.5kg±9.59

SLDS, single leg decline squat; VISA-P, Victorian Institute of Sport Questionnaire Patellar tendon

Reduction in pain between pre and post measures of every intervention session was greater for the isometric group (mean ± SD change = 1.8 ± 0.39) than it was for the isotonic group (0.9 ± 0.25, Cohens d = 2.75, p < 0.001; Figure 5.1). This corresponded to a greater volume of area under the curve (AUC) that is increased analgesia in the isometric group (AUC isometric 26.00, isotonic 14.23).
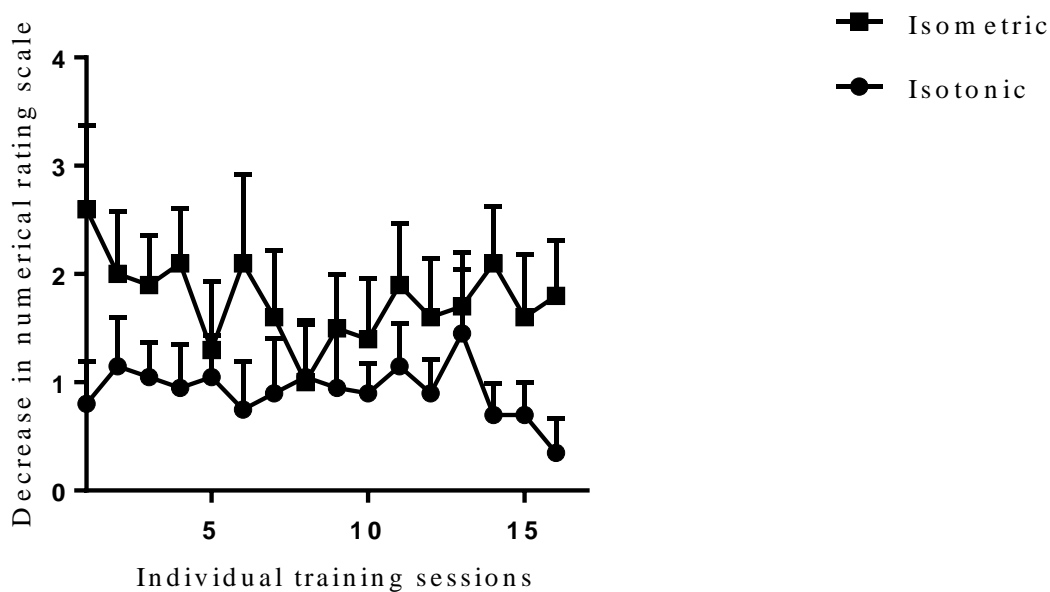
Figure 5.1 Mean±SEM decrease in pain between pre and post measures for the isotonic group (circles) and isometric group (squares) for each training session

Both groups improved their VISA-P over the 4-weeks and there were no significant differences between groups at follow up ($p = 0.99$). There was variability in the response including two athletes whose VISA-P score was worse in the isotonic group and two whose scores did not change (one in each group) (Figure 5.2). Neither group median was greater than the MCID, the isotonic group score change was 10.5 points and the isometric group change was 11.5 points. The median VISA-P in both groups was greater than 80/100 at the end of the four week intervention (isotonic group 80/100, range 60-94 and isometric group 84/100, range 41-100). Five athletes out of ten in the isotonic group achieved greater than 80/100 and seven athletes out of ten achieved greater than 80/100 at the end of 4-weeks.
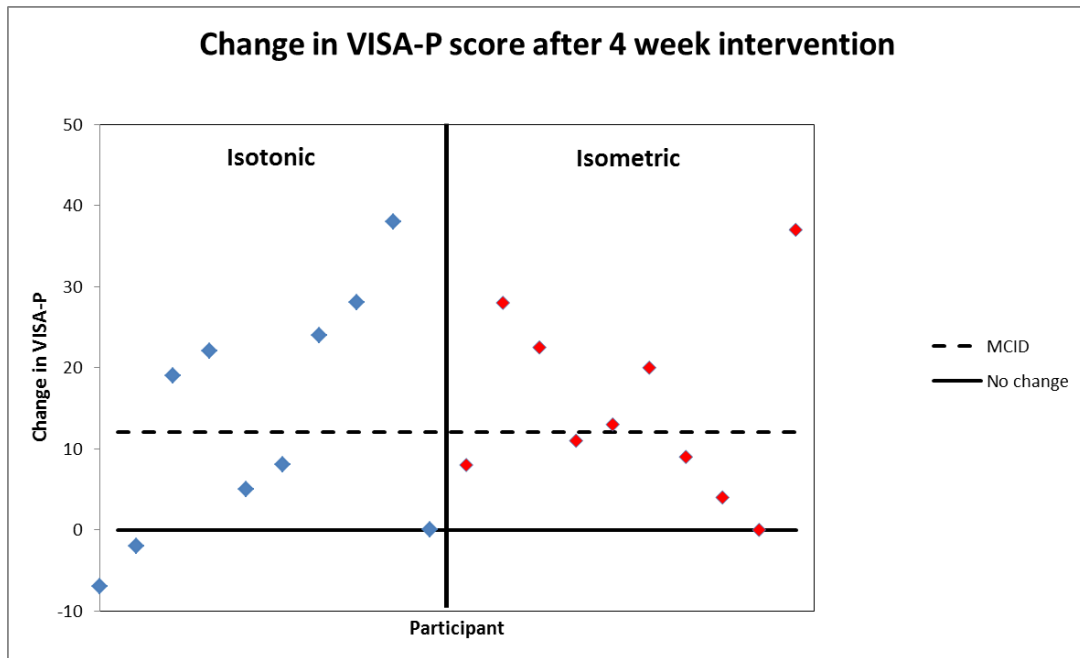
Figure 5.2 Change in VISA-P score

following 4-week intervention

MCID, minimum clinically important difference (13 points)

There was a moderate positive correlation between the mean change in NRS in week one and the change in VISA-P score ($r^2 = 0.64$). Approximately sixty percent of the variance in the VISA-P change from baseline to follow up was explained by the analgesic response to exercise in week one.

The starting weight for participants was mean 29.5 ± 9.6kg in the isometric group and 29.5 ± 9.9kg in the isotonic group. The weight increase was modest over 4 weeks; 0.9 ± 3.5kg for the isometric group and 1.45 ± 1.7kg for the isotonic group. If athletes had progressed according to the 2.5% increase, the overall increase would have been at least 3kg for both groups over the 4-weeks.

5.8 Discussion

Isometric muscle contractions resulted in significantly greater immediate analgesia than isotonic muscle contractions in a 4-week trial whilst athletes were playing and training. There are potential benefits to the increased immediate pain relief demonstrated by isometric exercise. First, less pain may lead to higher activity intensity or participation in more training sessions. It is also possible that athletes may spend less time in pain over the course of the week, particularly in light of previous research demonstrating at least a 45 minute effect associated with isometric but not isotonic exercise (Rio et al., *in press*). There are several additional benefits to reducing evoked pain with strength training including, removing fear of exercise (Vlaeyen and Linton, 2000), improved self efficacy in that they can modulate their own pain (and this is analgesic in itself) (Wiech et al., 2006) and an improved sense of control, as anxiety, closely linked to low sense of control, has differential and synergistic effects on pain (Wiech et al., 2014). At a tissue level there may be benefits to the quadriceps muscle architecture (Young et al., 1983), tendon properties (Kubo et al., 2002) and cortical drive to the quadriceps (Weier et al., 2012a). Analgesia from rehabilitation is also likely to promote increased adherence with completing the rehabilitation.

There are several potential centrally mediated mechanisms that may explain the anti-nociceptive effect of motor activation. Motor centres have direct projections to the dorsal horn (Kandel et al., 2012) and also to midbrain centres that are themselves powerful generators of descending inhibition. Completing maximal or near maximal effort without tissue damage reinforces positive effects (Butler, 2009). Furthermore, fatiguing tasks that require effort and demand attention compete with pain to influence the output generator (Nakagawa et al., 2013, Bantick et al., 2002). However, these mechanisms may not explain the differences between isometric and

isotonic muscle contractions as both protocols required fatiguing motor activation with cognitive demand. Therefore, they may also be differences in the local tissue response to the two types of contractions (such as nociceptive receptor stimulation or change to the biochemical environment) and / or unique differences in the cortical activation pattern between isometric and isotonic muscle contractions. Previous studies have reported a hypoalgesic effect of exercise depending upon the type; aerobic exercise reduced perception of experimentally induced pain in healthy people (effect size for threshold d = 0.41, intensity d = 0.59), dynamic / isotonic exercise (threshold d = 0.83, intensity d = 0.75) and isometric exercise (threshold d = 1.02, intensity d = 0.72) (Naugle et al., 2012).

There were no differences between groups in the VISA-P after 4-weeks and neither group median was greater than the MCID (a change score of 13 or 15.4% of their original score). The VISA-P is a robust measure and is not traditionally repeated in clinical practice or in research after only 4-weeks. There was variability in response as ten athletes (five in each group) improved more than 13 points, and 12 athletes scored more than 80 on their VISA-P at follow-up (five in the isotonic group and seven in the isometric group). A VISA-P score of less than 80 is considered to represent tendon pain that is causing impairment and reduced function (Visentini et al., 1998) indicating an important clinical shift in about half of the participants here in not just pain but also function.

There was a positive correlation between increased analgesia in the first four sessions (week one) and a greater increase in the VISA-P after four weeks. Early response to either intervention explained approximately 60% in the variance of the final VISA-P score. This may assist clinically with identifying those athletes that will respond to inseason load to induce analgesia.

The two athletes that scored lower in the VISA-P at the end of the intervention in the isotonic group reported pain reduction throughout the intervention in their pre- and post-exercise scores. It is difficult to reconcile these results and future studies may consider inclusion of qualitative data to better identify individual factors that lead to a positive outcome.

This pragmatic randomised clinical trial demonstrated that both isometric and isotonic exercise were well tolerated in the inseason athlete. Both protocols appear to be efficacious inseason in contrast with previous studies investigating eccentric exercise (Fredberg et al., 2008a, Visnes et al., 2005). Athletes did not miss any game or training sessions due to tendon pain, which is important as training sessions are sometimes sacrificed to prioritise games even at the sub-elite and elite levels.

The weight increase for both groups was small and half of what was calculated based upon a 2.5% weekly increase. The projected increase was based on hypertrophy studies and may not be possible on top of inseason loads or in a cohort with musculoskeletal pain. Alternatively, supervision of sessions actually may have assisted weight progression, as heavy load has been shown to be important in reducing tendon pain perception (Rio et al., 2015). It is possible that athletes were fearful of overload and too conservative. The most plausible explanation is that increments on the leg extension machines were more than 2.5% thus the next increment was too great and in many cases it was difficult to find small appropriate weights.

This study had multiple strengths that provide immediate clinical utility. First, it was an inseason intervention (when tendon pain is highest) that was specifically aimed at providing analgesia. Second, it was a short term study and this may have improved adherence, although adherence is likely to be high with an intervention that reduces pain. Athletes could choose

when to complete the intervention, thus making it convenient. They could also then utilise the analgesia at a time they considered most beneficial and that may be prior to games and/or following games. Third, it was a pragmatic trial, it reflects real life where training loads and game volume were uncontrolled; for example volleyball matches can be up to five sets but may only be three.

This study had limitations, most importantly the missing exercise booklets from athletes. The decision to use a zero change score is conservative as the median change score of both groups was positive. This approach can dilute the effect size, whereas using the group median may inflate the effect size. Importantly, these athletes were not drop outs (in which case it may be considered that they dropped out due to a negative effect). The VISA-P score for the athlete in the isotonic group was unchanged (so perhaps using a change score of zero is appropriate) but the two athletes in the isometric group for whom LOCF was used, VISA-P changed by four and 13 points thus using a change score of zero may not reflect their analgesic response. The two athletes that dropped out during the trial were also excluded as they were no longer playing / training three times per week and therefore scores may artificially improve due to reduced tendon load.

As this was a pragmatic trial, sessions were not supervised and thus may not have all been completed. As athletes chose when to complete the intervention sessions, it was not feasible to provide supervision. Athletes were reporting consistent pain reduction with the protocols (in both groups) therefore it is expected that adherence was high (as it was beneficial) and that the exercise diaries were completed accurately.

Athletes were requested to remove other quadriceps exercises from their training for four weeks. This was due to two factors. First, as part of this study, corticospinal responses were recorded from a subset of the population and other quadriceps training would have impacted upon those results. Second, it is a clinical observation that many of the other quadriceps exercises that people complete are actually provocative for patellar tendon pain, such as lunges where the knee is forward of the ankle. Therefore, it was preferable to reduce nociceptive drive where possible by limiting these and evaluating the effect of one non-provocative quadriceps exercise. It is possible athletes continued quadriceps exercises and did not inform researchers.

The audio file was provided to externally pace and counters the potential variability in the way the exercises were completed, but it is not known if this was used by all athletes for every session. It is also unknown if the same results would be observed without the use of the auditory pacing as this has been shown to be important for modifying both corticospinal excitability and inhibition (Leung et al., *in press*) and these process may underpin the results observed. Future studies should consider recording when the athletes completed the protocol in relation to pre/post training or games or on rest days. This would provide more information about when the timing of such interventions has the greatest benefit.

In conclusion, it is possible that both isometric and isotonic protocols have a role in the in season athlete and that individualised clinical decision making could further enhance athlete response. This is not possible in an RCT. This study however provides clinicians with two potential options in athletes with PT inseason without fear of increasing tendon pain. A pragmatic approach would be to select the protocol that provided more pain relief as this is likely to be preferable for the athlete and these data would support the use of isometric exercise in that instance. The NRS response in week one also appears to be correlated with VISA-P change at 4-

weeks. Exercise based analgesia could be used to reduce pain following high intensity sessions or prior to games/trainings. Future studies should attempt to record load beyond participation to determine if increased pain relief allows athletes to load more and if this has positive or negative ramifications.

Chapter 6. A novel concept in tendon rehabilitation

6.1 Declaration for thesis Chapter 6

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Tendon neuroplastic training: changing the way we think about tendon rehabilitation	70

The following co-authors contributed to this work:

Name	Nature of contribution
Kidgell D	Assistance with study design, input into methodology used and preparation of the manuscript
Moseley GL	Preparation of the manuscript
Purdam C	Assistance with protocol design and preparation of the manuscript
Docking, SI	Data collection and analysis of the US images, preparation of the manuscript
Gaida J	Preparation of the manuscript
	Preparation of the manuscript

Cook J	Senior supervision, assistance with protocol design and preparation of the manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidates and co-authors contributions to this work.

Candidate's signature (and date)

Main supervisor's signature (and date)

6.2 Chapter introduction

Patellar tendinopathy (PT) was shown to be associated with alteration in the corticospinal control of the quadriceps muscle, with both elevated corticospinal excitability (CSE) and increased cortical inhibition (reduced short-interval intra-cortical inhibition ratio [SICI] ratio). This finding further challenges current rehabilitation in that it may not adequately address these corticospinal control issues. Chapter 6 provides a concept of potential rehabilitation in tendinopathy that incorporates aspects of heavy strength training shown to be beneficial for tendon and muscle as well as external pacing shown to be essential for modulation of CSE and SICI. This manuscript has been submitted to the British Journal of Sports Medicine and the supplementary files are provided (Appendix AA). The aim of this study was to provide a potential framework for tendon rehabilitation based upon the findings from Chapters 2-5.

Tendon neuroplastic training: changing the way we think about tendon rehabilitation

6.3 Abstract

Tendinopathy can be resistant to treatment and often recurs, implying that we currently have suboptimal treatment approaches. Rehabilitation programs that have been shown to be successful in terms of pain and return to sport outcomes usually include strength training. Muscle activation can induce analgesia, improving self-efficacy associated with reducing one's own pain. Furthermore, strength training is beneficial for tendon matrix structure, muscle properties and limb biomechanics.

However, current tendon rehabilitation may not adequately address the corticospinal control of the muscle, which may result in altered control of muscle recruitment and consequent tendon load and this may contribute to recalcitrance or symptom recurrence. The aims of this concept paper are: (1) to review what is known about changes to the primary motor cortex and motor control in tendinopathy, (2) identify the parameters shown to induce neuroplasticity in strength training and (3) align these principles with tendon rehabilitation loading protocols to introduce a combination approach termed tendon neuroplastic training (TNT). Preliminary data of strength training in patellar tendinopathy that incorporated neuroplasticity paradigms are provided. Outcomes of interest include the effect on tendon pain, corticospinal excitability and short-interval intra-cortical inhibition.

Strength training is a powerful modulator of the central nervous system. In particular, corticospinal inputs are essential for motor unit recruitment and activation, however, specific strength training parameters are important for neuroplasticity. Strength training that is externally paced and akin to a skilled movement task has been shown to not only reduce tendon pain, but

modulate excitatory and inhibitory control of the muscle, and therefore potentially tendon load.

An improved understanding of the methods that maximise the opportunity for neuroplasticity

may be an important progression in how we prescribe exercise based rehabilitation in

tendinopathy for pain modulation and potentially restoration of the corticospinal control of the

muscle-tendon complex.

Summary – what are the new findings?

- Tendinopathy is associated with changes to motor control that appear to be bilateral and persistent even following rehabilitation
- Current rehabilitation may not adequately address motor control issues as self-paced strength training (the mainstay of treatment) does not alter corticospinal drive to muscle – this may contribute to recalcitrance and recurrence of tendinopathy
- Tendon neuroplastic training (TNT) proposes a concept of strength based loading that is an important stimulus for tendon and muscle, but with strategies known to optimise neuroplasticity of the motor cortex and drive to the muscle.

6.4 Introduction

The clinical outcomes of treatment of tendinopathy vary - there is currently no single effective treatment. Unimodal interventions aimed solely at peripheral tissue, in this case tendon, are unlikely to address complex corticospinal and neuromuscular adaptations associated with persistent pain. The term *corticospinal control of the muscle*, will in this paper refer to motor unit activation as a result of excitatory and inhibitory corticospinal inputs onto the spinal motor neuron pool, which will ultimately affect tendon loading and motor performance. Therefore, it is logical to explore the corticospinal pathway in people with tendinopathy.

Given the high incidence of bilateral tendinopathy (Cook et al., 1998) and bilateral pathology with predominantly unilateral load in animal (Andersson et al., 2011) and human studies (Miniaci et al., 2002), it is also important to consider the corticospinal control of the non-painful side in tendinopathy. A frequent and frustrating phenomenon is the clinical presentation of the previously unaffected side, following rehabilitation. These observations pose several clinical questions; what are the differences in motor control between those with tendinopathy and those without (that may predispose people to tendinopathy or may be adaptations)? Are there side to side differences associated with unilateral tendinopathy? How well does our current rehabilitation address these issues of motor control?

6.4.1 Motor control in people with and without tendinopathy

In tendon research, muscle strength, usually represented by maximal voluntary contraction (MVC), is far more often evaluated than motor control is. Interestingly, there is no consistent pattern of strength or performance change (either increase or decrease) that has been shown across those tendons that have been studied, which may conflict with clinical perception that pain is likely to result in strength loss due to disuse or willingness to protect the injured part

consciously or subconsciously. For example, people with Rotator Cuff (RC) tendinopathy have

been shown to be 15% stronger in measures of abduction on their symptomatic side than controls

(Brox et al., 1997) and this has also been shown in Lateral Epicondylagia (Bisset et al., 2006).

Athletes with jumper's knee have been shown to be better jumpers than athletes without jumpers

knee (Visnes et al., 2013), however several studies report less strength on the symptomatic side

than in controls (see (Heales et al., 2013) for review). Thus, there are conflicting data. People

with PT displayed greater cortical inhibition in their quadriceps responses (Rio et al., 2015) than

healthy individuals (Weier et al., 2012b). Increased cortical inhibition has been shown to be

associated with phasic nociceptive stimuli (Dube and Mercier, 2011), which describes tendon as

pain is consistently linked with loading and therefore often phasic rather than tonic for many

tendons. While there is increased cortical inhibition altering motor drive in PT, there was also

greater excitability than controls inferring differences in the balance of excitability and inhibition

of motor control compared with healthy controls. It may be that strength changes still represent

a decrease from that individual's potential performance.

A recent systematic review by Heales et al., (2013) on the sensory and motor deficits of the non-

injured side of patients with unilateral tendon pain included one study in the patellar tendon and

one study in the Achilles tendon, but 18 studies in the upper limb tendons. There is clearly a

paucity of literature investigating lower limb changes. The two included lower limb studies were

one on arch height in PT (Crossley et al., 2007) and an imaging paper of the Achilles tendon

(Grigg et al., 2012). It is not clear how arch height and imaging changes may relate to sensory or

motor changes, thus the sensory or motor changes in lower limb tendinopathy require further

investigation. Interestingly, a recent systematic review in complex regional pain syndrome

(CRPS) only identified suitable data from upper-extremity studies (Di Pietro et al., 2013). It is

possible that differences in functional reorganisation in the primary somatosensory (and/or M1) cortices following upper limb versus lower limb injury may exist that limit the extrapolation of upper limb findings to the lower limb. Given that the predominant role of the upper limb musculature is to position and control the hand in space, and that the hand is well represented on the somatosensory cortex and M1, injury to upper limb regions may have manifestations associated with chronicity that are different from those for the lower limb. There appears to be a bias towards investigations of upper limb conditions.

The cross sectional design of all studies that have investigated motor control in tendinopathy makes it difficult to infer causality and the potential impact of handedness or use-profiles (especially in upper limb studies) (Kloppel et al., 2007, Baumer et al., 2007, Volkmann et al., 1998). That is, there is a more complex relationship at play, as for example, talented jumpers are also more likely to play in positions that require more jumping (outside hitter in volleyball compared with setter) (Bahr and Bahr, 2014) and participants may be more vulnerable to tendon pain in their dominant limb, which is also likely to have been stronger to begin with. These factors will also affect measures of strength and the stimulus response characteristics of the corticospinal cells of the primary motor cortex (M1). Furthermore, maximal strength performance data are vulnerable to cognitive and motivational factors (Kroll, 1970, Peacock et al., 1981). Importantly, maximal strength measures may not discern the motor control resulting from a balance of excitatory input and the effect of inhibitory neurons synapsing on the M1.

Indices of maximum strength may not provide enough detail about muscle-tendon loading at sub-maximal levels, nor the ability to grade recruitment (St Clair Gibson et al., 2001) or appropriately timed patterns of activation according to the required task, especially in a painful state (for example see (Hodges and Richardson, 1999, Wadsworth and Bullock-Saxton, 1997),

all of which have significant implications for function and load attenuation (Seitz et al., 2011).

Athletes with patellar tendinopathy (PT) have greater excitability in their quadriceps (rectus

femoris) muscles responses to M1 stimulation that was not observed in controls (jumping

athletes without pain) (Rio et al., unpublished). As stated, athletes with PT also have greater

cortical inhibition (Rio et al., 2015) than healthy controls (Weier et al., 2012b). This reflects an

imbalance between the excitatory and inhibitory mechanisms that control muscle activation and

may be a protective response consequent to repeated nociceptive stimuli (such as jumping).

Jumping and landing mechanics will be influenced by motor control changes that include both

peripheral and central contributions to lower limb activation. People with patellar tendon

abnormality (pathology observable on ultrasound) have demonstrated landing patterns different

from those of controls and importantly, have less variability in movement than healthy controls

(Edwards et al., 2010). The invariable motor pattern implies that corticospinal control is altered

in some way and may be due to protective strategies underpinned by evaluative processes

relating to the consequence or meaning of the motor task (Moseley and Hodges, 2006). In the

case of patellar tendon abnormality, invariable motor patterns may reflect a strategy to avoid

pain during jumping (consequence) as well as the competing desire for optimal performance

(meaning). In fact, people with PT are better jumpers than those without - termed the 'jumpers

knee paradox'(Visnes et al., 2013).

Less variability has been observed in asymptomatic controls who demonstrate a protective

postural strategy when they expect their back to hurt (Moseley et al., 2004a) and people with

recurrent back pain who demonstrate a protective strategy even when they are pain free (Hodges

and Richardson, 1996). Moreover, a reduction in normal variability of postural adjustments has

been observed during experimentally induced pain, and failure to reinstate normal variability has

been proposed as a possible risk for recurrence (Moseley and Hodges, 2006). Such findings raise the possibility that an invariable motor pattern observed in PT may reflect a system less adaptable to environmental perturbations, - an undesirable state (Stergiou and Decker, 2011). Indeed, movement variability has been proposed as an important feature in actually preventing injury (Bartlett 2007).

Though the predicted goal of adopting a different motor strategy is protection, non-resolution of the strategy may in fact increase the likelihood of symptom recurrence (Moseley and Hodges, 2006). Given the high recurrence rate of tendinopathy, it is pertinent to consider that there may be non-resolution of motor strategies even in currently asymptomatic people with history of tendon pain, or tendon pathology that predispose to symptoms or symptom recurrence. This may also reflect the competing desire for optimal performance and this adds complexity to rehabilitation as the strategy adopted and that may be the default pattern, will reflect both the consequence and meaning unless there has been significant change to inputs (of which nociception is only one). The presence of a positive 'culture' of PT in jumping sports such as volleyball where playing with tendon pain is common (and may reinforce a concept that pain during activity doesn't equate to tissue damage) will probably serve to maintain the motor control strategy. These contextual factors are likely to further influence the experience of pain (Moseley and Arntz, 2007) and will vary depending upon the environment and one's own experiences.

Cross sectional studies do not allow elucidation of whether tendon pathology, or the presence of tendon pain, changes motor control, or vice versa. That pain will often be accompanied by altered motor output would be predicted on the basis that both pain and motor output can be effective at protecting us from bodily threat. A common finding in studies of motor control

during pain is altered corticospinal drive to the motor neuron/muscle. However, this phenomenon of greater CSE has also been observed during testing that was non-painful, in people with PT compared to activity matched controls and people with other anterior knee pain (Rio et al., unpublished). Furthermore, there were no differences between groups for activity, muscle strength (measured by maximal voluntary isometric contraction torque of the quadriceps), muscle activation (represented by surface electromyography) or measures of motor neuron activation (maximal femoral nerve stimulation), so it seems plausible that the increase in CSE was associated with the PT regardless of the fact that there was no pain during testing. It is possible that their net motor drive to the quadriceps muscle group is unaltered (or even that they may not be as good as they could be) however, controlled activation and the motor strategy may be affected. This also implies the motor task still has potential 'consequence' and 'meaning' in the absence of nociception, which fits with the invariable and abnormal landing strategy observed in people with tendon pathology.

Current tendon rehabilitation may fail to adequately address the multitude of contributing factors to altered motor control, which would include not only muscle strength and tendon capacity but corticospinal control encompassing excitability and inhibition as well as belief systems about pain and contextual factors.

6.4.2 Motor control changes may be bilateral

The lack of consistent abnormalities in muscle strength on the patient's affected leg may simply reflect similar abnormalities being present on the contralateral limb. Heales et al., (2013) reported that the contralateral asymptomatic side was weaker than controls in upper limb tendinopathy, though abduction in those with RC tendinopathy was an exception and no data were reported for the lower limb. Interestingly, data from low back pain studies are also variable

with some reporting both hypo-activity and others reporting hyperactivity, depending upon the muscles and tasks investigated (see (Hodges & Moseley 2003) for review). Strength deficits persist following surgery and rehabilitation in unilateral Achilles tendinopathy however the side-to-side strength difference was relatively low (7.2-8.8%) and may actually reflect a bilateral motor control deficit (Ohberg et al., 2001). However, while the direction of change (increases or decreases in muscle performance) is not consistent, it does appear that a change in motor control may occur bilaterally.

Regardless of whether motor control changes are a cause of pain or epiphenomena, changes to motor control may not just be bilateral but system-wide. There is an increasing body of evidence that multiple sites are frequently affected due to complex intrinsic and extrinsic factors, and contralateral pathology and/or the development of symptoms is common. That is, once tendon pain (or pathology) is established at one site, there appears to be the potential for increased risk of tendinopathy elsewhere. Notwithstanding systemic risk factors that predispose tendinopathy such as diabetes and elevated cholesterol, there may be other considerations including an increase in global sympathetic drive (Jewson et al., 2015). Whilst it is likely that loading is similar for both legs and bilaterality of pathology (and or pain) may be therefore somewhat expected, data from the upper limb with markedly different use profiles (such as baseball pitchers) (Miniaci et al., 2002) and unilaterally loaded animal models that demonstrate bilateral pathology (Andersson et al., 2011) implicate systemic or nervous system involvement in tendinopathy. The inter-hemispheric connections and potential for modulation at the spinal cord level are both potential avenues for bilateral changes outside of bilateral loading that have not been investigated.

It is possible that the other side may display differences in response to unilateral nociception (or insult) similar to what is observed in injury such as stroke. The adaptive response seen following stroke includes increased inhibition on the affected side and increased CSE to the unaffected limb (Butefisch et al., 2008). Furthermore, there is actually increased inter-hemispheric inhibition from the non-affected hemisphere to the lesioned hemisphere that further increases the inhibition on the affected side, during activation of the unaffected limb (Butefisch et al., 2008). This has a biological advantage to perhaps improve efficiency of the unaffected side, however remains a challenge in rehabilitation (as the affected side has significant inhibition and is further increased during activation of the unaffected limb).

To investigate the unaffected side in people with PT, 13 jumping athletes (six control participants, seven with unilateral PT) were recruited (Rio, unpublished data available as a supplementary file). Participants were tested bilaterally with transcranial magnetic stimulation (TMS) including their active motor threshold and a stimulus response curve as well as short-interval intra-cortical inhibition (SICI) using rectus femoris as the target muscle. When compared with healthy, activity matched controls, preliminary data in athletes with PT demonstrate hyper excitability on their affected side, supporting previous research (Rio et al., unpublished) and also displayed markedly increased cortical inhibition (n = 4 affected side SICI ratio 17.12%, n = 6 controls 58.78%). This motor control strategy may be likened to a novice driver controlling the speed of their car with one foot on the brake and one on the accelerator. Interestingly, the contralateral pathway controlling the unaffected side appears less excitable than both the affected side (similar to that observed in stroke), and controls, and also displays increased cortical inhibition (n = 4, unaffected side 19.13%) (where lower SICI percentage ratio represents greater cortical inhibition). These preliminary findings appear to replicate the

findings of unilateral stroke that affects the M1, in particular the plausibility of greater inter-hemispheric inhibition and involvement of bilateral changes. However, the sample size is small and warrants further investigation with greater numbers. It does highlight the danger of using the unaffected side as a control in studies of motor control, excitability or inhibition in people with tendinopathy. This also requires further evaluation as the clinical implications are considerable - strength training in the affected limb may continue to drive inhibition to the unaffected limb unless we can improve our understanding of techniques that modulate excess inhibition.

Given the propensity for lower limb activities to be bilateral and symmetrical for efficiency (ambulation, jumping etc), the changes in the unaffected side may be an attempt to achieve motor control homeostasis in a system trying to protect a region. That is, there are combined and perhaps competing demands of protecting a vulnerable, or apparently vulnerable tendon, and still producing torques sufficient for optimal performance. This may be argued for many tendinopathies not just in athletes but people involved in manual labour or any outcome dependent task.

The contralateral motor control changes may also contribute to, or explain the high injury rate of the contralateral tendon following rehabilitation as loading patterns are likely to be different (as corticospinal drive of the unaffected side is altered). This provides support for a rehabilitative strategy that targets the corticospinal control of both sides however; the strategies may need to be different. Strategies that modulate inhibition on the affected side as well as pain, such as isometric muscle contractions in patellar tendinopathy (Rio et al., 2015) should be evaluated for their potential effect on inter-hemispheric inhibition and inhibition of the ipsilateral M1. Rehabilitation that is capable of modulating pain *and* inhibition of both M1 may yield important advances in tendon management.

6.5 The key question is what happens first?

There are two theories about the relationship between pain and changes in muscle control (see (Hodges and Moseley, 2003) for review) and neither is supported unequivocally by the literature. They propose either, changes in muscle activity cause pain (sometimes termed pain-spasm-pain model or vicious cycle of pain in the pain literature) or that changes in muscle activity serve to protect the area by limiting movement (the pain adaptation model) (Lund et al., 1991).

Experimental pain studies that demonstrate transient changes to motor control after a transient nociceptive stimulus (Graven-Nielsen et al., 1997, Le Pera et al., 2001, Farina et al., 2001) as well as studies in a number of chronic conditions provide support for the pain adaptation model (Lund et al., 1991). The definitive study that studies motor control before the onset of pain remains elusive.

Hyper-excitability of the quadriceps in athletes with PT has been correlated with length of time of symptoms (Rio, unpublished data available as a supplementary file) and changes in infrapsinatus excitability in people with RC tendinopathy were correlated with chronicity (Ngomo et al., 2014). This does not exclude the possibility that aberrant motor control precedes the first onset of tendinopathy but provides a strong rationale that changes in motor control occur in response to nociceptive barrage. The potential for unilateral nociceptive input to drive motor control changes bilaterally (or even system wide) underlines the importance of improving our understanding of nociception-motor interactions (Nijs et al., 2012) particularly in a condition of chronic nociception where the nociceptive driver is unknown.

The pain adaptation model proposes that agonist activity is reduced and the antagonist activity is increased with pain (Lund et al., 1991). This may be the case in PT as there were no differences

in MVIC between athletes with PT and controls (Rio et al., unpublished). However in a separate study, following isometric exercise that reduced their pain, the MVC of the quadriceps of athletes with PT increased by 18.7% implying their agonist activity (the quadriceps) was in fact inhibited (reduced) prior to isometric exercise (Rio et al., 2015). The hamstrings that serve as the antagonists have not been measured. Most testing is completed in the laboratory with a single joint movement for simplicity, for example leg extension however, agonists and antagonists would change during a more complex movement such as a counter movement jump.

The threat to tissue (as far as the brain is concerned) may remain even after pain reduction and return to sport, as tendon may not have 'healed' (many consider tendinopathy to be failed healing) (see (Cook and Purdam, 2009) for review). In this context, there may be ongoing monitoring and persistent changes to corticospinal control of muscle (to protect the tendon) as the M1 and its projections may consider it to be vulnerable. Alternatively, the motor control changes that occur in tendinopathy may not spontaneously resolve or normalise following recovery indicating rehabilitation may not address motor activation leaving people vulnerable to recurrence of symptoms.

People can and do recover in terms of pain and function despite tendon pathology remaining unchanged on clinical imaging (Drew et al., 2014). One plausible explanation for this at a tissue level is that the tendon may structurally compensate in the area around the pathological lesion. That is, the volume of structurally intact tissue increases as an adaptive response (Docking and Cook, 2015). This tendon may be thicker but potentially amenable to improvements in mechanical strength (Docking and Cook, 2015) through graded rehabilitation that would also alter muscle properties. Non-painful motor activation would also improve self efficacy so there are a number of potential mechanisms linking rehabilitation (in particular strength training) to

improvements in symptoms. However, given the clinical observation that "once a tendon, always a tendon" reflecting the strong tendency for symptom recurrence, there is clearly room for improvement in our strategic approach. Given the differences in motor control observed across tendinopathies, how well does current rehabilitation address motor control?

6.6 Strength training and motor control

Self-paced strength training describes a process without external timing cues (such as visual or auditory) and involves activation of broader cortical and sub-cortical regions (Cohen et al., 1998, Gerloff et al., 1998). Studies that have used external pacing, for example with a metronome, have demonstrated increases in excitability in both skill (visuomotor tracking) (Ackerley et al., 2011) or short term strength training (Kidgell and Pearce, 2010, Kidgell et al., 2010). Leung (*in press, 2015)* investigated the effects on excitability and inhibition of a single bout of visuomotor tracking with self-paced strength training and metronome based strength training. They found that both skilled training and metronome paced strength training, but not self paced strength training increased excitability and released inhibition in both the trained limb and in the untrained limb. This has implications for tendinopathy rehabilitation as both CSE and inhibition have been shown to be different compared with controls.

6.7 Current tendon rehabilitation and proposed concept

Current rehabilitation aims to restore tendon and muscle properties using exercise with a variety of paradigms. There is evidence for the efficacy of eccentric only contractions (Frohm et al., 2007a, Frohm et al., 2007b, Jensen and Di Fabio, 1989, Jonsson et al., 2008, Kongsgaard et al., 2006, Mafi et al., 2001a) and heavy slow strength (involving both a concentric and eccentric component) (Kongsgaard et al., 2009) in improving pain and function in Achilles and Patellar

tendinopathy. Protocols that include strength training (load) appear to have the greatest stimulus for the tendon and muscle.

However, deficits in muscle performance have been shown to persist following surgical intervention plus rehabilitation or rehabilitation alone for tendinopathy, despite positive clinical outcomes (Ohberg et al., 2001, Paavola et al., 2000). Current prescription of tendinopathy rehabilitation is best described as self paced where patients are provided exercises with guidance of repetitions, sets and load (all of these are variable and no gold standard exists) but importantly, without external pacing. Given the high recurrence rate of tendinopathy and persistent motor changes following rehabilitation (Paavola et al., 2000), it is possible current rehabilitation fails to restore corticospinal control of the muscle-tendon complex(s).

Rehabilitation protocols are historically directed at local tissue adaptation (muscle hypertrophy and tendon) and there has been little if any focus on modulating corticospinal control. It is possible that these approaches therefore only address some of the neuromuscular and muscle-tendon changes in tendinopathy. Furthermore, passive uni-model treatments such as injections are unlikely to address any of the local or central deficits (Figure 6.1a-d).
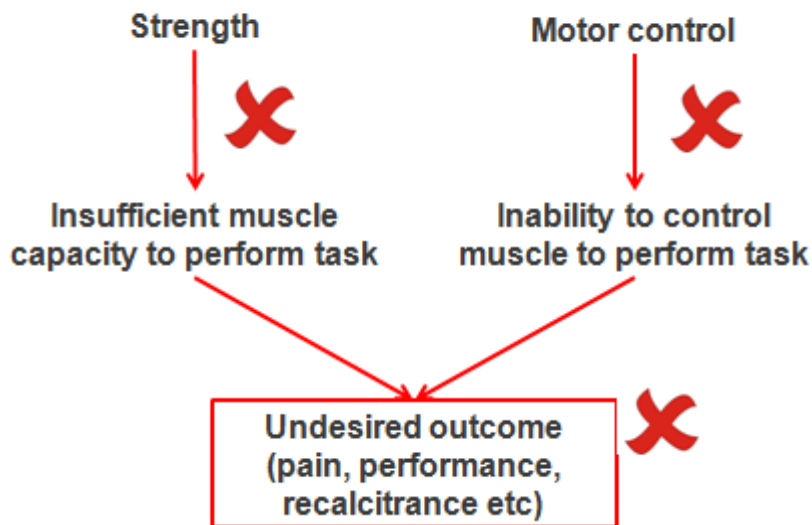
(a) A passive intervention fails to address strength and capacity of the tendon or muscle as load is required to stimulate these tissues, this leads to an inability to perform the task and an undesired outcome on the left. An example may be an injection into the tendon aimed at restoring tendon structure. Simultaneously, motor control has not been addressed thus the drive to the muscle may be unchanged and the outcome remains undesirable.
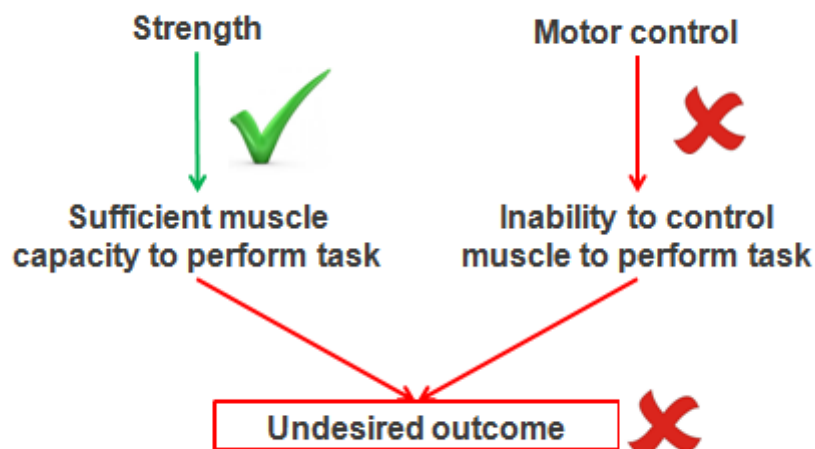
(b) This likely describes most current clinical rehabilitative approaches that focus on strength. The local tissue has probably improved in its characteristics (tendon mechanical properties, muscle strength) however the

drive to the muscle has not been addressed due to the nature of self paced strength training thus the outcome may still be undesired (perhaps in terms of recurrence).

Strength   **Motor control**

Insufficient muscle capacity to perform task   Ability to control muscle to perform task

Inability to perform task
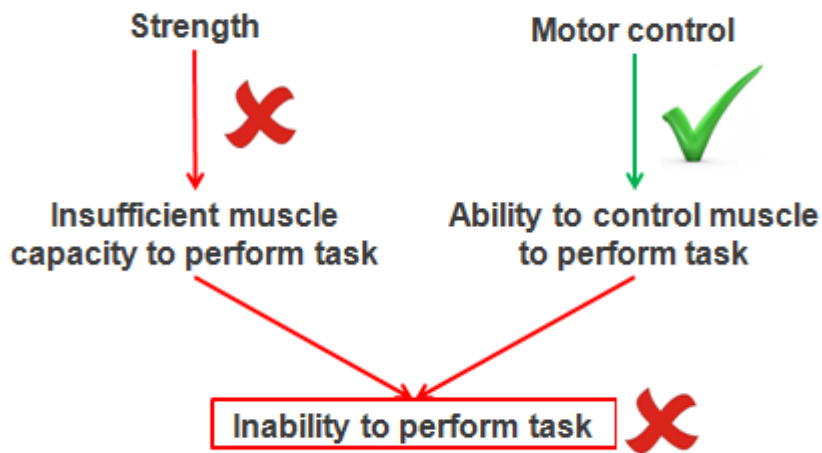
(c)   In this example, the focus may be purely on trying to alter the biomechanics or motor control with repetition and feedback about the task (for example proprioception exercises). This not only has been shown to have poor integration into the sporting environment, it also has not addressed the tissue capacity. Therefore, the local feedback to the CNS is likely to maintain the motor control pattern as an ongoing protective or adaptive strategy.

Strength   **Motor control**

Sufficient muscle capacity to perform task   Ability to control muscle to perform task

Ability to perform task
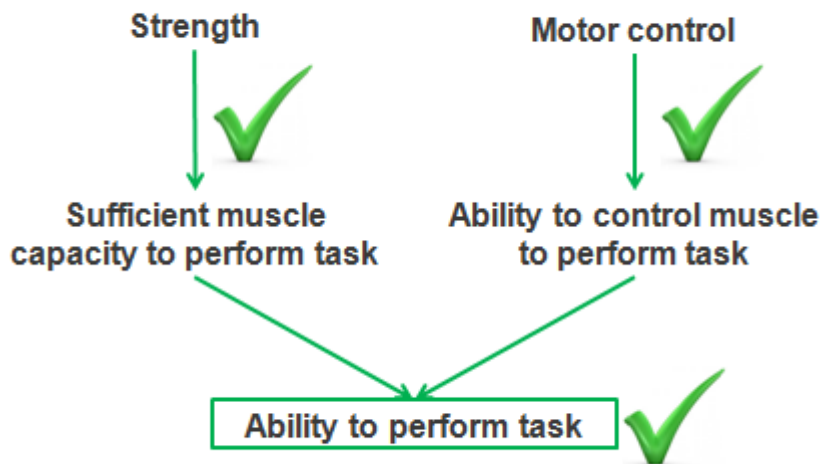
(d) The concept of TNT includes using strength training to address tendon as load is the only stimulus shown to promote the matrix. Furthermore, strength training improves muscle architecture. In this example, the external pacing of strength training also serves to address cortical muscle control in an attempt to improve the muscle recruitment pattern and therefore also tendon load.

Figure 6.1 Summary of different approaches of tendon rehabilitation and effects on strength and motor control

Externally paced strength training, such as with the use of a metronome, is capable of inducing ipsilateral and contralateral changes to the excitability and inhibition in healthy participants (Kidgell and Pearce, 2010, Kidgell et al., 2011, Latella et al., 2012b, Pearce et al., 2013b, Weier et al., 2012a). To investigate this concept in a PT model, a protocol was developed that used externally paced strength training, termed Tendon Neuroplastic training (TNT) (protocol available in Rio et al., unpublished). Two strategies were trialled, either isometric or isotonic quadriceps muscle contractions, using TNT (the combination of heavy strength training and externally pacing) due to a lack of efficacious inseason loading options and both active treatments. This had a clinical basis to answer the questions: which program may reduce pain immediately inseason and was there any difference between them over a four week trial. As both groups were externally paced with the training, it was hypothesised they would both improve in excitability and inhibitory control. However, one protocol may be better for analgesia and this may also affect control, particularly cortical inhibition.

A subgroup of nine athletes completed the corticospinal testing before and after the 4-week TNT intervention (that recruited 29 athletes) and one of the athletes completed weekly testing (Figure 6.2). A supplemental file is available with the method and full data-set.

Isometric exercise provided greater immediate analgesia (Rio, et al., unpublished data) and both protocols reduced pain significantly over the 4-week trial (van Ark et al., unpublished data). There were no differences between groups after 4-weeks. A case study demonstrates that there are changes in excitability over the course of 4-weeks and week 4 most closely represents normal CSE in jumping athletes without PT.
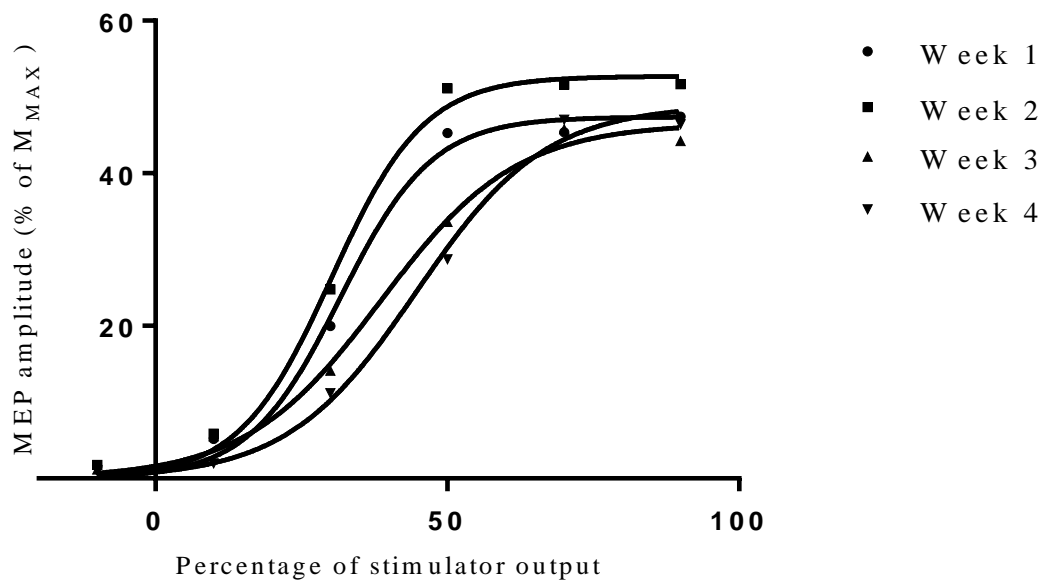
Figure 6.2 Individual weekly response to tendon neuroplastic training (isometric protocol) Mean ± SEM MEP amplitude

(note error bars are too small to be seen) MEP, motor evoked potential

Testing showed that TNT, using either isometric or isotonic muscle contractions changed inhibition (p = 0.008) (Figure 6.3). Preliminary data for the individuals and group responses are provided. The values are a percentage representing cortical inhibition of the quadriceps where normative values (for those without PT) are 50-70% (Weier et al., 2012a). All athletes improved to be within the normal range following the intervention so this represents a physiologically

important change. There were differences between the isometric and isotonic group (Figure. 6.3), however clinical implications are limited based on small sample size. Furthermore, a larger study that compared self paced with externally paced would elucidate if the effects are associated with a reduction in nociception or the use of external pacing or a combination. Data in healthy participants would support the use of external pacing over self pacing in targeting the M1 and given nociception-motor interactions (Nijs et al., 2012), external pacing may augment changes.
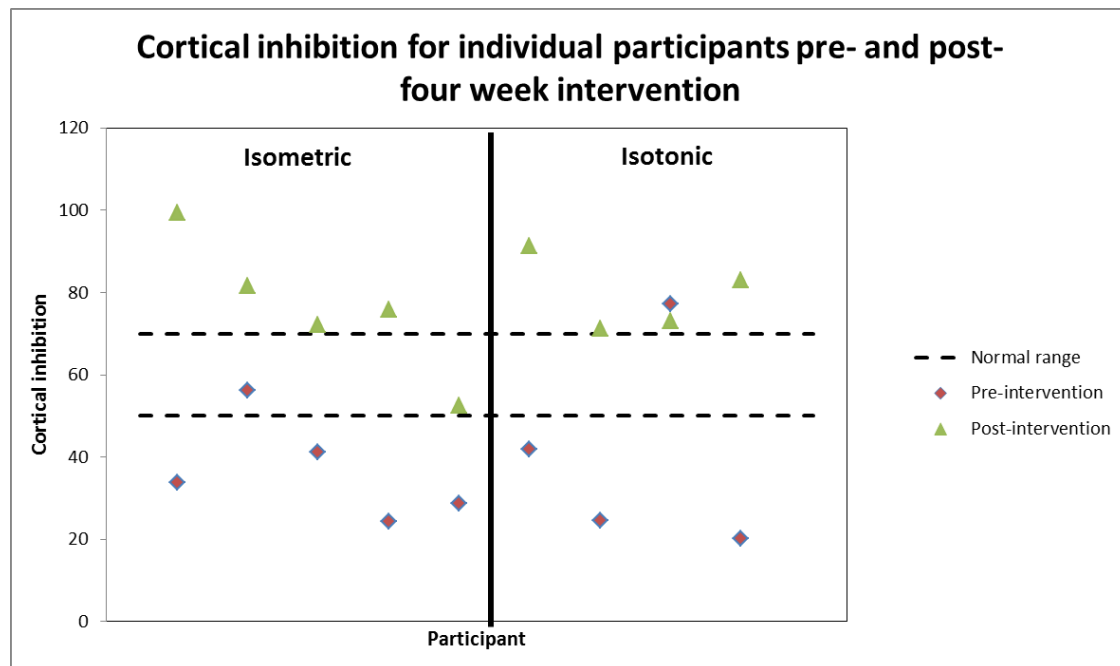
Figure 6.3 Individual cortical inhibition responses to tendon neuroplastic training by muscle contraction type

Isometric: p = 0.06, Isotonic: p = 0.25, TNT group including both paradigms: p = 0.008. Each individual participants data are provided with diamond denoting pre-intervention and triangle denoting post-intervention for that person.

6.8 Conclusion and clinical implications

Self paced strength training targeted to improving muscle architecture, which would describe the current prescription of most clinical programs, may not adequately address the differences in excitability and inhibition that has been observed in PT and may be a feature of other tendinopathies. The alterations to corticospinal control of muscle may manifest as a different motor strategy (for protection) however, this could contribute to ongoing morbidity or vulnerability to symptom recurrence. Movement variability is important and is sometimes lost in

musculoskeletal pain conditions even if nociceptive input is absent. Aberrant tendon load from altered motor control may be transmitted to tendon causing perpetuation of nociceptive input. However, the altered pattern also appears to serve the desire for performance because many studies demonstrate that people with tendinopathy display superior strength or performance. Current rehabilitation for tendinopathy focuses on strength training because it stimulates the physiological adaptation of muscle and tendon. However, strength training that is externally paced has also been shown to be able to modulate tendon pain and corticospinal control of muscle. The concept of TNT incorporates loading that has been shown to be efficacious both in the short and long term for tendinopathy, in a painfree protocol, which is tolerated by athletes in a competitive environment as well as those parameters that promote changes to corticospinal muscle control. The current program may induce change by reducing tendon pain. As clinicians and scientists, it is important that we progress our understanding of the mechanisms behind improvement (or lack thereof) to improve patient outcomes in tendinopathy. This will need to also consider rehabilitation that addresses the unaffected side, which appears to display motor adaptations as well as explore how belief systems may impact the prognosis of people with tendinopathy.

Chapter 7. General Discussion

The studies in this thesis used transcranial magnetic stimulation (TMS) to investigate the corticospinal responses of the rectus femoris muscle in people with patellar tendinopathy (PT) as well as the ability of heavy, externally paced strength training to modulate tendon pain, corticospinal excitability (CSE) and short-interval intra-cortical inhibition (SICI) both immediately, and as a 4-week inseason intervention. The publications that contributed to this thesis, by chapter, found (1) that the local nociceptive driver of tendon pain is unknown and there are features of tendon pain consistent with both physiological and pathophysiological mechanisms, and that while tendinopathy may represent a disruption to internal load sensing, the corticospinal control of muscle in people with tendinopathy had not been explored, (2) that the CSE was greater in jumping athletes with PT than it was in control participants and those with other anterior knee pain (AKP), (3) externally paced isometric muscle contractions induced immediate analgesia, which lasted at least 45 minutes and decreased cortical inhibition thereby improving quadriceps muscle torque, (4) externally paced isometric muscle contractions induced greater immediate analgesia than isotonic muscle contractions in a 4-week inseason intervention, though both were well tolerated and, finally (5) that the studies in this thesis support the concept of strength training that is externally paced for the modulation of tendon pain and corticospinal control of muscle.

7.1 Patellar tendon pain is associated with greater corticospinal excitability and greater inhibition of the quadriceps

Chapter 3 focussed on the corticospinal control of the rectus femoris muscle in people with PT. The hypothesis was partially supported, in that jumping athletes with PT exhibited hyper-excitability in the corticospinal responses of their quadriceps to M1 stimulation, and this was not

observed in control participants or participants with other AKP. Furthermore, there were no differences between groups in M_{MAX}, which is a measure of the α-motorneuron pool, thus changes were confined to the M1. The increased slope of the stimulus response curve in people with PT represents an increase in the strength of corticospinal projections onto the quadriceps motorneuron pool, increased membrane excitability and corticospinal cell recruitment (Smith et al., 2011) and is indicative of the extent of motor representation on the M1. There were no differences between the three groups in the top of the curve, which represents MEP_{MAX}, or group MVIC torques. Therefore, people with PT have the ability to produce high force, evidenced by no group differences in MVIC and normal peripheral drive (evidenced by no group differences in M_{MAX}) however excitability demonstrated an adaptive plasticity associated with PT.

This may represent maladaptive plasticity as it may perpetuate symptoms, however it can equally reflect an adaptive strategy given the balance of task demands includes high performance. It is unlikely to be simply use-dependent plasticity as participants in all groups were jumping athletes. To put this in a clinical context, when an athlete with PT jumps they may have increased corticospinal drive and recruitment from their quadriceps motorneuron pool by activating maximally, or near maximally once a threshold is reached. That is, small jumps may only recruit an appropriate level of motorneuron activity but at a certain point, an athlete with PT will recruit maximally when an athlete without PT would still be recruiting sub-maximally and appropriately to the level of the task. This supports the concept of a disruption of internal load sensing (Chapter 2) and an inability to match motor output with task demand. It is important to note that jumping is a complex task and is also influenced by other factors that determine motor unit activation and activation of other muscles.

The sharp slope in the curve followed by plateau, rather than smooth graded recruitment to increasing stimulation was observed in all participants with PT and with small SD. This pattern of recruitment may also result in an invariable pattern (as their quadriceps may be recruited at high levels each time for a given task) and this concept is supported by a review by Van der Worp et al., (2014) who reported an invariable landing pattern was associated with re-development of PT symptoms in those with a past history of tendon pain. However, force steadiness studies would be required to provide further information about how corticospinal responses may affect function.

An invariable strategy with differences to the balance of CSE and SICI may also result in quadriceps muscle fatigue or central fatigue earlier than a painfree athlete and importantly, is likely to transmit different forces to the patellar tendon than a painfree athlete. Whilst tendon forces were not measured in this study, they are directly related to the level of quadriceps activation. The concept of tendon overload, especially during jumping has been examined by a number of studies.

Lian et al., (2003) found that high level volleyball players with PT (n = 24) performed better than an asymptomatic control group (n = 23) in a counter movement jump and this phenomenon is also reported in people with RC tendinopathy who were stronger on their symptomatic side compared with controls in measures of abduction. However, in the Lian et al. study (2003), the PT group completed significantly more hours of weight training during each week and were heavier, thus jumping ability may have been linked to strength and muscle mass (Visnes et al., 2013). Equally, increased body mass may have also been a factor in the development of PT (Gaida et al., 2004). What is clear from the studies demonstrating superior jumping ability is that despite patellar tendon pain, athletes were still able to load maximally (or at very high

levels), supporting data from this thesis where MVIC and the top of the curve were comparable to controls. However, this still may represent a deficit when compared to their potential. Athletes with previous PT have demonstrated a stiffer landing strategy, that is, less knee joint flexion during the first part of landing impact (Bisseling et al., 2008) that may have contributions from the greater CSE observed in the studies in this thesis. This adaptation may serve to limit knee joint flexion range (thus limiting eccentric to concentric turnaround range) and would be supported by the pain adaptation model as a protective strategy (Lund et al., 1991). That is, if rehabilitation has failed to change the corticospinal control of their quadriceps, even if they were currently asymptomatic, it is possible that a stiff landing strategy is driven by persistent alterations in their corticospinal activation. This pattern of altered quadriceps recruitment may continue to transmit abnormal loads to the tendon, thus may partly explain why recurrence of tendinopathy is so high. Recurrence may also be related to positional load within the athletic environment.

Jumping load can be different even within a sport depending upon the positional demands (Bahr and Bahr, 2014). Within the volleyball population PT is more common in outside hitters and middle blockers as they perform a higher number of maximal jumps than setters and utility players (Bahr and Bahr, 2014). One of the challenges is that even within a volleyball cohort, the middle blockers and outside hitters, who are prone to PT due to load, are also most likely going to outperform other positions (such as setters) in a jumping test, as that is the strength of their game. Visnes et al., (2013) in a 5-year prospective study demonstrated that jumping ability was a risk factor for developing PT. However, it is likely that the better jumpers on entry to an elite program will complete more jumping during training sessions throughout the program as they

will be blockers and hitters. It seems that better jumpers are also more likely to jump more often and these combined factors lead to patellar tendon pain.

Only jumping athletes were recruited for the studies in this thesis as they were shown to have different CSE compared with active non-jumpers in pilot testing (Appendix Z). In Chapter 2 they were then classified as controls, PT or other AKP. Better jumping ability or volume of jumping (due to positional demands) may contribute to the increased excitability observed in people with PT, though it is unlikely as all of the included volleyball players were hitters and blockers and competing at an elite or sub-elite level. However, jumping ability and jumping load (as in number of jumps) were not measured in this study (and a range of jumping sports were included). It is worth noting that volleyball athletes comprised majority of the sample in each group and no setters were included in the studies in this thesis (neither in controls nor other groups). The groups were matched on key factors reported to influence the M1, specifically number of sessions per week that included jumping activity and recruited from elite and sub-elite competitions with high loads and were not different in age, sex or length of time of symptoms in the two groups with pain.

Higher MVIC has been previously associated with better jumping performance and increased excitability (Heroux and Tremblay, 2006) however there were no differences in MVIC between groups, thus differences observed in CSE were not a function of the group with PT being stronger. The increase in excitability observed, and quadriceps muscle representation on the M1, is most likely to be associated with patellar tendon pain. Whilst PT and other AKP conditions, such as PFJ pain, share many clinical similarities in presentation, it appears from these data there are differences in the corticospinal activation of the rectus femoris muscle dependent on nociceptive specificity.

No previous study has investigated nociceptive specificity. The corticospinal control of the quadriceps muscle group has been previously compared between control participants and those with PFJ pain (On et al., 2004). Patellofemoral pain was associated with increased excitability of the VL and VMO, evidenced by higher MEP / M_{MAX} ratio however, the M_{MAX} reported by On et al., (2004) was significantly lower in the PFP group than the control group (approximately half), which is not easily explained. Maximal stimulation of the peripheral nerve should recruit the entire motor neuron pool and has been shown to not change with strength training (Aagaard et al., 2002b). The participants in the PFP group in the On et al., (2004) study may have had significant muscle atrophy, however M_{MAX} changes have been reported in conditions such as motorneuron disease (de Carvalho et al., 2007), no studies were located that reported decreased M_{MAX} associated with musculoskeletal pain. The significantly lower M_{MAX} in the PFP group may reflect factors outside of their pain condition, such as a genetically predetermined difference, equipment issues or potentially a lack of blinding during data collection. There were no differences between groups in M_{MAX} in any of the studies in this thesis, including in those with other AKP that would almost certainly include PFP.

There are several key differences between PT and other AKP, first tendon pain has a precise location regardless of length of time of symptoms in those with PT. There may be receptors isolated to the tendon that transmit noxious stimuli, as well as potentially different noxious stimuli in tendon (the local driver is unknown but appears unrelated to traditional triphasic inflammation). These local factors may contrast to other AKP conditions and impact on the manifestations of chronic nociception within the M1. For example, inflammation is linked with wind-up and secondary hyperalgesia (Latremoliere and Woolf, 2010); inflammation does not appear to be a feature of PT, nor is wind-up or secondary hyperalgesia observed in PT (Chapter

2). Furthermore, the primary afferent neuron in PT may synapse with either a nociceptive specific or wide dynamic range neurons in the spinal cord. This may influence modulation of both intensity as well as the lack of spreading of pain in PT as radiation and referral of pain is linked with progressive recruitment of wide dynamic range neurons spreading along the spinal cord (Jensen et al., 2001). It would appear that the corticospinal response is diverse in different conditions and not simply related to nociception itself.

It is possible these corticospinal changes are present in a proportion of the population and that they predispose people to develop PT symptoms. This is a novel theory in some chronic pain conditions based on the normal distribution of responses to noxious stimuli and the small body of data indicating some people may experience increased risk of developing chronic pain conditions (Edwards, 2005). Response to sensory testing studies demonstrate population wide distributions of normal responses, and given the wide spread of responses it is possible that people who are more sensitive in these studies would be at an increased risk of developing chronic pain (Edwards, 2005). Theoretically, these people would be then more vulnerable to persistent pain than someone without this underlying risk profile of sensory sensitivity, if they sustained an injury (that is, it appears nociception is still an important initial driver of chronic pain) (Gracely et al., 1992, Woolf, 2011). However, it may not be possible to extrapolate the sensory sensitivities studies directly to motor control. If underlying changes to CSE pre-disposed people to PT, it would be expected that a wider distribution of excitability would have been observed in the control population including individuals with CSE similar to that observed in the PT group, which was not the case. The controls in this work (n = 13 people across studies, data for n = 19 M1 as bilateral data were collected in some) would have included (presumably) people that have increased future risk of developing PT if it were a consequence of pre-existing CSE, though

greater numbers would be needed to support this statement. There is evidence in LBP from a prospective cohort study with follow up at 4 and 8 years that low PPT were associated with, but did not predispose people to, low back pain (LBP) (O'Neill et al., 2011).

The answer to the question of 'cause or consequence' would only be possible with a large prospective study that included ongoing and regular measures of CSE, load (both jumping and weights) and MVIC in young athletes. Transcranial magnetic stimulation despite being non-invasive can be uncomfortable, isn't appropriate for some people (Chipchase et al., 2012) and obtaining measures such as stimulus response curves is time consuming, thus large participant numbers can be challenging. Furthermore, studies have demonstrated that tendinopathy and tendon pathology is present in children and adolescents (Cook et al., 2000b), so the age of inclusion for such a study would ideally be pre-pubertal, raising ethical concerns. While it cannot be concluded that it was *tendon pain* that caused increased CSE from a cross-sectional study, the important clinical question would be: how can we modulate tendon pain?

7.2 Isometric exercise induces immediate analgesia

Chapter 4 compared an acute bout of two types of strength training, isometric or isotonic muscle contractions. The clinical outcome measure was the effect on patellar tendon pain using the SLDS. Hypothesis one was supported as isometric muscle contractions induced greater analgesia immediately than isotonic muscle contractions and this effect was sustained at 45 minutes. This is the first study to investigate immediate analgesia using muscle contractions in tendinopathy. The mechanisms behind the analgesia are unknown and may involve combinations of changes to the local biochemical environment reducing nociceptive drive or modulation at spinal or supraspinal levels.

Spinal and supraspinal contributions to inhibitory modulation of noxious stimuli have been termed endogenous pain inhibition (Knauf and Koltyn, 2014, Lannersten and Kosek, 2010, van Wijk and Veldhuijzen, 2010). Although local changes in the tendon, surrounding tissue or its receptors, cannot be investigated easily in human participants the key question is: is the analgesic effect of isometric exercise in PT driven by changes that are generated in the CNS (top down) at the tendon level (bottom up)?

7.2.1 'Top down' versus 'bottom up' pain modulation in persistent musculoskeletal pain

Gwilym et al., (2010) demonstrated restoration of thalamic grey matter volume in patients following hip replacement surgery for osteoarthritis (OA). This implies that modification of the nociceptive drive (that is removal of the nociceptive stimulus) reversed functional grey matter changes (and potentially changes along the neuroaxis) in a chronic nociceptive condition. Hip OA is an interesting model the nociceptive drive is removed with total hip joint replacement (unless functional nervous system changes have a predominant contribution to pain perception, in which case surgery may not change pain). However, removal of nociceptive information with denervation of tendon or local anaesthetic may actually place the tissue at risk of further damage as it is still responsible for load transmission. A surgical scraping technique that de-innervates tendon by debriding the richly innervated peritendon and separating the underlying nerves and fat reduces pain (Alfredson, 2011) and this technique has been shown to improve both unilateral and contralateral symptoms even when conducted on only side (Achilles tendon) (Alfredson et al., 2014). Denervation of a tendon appears to remove the feedback from the periphery thus removing nociceptive drive but may also remove other important functions such as load sensing. It is unclear if this surgery (and removal of nociception) would restore corticospinal control of

muscle. It is important to investigate non-invasive methods of analgesia and exercise, specifically strength training as it is a simple clinical intervention for tendon pain.

7.2.2 Isometric exercise in patellar tendinopathy: endogenous pain inhibition?

Modulation of nociceptive input to alter evoked pain can occur with goal directed behaviour (Lorenz et al., 2003), which reduces the amount of attention given to the nociceptive stimulus that in turn reduces pain (Moseley et al., 2004b, Defrin et al., 2010, Van Damme et al., 2010, Van Ryckeghem et al., 2011). The isometric muscle contraction task required visual and auditory attention as the protocol was externally paced and represents endogenous pain inhibition (EPI). The addition of an attention demanding component activates areas such as the dorsolateral prefrontal cortex, important for continuous monitoring of the external world, maintenance of information in short term memory and governing efficient performance control in the presence of interfering stimuli (Lorenz et al., 2003) as well as areas involved during cognitively demanding tasks such as the perigenual anterior cingulated cortex. However, the same external pacing cues were also used during the isotonic protocol (metronome and verbal attention to task), thus competing attention is unlikely to explain the difference between the two muscle contraction types. With sustained sub-maximal contractions, there are changes to group III and IV muscle afferent (both are mechanically sensitive fibres) firing rates particularly with peripheral and central fatigue, and this alters excitability and inhibition (Taylor et al., 2000) that may be involved in the nociception-motor interaction. Protocols were also matched for time under load, rest between sets and pilot studies were used to match them on rating of perceived exertion for load and muscle effort. Therefore, the key difference appears to be the type of contraction.

Many different types of exercise have been shown to have a hypoalgesic effect and the magnitude appears to be dependent on the mode of exercise; aerobic exercise reduced perception of experimentally induced pain in healthy people (effect size for threshold d = 0.41, intensity d = 0.59), dynamic / isotonic exercise (threshold d = 0.83, intensity d = 0.75) and isometric exercise (threshold d = 1.02, intensity d = 0.72) (Naugle et al., 2012). However, the duration of change to pain perception was not measured in the Naugle et al. (2012) study thus their results cannot be compared with the 45 minutes of induced analgesia following isometric exercise in PT.

In normal healthy participants (12 men, 12 women), sub-maximal isometric exercise resulted in increased PPTs, over the contracting muscle, the contralateral muscle and a distant resting muscle, indicative of endogenous pain inhibition (Kosek and Lundberg, 2003) or exercise induced hypoalgesia (EIH) (Koltyn and Umeda, 2007). There was a significant difference between the PPTs, being higher at the contracting site than distal sites (Kosek and Lundberg, 2003). However, following cessation of exercise the PPTs returned to baseline. This contrasts with the study presented in this thesis demonstrating sustained analgesia at 45 minutes, therefore the mechanisms behind analgesia in people with PT may be different to experimentally induced pain. The studies in this thesis did not measure PPTs (sensory) but instead used a pain provocation test during an active task.

Bilateral EIH, evidenced by increased PPTs in healthy women was recorded following unilateral short duration sub-maximal isometric exercise (40-50% of maximum) (Koltyn and Umeda, 2007). This was not observed in the present tendon study where only unilateral pain was reduced in people with bilateral tendinopathy (n = 3). Isometric load was heavier (70% of maximum) and the protocol was different (5 x 45 seconds compared with 2 x 2 minutes used by Koltyn (2007)). It is possible that the nociceptive stimulus used in the PPT study (pressure to

elicit pain) may be an example of conditioned pain modulation (CPM) (crudely 'pain inhibits pain') (Ellingson et al., 2014, Moont et al., 2010) that altered pain perception rather than, or as well as, the isometric exercise.

When populations with chronic pain are studied, data on the effect of exercise and analgesia are highly variable, implicating some dysfunction of their normal sensory processing and potentially endogenous pain inhibition strategies. For example, women with a diagnosis of fibromyalgia report reduced PPTs, indicative of increased pain perception to a lower nociceptive stimuli following sub-maximal isometric exercise (Kosek et al., 1996). The response to isometric exercise appears to be different in people with PT than fibromyalgia (though tendinopathy is a persistent pain state) as pain was reduced, however sensory testing was not conducted. Despite small numbers of participants with bilateral PT (n = 3), analgesic effects were not reported bilaterally in a unilateral isometric contraction protocol, in fact there was no change in their contralateral SLDS score following isometric exercise. Whilst this study needs to be repeated with greater numbers, this implies the effect was unlikely to be EIH as classically described (Koltyn, 2000) as widespread analgesia would be expected. Furthermore, the lack of bilateral effect would imply that widespread inhibitory drive was not the mechanism behind analgesia in PT with isometric exercise. It is not known if these endogenous mechanisms are disrupted in tendinopathy.

Modulation of noxious stimuli is influenced by a range of factors outside of the nociceptive characteristics. Modulation of noxious stimuli by contextual factors has been demonstrated in a number of studies and can manipulate pain perception including both inhibition and enhancement (Moseley and Arntz, 2007). The participants in the cross over study (Chapter 4) that examined isometric and isotonic exercise were provided with identical instructions

regardless of intervention (isometric or isotonic) thus it is unlikely that they had expectations of one type of contraction over the other. Furthermore, there are no studies of this kind, nor are these muscle contraction types used extensively clinically (eccentric only exercise still dominates clinical practise) so it would also be unlikely they would present for the study with preconceived bias towards one type of muscle contraction over the other for its analgesic effect. All testing was conducted in the same laboratory and the same time of day exactly 1 week apart to minimise the possible influence of circadian rhythms on pain that has been observed in other chronic nociceptive conditions (Bellamy et al., 2002) and stabilise the previous days loading, which also alters tendon pain (Kountouris and Cook, 2007).

Padawer and Levine (1992) proposed that pre-testing the painful stimulus, (in Chapter 4-5 this would be the pain provocation test, the SLDS) causes the resultant reduction in pain in the post test (repeated SLDS) rather than the exercise intervention. Their study, using a Soloman design where only some of the participants complete both pre and post test, provided compelling evidence to support this hypothesis. However, the cross over design utilised in Chapter 4 provided equal exposure of all participants to the SLDS testing. If the induced analgesia was a pain test artefact, it would be expected that there would be no difference between the isometric and isotonic conditions. Furthermore, based on this hypothesis, the NRS for the SLDS should be lowest 45 minutes after the exercise due to several exposures to the painful SLDS test when in fact it had returned to baseline in the isotonic condition.

The immediate analgesic effect in the isotonic condition is consistent with the study by Koltyn and Arbogast (1998). Similarly, they reported that pain perception (measured with PPT) returned to baseline within 15-20 minutes. Given the lack of reduction in cortical inhibition

following the isotonic condition, it is possible that the mechanisms behind the analgesic effect were different for isotonic and isometric conditions.

This is supported by Kosek & Ekholm (1995) who reported PPTs remained elevated in the recovery period following long duration isometric quadriceps contraction in healthy participants indicating an analgesic effect. However, no study has previously compared isotonic and isometric exercise in a population with MSK pain for the immediate effect on pain. Furthermore, the literature has used sensory testing (usually PPT) as it is the only possible method in someone without a current pain condition. The study in Chapter 4 is the first study to investigate the use of strength training for its immediate effect on a pain provocation test.

7.2.3 Generalisability of isometric exercise in patellar tendinopathy to other tendons

Interestingly, the protocol used by Kosek and Lundberg (2003) to investigate isometric exercise tested different contraction sites of the upper and lower limb. Contraction of infrapsinatus but not quadratus femoris gave rise to additional activation of unilateral segmental nociceptive effects. This implies there may be some upper and lower limb differences in endogenous modulation or sensory processing. As PT was the focus of this thesis, the results may not be generalisable to other tendons, especially those of the upper limb.

Some of the upper limb tendons, such as supraspinatus may have a different function and composition, for example the patellar tendon is an energy storage tendon and supraspinatus appears to be better defined as a positional tendon and these have been shown to have a different matrix structure (Screen et al., 2013). Upper limb tendons have different motor and sensory representations and use profiles influenced by handedness, the upper limb neurons are shorter thus conduction time from the periphery is less and this may influence features such as wind-up

(Chapter 2). However, these data may be reflective of other lower limb tendons such as the Achilles tendon, which is also an energy storage tendon. The clinical utility of isometric exercise lies not only in its ability to induce analgesia immediately but for its immediate modulation of corticospinal control and warrants investigation in other tendons.

7.3 Isometric exercise reduces cortical inhibition

It is not known where along the neuroaxis that the nociceptive input was altered or modulated following the isometric muscle contraction protocol. However, the reduction in pain following isometric exercise was paralleled by a release of cortical inhibition, in this case SICI, which partially supported hypothesis two. This would imply an alteration in the number or intensity of inhibitory neurons synapsing on the corticospinal cells within the motor cortex or the amount of neurotransmitter ($GABA_A$). If we consider the pain adaptation model, this suggests a reduction in peripheral nociceptive input from the isometric contraction that enabled a release of SICI. Conversely, it is possible that isometric exercise may have caused a release of inhibition that altered muscle activation reducing nociceptive drive. However, it does not appear that isometric exercise is purely exercised induced hyperalgesia in PT as discussed in the previous section as logically, you would expect to see bilateral pain reduction, and potentially but not necessarily, the same effect in the isotonic group. In contrast, isotonic exercise showed no effect on SICI. The local analgesic effect indicates that the tendon, muscle and corticospinal pathway needed to be stimulated thus the precise changes at all these levels are unknown. Furthermore, the increased cortical inhibition observed in people with PT prior to isometric exercise may be protective, so it would follow that this would only be released following a reduction in nociceptive drive.

The increased inhibition in people with PT contrasts to the study by Kittelson et al., (2014) who found no difference in SICI between people with knee OA and matched controls. It is possible that the competing demands in PT of protection and optimal performance result in a different characteristic corticospinal response compared with OA where competing demands may be protection and function. Participants with OA and matched controls were also older adults and thus may have age related changes in corticospinal control.

A single bout of isometric exercise reduced patellar tendon pain, however the cumulative effects of repeated bouts on pain and cortical control warranted investigation. Furthermore, there were no efficacious rehabilitative options for athletes inseason. Therefore, it was important to establish in a real world environment if repeated isometric exercise training was tolerated by athletes with PT inseason. Isotonic exercise also showed a smaller but still significant analgesic effect and was therefore an appropriate comparator for an RCT.

7.4 Isometric exercise induces greater analgesia than isotonic contractions inseason

There are clear benefits to reducing pain immediately in an athletic environment where the primary goal is performance. Whilst isometric and isotonic muscle contractions were both shown to reduce pain, isometric exercise resulted in increased immediate analgesia, which supported the study's hypothesis. Muscle contractions that cause greater immediate analgesia may be the athletes' choice.

Importantly, all of the studies in this thesis utilised principles of externally paced strength training to exploit the processes leading to neuroplasticity. This contrasts with clinical practice where rehabilitation is traditionally self paced. It stands to reason that current rehabilitation may not adequately address motor changes in PT. However, it is also possible that isometric exercise (regardless of whether it is self or externally paced) reduces nociceptive drive and this alters

inhibition outside of plastic changes to cortical control. Future studies should compare these training conditions (self paced and externally paced) to establish the mechanism behind changes in pain.

7.5 Limitations of the thesis

The greatest challenge and limitation of the studies in this thesis pertain to sample size. Though TMS is non-invasive, it is uncomfortable and can be time consuming to conduct. It can be difficult to schedule participants repeatedly at the same time of day and this is important to avoid the effect of circadian rhythms and also variations in tendon pain and tendon load. For example, all participants who were included in the intervention studies and underwent repeated testing (Chapters 4-6) were tested on the same day of the week and time of day. This meant their previous day loading was as stable as possible (i.e. following a volleyball game) as the 24 hour response to tendon load can influence SLDS pain substantially. This ensured that any changes were associated with the intervention and not fluctuations in load. In the cross over study (Chapter 4), the same timing of testing was used to ensure baseline SLDS scores did not vary week to week. These were considered important variables to control, even in a pragmatic and clinically relevant study such as the RCT. Study 2 was a cross over study to ascertain the effects by comparing each individual with themselves in two separate interventions as well as a baseline with no intervention. Though it was robustly conducted, it would have been improved with greater numbers.

Greater numbers would also enable detailed analysis of pain and pathology subgroups and their combinations on corticospinal control. The LBP and stroke literature indicate that inter-hemispheric inhibition and changes in the ipsilateral M1 are present in those conditions, thus

greater numbers of participants and the ability to collect inter-hemispheric measures would have enhanced the studies.

The RCT used an auditory file for external pacing. The rest period was not as long as the protocol for the acute cross over study. The exercise was continuous, alternating from leg to leg and immediate change of leg was used to try to avoid participants fast-forwarding through an enforced rest period. This reduced the rest period to 1 minute per leg compared with 2 minutes per leg, which should have been sufficient for muscle recovery but may have induced aspects of central fatigue (Gandevia, 2001, Taylor and Gandevia, 2008).

Ideally, participants would have completed supervised training to check technique and assist with increasing their weights in the RCT. However, this was not possible with 20 participants. The lack of individual supervision does mimic real life where athlete's complete exercises unsupervised. Further follow up testing sessions, especially with those that had undergone TMS testing, to establish the longer term effects of the interventions would have improved the study.

The RCT was conducted towards the end of the volleyball season and many athletes do not continue to load their patellar tendons in the off –season so it would have also been interesting to retest TMS responses in their off-season to observe whether corticospinal changes from the intervention were retained. A control group would have provided detail about how corticospinal control may or may not change over the course of a competitive season.

The precision and consistency of TMS can be improved with equipment that ensures the location of stimulation is the same each time. Participant's heads were measured according to published protocols, an accepted criterion was used to establish AMT and each trial was repeated if rmsEMG was high or there was variability in the size of the MEP amplitude compared with other

trials at the same intensity, however such equipment would enhance the reliability of delivering the stimulus to the exact spot each time.

A number of other factors including genetic variants are associated with tendinopathy and neuroplasticity, however this was outside the scope of this thesis. Finally, the findings in these studies may not be generalisable to other tendons and further research is required.

7.6 Clinical implications and strengths of the thesis

The studies in this thesis investigated a novel concept in PT. The corticospinal control of the quadriceps including the CSE and SICI was different to controls and modifiable with heavy, externally paced strength training. Corticospinal control of the quadriceps would influence the load transmission to tendon in functional activities. Differences compared with healthy controls may indicate an abnormal balance of CSE and SICI that may balance demands of protection and performance. Addressing these changes may provide novel directions for rehabilitation. Conversely, these data may indicate that some people are vulnerable to PT due to pre-existing motor control differences and this would provide a basis for considering the risk factors for developing PT. It is plausible that strength training may be used to modify nociceptive drive, which may in turn alter corticospinal control. Merely addressing CSE or SICI without attempting to modify nociceptive drive in what appears to be a chronic nociceptive condition may be futile.

There are a number of strengths of the studies in this thesis that enhance clinical relevance. All studies in this thesis included athletes, and groups that were compared were matched for many important factors known to influence the M1, and timing of TMS sessions was tightly controlled to minimise changes in preceding load that may affect tendon pain and potentially TMS responses. Substantial pilot testing was undertaken including measuring the effect of jumping

load on CSE in an active population as well as the interventions used throughout the studies.

Therefore, these results may be considered reflective of athletes with PT and healthy jumping

control participants and include interventions that are relevant to athletes playing and training

with tendon pain. Furthermore, Chapter 4-6 pertain to interventions conducted inseason.

These are the first studies to demonstrate two efficacious strength training programs for inseason

PT management. This is also the first study to demonstrate an analgesic effect of isometric

loading that may be used to reduce tendon pain but not reduce muscle performance. This has

immediate beneficial clinical implications.

The interventions used in this thesis were not only pilot tested but based upon the tendon, muscle

and neuroscience literature to try to optimise the protocols. Importantly, externally paced, but

not self paced strength training has been shown to alter corticospinal control of muscle in healthy

people mainly via a release in SICI. The alteration to corticospinal control, in particular changes

to SICI in people with PT was demonstrated in this thesis following an intervention that used

externally paced strength training. All TMS testing and analysis were conducted blinded to

group. While sub-grouping reduced numbers, it also enhances the validity of the findings as the

contralateral limb was never used as a control and separating unilateral and bilateral

presentations of pain and pathology will enable an improved understanding of how these factors

influence the M1. In particular, Chapter 6 provides preliminary data to build on to test these

potentially exciting new avenues for tendon rehabilitation.

7.7 Conclusions and future directions

Studies in this thesis found increased CSE and cortical inhibition responses of the M1 were

associated with PT. This may represent imbalanced corticospinal control of the quadriceps

muscle, which may contribute to persistent altered motor control and invariability that has been

reported in PT. It may have negative implications; changes to motor control may contribute to treatment resistance and symptom recurrence through aberrant load transmission to tendon. However it is also possible that the motor control changes reflect the complex demands for both performance and protection. Differences in corticospinal control of muscle may exist in some individuals and this may precede tendon pathology or pain and contribute to an increased risk of developing pathology or pain, however the cross sectional study design used in this thesis did not enable cause and effect to be determined. Future studies with prospective design may enable a better understanding of these factors.

Isometric muscle contractions were more analgesic for PT than isotonic muscle contractions, and isometric contractions modulated SICI, which resulted in increased quadriceps MVIC torque. This finding has positive implications for clinical utility in PT as isometric muscle contractions may be used prior to sport to reduce pain without a decline in quadriceps MVIC (representative of muscle performance) and this warrants investigations in other tendons. Furthermore, studies in this thesis also demonstrated two efficacious inseason programs though isometric exercise provided greater immediate analgesia thus may be the athlete's choice.

Finally, if external pacing is important in the rehabilitation of tendinopathy to address corticospinal drive to the muscle, we may need to change the way we prescribe strength based rehabilitation. The parameters that stimulate muscle and tendon remain important, however, the precise application of these including the use of auditory or visual cueing would be equally important.

Appendix A. Monash University Ethics approval, Explanatory statement and Informed consent

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	20 March 2012
Project Number:	CF12/0230 - 2012000067
Project Title:	Cortical changes associated with patellar tendinopathy and effects on rehabilitation
Chief Investigator:	Prof Jill Cook
Approved:	From 20 March 2012 to 20 March 2017

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.**
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.
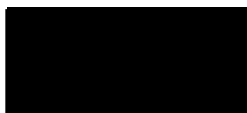
Professor Ben Canny
Chair, MUHREC

cc: Ms Ebonie Scase

1

Explanatory Statement

To Participant

Date:

Title: Cortical changes associated with patellar tendinopathy and effects of rehabilitation

This information sheet is for you to keep.

Student Research Project

My name is Ebonie Scase I am conducting a research project with Professor Jill Cook, Dr.Shapour Jaberzadeh and Dr. Dawson Kidgell towards a PhD at Monash University. This means that I will be writing several articles based on the findings and a research thesis.

Why have you been asked to participate in this project?

You have been invited to participate because you have responded to the related advertisement and met the following inclusion criteria:

• You are at least 18 years old.
• You can speak, read and understand English.
• Your responses to our screening questions indicate that are eligible to participate in this study.

The aim/purpose of the research

The study aims to compare the motor and sensory changes in people with patellar tendon pain compared with pain free individuals.

Possible benefits

There are possible direct benefits for the participants from this study. People with patellar tendon pain will be randomly assigned to an intervention group and receive one of three commonly utilised treatments. . Following completion of all data collection, all groups shall be offered the intervention which was the most effective. We hope the study will benefit the advancement of the understanding of tendon pain and rehabilitation.

What does the research involve?

You will be invited to either Deakin University laboratory (Burwood) or Monash University laboratory (Frankston) for testing (whichever is more conveniently located for you.) You will be asked to complete several questionnaires to gather information about past injury, demographics, quality of life, depressive score and a cognitive test. You will complete a lower limb assessment (which includes measurements of height, weight, waist circumference, calf strength, ankle range, single leg squat test & hop test) and ultrasound assessment of your patellar tendon. Baseline testing will also include transcranial magnetic stimulation (TMS) quantitative sensory testing (QST) and stimulating your femoral nerve called a somatosensory evoked potential.

TMS is a safe and painless technique which is widely used in different laboratories for both therapeutic and research purposes. TMS will be applied in sitting position through a magnetic coil which will be held over your head. Muscle responses will be recorded from the quadriceps muscles with surface electrodes. During the session, a current will also be applied to the femoral nerve to allow the sensory representation to be recorded for your quadriceps and tendon (called the somatosensory evoked potential). The final TMS testing will include a stimulation given during a quadriceps maximal contraction. During testing it is common to feel your quadriceps muscle contracting and painless twitch of facial muscles.

QST involves testing your sensitivity to thermal (hot / cold) and mechanical (pressure) stimuli over your legs, arms & torso. This is a safe, quick and painless test.

If you have patellar tendinopathy you will be invited to participate in a rehabilitation intervention. You will be randomised to one of three rehabilitation groups for an eight week period. You will be taught all exercises and can contact the researcher at any time. Follow up testing will include the questionnaires, TMS and QST. People without patella tendinopathy who are not part of the intervention will be invited back for follow up testing also.

How much time will the research take?

Testing will take approximately three hours at baseline (which does not have to be at one time). The intervention (if you are part of it) will take approximately 15-20 mins three times per week over eight weeks and follow up testing will require approximately two to three hours (which does not have to be at one time) up to a maximum of two testing occasions.

Are there any risks to people in this study?

All of the procedures that will be used in this study have been thoroughly tested in previous studies and are used as standard tests of nervous system function in clinical neurophysiology and neurology. As a matter of precaution, we exclude any persons from our study who have had a seizure or suffer from epilepsy, or a family history of epilepsy. Also, anyone who has had a stroke, metal implants in the skull, or cardiac pacemakers is excluded from these experiments. There may be a very small risk of seizure if there is a pre-existing congenital condition. Please advise the people conducting the study if any of these medical conditions apply.

Who can't be in this study?

You are unable to participate in this study if you have had a brain injury or if you have had a seizure or suffer from epilepsy, or a family history of epilepsy. Also, anyone who has had a stroke, metal implants in the skull, or cardiac pacemakers is excluded from this study. If you are unable to commit to the timeframes, because of things such as overseas travel, please discuss this with the researcher as you may need to be excluded from the study.

Can I withdraw from the study?

Participation in this study is voluntary. You are free to withdraw consent and to discontinue participation in the research at any time. Furthermore, you have the right to request that all traces of your participation be removed from the project records.

How will I know the results of this study?

You will receive an individual report of your results following your baseline and followup testing.

What will happen to my information?

You will be assigned a code and all information recorded will be coded under this. Your contact information will only be used to enable communication with myself during the weekly followup and to make mutually convenient testing times. The questionaires and recorded information will be de-identified and pooled with the data from other participants. All forms and information sheets will be stored in a locked filing cabinet in a locked office at Monash University for the duration of the study.

Data stored on computers will be protected by security passwords. The results of this study will be the basis part of a PhD thesis that will, in several years time, probably be available via the internet. Papers arising from the thesis will be submitted for publication in scientific journals and will also be presented at conferences. No publications arising from this work will enable any participant to be identified.

At the completion of the study, all forms and questionnaires (including consent forms) will be filed in a locked cabinet in a locked office for 6 years, after which time they will be destroyed in a confidential manner: paper by shredding, electronic by deleting from the hard drive and back up files. No one other than the research team will have access to these files at any stage. You may request a copy of personal information collected in the course of the research at any stage of the study up to the point where the link between the code and the identity of individuals is broken. This will occur when all information from the other participants have been entered and is anticipated to

occur within 4 weeks of the completion of each measurement session. After this point you will only be able to access pooled and de-identified data.

<div style="background-color: #8CC63F; padding: 4px;">Storage of data</div>

Storage of the data collected will adhere to the University regulations and kept on Monash University premises in a locked cupboard/filing cabinet for 5 years. A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report.

Any questions regarding this project may be directed to

1.　　Ebonie Scase Physiotherapist, PhD Candidate, Physiotherapy Department, School of Primary Health Care, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne – Peninsula Campus, ███████████████████████████████████ ████████████████████

2.Professor Jill Cook, Research Fellow, School of Primary Health Care, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne - Peninsula Campus ███████████████ ████████████████

Should you have any complaint concerning the manner in which this research is conducted, please do not hesitate to contact the Monash University Human Research Ethics Committee at the following address:

Executive Officer, Human Research Ethics

Monash University Human Research Ethics Committee (MUHREC)

Building 3e Room 111

Research Office

Monash University VIC 3800

████████████████████████████████████
████████████████████████████████████

Thank you.

Ebonie Scase

Title: Cortical changes associated with patellar tendinopathy and effects of rehabilitation

NOTE: This consent form will remain with the Monash University researcher for their records

I agree to take part in the Monash University research project specified above. I have had the project explained to me, and I have read the Explanatory Statement, which I keep for my records. I understand that agreeing to take part means that:

List all procedures relevant to your data collection – delete those not applicable

I agree to complete questionnaires asking me about pain experience, quality of life and cognitive function.   ☐ **Yes**   ☐ **No**

I agree to undergo testing that will involve the use of transcranial magnetic stimulation

☐ **Yes**   ☐ **No**

I agree to undergo testing that will involve stimulation of peripheral nerves

☐ **Yes**   ☐ **No**

I agree to undergo sensory testing that will involve the use of quantitative sensory testing measures of temperature and pressure

☐ **Yes**   ☐ **No**

and/or

I understand that my participation is voluntary, that I can choose not to participate in part or all of the project, and that I can withdraw at any stage of the project without being penalised or disadvantaged in any way.

and/or

I understand that any data that the researcher extracts from the questionnaire and assessment for use in reports or published findings will not, under any circumstances, contain names or identifying characteristics.

and/or

I understand that I will be given a transcript of data concerning me for my approval before it is included in the write up of the research.

and/or

I understand that any information I provide is confidential, and that no information that could lead to the identification of any individual will be disclosed in any reports on the project, or to any other party.

and/or

I understand that data from the questionnaire and assessment will be kept in a secure storage and accessible to the research team. I also understand that the data will be destroyed after a 5 year period unless I consent to it being used in future research.

Participant's name

Signature

Date

Appendix B. Deakin University Ethics Approval

Human Research Ethics

DEAKIN
UNIVERSITY AUSTRALIA

Deakin Research Integrity
70 Elgar Road Burwood Victoria
Postal: 221 Burwood Highway
Burwood Victoria 3125 Australia

Memorandum

To: Dr Dawson Kidgell

School of Exercise and Nutrition Sciences

B

cc:

From: Deakin University Human Research Ethics Committee (DUHREC)

Date: 19 April, 2012

Subject: 2012-090

Cortical changes associated with patellar tendinopathy and effects of rehabilitation

Please quote this project number in all future communications

Approval for this project was granted by the Deakin University Human Research Ethics Committee Executive on 19/04/2012.

Approval has been given for Dr Dawson Kidgell, School of Exercise and Nutrition Sciences, to undertake this project for four years from 19/04/2012.

The approval given by the Deakin University Human Research Ethics Committee is given only for the project and for the period as stated in the approval. It is your responsibility to contact the Human Research Ethics Unit immediately should any of the following occur:

- Serious or unexpected adverse effects on the participants
- Any proposed changes in the protocol, including extensions of time.
- Any events which might affect the continuing ethical acceptability of the project.
- The project is discontinued before the expected date of completion.
- Modifications are requested by other HRECs.

In addition you will be required to report on the progress of your project at least once every year and at the conclusion of the project. Failure to report as required will result in suspension of your approval to proceed with the project.

DUHREC may need to audit this project as part of the requirements for monitoring set out in the National Statement on Ethical Conduct in Human Research (2007).

Human Research Ethics Unit

REVIEW ARTICLE

The Pain of Tendinopathy: Physiological or Pathophysiological?

Ebonie Rio · Lorimer Moseley · Craig Purdam ·
Tom Samiric · Dawson Kidgell · Alan J. Pearce ·
Shapour Jaberzadeh · Jill Cook

Abstract   Tendon pain remains an enigma. Many clinical features are consistent with tissue disruption—the pain is localised, persistent and specifically associated with tendon loading, whereas others are not—investigations do not always match symptoms and painless tendons can be catastrophically degenerated. As such, the question 'what causes a tendon to be painful?' remains unanswered. Without a proper understanding of the mechanism behind tendon pain, it is no surprise that treatments are often ineffective. Tendon pain certainly serves to protect the area—this is a defining characteristic of pain—and there is often a plausible nociceptive contributor. However, the problem of tendon pain is that the relation between pain and evidence of tissue disruption is variable. The investigation into mechanisms for tendon pain should extend beyond local tissue changes and include peripheral and central mechanisms of nociception modulation. This review integrates recent discoveries in diverse fields such as histology, physiology and neuroscience with clinical insight to present a current state of the art in tendon pain. New hypotheses for this condition are proposed, which focus on the potential role of tenocytes, mechanosensitive and chemosensitive receptors, the role of ion channels in nociception and pain and central mechanisms associated with load and threat monitoring.

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1 Introduction

Tendon pain is baffling for clinicians and scientists alike. It is difficult to understand why it is so persistent and why it comes and goes with little reason. Scientifically this translates to the absence of a clear mechanism that can explain the clinical features of tendon pain. It is therefore no surprise that treatments for tendon pain are often ineffective [1–4].

Tendinopathy, the clinical syndrome of pain and dysfunction in a tendon, is often a chronic condition. Like other chronic pain conditions, in tendinopathy there is disconnect between tissue damage seen on clinical imaging and clinical presentation, which creates confusion for both patients and clinicians. However, key features of tendon pain are different from other chronic pain conditions. The purpose of this review is to (i) explore the clinical questions surrounding tendon pain; (ii) summarise what is known about tendon pain; and (iii) examine evidence from relevant fields to provide direction for future research.

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1.1 Clinical Features of Tendon Pain

The clinical presentation of tendinopathy includes localised tendon pain with loading [5–7], tenderness to palpation [8] and impaired function [9–11]. Pain defines the clinical presentation [10], regardless of the degree of tendon pathology. Tendinopathy, despite being an umbrella term, is usually limited to intra-tendinous presentations, with more specific terminology being applied to pathology in surrounding tissue with different disease processes, such as paratendinitis [10]. Microscopic examination of tissue biopsies from painful tendon reveals variable features of tendon pathology, including collagen disorientation, disorganisation and fibre separation, increased proteoglycans (PG) and water, increased prominence of cells, and areas with or without neovascularisation, which collectively are termed tendinosis [12]. Many imaging studies (i.e. ultrasound, magnetic resonance imaging) indicate that these changes can exist in the tendon without pain, and people without symptoms rarely present clinically. Therefore, tendinosis may be an incidental examination finding and does not in itself constitute the diagnosis of tendinopathy, which requires clinical symptoms [10].

Tendon pain has a transient on/off nature closely linked to loading, and excessive energy storage and release in the tendon most commonly precedes symptoms [13–16]. Pain is rarely experienced at rest or during low-load tendon activities; for example, a person with patellar tendinopathy will describe jumping as exquisitely painful yet not experience pain with cycling because of the different demands on the musculotendinous unit. A further characteristic pain pattern is that the tendon 'warms up', becoming less painful over the course of an activity, only to become very painful at variable times after exercise [7].

1.2 Defining Pain Concepts

Clinicians and researchers distinguish between physiological and pathophysiological pain. Physiological or 'nociceptive' pain is considered to reflect activation of primary nociceptors following actual or impending tissue damage or in association with inflammation. This type of pain is a helpful warning sign and is considered to be of evolutionary importance. Pathophysiological pain is associated with functional changes within the nervous system, such as ectopic generation of action potentials, facilitation of synaptic transmission, loss of synaptic connectivity, formation of new synaptic circuits, and neuroimmune interactions as well as cortical topographical changes [17], making it resistant to tissue-based treatments and it appears to provide no evolutionary advantage or helpful warning.

Some aspects of tendinopathy fit more clearly into pathophysiological pain. Painful tendons can have little pathology [18, 19] and pain can persist for years [20]. Furthermore, pain during tendon rehabilitation exercises has been encouraged [21–24] and may not be deleterious [25], providing evidence that tendon pain does not necessarily equate with tissue damage. Overuse tendon injury does not involve an inflammatory process with a clear endpoint that underpins most physiological pain (see Sect. 2.3 for more detail). However, other aspects of tendinopathy fit more clearly into physiological pain—pain remains confined to the tendon [8] and is closely linked temporally to tissue loading [26]. A clinical presentation that fails to be explained by either pain state classification is the rupture of a pathological yet pain-free tendon, where nociceptive input would have been advantageous.

In order to explore the cause of tendon pain, it is helpful to briefly review newer concepts of pain. Modern understanding of pain suggests that nociception is neither sufficient nor necessary for pain [27]. Nociception refers to activity in primary afferent nociceptors—unmyelinated C fibres and thinly myelinated Aδ fibres—and their projections to the cortex via the lateral spinothalamic tract (Fig. 1). The projections terminate in multiple regions but predominantly the thalamus, which transmits impulses to the somatosensory cortex. Primary nociceptors respond to thermal, mechanical or chemical stimuli. In contrast, neuralgia describes pain in association with demonstrable nerve damage and is often felt, along with other sensory symptoms, along the length of the nerve or its peripheral distribution.

Pain, on the other hand, is an emergent property of the brain of the person in pain [28]. A useful conceptualisation is that pain emerges into consciousness in association with an individually specific pattern of activity across cortical and subcortical brain cells [29]. Innumerable experiments and common everyday experiences show that pain is most often triggered by nociceptive input. However, carefully designed experiments in healthy volunteers show that pain can be evoked without activating nociceptors [30] and that pain is readily modulated by a range of contextual and cognitive factors [31].

The relationship between nociception and pain becomes more tenuous as pain persists, and research has uncovered profound changes in the response profile of neurons within the nociceptive neuraxis. The mechanisms that underlie these changes have been extensively reviewed [32–34]. The clinical manifestations of these changes—sensitisation and disinhibition (or 'imprecision')—are important because they can be compared and contrasted with the clinical presentation of tendinopathy. Sensitisation refers to an upregulation of the relationship between stimulus and response where pain is evoked by stimuli that do not normally evoke pain—allodynia—and stimuli that normally evoke pain evoke more pain than normal—hyperalgesia.
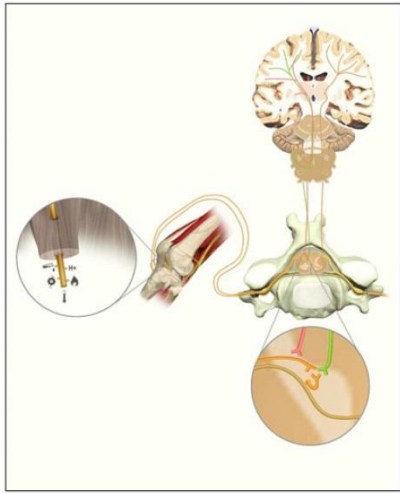
Fig. 1 Schematic representation of the basic physiology of tendon pain. The peripheral end of nociceptors, or free nerve endings, on thin unmyelinated (type C fibres) or thinly myelinated (type A delta fibres) situated in the peritendon and the peripheral portions of tendon tissue contain thermal, heat and mechanically activated ion channels. Changes in the chemical thermal or mechanical environment are transformed here to elicit signals or action potentials in the nociceptor. The signal travels to the dorsal horn of the spinal cord (in the superficial laminae I and II), where the nociceptor synapses with second order or spinal nociceptor. The spinal nociceptor sends a signal to the thalamus via the lateral spinothalamic tract and thence the brain. The medial aspect of the spinothalamic tract and the spinoparabrachial tract project to medial thalamus and limbic structures and are believed to mediate the emotional component of pain. A complex evaluative process occurs across multiple brain areas and protective outputs are activated. One such output is pain. Others include motor output, autonomic, endocrine and immune activation. In addition, descending projections (shown here in *red* and *green*) modulate nuclei in the brainstem, which in turn send signals down the spinal cord to modulate the same synapse in the dorsal horn. These neurons are activated to either facilitate or inhibit the spinal synapse, thereby either turning nociception up or turning it down. The manner of modulation here depends on the brain's evaluation of the need for pain and protection. As such, the spinal cord represents the first stage of integration and processing of the nociceptive signal

Allodynia and primary hyperalgesia are attributed to sensitisation of the primary nociceptor and relate to the area of usual pain. In tendinopathy, if normally pain-free movements, for example jumping, evoke tendon pain, this can be termed allodynia. If palpation of the Achilles tendon evokes more pain than usual, this can be termed primary hyperalgesia. In both scenarios, the tendon pain mechanism is over-sensitive. Notably, tendon palpation is only a moderately sensitive clinical test [35] and tenderness, or primary hyperalgesia does not correlate with tendon function.

Secondary hyperalgesia and allodynia are attributed to sensitisation of nociceptive neurons within the central nervous system (CNS), collectively called central sensitisation, and relate clinically to areas away from the primary 'zone'. Tenderness and evoked pain that spread, in a non-dermatomal, non-peripheral nerve distribution is best explained by central sensitisation [36].

The astute clinician will observe that, in the clinical presentation of tendinopathy, there is clear evidence of allodynia and primary, but not secondary, hyperalgesia [37]. This observation strongly implies the tendon tissue or the primary nociceptors that innervate it, are the nociceptive driver of tendon pain. We must look then more closely for potential local sources of nociception. However, tendinopathy is a chronic and persistent pain state and thus a scientist will ponder whether tendinopathy exhibits subclinical signs of central sensitisation and disinhibition identified in other chronic painful conditions [38–40]. We must then also look for potential central contributions to tendinopathy that may promote chronicity but not manifest in secondary hyperalgesia. To do this it is important to understand normal and pathological tendon structure.

2 Tendon Histology and Pathology

2.1 Normal Tendon

Normal tendons are mainly composed of fibroblastic tendon cells, called tenocytes, surrounded by extensive extracellular matrix (ECM). The ECM is predominantly made up of tightly packed collagen fibres (mainly Type I) that are orientated along the primary loading direction [41]. Also present are several PG (mainly small molecular weight decorin) and other non-collagenous proteins. Connective tissue both surrounds the tendon (peritendon) and infiltrates the tendon (endotendon).

Tenocytes manufacture all of the components of the ECM. Tenocytes lie end-to-end in channels between collagen fibres, with cell processes linking the cells within and between rows allowing communication [42]. Gap junctions that link cell processes are capable of being remodelled in hours [43], and appear to couple cells metabolically, chemically and electrically [42–44]. They allow rapid exchange of ions and small metabolites between cells, and different types have shown to be stimulatory and inhibitory in response to load [45]. Gap junction channels are gated open more often than closed, therefore it is the selectivity of the channel that dictates what passes from cell to cell [46]. The probability of gap junction channels being open or closed is influenced by pH, calcium concentration, the voltage across the gap junction and mechanical load [43, 47].

Whilst tenocytes have important roles in manufacturing ECM and load sensing, there are other cell types in tendon whose role is currently unclear, including a multi-potent population capable of differentiation [48, 49]. Mast cells, associated with immune function and found near blood vessels in tendon [50] are bone marrow derived and capable of phagocytosis, cytokine production, vasoactive substance release and immune receptor expression. Glial cells, not yet investigated in tendon but evident in other connective tissues [51], share a bone marrow lineage [52] and an immune role. Glial cells, which are capable of neurotransmission in chronic injury [53], communicate information between the peripheral nervous system (PNS) and CNS [54, 55] and when activated are implicated in ongoing pain [56] and may be another cell type potentially involved in tendon pain. Classic inflammatory cell types have been associated with rupture [57, 58] but have been infrequently shown in chronic tendinopathy [59].

2.1.1 What is the Neural Supply to the Tendon?

Tendon pain is well localised (implying small receptive fields) [60], occurs instantly with loading (implicating the involvement of myelinated/fast fibres) yet 'warms up' (implying a gating mechanism or exercise-induced inhibition); however, few studies have investigated these neural pathways.

Innervation studies in human tendon show scant innervation in the tendon proper; however, tendon connective tissue and blood vessels are well innervated [61, 62] with three neuronal signalling pathways: autonomic, sensory and glutamatergic [62–64]. Autonomic nerves, particularly sympathetic nerve endings in blood vessel walls [65], have been reported in the tendon, peritendon and endotendon of the patellar tendon [66, 67]. Sensory and sympathetic perivascular innervation of the walls of large and small blood vessels occur in peritendinous loose connective tissue, and there are some sensory nerve endings in the superficial endotendon [61]. Sparse sensory nerves have been identified in the body of the patellar tendon [64, 65]; in contrast, surrounding structures such as retinaculum and fat pad are richly innervated [68–70]. Mechanoreceptors are concentrated at myotendinous junctions and tendon insertions.

2.2 Tendon Pathology

Tendon pathology results in cell activation and proliferation, matrix change (collagen disorganisation and increased large PG) and neovascularisation, in various combinations and severity [18, 71, 72]. Tendon pathology is not always painful [73] but clinical presentation of tendinopathy is almost always associated with pain (tendon rupture may have been previously pain free). Change in collagen structure is the most obvious candidate for nociception because it is the load-bearing structure in tendon, but loss of collagen integrity does not correlate with tendon pain [18]. In fact, pain-free tendons can have sufficient structural disorganisation that they rupture [74].

2.2.1 Does the Innervation Pattern Change with Pathology?

There are few afferent nerves within tendon, and innervation patterns do not change with pathology [61, 75]. New vessels primarily bring autonomic vasomotor nerves (and some sensory nerves) but neovascularisation is not present in every painful tendon. Tendon pain may be associated with nerve-ending sprouting, or changes to nerve function rather than type; for example, Aβ fibre activation can cause pain when there is production of nociceptive substances and/or central sensitisation [34, 36, 76].

Innervation may not be uniform throughout a pathological tendon. The area dorsal to the proximal patellar tendon, which is targeted in some injectable and surgical interventions because of the neovascularity in this area, has mainly sympathetic nerves and few sensory nerves [67]. The vessels displayed marked perivascular innervations and adrenoreceptor immunoreactions [67].

These changes to innervation do not appear to explain the clinical features of tendon pain. To reflect all the clinical features, the local nociceptor must have a threshold for activation, be responsive to mechanical stimuli and exhibit saturation. Tendon pain may result from non-nociceptive pathways playing nociceptive roles.

2.3 Potential Contributors to Pain

If local nociception drives tendon pain then the nociceptive signal needs to be relayed to the CNS. One way to interrogate the nociceptive capability of tissue is via experimentally induced pain. Hypertonic saline activates nociceptors via chemically-driven ion channels. Hypertonic saline injected into healthy tendon induces pain and mechanical sensitivity but no pain referral—a pain pattern similar to that of load-induced tendinopathy [77]. In contrast, hypertonic saline injected intramuscularly evokes referred pain [78], which clearly implicates convergence within the CNS. However, chemically induced experimental pain studies do not mimic the characteristic load-dependent nature of tendinopathy pain [79]. A complementary approach is to look more closely at the tendon itself. As classical (i.e. cell-mediated/prostaglandin-driven) inflammation has not been associated with tendinopathy and as the innervation pattern does not differ greatly for normal and pathological tendon, potential sources of

nociception in tendon include changes in the matrix, vascular supply, cell function, bioactive substance production, ion channel expression, cytokine and neurotransmitter expression, metabolism and mechanotransduction, or a combination of these.

2.3.1 Matrix Changes

The increased production of large PGs seen with tendon pathology, most notably aggrecan, may compromise cell adhesion, migration and proliferation and interfere with cell–matrix interaction [80]. Large PGs, particularly aggrecan, attract and bind water causing the tendon to swell, which will stimulate local C fibres [81] and increase interstitial potassium (K+) and hydrogen (H+) concentrations. This in turn can stimulate nociceptors and influence ion channel expression and/or activation. Kubo et al. [82] reported that nociceptive neurons were sensitised by low pH through augmenting the mechanical response of thin fibre afferents, and that this sensitisation was attenuated by versican, but not by blocking intracellular signalling pathways.

Larger PGs may also disrupt mechanotransduction, reducing communication between cells and between the cells and the ECM [45]. This may result in a loss of gap junctions between parallel rows of tenocytes (mediated by connexin 43) and even between longitudinal cells. It is feasible that disruption of gap junctions alters tendon homeostasis sufficiently to activate nociceptors. Cell and consequent matrix changes may also compromise gap junction permeability and ion channels that regulate neuronal excitability [83]. Conversely, the disruption of communication in a disordered matrix may protect the tendon by isolating the cell and preventing toxic communication of substances to healthy neighbours.

2.3.2 Vascular Change

Increased vascularity has been reported to be a source of nociception in tendinopathy [84, 85]. Nerves, and receptors such as adrenoreceptors, are found in vessel walls in tendinosis and are likely to be associated with angiogenesis and blood flow rather than having any role in nociception. As the tenocyte is responsible for producing the components of the ECM, stimulation of tenocyte receptors may drive structural change rather than be involved in nociception [86].

Neovascularisation has been associated with degenerative tendinopathy but is not a feature of early pathology [18]. Not all painful tendons have increased vascularity [18, 87] and vice versa [18], therefore the vessels or the nerves and receptors on vessel walls fail to explain tendon pain across all pathological presentations. Sclerosing

treatment of neovascularity has resulted in variable improvements in pain and vascularity [88–91]. Sclerosants may work by changing the biochemical environment or disrupting neural pathways. If local nociceptors are critical to tendon pain, then they must be present across all stages of pathological change, in which case the tenocyte may be the key.

2.3.3 Tenocyte Changes in Structure and Function

Tenocytes respond to changes in their mechanical, ionic and osmotic environment [92–94]. In tendinopathy, tenocytes proliferate, become more rounded, and contain a higher proportion of protein-producing organelles [18]. These changes appear to increase production of substances and receptors involved in nociception (Sect. 2.3.4). Cell changes may also alter gap junction function and affect cell communication, nociception transmission or mechanotransduction, affecting tendon homeostasis and possibly nociceptive communication [45]. In addition to changes in cell structure and communication, the biochemical environment in tendinopathy has a myriad of substances that may be involved in nociception and further alter cell function.

2.3.4 Biochemical Changes: Cytokines, Neuropeptides and Neurotransmitters

There are many biochemical changes in tendinopathy, none of which can fully explain tendon pain. Bioactive substances and their receptors may be important in pain behaviour. Neuropeptides and neurotransmitters, formerly attributed only to neurons, are now known to also be produced by tenocytes.

Autocrine signalling occurs when a signalling molecule binds to a receptor on the same cell type. Paracrine cell signalling functions by signalling to another cell type. Signalling agents can have very short half-lives [for example nitric oxide (NO) is less than 0.1 s] and be influenced by the presence of concurrent substances such as glutamate and calcium ions (Ca^{2+}) [95]. It is not clear whether autocrine or paracrine signalling has a role in tendon pain.

Tendon pain is likely mediated by substances that have pro- and anti-inflammatory effects, for example cytokines [tumour necrosis factor-alpha (TNFα) and interleukin (IL)-1β], signalling molecules [Ca^{2+}, adenosine triphosphate (ATP)], neuropeptides [substance P (SP), neuropeptide Y] and neurotransmitters such as glutamate. These substances have been studied in other chronic pain conditions [96] and may be important contributors to tendinopathy (both pain and pathology). Cytokines are involved in intercellular communication and modulation of gene expression. The TNFα system, implicated in tendinopathy and possibly

activated by mechanotransduction, seems to be involved in matrix structure change and is capable of inducing apoptosis [97–101]. TNFα also causes a dose-dependent increase in afferent Aδ and C firing and may have a role in tendinopathy nociception [102]. IL-1β, upregulated in a human tendon cell culture model, is capable of causing cell proliferation and apoptosis [103]. These cytokines do not show rapid on/off response profiles, but that does not exclude them from being important in tendinopathy. Substances such as TNFα and IL-6 are among those that have thus far been studied in tendinopathy, yet there are many other cytokines that might play a role. Glial cells, a primary expressor of such cytokines, are critical for synaptic transmission [104] in spinal or supraspinal communication [105], and may be a feasible mechanism by which nociception could be upregulated at the level of the CNS.

Neuropeptides such as SP and calcitonin gene-related peptide (CGRP) transmit signals across a synapse. Both SP and CGRP are released by the terminals of nociceptors and SP has been shown to be released by tenocytes. SP afferent immunoreactivity has been demonstrated at the enthesis [106] and in tendon tissue [61, 64], which indicates thin fibre sensory innervation, most likely serving a nociceptive function. SP [and its receptor, neurokinin-1 receptor (NK-1 R)] and CGRP have also been identified in nerve fascicles in large and small blood vessels in tendinopathy [107]. Binding of SP to its receptor has been associated with the transmission of nociception [108].

SP can cause vasodilation and protein extravasation in surrounding tissue—a process termed neurogenic or peptidergic inflammation. SP increases cell metabolism, cell viability and cell proliferation in tenocytes [109]. The peptidergic inflammatory mechanism of nociceptors is initiated by nociceptor activation. However, antidromic mechanisms driven within the CNS can lead to peptidergic inflammation and this raises the possibility that central mechanisms influence tendon pain.

Acetylcholine (ACh), a neurotransmitter in the CNS and PNS that is also produced by activated tenocytes [94], is capable of modulating nociceptive input, influencing collagen production, inducing cell proliferation and regulating vessel tone [94, 110]. Muscarinic ACh receptors of subtype M2 (M2Rs) have been found on tenocytes (in tendons with hypercellularity), nerve fascicles and the local blood vessel walls [94]. Upregulation in the cholinergic patterning also correlated with recalcitrance to treatment [94].

Immunoreactions for adrenergic receptors have been found in blood vessel walls, tenocytes and in some of the nerve fascicles in the patellar tendon [66]. Increases in nerve fibres showing neuropeptide Y immunoreactions as well as those involved in synthesis pathway of norepinephrine and epinephrine and their receptors have been observed in vessels in pathological tendon [66, 67].

ATP can be released by neurons and has been implicated in both central and peripheral pain mechanisms as it functions as a signalling molecule [111]. ATP facilitates nociceptive behaviour and electrolyte transmission, elicits glutamate release [112, 113], acts directly on dorsal horn, regulates cell death and vascular tone, degranulates mast cells and induces prostaglandin synthesis. ATP is released from damaged cells [114] and could activate primary afferent nociceptors.

High intratendinous levels of glutamate and its receptor, the N-methyl-D-aspartic acid or N-methyl-D-aspartate (NMDA) receptor, have been demonstrated in tendinopathy [115, 116]. Glutamate, also produced by the tenocyte, is involved in nociceptive modulation in other persistent pain states, is involved in vasomodulation, is capable of inducing oxidative stress, has a role in ECM metabolism and is associated with tenocyte proliferation and apoptosis [117, 118]. Glutamate receptors can be activated by SP and it is the major neurotransmitter mediating fast excitatory transmission in the CNS. These factors seem to implicate glutamate in tendinopathy; however, resolution of tendon pain with rehabilitation did not change glutamate levels [119]. However, NMDA receptors require glutamate and glycine (also a neurotransmitter) interaction [120] so perhaps it is glycine levels that change (or another substance not examined). Notably, prolonged firing of C fibres is thought to increase glutamate release, which seems inconsistent with the on/off non-spreading nature of tendinopathy pain.

2.3.5 Biochemical Changes: Metabolites

All cells and tissues require the maintenance of intracellular and tissue pH, as many processes and proteins only function within specific pH ranges [44]. Cell membrane potential, which is the difference in voltage between the inside and outside of the cell, determines the excitability of the cell and is influenced by tissue pH. Lactate can decrease pH, and microdialysis of tendinopathic tissue showed lactate levels at rest were double that shown in healthy control tendon [121]. Increased lactate, due to a predominant anaerobic metabolism, occurs in tendons of older people as well as tendinopathy [122, 123], and is compounded by the high metabolic rate in tendon pathology (25 times that of normal tendon) [124].

At physiological pH, lactic acid almost completely dissociates to lactate and hydrogen ions; the latter are known to modulate nociceptor activity and alter ion channel expression. Lactate is not just a waste product—it is an active metabolite, capable of moving between cells, tissues and organs. Lactate can stimulate collagen production and deposition, activate tenocytes [125] and increase vascular endothelial growth factor (VEGF) and neovascularisation

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[126]. Lactate also closes the inhibitory gap junctions between rows of tenocytes, which may exaggerate response to loading [127].

Accumulated lactate has been associated with pain in other tissues such as cardiac and skeletal muscle and the intervertebral disc (IVD), but it has not been fully investigated for tendons. It is notable that tendon pain has some features that are consistent with accumulated lactate: rapid easing in symptoms after a change of posture (sustained positions are painful in tendinopathy), poor response to anti-inflammatory medication (true in tendons for most anti-inflammatory medications, those that alter pain and function appear to do so by tenocyte down-regulation and PG inhibition [128, 129] and sometimes no evidence of clear pathology [76]. However, other features require further explanation—transient load-dependent pain (requires gating) and decreasing pain with ongoing activity (implies saturation).

2.3.6 Cell Changes: Ion Channels

Ion channels, present in cell membranes, alter the flow of ions in and out of a cell and respond to voltage, movement or chemicals. Ion channels in tenocytes may perform a number of roles, including mediation of calcium signalling, osmoregulation and cell volume control, control of resting membrane potential levels and the detection of mechanical stimuli [130]. Ion channels are important in tendon pain; they may be involved in sensing the nociceptive stimuli, communicating with the afferent nerves and neuronal transmission to and within the cortex.

Ion channels are often linked to the cytoskeleton and to an extracellular structure, allowing them to be directly gated by mechanical deformation and almost certainly altered with a change to tenocyte shape with tendinopathy. On nerve cells they enable neuronal communication (in both the PNS and CNS), communication between different tissue types and the conversion of a force or load into an action potential in a nerve.

2.3.6.1 Ion Channels: Sensing the Stimulus
Ion channel expression is likely to change in tendinopathy because of a more acidic environment due to excess lactate. A decrease of the extracellular pH influences the expression of acid-sensing ion channels (ASICs) [131]. The magnitude of currents in ASICs is sufficient to initiate action potentials in neurons [131]; ASICs are activated quickly by hydrogen ions and inactivate rapidly despite continued presence of low pH, exhibiting features of saturation.

ASICs have been associated with painful conditions that have accompanying tissue acidosis and ischaemia, and they were therefore originally thought to only be expressed by neurons. However, connective tissue cells of the IVD [132,

133] bone cells [134], chondrocytes and synoviocytes [135–138] have been shown to express ASICs. These connective tissues share similarities with tendon; low blood supply, few nerves, subject to compression and tension and pain that is not always correlated with tissue damage [139]. In IVDs and articular cartilage, cell metabolism is almost entirely anaerobic [140, 141] and the tissues have high lactate levels and low pH, similar to tendinopathy. In bone, an acidic environment directly impedes osteocyte activity [142], thus ASICs have a role not only in nociception but also cell activity.

Other ion channels in tendons may be important in nociception. The transient receptor potential cation channel subfamily V member 1 ion channel (TrpV1) is believed to function as a molecular integrator of noxious stimuli, including heat, acid and endogenous pro-inflammatory substances [143]. Stretch-activated ion channels (SAC), voltage-operated ion channels [144, 145] or other mechanically gated channels may be implicated in nociception sensing and transmission [146]. Activation of SACs would fit the load based on/off nature of tendon pain and the clinical observation that pain gets stronger with increased loading (which would correlate with increased channel activation) and the 'warming up' phenomenon as ion channels become saturated. Mechanosensitivity (membrane stretch, fluid flow, etc.) is phenotypic [146] and therefore SACs are likely to be selective to other stimuli such as voltage or acid. SACs have been shown to be blocked by gadolinium and, more specifically, by mechanotoxin 4 (GsMTx4); a peptide that modulates ionic currents across calcium, sodium or potassium ion channels and blocks capsaicin receptor channels. Investigation of these blockers may lead to identification of potential treatment options for tendinopathy that may address both pain and the pathological process.

Voltage operated calcium channels (VOCC) have been demonstrated in human tenocytes, as well as the mechanosensitive tandem pore domain potassium channel [2PK (+)] TREK-1, which is sensitive to membrane stretch, intracellular pH and temperature [130]. Importantly, these channels are known to be associated with electrically excitable cells [147] so tenocytes may be capable of conducting an electrical potential as they open and close in response to voltage across the membrane.

2.3.7 Ion Channels: Communicating with Nerves

To activate neuronal pathways, receptors and ion channels are required. Ion channel expression in tenocytes may change, but ion channel expression in the afferent nerve may also change in response to repeated activation [36]. This sensitises the primary neuron to the very stimulus that evoked the adjustment. Ion channels transduce noxious

stimuli into neuron membrane depolarisations that trigger and conduct action potentials from the peripheral site to the synapse in the CNS [148]. As there is a limited relationship between pain and the presence of neural ingrowth in humans [18], additional mechanisms may be performing a nociceptive function. Intercellular signalling via non-synaptic mechanisms are important in the nervous system and between tissues and the nervous system but are not as clearly understood as synaptic communication[149]. In fact, cells may communicate with glial cells [150] via neurotransmitters through neurotransmitter-gated ion channels [151, 152] and voltage-gated ion channels [152]; glial cells may also communicate among themselves. Cell–cell communication within a tendon and with the nearest sensory nerve may well occur via this form of signalling. Alternatively, perhaps load-sensing mechanisms within, or separate from, the tendon play a nociceptive function. If so, they would utilise complex threat-evaluation systems within the CNS.

2.4 How Might These Changes Relate to Tendon Pain?

The presence of stretch and ion-activated channels in either neurons or tenocytes would fit many features of tendon pain. Ion channels are normally closed in the absence of a stimulus, but open for a few milliseconds to allow equalisation along an electrical gradient [153]. With prolonged (chemical or electrical) stimulation, many of these channels close and desensitise, leaving them refractory to further opening unless the stimulus is removed.

Although ASICs have not been studied in normal, pathological or painful tendons, the tendon environment can become acidic [121] to levels that would open ASIC channels if they were expressed by tenocytes or neurons. Desensitisation occurs with persistent stimulation of ASICs after approximately 3 min [154], which may explain the clinical feature of tendons being initially painful during activity then warming up. Recovery from desensitisation occurs slowly, over many hours, which may fit with later pain and stiffness. ASICs are rapidly activating and inactivating (<5 ms to activate, 400 ms to deactivate) [155] which may also fit with the on/off nature of tendon pain. Further investigation of the presence and role of ion channels in tendon pain is warranted.

To be a practical theory, tendon pain must be explained across the range of clinical presentations. These presentations may be a combined result of changes in structure, biochemical levels and cell function that interact to cause pain. Theoretically, in reactive tendinopathy (as described by Cook and Purdam [156]) there may be increased expression of nociceptive substances because of cell activation and proliferation, but no change in innervation. In degenerative tendinopathy there may be little expression of nociceptive substances due to cell inactivation or death but greater innervation. At both ends of the spectrum pain is possible. The pain-free tendon may have substantial matrix disorganisation and cell compromise, but insufficient production of nociceptive substances and/or the neural network to reach a threshold to cause pain. An example is tendon rupture in asymptomatic people, where tissue threatening loads are not communicated to the CNS as pain prior to tendon rupture.

3 Central Mechanisms: the Spinal Cord and Brain

Primary nociceptors have their proximal synapse in the dorsal horn of the spinal cord where they communicate with spinal nociceptors, using glutamate or SP. The spinal nociceptor projects to the thalamus and then onward to access the network of cortical and subcortical areas associated with pain [157]. Experimental pain studies reveal that the contralateral insular cortex, the anterior cingulate cortex, cerebellum, the contralateral thalamus, the putamen, primary and secondary somatosensory cortex, prefrontal cortex and premotor cortex are involved in the pain experience, although much variability exists [158–162].

There is no theoretical or clinical reason to conclude that tendon pain serves an alternative purpose to other types of pain—to protect the painful part. This rather pragmatic view requires acceptance that the entire evaluation of whether or not a tendon is in danger occurs outside of consciousness, and that the spinal nociceptor is just one contributor to this evaluation. Theoretical models that attempt to integrate the research on pain all emphasise the multifactorial nature of pain and the complex and bidirectional interactions that occur between the state of the body and pain. This brings challenges because it raises the possibility that higher centres can target local tissues, if the brain concludes that they are in danger.

The tendon, attached bone and muscle, and overlying skin are all represented within the brain. All bodily representation (including motor, sensory, visual and auditory) is plastic and is influenced by use, injury, pain and disease [163–168]. Although motor and sensory representations, cortical excitability (or descending inhibition) and cognitive modulation of pain have all been well studied in other pain states, little research has been undertaken on tendon pain.

3.1 Does Tendon Pain Centralise?

The PNS and CNS neural networks that mediate nociception demonstrate plasticity in pathological states [169]. The regions that are most likely upregulated are the tendon itself, the nociceptor, the dorsal horn or in the brain.

Sustained peripheral nociceptive activity may lead to the development of central sensitisation [76]. Although central sensitisation accounts for widespread pain and hyperalgesia/allodynia in chronic pain patients, excessive pain response is not a clinical feature of tendon pain regardless of symptom chronicity. This may be explained by the on/off nature of tendon pain, reducing the likelihood of long-term potentiation or depression, or local saturation of the receptor that would then fail to stimulate the afferent nerve.

Few studies have examined if central pain processes are involved in tendon pain states [77, 170]. Tendinopathy pain would seem a unique chronic pain because pain generally occurs during loading, and although there is more pain with increasing load, it disappears once the load is removed. Spreading of pain (for example secondary hyperalgesia) is not a common clinical feature of tendinopathy, especially in the lower limb. However, developing symptoms on the other side is common [171] and this mirroring is often attributed to bilateral loading patterns, although CNS neuroimmune mechanisms offer an equally feasible explanation [104]. The odds ratio of rupturing the other Achilles tendon after a unilateral rupture is 176, when compared with the general population (6 % of the participants ruptured the contralateral tendon) [172]. This may be due to high bilateral loads, but may also indicate central drivers to pathology and/or pain or systemic or genetic factors. Bilateral tendinopathy in both the loaded and unloaded limb of baseball pitchers would support this [173]. This view is further strengthened by data from an animal model where bilateral cell changes were observed in unilaterally loaded rabbits [174] and a unilateral chemically induced model of tendinopathy in horses [175].

There are several features of tendon pain that suggest cortical changes. High frequency train of input (e.g. repetitive high tendon load) strengthens synaptic transmission, and makes the next cell within the CNS more excitable for several days. In tendinopathy, substantial time between high loads is important to control pain [7]. It is possible that this may be not only related to local tendon adaptation such as collagen production and local cellular responses [176], but also to the sensitivity of the pathway.

Tendon pain has been associated with local sensory change such as increased mechanical sensitivity (pain with activity and tendon pressure) [177, 178]. Individuals with unilateral lateral epicondylalgia (LE) demonstrated hyperalgesia and bilateral changes to pressure pain thresholds [179]. The affected side was worse than the unaffected side, and both sides were worse than controls. Individuals also showed bilateral changes to thermal sensitivity [180]. These differences in mechanical and thermal hyperalgesia may indicate central sensitisation. However, another study in tendons demonstrated no differences in cold and heat pain, cold and warm detection thresholds [170].

van Wilgen et al. [170] completed quantitative sensory testing in people with and without patellar tendinopathy to assess central sensitisation. The pressure pain thresholds of asymptomatic athletes differed significantly from athletes with a diagnosis of patellar tendinopathy [181]. Mechanical pain threshold and vibration threshold were found to be significantly lower in people with patellar tendinopathy. Reduced mechanical pain thresholds or pinprick allodynia may reflect the involvement of central sensitization (myelinated Aδ-fibres).

If there are minimal cortical changes in tendinopathy, it is important to know if a tendon transmits pain in a way that protects the brain from central change. First, long-term cortical plasticity changes involve long-term potentiation (repetitive increase in the strength of synaptic transmission that lasts for more than a few mins) [76] or long-term depression (involving GABAergic pathways). The nature of tendon pain, being on/off may prevent long-term potentiation or long-term depression. Second, local inflammation, which is not a feature of tendinopathy, is an important event in the onset of many chronic pain states [182–187]. During inflammatory processes, pro-inflammatory mediators (e.g. prostaglandins, etc.) that are released from damaged tissues activate receptors, stimulate mast cells to release further pro-inflammatory cytokines, which lowers nociceptive threshold firing and increases the rate of firing. Third, the activation of intracellular second messengers is required and subsequent alterations to gene and ion channel expression may be a more transient change with expression changing with the removal of the painful load.

3.2 Central Mechanisms: Future Directions

There may be non-nociceptive mechanisms that play a nociceptive role in tendon pain. One such mechanism may be related to an internal calculation of tendon load. This idea is consistent with the modern idea of pain being about protection and not dependent on nociception, and shares characteristics with the central governor theory of fatigue [188]. Alternatively, tendon pain may reflect an error in the internal calculation of tendon load. Several of the local dysregulations discussed here could contribute to erroneous load information. These ideas are speculative but not outrageous—that central evaluation of danger to body tissue modulates pain is well accepted (see Butler and Moseley [27] for review), and that internal comparators evaluate predicted and actual motor responses has been established for some time [189].

4 Conclusions

The molecular biology of tendon in pathological and healthy states highlights many potential contributors to

pain and the search for these needs to extend beyond the tendon. Nociception could occur from cell–cell signalling via ion channels that communicate with an afferent neuron that could transmit, suppress or amplify the nociceptive signal. Nociception may be modulated spinally or above and descending mechanisms may exert nociceptive pressure that manifest locally. Finally, pain could be evoked via non-nociceptive mechanisms through a load detection system, which itself could be disrupted via local or central dysfunction. The question of the pain of tendinopathy, physiological or pathophysiological, remains unanswered; however, there is evidence for both—tendon based nociceptive contributions and extensive mechanisms within the periphery and the CNS. Importantly for clinicians, tendon pain is complex and requires thorough assessment of both musculoskeletal and neural contributors as well as excellent clinical reasoning to account for nociceptive input from local tendon pathology as well as potential central mechanisms.

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Appendix D. Publication: Do isometric and isotonic exercise programs reduce pain in athletes with patellar tendinopathy inseason? A randomised clinical trial

Abstract

Objectives: Many athletes with patellar tendinopathy participate in sports with symptoms during or after activities. Current treatments do not decrease pain inseason; eccentric exercises inseason result in an increase in pain. This study examined if isometric and isotonic exercises relieved pain in competing athletes with patellar tendinopathy.

Design: Randomised clinical trial

Methods: Jumping athletes with patellar tendinopathy playing at least three times per week participated in this study. Athletes were randomised into an isometric or isotonic exercise group. The exercise programs consisted of four isometric or isotonic exercise sessions per week for 4-weeks. Pain during a single leg decline squat (SLDS) on a Numeric Rating Scale (NRS; 0-10) was used as the main outcome measure; measurements were completed at baseline and at 4-week follow-up.

Results: Twenty-nine athletes were included in this study. Median pain scores improved significantly over the 4-week intervention period in both the isometric group (Z=-2.527. p=0.012, r = -0.63) and isotonic group (Z=-2.952, p=0.003, r= -0.63). There was no significant difference in NRS pain score change (U = 29.0 p=0.208 r=0.29) between the isometric group (median (IQR), 2.5 (1-4.5)) and isotonic group (median (IQR), 3.0 (2-6)).

Conclusions: This is the first study to show a decrease in patellar tendon pain without a modification of training and competition load and the first study to investigate isometric exercises in a clinical setting. Both isometric and isotonic exercise programs are easy-to-use exercises that can reduce pain from patellar tendinopathy for athletes inseason.

Introduction

Patellar tendinopathy, also known as jumper's knee, is an overuse injury of the patellar tendon that causes pain and dysfunction. It is a common injury in sports that involve explosive movements that load the extensor mechanism of the knee.[1] High prevalence rates are reported in jumping sports such as volleyball and basketball (45% and 32% in elite athletes respectively).[1]

Many different modalities are used for the treatment of patellar tendinopathy, however treatments like injections, shockwave and surgery require athletes to cease sporting activities [2-4]. Exercise may be the best treatment for tendinopathies as histopathological changes and clinical improvements in pain and function have been demonstrated.[5] Most studies have been conducted using eccentric exercise protocols[6-8] and early studies showed positive results. However, eccentric exercises are not effective when used inseason and might even make symptoms worse in athletes with patellar tendinopathy.[7,9,10] Moreover, when eccentric exercise was used prophylactically inseason in asymptomatic soccer players with pathology on imaging, there was a higher risk of developing a jumper's knee.[11]

Many athletes play with jumper's knee symptoms and pain negatively affects capacity to train and perform in matches. They cope with their injury because pain often decreases after warm-up but returns and is worse the day after activity. Isometric and isotonic exercises have the potential to decrease pain while continuing sport activities.[12,13] Isotonic muscle contractions (heavy slow strength training 3-5 times per week) resulted in a significant reduction in pain after a 12-week program.[14,15] Isometric exercises have been found to decrease tendon pain in athletes with patellar tendinopathy in the short-term (45 minutes).[16] It is unknown if isometric exercises can decrease tendon pain over a longer period of time and if repeated isometric exercises are beneficial.

The aim of this study was to examine whether isometric and isotonic exercises relieve pain in competing athletes with patellar tendinopathy. It was hypothesised that both isometric and

isotonic exercises would decrease pain in athletes with patellar tendinopathy inseason and that isometric exercises would decrease patellar tendon pain more than isotonic exercises.

Methods

This study was a randomised trial of two interventions – participants were randomly assigned to one of two exercise intervention groups. The study was approved by the Monash University Human Research Ethics Committee (MUHREC), Australia (CF12/0230 – 2012000067). All participants provided written informed consent. This trial was registered in the Australian New Zealand Clinical Trial Registry (ACTRN12613000871741).

Participants were volleyball and basketball players (16-32 years) playing or training at least three times per week, presenting with patellar tendinopathy diagnosed by an experienced physiotherapist. Inclusion criteria consisted of focal tendon pain at the inferior or superior pole of the patella and a history of exercise associated knee pain at the same spot. Exclusion criteria were existence of other knee pathology, previous patellar tendon rupture, previous patellar tendon surgery, inflammatory disorders, metabolic bone diseases, type II diabetes, use of fluroquinolones or corticosteroids in the last 12 months, known familial hypercholesterolemia and chronic pain conditions.

Players from Victorian volleyball leagues and basketball leagues who played or trained at least three times per week were approached at their game or training venue. After baseline measurements were performed, participants were given an exercise program. Participants were randomised to an exercise program by the draw of a sealed opaque envelope from 40 identical envelopes that were randomised using a randomisation table created by computer software (20 in each group). The program was demonstrated (including repetition maximum testing) at the gym where they were going to perform their exercises. Every week participants

were followed-up in person or by phone, asking participants if they encountered any problems with the exercise program. After the 4-week exercise program baseline measurements were repeated.

Both groups performed a 4-week exercise program with exercises performed four times per week. The isometric and isotonic exercise program were matched for time under tension and rest. Pilot testing was used to ensure that the protocols were matched for rate of perceived exertion. The isometric exercise consisted of 5 x 45 second single leg isometric contractions of each leg on a leg extension machine. Isometric contractions were performed at 80% of maximal voluntary contraction with a knee joint angle of 60 degrees.

Isotonic exercise consisted of four sets of eight repetitions of single leg isotonic contractions of each leg on a leg extension machine. Isotonic contractions consisted of a three second concentric phase immediately followed by a four second eccentric phase and were performed on 80% of 8 repetitions maximum. After performing the exercises for each leg, participants rested for 15 seconds before continuing with the first leg again.

Weight was increased by 2.5% every week if possible. If pain was experienced during an exercise or if participants were not able to complete their repetitions with proper execution (e.g. shaking during the contraction), they were instructed to lower the weight for the following repetitions and complete the entire session (equal time under tension). Audio files that counted the timing of the exercises were provided for use during their exercises to standardise the speed of repetition and rest and therefore time under tension for all participants.

The primary outcome measure was pain during a single leg decline squat (SLDS) scored on a numeric rating scale (NRS) (0 -10), which is a provocative clinical test to monitor tendon pain.[17,18] The VISA-P, a questionnaire on pain and function of the knee,[19] was also completed. The score on the VISA-P ranges from 0-100, 100 being a completely asymptomatic and fully functioning athlete. Participants were asked about their average tendon pain compared to the

beginning of the exercise program on a global rating of change scale from very much worse (-4) to very much better (+4).

All outcome measures were administered at baseline and four weeks later at the end of the program. Only the worst knee was used in the analysis of the data in athletes with bilateral patellar tendinopathy.

NRS pain scores on the SLDS had a non-normal distribution, and non-parametric tests were used to test for differences. A Wilcoxon signed rank test was conducted to test for differences between baseline and follow-up measurements for NRS pain score during SLDS within each group. A Mann-Whitney U test was used to test for differences between the isometric and isotonic intervention group. As secondary analyses, the same tests were performed for the VISA-P score. Analyses were conducted using IBM SPSS Statistics 20 software and an alpha of 0.05 was considered significant.

Results

Participants were included in the trial between August 2013 and July 2014 (Figure 1). Thirteen participants were randomised to the isometric group and 16 to the isotonic group. Group characteristics did not differ at baseline (Table 1) and mean adherence to the exercise program was 81%. Median pain scores improved significantly over the 4-week intervention period within the isometric group (Z=-2.527. p=0.012, r = -0.63) and within the isotonic group (Z=-2.952, p=0.003, r= -0.63) (Table 2). There was no significant difference in NRS pain score change (U = 29.0 p=0.208 r=0.29) between the isometric group (median (IQR), 2.5 (1-4.5)) and isotonic group (median (IQR), 3.0 (2-6)) (Table 2). Median VISA-P scores also improved significantly over the 4 week intervention period within the isometric group (Z= -2.201, p=0.028, r=-0.55) and within the isotonic group (Z=-2.952, p=0.003, r=-0.66). There was no significant difference in VISA-P score change (U = 39.5 p=0.965 r=-0.01) between the isometric group and isotonic group (Table 2). The median perceived global rating of

change (-4 to +4) for tendon pain at follow-up compared to pre-intervention was +2.3 (2.0-3.0).

Discussion

This study showed a decrease in pain in athletes with patellar tendinopathy during a season with both isometric and isotonic exercises. The VISA-P also showed a significant improvement over time, which indicates that not only pain but also function of the knee improved in this population. No significant difference between the isometric and isotonic exercise group was found.

In the field of tendinopathy, where exercise is the primary and most effective treatment available,[20,21] relatively few studies have been conducted on exercise programs for patellar tendinopathy.[22] Improvements in pain have been reported when strength exercise/training is used as rehabilitation. Kongsgaard et al[14] showed a similar improvement in pain after 12 weeks of heavy slow strength training as our study. After 6 weeks of a heavy slow isotonic exercise rehabilitation program, Cannell et al[15] also found a decrease in pain. Other studies have focussed on eccentric exercises as rehabilitation, and these exercise protocols also relieved pain in non-competing athletes.[7,23,24] Eccentric exercise inseason has no effect or even worsens patellar tendinopathy symptoms.[7,9,10] The findings of our study using isotonic and isometric exercise are in contrast with eccentric exercises inseason.

Previous studies investigating short-term effects of isometric and isotonic exercises on (tendon) pain[12,16] have found a decrease in pain post exercise. Isometric exercises resulted in a significant decrease in tendon pain and cortical inhibition (present at elevated levels in patellar tendinopathy); pain relief lasted for at least 45 minutes after isometric exercises, while a much smaller decrease in pain and no change in cortical inhibition was found after isotonic exercises.[16] In contrast to these studies on the acute effects of isometric and isotonic exercise, our study found no difference between isotonic and isometric exercise after 4 weeks. Previous studies suggest it may be that isometric exercises have a greater effect in reducing

acute pain, while isotonic exercise may cause a more gradual decrease in pain.[15,16] How exercises affect pain is still unclear. An ongoing debate about pain in (patellar) tendinopathy exists; it is still unclear if pain is physiological or pathophysiological or a combination in patellar tendinopathy.[25]

Our study has an important contribution to the conservative management of patellar tendinopathy, in particular for inseason athletes with patellar tendinopathy. It also confirms the recent shift in the literature away from isolated eccentrics for the rehabilitation of patellar tendinopathy.[26,27] More high quality research in this field is needed to find the best treatment strategy for every phase of tendinopathy.[28]

The dosage and type of exercise are important characteristics of an exercise program. A high percentage of repetition maximum (RM) has been used in our study for the isometric (80% 1RM) as well as the isotonic exercises (80% 8RM). Beneficial effects from physical training for tendons require high load per repetition.[29] Furthermore, a high percentage of RM in leg extension exercises has been shown to improve muscle strength and neural activation.[30] The leg extension machine was used to isolate the load through the rectus femoris and patellar tendon as much as possible. The optimal dosage and loading strategy to reduce tendon pain still have yet to be determined. Despite the positive effect of exercise for tendinopathy, both in research labs and in the clinic, the precise mechanism of effect has not yet been determined and further research is required.

Our study had relatively small numbers in the intervention groups. Despite small group sizes, we found significant improvements in pain scores in both groups. There were no data on which to base an a priori sample size calculation, as this was the first study to compare these exercise programs. The group sizes in this study are similar to other studies investigating exercise programs for patellar tendinopathy.[22] The 4-week follow-up was relatively short as the study was designed to investigate if an (initial) decrease in patellar tendon pain could be

achieved in competing athletes. Another limitation was that sessions were not supervised and no random checks for compliance in the gym were performed. This was a real-life study, supervision of all patients was therefore not feasible and it reflects what is done in clinical practice. The chance to successfully implement the exercise programs in practice with a high adherence of the patient might also be greater than in studies with a more controlled environment.

Conclusion

This study was, to our knowledge, the first to find positive results for athletes with patellar tendinopathy without modification of the training and competition load and it was the first study to investigate isometric exercises in a clinical setting. Both isometric and isotonic exercise programs can reduce pain and improve function in athletes with patellar tendinopathy inseason.

Practical implications

- This study shows that isometric and isotonic exercises can decrease pain in athletes with patellar tendinopathy inseason.

- The exercises are easy to perform and also have the advantage over conventional eccentric training that they are less time-consuming for the athlete.

- The programs should be applied in a situation in which an athlete has pain inseason or in the first weeks after a patient comes to a sports medicine/physiotherapy clinic with patellar tendinopathy symptoms.

- Pain decrease in the relatively short term possibly increases the adherence of patients with a program and reduces the chance of transition to invasive and more expensive treatments.

Acknowledgements

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Table 1. Characteristics of the population

Characteristics	Isometric group *n=13*	Isotonic group *n=16*	Total *n=29*
Age, yr mean ± SD (range)	22.9 ± 4.9 (16-30)	23.1 ± 4.7 (17-32)	23.0 ± 4.7 (16-32)
Sex (male/female)	12/1	15/1	27/2
Duration of symptoms, months mean ± SD (range)	30.8 ± 26.1 (1-84)	39.6 ± 39.1 (1-120)	35.8 ± 33.8 (1-120)
BMI, kg/m^2 mean ± SD (range)	23.7 ± 2.0 (19.8-26.5)	24.2 ± 3.7 (18.9-34.7)	24.0 ± 3.0 (18.9-34.7)
Unilateral/bilateral symptoms	6/7	7/9	13/16

Table 2. Main outcome measures at baseline and follow-up for the intervention groups and
total population.

measurements	Isometric group	Isotonic group	Total
NRS pain SLDS – baseline median (IQR)	6.3 (5.3-7.0) *n=8*	5.5 (4.0-6.0) *n=11*	6.0 (4.0-7.0) *n= 19*
NRS pain SLDS – 4wk median (IQR)	4.0 (2.0-5.0)* *n=8*	2.0 (1.0-3.0)* *n=11*	2.0 (2.0-3.8)* *n=19*
VISA-P – baseline mean ± SD (range)	63.1 ± 22.4 (13-88) *n=8*	66.6 ± 12.1 (46-83) *n=10*	65.1 ± 16.9 (13-88) *n=18*
VISA-P – 4wk mean ± SD (range)	76.1 ± 17.0^* (41-100) *n=8*	78.7 ± 13.3* (59-98) *n=10*	77.6 ± 14.7* (41-100) *n=18*
Number of exercise performed per week, median (IQR)	3.0 (2.5-3.9) *n=9*	3 (2.75-3.75) *n=11*	3.1 (2.8-3.8) *n=20*
Tendon pain change compared to pre-intervention on GRC (-4 - +4), median (IQR)	+2.5 (.5-3.0) *n=9*	+2 (2-3) *n=11*	+2.3 (2.0-3.0) *n=20*

* Significant difference from baseline (p<0.05) ^Minimal clinical important difference from

baseline

IQR = Inter quartile range, GRC = global rating of change scale

Heel pain: a practical approach

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CPD

Background

Heel pain is a common presentation in primary care and the risk of developing pain is higher with increasing body mass index and age.[1] This is troubling given the increasing prevalence of obesity and an ageing population.

Objective

This article aims to assist with differential diagnosis of heel pain, which is critical as there are many structures in the heel area that can cause pain, and each requires a tailored treatment.

Discussion

Structures affected by pain vary with age, although the more common diagnoses such as Achilles insertional tendinopathy and plantar fascia pain can occur at any age. The use of diagnostic imaging must be considered in the context of clinical presentation as asymptomatic pathology occurs in many tissues. Evidence-based treatment for common causes of heel pain are limited. As with all presentations to clinicians, the potential for non-musculoskeletal, more sinister causes of pain and systemic disease must be considered.

Keywords

heel; pain; diagnosis; therapeutics

Heel pain is a vague term describing pain surrounding the calcaneus, most commonly felt posteriorly or inferiorly. Anatomically, the heel refers to the fatty tissue that forms a pad under and around the calcaneus to protect structures of the foot during weight-bearing activity.[2] However, patients consider a more broad area as their heel. This review, therefore, will consider the structures that may cause pain from the calcaneus, extending to both lateral and medial perimalleolar regions, the Achilles enthesis and proximal plantar fascia attachment. Most pain arises from pathology in soft tissue structures (tendons, fascia and nerves); apophyses and other sources of bony pain are less common. As with other soft tissue structures, pathology on imaging is not always correlated with pain and a good clinical examination is required to reveal the painful structure. Palpation pain is a poor diagnostic test in isolation, as many structures are painful on palpation without being the cause of symptoms. The history and further clinical examination remain important.

Sources of pain by structure

Tendons

The key tendons that may be involved in heel pain are the Achilles tendon at its insertion, flexor hallucis longus (FHL), tibialis posterior and the peroneal tendons (*Figure 1*). The medial and lateral tendons are surrounded by tenosynovial sheaths that can be irritated by friction or compression at the malleolus. Tibialis posterior pain (tendon and/or sheath) is most commonly seen in older women.[3,4] FHL tenosynovitis is seen in younger people, especially dancers because of the repetitive movement of the ankle and foot between extremes of plantarflexion and dorsiflexion.[5]

The Achilles insertion is a complex structure that includes the retrocalcaneal bursa.[6] All insertional pain should be treated

Table 1. Possible structures and sites of pain		
Site/type of pain	**Common sources of pain**	**Less common sources of pain**
Posterior	• Achilles tendon insertion • Superficial calcaneal bursa • Posterior impingement of soft-tissues/os trigonum in active people • Calcaneal apophysis in adolescents	• Sural nerve
Inferior	• Plantar fascia • Calcaneal fat pad	• Medial or lateral calcaneal nerve, especially as they split from the tibial branch
Medial	• Tibialis posterior tendon and sheath • Tibialis posterior insertion and apophysis in adolescents	• FHL and sheath • Abductor hallucis • Deltoid and spring ligaments • Posterior tibial nerve in tarsal tunnel (is associated with neural symptoms such as tingling) • Bone: medial malleolus
Lateral	• Lateral ligaments of the ankle • Sinus tarsi	• Peroneal tendinopathy or tenosynovitis associated with subluxation • Cubometatarsal joint • Peroneus brevis insertion/apophysis of base of 5th metatarsal in adolescents or after ankle sprain
Deep, vague pain	• Subtalar joint	• Bone pain: calcaneus, talus, navicular

FHL, flexor hallucis longus

Figure 1. Relationship of the calcaneus to neural structures and tendons (transverse view)

holistically as a tendinopathy, as the bursa is rarely affected in isolation.[7] The mid-substance and insertional Achilles tendon undergo similar histopathological change.[8] Excess compression of the tendon against the superior calcaneus in dorsiflexion is the provocative load; however, a Haglund morphology (a square superior prominence of the calcaneus) is common and complete resolution of symptoms can occur despite the anatomy.[9]

Peroneal tendinopathy is less common and is seen after acute ankle sprain or provoked by an insufficient retinaculum at the lateral malleolus, again increasing compression and friction loads. The plantar fascia, histologically indistinguishable from a tendon, is also a common source of pain, especially in older women who are more obese.[10]

Neural sources of heel pain: entrapment and referred pain

Pain from a neural source can mimic soft tissue pain. Neural sources of heel pain may include an entrapment that can occur proximally, for example, in the lower lumbar spine and gluteal region, or distally at the ankle retinacula. The posterior tibial nerve ends deep to the flexor retinaculum, then divides into the medial and lateral plantar (also termed calcaneal) nerves, where it is especially vulnerable. Pain from this source can mimic plantar heel pain.[11] Tarsal tunnel syndrome is an entrapment of the posterior tibial nerve under the flexor retinaculum. Rarely, sural nerve symptoms can be related to Achilles tendinopathy, resulting in posterior heel neural signs.

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Bone and joints

Calcaneal bone injury is rare in adults but can cause heel pain following either a traumatic fall from a height (fracture) or excessive weight-bearing such as running or marching (bone stress reaction or stress fracture).[12,13] Talar and navicular stress fractures are infrequent but considered high risk because of their propensity to progress to full fracture or result in non-union or delayed union,[14] which require lengthy periods of non-weight bearing or surgical management. The subtalar joint or the transverse tarsal joint may cause pain due to acute injury or arthritis.

Sources of pain by site

Differential diagnosis is complex, as there may be pain from more than one structure. The site of pain may be a guide to the structures involved (Table 1) and there are several key clinical history questions that will guide the clinician to the likely source of pain (Table 2). The most important questions to ask are 'Where is your pain? When did it start and what were you doing when it started?' Mechanical causes of heel pain are often brought on by a change in activity or a change in shoes. A specific incident or trauma to the region will guide further questioning around the forces and potential sources of pain.

Table 2. Subjective assessment questions to direct clinical reasoning		
Question	**Common responses**	**Diagnoses to consider**
Age	Young	Common: Sever's disease (calcaneal apophysitis) Uncommon: calcaneal stress or tumour
	Middle-aged	Common: Achilles insertion tendinopathy, plantar fascia pain
	Older	Common: tibialis posterior tendinopathy and lengthening
What aggravates the pain?	Mechanical causes (eg walking, running)	Insertional Achilles tendinopathy (note, a warm-up phenomenon with activity is reported) Pain that increases with activity may indicate: • involvement of sheath (paratendinitis) • bone (stress reaction or stress fracture) • sinus tarsi or neural sources (including tarsal tunnel); prolonged standing can irritate tarsal tunnel.
	Non-mechanical	Pain at rest should be questioned further in terms of positioning and neural symptoms Tendon pain at rest is uncommon but pain on rising after sitting is a hallmark sign of tendinopathy
Was the onset of pain associated with an incident?	Yes: change to weight-bearing load (eg running or footwear)	Achilles tendinopathy Calcaneal bone stress
	No	Consider arthritic causes
Pain behaviour	Morning pain and stiffness	Achilles tendinopathy, FHL tenosynovitis, plantar fascia pain Long time to warm up (>60 minutes): consider rheumatological cause
	Night pain	Bone stress (eg calcaneal stress or more sinister causes)
General health questions and red flags	Night pain Other flags such as loss of weight, night sweats, joint pain and swelling	Tumour Consider non-musculoskeletal cause and include rheumatoid arthritis, gout, spondyarthopathies, infection
	Past injury	Repeated ankle sprains can commonly cause posterior impingement and sinus tarsi syndromes
Other	Cramping (calf and feet)	Vascular claudication Can be an early indicator of bone stress
	Neural symptoms	Sharp pain, burning, 'pins and needles' or numbness indicate neural involvement (eg tarsal tunnel syndrome (posterior tibial nerve and branches) present with symptoms in posteromedial ankle and heel and may extend to distal sole and toes)

Figure 2. Simmonds' calf squeeze

With the foot relaxed squeezing the calf should elicit plantar flexion of the foot with an intact Achilles tendon

Figure 3. Posterior impingement test

Firm and slow compression of the calcaneus into the tibia will cause symptoms

Figure 4. FHL test

Active or resisted plantarflexion of the great toe in full ankle plantarflexion will provoke crepitus and possible pain

Table 3. Objective assessment	
Site/type of pain	**Common sources of pain**
Observation	Skin – colour, bruising, swelling, abrasions, rashes, Achilles tendon swelling / thickening or obvious deformity, muscle wasting
Functional – walking	Limping, avoiding joint movement or loading
Calf raise – double or single	Should be capable of lifting body weight on each leg at least 10 times. Inability to do this consider Achilles tendon rupture or tibialis posterior tear
Palpation	The sural nerve can be easily palpated lateral to the Achilles tendon with the ankle in dorsiflexion Sinus tarsi pain can indicate local and subtalar joint synovitis Plantar fascia attachment on the medial process of the calcaneal tuberosity Tibialis posterior and FHL tendons posteromedial to medial malleolus Apophyses such as calcaneal, navicular, base of 5th metatarsal • Note the Achilles tendon squeeze can be painful when the tendon is not the source of heel pain and is a poor diagnostic test Sites of bone stress: calcaneal squeeze for calcaneus, dorsal navicular and talar neck
Muscle strength	Resisted inversion in plantarflexion for tibialis posterior Resisted eversion for peroneals. Observe peroneal tendon does not sublux around lateral malleolus
Other – special tests	Specific tests such as the Simmonds' calf squeeze test for suspected Achilles tendon rupture (*Figure 2*) Posterior impingement test (*Figure 3*) and FHL testing (*Figure 4*) should reproduce symptoms Crepitus and clicking not always associated with symptoms Gentle palpation of the Achilles during active plantarflexion and dorsiflexion may demonstrate crepitus consistent with Achilles paratendinitis (sheath inflammation) Tinel's sign is well described and involves 4–6 taps over the nerve (such as sural or tibial) and should elicit 'pins and needles' or tingling
Neural testing	Straight leg raise with bias for peroneal nerve (add adduction, ankle plantar flexion and inversion) or tibial nerve (add dorsiflexion and eversion) Commonly – this may not reproduce the pain but an asymmetry can be noted Seated slump with lumbar kyphosis or lordosis

Following a thorough history taking, the potential sources of pain are identified and further objective assessment conducted to confirm the diagnosis (*Table 3*). Although some diagnoses are uncommon, they are important to recognise. Examples of these diagnoses include Achilles tendon rupture, which can be recent or chronic and presents with pain due to blood pooling distal to rupture, progressive tibialis posterior lengthening, seronegative arthropathies presenting as Achilles insertional tendinopathy, stress fractures, osteoid osteoma and tarsal coalition.

Bony presentations may require imaging when there is a high index of suspicion. Tarsal coalition may present with flat foot and pain, and requires imaging to confirm it, especially if the patient has a family history of the condition. Osteoid osteoma should be considered when night pain is reported.

The role of diagnostic imaging in heel pain

Clinical assessment remains the most important diagnostic tool as imaging identifies pathology and structural abnormality.

Table 4. Evidence-based and clinical opinion for management by cause		
Cause of pain	**Recommendations**	**No evidence or not advised**
Achilles tendon insertion pain or retrocalcaneal bursitis	Heel raises in shoes or added externally to shoes (to reduce compression at the Haglund prominence)	Avoid stretching and the eccentric heel drop program (due to compression). May be completed to plantargrade
	Graded strength rehabilitation from flat ground into plantar flexion	Intra-tendinous injections
	Other: polypill (ibuprofen, epigallocatechin gallate and doxycycline)[18]	Rest/ice/anti-inflammatory medications have limited efficacy: there is no evidence of inflammation in chronic tendinopathy
Posterior impingement syndrome	Calf strengthening – single leg heel raises, 25+ repetitions in a painfree range of motion in younger people Manual techniques that involve sub-talar joint distraction	Compressive positions or forced ankle joint plantar flexion
FHL (usually tenosynovitis)	Calf strengthening – single leg heel raises, 25+ repetitions in a pain-free range of movement in younger people Hirrudoid/diclofenac gel wrap – good clinical results with physiological justification (heparin based treatments block the formation of fibrin associated with crepitus[17]	Eccentric exercises and stretches in full dorsiflexion or heel off step
Neural – entrapment (including tarsal tunnel)	Neural mobilisation	Neural tension exercise
	Check for direct compression (eg footware)	
	Treat underlying pathology of FHL	
Plantar fascia pain	Taping and orthotics may offer relief Strengthening of the foot intrinsics, calf and kinetic chain Low height isometric heel raise sustained hold	
Tibialis posterior tendinopathy (may be tenosynovitis)	Taping and orthotics Heel raise Strengthening in good ankle alignment	Eccentric exercise often increases the friction around the medial malleolus and exacerbates symptoms
Calcaneal bone stress Talar stress fracture Navicular stress fracture	Reduction in load and may require non-weight bearing	
Apophysitis	Reduction in load May benefit from a heel cup with heel raise in shoes to reduce traction of the apophysis Taping and orthotics Graded strengthening program Improving muscle compliance of the gastrocnemius, soleus and tibialis posterior	Though stretching is regularly recommended, initially it is painful especially if felt at the insertion
FHL, flexor hallucis longus		

However, tendon and joint pathology can be present without pain. Therefore, pathology on imaging can mislead the clinician into thinking that imaging has confirmed the source of pain. Common examples include the presence of an os trigonum and heel spurs at the attachment of the plantar fascia and peroneal tendon pathology, seen as an increased signal on magnetic resonance imaging (MRI), which is common following an ankle inversion injury. Posterior ankle impingement syndrome and subtalar joint synovitis following an ankle sprain is a more likely source of pain (*Figure 3*). Similarly, pathology in the retrocalcaneal bursa and Achilles tendon, together with a Haglund morphology can be present in people who are pain-free.[15]

Treatment of heel pain

An overview of the available evidence and expert clinical opinion for the conservative treatment of common causes of heel pain is not intended to be comprehensive or prescriptive (*Table 4*). Clinical experience, for example neural mobilisation techniques,[16] has been included as there is a lack of published evidence for efficacious treatment. Furthermore, the decision to include analgesia or anti-inflammatory medication is discussed only where its use has been shown to be detrimental or to have an off-label effect (eg heparin-based treatments for paratendinitis[17] and the polypill).[18] Consideration of the kinetic chain is vital for the successful rehabilitation of many conditions and is outside the scope of this paper. Referral to allied health professionals such as physiotherapists or podiatrists may be necessary.

Conclusion

Heel pain is usually of mechanical origin and the most valuable approach for the clinician is to use the site of pain to narrow potential diagnoses. Imaging can assist, however should not replace clinician assessment. Treatments vary with presentation and require thoughtful prescription.

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Appendix F. Publication: Does the adolescent patellar tendon respond to five days of cumulative load during a volleyball tournament?

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Does the adolescent patellar tendon respond to 5 days of cumulative load during a volleyball tournament?

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Patellar tendinopathy (jumper's knee) has a high prevalence in jumping athletes. Excessive load on the patellar tendon through high volumes of training and competition is an important risk factor. Structural changes in the tendon are related to a higher risk of developing patellar tendinopathy. The critical tendon load that affects tendon structure is unknown. The aim of this study was to investigate patellar tendon structure on each day of a 5-day volleyball tournament in an adolescent population (16–18 years). The right patellar tendon of 41 players in the Australian Volleyball Schools Cup was scanned with ultrasound tissue characterization (UTC) on every day of the tournament (Monday to Friday). UTC can quantify structure of a tendon into four echo types based on the stability of the echo pattern. Generalized estimating equations (GEE) were used to test for change of echo type I and II over the tournament days. Participants played between eight and nine matches during the tournament. GEE analysis showed no significant change of echo type percentages of echo type I (Wald chi-square = 4.603, d.f. = 4, $P = 0.331$) and echo type II (Wald chi-square = 6.070, d.f. = 4, $P = 0.194$) over time. This study shows that patellar tendon structure of 16–18-year-old volleyball players is not affected during 5 days of cumulative loading during a volleyball tournament.

Patellar tendinopathy, also known as jumper's knee, is an overuse injury of the patellar tendon that causes load-related focal pain usually at the tendon insertion to the patella. Patellar tendinopathy causes pain and dysfunction predominantly in jumping athletes (Ferretti et al., 1984; Zwerver et al., 2011), which may result in cessation of sport (Kettunen et al., 2002). The prevalence in elite volleyball athletes is as high as 45% (Lian et al., 2005), while a prevalence of 14.4% has been reported in recreational volleyball players (Zwerver et al., 2011).

Patellar tendinopathy is diagnosed clinically, and confirmed with ultrasound imaging or magnetic resonance imaging. Although the presence of ultrasound abnormalities in a tendon is not directly correlated with pain (Khan et al., 1996; Lian et al., 1996), current literature suggests that athletes with structural changes in their tendon have a higher risk of developing patellar tendinopathy than athletes without structural changes (Cook et al., 2000b; Fredberg & Bolvig, 2002; Gisslen & Alfredson, 2005; Gisslen et al., 2007; Fredberg et al., 2008; Comin et al., 2013; Giombini et al., 2013; Visnes et al., 2014).

Tendon structure has been difficult to measure until recently, where higher level analysis of ultrasound images has allowed quantification of tendon structure. Kulig et al. (2013) used fast Fourier transformation of ultrasound images and showed that tendon structure on ultrasound (peak spatial frequency) could discriminate between athletes with and without patellar tendinopathy. Similarly, van Schie et al. (2003) developed an algorithmic enhanced ultrasound analysis [ultrasound tissue characterization (UTC)] that can quantify the structure of a tendon based on the stability of the echo pattern by calculating percentages of four echo types (echo type I being the most stable and echo type IV being the least stable echo type). UTC has been found to have good inter-tester reliability [intraclass correlation coefficient (ICC) > 0.9] in quantifying tendon structure (van Schie et al., 2010). It has also been shown that UTC can discriminate between symptomatic and asymptomatic Achilles tendons (van Schie et al., 2003); other validity data in humans are not yet available.

Many intrinsic and extrinsic factors may contribute to patellar tendinopathy and structural change. Extrinsic factors, especially excessive load through a high volume of training and competition, seem to be the most important risk factors (Visnes & Bahr, 2013). The amount of mechanical load placed on the tendon in sporting activities includes the intensity, volume, and frequency of patellar tendon loading; in this paper, this will be called tendon load. It is unknown how much tendon load it takes to result in patellar tendinopathy and structural

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change. Insufficient rest of the tendon after an acute bout of load might result in cumulative structural changes (Magnusson et al., 2010). The acute response of a tendon to load in a competitive sport setting has only recently been investigated in the Achilles tendon; structural changes were reported 2 days after an Australian football match (Rosengarten et al., 2015).

Intrinsic factors to be considered include age, body composition, and genetics (van der Worp et al., 2011; Salles et al., 2015). Of these factors, age seems to be an important factor. The relationship between structural changes and development of patellar tendinopathy symptoms seems more closely related in younger athletes than adults (Visnes et al., 2014). Additionally, several studies show a high prevalence of patellar tendinopathy in teenage athletes, which might indicate that young athletes are prone to develop patellar tendinopathy (Cook et al., 2000a; Gisslen et al., 2007; Cassel et al., 2014). Another intrinsic risk factor to be considered is sex; a different prevalence has been reported between male and female athletes (Lian et al., 2005; Zwerver et al., 2011).

The response of the patellar tendon to tendon load, how tendons react to a bout of cumulative high load, and if adolescents are susceptible to acute load-induced structural changes is unknown. To our knowledge, no previous studies investigated the response of a tendon during cumulative high bouts of loading during several days. The aim of this study was to investigate the response of the patellar tendon on UTC imaging during a 5-day volleyball tournament in an adolescent population (16–18 years old). Secondary aims of the study were to examine if patellar tendons of participants with hypoechoic abnormalities respond differently to tendon load than players without hypoechoic abnormalities and if the response to load varies by sex. A change in tendon structure during the tournament expressed by a decrease in echo type I and a coinciding increase in echo type II were hypothesized.

Materials and methods

Victorian teams playing in the top division in the Australian Volleyball Schools Cup (AVSC) were approached to participate in the study. AVSC is a competitive 5-day schools volleyball tournament. Six teams agreed to allow recruitment of players in their team. All participants provided informed consent and players aged 16 years or more were able to provide consent without parental approval. The study was approved by the Monash University Human Research Ethics Committee, Australia (CF13/2202 – 2013001164).

Standard anthropometric measures (height, weight, waist circumference) and a UTC scan were obtained at baseline (week before the tournament). Participants were asked if they had any knee pain and when answered "yes," their knee was assessed by a physiotherapist to establish if the participant had patellar tendon pain or another knee injury. The clinical assessment was done by taking a history and testing the pain location on a single leg decline squat (Purdam et al., 2003; Zwerver et al., 2007). Hypoechoic abnormalities in the patellar tendon were also recorded.

Hypoechoic abnormality was defined as a hypoechoic zone visible on gray-scale ultrasound image of the tendon in the transverse and sagittal plane.

A UTC scan of the patellar tendon was performed on every day of the tournament. Furthermore, participants were asked about their knee pain on each day. When participants indicated that they had pain on a particular day, the single leg decline squat was used as a patellar tendon pain provocation test. Participants were asked to estimate the percentage of points that they were playing (not substituted) and the number of sets and points played by their team was recorded. On the final day, the question "What was last week like compared to physical activity loading your knee in the last three months?" was asked to measure the subjective load on the knee. Participants were asked to answer this question on a 9-point global rating of change scale ranging from −4 (very much less activity) to +4 (very much more activity).

The UTC scan was obtained during the tournament days at one of three playing venues. A UTC machine has an ultrasound probe (SmartProbe 12L5-V, Terason 2000+; Teratech, Burlington, Maryland, USA) fixed in a tracking device (UTC Tracker, UTC Imaging, Stein, The Netherlands) to ensure a consistent transducer tilt angle in relation to the tendon. The tracker device moves the ultrasound probe automatically with a consistent speed perpendicular along the tendon long axis. An ultrasound image of the transverse plane of the tendon is captured every 0.2 mm over the length of the patellar tendon. The UTC software (UTC 2011, UTC Imaging) constructs the sagittal and coronal planes from the transverse images creating a 3D ultrasound data block (van Schie et al., 2010). The right knees of participants were scanned based on previous studies that showed that a majority of patellar tendinopathies in volleyball players occur in the right patellar tendon (Lian et al., 2003; Malliaras et al., 2006; Bisseling et al., 2008; Helland et al., 2013). Participants were scanned by one of two trained researchers (M. v. A., S. D.). Participants lay supine on a treatment bench; their knee was bent to an approximate 100° of knee flexion in which a clear image could be obtained with the ultrasound probe in the tracker perpendicular to the long axis of the tendon. A picture of the UTC scan set up is shown in Fig. 1.

The consistency of intensity and distribution of gray levels of images over a length of 4.8 mm (25 images) was quantified by using computer algorithms. Based on the consistency, four echo types were created for every transverse image. The four echo types range from the most stable echo pattern (echo type I) to the least stable echo pattern (echo type IV; van Schie et al., 2003, 2010). The tendon was analyzed from the apex of the patella to 20 mm distally; percentages of these echo types in this region of interest (RoI) were calculated. This RoI was chosen because pain and change of structure are normally localized in this area. To quantify echo types in this area, tendon contours were marked by a trained researcher (M. v. A.). All scans were de-identified before marking the contours to ensure the researcher was blind to participant and day of the scan. All scan contours were reviewed by both trained researchers to ensure consistency and poor quality scans were excluded. If consensus was not reached a third assessor made a final decision (6% of the scans).

This study examined echo types I and II because short-term changes in these echo types have been shown in previous studies (Rosengarten et al., 2015). Inter- and intra-observer reliability was assessed in 18 tendons.

Statistical analysis

Data were analyzed for normality, distribution of echo types I and II were found to be normal (Q-Q plots were assessed and Shapiro–Wilk tests were not significant). To establish if tendon structure was not fluctuating in the days before the tournament, a paired t-test was run. Echo type percentages from baseline and day 1 (Monday) measurements were compared.

Fig. 1. Setup of ultrasound tissue characterization scan of the patellar tendon.

Generalized estimating equations were used to test for change of echo type I and II over the tournament days. Separate models were run for echo type I and echo type II, with echo type as dependent variable. Participant (ID number) was used as subject variable. Main effect of time (days of the tournament) was determined. An exchangeable working correlation matrix was used.

To test for the secondary aims of the study, two models were run. In a second model, hypoechoic abnormality was added to the first model; the main effect of hypoechoic abnormality and interaction effect time by hypoechoic abnormality was determined. A third model was run adding sex to the first model; its main effect together with the interaction effect time by sex was determined.

Results

Forty-one players from six different teams were recruited (Table 1). Two participants were excluded from all data analyses because of poor quality scans due to anisotropy or imaging artifacts; each day, some scans were not analyzed because of their quality (Table 2). No significant changes were found between echo types on baseline and the first day of the tournament [echo type I: $t(27) = 1.441$, $P = 0.161$; echo type II: $t(27) = -1.083$, $P = 0.288$].

Every team played eight or nine matches during the tournament, with a mean (SD) of 28.0(2.8) sets. The mean estimated number of points played (not substituted) by an individual athlete was 871 ± 308 points. The subjective load on the knee during the tournament week compared with normal physical activity in the last 3 months was $+1.8 \pm 1.6$ on a 9-point global rating of

Table 1. Baseline participant demographics and tendon characteristics

Measure	Mean (SD)
Sex (M:W)	30:11
Age (years)	17.2 (0.8)
Height (cm)	180.8 (7.3)
Weight (kg)	73.6 (11.2)
Number of times volleyball normal week	2.7 (1.5)
Hypoechoic abnormality (yes:no)	14:25
Patellar tendon pain before tournament (yes:no)	8:33
Patellar tendon pain at least 1 day of tournament (yes:no)	15:26
Echo type I (%) $n = 30$	58.7 (11.4)
Echo type II (%) $n = 30$	39.4 (9.8)
Echo type III (%) $n = 30$	1.6 (2.8)
Echo type IV (%) $n = 30$	0.3 (0.5)

SD, standard deviation.

change scale, indicating an increase in knee load. Four participants indicated that the tournament week was less physical activity loading their knee.

Eight participants reported patellar tendon pain at baseline; an additional seven reported patellar tendon pain on one or more days during the tournament. Fourteen of the 39 analyzed tendons showed hypoechoic abnormalities. Eleven of those 14 also reported pain on at least 1 day of the tournament. Four participants reported patellar tendon pain but did not show hypoechoic abnormalities. Twenty-one participants did not have patellar tendon pain or hypoechoic abnormalities.

The echo type percentages were calculated for each day of the tournament (Table 3). There was no

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Table 2. Number of scans completed each day of the tournament

	Scans completed	Scans included	Scans excluded (low quality)*
Baseline	41/41	30/41	11/41
Monday	41/41	37/41	4/41
Tuesday	41/41	37/41	4/41
Wednesday	39/41	36/39	3/39
Thursday	40/41	32/40	8/40
Friday	38/41	32/38	6/38
Total	240/246	204/240	36/240

*It was not possible to obtain a good scan on every day for two participants.

significant change in echo types over the 5 days of the study [echo type I: Wald chi-square = 4.603, d.f. = 4, $P = 0.331$; echo type II: Wald chi-square = 6.070, d.f. = 4, $P = 0.194$ (Fig. 2)].

When hypoechoic abnormality was added to the model, a significant difference in echo type I percentages in those with and without a hypoechoic abnormality was found (Wald chi-square = 16.545, d.f. = 1, $P < 0.001$); however, this was not the case for echo type II (Wald chi-square = 2.864, d.f. = 1, $P = 0.091$). The way echo type I (Wald chi-square = 3.853, d.f. = 4, $P = 0.426$, Fig. 3) and echo type II (Wald chi-square = 4.205, d.f. = 4, $P = 0.379$) changed over time was not significantly different between participants with and without hypoechoic abnormalities.

There were no significant differences between men and women for echo type I (Wald chi-square = 1.818, d.f. = 1, $P = 0.178$) and echo type II (Wald chi-square = 3.401, d.f. = 1, $P = 0.065$). No difference between men and women in the way echo type I percentages changed over time was found (Wald chi-square = 3.457, d.f. = 4, $P = 0.484$); however, the way echo type II percentages changed over time was significantly different for men and women (Wald chi-square = 12.270, d.f. = 4, $P = 0.015$). They showed a similar minor increase over 5 days but day-to-day differences between men and women.

Reliability tested in 18 tendons showed an ICC for intra-observer reliability of 0.82 (0.66–0.91) for echo type I and 0.82 (0.65–0.91) for echo type II with a mean difference of 0.6% and a SD of 5.8 for echo type I and the same mean difference with a SD of 5.9 for echo type II. The ICC for Inter observer reliability was 0.73 (0.49–0.91) with a mean difference of 2.2% for echo type I and 0.73 (0.49–0.87) with a mean difference of 2.1% for echo type II and a SD of 7.1 for both echo types.

Discussion

This study investigated the effect on tendon structure of cumulative loading of the patellar tendon in a competitive high loading volleyball environment. This study showed no change in the echo pattern of the

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Table 3. Mean (SD) percentage of echo types I and II during tournament days

	Total population		No hypoechoic abnormality		Hypoechoic abnormality		Men		Women	
	% Echo type I	% Echo type II	% Echo type I	% Echo type II	% Echo type I	% Echo type II	% Echo type I	% Echo type II	% Echo type I	% Echo type II
Monday	54.5 (10.3) n = 37	43.2 (8.9) n = 37	57.3 (9.0) n = 24	42.3 (8.8) n = 24	49.4 (11.1) n = 13	44.9 (9.1) n = 13	55.8 (10.2) n = 28	42.2 (9.3) n = 28	50.7 (10.3) n = 9	46.2 (7.0) n = 9
Tuesday	53.3 (8.9) n = 37	44.2 (8.2) n = 37	55.6 (8.1) n = 23	44.0 (7.8) n = 23	49.6 (9.2) n = 14	44.5 (9.2) n = 14	54.0 (9.4) n = 28	43.9 (9.1) n = 28	51.2 (7.2) n = 9	45.0 (5.4) n = 9
Wednesday	54.3 (9.1) n = 36	43.1 (8.0) n = 36	57.8 (8.0) n = 23	41.6 (7.7) n = 23	48.0 (7.7) n = 13	45.7 (8.2) n = 13	55.6 (9.5) n = 28	41.5 (8.0) n = 28	49.5 (5.4) n = 8	48.7 (5.5) n = 8
Thursday	51.7 (11.4) n = 32	45.6 (9.5) n = 32	55.3 (11.0) n = 21	44.3 (10.7) n = 21	44.9 (9.2) n = 11	48.2 (6.3) n = 11	52.7 (10.8) n = 25	44.8 (9.6) n = 25	48.3 (14.0) n = 7	48.5 (9.0) n = 7
Friday	52.4 (12.3) n = 32	45.1 (10.2) n = 32	57.9 (7.9) n = 20	41.8 (7.7) n = 20	43.3 (13.3) n = 12	50.5 (11.8) n = 12	53.0 (12.9) n = 24	44.3 (10.4) n = 24	50.7 (11.0) n = 8	47.4 (9.7) n = 8

SD, standard deviation.

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A significantly different change of echo type II over time was found between men and women. When looking at the descriptive statistics, men and women seem to show the same trend for echo type II percentages over time. Small day-to-day differences in echo type II between male and female participants might have caused this significant finding by chance.

Limitations

A small number of scans were not good enough to analyze. Any ultrasound scan can vary in quality because of movement artifact, poor contact, hair, sweat, and skin contour. A UTC scan of insufficient quality will have an overrepresentation of echo types II, III, and IV because artifacts and not the structure of the tendon will cause inconsistencies. Therefore, poor quality scans (15%) were excluded from the analysis.

Furthermore, although previous studies on the Achilles tendon (van Schie et al., 2010) and current data on the patellar tendon show good reliability, we recommend further research on the reliability of the UTC in the patellar tendon on a larger population.

Perspectives

This is the first study to investigate the effect of cumulative loading over several days in the patellar tendon in a real-life setting. Similar research has been completed in the Achilles tendon (Rosengarten et al., 2015). The current study shows that 5 days of cumulative loading during a schools volleyball tournament is not detrimental for the structure of the tendon of 16–18-year-old athletes. However, sub-groups that show a decrease in structure of the echo pattern after cumulative loading might exist, for example, athletes with preexisting hypoechoic abnormalities. An implication for volleyball organizations is that 5 days of consecutive loading is not detrimental to patellar tendon structure. Further research in this area should focus on different tendon loads and subgroups to find out what the critical load for tendon structure change is. This study should, for example, be replicated in elite athletes and a population with patellar tendinopathy to see if this shows different results.

Key words: Patella, tendinosis, grayscale, hypoechoic, pain, sports medicine.

Conflicts of interest

Jill Cook is a director and shareholder in Trackside Technologies, the applicant of a patent directed to using ultrasound to monitor connective tissue and compositions for treating connective tissue.

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pain; other studies had subjects with tendon pain and abnormality in their study. Another reason for different findings might be that this is the first UTC study on the patellar tendon; all other studies in humans have been performed on the Achilles tendon. It is likely that a different echo type distribution exists between tendons; more research is needed to confirm this. Furthermore, the number of studies using UTC is still small. Values for percentages of echo types I and II also differ per study performed with UTC. This study showed a higher percentage echo type II than any of the other studies using UTC (van Schie et al., 2010; de Vos et al., 2011, 2012; Rosengarten et al., 2015). Rosengarten et al. (2015) showed a much higher percentage of echo type I (92%) compared with this study, other studies showed lower percentages of echo type I (34–49%). It is not possible to draw conclusion from these differences because UTC echo type percentages are not comparable between studies unless exactly the same settings and UTC model have been used.

The results of the analyses with window size 25 were used in this study because this window size was also used in previous studies using UTC. Post-hoc analyses were also performed with window sizes 17 and 9. Change in echo type percentages over time was not statistically different when analysis was performed using different window sizes (results not shown).

Many practical issues are involved in conducting a cohort study such as this where the environment is hard to control. However, the advantage of investigating the response of a real-life tendon load outweighs the disadvantage of not being able to control all aspects. Access to players was sometimes hampered by coaches who wanted to instruct their players, who in turn were distracted by the tournament environment and the varying duration and venues of games. Finding a suitable time for a UTC scan of participants was one of the logistical challenges. Most scans were performed after the first match of the day. Although previous studies have shown an immediate decrease in anterior-posterior tendon diameter immediately post-exercise (Wearing et al., 2014), mechanical loading seems to take some time to exert effect on the structure of the tendon detected by UTC. A review on the response of a tendon to loading proposed that the metabolic response peaks only 24 h after mechanical loading (Magnusson et al., 2010) In addition, no changes in echo types were found 1 day after an Australian football game, while there was a change in structure 2 days after a game (Rosengarten et al., 2015). As tendon structure is not immediately affected by exercise as tendon dimensions are, a variable time of day (of the UTC scans) will probably not have influenced the outcome for this study.

One of the most important variables to influence tendon structure is the load on the patellar tendon (Visnes & Bahr, 2013). Objective and subjective data showed that the tournament was a heavy load. We objectified the tendon load by calculating the total number of games, sets, and points played including an individual estimation of total number of points played every day. This showed that on average, 871 ± 308 points were actually played by an individual during the 5 days of the tournament over eight or nine matches. This was much more than the participants' average number of times playing volleyball in a normal week (2.7 ± 1.5), often including only one match. To see if the participants also subjectively reported a high load a question was asked about their perceived knee loading during the tournament compared with a normal week. The results showed that most participants also perceived the tournament as a high load for their knees. Tendon load will have differed between participants of the study because the number of jumps varies between players (Bahr & Bahr, 2014); however, the data showed that overall the tournament was a high load for the participants.

Preexisting hypoechoic abnormalities on ultrasound might cause a different response of the patellar tendon to tendon load. Secondary analyses showed a significant difference in echo type I percentage between athletes with and without hypoechoic abnormality. This confirms the relation between UTC and gray-scale images. It also seems to be in line with van Schie et al. (2010), when taking into consideration that 11 of the 14 athletes also experienced patellar tendon pain. van Schie et al. (2010) found that UTC discriminated between symptomatic and asymptomatic Achilles tendons. The difference between athletes with and without hypoechoic abnormalities was not significant for echo type II, the difference in findings between echo types I and II might be explained by the fact that symptomatic tendons show higher values of echo type III and IV than controls (van Schie et al., 2010). A lower percentage of echo type I is not necessarily related to an increase in echo type II. Although the effect of preexisting hypoechoic abnormalities over time was not significant, it is worth noticing that a tendency was seen for athletes with hypoechoic abnormalities to have a different response to tendon load than athletes without hypoechoic abnormalities. Cumulative tendon load seems to decrease the stability of echo patterns in athletes with existing hypoechoic abnormalities while athletes without abnormalities do not seem to change in overall echo pattern. This seems to confirm previous findings that the presence of ultrasound changes increases the risk of developing patellar tendinopathy symptoms (Cook et al., 2000b; Fredberg & Bolvig, 2002; Gisslen & Alfredson, 2005; Gisslen et al., 2007; Fredberg et al., 2008; Comin et al., 2013; Giombini et al., 2013; Visnes et al., 2014). When comparing participants with and without tendon pain at least 1 day of the tournament post-hoc, the same trend was observed. This is not surprising because 79% of the participants with hypoechoic abnormalities also reported tendon pain.

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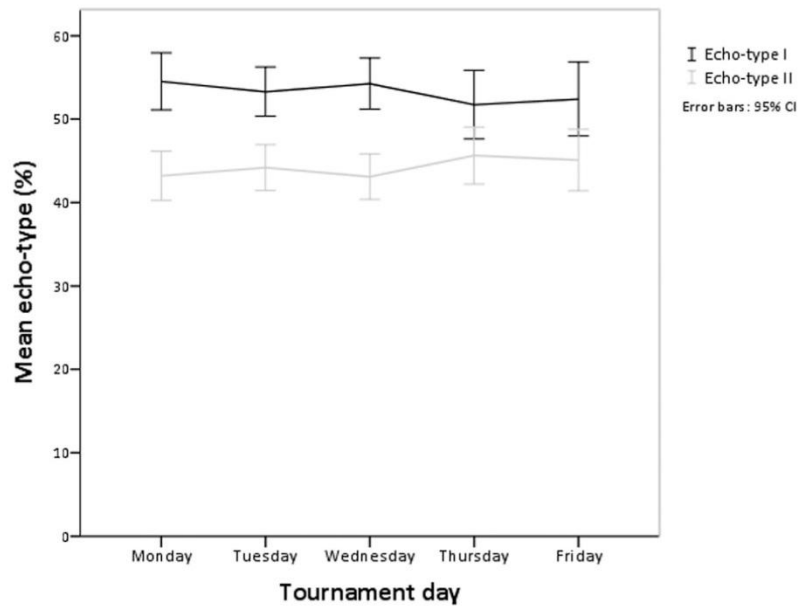
Fig. 2. Mean echo type I and II percentages during tournament days.
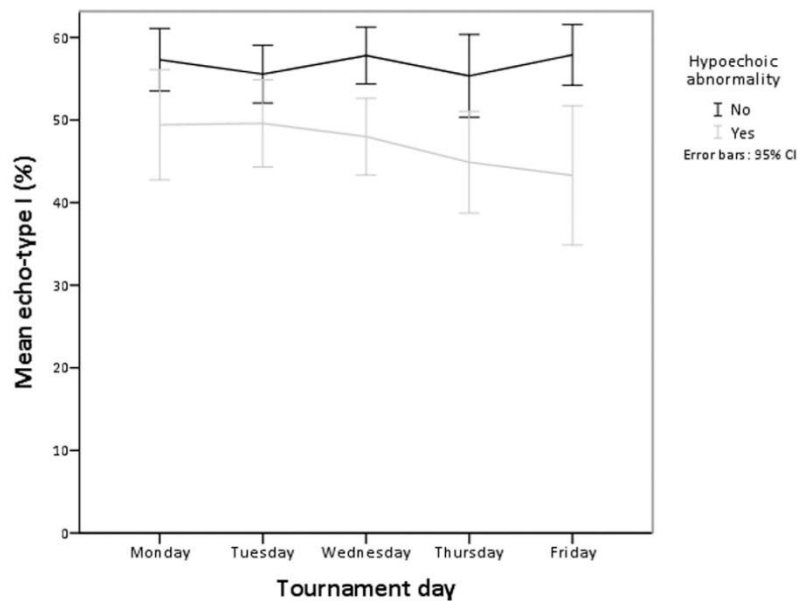
Fig. 3. Mean echo type I during tournament days for athletes with and without hypoechoic abnormalities at the start of the tournament.

patellar tendon of adolescent volleyball players over several days of cumulative loading during a volleyball tournament.

Based on previous studies, we hypothesized change in tendon structure during the tournament expressed by a decrease in echo type I and a coinciding increase in echo type II. Achilles tendon structure on UTC after an Australian football match showed a decrease in echo type I and an increase in echo type II after 2 days and a return to baseline values 4 days after the match (Rosengarten

et al., 2015). A similar change in echo types on UTC imaging was found in superficial digital flexor tendons of thoroughbred racehorses after loading (Docking et al., 2012). On the contrary, in recreational runners, a difference in Achilles tendon structure on UTC imaging 2 and 4 days after a 10-km run was not found (Wong et al., 2014). The differences in findings between the studies can partly be explained by the difference in characteristics of the population. For example, Rosengarten et al. (2015) investigated participants without Achilles tendon

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Original article

Relationship between compressive loading and ECM changes in tendons

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Summary

Tendons are designed to absorb and transfer large amounts of tensile load. The well organised, strong yet flexible, extracellular matrix allows for this function. Many tendons are also subject to compressive loads, such as at the entheses, as the tendon wraps around bony protuberances or from internal compression during tensile loading or twisting. Tendinopathy, the clinical syndrome of pain and dysfunction in a tendon is usually the result of overload. However, it is not only the tensile overload that should be considered, as it has been shown that compressive loads change tendon structure and that combination loads can induce tendon pathology. This review summarises how load is detected by the tenocytes, how they respond to compressive load and the resulting extracellular matrix changes that occur. Understanding the effect of compression on tendon structure and function may provide directions for future matrix based interventions.

KEY WORDS: compression, extracellular matrix, tendon, tendinopathy.

Tendon ECM changes and compression

Tendons are exposed to different types of load during normal function. Tensile load is the prime load that tendons endure, often functioning as elastic tissue to decrease the metabolic costs of high level function. In addition to tensile loads, compressive load is high at the enthesis and at points where the tendon has bony contact[1]. Pathology at these points of compression is common and some features of pathology in tensile and compressed regions are similar to fibrocartilage, which is a normal response to compressive load. To fully understand this response to compressive load, it is important to briefly review the structure of normal tendon.

Normal tendons are a three dimensional network of tendon cells (tenocytes), interspersed between tightly packed collagen fibres that are orientated along the line of tensile loading[2]. Also present in the extracellular matrix (ECM) are proteoglycans, glycoproteins and water as well as a range of enzymes, growth factors and cytokines.

Tenocytes synthesise all ECM proteins of tendon tissue[3] and are capable of expressing different phenotypes in response to differing mechanical stimuli[4]. The synthesis of the ECM components is based on load applied, therefore there is variation in tendon architecture and composition along the length of tendons and in tendons with different functions (e.g. elastic storage compared to positional tendons)[5]. The difference in structure in tendons that are subjected to differing mechanical stimuli clearly demonstrates a capacity of the tendon and its cell to detect and respond to load.

Cook and Purdam[1] examined the evidence for compression in the development of overuse tendinopathy and highlighted the many tendons subject to compression, particularly close to their insertion into bone. Tendons that develop tendinopathy where compression is an important factor include the Achilles insertion, proximal hamstring, tibialis posterior, biceps long head, supraspinatus, gluteus medius and minimus, adductor longus/rectus abdominus, peroneal tendons, quadriceps and pectorals. Given that most tendons are affected by compression, it is timely to review the cellular and matrix response to compressive loads. To understand the response, it is important to first appreciate how tendons detect, respond and transduce mechanical stimuli.

Overview of mechanotransduction in tendons

Mechanotransduction describes the conversion of a mechanical stimulus to a biochemical response and is important in tendon remodelling. The exact mechanisms by which tenocytes detect mechanical stimuli and thereby alter the ECM remains poorly understood[2]. It has been shown that the composition and tendon mi-

cro-architecture is continually adapting to the loads applied or removed, and that this adaptive process is driven by the tenocyte.

Tenocytes are sparsely distributed spindle shaped cells located end to end in rows in channels between collagen fibres. Tenocytes possess numerous cell processes extending between the cells in the rows and between rows of cells allowing communication between cells via the cell processes and gap junctions[6]. These gap junctions allow rapid exchange of ions and signalling molecules between cells, which can induce stimulatory and inhibitory responses to tensile load[7]. Whether these gap junctions play a role in compressive load is yet to be determined.

Tenocytes not only respond to mechanical loads[8] but to local stimuli (e.g., hydrostatic pressure changes, cytokines and growth factors)[9]. Different types of mechanical load may activate tenocytes differently (e.g. shear stress compared with substrate strain)[10]. That is, both the type and magnitude of the load may elicit a different cellular response.

The tenocyte has a number of mechanisms for detecting the mechanical environment such as their internal cytoskeleton, cellular projections (cilia), cell-cell communication and local/circulating chemical messengers. In the 1990's, Ingber described the 'tensegrity' model in an attempt to understand mechanotransduction and the role of cell deformation and the cytoskeleton[11-13]. The internal cytoskeletal structure forms a network of struts and cables that are placed in a state of isometric tension, due to the forces applied on the cell by the surrounding ECM, allowing the cell to be responsive to mechanical stresses. When under tensile strain, Type I collagen production is up-regulated in cultured tenocytes, however when the cytoskeleton is disrupted with cytochalasin D, collagenase mRNA expression is shown to be upregulated indicating increased catabolism[14]. This three dimensional internal network can detect and respond to tensile strain; however the ability of the cytoskeleton to detect compressive stresses has not been investigated.

Primary cilia, solitary finger-like immotile projections that extend from the cell surface into the extracellular environment, have been observed in almost two-thirds of all tenocytes[2] and have a role in detecting tensile load. Cilia are microtubule based sensory organelles and shown to be aligned parallel to the collagen fibres forming a cantilevered beam with adhesions to the fibrillar matrix[2]. The cilia have been shown to deflect in response to tensile loading and lengthen when deprived of stress suggesting these cellular projections play an important role in detecting load[15, 16]. Although, it is not known how cilia react to compressive load in the tendon. In other tissues such as bone, cilia has been shown to detect fluid flow[17, 18], and this may be increased with compressive load.

How does tendon react to compression?

Pauwels[19] described connective tissue differentiation (fibrous, fibrocartilage, cartilage and bone) in response to differing mechanical stimuli, which as a result deter-mines the expression of an appropriate form of connective tissue. Tissues respond to different loading parameters by altering their matrix structure to be suitable to transmit and absorb the applied loads[20]. Tendon, designed primarily to withstand tensile load, demonstrates several adaptive responses when subjected to compression. A substantial change in tendon composition and structure adjacent to a bony prominence has been described where the tendon is subjected to compressive forces. Gillard et al.[21] demonstrated fibrocartilage at the compressive region (where the tendon wraps around the calcaneus and talus) within the normal flexor digitorum profundus tendon of the rabbit, with a return to normal fibrous tissue upon removal of compression through surgical intervention. Milz et al.[22] also showed in the Achilles tendon that areas of fibrocartilage at, and proximal to, the insertion were normal adaptive changes.

What is the structure of compressed tendon (fibrocartilage)?

Tenocytes alter their phenotype as a result of compressive forces by becoming more rounded (chondrocytic) and express cartilage-like matrix proteins such as large proteoglycans and Type II collagen. They protect themselves by their position in lacunae and also by releasing large proteoglycans that slow the dissipation of fluid and reduce fluid shear stress (CJ Handley, personal communication[23]). Large proteoglycans such as aggrecan and versican are found in higher concentrations in both compressed and pathological tendon. This suggests that compression may be critical in the overload that drives the onset of pathology. These large proteoglycans may help with cell and/or tendon protection by limiting loads on the cell and decreasing stress on the tendon. Small proteoglycans are still synthesised by the tenocytes, but there is a greater predominance of large proteoglycans. In addition to the ongoing slow production of Type I collagen, there is some production of Type II collagen in the areas subject to compression within tendons[24]. Whether this production also exists in tendon pathology where compressive overload is a factor, is not yet known.

When does adaptation to compression become pathological?

A naturally occurring response to compressive load resulting in fibrocartilage occurs when tendon sustains compressive loads near a bony prominence that are not excessive but due to the normal positional and functional demands. The fibrocartilage is essential to allow the tendon to both tolerate the compressive load and maintain capacity to act in conjunction with the tensile load bearing part of the tendon.

When the compressive loads are excessive and/or suddenly increased in magnitude or volume, then tendinopathic changes occur. The cell and matrix changes in tendon pathology are described extensively. These

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Table 1. Differences between fibrocartilage and tendon pathology (Reproduced with permission from Cook and Purdam: Is compressive load a factor in the development of tendinopathy?. British Journal of Sport Medicine 2012; 46:53).

	Normal tendon	Fibrocartilage	Pathological tendon
Cells	Few spindle shaped cells	No cell proliferation Cells rounder	Cell proliferation Cells rounder, more endoplasmic reticulum
Proteoglycans	Minimal mostly decorin and biglycan	5-10-fold higher than in tensile tissue, mostly aggrecan	3-fold higher than tensile tissue, 25-fold higher metabolic rate of normal tendon[32] Biglycan and aggrecan increase, decorin maintained[33]
Collagen	Predominately Type I	Type I & II	Type I collagen, some Type II, substantial increase in Type III collagen
Collagen structure	Ordered collagen network	Ordered collagen network	Disorganised collagen network
Vascularity	Minimal	None to minimal	Variable but can be abundant

changes include cell activation and proliferation, which leads to substantial matrix changes[25]. The cell proliferation drives a rapid increase in the production and degradation of large proteoglycans, with a half-life of around 2-3 days[26, 27]. The cells preferentially synthesise Type III collagen (some Type I and II is produced also) leading to increased collagen turnover. As Type III collagen is thinner and less capable of fibril formation, collagen disorganisation and neurovascular ingrowth results[28].

These changes associated with pathology are sometimes referred to as fibrocartilaginous metaplasia[29, 30] due to the similarity to fibrocartilage[31]. However, despite the role of compressive stresses in pathology and the obvious similarities between tendon pathology and fibrocartilage, the term fibrocartilaginous metaplasia in reference to pathology is incorrect due to key differences as listed in Table 1.

Compressive loads, in isolation and in combination with tensile load have been investigated for their ability to induce tendon pathology. Soslowsky et al.[34] investigated the effect of different loads on rat supraspinatus tendon and examined the effect of compressive load, tensile load and the combination of both. They showed that compressive load (by interposing tissue between the tendon and acromion) in itself had minimal effect in the tendon, tensile load (running downhill) was clearly detrimental, but the combination of loads was especially damaging to the tendon[35]. Increased cross-sectional area and decreased mechanical properties were maximal in tendons exposed to both compressive and tensile loads. This has immediate clinical relevance as many tendons are subject to an environment of both tensile and compressive loads in relative combinations.

How does this relate to tendinopathy?

Normal adaptation to compression is present within the tibialis posterior tendon as it passes posterior to the medial malleolus and presents as an appropriate model for understanding compression in the development of tendinopathy[36, 37]. Within these areas of fibrocartilage the presence of aggrecan binds with water, slowing the permeability of fluid and protecting the fibrillar and cellular components of the tendon from lateral forces[23]. In contrast, the tensile region of the tendon is proposed to have higher fluid permeability due to low concentrations of aggrecan, allowing the tendon to withstand high tensile load. However, this zone of fibrocartilage is not well demarcated and a zone of transitional tissue exists between the two mechanical distinct regions. As this transitional zone is unsuited to compressive loads, this area of tendon may be implicated in the development of tendinopathy. If excessive loading (tensile, compressive or more likely combination load) is placed upon tendon, this may lead to the flow of fluid and the depletion of bound water within the high fluid permeability areas (tensile and transitional zones). Grigg et al.[38] reported a reduction in the Achilles tendon AP diameter at these high fluid permeability areas (mid-substance of the tendon) as a result of repeated eccentric load. In pathological tendons, which have been shown to contain high levels of aggrecan, this alteration in AP diameter was not observed[38].

The movement and loss of water through the tendon may expose the tenocyte to compressive load. In response to the loss of water from the tendon, the tendon may synthesise and release large water binding proteoglycans in an attempt to maintain homeostasis. This process has been shown to occur in a pathological state and occurs within days[39]. As previously discussed, this would bind water to the matrix and protect the cellular and fibrillar components of the tendon against future insult by reducing the permeability of water through the matrix. Further loading to the tendon may perpetuate the response and result in extensive disorganisation of structure[40]. Pathological features similar to fibrocartilage (cell rounding, aggrecan deposition) have been induced in the supraspinatus tendon in the rat within the transitional zones normally occupied by normal spindle shaped tenocytes[41].

Compression may not only occur as a result of the tendon being adjacent to a bony prominence, but occur

during tensile loading such as in the midsubstance of the Achilles tendon. Lavagnino et al.[42] developed a finite computational model to measure mechanical stresses placed on the cell during tensile strain. Cellular tensile strain was suggested to be similar to the strain on the tendon yet shear stress (perpendicular to the long axis of the tendon) was significantly increased when strain rate was increased. The reason for this lateral shear stress was suggested to be due to fluid flow perpendicular to tensile strain. This increase in lateral compression placed on to the tenocyte may help explain why high elastic storage (high strain rate) movements are deleterious to the tendon and implicated in tendinopathy[34, 43] yet heavy slow resistance loads (low strain rate) are more beneficial[44].

In summary, tendons adapt to the loads placed on them either with normal adaptive responses or with a pathological response. The exact mechanisms that lead to adaptation versus pathological change are not completely understood but are likely to be related to the frequency and type of load (with a combination of tensile and compression load being the most provocative). Characterisation studies of the clinical and imaging presentation of tendinopathy at various tendons[45, 46] identify the site of compression adjacent to the tendon insertion as a predominant site of pathology, strongly suggesting that compression is an important consideration in the development and management of tendinopathy. Compression to the tendon is not solely isolated to the insertion and can occur due to normal anatomical bony prominences away from the insertion, due to alterations in biomechanics that induce compression from an adjacent bony prominence or changes to fluid flow and matrix structure. Compression is not responsible for all tendinopathies as some tendons lack a nearby bony prominence (e.g. flexor tendons of the forearm, proximal insertion of the patellar tendon). However, clearly compression appears to be implicated in pathology and results in substantial changes to the structure and function of the ECM and therefore of the tendon. Opportunities to reduce compressive loads on the tendon, especially when in combination with tensile loads may prevent a deleterious tendon response.

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Appendix H. Publication: Junior Australian football injury research:

Are we moving forward?

Literature review

Junior Australian football injury research: Are we moving forward?

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ABSTRACT

Summarise the progress of junior Australian football (AF) injury research in line with the six stages of the 'Translating Research into Injury Prevention Practice' (TRIPP) model, in order to direct future research for the area. Systematically searched narrative review. Bibliographic research databases (Medline, PubMed, Scopus, and SPORTDiscus™) were used to search for original studies in which injuries in junior AF players were investigated. 18 studies (NHMRC levels of evidence ranging from NHMRC II–IV) addressed junior AF injuries within the TRIPP model. Injury surveillance (stage 1) was represented by five studies, aetiology and mechanism of injury (stage 2) was represented by various contributions from 12 studies, and injury prevention (stages 3–6) was represented by five papers. All papers addressing TRIPP stage 1 suffered from methodological discrepancies and inconsistencies in the data that are reported. Hence, a consistent injury definition and ongoing injury surveillance remains a priority. Injury research at the junior level of AF is predominantly situated at stage 2 of the TRIPP process. It can be postulated that most junior AF injury prevention programs are based upon senior AF research and anecdotal evidence due to the paucity of studies addressing stages 3–6.

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1. Introduction

Australian football (AF) is a collision sport played on natural grass with very high injury rates in senior (36.4 new injuries/club/season) (Orchard, Seward, & Orchard, 2013) and junior (17.1 new injuries/club/season) (Scase, Magarey, Chalmers, Heynen, Petkov, & Bailey, 2012) competition. The game is primarily played in Australia and involves strenuous running and cutting combined with ball handling and body contact. Injury prevention practices in junior AF are currently not consistent and therefore an update on current processes and directions for the future is warranted.

In 1987, Van Mechelen et al. proposed a framework for sports injury research (Van Mechelen, Hlobil, & Kemper, 1992). In 2006, Finch built upon this model by identifying the deficiencies and further outlined the required directions for injury prevention research. The model was titled 'Translating Research into Injury Prevention Practice' (TRIPP) framework and is defined by six stages:

1. Injury surveillance
2. Establishing the aetiology and mechanisms of injury
3. Developing preventative measures
4. An evaluation of the prevention model in 'ideal conditions'
5. Describe the intervention context to inform implementation strategies
6. Evaluate the effectiveness of preventative measures in implementation context

It seems appropriate to identify the progress of injury prevention research in junior AF at a time when more draftees are required, due to the addition of two national clubs into the senior Australian Football League (AFL). In addition with rising financial rewards, there is growing pressure amongst sporting teams to develop young players into elite professionals, preferably free of injury (Burgess, Naughton, & Norton, 2012; Johnson, Doherty, & Freemont, 2009).

At the elite senior AFL level, injury surveillance has been mandatory since 1992, however, limited injury data collection systems are in place at junior levels (Grimmer & Williams, 2003; McMahon, Nolan, Bennett, & Carlin, 1993; Orchard, Wood, Seward, & Broad, 1998; Romiti, Finch, & Gabbe, 2008; Scase et al., 2012) (TRIPP stage 1). The results from the AFL injury surveillance program cannot be directly transferred to other levels of football because of difference in factors such as fitness, exposure, skill, participant maturity and match demands (Burgess et al., 2012; Gabbe, Finch, & Cameron, 2007; Veale, Pearce, Buttifant, & Carlson, 2010).

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As outlined by the TRIPP model, the aim of injury surveillance should be to move beyond descriptive surveillance (TRIPP stage 1) to identifying mechanisms (Grimmer & Williams, 2003; McMahon et al., 1993; Orchard et al., 1998; Romiti et al., 2008; Scase et al., 2012) and risk factors (Banky & McCrory 1999; Chalmers, Magarey, Esterman, Speechley, Scase, & Heynen, 2012; Crow, Pearce, Veale, VanderWesthuizen, Coburn, & Pizzari, 2010; Finch, Donohue, Garnham, & Seward, 2002; Gabbe et al., 2010; Gastin, Bennett, & Cook, 2013; Taylor, Pizzari, Ames, Orchard, Gabbe, & Cook, 2011) (TRIPP stage 2), which lead to the development of injury prevention strategies (TRIPP stages 3–6) (Casey, Finch, Mahoney, & Townsend 2004; Finch, Donohue, & Garnham, 2002; Mitchell, 2000; Osborne, Quinlan, & Allison, 2012; Scase, Cook, Makdissi, Gabbe, & Shuck, 2006) that are appropriate to the intervention context. Therefore, the purpose of this review was to; first, present the available evidence regarding junior AF injury research in line with the TRIPP model, and second, provide recommendations for future research that will strengthen this field.

2. Methods

2.1. Information sources

To overcome the subjective nature of a traditional narrative review search strategy, the literature was systematically searched. A broad approach was necessary to confer a full scan of all published junior AF injury research. The narrative review style discussion permits the two primary aims of this review; first, summarise the available literature on junior AF injuries into the TRIPP model. Second, based upon the available evidence, provide recommendations for future research. Previously, the TRIPP model has been used in a narrative review to summarise injury research in triathlon (Gosling, Gabbe, & Forbes 2008). A critical appraisal tool was not used to ascertain the quality of papers. The reasoning for this is; first, the TRIPP model necessitates varying research methodologies on a whole, and within each individual stage. Thus, no single critical appraisal tool could fairly be used to critique and rank studies within the paper as a whole, or within each individual TRIPP stage. Therefore, to provide a subjective appraisal of the available evidence, the Australian National Health and Medical Research Council (NHMRC) (2008) level of evidence guidelines (Appendix 1) were used to identify the strength of the published literature within each stage of the TRIPP model. Two independent reviewers categorised each study that met the inclusion criteria for the review. In the event of a disagreement, a third independent reviewer examined the studies.

Medline, PubMed, Scopus, and SPORTDiscus™ databases were searched for available literature from their respective inception through to December 2012. The search strategy included; 'Australian football', 'junior', 'adolescent', 'injury', 'surveillance', 'risk', 'mechanism', 'intervention'. The relevant subject headings and keywords were used in isolation, and combination in each database (Appendix 2). For example, the complete Medline search strategy is provided in Appendix 2 (the same search strategy was used for each database). The references of all relevant articles were pearled for further papers.

2.2. Study selection

Papers were not excluded based upon the level of evidence. This relates to the first aim of the paper (summarise all the available published evidence). Furthermore, the TRIPP model incorporates all levels of evidence, therefore, excluding articles based upon the level of evidence would be opposing the intent of the TRIPP model and the first aim of the review. The process for study selection and exclusion is described in Fig. 1.

3. Results

3.1. TRIPP stage 1: injury surveillance

In the junior AF research field, TRIPP stage 1 is represented by five surveillance studies (Table 1), which have a strong level of evidence (Level II per NHMRC guidelines) and can be trusted to guide practice (Table 2).

3.1.1. Injury definition

A common problem in sports injury research is the variability of the injury definition. It is difficult to compare different junior AF injury studies due to the implementation of inconsistent injury
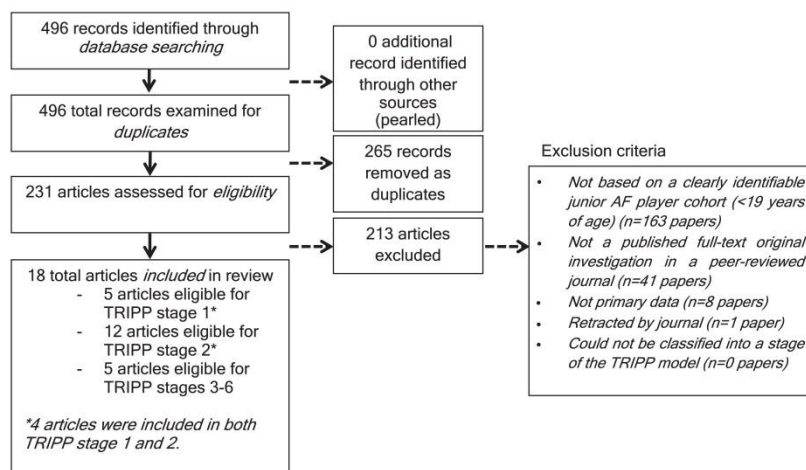
Fig. 1. Methodology of literature searching.

Table 1
Results from prospective cohort injury surveillance studies (TRIPP stage 1).

Study	Participants	Injury definition	Injury incidence	Most frequent injury type	Average injury severity	Average injury recurrence	Most common injury mechanism
Scase et al. (2012)	532 U18 South Australian National Football League	Any injury that resulted in a missed game	17.1 new injuries/40 player club/season	Ankle sprain/joint (2.6 injuries/40 player club/season)	3.3 games/injury	2.2/club (12.8%)	Collision with player (29%)
Romiti et al. (2008)	51 U9–U17 teams	Any trauma causing disability and/or pain	Overall: 18.0 injuries/1000 h of exposure	Knee (12.9% of all injuries)	Most common injury severity category was 'player left field' at a rate of 13.1 injuries/1000 h	Not reported	Being tackled (23.6%)
Grimmer and Williams (2003)	697 boys aged 7-17	Anything that significantly interferes with enjoyment of, or participation in, the sport	19.5% of participants sustained injuries	Knee (13.7% of all injuries)	Not reported	Not reported	Collision (43.2%)
Orchard et al. (1998)	5, 10 & 9 clubs participated in the survey over the three years of data collection U18 Victorian State Football League (VSFL)	1) Any injury which caused a player to be unavailable for selection in a match or participation in a training session 2) Any other injury which required specific medical treatment, other than routine conservative measures	797.8 injuries per 10 000 player hours	Thigh haematomas (52.5 injuries/10 000 player hours)	135.4 missed hours/10 000 h	Not reported	Not reported
McMahon et al. (1993)	1253 Vickick/U10 & U15	Any trauma that caused some disability or pain	Overall: 8.08 injuries/1000 player hours	Lower limb	Vickick: 0 days U10: 7 days U15: 10 days	Not reported	Collision with player

Table 2
NHMRC level of evidence for studies in TRIPP stage 1.

Study	Type of study	Level of evidence	TRIPP stage
Chalmers et al. (2013)	Aetiology	II	2
Gastin, Bennett, & Cook (2013)	Aetiology	IV	2
Osborne et al. (2012)	Intervention	II	3–6
Scase et al. (2012)	Aetiology	II	1 & 2
Taylor et al. (2011)	Screening	III-3	2
Crow et al. (2010)	Aetiology	II	2
Gabbe et al. (2010)	Aetiology	III-2	2
Romiti et al. (2008)	Aetiology	II	1 & 2
Burton and Fenton (2007)	Aetiology	IV	2
Scase et al. (2006)	Intervention	III-2	3–6
Casey et al. (2004)	Aetiology	IV	3–6
Grimmer and Williams (2003)	Aetiology	II	1 & 2
Finch, Donohue, Garnham, and Seward (2002)	Aetiology	IV	2
Finch, Donohue, and Garnham (2002)	Aetiology	IV	3–6
Mitchell (2000)	Intervention	III-2	3–6
Banky and McCrory (1999)	Aetiology	IV	2
Orchard et al. (1998)	Aetiology	II	1
McMahon et al. (1993)	Aetiology	II	1 & 2

definitions. Overall, the injury definitions of four studies were defined as 'broad' (Grimmer & Williams, 2003; McMahon et al., 1993; Orchard et al., 1998; Romiti et al., 2008), whilst the definition of one study was defined as 'narrow' (missed game-only) (Scase et al., 2012) (Table 1). For a comprehensive overview of the narrow versus broad injury definition debate, refer to Orchard and Hoskins (2007) and Hodgson, Gissane, Gabbett, and King (2007).

According to Van Mechelen (1997), an injury surveillance system should enable the assessment of injury incidence (inclusive of recurrence incidence), the prevalence and duration of sport injuries.

3.1.2. Injury incidence

The 'new' injury incidence has been well reported in the literature. From the studies that used a similar broad injury definition (injuries/hours of exposure), the injury incidence rate was comparable between McMahon et al. (1993) and Romiti et al. (2008), however, the injury rate of Orchard et al. (1998) was higher. This discrepancy may be due to the differences in cohorts studied; Orchard et al. (1998) recorded the injury profile of elite junior players (U18 years) whereas broader age ranges were included in the two former studies. Previous research has demonstrated an increased injury risk for 'older' junior AF players (Grimmer & Williams, 2003; Romiti et al., 2008). The injury incidence reported by Grimmer and Williams (2003) and Scase et al. (2012) could not be compared with the aforementioned papers due to variation in the implemented injury definitions. A limitation of the Grimmer and Williams (2003) study was that injury incidence was not reported in relation to an exposure measure. Scase et al. (2012) provided injury incidence by 'new injuries/40 player club', to allow for direct comparison with the AFL.

The injury incidence in the senior AFL could be presumed to be higher than junior competitions, primarily relating to the faster game speed and intensity (Burgess et al., 2012; Norton, Schwerdt, & Lange, 2001). However, study results are equivocal. Orchard et al. (1998) directly compared elite junior and elite senior (AFL) injury rates and demonstrated the elite junior competition to have an incidence rate of 797.8/10 000 h whilst the senior competition had a rate of only 657.8/10 000 h. In contrast to these results, Scase et al. (2012) (using the same injury definition as the AFL), reported the injury incidence to be much lower in elite junior

(17.1 injuries/standardised club) than the average seasonal injury incidence in elite senior AFL from 2003 to 2012 (36.4/club) (Orchard et al., 2013). Due to differing injury definitions, it is not possible to directly compare the absolute injury incidence of the Grimmer and Williams (2003), McMahon et al. (1993), and Romiti et al., (2008) studies to that of the senior AFL. It is clear that the lack of consistent injury definition makes comparison of the injury incidence difficult across studies.

The injury incidence data from all the aforementioned studies demonstrates that although the absolute numbers are different, the pattern of injury profile amongst junior and senior AF is similar with high rates of ankle, knee and thigh injuries (Grimmer & Williams, 2003; McMahon et al., 1993; Orchard et al., 1998, 2013; Romiti et al., 2008; Scase et al., 2012). These results suggest that the physical demand placed on the lower limb through high intensity repeated running, kicking, jumping and tackling results in a high injury risk to the region, irrespective of competition level.

3.1.3. Injury severity

All four papers in which injury severity was documented utilised different definitions, making comparison difficult (McMahon et al., 1993; Orchard et al., 1998; Romiti et al., 2008; Scase et al., 2012). The studies by McMahon et al. (1993), Orchard et al. (1998), and Romiti et al. (2008) utilised definitions that incorporated a player missing any football involvement (training and/or match), however, the outcome variable for the studies was different. The outcome variable of the McMahon et al. (1993) study was *'days unable to participate in football due to an injury'* whilst the Orchard et al. (1998) study was *'hours missed due to an injury per 1000 exposure hours'*. Romiti et al. (2008) classed each injury into different severity categories of; *'player left field, player stayed off the field, player was advised to seek off-field medical advice, and player was taken to hospital.'* Each category was reported as injuries per 1000 exposure hours (Romiti et al., 2008). It may be appropriate to classify the severity of injury 'per hours of exposure' at the elite junior level (U18) because training and match exposure time become more organised and documented than in younger cohorts. However, player commitments may fluctuate at the younger levels for a variety of reasons. If direct comparison of injury statistics with the senior AFL is of interest, then the injury severity definition should only incorporate *'missed games per injury'* since this is the definition used in the AFL Injury Report. An example of the implementation of this definition is the study by Scase et al. (2012), in which a lower injury severity was demonstrated in elite junior (3.3 matches/injury) than elite senior (AFL) players (3.6 matches/injury).

3.1.4. Injury recurrence

The injury recurrence rate is a seemingly important injury statistic that has the potential to provide valuable feedback to club medical staff from which they can assess when players could return to play without a high risk of an injury recurrence. However, it is a statistic that has been significantly underreported in the literature. The only junior AF study in which the injury recurrence rate is reported is that by Scase et al. (2012), demonstrating the yearly injury recurrence rate of elite junior AF players (12.8%) to be slightly higher than the seasonal average in senior elite AF players from 2003 to 2012 (12%) (Orchard et al., 2013).

In summary, a consistently implemented injury definition would enable ongoing and direct comparison. Furthermore, continual and consistent injury surveillance should be established at the junior level to monitor the effects of any interventions and satisfy stage 1 of the TRIPP model. Previous studies have provided a snapshot of the injury profile.

3.2. TRIPP stage 2: establishing the aetiology and mechanisms of injury

12 papers were eligible for TRIPP stage 2 (Table 2). The categorisation indicates a large spread in the quality of available evidence.

3.2.1. Injury mechanisms

Firstly, four injury incidence studies have helped guide research into the mechanism of injuries at the junior AF level. Although the classification of injury mechanisms differs between papers, it is still possible to identify themes. All four studies in which the injury mechanism was reported identified that 'contact/collision' was the main cause of injury (Grimmer & Williams, 2003; McMahon et al., 1993; Romiti et al., 2008; Scase et al., 2012). In some respects, this result is not surprising due to the high intensity, contact nature of the sport. AF is a sport in which the ball carrier can be hit from any angle by another player, resulting in many players not being able to brace before contact. Junior injury surveillance programs (Grimmer & Williams, 2003; McMahon et al., 1993; Orchard et al., 1998; Romiti et al., 2008; Scase et al., 2012) have not yet documented the precise mechanism of specific injuries (and this may be difficult due to differences in club medical support staff).

Other factors that help define the aetiology of injuries have been inconsistently reported throughout the junior AF injury surveillance literature (Table 3). The relationship between many of these extrinsic risk factors and injury risk remains ambiguous and therefore difficult to address.

3.2.2. Injury risk factors

Banky and McCrory (1999) reported that 64% of junior players wore mouthguards during matches, but only 1% wore mouthguards during training. Education and injury awareness programs should be specifically directed at this age group to help reduce to the risk of dental injuries (Banky & McCrory, 1999).

Chalmers et al. (2012) explored the relationship between certain physical fitness qualities and injury, discovering a lower aerobic endurance, faster 5-m acceleration, and faster planned agility to be associated with the incidence of several injuries. A higher left foot running vertical jump, and faster 5-m acceleration was associated with a greater severity of injury (Chalmers et al., 2012). The authors postulated that these results might relate to a greater work capacity placing a higher load upon the musculoskeletal system in contact and non-contact situations (Chalmers et al., 2012). Unfortunately, these are predominantly (besides lower aerobic endurance) coveted physical capabilities, thus the only viable option could be close monitoring of these 'high risk' players (Chalmers et al., 2012).

Table 3
Other extrinsic risk factors for injury as reported by injury surveillance programs.

Factors associated with increased risk of injury	Paper in which increased risk is reported
During matches > training	Scase et al., 2012; Romiti et al., 2008; Grimmer & Williams, 2003; McMahon et al., 1993
Older playing age	Romiti et al., 2008; Grimmer & Williams, 2003; McMahon et al., 1993
Both 'firm' and 'soft' playing surface	Grimmer & Williams, 2003; McMahon et al., 1993
During the second half of a match	Grimmer & Williams, 2003
During May and August	McMahon et al., 1993
With a shorter warm-up (<11 min)	McMahon et al., 1993
In competitions that do not have rule modifications during matches	McMahon et al., 1993

Gastin et al. (2013) identified that within the same chronological junior age group there is a range of biological maturity within individuals. This could place more mature players at a performance advantage and influence injury rates (Gastin et al., 2013).

Taylor et al. (2011) identified that elite junior indigenous players achieve less range of passive hip internal rotation with the hip in neutral, reduced adductor squeeze force and higher levels of groin pain with the squeeze test at 90° than their non-indigenous contemporaries. Taylor et al. (2011) suggested that these findings indicate that indigenous players may be at greater risk of hip and groin injuries than non-indigenous players. The authors did not suggest a definitive reason for the difference in injury risk, however, they postulated the increased risk to be a result of intrinsic morphological and physiological differences in the indigenous population, and the warmer climate in the regions from which the majority of indigenous players originate (Taylor et al., 2011). Future studies should examine whether there is consistently greater risk of groin injury, whether these intrinsic differences cause altered biomechanics and ameliorate risk, or whether 'prehabilitation' can reduce risk.

Gabbe et al. (2010) identified that elite junior players reporting groin injuries prior to senior AFL recruitment had a risk of groin injuries in senior AF more than six times higher than those without previous groin injuries. This is a worrying statistic and creates a treatment and management problem for medical personnel due to the paucity of evidence based rehabilitation programs (Gabbe et al., 2010).

Crow et al. (2010) identified that hip adductor muscle strength is reduced preceding and during the onset of a groin injury in elite junior AF players. The study concluded by supporting the use of regular screening with a hand held dynamometer for the early identification of a potential groin injury (Crow et al., 2010).

In a case study paper, Burton and Fenton (2007) detailed three occurrences of blunt pancreatic injury during under-age Australian rules football matches. Burton and Fenton (2007) suggest that the risk of pancreatic injuries in under-age footballers is reduced because of the smaller force generated in collisions.

Finch, Donohue, Garnham, and Seward (2002) investigated the playing habits and other commitments of elite junior players following anecdotal evidence that they have considerable sporting commitments, coupled with previous research by Van Mechelen, Twisk, Molendijk, Blom, Snel, and Kemper (1996) demonstrating that high exposure time results in an increased risk of injury. Elite junior players undertake 3—4 football training sessions per week and compete in 1—2 matches per week, potentially increasing the risk of overuse and match-related injuries (Finch, Donohue, Garnham, & Seward, 2002). Overall load is a major issue for junior athletes who are selected and sought after by club, school and state teams and want to maximise their drafting chances. This provides a challenging musculoskeletal training regime, and efforts must be ensured to reduce the risk of overuse injuries.

In summary, few studies have provided detailed information about injury mechanisms, making targeted intervention challenging. Individual risk factors have been investigated and recommendations made regarding some modifiable risk factors such as overall load, attitudes and muscle strength. However, at a time when more junior AF players are sought after for a professional career than ever before, further research is needed to inform evidence based injury prevention programs so these players can have the greatest chance of forging a successful career.

3.3. TRIPP stages 3—6: describing the intervention context and developing preventative measures with scientific evaluation

To-date, research that has moved beyond TRIPP stage 1 & 2 at the junior level of AF is limited (Table 2). There is a lack of consistent high quality studies in this stage of the TRIPP model.

Osborne et al. (2012) observed elite junior footballers to have deficiencies in hip abduction performance. The authors suggest that the risk of injury in players could be reduced following a relatively short period of hip abduction training (Osborne et al., 2012).

After identifying that landing injuries were common amongst adult football codes, Scase et al. (2006) implemented a landing and falls injury intervention program in elite junior AF players. The intervention significantly reduced the risk of players sustaining an injury resulting from mechanisms associated with landing and falling.

Casey et al. (2004) reported that junior football clubs in rural areas lack comprehensive safety policies and practices to reduce the risk of injury. A shortage of volunteers and players was identified as the main barrier to implementing sports safety (Casey et al., 2004).

Finch, Donohue, and Garnham (2002) conducted a qualitative study to determine the safety attitudes and beliefs of junior AF players in the hope of providing an understanding of the behaviour of athletes in the context in which future injury prevention programs can be implemented. The authors reported 58.3% of elite junior players were willing to play with an injury whilst 76.6% were willing to risk playing with an injury if they thought their chances of selection for the AFL draft would be affected if they did not play (Finch, Donohue, & Garnham, 2002). Clearly there needs to be further investigation of player and coach attitudes, and potentially interventions aimed at education if they are a barrier.

Mitchell (2000) demonstrated that players who wore a thigh protector sustained significantly fewer thigh haematomas. Mitchell (2000) suggests that the missed training and match time subsequent to the thigh haematoma results in deconditioning of the muscle and an increase in injury risk. The thigh protectors were reported to be comfortable whilst playing, except in hot conditions (Mitchell, 2000).

Research in TRIPP stages 3—6 remains sparse, emphasising the need for further investigations in line with suggestions raised in the next section of the manuscript.

4. Discussion

4.1. Guidelines for future research and practical applications in junior AF research

4.1.1. Injury definition

A consistent injury definition should be agreed upon by all stakeholders to ensure comparison between studies and consistent injury reporting. Whilst all definitions have limitations, failure to use a consensus injury definition only stunts injury prevention research. The strength of the narrow, missed game-only injury definition adopted by the AFL is in its simplicity, and reliability across a large number of clubs over a long period of time (Orchard & Hoskins, 2007). Such strengths are also evident when collecting injury data from those involved at junior level because the reporting is simple and straightforward, thus enhancing compliance of officials (Orchard & Hoskins, 2007) who are predominantly volunteers or part-time staff members. However, the lack of information related to mechanisms of specific injuries, influence of the decision makers about return to sport (conservative versus aggressive), availability of a consistent professional injury management team to enhance recovery and reduce time away from the sport associated with injury, management of injuries from the previous season or pre-season period, reporting of long term injuries where the period of non-participation falls outside the competition period all limit

the strength of the injury surveillance protocol (Orchard & Hoskins, 2007).

Further research to determine whether a more detailed reporting system that includes consideration of at least some of the factors described above, while retaining consistency across clubs and seasons is warranted to ascertain the overall injury status of junior AF players. It is feasible that some compromise of definitions or reporting methods may provide a more accurate and detailed injury profile in the junior cohort without losing the essence of simplicity and reliability. A consensus approach between research teams in the field would greatly strengthen results, leading to better-targeted injury prevention programs with more chance of successful implementation.

4.1.2. Ongoing injury surveillance

Once a consistent definition has been established, ongoing injury surveillance should be implemented. Due to the elite U18 leagues being feeder competitions for the senior AFL, combined with the medical support available to each club, this would be an ideal setting to implement organised, continuous and reliable injury surveillance. In addition to establishing the injury profile, further investigation into the underlying causes of injury (Stage 2 of the TRIPP model) is still required. Evaluation of potential associated risk factors, such as age, body composition, kicking leg dominance, playing position, musculoskeletal impairments or asymmetries, player training and match load, impact of playing outside their age group level and impact of previous injury is required. Once relevance is established, investigation into potential interventions to address those factors that are modifiable (TRIPP stage 3) will start to address some of the knowledge gaps.

Continuation of research to determine differences in injury rates and mechanisms between junior and senior ranks (also Stage 2 of the TRIPP model) will allow more targeted programs aimed at injury reduction. Theoretically, due to the increased speed, length of the game, size of the players, and longer exposure hours (Burgess et al., 2012; Veale et al., 2010), the injury risk should be higher for elite senior AFL players. However, as previously discussed, there is evidence to the contrary (Orchard et al., 1998). Junior football research that shares the same definition as the AFL injury report will enable reliable comparison between the profiles and help to identify where senior research can be directly applied to the junior level, and where a different emphasis for investigations is required.

4.1.3. Relationship between exposure and injury

Increased training and playing loads have been demonstrated to increase injury rates in rugby (Gabbett & Jenkins, 2011). Adolescent AF players are frequently skilled in other sports and potentially, participate in more than one sport throughout the year. Equally, the more elite among the cohort may be selected to play in senior competitions and/or the state team competition. Training and playing in senior competition exposes young players to the stronger tackling and the higher pace of the game played by adult men (Burgess et al., 2012). Furthermore, those who are selected to represent their state undertake a period of six weeks of two additional training sessions/week with the state squad and up to four additional matches. Injury data have been analysed for the South Australian U18 state squad cohort over two seasons (Dunsford, Magarey, Chalmers, & Boesch, 2011), with some evidence of increased incidence of injury through the remainder of the season following the state competition, although small numbers limit the strength of the analysis. Clearly, further research into the effect of playing and training load on injury would help inform the sport's

governing bodies on the value of establishment of player load limits.

4.1.4. Attitudes, beliefs and contextual barriers

The successful implementation of junior AF injury prevention strategies is difficult as we have limited understanding of the potential barriers and considerations including; coach attitudes to injury prevention programs and whether they see them as a priority and how to affect this, player and coach attitudes to injury prevention equipment and compliance including cost effectiveness studies. Education is a powerful tool and changing belief systems in players, coaches and selectors will be a significant challenge. The forum in which education is delivered must include collaboration with all parties and stakeholders to ensure the best chance of success. Further education of coaches, players and medical staff could help bridge the gap between research findings and successful practical sporting practice.

5. Conclusion

Injuries have the potential to affect a young athlete throughout their career (Gabbe et al., 2010). Thus, injury prevention should be seen as a priority, especially at a young age (Grimmer & Williams, 2003). However, a paucity of research is available which aims to reduce the risk of injury in junior AF players or investigate the context and culture, knowledge which is vital for effective implementation (TRIPP stages 3–6). Injury research at the junior level of AF is currently predominantly situated at stage 2 of the TRIPP process. However, even though evidence from TRIPP stage 1 is high quality, the research suffers from large methodological discrepancies, and inconsistencies in the data that is reported. The researchers reporting in these papers and other articles have made a positive attempt to achieve TRIPP stage 2, although, still more research is needed in line with the recommendations in this paper. It can be postulated that most injury prevention programs are based upon senior AF research and anecdotal evidence as TRIPP stages 3–6 is represented by only five papers. Hence, researchers should begin to identify TRIPP stages 3–6 as a priority for the formulation of high quality studies.

This review summarises the junior AF research into the TRIPP framework to identify gaps and direct future research. Clearly, a consistent injury definition and ongoing injury surveillance remains a priority, however, further studies identifying risk factors, attitudes and contextual barriers are necessary for the success of future injury prevention efforts. Injury research aimed at the junior and community level could have the greatest impact on the overall safety of AF, due to the larger levels of participation than at the AFL level (Gabbe et al., 2007).

Appendix 1. NHMRC level of evidence guideline table (NHMRC, 2008).

Table 1
NHMRC Evidence Hierarchy: designations of 'Levels of evidence' according to type of research question (including explanatory notes).

Level	Intervention[a]	Diagnostic accuracy[b]	Prognosis	Aetiology[c]	Screening intervention
1[d]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[e] among consecutive persons with a defined clinical presentation[f]	A prospective cohort study[g]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[e] among non-consecutive persons with a defined clinical presentation[f]	All or none[h]	All or none[h]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial[i] • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study[j] • Interrupted time series without a parallel control group	Diagnostic case-control study[f]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[k]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

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Appendix 2. Example database search strategy from Medline.

Search number	Search	Results
1	Australian football.mp.	170
2	Junior.mp.	8557
3	Adolescent/in [Injuries]	3
4	Injury.mp.	415 812
5	Surveillance.mp.	120 240
6	Risk.mp.	1 335 178
7	Mechanism.mp.	679 444
8	Intervention.mp.	280 137
9	Australian football AND injury AND surveillance	16
10	Australian football AND injury AND risk	53
11	Australian football AND injury AND mechanism	4
12	Australian football AND injury AND intervention	14
13	(Australian football AND injury AND surveillance) OR (Australian football AND injury AND risk) OR (Australian football AND injury AND mechanism) OR (Australian football AND injury AND intervention)	64
14	Australian football AND junior AND injury	12
15	(Australian football AND junior AND injury) OR ((Australian football AND injury AND surveillance) OR (Australian football AND injury AND risk) OR (Australian football AND injury AND mechanism) OR (Australian football AND injury AND intervention))	67

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Original research

The epidemiology of injury for an elite junior Australian Football cohort

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Abstract

Objectives: To implement an injury recording protocol in a junior elite Australian Football competition and determine the injury profile of this population.

Design: Longitudinal cohort study.

Methods: Players from an elite Under 18 Australian Football competition were tracked throughout one football season in terms of participation or non-participation in the football competition. Injury reporting forms were collected for all players who were not available for selection as a result of injury.

Results: The cohort consisted of 532 players who provided consent for inclusion in the study (100% of players in the competition). There were 256 injuries sustained during the season. Results were standardised to a 40 man team to allow comparison with results from the Australian Football League. The injury incidence was 17.1 new injuries per club (95% CI 14.1–19.4), and prevalence 63.3 missed matches per club (95% CI 59.1–67.1). The category "Ankle joint injuries" was the most commonly reported ($n = 34$) and "Collision with another player" was the main injury mechanism ($n = 75$).

Conclusions: The most commonly injured region in junior elite Australian Football was the ankle and collision with another player was the most common injury mechanism. As with previous reports on junior Australian Football, injury incidence was low in comparison to the senior elite competition. Defining the injury profile guides injury prevention strategies. Analysis of injury in junior elite football may provide a unique opportunity to affect both junior and senior injury rates.

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Keywords: Sports injury; Australian Football; Junior

1. Introduction

Australian Football (AF) is a full contact, dynamic sport involving explosive running, change of direction, jumping, stopping, aggressive tackling, sudden and severe collisions, as well as kicking and handballing skills.[1] It is played at an elite level in junior and senior competitions with an established and standardised injury data collection protocol completed at the elite professional senior level since

1992.[2] The results of the annual Australian Football League (AFL) Injury Report guide injury prevention strategies at this level.[2] Interest in junior competitions has been reported previously, including epidemiological studies[1,3,4] qualitative investigation into player attitudes,[5] loading,[6,7] and specific injury prevalence.[8–10] However, despite Under 18 (U18) elite competition acting as a feeder to the senior competition, no consistent comprehensive injury surveillance has been reported for this population.

Talented junior athletes often participate for club, school and state teams and may even be involved with other sports placing high demand on a growing body.[6] Injury during junior

playing years may generate greater susceptibility to injury at senior level, with the potential to limit long term playing potential.[8] Differences have been demonstrated between senior and junior players in physical fitness, exposure, skill and participant physical and psychological maturity.[7,11] Interpretation of results from the AFL injury surveillance programme may not be transferable to the elite junior level and injury prevention at this age group should be seen as a priority.[8,12,13]

Injury prevention strategies seem warranted in contact sports such as AF as a result of the significant medical and economic cost associated with sports injury.[12] Intervention in junior levels may reduce attrition associated with sports injury, reduce economic costs of diagnosis and treatment, potentially affect future injury risk for players drafted into the senior competition,[8,14] and have long-term health implications for retired athletes.[15,16]

However, if an injury prevention package is to be effective, it should be based on knowledge of the injury profile of the population. The TRIPP (Translating Research into Injury Prevention Practice) model[17] of injury prevention research provides a well-recognised process of addressing injury prevention that encompasses the steps of:

1. Injury surveillance
2. Establish aetiology and mechanisms of injury
3. Develop preventative measures
4. "Ideal conditions"/scientific evaluation
5. Describe intervention context to inform implementation strategies
6. Evaluate effectiveness of preventative measures in implementation context.

This study represents Stage 1 of the TRIPP process as it provides injury data for junior AF players in the South Australian National Football League (SANFL) throughout season 2009. Season 2009 marked the commencement of a new competition for U18 players by the SANFL and therefore, provided a unique opportunity to trial the AFL surveillance system to determine the nature and mechanisms of injuries within this cohort of players.

The aims of this study were:

● To implement an injury recording protocol in a cohort of junior elite football
● To establish the injury profile of the SANFL U18 competition players over one season.

2. Methods

The study was approved by the University of South Australia Human Research Ethics Committee. Every player from all nine teams participating in the elite U18 SANFL competition was invited to participate in this study. Before participation, informed written consent was obtained from the SANFL, officials from each participating club, players

Table 1
Definitions used in the present study.

Parameter	Definition
Injury definition	Any physical or medical condition that resulted in a player missing one or more elite competition matches
Injury incidence	Number of new injuries per club per season (n, %)
Injury prevalence	Number of missed games per club per season (n, %)
Injury severity	Number of games missed per injury (n, %)
Injury recurrence	The recurrence rate was the number of recurrent injuries expressed as a percentage of the number of new injuries (%). A recurrent injury is an injury in the same injury category occurring on the same side of the body in a player during the same season.
Overuse injury	An injury resulting from repetitive strain/overtraining

and their parent/guardian for players aged under 18 years. The study was conducted during season 2009 (regular season only, no finals matches) and consisted of 20 matches. Each week, 22 players from the squad were chosen to compete for each team. Players were included in the study if they played at least one match during the 2009 season. Player data were de-identified to maintain confidentiality.

Injury data were collected using an injury surveillance system modeled on that of the AFL to allow comparison of the injury profiles with minimal methodological differences. Exposure data, defined as match participation, were collected for each player for the regular 2009 season. Training exposure data were not recorded to model the AFL exposure definition. Injury definitions used in this study (Table 1) are consistent with those used in the AFL Injury Report.[2] Injuries were captured whether they occurred in trainings, matches or away from football but were included in results only if they resulted in a missed match – i.e. if the player were unavailable for selection as a result of injury. All injuries reported for the first time were classified as 'new injuries', even if they were ongoing from the pre-season period or previous year, again, in line with the AFL protocol. The injury headings used in the Orchard Sports Injury Classification System (OSICS): Version 10[18] were used in this study, again to allow direct comparison with the manner in which data are reported in the annual AFL Injury Report. However, injuries were not further classified into the OSICS subgrouping system, hence the OSICS codes are not reported in this study.

A standardised Injury Report Form (IRF) (Supplementary Material 1) was completed by designated club health personnel (physiotherapist or sports trainer) for every player who missed a match as a result of injury. The injury report form included information related to; injury type, mechanism, and whether the injury was new or recurrent. Recognition of the potential differences in qualifications of those completing the form at different participating clubs, with physiotherapists available at some clubs and sports trainers at others, required that the injury reporting system be clear and straightforward.

Education sessions were provided to clubs to assist with completion of the IRFs. Completion of the IRF required no advanced diagnostic skills.

Player participation in football matches (exposure) was monitored using a tool termed a Player Movement Record (PMR) completed by a designated club official. Each week, player participation or non-participation was recorded. Information included whether players were competing for their elite team or elsewhere (for example, local club or school), or if they were injured, ill, suspended or absent for another personal reason. The PMR was used to crosscheck with IRFs to ensure that a form was completed for all situations meeting the injury definition.

With a target population of approximately 2340 U18 elite AF players in Australia and an initial injury incidence estimate of 45%, based on data from a previous study,[3] a sample size of 475 players would provide an incidence proportion with ±4% accuracy with 95% confidence.

To allow direct comparison with the data from the AFL Injury Report, data were standardised to a 40-man team. Descriptive statistics such as absolute numbers, averages and percentages for the desired outcome measures – incidence, prevalence, recurrence, site and mechanism – were calculated in Excel version 2007.

Severity of injury was defined in relation to the number of missed matches for a single injury, with the most severe being the injury that resulted in the most missed matches. The injury types that caused the most missed matches were compared using SPSS version 15.0. Since injury data were not normal but right-skewed, a Generalised Linear Model with a Gamma distribution was used for analysis. A Chi-Square Goodness of Fit test was used to determine whether more injuries occurred in matches or at training.

3. Results

The PMR for each club for the season included a total of 532 players. All players gave consent to participate in the study ($n = 532$), age range 15–18 years. The majority of players were under 18 years of age on January 1st 2009, however, clubs were entitled to field six players each week who were already 18 years old on January 1st 2009.

During the season, 227 injuries were sustained with an average of 17.1 new injuries/standardised club (95% CI 14.9–19.4). There was an overall average of 19.3 injuries/club (95% CI 17.0–21.7) as there were also 2.2 recurrent injuries/club (95% CI 1.4–3.0). There were 841 matches missed due to injury by participants in the competition equating to an average of 63.3 missed matches/club in season 2009 (95% CI 59.1–67.6). On average 3.3 matches were missed per injury (95% CI 3.1–3.6).

The majority of new injuries (injury incidence) were to the lower limb ($n = 164$, 72.2%); 'Hip/groin/thigh' ($n = 80$, 35.2%), 'Shin/ankle/foot' ($n = 54$, 23.7%) and the 'Knee'

($n = 30$, 13.2%). 'Upper limb injuries' accounted for 33.9% ($n = 77$) and 'Medical illness' for 5.8% of injuries.

The most frequently reported injury was to the 'Ankle joint' with an average of 2.6 injuries/club, followed by 'Hamstring strains' and 'Groin strains/osteitis pubis', both of which had an average of 1.9 new injuries/club.

The majority of the injuries resulted from non-contact mechanisms (49%), overuse injuries accounted for 17% and the remainder were contact injuries including collision with another player (34%). The Chi-Square Goodness of Fit test showed that injuries were more likely to occur during matches (64%) than at training (22%) or elsewhere (14%) ($\chi^2 = 229.23$, df = 2, $p < 0.0001$). On average 3.8 players were unavailable for selection each week due to injury. An average of 11.9 players did not play each week for another reason, an average of 21.9 players played elsewhere and 22 players/club played SANFL U18 competition.

The Generalised Linear Model showed that two injuries were significantly associated with matches missed. Overall the model is significant (Wald = 37.68, df = 7, $p = 0.0000$). 'Knee injuries' were significantly associated (Wald = 18.92, $p < 0.0001$). 'Shoulder/arm/elbow injuries' were also significant (Wald = 5.93, $p = 0.015$). The average number of games missed due to knee and shoulder injuries were 5.44 and 4.41 respectively.

The injury recurrence rate was 12.8%/club (2.2/club). The body area classified as 'Other leg/foot/ankle' experienced the highest recurrence rate of 29%, followed by 'Other hip/groin/thigh' (27%).

4. Discussion

This study has established the injury profile for a junior elite AF cohort across a complete playing season and enables comparison with other cohorts that have employed the same methodology.[2,3] The sample size of 532 players satisfied the criteria to provide an incidence proportion with ±4.0% accuracy with 95% confidence.

The rate of injury in this cohort was lower than that of the elite senior competition at 17.1 new injuries/club and 2.2 recurrent injuries/club, supporting previous findings from comparative AF studies.[2,19] The similarities in the results of Scase et al.[3] and the present study, both undertaken on players of the same age, playing in an equivalent level of competition and using a similar data collection protocol, support use of the methodology in this study and reflect a degree of consistency in injury trends in junior AF players. Direct comparison with the results reported by Orchard et al.[1] and Romiti et al.[10] is not possible because of methodological differences in injury reporting between the respective studies. In both papers, a broader injury definition was used than in the current study and in the AFL Injury Report since 1997.[19] Whilst the relative consistency between the results of Scase et al.[3] and the present study is encouraging, data collection over further seasons is required to determine whether patterns of injury are

consistent, thus strengthening evidence that Stage 1 of the TRIPP model was achieved.

Injury incidence, both of new and recurrent injuries, prevalence and severity were lower in the present study than in the AFL in season 2009, potentially reflecting higher playing intensity in the senior competition, although the recurrence rate was very similar (12.7% compared with AFL 13%).[2]

The pattern of injuries was similar across this junior cohort and the AFL, despite differences in the competition, age, development, skill and medical support available to the players. The lower injury incidence demonstrated in the junior cohort is to be expected. Whilst the AFL players are professional athletes with years of training, experience and skill, the greater number of hours and higher intensity of training and matches could be expected to lead to a higher injury incidence.[6,7] Despite the similarities in injury pattern, factors relevant in junior athletes, such as skeletal, physiological, psychological and hormonal maturity, physical fitness, skill level (landing, tackling, ball handling) and participant exposure, mean that attention to these factors may be relevant in development of prevention programmes.[20,21] The players in this cohort compete in a feeder competition for the AFL. Establishing the injury profile and developing an understanding of the injury mechanisms in this junior elite cohort may assist in the goal of reducing injury at the elite professional rookie level of AF.[7,8]

Injuries occurring during matches (64%) rather than training (22%) or elsewhere (14%) are comparable to figures from similar contact sports most likely reflecting the lower intensity and fewer episodes of high impact body contact during training in these sports.[22,23] The lower limb (72.2%) was the site of most injuries, suggesting that this region, especially the ankle, should be a high priority for future intervention in relation to injury prevention strategies. A similar bias in injury location has been demonstrated in both senior and junior AF cohorts.[1,2]

Of particular interest in this study is the high incidence of hamstring and groin injuries, reflective of the results in the AFL and two areas of concern highlighted by Orchard and Seward.[19] A high incidence of similar injuries in the junior cohort indicates the need for further investigation of injury predictors potentially identified by standardised musculoskeletal screening.[24] Injury prevention programmes may then be implemented and evaluated for effectiveness in this age group. Since Gabbe et al.[8] demonstrated that players entering the AFL competition with a previous history of groin strain are six times more likely to suffer a further groin injury than their previously non-injured counterparts, such programmes may have the effect of reducing the incidence of groin injuries at both junior and senior level. Equally, observation of a high incidence of hamstring injuries in a feeder competition for the AFL provides an opportunity to explore the hamstring risk factors in a younger population with the goal of prevention prior to the players' advent in the senior game.

'Ankle sprain/injury' was the most frequent specific injury reported in the present study (13%, AFL 2.6%), a key difference from the AFL. The data on use of prophylactic ankle taping in our study were incomplete nor were data collected around potential risk factors such as past injury history, balance or strength which may be associated with ankle injury. Injury profile information, provided through injury surveillance, may potentially guide future injury prevention programmes. Lower limb training programmes have demonstrated success as measured by a reduction in injury incidence for many injuries.[3,25,26]

The AFL does not report mechanism of injury, however the proportion of injuries associated with contact, overuse and non-contact was very similar between the present study and that of Scase et al.[3] The high incidence of contact injuries reflects the high risk nature of contact sports. Several studies have addressed non-contact injury prevention such as landing and falling intervention training,[3] the FIFA 11+ dynamic warm-up,[27] and the protocol proposed by Finch et al.[28] for example. Addressing injuries from contact mechanisms may require further investigation.[10]

The research design of this study deliberately mirrored that of the AFL injury reporting process, with use of the same definitions and methodology, so that the results could be directly compared with those of the senior level of the sport. Several limitations are acknowledged of the injury surveillance methodology.[29] A narrow injury definition (missed match) may lead to under reporting of minor injuries and the number of games missed due to injury is affected by the time in season when the injury occurred. Future studies could be improved by collecting and linking screening data in which information is gathered about aspects of physical maturity to risk of specific injury for this population.

There may be differences in the quality and detail of reports on the IRFs depending upon the expertise of the recorder. However, the IRF was deliberately designed to allow for such difference in expertise – physiotherapist compared with sports trainer. In future studies, establishment of reliability of completion of the IRF will strengthen the results. Further education about study aims may limit incomplete data by improving compliance. At junior level, the player list may change from week to week, with up to 59 players used by some clubs through the season, in comparison to the AFL, where clubs have a fixed list. With such a large number of players moving in and out of the elite junior teams through the season, some players may not have undertaken appropriate training at the elite level, potentially putting them at higher injury risk than those involved throughout the programme.[30] In contrast, those players involved through the entire pre-season and competition may be affected by fatigue by the end of the season. Analysis of the influence of such factors on injury would strengthen the data. This difference between the U18 and AFL cohorts must be acknowledged. Finally, whilst establishing an injury profile for the U18 cohort through one season provides a baseline, without further investigation, these results hold limited value. Ongoing monitoring

of injuries through further seasons and linking injury surveillance information with the results of pre-season fitness testing and musculoskeletal screening will provide greater benefit.

5. Conclusions

The principal aim of this study was to implement data collection on occurrence of injuries for a cohort of junior AF players and to describe the injury profile across a full season of football. The data collected, with acknowledged limitations, have advanced our knowledge of injury profiles in junior footballers and established a baseline against which to compare results of future years' injury reports and to assist in identifying risk factors that may be amenable to preventative intervention. By achieving this aim, the study has fulfilled the first stage of the TRIPP model,[17] that of initial injury surveillance. Our continued research aims to expand information on the injury profile and work to address the other stages of the process.

6. Practical implications

- This study has established injury data collection across a large cohort of junior football players providing baseline data towards development of injury prevention strategies.
- Investigation of the factors associated with the high incidence of ankle, hip/groin and hamstring injury such as evaluation of balance and lower limb strength, coordination and/or use of prophylactic taping (cost vs benefit) should be included in future studies.
- Identified risk factors should then be targeted in future injury prevention and injury incidence in an intervention group compared against this injury profile.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jsams.2011.12.002.

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Original research

The relationship between pre-season fitness testing and injury in elite junior Australian football players

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ABSTRACT

Objectives: Australian Football (AF) is a collision sport containing high injury rates in junior competition. Successful performance at the elite junior level not only requires superior specific football knowledge and skills, but also well developed fitness qualities. However, no studies have examined the link between physical fitness qualities and injury in AF.
Design: Prospective cohort.
Methods: Injury data were collected through the use of a Player Movement Record (PMR) and a standardized Injury Report Form (IRF). Fitness test data was collected during the pre-season of the 2010 and 2011 seasons.
Results: 382 players consented to participate in the study. The cohort experienced an injury incidence rate of 24.29/standardized club (40 players/club). A faster 5-m sprint was associated with 'injury status' ($p = 0.016$) and a 'knee' region ($p \leq 0.001$) injury. A faster planned agility score was associated with an increased risk of a 'hip/groin/thigh' region ($p = 0.010$) injury, and specifically a 'quadriceps strain' ($p = 0.005$). A lower 20-m shuttle run was associated with an increased risk of a 'shin/ankle/foot' ($p = 0.045$) injury. Increased injury severity was associated with a higher left foot running vertical jump (VJ) ($p = 0.040$), and faster 5-m sprint ($p = 0.043$).
Conclusions: Lower aerobic endurance, faster 5-m acceleration and greater planned agility were associated with an increased risk of various injury types in elite junior AF players. Furthermore, a higher left foot running VJ and faster 5-m acceleration were associated with injury severity. These results may largely relate to a greater work capacity placing a higher load upon the musculoskeletal system in contact and non-contact situations.

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1. Introduction

Australian Football (AF) is a collision sport containing high injury rates in senior[1,2] and junior[1,3] competition. The game is primarily played in Australia on a large sized field involving strenuous running and cutting combined with ball handling and body contact. Elite junior players complete an average total distance of 13.6 km and 140 high intensity efforts (running and sprinting) per match.[4] The South Australian National Football League (SANFL) is the state competition for South Australia in which nine teams participate in the elite Under 18 (U18) league. Nation-wide, the elite state U18 competitions act as primary feeder leagues to the professional Australian Football League (AFL) competition.

Successful performance at the elite junior and senior level not only requires superior specific football knowledge and skills, but also well-developed fitness qualities of muscular power, strength, speed, acceleration, agility and aerobic endurance.[5–7] However, no studies have examined the link between physical fitness qualities and injury in AF.

The testing of physical fitness qualities provides an accessible means to potentially predict injury risk. The AFL currently recommends a standard battery of fitness tests that includes standing and running vertical jumps (VJ), sprinting, planned agility and 20-m multi stage shuttle run tests.

The use of physical fitness qualities to predict injury has had mixed success in the similar sports of soccer[8–10] and rugby.[11,12]

Studies have failed to demonstrate a relationship between physical fitness qualities and within-season injury.[8] However, other studies have demonstrated a link, for example, in soccer, Engebretsen et al.[10] identified slower speed to increase the risk of acute groin injury in amateur players. In rugby, Gabbett and Domrow[12] identified reduced speed and aerobic endurance to be linked with increased injury rates in sub-elite players.

The aim of the research was to investigate the relationship between physical fitness qualities and injury in elite junior AF players. Based upon results from previous research, we hypothesized that players with lower physical fitness qualities would be at an increased risk of injury.

2. Methods

The SANFL was approached to give their approval and consent for participation of their players in this prospective cohort study. All players registered for the SANFL U18 competition over the 2010 and 2011 competitive seasons were then approached for inclusion within the study. Informed consent was obtained from individual players, or their parent/guardian if under 18 years old. All players were de-identified when placed in the injury database by assigning each player a study number. Ethical clearance for the research was obtained from the University of South Australia Human Research Ethics Committee.

An injury was defined as an 'injury or medical condition which causes a player to miss a match', maintaining consistency with the AFL injury Report.[2]

Each team in the U18 SANFL league competes in 20 regular season matches from March to September. Data were not collected during the pre-season period or the end of season finals series. The instruments used in the study included a Player Movement Record (PMR) and a standardized Injury Report Form (IRF), as used in similar studies by Scase et al.[3,13] with similar elite junior cohorts and comparable medical facilities. The PMR was a coded spreadsheet that recorded player participation data. The possible participation options were:

1. Competing for their SANFL club, local club or school team, or
2. Not competing because of injury, illness, suspension or other reasons.

Following a competitive match, a hard copy or electronic PMR and IRF were submitted to the principal investigator by a designated person at each club (e.g. physiotherapist or head trainer).

Through the combined use of the PMR and IRF, the 'injury status' of a player could be determined. For the purpose of data analysis, 'injury status' was defined as "a count variable, which identified whether a player had been injured (yes/no), irrespective of injury type." 'Injury status' was inclusive of upper and lower limb injuries. Next, the IRF enabled classification of an injury into several categories: the 'injury region' category enabled classification of all lower limb injuries (comprising 'hip/groin/thigh', 'knee' and 'shin/ankle/foot'), whilst the 'specific injury type' category comprised four injuries (ankle sprains', 'hamstring strain', 'quadriceps strain' and 'groin strains'). The four specific injuries have been identified to be highly common injuries in junior AF players[3] and were representative of the main muscle groups that are utilized during game conditions and the fitness tests.

In addition, injury severity was reported on the IRF. 'Injury severity' was defined as "the number of games a player missed per injury".

During the 2010 and 2011 pre-season periods, players participated in an AFL recommended standard battery of fitness tests. The sum of seven skinfolds, consistent with the protocol of the International Society of Kinanthropometry[14] was used to establish the body fat percentage of a player. The skinfold sites included the triceps, biceps, subscapular, supraspinale, abdominal, medial calf and front thigh. The measurement was recorded to the nearest 0.1 mm. The maximal muscular power of the lower limb was evaluated using VJ tests. VJ was measured by a 'jump and reach' protocol from a standing start and running jumps (within 5 m) from the left and right foot. A Vertec yardstick device (Swift Performance Equipment, New South Wales, Australia) measured the height to the closest 0.1 cm. The acceleration of a player was evaluated using a maximal high intensity run over a 5- and 20-m distance from a stationary start. Players were timed to the closest 0.01 s using a dual beam electronic timing system (Swift Performance Equipment, New South Wales, Australia). Planned agility was evaluated using the protocol termed 'AFL unique agility test'. The test consists of a series of five pre-planned changes of direction each greater than 90°. The changes of direction are marked with cones that the players run around. Players began from a standing start and performance was timed to the closest 0.01 s using a dual beam electronic timing system (Swift Performance Equipment, New South Wales, Australia) positioned at the end of the course. Aerobic endurance was estimated using the standard protocol for the 20-m multi stage shuttle run, as outlined in a recent reliability re-appraisal of the test by Lamb and Rogers.[15] The final stage achieved was recorded rather than a calculated estimate of $\dot{V}O_{2max}$. Error and reliability data were not available for the planned agility and 20-m shuttle run tests.

Injury data were standardized to a '40 player club' to maintain consistency with the established protocol of the AFL.[2] No recurrent injuries were included in the data. The 'injury status' of each player was only examined against fitness test results from the current year. Thus, if a player participated in the first year of the study, and were eligible and consented to participate for the second year, they participated in another round of pre-season fitness testing.

Statistical analysis was performed in Stata version 11. To determine the impact of confounding variables, the relationship between demographic variables and injury was first established. A log binomial generalized linear model (GLM) was used which modeled the risk ratios (RRs) with 95% confidence intervals (CIs), to determine which factors increased or decreased the risk of injury. In cases where the log binomial GLM failed to converge, a robust Poisson regression model was used instead.

Secondly, to examine the relationship between fitness test results and 'injury status', injury region and specific injury types, a log binomial GLM was again used. RRs were calculated in the model, combined with 95% CIs. If two or more factors were identified to be statistically significant ($p \le 0.05$) in the adjusted univariate analysis, a multivariate analysis was performed using backward elimination.

Thirdly, a negative binomial regression equation that accounted for player clustering was used to examine the relationship between injury severity and fitness test results. RRs with 95% confidence intervals were established. If two or more factors were identified to be statistically significant ($p \le 0.05$) in the adjusted univariate analysis, a multivariate analysis was performed.

3. Results

Over the course of the two seasons, 382 males aged between 14 and 19 years consented to participate in the study. The average age was 17.1 ± 0.8 years. Injury incidence for the cohort is described in Table 1. The average injury severity was 2.8 missed matches/injury.

The average fitness test scores are recorded in Table 2.

The first aim of the study was to determine whether any of the physical fitness variables were related to 'injury status'. A univariate analysis determined whether any of the demographic

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Table 1
Injury statistics.

Classification	Injury	Incidence	Incidence/standardized club (40 player club)
	Total injury incidence (including upper limb injuries)	232	24.29
Body region	Hip/groin/thigh	71	7.43
	Knee	32	3.35
	Shin/ankle/foot	54	5.65
Specific injury types	Groin strains	32	3.35
	Quadriceps strain	21	2.20
	Hamstring strain	16	1.68
	Ankle sprain	42	4.40

variables of age, height, mass and BMI were related to any of the injury variables. Older age was associated with 'injury status' ($p \leq 0.001$), a 'knee region' ($p = 0.010$) injury, a 'shin/ankle/foot' region injury ($p = 0.003$), an 'ankle sprain' ($p = 0.004$) and injury severity ($p = 0.001$). Shorter height was associated with a 'quadriceps' injury ($p = 0.025$) whilst mass was not associated with any of the injury variables. Larger BMI was associated with injury severity ($p = 0.006$) (see supplementary Table 1).

Once the relationship between injuries and demographic variables was established, a univariate analysis (adjusted for age) determined that a faster 5-m sprint ($p = 0.003$), 20-m sprint ($p = 0.025$) and agility ($p = 0.015$) were linked with 'injury status'. A multivariate analysis revealed that a faster 5-m sprint ($p = 0.016$) was associated with 'injury status' (see supplementary Table 2).

The physical fitness qualities were then compared against injuries of certain lower limb regions. First, a univariate analysis (did not require any adjusting for confounding factors) demonstrated that a faster planned agility was associated with a greater risk of a 'hip/groin/thigh' region ($p = 0.010$). Second, a univariate analysis (adjusted for age) identified that a faster 5-m sprint was associated with a greater risk of a 'knee' region injury ($p \leq 0.001$). Finally, a univariate analysis (adjusted for age) revealed that a lower 20-m shuttle run resulted in an increased risk of a 'shin/ankle/foot' region injury ($p = 0.045$) (see supplementary Table 3).

The physical fitness qualities were then compared against four specific injury types. Univariate analyses indicated that an 'ankle sprain' (adjusted for age), 'hamstring strain' or 'groin strain' injury were not associated with any physical fitness qualities. However, a univariate analysis demonstrated that a 'quadriceps strain' (adjusted for height) to be associated with a higher running left foot VJ ($p = 0.034$) and faster planned agility ($p = 0.001$) scores (see supplementary Table 4). A multivariate analysis revealed only a

Table 2
The fitness test results of the cohort.

Fitness quality	Average	Technical error measurement (TEM)	Intraclass coefficient (ICC)
Height (cm)	181.9 ± 7.2	1.03	0.97
Mass (kg)	75.0 ± 8.1	0.59	0.99
BMI	22.6 ± 1.8	na	na
Sum of 7 skinfolds (mm)	60.4 ± 18.2	na	na
Standing VJ (cm)	58.1 ± 5.5	1.98	0.88
Left foot run VJ (cm)	70.7 ± 7.8	1.75	0.93
Right foot run VJ (cm)	66.4 ± 7.9	3.26	0.86
5-m sprint (s)	1.13 ± 0.05	0.02	0.62
20-m sprint (s)	3.14 ± 0.10	0.04	0.78
Agility (s)	8.63 ± 0.29	na	na
20-m shuttle run (level.lap)	12.7 ± 1.1	na	na

faster planned agility to increase the risk of a 'quadriceps strain' ($p = 0.005$) (see supplementary Table 5).

Finally, physical fitness qualities were analyzed against injury severity. A faster 5-m sprint ($p = 0.018$), 20-m sprint ($p = 0.024$), planned agility ($p = 0.013$), and a higher left run VJ ($p = 0.038$) were found to have a relationship with injury severity (adjusted for age and BMI). A multivariate analysis revealed that only a higher left foot run VJ ($p = 0.040$) and a faster 5-m sprint ($p = 0.043$) were significantly associated with injury severity (see supplementary Table 6).

4. Discussion

This study supports ongoing research into elite junior AF injuries, for which there are limited data available for the development of injury prevention programs. The present study is the first in which the relationship between physical fitness qualities and injury in AF players has been investigated. The main finding of the study was that lower aerobic endurance, faster 5-m acceleration, and faster agility were associated with an increased risk of various injury types. The secondary finding of the study was that a higher left foot running VJ, and faster 5-m acceleration were associated with a greater severity of injury.

Whilst the aetiology of an injury in contact sports is multifactorial,[16] it is possible to identify intrinsic factors which may increase the injury risk of a player. In this study, the demographic variables of age, height, mass and BMI were included in the analysis. Older age was found to be associated with 'injury status' (RR = 1.343), 'knee' (RR = 1.906) and 'shin/ankle/foot' (RR = 1.743) region injuries, and 'ankle sprains' (RR = 1.843) specifically. However, the general homogeneity of the cohort must be acknowledged. Shorter players were found to be at a higher risk of a quadriceps injury, a result that replicates findings from the elite senior level of AF.[17] Larger BMI (RR = 1.14) was associated with increased injury severity. The increased size and mass of players could place their body at a greater risk of more severe injury resulting from the absorption of larger forces through joints and soft tissue.[9] Players with larger BMI's may also have an increased level of repetitive accumulated physical trauma,[12] possibly increasing the risk of severe overuse injuries.

Faster acceleration (5-m sprint) was found to be a predictor of 'injury status' (RR = 0.013) and 'knee' (RR ≤ 0.001/s; RR = 0.989/ms) region injuries. Norton et al.[18] proposed that increasing match speed is a central component to an increased injury risk in AF. Faster players could be at an increased risk of injury in both contact and non-contact situations for a variety of reasons. First, previous authors have suggested that fast twitch dominated athletes and players with a greater work capacity may compete with a greater playing intensity (i.e. acceleration and deceleration forces), increasing physiological strain upon the musculoskeletal system.[10,12,19] Secondly, faster players may be able to place themselves in more game involvements, increasing their risk of injury. Engebretsen et al.[10] demonstrated an increased risk of acute groin injuries in explosive players.

Players who were faster at the planned agility run were at a greater risk of developing a 'hip/groin/thigh' (RR = 0.341) region injury and more specifically, a 'quadriceps strain' (RR = 0.073). Hip and groin injuries most commonly occur during movements that are associated with the planned agility test; side-to-side cutting, quick accelerations and decelerations, and sudden directional changes.[20] Pyne et al.[21] identified midfield players to have the greatest levels of agility, indicating that this could be the positional group at the greatest risk. This hypothesis could relate to the increased physical capacity of these players to change direction, cut and maneuver with higher intensity, placing a greater

level of physiological strain on the lower limb. This observation is especially relevant for an acute 'quadriceps strain', because the quadriceps muscle group plays an important role in force generation and absorption.[22]

Players with lower levels of aerobic endurance (20-m multi stage shuttle run) were at a greater risk of 'shin/ankle/foot' region injuries (RR = 0.752), possibly due to these players experiencing higher levels of fatigue at a comparative workload.[12] Due to the greater level of fatigue, those players may struggle to avoid potentially dangerous contact situations in the later stages of quarters. AF is a sport that is highly demanding on the elite athlete. On average, elite junior players undertake 3–4 football training sessions per week and compete in 1–2 matches per week, covering a mean distance of 13.62 km per match.[4,23] This workload may expose players with lower aerobic endurance and poorer ability to cope with the high running workload demands to more shin, ankle and foot injuries, especially those injuries related to repetitive loading. Increasing the aerobic endurance of players may act as a viable method to reduce the risk of shin, ankle or foot injuries. However, it is unclear why the upper leg was not a significantly greater risk of injury in players with a lower 20-m shuttle run.

The second part of the study was to identify if severity of injury was linked with any physical fitness qualities. First, a higher left foot running VJ (RR = 1.022) was associated with increased injury severity. This increase could be associated with the greater muscular and joint strain to jump higher and in turn, the increased load upon landing. Data were not collected on leg dominance; thus, the reason for a lack of relationship with right foot running jump is unclear. However, it is feasible that the predominance of athletes were right foot dominant. As such, the non-dominant left leg would be loaded in stance at a greater level with high intensity movements (kicking, sprinting, running, jumping).

Second, a faster 5-m sprint (RR = 0.021) may be related to an increase in the severity of both contact and non-contact injuries. Faster players may be prone to greater impact forces upon contact with other players, potentially increasing the risk of long term contact injuries such as fractures and ruptured ligaments through being tackled, bumped or in a marking contest. Faster players might also be at an increased risk of more severe non-contact injuries during running and sprinting, as a result of the increased forces absorbed by the lower limb musculature. In relation to the general trend of an increase in injury incidence and injury severity for players with superior fitness test scores, close physical monitoring of this 'high risk' group may be the only viable option.

The main limitation of the study was that the time between fitness testing and injury was not considered. Pre-season fitness testing may only be reflective of injuries sustained early in the season, as a result of the natural fluctuations of player fitness levels over the course of the season. The limitations of the narrow 'missed match only' injury definition and its bias towards more severe injuries are outlined by Orchard and Hoskins.[24] It may be possible that some of the findings presented here are as a result of chance rather than being genuinely causal. Future research should examine the classification of leg dominance, as this may be a key component in determining the different results for left and right foot VJ jump and injury severity. Determination whether there is a relationship between pre-season fitness test scores and results of musculoskeletal screening may provide a greater level of understanding of the factors influencing injury in junior AF players.

5. Conclusion

Lower aerobic endurance, faster 5-m acceleration and greater agility were associated with an increased risk of various injury types in elite junior AF players. Furthermore, a higher left foot running VJ and faster 5-m acceleration were associated with injury severity. This result may largely relate to a greater work capacity placing a higher load upon their musculoskeletal system in contact and non-contact situations.

Practical implications

- Increase the aerobic endurance of players, in an effort to reduce 'shin/ankle/foot' injuries.
- In relation to the general trend of an increase in injury incidence and injury severity for players with superior fitness test scores, close physical monitoring of this 'high risk' group may be the only viable option.
- This study supports ongoing research into elite junior AF injuries, for which there are limited data available, for the development of injury prevention programs.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsams.2012.09.005.

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Appendix K. Publication: The juxtaposition of science and medicine in sport.

Editorials

The juxtaposition of science and medicine in sport. Can we all play together nicely?

David A Opar,[1] Ebonie Rio[2]

The growth in the physical performance team in the elite sport environment has been exponential in recent times. There have never been more personnel involved in the preparation, recovery and injury management of athletes. The practitioners, all with varying and vast skill sets, often include sports physicians, physiotherapists, rehabilitation co-ordinators, strength and conditioning coaches and sports scientists. In some instances, the quest for elite performance has never been so well resourced. Though it must be said, this not true in all sports, including those with less public profile and funding, especially women's sports, which still lacks parity in many facets including the depth of the physical performance team. For the purposes of this editorial, we wish to turn our focus to the juxtaposition of science and medicine in sport and those environments where substantial physical performance teams exist.

Striving for improved performance often involves pushing the athlete to the limit of their capacity, with the ever-present risk of injury. In the perfect world, managing and minimising the risk of injury in athletes would be a collaborative effort, using all the expertise available within the physical performance team; using the experience and learnings from the diverse backgrounds of the team to identify at-risk athletes; instigate interventions to reduce the likelihood of injury and implementing screening and monitoring systems to give daily or weekly information to vindicate your approach or alert you to the need for closer re-examination.

All great in theory.

Anyone who has been involved, in any extent, in an elite sporting environment knows all too well the friction that can exist within the physical performance team. Often there are divergent viewpoints, typically, but not exclusively, between medical (doctor/physio) and performance (S&C and sport scientists) departments (and not to mention the coaching department!). Of course this diversity and robust debate should be encouraged and fostered, as the benefit of many well-considered, evidence-based opinions combined with astute leadership should lead to the most appropriate course of action, given the available information. But too often, the 'battle' can become fierce and one-eyed. Strong ideologies and philosophies are juxtaposed, all with the best intention for the athlete, but with disagreement that can fracture relationships and remove the focus from the ultimate aim.

The evidence from sports around the world suggests that the incidence of our major sporting injuries (ie, hamstring injury) is not on the decline. So despite the best intentions and proliferation in scientific endeavour, the curse of injury still remains. So the question then must be posed, given all the money spent to maximise performance and minimise the risk of injury in athletes, where did it all go wrong?

To use a horse racing idiom, perhaps we start by removing the blinkers. Often our view point of the evidence in front of us is influenced by our education and experience. While medical staff deal with a barrage of ill and injured, and guiding the necessary rehabilitation, performance staff are so often focused on augmenting physical capabilities to maximise output. While both sides are likely to have the same end goal in mind, there can easily be a divide in opinion of how to get there, particularly when the athlete sustains an injury. To appreciate the opinions and expertise of others is such a valuable commodity that might require practitioners from both sides to swallow their pride at times, but this is such a strength of the multidisciplinary performance staff era. What can be learnt from those with different mindsets could reveal insights that might have never been considered.

Ultimately the physical performance team needs to work as a cohesive unit. How do we achieve this? Is it too simplistic to remain within well-defined roles, where overlap exists across positions? Or is this a case of too many chiefs? The answer to these conundrums is likely to be different for every sporting environment, but is a major challenge facing many elite clubs, and ultimately impairing the ability of the physical performance team to provide the best sports medicine and sports science support possible. In an era where the investment in physical preparation and sports medicine in high-profile sports around the world continues to grow, perhaps the time for some reflection into the internal mechanics of the physical performance team is required to ensure that all of that outlay, of both money and time, does not result in more problems than answers.

RESEARCH AT THE COAL FACE OF CLINICAL SPORTS MEDICINE

Clinicians have long been pushing for a shift towards clinically based, clinically applicable and clinically relevant research with a pragmatic approach that can be implemented at the coal face. The elite sporting environment places constant pressure on sports medicine and sports science (both researchers and clinicians) to provide the answers. There is now increased involvement of stakeholders demanding faster translation to clinical practice than we have ever seen before. This has resulted in a significant change over the past few years. Australian football is a perfect example, where research is conducted at clubs and by clubs—who are not waiting for the paper to be published in a few years time after two journal rejections and pages of reviewer comments. They often have immediate access to the latest technology and in-house expertise to answer the questions that plaque their unique environment. With the ever-increasing scrutiny on research quality, it has never been more difficult to publish applied research, which can further slow the translation of this research to practice.

We have both been fortunate enough to tap into these situations (the elite sporting environment) and conduct research. This enables a relationship between the people on the ground with the questions (clinicians) and the people that have the knowledge to design a study to provide an answer (researchers) or, in most cases, usually uncover more questions! It is immensely satisfying for all to be able to contribute in this way.

However, this can have pitfalls. Clinicians may be quick to accept or reject findings and integrate into their practice prematurely and researchers can be guilty of being slaves to p values, without the consideration for clinical relevance.

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Unfortunately this type of research may be limited and lack scientific rigour depending on whether the personnel have the necessary research skills. There is the risk of commercial interest outweighing or influencing good science. It remains imperative that we continue to conduct research of the highest quality within the applied environment. Quality research, however, does not have to always be a randomised controlled trial. There has never been a randomised controlled trial demonstrating that parachutes are advantageous if you jump out of a plane (Thanks Peter Blanch!). Similarly to jumping out of a plane, the elite sporting environment is usually not conducive to rigid controlled trials with a sham control group. This means a compromise (sometimes) between the ideal and the reality. We should not see this as a negative, as ultimately a pragmatic approach may enable us to be one step closer to clinical translation (or more questions!)

ONE CONFERENCE TO RULE THEM ALL...

The issues raised in the editorials[1 2] draw into focus two of the great strengths of Sports Medicine Australia, the strong collaborative focus across disciplines and the need for access to cutting edge clinically applicable research. To this end, the ASICS Sports Medicine Australia Conference to be held at the Intercontinental Sanctuary Cove —Gold Coast, Queensland, 21–24 October 2015 will be no exception. Why is it such a great conference? Apart from a strong scientific programme, an impressive list of internationally renowned keynote speakers,

daily workshops offering practical tips and tricks from experts in the field of sports science and sports medicine, what better than doing all this in the idyllic surrounds of Sanctuary Cove. All of this makes the ASICS Sports Medicine Australia conference a one stop shop to update your knowledge and skills, to connect with colleagues and network.

As a researcher, this conference offers one of the richest sports medicine and science conference awards scheme with over $AUD23 000 on offer as recognition and encouragement for some of the wonderful research presented. For those involved in research, it is a fantastic exposure to a broad audience of researchers and practitioners alike. Perhaps most encouraging, particularly for emerging researchers, is that up to three new investigators are offered the amazing opportunity to travel to an international conference to present their research to the world! Both ER and DAO have been talented recipients of awards at previous ASICS Sports Medicine Australia Conferences and encourage other researchers to submit abstracts by visiting http://sma.org.au/conferences-events/conference/ and follow the prompts.

ER was awarded the New Investigator Award in Clinical Sports Medicine 2013 and the travel grant allowed her to attend and present her research on isometric exercise to reduce pain in tendinopathy at the International Scientific Tendon Symposium in Oxford 2014. DAO was a recipient of the Best New Investigator in Injury Prevention in 2013 and Best Paper in Clinical Sports Medicine in 2014 and has used this money to support his

ongoing research endeavours in hamstring injury. These are fantastic opportunities for early career researcher to link with colleagues on the world stage. These awards provide unique opportunities to obtain support for attending international conferences which while so important, can be cost prohibitive. Even if you are not so 'young' or new, we would encourage all researchers and clinicians to mark this conference in your diary. Cocktail anyone? http://www.intercontinentalsanctuarycove.com/

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The juxtaposition of science and medicine in sport. Can we all play together nicely?

David A Opar and Ebonie Rio

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Journal of Orthopaedic & Sports Physical Therapy

Patellar tendinopathy: Management strategies for difficult presentations

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Patellar tendinopathy: strategies for difficult presentations

1   **Abstract**

2   Anterior knee pain may be caused by several structures including the fat pad, patellar tendon,

3   patellofemoral joint, bursae and less commonly neural irritation or joint plica. Whilst imaging

4   may assist in differential diagnosis, the diagnosis of patellar tendinopathy remains clinical, as

5   asymptomatic tendon pathology may coexist in people who have pain from other anterior knee

6   sources. The two hallmark features of patellar tendinopathy are (1) pain localised to the inferior

7   pole of the patella and (2) dose dependent load related pain that occurs with activities that

8   require the patellar tendon to store and release energy (jumping and change of direction). A

9   thorough ~~subjective and objective evaluation~~ will generally determine the source of pain.

10 Management of patellar tendinopathy should focus on progressively developing load-tolerance

11 of the tendon, the musculoskeletal unit and the kinetic chain. Rehabilitation can be a slow and

12 sometimes frustrating. Common pitfalls involve inadequate rehabilitation time or progression,

13 over-reliance on passive treatments, a lack of individualisation, or not addressing specific

14 muscle, biomechanical and kinetic chain deficits. This review will assist clinicians with the more

15 ~~difficult~~ presentations ~~and~~ outlin~~e the challenges and~~ common ~~errors~~ in treating patellar

16 tendinopathy.

17

Introduction

19   Anterior knee pain is a common clinical presentation and is prevalent in athletes who jump and

20   land, run or cycle. Anterior knee pain can originate from the joint, the tendon and the

21   surrounding structures of the knee. Proximal patellar tendinopathy, one diagnosis of anterior

22   knee pain, is not a self-limiting condition and often results in prolonged time away from sport.

23   Cook et al. [8] found that more than a third of athletes presenting for treatment for patellar

24   tendinopathy were not able to return to sport within 6 months. Patellar tendinopathy is

25   primarily a condition of relatively young (15-30 year old) athletes especially men who perform

26   repetitive loading in sports such as basketball, volleyball, athletic jump events, tennis and

27   football. Movements in these sports involve jumping, landing and change of direction, which

28   require energy storage and release in the tendon, that is, high tendon load.[22]

Assessment of patellar tendinopathy

30   Tendinopathy can be either missed as a diagnosis or incorrectly diagnosed when another

31   structure is responsible for the pain. Patellar tendinopathy is one of many potential diagnoses

32   producing anterior knee pain and has specific and defining clinical features. The two hallmark

33   features of patellar tendinopathy are (1) pain localised to the inferior pole of the patella and (2)

34   dose dependent load related pain that occurs with activities that store and release energy in the

35   patellar tendon.[21] Tendon pain occurs instantly with loading and ceases when the load is

36   removed (again, very quickly).[35]

37   Key points of the ~~subjective evaluation~~ can reveal a "warm up" phenomenon where pain

38   decreases as activity continues, but is followed by increased pain the day after high tendon load

39   activities [35]. The ~~objective~~ assessment should demonstrate that the pain increases as the load

40   on the tendon increases.[21] This means a single leg hop will hurt more than a double leg jump

41   and increasing hop/land height will be more painful again. Strategies to reduce tendon loading

42   (e.g a stiff knee in hopping) are characteristic of patellar tendinopathy.[41] ~~In fact~~, the athlete who

43   is willing to flex the knee during hopping is likely to have an alternate source of pain. Deficits in

44   the kinetic chain most commonly include gluteal and quadriceps atrophy, poor calf endurance,

45   and limited capacity to attenuate or store and release energy in the kinetic chain. Many of

46   these features (especially the stiff knee strategy) are unique to tendon pain and assist with

47   differential diagnosis of anterior knee pain.

48   Aside from pain at the inferior patella pole, tendinopathy of the extensor mechanism can occur

49   at the quadriceps tendon or distal insertion at the tibial tuberosity. These less common clinical

50   presentations also have unique features. Quadriceps tendinopathy, seen in athletes such as

51   weight lifters who use deep knee flexion (thus have tendon compression against the condyles),

52   will have pain localised to the superior patellar quadriceps tendon insertion.[39] Distal patellar

53   tendon pain, often seen in distance runners, is generally localised to the tibial tuberosity.[39] The

54   infrapatellar bursa is an intimate part of the distal patellar tendon attachment[4] and should be

55   treated in conjunction with the tendon. Mid tendon patellar tendinopathy is generally only

56   secondary to intratendinous interventions or caused by trauma from a direct blow[15, 40]

57   (however this also requires careful differential diagnosis as other structures be injured in a

58   direct blow).

59   *Differential diagnosis*

60   Pain will be more variable in nature and site if nearby structures are the source of pain. The

61   contribution of Hoffa's fat pad to anterior knee pain is poorly understood. It is known to be

62   active in cytokine production[40], have vascular connections to the tendon[31] and fascial

63   connections with knee joint (patellofemoral and tibiofemoral) ligaments and patellar tendon.[7] It

64   can be impinged traumatically, usually in a tibiofemoral hyperextension incident. Isolated fat

65   pad pain of insidious onset is often associated with chronic uncontrolled extension and is

66   common in some populations (e.g. young gymnasts). Infrapatellar fat pad hypertrophy has been

67   described in association with patellar tendinopathy.[11] The main differential diagnosis is the site

68   of pain, fat pad pain is not localised to the inferior pole, but more likely diffuse anterior inferior

69   knee pain, especially during loading tests that accentuate knee extension.

70   Patellofemoral pain syndrome (PFPS) may also present as anterior knee pain among jumping

71   athletes and is a key differential diagnosis. PFPS will generally become even more diffuse when

72   loaded and not increase as tendon load increases.[6] The athlete may often complain of

73   aggravating activates that are low tendon load, such as walking, running or cycling[6], thus pain

74   from these activities should cause a high index of suspicion for a diagnosis other than patellar

75   tendinopathy. On a clinical note, patellar tendinopathy and PFPS rarely co-exist, that is, one or

76   the other is the primary source of pain and rehabilitation should be consistent with that

77   diagnosis. Abnormality in the patellar tendon on ultrasound or magnetic resonance imaging

78   does not constitute a diagnosis of patellar tendinopathy.

79   Pain from the joint such as a plica and chondral surface pathology may also present as anterior

80   knee pain. These may result from trauma and can produce pain at rest and at night, which is

81   uncommon in tendons [9]. Localised osteochondral lesions of the inferior patella or trochlear may

82   sometimes closely mimic patellar tendinopathy.   Joint effusion is an indicator of intra-articular

83   injury and does not occur in either patellar or quadriceps tendinopathy. Palpation of the

84   common sites for plicae, a history of snapping sensation and MRI often assist in the diagnosis.

85   Superior plica may be confused with quadriceps tendinopathy both clinically and radiologically.

86   A delineated lesion deep to the quadriceps tendon proper raises a high index of suspicion for

87   superior plica.[16]

88   <u>Differential diagnoses through the lifespan</u>

89   Developing growth plates may cause anterior knee pain during puberty, resulting in Osgood-

90   Schlatter syndrome (common) and Sinding-Larsen--Johansson Syndrome (rare).[17] Both patellar

91   tendinopathy and isolated fat pad irritation are common in adolescents. Children and

92   adolescents are also vulnerable to systemic and sinister causes of pain and symptoms that

93   suggest non-mechanical pain should be referred appropriately.[6] Conversely, patellar

94   tendinopathy almost never occurs in older people (>40 years), it seems even in the face of

95   continued jumping in the occasional athlete, that the load on the tendon is below a provocative

96   threshold.

97   **Management of patellar tendinopathy**

98   Management of patellar tendinopathy should focus on progressively developing load-tolerance

99   of the tendon, the musculoskeletal unit and the kinetic chain through four stages. Rehabilitation

100   progression criteria should be based on pain and strength (Table 1). Loading modification is

101   used first to reduce pain, then progressive loading is used to restore function in the kinetic

102   chain and muscle-tendon unit. Minimal pain or awareness is acceptable during and after

103   exercise, but symptoms should settle reasonably quickly after exercise (within a few hours) and

104   should not progressively worsen over the course of the loading program.[20] In particular, the

105   pain 24 hours after activity is a good indication of the tendon's response to the load, if pain is

106   stable or improved the load has been tolerated, if it is worse it suggests the load exceeded the

107   tendon's tolerance.

108   Key rehabilitation exercises and progression criteria for patellar tendinopathy requires a

109   comprehensive rehabilitation progression in the presence of high levels of pain and dysfunction

110   (Figure 1). It can be modified to individual needs, for example, more or less stage 2 or 3

111   exercises is dependent on strength and energy storage deficits, respectively. In the initial phases

112   of rehabilitation the goal is to reduce pain with isometric exercise and other adjuncts. In later

113   phases pain may still be present but needs to be stable. Whether pain is reducing or remaining

114   stable is best assessed with a provocative load test at the same time every day. This may include

115   a forward hop, single leg decline squat, or split jump.

116

117   [Table 1 around here]

118

119   Stage 1: Isometric mid-range quadriceps exercise have been shown to reduce patellar tendon

120   pain for 45 minutes post exercise and this was associated with reduced motor cortex

121   inhibition.[35] They are indicated to reduce and manage tendon pain and commence muscle-

122   tendon unit loading when pain limits the ability to perform isotonic exercise. Leg extension

123   isometrics (30° knee flexion) are ideal for patellar tendon as they isolate the quadriceps ~~and do~~

124   ~~not allow other muscles to take over (e.g gluteus maximus in leg press) if the quadriceps are~~

125   ~~pain inhibited.~~ Importantly resistance should be added fairly quickly and progressed to single

126   leg for optimum effect. An alternative is the Spanish squat[2] that can be useful especially when

127   there is limited or no access to gym equipment (e.g the travelling athlete). The dosage for either

128   exercise above will depend upon individual factors but clinically the aim is 4 sets of 45 seconds

129   performed 2-3 times per day[9, 35]. It is important that there is no muscle fasciculation or

130   "bounce" and that there is sufficient (at least 60-90 seconds) rest between sets to allow muscle

131   recovery. A good prognostic sign for isometrics is an immediate reduction in pain with loading

132   tests post exercise. Furthermore, the authors have used isometric exercise as part of differential

133   diagnosis, a tendinopathy will demonstrate an immediate reduction in pain on a loading test.

134   Stage 2: Isotonic load is commenced when it can be performed with minimal pain with low load.

135   Isotonic load is important to restore muscle bulk and strength in functional joint ranges. Knee

136   flexion beyond 90° and full extension are avoided as it can be provocative. Initially, flexion may

137   be limited from 10-60°, and progressed towards 90° as pain permits. Leg press, leg extension,

138   squats and split squats are suitable exercises. The focus is on heavy (8 to 6 repetition maximum)

139   and slow isotonic (concentric-eccentric) loading, 3-4 sets performed every other day. There

140   should be a significant single leg exercise component in order to address strength asymmetries.

141   Evidence suggests heavy isotonic training may be superior to traditional decline squatting[20].

142   Stage 1 exercises can be continued on the "off" days, particularly if symptoms are still present

143   and isometrics have an immediate positive effect on symptoms. Stage 2 strengthening

144   exercises, preferably weight-based, are maintained throughout rehabilitation and return to

145   sport

146   Stage 3: Reintroduction of energy storage loads on the myotendinous unit is critical to increase

147   load tolerance and improve power as a progression to return to sport. Energy storage is

87

148   commenced when there is good strength consistent with the other side (for example will need

149   to be able to leg press at least 120% bodyweight <mark>8RM</mark> for most jumping athletes but higher

150   needed at elite level) <mark>and minimal pain during and minimal or no flare in the 24-hours following</mark>

<mark>151</mark>   <mark>energy storage e.g. slow hop (e.g. 1.5Hz to ensure adequate knee flexion) or split jumps</mark>. The

152   start point for energy storage rehabilitation will depend on pain response to load and function

153   during energy storage testing (e.g. hopping). Initially the tendon may only be tolerant to a few

154   low intensity jumps (e.g. double leg jumps or small depth split squat jumps) and the volume can

155   be progressed as tolerance increases. Eventually higher intensity jumps can be added (e.g.

156   single leg hops, forward hops, deeper split squat jumps). Progressions are always guided by the

157   24-hour response to load. Pain with load is monitored at the same time daily with a single leg

158   decline squat, <mark>recording pain</mark> out of 10. If pain <mark>remains minimal</mark> and stable, loads can be

159   progressed, but requires modification if pain increases. This is often the most provocative stage,

160   so loading is performed every third day and should be followed by a low load tendon day (e.g.

161   stage 1 isometric loads, non-impact cross training), followed by a strengthening (stage 2) day to

162   form a three day high-low-medium tendon load cycles twice a week with a rest day allowed.

163   Some athletes feel worse the day after a rest, requiring a program that loads the tendon

164   everyday. Accurate quantification of load is important at this stage. The number and intensity

165   of jumps and all other energy storage activities should be captured to ensure that loads are

166   progressively applied to meet the ultimate demands of the sport. Although highly individual,

167   this process can take several weeks to months for some athletes. Energy storage options include

168   jumping and hopping variations, acceleration, deceleration and cutting (Figure 1). Choice of

169   exercise will depend on individual sports demands so <mark>energy storage programs</mark> can vary greatly

170   in individuals in different sports and even between positions of the same sport.

171   Stage 4: Progression back to sports specific training can be commenced when the tendon is

172   tolerant to stage three <mark>energy storage load progressions.</mark> These replace the stage three

173   exercises but stage two exercises are continued. <mark>Stage one (isometrics) can be utilised but</mark>

<mark>174</mark>   <mark>increased pain after loading requires load modifications</mark>.   Controlled volume and intensity of

175   load on re-introduction to training is essential and should be consistent with stage three

176   exercises in the early phases. Ideally sports loads (competition and training) are performed

177   every two to three days, but this can vary depending on symptom response and demands of

178   individual sports/teams.

179

180   Figure 1: Progression of patellar tendinopathy rehabilitation

181   **Common management pitfalls**

182   Rehabilitation can be a slow and frustrating process and management pitfalls involve either

183   inadequate rehabilitation time or progression and an over-reliance on non-load (passive)

184   treatments. Some clinical presentations are associated with slower response to rehabilitation,

185   such as extremely load-sensitive tendons usually in young jumping athletes.

186   *Unrealistic rehabilitation timeframes*

187   The temptation or pressure to shorten rehabilitation time is understandable given athletes'

188   eagerness to return to sport, and the demands of competing in elite sport. Progression of

189   rehabilitation is related to symptom response to load and neuromuscular function, both of

190   which also determine capacity to return to play. Progression can be slow, sometimes taking 6

191   months or longer, particularly among athletes with poor baseline neuromuscular function,

192   muscle atrophy and irritable symptoms or after multiple intra-tendinous interventions. It is

193   important to educate patients and other stakeholders (parents, coaches) about realistic

194   timeframes. All stakeholders should be involved in setting short and longer-term goals based on

195   functional targets (e.g. restoring leg extension strength on the affected side, equal hop for height

196   on both sides) as these serve to motivate athletes, monitor progress and provide objective

197   measures for progression.

198   *Beliefs and expectations about pain*

199   Some athletes with patellar tendinopathy are unable to continue competing with symptoms,

200   whereas others can continue with substantial pain and kinetic chain deficits.[9, 26] In some sports

201   where patellar tendinopathy is prevalent, such as volleyball, there is a culture of playing with

202   pain. Beliefs about pain and pathology may influence the development and management of

203   unresponsive symptoms.[3, 29] Some athletes may have been told that 'tears' and 'degeneration'

204   have caused permanent tendon 'weakening', increasing the risk of rupture. Patellar tendon

205   rupture (in the absence of systemic disease) in sport is rare.[23] Education about pain and tendon

206   remodelling is important. Athletes need to be aware that pain is not necessarily equal to harm,

207   and some pain during rehabilitation is acceptable, and athletes may return to sport managing

208   some pain. Symptoms during rehabilitation are less important than response to a load test the

209   next day.[20, 38] Features of central sensitisation are not common in athletes with patellar

210   tendinopathy, however patients who have undergone multiple invasive procedures are

211   vulnerable. Extra care in differential diagnosis must be taken with the athlete with many years

212   of symptoms, vague anterior knee pain or changes in imaging as they are frequently mistreated

213   as patellar tendinopathy that has "central sensitisation features" such as spreading of pain and

214   do not benefit from a tendon rehabilitation approach.

215   *Over-reliance on non-load treatments*

216   Common non-load or adjunct interventions include manual therapy such as transverse frictions,

217   electrotherapy (e.g. ultrasound), shockwave therapy, injections (sclerosing, steroid, platelet rich

218   plasma) and surgery. There are three key issues with passive adjuncts, 1) there is progressive

219   tendon and kinetic chain deconditioning due to enforced rest following the intervention 2)

220   passive therapy fails to address musculoskeletal and kinetic chain dysfunction 3) the potential

221   for pain sensitisation that further complicates management. Evidence for effectiveness is

222   lacking for most adjunct treatments, particularly when compared to exercise [14]. Injections and

223   surgery are commonly offered when rehabilitation plateaus or fails, unfortunately many

224   rehabilitation programs ensure failure because they are incomplete or have not allowed

225   sufficient time for adaptation.[37] Multiple adjuncts without an individualised and progressive

226   rehabilitation program is a poor management strategy for patellar tendinopathy. The key

227   strategy for avoiding this is setting realistic goals based on a sound understanding of the

228   condition and its rehabilitation.

229   *Inappropriate rehabilitation progression*

230   Rehabilitation choices may be inappropriate at any of the four stages. Failure to gain control of

231   pain, normalise muscle capacity, progress and accommodate elastic loading and absorb

232   functional challenges at normal training volumes generally explain rehabilitation failures.

233   Tissue loading and adaptation to meet the demands of the sport can only be progressed in a

234   stepwise manner and at a finite rate that matches the tendon's capacity to adapt (indicated by

235   the response to load the next day).

236   Progression to each stage and inappropriate rehabilitation can be assessed clinically. Stage one

237   isometric exercises are for pain management and should be used in isolation only in the first

238   few weeks of the program before progressing to stage two exercises. Occasionally, highly

239   reactive tendons require more time in this stage. These exercises are not effective for tendon

240   pain relief if they are loaded too little (eg static quads over fulcrum) or too much (200kg on a leg

241   press), leaving both athlete and clinician frustrated.

242   The key in the stage two is a formal strengthening approach, three to four sessions per week,

243   with a focus on progressive overload of the atrophic muscle groups with multiple sets of two to

244   three varied exercises in the session (generally performed with no provocation of symptoms on

245   decline squat testing the next day). A common pitfall is including only double leg, multi-joint

246   exercises (eg squats) that continue to offer an opportunity for the painful patellar tendon to be

247   unloaded.

248   Stage three (energy storage loading) offers greater risk of symptom provocation and should

249   only be commenced when neuromuscular function (e.g. strength), or load distribution through

250   the kinetic chain is adequate and symptoms are not irritable. Most athletes with patellar

251   tendinopathy will benefit from gradual reintroduction of energy storage loads over 6-8 weeks to

252   enable the tendon to develop sufficient load tolerance (volume and intensity) before building to

253   sports specific rehab in stage four. Volleyball presents one of the greatest challenges to

254   regaining tendon tolerance as they can have up to 300 jump-landing cycles in a session. Our

255   recommendation would be no more than three energy storage loading sessions (stage three and

256   four) within a week in the recovering tendon, which in elite sport is continued as a principle for

257   the first year of return.

258   *Over-reliance on a decline board exercise program*

259   The single leg decline board squat was developed to focus load more on the patellar tendon in

260   assessment or rehabilitation.[19, 33, 42] A high quality study with low numbers showed equivalent

261   outcomes with heavy slow resistance training (double leg hack squats, leg press, squats).[20, 25]

262   Clinically, the decline squat program (that is an eccentric focus program) may be too aggressive

263   for patients with symptoms and is a poor choice in season as it is designed to maximise patellar

264   tendon load[42] and often provokes pain. Further, reliance on decline board squatting as the

265   singular means of muscle-tendon overload and progression falls well short of the demands of

266   sport.

267   *Not addressing isolated muscle deficits*

268   Rio et al. [35] found that patellar tendinopathy was associated with substantial motor cortex

269   inhibition, which may explain persistent muscle atrophy with symptoms. Altered

270   neuromuscular output is likely to be a response to pain but may persist even after symptoms

271   have resolved.[18] Compound rehabilitation exercises, such as single leg squatting, single leg

272   decline squats and compound gym-based exercise such as leg press and squats may not

273   adequately address quadriceps atrophy. They can be counter-productive in early stages when

274   quadriceps muscle weakness and inhibition is a predominant feature; in this instance

275   compensatory patterns may spare the very muscle group targeted. Leg extension is an ideal

276   exercise option for patellar tendinopathy as it can isolate quadriceps function.

277   *Failure to address kinetic chain deficits*

278   In rehabilitation there is a temptation to focus on the injured site, in this case the patellar

279   tendon. Addressing kinetic chain factors is essential for successful resumption of sporting

280   activity. In the distal kinetic chain, the calf-Achilles complex has an important role in producing

281   power and absorbing load in landing and jumping[5], hence calf strength, endurance and power

282   are critical. Limited ankle dorsiflexion has been associated with patellar tendinopathy [27].

283   Stretching, mobilising the ankle joint and end range isotonic loading (e.g. eccentric calf muscle

284   training) may increase dorsiflexion range.[24, 30, 34] Proximal kinetic chain deficits contributing to

285   patellar tendinopathy more commonly involve poor sagittal plane capacity (hip extensor

286   function) rather than coronal and transverse plane dysfunction.[36]

287   *Not adequately addressing biomechanics*

288   Athletes with patellar tendinopathy may require progressive jump-land retraining, focusing on

289   'soft' landings on the fore-mid foot with greater ankle, knee and hip range of motion[32] to reduce

290   vertical ground reaction forces. This generally commences with double and progressing to

291   single leg landings. Landing with a 'stiff' knee strategy[41] and reduced hip flexion in horizontal

292   jump landing [12] are associated with higher patellar tendon forces. Importantly, changes to jump-

293   landing mechanics should not be attempted prior to adequate rehabilitation (i.e. meeting

294   criteria to progress to stage three, and mild (less than 24 hours) or no symptom provocation

295   following energy storage exercise). Pain and weakness are commonly the cause of changes to

296   strategies and these must be addressed first.

297   **Difficult patient presentations**

298   *Highly irritable tendon symptoms*

299   Poor outcomes occur when progression of rehabilitation fails to respect pain severity and

300   irritability. The patellar tendon that is very irritable may require bilateral loading early,

301   however progression to single leg isometric loading with resistance should remain a short-term

302   aim guided by 24 hour response to load. Adjunct interventions (avoiding intratendinous

303   injection) may be very useful in reducing symptoms to allow load progression within a

304   controlled rehabilitation program.

305   *In-season athletes*

306   In-season athletes with patellar tendinopathy can be difficult to manage[9], mainly because it is

307   difficult to adequately reduce their volume of energy storage loading to allow symptoms to

308   settle. In addition, it is a challenge to address underlying muscle strength deficiencies, and

309   persistent symptoms will restrict training and competition. In these athletes, the principal focus

310   is on managing pain through the use of isometric leg extensions, coupled with load management

311   by reducing or removing training drills that involve maximal jumping, landing or change of

312   direction and intrinsic unloading through better distribution of energy absorption across the

313   kinetic chain. Anti-inflammatories, the tendon polypill[13], corticosteroid (oral or injectable)[20] and

314   high volume injection[10] may have an adjunct role, for example, leading into a tournament or

315   towards the end of the season. Preference should be given to the least provocative and invasive

316   options first. Maintenance and progression of isometric (daily) and slow isotonic loading (two

317   to three times a week), optimally timetabled around training loads, remains a key element in in-

318   season management.

319   *Deconditioned athletes*

320   Athletes who return to training and playing after a layoff are susceptible to patellar

321   tendinopathy symptoms, particularly those with a past history of patellar tendinopathy. The

322   layoff may be short, due to acute injury or the off-season, or ~~longer~~ on return from any longer-

323   term injury. The principal issue is deconditioning of the kinetic chain, quadriceps and tendon

324   tolerance to load, which generally require significant time to restore. Setting a realistic

325   management timeline on return to sport is critical. Where the practitioner has influence over

326   the athlete during prolonged absences from training, maintenance of adequate muscle, tendon

327   and kinetic chain loading is essential.

328   *Young jumping athletes*

329   Patellar tendinopathy can be very difficult to manage among young jumping athletes. The onset

330   is usually in boys between 14 and 17 years old, coinciding with an increase in training volume,

331   such as starting to play for representative as well as local teams. The talented young athlete is

332   highly committed, both in terms of training and playing, not uncommonly across more than one

333   sport. Young athletes require all the strategies of initial unloading followed by progressive

334   loading and rehabilitation, and are typically more reactive at this stage than in older athletes.

335   *Systemic drivers*

336   The aetiology of patellar tendinopathy is multifactorial, including both load-related and

337   systemic drivers. Systemic drivers associated with patellar tendinopathy include increased

338   central adiposity and insulin resistance, even in the young and active patellar tendinopathy

339   population.[28] Although uncommon, symptomatic patellar tendinopathy may be associated with

340   auto-immune or connective tissue disease (e.g. systemic lupus erythematosus, psoriatic

341   arthritis).[1] Symptoms are often bilateral and irritable. Clinicians should suspect a

342   rheumatological contribution to patellar tendinopathy where it is difficult to attribute the

343   tendon load history to the apparent tendinopathy (i.e. when there is a complete absence of high

344   patellar tendon energy storage load).

345   **Conclusion**

346   Patellar tendinopathy can be difficult to manage. This review highlights key clinical aspects in

347   both diagnosis and management, and common pitfalls. More commonly management fails

348   because diagnosis is inaccurate or rehabilitation is inadequate (e.g. rushed, not progressive

349   enough, not addressing key deficits in a systematic manner). The cornerstone of patellar tendon

350   management and rehabilitation remains a highly specific and thorough approach to progressive

351   loading of the kinetic chain, muscle-tendon unit and tendon matrix.

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Table 1: Rehabilitation stages and progression criteria

Stage	Indication
1=Isometrics	Tendon pain Can be used in-season or in the initial stages of rehabilitation to reduce tendon pain, suggested range 30°-60° degrees knee flexion
2=Isotonic	Minimal pain with isotonic load e.g. leg press to a maximum of 90° degrees knee flexion or less, leg extension to suggested 20-70 degrees (usually need avoid full extension and 90 degrees knee flexion)
3=Energy storage	FUNCTION Good strength consistent with other side (for example will need to be able to leg press at least 120% bodyweight 8RM for most jumping athletes but higher needed at elite level) PAIN Minimal pain during and minimal or no flare in the 24-hours following energy storage e.g. slow hop (e.g. 1.5Hz to ensure adequate knee flexion) or split jumps
4=Sport	No reaction to progressive energy storage, and progressive training prior to competition

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STAGE 1: Isometrics: indicated if pain prohibits isotonic exercise
Dosage: 4 x 45 seconds, 2-3 x /day, progress to 70% MVC

a) Leg extension 30°-60° knee flexion or 'Spanish squat'
b) Spanish squat is an alternative
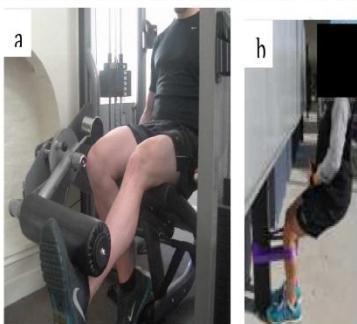
STAGE 2: Isotonic: commence when minimal pain in their execution
Dosage: 3-4 x 6-8 repetitions, every 2nd day, fatiguing load

a) leg extension; b) leg press; c) split squat
Other examples include step up, walking lunges
20°-70° knee flexion for leg extension, maximum 90° for other exercises
Care with tibia angle to ground no less than 90°
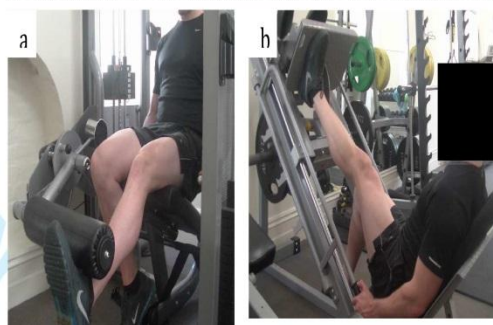
STAGE 3: Energy storage: commence when strength recovered and no
pain 'reaction' to energy storage exercise

Add 1-2 sports and deficit specific tasks over a 6-8 week period in order
to replicate demands of sport, low to high intensity

Example progressions:
Jumping/hopping e.g. vertical jump/hop, forward hop, split jump
Acceleration e.g. run throughs
Deceleration e.g. stop jumps
Cutting e.g. 60° turns
Sports specific training i.e. gradual training resumption
NB low intensity sports specific skills training can commence earlier
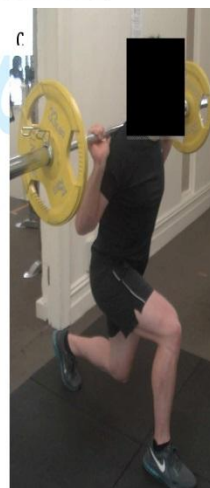
No reaction to progressive energy storage, and progressive training
prior to competition

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Appendix M. Publication: At what age do children and adolescents develop lower limb tendon pathology or tendinopathy? A systematic review and meta-analysis

Title:

At what age do children and adolescents develop lower limb tendon pathology or tendinopathy? A systematic review and meta-analysis.

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Short title: Tendinopathy in children and adolescents

Abbreviations: QA – Quality Assessment; PE – Physical Examination; US – Ultrasound

Key words: Tendinopathy, children, adolescents, puberty, gender, development, tendon

Contributor's statements:

Mitchell Simpson: Mr Simpson designed the review, completed the search of literature, designed and completed the quality assessment of all studies, drafted the initial manuscript, and approved the final manuscript as submitted.

Ebonie Rio: Mrs Rio assisted with the design of the review and search terms, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Jill Cook: Prof Cook assisted with the design of the review and search terms, assessed the quality of the studies, supervised the initial draft of the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Background: Tendon pathology and tendinopathy have been reported in children and adolescents; however, the age of onset and prevalence of the conditions have not been examined systematically.

Objective: To examine the prevalence of lower limb tendon pathology and tendinopathy in children and adolescents and the factors associated with the conditions in this population.

Methods: Six databases were searched (Medline, CENTRAL, EMBASE, Scopus, Web of Science and AMED). Studies were included if the prevalence of lower limb tendon pathology and/or tendinopathy were reported in humans under the age of 18. Studies were divided into method of diagnosis (physical examination, ultrasound and questionnaire) and further into studies that reported prevalence data by tendon (reported two data points (right and left) for each participant) and those that reported prevalence data for participant (reporting one data point (right or left) per participant).

Results: Sixteen studies met the inclusion criteria. Lower limb tendinopathy prevalence (presence of pain and dysfunction) ranged between 8.2% and 33.3%, and increased in prevalence as age increased up to 18 years. The odds ratio for studies reporting tendinopathy by tendon was 0.37 [0.20, 0.69] in favour of boys presenting with tendinopathy. Study aims and reporting methods were heterogeneous.

Conclusions: The onset age of lower limb tendinopathy in children and adolescents has not been widely studied. The systematic review found that tendinopathy is present in children and adolescents and increased in prevalence with age up to 18 years. Male sex was significantly associated with tendinopathy in studies that reported tendinopathy by tendon.

Key points

- Lower limb tendon pathology and tendinopathy is present in children and adolescents, which coincides with the ages of puberty and biological maturation.

- Male sex is significantly associated with tendinopathy in studies that reported tendinopathy by tendon.

- The findings indicate a need for longitudinal investigations into age of tendon pathology and tendinopathy onset, as well as further research into whether puberty is associated with tendon pathology and tendinopathy development.

Introduction

Tendinopathy is a debilitating musculoskeletal condition in the work place and on the sporting field that can result in substantial morbidity and disability [1-4]. Tendon pathology is the term used for the presence of tendon injury seen on clinical imaging, and can occur with or without pain (Fig1)[1, 3]. Tendon pathology in the presence of pain is known as tendinopathy [1, 5, 6]. For the purpose of this systematic review the term tendon pathology will refer to tendon injury diagnosed on imaging (hypoechoic areas or vascularity on ultraound), irrespective of the clinical diagnosis. The term tendinopathy will only include those clinically diagnosed with tendon pain with or without pathology.

Tendinopathy is defined as the clinical syndrome of pain and dysfunction within a tendon, and while it is currently the preferred term used to describe symptomatic tendon pathology [3], other terms have been used to describe this presentation in the past [1, 5]. Tendonitis was the term originally used to describe an inflamed and painful tendon [5, 7, 8], however this definition assumes the injury is accompanied by an inflammatory response [1]. A number of histopathological, biochemical and molecular research papers have reported the limited inflammation, with the lesion best described as non-inflammatory tendinosis [8]. Inflammation has rarely been shown to be a leading component of tendon pathology however it may be a characteristic at some point [9]. The term tendinopathy is therefore recommended for the clinical presentation of tendon pathology [5, 7, 8].

Ultrasound and magnetic resonance imaging are commonly used to diagnose tendon pathology [10], and ultrasound has been found to be a valid measure of tendon pathology [1, 11]. The presence of abnormalities (hypoechoic areas or vascularity) is not always associated with tendinopathy because asymptomatic pathology exists in a large proportion of the active population [12]. Therefore ultrasound diagnosis of tendon pathology will give a different prevalence rate to diagnosing tendinopathy by recording pain and dysfunction through physical examination and questionnaires. Further inconsistencies in tendinopathy diagnosis can exist due to tendon pathology and pain occurring at different areas of the muscle-tendon-bone complex.

A common area for a tendon to be injured in adults is at its bony insertion [13]. This is known as the enthesis, or osteotendinous junction, and is the site of concentrated force between the tendon and bone [13, 14]. In children, an apophysis is a growth centre at the osteotendinous junction. Apophyseal

injuries are common (apophysitis), particularly during development, however they are different to injuries that occur at the enthesis (enthesopathy) in adults [13, 15].

At the patellar tendon, injury occurs at both bony ends of tendon; the enthesis in adults or apophysis in children. Tendon injuries also commonly occur at the Achilles, tibialis posterior, hamstrings, supraspinatus and both the flexor and extensor tendons of the elbow [7]. Tendon pathology and tendinopathy commonly occur later in life in the supraspinatus tendon and extensor tendons of the elbow [16-19], however this is not true of all tendons. Pathology and tendinopathy in the Achilles and the patellar tendons have been reported earlier in life among athletes [20-23].

The prevalence of tendon pathology and tendinopathy in children has been poorly investigated. However recent cross-sectional and prospective studies have reported cases of both patellar tendon pathology and tendinopathy between the ages of 14 – 19 years [23-25]. Gisslen et al. [25] reported patellar tendon pathology in 39.2% of 14 – 18 year old volleyball players, and diagnosed patellar tendinopathy clinically in 14.2% of the same population. Although puberty usually begins just prior to these ages, the most significant physical growth and development occurs during the adolescent years [26].

Biological development occurs at different ages in boys and girls. Girls typically reach puberty between the ages of 9 – 13 years, while boys are generally later to reach puberty (10 – 14 years) and two to three years later to complete it [26, 27]. More recently, studies into children and adolescents have been investigating the role of puberty in sports injury and performance to establish if it is a more reliable determinant than age alone. A six-year prospective study by Johnson et al. [28] investigated growth and developmental factors associated with injury in elite schoolboy soccer players and found that skeletal age is a factor in injury. Similarly Gastin et al. [29] investigated junior Australian football players and discovered that running fitness, speed, and functional performance all increased significantly with biological maturity. With tendon load and sex as known risk factors for tendinopathy [3], puberty should be investigated in tendon development.

As a result, there is a need to systematically review the current literature on tendon pathology and tendinopathy in children and adolescents. Determining the age at which onset of pathology and symptoms occur, as well as synthesising current data on risk factors for tendon pathology and

tendinopathy in children and adolescents would enable future studies to target the populations most at risk of tendon pathology and tendinopathy.

The impact of puberty, sex and age on the development of tendon pathology and tendinopathy is not clear. This review seeks to synthesise existing knowledge of tendon pathology and tendinopathy in children and adolescents, and investigate if the age of development of these conditions is known.

The primary aim of the systematic review was to examine the age lower limb tendinopathy and tendon pathology was reported in children and adolescents. The secondary aims were to examine if puberty or gender were associated with the development of lower limb tendinopathy in children and adolescents.

Methods

Search strategy

The electronic literature search was conducted in June 2014, utilising the entire holdings of Medline, CENTRAL, EMBASE, Scopus, Web of Science and AMED to identify studies examining tendinopathy and/or tendon pathology in children and adolescents. No limitations were applied to publication year, however only studies in English were considered. The medical subject headings used included tendon injuries and tendinopathy and plain text searching used (Tend#nopath*, Tend#nitis, Tend#nos#s, (Jumper* ADJ1 Knee*), (Tendon ADJ1 Pain*), (Tendon ADJ1 Strain*), Child*, Adolescent*, Prepubescent*, Peripubescent*, Postpubescent*, Pubescent*, Youth*, Teen*) as given in Online Resources 1 and 2. Articles were imported into referencing software (Endnote X7.1, Thomson, New York, NY).

Eligibility criteria

Case series, case reports and case studies were excluded. To be eligible, a study had to have more than 80% of participants under the age of 18 years and report prevalence data on lower limb tendinopathy in humans. Studies were excluded if their population all had pathology (eg: studies on treatment), or where no baseline prevalence data could be extracted. Studies were also excluded if the cause of tendinopathy was related to medication/drug, congenital conditions, trauma or systemic condition. If multiple publications occurred using the same population, the study that had the largest participant number was used. If the number of participants were the same, the most recent study was included.

Quality assessment

Methodological quality was examined with a quality assessment tool that was developed by the authors to identify sources of bias in the four study designs (cohort, cross-sectional, case-control, and a prospective case-control). It was designed with reference to the Critical Appraisal Skills Programme [CASP] [31], Downs & Black [32] and the PEDro Scale [33] as shown in Online Resource 3. The papers were assessed by one reviewer (MS). Scores were represented as a percentage as three questions were not applicable to cross-sectional studies.

Data extraction

Data were extracted from the included papers by one researcher (MS). In prospective studies that examined onset of tendinopathy, baseline and follow up data were included. In prospective studies that investigated treatments or risk factors, only baseline prevalence data were extracted.

Statistical analysis

Meta-analysis for age of tendinopathy onset was not possible as the papers were heterogeneous in data measured and reported. Where possible the mean, standard deviation and range of the participants' age were synthesised to address the review's primary aim. To ensure that diagnosis did not bias the findings, the papers were separated by their method of diagnosis that included physical examination, ultrasound imaging, questionnaire or a combination of methods. Studies that reported prevalence data for each tendon (reported two data points (right and left) for each participant) and those who reported prevalence data for participant (reporting one data point (right or left) for each participant) were also separated for analysis [34]. Due to the diverse study periods and designs, only baseline data from prospective studies were synthesised.

Results

The search of six databases yielded 696 unique papers from which 669 were excluded based on title and abstract using the inclusion and exclusion criteria. The remaining 27 papers were obtained and read in full; eleven did not meet the inclusion criteria and were excluded leaving 16 papers included in the review ([12, 21-25, 30, 35-43], Fig2). The studies scored from 44% to 100 % on the quality assessment tool, indicating variability in the quality of included studies.

Six studies utilised a longitudinal cohort design [21, 23, 25, 35, 37, 41] that followed participants prospectively from 7 months to 3 years. Four studies were of cross-sectional study design [22, 38, 39, 43]; six were case-control studies [12, 24, 30, 40, 42], one of which followed participants prospectively over one year [36]. Of the studies included, five examined basketball players [12, 24, 35, 37, 38], five examined volleyball players [23, 25, 30, 41, 42] and two studies evaluated dancers [22, 43]. The remaining four studies included participants in skiing [36], American football [21], figure skating [39] and general activity ([40], Table 1).

The methods of diagnosis included ultrasound, physical examination and questionnaire. This was dependent on the study's intended outcome, which varied between using imaging to diagnose all tendon pathology in basketball players, to reporting prevalence of self-reported injuries in sport. These different diagnostic strategies provided very different prevalence rates (Tables 2-5).

Primary outcomes

Five papers diagnosed tendinopathy using physical examination, their diagnostic criteria differed yet was primarily based around provoking tenderness and pain when palpating the tendon ([21, 22, 35, 36, 40], Table 2). The prevalence ranged from 8% to 33%, while the age of participants ranged between 14 and 20 years. The mean age and tendinopathy prevalence were plotted for all five studies, which suggested that tendinopathy prevalence increased with age up to 18 years (Fig3).

Two papers investigated tendon pathology using ultrasound [12, 37]. Neither paper reported outcomes by age and the prevalence of pathology ranged from 19% to 36% (Table 3).

A questionnaire was used by two papers to investigate the type and prevalence of injuries among junior elite figure skaters and dancers ([39, 43], Table 4). Both questionnaires requested information on past or present injuries (frequency, site and type) and training history. Due to the nature of the studies, neither described the method used for tendinopathy diagnosis and subsequently scored poorly on the quality assessment. The prevalence of tendinopathy ranged from 19% to 36% between the ages of 14 and 18 years.

Seven papers investigated tendinopathy and tendon pathology diagnosed by physical examination and ultrasound [23-25, 30, 38, 41, 42]. Extracted data were synthesised with data from other papers by age range and tendinopathy prevalence. There was a higher prevalence of tendon pathology identified on

US compared to tendinopathy clinically diagnosed, demonstrated by the seven papers that investigated both pathology and tendinopathy (Table 5, Fig4).

3.2   Secondary outcomes

Seven papers investigated the association between gender and tendinopathy and were synthesised in a meta-analysis. Four of the papers reported prevalence using two data points per participant (by tendon), whilst three papers reported prevalence using one data point per participant (by participant). The odds ratio for studies reporting tendinopathy by tendon was 0.37 [0.20, 0.69] in favor of boys presenting with tendinopathy (Fig5). The odds ratio for the three studies investigating tendinopathy by participant was not significant. No studies reported data on puberty or biological age of participants.

4   Discussion and limitations

This review showed that children and adolescents can have tendon pathology and tendinopathy, and that the prevalence of tendinopathy was significantly higher in boys when investigated by tendon. When investigating by participant, the relationship was not significant. No studies reported data on puberty.

With a significant difference in tendinopathy shown between boys and girls when analysing data by tendon, and with no significant difference when analysing data by participant, boys may be more likely to develop bilateral symptoms than girls. This finding is in contrast to studies on adult tendinopathy [44]. Cook et al. [44] examined unilateral and bilateral tendinopathy between men and women and found no differences between men and women for bilateral symptoms, but instead found men to be twice as likely as women to have unilateral patellar tendinopathy [44].

However the analysis of data by limb rather than by person (use of both tendons as data) has limitations [34]. Statistical analysis relies on each data point representing an independent unit however this is compromised if multiple data points are collected from the same person, which is what occurred in six of the 16 included papers. There are systemic factors that relate to both limbs in tendinopathy and instead of doubling the sample size, the independence assumption is compromised [34]. Analysing data by limb can result in an over-reporting bias and the significance of boys having more tendinopathy has to be questioned due to the method of data analysis.

4.1   Heterogeneity

The difference in diagnostic criteria between studies made it difficult to synthesise findings. Six of the 16 papers reported data from each tendon while the remaining ten papers recorded one data point per participant (either right or left). Two papers that investigated tendon pathology diagnosed with US also used the same sport and age group yet reported a different prevalence of tendon pathology. The prospective imaging study by Cook et al. [37] reported a prevalence of tendon pathology in 19% of tendons, while the cross-sectional study by Cook et al. [12] investigated pathology by participant and calculated the prevalence of tendon pathology as 36%. Diagnosing and reporting tendon pathology data by tendon instead of by participant may have contributed to the difference between these two findings. An alternate explanation may be the difference in sex distribution between studies, with the prospective imaging study by Cook et al. [37] recruiting 8 boys and 18 girls compared to the cross-sectional study by Cook et al. [12] which recruited 71 boys and 64 girls.

There was considerable variation in reported tendon pathology and tendinopathy prevalence between the 16 studies. This may have been due to the broad age ranges investigated by the studies (from 8 to 20 years). Tendon pathology was more prevalent than symptomatic tendinopathy, which supports previous studies that describe asymptomatic tendon pathology [2, 23, 37, 44]. This is demonstrated by the seven studies that investigated tendinopathy through both methods of diagnosis. Gisslen & Alfredson [25] reported the prevalence of symptomatic tendinopathy identified on physical examination to be 14%. For that same population, tendon pathology was identified on ultrasound in 39% of the tendons examined. Similarly, Visnes et al. [23] reported tendinopathy prevalence in 10% of the population, whilst tendon pathology was reported at 29%.

Cook et al. [44] showed in a prospective study that not all tendons with pathology on US will become symptomatic, however many studies have shown an increased risk of developing symptoms if you have tendon pathology [2]. The prevalence of adult tendinopathy in high loading sports such as volleyball and basketball, is estimated between 40-50% [45-47], which is similar to the US results of the Gisslen & Alfredson [25].

Not all studies aimed to examine the prevalence of tendinopathy or tendon pathology. Some studies aimed to examine sporting injuries in general [21, 22, 36, 39, 40, 43]. Aside from Galanty et al. [40], these studies reported substantially lower prevalence than studies that investigated tendon pathology

and tendinopathy alone. Studies investigating sporting injury may have underestimated the prevalence of tendon pathology and tendinopathy as the methods of diagnosing injury are not sensitive to tendon symptoms. However Galanty et al. [40] reported a tendinopathy prevalence of 33.1% despite investigating all injury prevalence and type. This prevalence was greater than many papers that investigated tendinopathy and tendon pathology alone [24, 25, 37, 41, 42] and may be attributed to the recruitment bias [40]. The study advertised a no charge consultation, diagnosis and rehabilitation advice by a qualified physician and it was possible that students would volunteer if they already had knee pain.

4.2   Tendon load

Tendon load is a known risk factor for tendon pathology and tendinopathy [48, 49] and tendon load may have varied between the study populations and affected the prevalence of tendon pathology and tendinopathy. The prevalence of adult tendinopathy in jumping sports has been reported to be between 40% and 50% [45-47]. Studies by Cook et al. [12] and Gisslen & Alfredson [25] reported the prevalence of tendon pathology between 36% and 39% in high loading (basketball and volleyball) adolescents. In contrast, the study by Le Gall et al. [21] investigated American football and identified a tendinopathy prevalence of 8%. American football typically has a lower prevalence of patellar tendinopathy compared with volleyball and basketball players [50], again possibly attributed to less jumping load.

4.3   Implications for future research

Few studies have investigated tendon pathology and tendinopathy development in children and adolescents. The systematic review identified the need for longitudinal investigations into age of tendon pathology and tendinopathy onset in children and adolescents, as well as further research into whether puberty is associated with tendon pathology and tendinopathy development. The review also emphasised the need for a clear set of guidelines in terms of diagnosing tendinopathy. This would then allow for a more synthesis of results across studies. Further investigation also needs to be conducted into whether tendinopathy is primarily a bilateral or unilateral condition, and what risk factors predispose people to developing tendinopathy in both or one side. Up to this point, few studies have investigated the long-term effects of tendon pathology, as identified on ultrasound imaging, and its likelihood of progressing to symptomatic tendinopathy in children and adolescents. Prospective cohort studies are required to further answer this question.

Future studies should aim to consolidate current patellar tendon pathology literature in children and adolescents due to the prevalence and morbidity of this condition. Investigating not only patellar tendon pathology but also the development and maturation of the patellar tendon through puberty, will enable a better understanding of the condition, and help with future prevention and treatment in children and adolescents.

5   Conclusion

The onset age of tendon pathology and tendinopathy in children and adolescents has not been widely studied. The systematic review of current literature suggests that tendinopathy is present in children and adolescents and differs in prevalence across these ages. Male sex was significantly associated with tendinopathy in children and adolescents in studies that reported prevalence by tendon. Further research is needed to determine the role that puberty plays in tendinopathy development. As this systematic review demonstrates the presence of the conditions during the developmental years, tendon pathology and tendinopathy may occur much earlier than previously thought, in which case future research could prevent the progression of tendinopathy at a much earlier stage.

Acknowledgements

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Tables

Table 1: Study characteristics and key findings of included papers

Study	Method of diagnosis	QA	Study design	Sport	Tendon	Cohort size	Sex	Key findings
Backman (2011)	PE	89%	Cohort study	Basketball	Patellar tendon	75	Both	Patellar tendinopathy was present in junior elite basketball players, more so in those with low ankle dorsi flexion range.
Bergstrom (2001)	PE	83%	Case-control – prospective study	Skiing	Patellar tendon	45	Both	"… jumper's knee seemed to be related to growth and an increased level of activity." Page 148*
Galanty (1994)	PE	75%	Case-control study	Not specified	Patellar tendon	142	Both	Tendinopathy was present in children and adolescents, more so in the active population.
Steinberg (2011)	PE	78%	Cross-sectional study	Dance	Achilles tendon	1336	Female	Tendinopathy was present in children and adolescent dancers.
Le Gall (2007)	PE	44%	Cohort study	American football	Achilles, patellar and adductor tendons	233	Male	Tendinopathy was present in children and adolescent American football players.
Cook (2004)	US	89%	Case-control study	Basketball	Patellar tendon	135	Both	Asymptomatic tendons (sonographic changes) were shown to progress to symptomatic tendinopathy.
Cook (2000)b	US	78%	Cohort study	Basketball	Patellar tendon	26	Both	Tendinopathy and tendon changes were present in junior elite basketball players.

Table 1: *(Continued)*

Study	Method of diagnosis	Quality assessment	Study design	Sport	Tendon	Cohort size	Sex	Key findings
Gisslen (2005)a	PE and US	100%	Cohort study	Volleyball	Patellar tendon	60	Both	Tendinopathy and tendon changes were present in children and adolescent volleyball players, more prevalent in males.
Gisslen (2007)	PE & US	100%	Cohort study	Volleyball	Patellar tendon	22	Both	Tendinopathy and tendon changes were present in children and adolescent volleyball players.
Cook (2000)a	PE and US	92%	Case-control study	Basketball	Patellar tendon	163	Both	Tendinopathy and tendon changes were present in junior elite basketball players, more prevalent in boys
Gisslen (2005)b	PE and US	92%	Case-control study	Volleyball	Patellar tendon	112	Both	Tendinopathy and tendon changes were present in children and adolescent volleyball players, more prevalent in males.
Toprak (2012)	PE and US	92%	Case-control study	Volleyball	Patellar tendon	120	Female	Tendinopathy and tendon changes were present in junior elite female volleyball players.
Cook (2001)	PE and US	78%	Cross-sectional study	Basketball	Patellar tendon	163	Both	Tendinopathy and tendon changes were present in junior elite basketball players.
Visnes (2014)	PE and US	78%	Cohort study	Volleyball	Patellar and quadriceps tendon	68	Both	Tendinopathy and tendon changes were present in junior male & female volleyball players; sex, training volume, match exposure and jumping ability are significant risk factors in jumper's knee.
Dubravcic-Simunjak (2003)	Questionnaire	67%	Cross-sectional study	Figure skating	Achilles and patellar tendon	469	Both	Tendinopathy was present in junior elite figure skaters.
Kish (2003)	Questionnaire	56%	Cross-sectional study	Dance	Undefined	173	Both	Tendinopathy was present in young dancers.

Cook (2000)a – Patellar Tendinopathy in Junior Basketball Players; Cook (2000)b – Prospective Imaging Study of Asymptomatic Patellar Tendinopathy in Elite Junior Basketball Players

Gisslen (2005)a – Neurovascularisation & Pain in Jumper's Knee; Gisslen (2005)b – High Prevalence of Jumper's Knee and Sonographic Changes in Swedish Elite Junior Volleyball Players

* a direct quote was used due to the study not presenting any statistically significant findings for patellar tendinopathy yet their findings concluded that the study "seemed' to show a trend.

Table 2: Tendinopathy diagnosis – Physical Examination

Author (year)	QA %	Definition	Control/ tendinopathy	Chronological Age	Age of population	Nº·	M:F	Other
Backman et al. (2011)	89	History of activity-related anterior knee pain and reduced function of the knee, distinct palpation tenderness corresponding to the painful area, and knee pain provoked by a previously described single-legged decline squat test.	Tendinopathy	17.4 ± 1.3	17.8 ± 1.6; range = 14.4-20.6	12	38:37	N/A
			Control	17.9 ± 1.7		63		
Bergstrom et al. (2001)	83	Pain at the inferior pole of the patellar. Undefined how pain was provoked.	Tendinopathy	N/A	17; range = 15-19	15	7:8	Tendinopathy in 5/21 Males, 10/24 Females
			Control	N/A		30		
Galanty et al. (1994)	75	Anterior knee pain defined clinically as peripatellar, patellar tendon, or tibial tuberosity diagnosed by pain on physical exam.	Tendinopathy	N/A	16.6 ± 1.5; range = 10-18	47	79:63	26/79 Males, 21/63 Females
			Control	N/A		95		
Le Gall et al. (2007)	44	Undefined. Physical examination.	Tendinopathy	N/A	13.3 ± 0.3; range = 12.3-14.4	19	233:0	N calculated from "8.1% had tendinopathy"
			Control	N/A		214		
Steinberg et al. (2011)	78	Tendonitis in the ankle or foot. Note that this does not take into account patellar tendinopathy, assumed to be included in "knee injuries" category.	Tendinopathy	N/A	13.3; range = 8-16	251	0:1336	Knee tendinopathy excluded as not differentiated in results
			Control	N/A		1085		

Table 3: Tendon pathology diagnosis – Ultrasound

Author (year)	QA %	Definition	Hypoechoic / control	Chronological age	N°.	M:F	Other
Cook et al. (2000)b	78	An ultrasonographic abnormality was defined as either (1) a hypoechoic region, evident in both the longitudinal and the transverse scans or (2) a fusiform swelling without hypoechoic areas.	Hypoechoic	Range = 14-18	10 tendons (19.2%)	8:18	No mean age was given. Note: Five people were excluded as they had 'jumper's knee-like symptoms'
			Control		42 tendons		
Cook et al. (2004)	89	An ultrasonographic abnormality was defined as abnormality in the fibre structure of the tendon evident in both the longitudinal and the transverse scans.	Hypoechoic	Range = 14-18	49 (36.3%)	71:64	No mean age was given
			Control		86		

Cook (2000)a – Patellar Tendinopathy in Junior Basketball Players; Cook (2000)b – Prospective Imaging Study of Asymptomatic Patellar Tendinopathy in Elite Junior Basketball Players

Gisslen (2005)a – Neurovascularisation & Pain in Jumper's Knee; Gisslen (2005)b – High Prevalence of Jumper's Knee and Sonographic Changes in Swedish Elite Junior Volleyball Players

Table 4: Tendinopathy diagnosis – Questionnaire

Author (year)	QA %	Chronological age	Prevalence reported	M:F	Other
Dubravcic-Simunjak et al. (2003)	67	Range = 13-20	48/469 participants (10.2%)	233:236	Jumper's knee and Achilles tendonitis results were included across single, pair and ice dancing divisions
Kish et al. (2003)	56	15.2 ± 3.23; range = 8-18	7%	6:167	Pathology was reported at 'tendonitis'

Table 5: Tendinopathy diagnosis – Physical examination and ultrasound

Author (year)	QA %	Chronological age (SD)	Physical examination				Ultrasound			
			Definition of diagnosis	Group	Prevalence of symptoms	Other	Definition of diagnosis	Group	Prevalence of pathology	Other
Cook (2000)[1]	92	16.3; range = 14-18	Palpation of knee, tendon attachment to inferior pole of patellar	Male Basketball Players	15/140 tendons (11%)	N calculated from "2% and 11% in tendons..."	Hypoechoic regions observed in axial and longitudinal planes	Abnormal tendons	71/268 tendons (26%)	N calculated from "26% of the basketball players..."
				Female Basketball Players	3/128 tendons (2%)			Normal tendons	197/268 tendons (74%)	
Cook (2001)	78	16.4 (1.0); range = 14.2-18.7	Pain moderate-severe on palpation of inferior pole of patellar	Basketball players	62/299 tendons (21%)	Age converted from months to years.	Hypoechoic regions observed in axial and longitudinal planes	Abnormal tendons	63/299 tendons (21%)	N/A
								Normal tendons	236/299 tendons (79%)	
Gisslen (2005)[1]	100	Range = 15-19	Tender on palpation of inferior pole of patellar and pain during provocative tests knee extensors	Male volleyball players	10/58 tendons (17%)	Baseline data was used	Hypoechoic regions observed in transverse and longitudinal planes	Male volleyball players	26/58 tendons (45%)	Baseline data was used
				Female volleyball players	7/62 tendons (11%)			Female volleyball players	21/62 tendons (34%)	
Gisslen (2005)[2]	92	Range = 15-19	Tender on palpation of inferior pole of patellar and pain during provocative tests of knee extensors	Male volleyball players	10/58 tendons (17%)	Control group was not used as no tendinopathy was present	Hypoechoic regions observed in transverse and longitudinal planes	Male volleyball players	22/58 tendons (38%)	N/A
				Female volleyball players	2/56 tendons (3%)			Female volleyball players	11/56 tendons (20%)	

Table 5: *(Continued)*

Author (year)	QA %	Chronological age (SD)	Physical examination				Ultrasound			
			Definition of diagnosis	Group	Prevalence of symptoms	Other	Definition of diagnosis	Group	Prevalence of pathology	Other
Gisslen (2007)	100	Range = 15-16	Tender on palpation of inferior pole of patellar and pain during provocative tests of knee extensors	Baseline Male Volleyball Baseline Female Volleyball	4/22 tendons 18%) 4/22 tendons (18%)	Baseline data was used	N/A	N/A N/A	N/A N/A	N/A
Toprak (2012)	92	Range = 11-16	Knee joint extensor provocative test and lower pole of patellar palpated	Active Volleyball Female	13/60 participants (22%)	Control group was not used as no pathology data was present	N/A	N/A	N/A	N/A
Visnes (2014)	78	Range = 15-16	a) history of pain in patellar tendon; b) tenderness on palpation over described area	Baseline Male Volleyball Baseline Female Volleyball	11/74 participants (15%) 6/84 participants (7%)	Baseline data was used	Clearly defined hypoechoic areas seen in both longitudinal and transverse US scans	Abnormal tendons Normal tendons	46/158 participants (29%) 112/158 participants (71%)	Baseline data was used and interpreted from results and discussion

Cook (2000)a – Patellar Tendinopathy in Junior Basketball Players; Cook (2000)b – Prospective Imaging Study of Asymptomatic Patellar Tendinopathy in Elite Junior Basketball Players

Gisslen (2005)a – Neurovascularisation & Pain in Jumper's Knee; Gisslen (2005)b – High Prevalence of Jumper's Knee and Sonographic Changes in Swedish Elite Junior Volleyball Players

Figure legends

All figure files were created using MSOffice Word.

Fig1 Tendon pathology flow chart

Fig2 PRISMA flow diagram

Fig3 The relationship between age and tendinopathy prevalence as diagnosed by physical examination

The bar width indicates the age range of the study's population, whilst the number within the bar is the tendon pathology or tendinopathy prevalence

Fig4 The comparison of age and tendinopathy prevalence across studies

Fig5 The comparison between participant sex and tendinopathy prevalence between the ages of 14 and 19 years (tendon)

Electronic Supplementary Material (Online Resources)

All ESM files were created using MSOffice Word.

ESM_1 Terms used to search databases

ESM_2 Sample electronic database search in full

ESM_3 Quality assessment tool

Warm up

Lower limb injury: improving our translation of research into clinical practice for acute injuries and long-term sequelae

Ebonie Rio,[1] David A Opar[2]

BETTER UNDERSTANDING OF THE EFFECT OF SOCCER IN MRI FINDINGS IN THE CONTEXT OF GROIN PAIN

Adductor-related groin pain remains the bane of the soccer medical team's existence. While MRI is commonly used to assist in diagnosis of groin pain (acute and long standing), few studies have compared symptomatic athletes with matched controls. Imaging is known to uncover pathologies that may not fit with the clinical picture and MRI is no exception. The paper by Branci *et al* (*see page 681*) provides insight into the MRI findings that may be associated with soccer participation and reminds us that caution and clinical judgment must be used when interpreting the MRI of an athlete with adductor-related groin pain.

In a second paper, Branci *et al* try to standardise criteria to evaluate key findings in pubic and groin MRIs in athletes (*see page 692*). It reminds us that the findings should continue to be placed in a clinical context as there is still variability around reporting on some pathologies such as the adductor tendons. Studies should continue to strive for standardised criteria for MRI reporting as this will improve clinical utility and consistency for athletes everywhere.

ACL RUPTURE AND CUTTING—CAN WE IMPROVE THE BIOMECHANICS OF THE TASK WITH TRAINING?

Injury prevention programmes that aim to target and alter biomechanics are popular. However, it is not known how effective they are at changing a movement pattern considered to be high risk. Pappas *et al* conducted a systematic review and

meta-analysis on this very important topic (*see page 673*) and found that injury prevention programmes focused on altering cutting task biomechanics leads to a decreased lateral hamstring electromyographical activity. Single studies have found a number of other benefits related to muscle activity, kinetics and kinematics.

ACL RECONSTRUCTION—DOES DELAYING IT AFFECT OUTCOME?

First, it must be said only one patient was lost to follow-up in 5 years out of a cohort of more than 100! Frobell *et al* conducted a high quality randomised controlled trial with long-term follow-up and clinically important outcome measures that provides evidence for clinicians to use when educating patients about their rehabilitative options. The cohort of young active adult patients reflects the most common presentation of ACL injury to practitioners thus this is highly translatable and food for thought (*see page 700*).

Continuing the ACL theme, this editorial by Engebretsen discusses the need for widespread and transparent ACL registers (*see page 636*). This enables collation of huge amounts of data that may drive important decisions on surgical procedures, fixation devices and rehabilitation protocols.

PAIN IN OSTEOARTHRITIS

Injection based treatments for osteoarthritis is popular and the research is lagging behind their widespread clinical use. Laudy *et al* detected a positive result for platelet rich plasma injections compared with placebo and hyaluronic acid injections for pain at 6 months (*see page 649*). However, there is a high level of bias in the studies that were identified. It is imperative that we strive for good quality evidence so that we can be confident in translating research into clinical practice and also aim for long-term follow-up of patient outcomes and satisfaction.

"LOAD ME UP, SCOTTY": MECHANOTHERAPY FOR PLANTAR FASCIOPATHY (FORMERLY KNOWN AS PLANTAR FASCIITIS)

Plantar fasciopathy is a common clinical presentation. Previous treatments have been predominantly passive including orthotics, stretching and massage. The shift towards a mechanotherapy based loading regime has perhaps been slower to reach the plantar fascia than for its tendon cousins, but it has arrived and shown to be more effective than stretching. This editorial by Rathleff *et al* outlines the justification behind a loading approach for the treatment of plantar fascia as well as highlighting new commercially available technologies that may make it easier for the clinician to implement effective protocols (*see page 638*).

THE ASICS SPORTS MEDICINE AUSTRALIA CONFERENCE, 21–24 OCTOBER 2015

This edition of *BJSM*, on lower limb injury and translation of evidence to practice, draws to attention one of the key foci of the annual ASICS Sports Medicine Australia Conference. As well as a strong scientific programme, an impressive list of internationally renowned keynote speakers, daily workshops offering practical tips and tricks from experts in the field of sports science and sports medicine, in recent times there has also been the introduction of a specific series of oral presentations on 'Clinical and Cutting Edge'. These presentations are selected particularly for their relevance and translation to clinical practice. Check out the website (http://sma.org.au/conferences-events/conference/) or follow on Twitter (@SMA_Events) and join us at the Intercontinental Sanctuary Cove—Gold Coast, Queensland, 21–24 October 2015.

CrossMark

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Rio E, *et al. Br J Sports Med* May 2015 Vol 49 No 10

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Appendix O. Publication: Patellar tendinopathy and its diagnosis

Patellar tendinopathy and its diagnosis
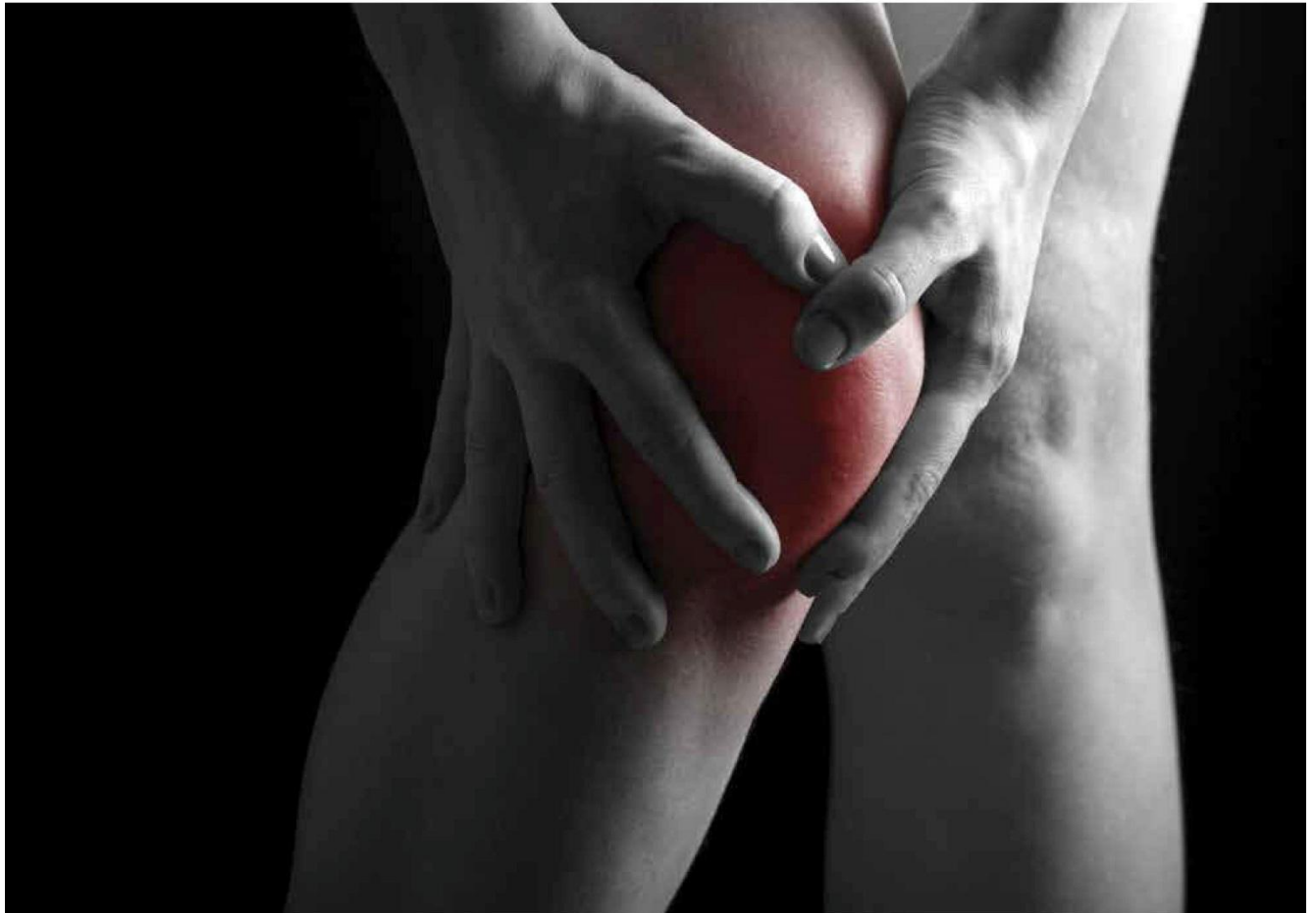
Professor Jill Cook and PhD candidates Ebonie Rio and Sean Docking of Monash University's Monash Tendon Research group examine the diagnosis of patellar tendinopathy.

Anterior knee pain in the jumping athlete requires careful examination.

Despite the high prevalence of tendon pathology and tendon pain in these athletes that is reported in the literature, the diagnosis of patellar tendinopathy should not be assumed. During recruitment for a recent randomised trial in a volleyball cohort, we had to exclude approximately 50% of the athletes who presented with anterior knee pain. Many of these were being treated at that time for patellar tendinopathy; however

clinical questioning and testing revealed that the tendon was not the source of symptoms in that athlete. The differential diagnosis for anterior knee pain is extensive so the purpose of this article is to help clinicians recognise if the tendon is the source of symptoms in the athlete. We will also illustrate how imaging may assist diagnosis, but it can also be misleading, especially in an athletic population. Importantly, tendinopathy remains a clinical diagnosis.

"The differential diagnosis for anterior knee pain is extensive so the purpose of this article is to help clinicians recognise if the tendon is the source of symptoms in the athlete."

Figure 1: Patellar tendon pain is most commonly at the inferior pole of the patella (A), it is also localised to this area when doing a decline squat (B).

"The single leg decline squat is the best clinical assessment tool."

Diagnosis

The key clinical features of patellar tendinopathy are localised pain most commonly at the inferior pole that occurs with patellar tendon energy storage and release (e.g jumping and change of direction), and a single leg decline squat test that reproduces pain at that site (Figure 1). Patellar tendon pain does not refer or spread over time or with additional load and people point to the area of pain with one finger. It is so specific that they don't move their finger and this subtlety is very important. Furthermore, loading causes a dose dependent increase in pain in patellar tendinopathy presentations, so pain will increase as the demand on the patellar tendon is increased. Another important and often distinguishing feature is the fact that they are usually worse the day after excessive loading, whereas this is variable in PFJ, fat pad or plica presentations.

In addition to localised pain, it is important to remember that tendinopathy reduces power and therefore clinical examination is likely to reveal a poorly functioning and powerless kinetic chain. Athletes will land with limited knee flexion in tasks such as hopping or dynamic change of direction tasks.

Differential diagnosis

Patellar tendinopathy is not usually associated with running as this is not a high load activity for the patellar tendon. Extra care with diagnosis needs to be given to the running athlete with anterior knee pain who are frequently treated for their tendon, however it may not be the source of their pain. Furthermore, volleyball and basketball athletes spend long periods of time in knee flexion and may also land on their knees leaving their patellofemoral joint (PFJ) vulnerable to compression that can present as anterior knee pain (the pain is less localised but can mimic aspects of patellar tendinopathy thus careful examination is vital). Both diagnoses usually have pain with stairs and prolonged sitting therefore these features do not distinguish between conditions. Another common clinical challenge is the athlete that complains of pain with cycling. Cycling requires no elastic energy storage of the patellar tendon so clinicians should look for a differential diagnosis or other activities in their training that may be causing tendinopathy.

Clearly there are a number of features that distinguish tendon from other sources of pain. Another difference is that taping to unload the PFJ will fail to change the SLDS pain in people with patellar tendon pain. PFJ taping that changes their squat pain almost certainly indicates the tendon is not involved as the pain source as these techniques offer little in the way of immediate relief for tendons. The best taping we have found to do this provides a diamond around the patella that aims to change sensory input and reduce retropatellar compression – taping with medial glides etc rarely help as it is direct compression in knee flexion that we are trying to unload.

Many clinicians wonder if PFJ and patellar tendinopathy can co-exist. They usually do not. Someone may have tendon pathology on ultrasound and PFJ symptoms – they should be managed as a PFJ presentation as loading for their tendon may exacerbate the PFJ compression and cause ongoing pain. An example of this is the athlete given Spanish squat isometric holds or wall sits that makes their anterior knee pain worse. This position will irritate the PFJ as it is in compression however someone with tendon pain is likely to get relief with this isometric loading. A more extreme example of this is the person given multiple injections into their tendon but who never had tendon symptoms. Tendon pathology on imaging should not change the clinical diagnosis.

"Many clinicians wonder if PFJ and patellar tendinopathy can co-exist. They usually do not. Someone may have tendon pathology on ultrasound and PFJ symptoms – they should be managed as a PFJ presentation as loading for their tendon may exacerbate the PFJ compression and cause ongoing pain."

Imaging

Use of conventional imaging modalities such as ultrasound (US) and magnetic resonance (MR) imaging have been shown to have good-to-excellent accuracy in detecting structural abnormalities[2–4]. Changes within the tendon are described as thickening of the tendon, focal areas of hypoechogenicity on US or increased signal on MR, and infiltration of blood vessels. However, caution is advised in basing a diagnosis of patellar tendinopathy

solely on imaging. Like other soft tissue structures (ie intervertebral discs and cartilage), there is a disconnect between structural abnormalities and clinical symptoms. This is demonstrated by previous studies showing that 22% of volleyball players have pathological patellar tendons despite a lack of anterior knee pain[5]. Imaging should not be utilised as a test to exclude the tendon as the source of symptoms. Clinically, we frequently have seen structural changes on imaging in patients with patellofemoral joint pain, which can be misleading. New imaging modalities, such as ultrasound tissue characterisation (UTC), may be useful in assessing and monitoring the extent of structural pathology once a clinical diagnosis of tendinopathy is ascertained[6].

"The key clinical features of patellar tendinopathy are localised pain most commonly at the inferior pole that occurs with patellar tendon energy storage and release (e.g jumping and change of direction), and a single leg decline squat test that reproduces pain at that site."

A number of authors have frequently described the limitation of conventional imaging modalities in differentiating areas of pathology and partial tears[7]. There is no general consensus on the features and parameters in differentiating between tendinosis and partial tears with the differential often relying on clinical history (sudden vs. insidious onset of pain). Partial tears in the normal part of the patellar tendon are exceedingly rare, yet microtears can occur within the degenerative lesion, which are of little clinical importance and should be managed as a tendinopathy.

Categorising patellar tendinopathy in the continuum of tendinopathy[8], one of the most common presentations in the patellar tendon is reactive-on-degenerative (Figure 2). A focal area of disorganisation is observed within the central
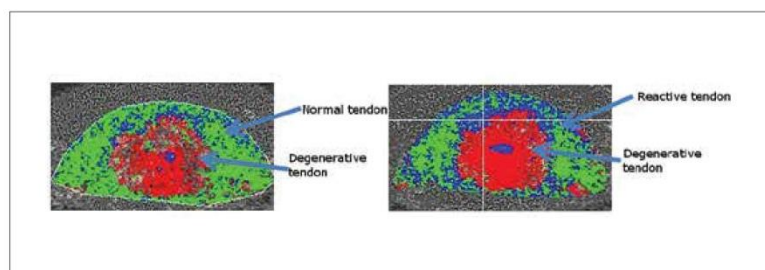
Figure 2: Example degenerative and reactive-on-degenerative patellar tendon over time. The degenerative lesion of the tendon has not altered, with diffuse reactive changes observed in the normal part of the tendon coinciding with an flare in symptoms.

portion of the tendon at the patellar insertion. It had been theorised that an acute onset of pain coincides with reactive changes in the surrounding normal tendon. Conventional imaging modalities have been unable to detect these reactive changes in the normal tendon. As UTC is sensitive to subtle changes in tendon structure, these reactive changes in the surrounding tissue can be seen. Identifying these changes has a substantial role in athlete management, as treatment can be directed at settling down the reactive portion.

"Whilst the diagnosis remains clinical, new imaging modalities such as UTC offer the clinician greater insight into common tendon presentations such as the reactive on degenerative tendon."

Conclusion and clinical message

Patellar tendinopathy is a clinical diagnosis of localised tendon pain that is exacerbated by activities that load the patellar tendon such as jumping and change of direction. However, even in jumping athletes anterior knee pain may be caused by a number of other structures. The single leg decline squat is the best clinical assessment tool. People that have changes on ultrasound but no clinical tendon symptoms should avoid interventions for their tendon and be managed according to the clinical diagnosis. Whilst the diagnosis remains clinical, new imaging modalities such as UTC offer the clinician greater insight into common tendon presentations such as the reactive on degenerative tendon.

References, as indicated within the article, are available at sma.org.au/publications/sport-health

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Tendinopathy: What about the pain?
By Ebonie Rio & Prof. Jill Cook

Tendinopathy is the clinical syndrome of pain and dysfunction in a tendon. It is a common and often chronic condition that continues to baffle both scientists and clinicians. The drivers of tendon pain and modulation by the central nervous system are poorly understood. These limitations affect our ability to effectively treat people with tendon pain – we don't know where the pain comes from.

Many features of tendon pain are consistent with tissue disruption - the pain is well localised, persistent and specifically associated with tendon loading, whereas others are not, however investigations do not always match symptoms and painless tendons can be catastrophically degenerated and even rupture. This review will briefly summarise the clinical features, current research into pain drivers and central nervous system contribution. Exercise based rehabilitation remains the most potent method of stimulating the tendon matrix and new evidence indicates certain types of exercise can also provide acute pain relief.

Note: *Tendonitis* is not a commonly accepted term as no inflammatory cells have been demonstrated and the changes appear to be a cell driven response. Tendinopathy is the term that is accepted and refers to a continuum of pathological change with pain. Note that collagen tearing has not been shown to be a primary event.

What are the clinical features of tendon pain?

The clinical presentation of tendinopathy includes localised tendon pain with loading [1], tenderness to palpation [2] and impaired function [3, 4]. The tendons most commonly affected by tendon pain include the patellar, Achilles, lateral elbow, adductor and gluteus

Figure 1. Patellar tendon pain is most commonly felt at the inferior pole.

medius. Pain defines the clinical presentation, regardless of the degree of tendon pathology. In fact, tendon pathology can be present (ie changes on ultrasound) without the tendon being the cause of symptoms in the presentation. Tendinopathy, despite being an umbrella term, is usually limited to intra-tendinous presentations, with more specific terminology being applied to pathology in surrounding tissue with different disease processes, such as peritendinitis. These also require a different treatment approach, thus differential diagnosis is key.

Tendon pain has an on/off nature linked to loading, and excessive energy storage and release in the tendon most commonly precedes symptoms [5, 6]. For example, the pain in patellar tendinopathy is most commonly at the inferior pole (Figure 1) and activities that require energy storage and release in this tendon, such as jumping are both painful and impaired. Pain is rarely experienced at rest or during low load tendon activities; for example, a person with patellar tendi-

nopathy will describe jumping as exquisitely painful yet not experience pain with cycling due to the different demands on the musculotendinous unit. A further characteristic pain pattern is that the tendon "warms up", becoming less painful over the course of an activity, only to become very painful at variable times after exercise [7].

Modern concepts of pain

Physiological or 'nociceptive' pain reflects activation of primary nociceptors following actual or impending tissue damage or in association with inflammation. Pathophysiological pain is associated with functional changes within the nervous system making it resistant to tissue-based treatments. The distinction between these is important clinically as they may require different approaches. However, it is important to remember that pain is an output and modulation by the central nervous system, it occurs even with clear physiological input.

Some aspects of tendinopathy fit more clearly into pathophysiological pain. Painful tendons can have little pathology [8, 9] and pain can persist for years [10]. Furthermore, pain during tendon rehabilitation exercises has been encouraged [11-14] and may not be deleterious [15], demonstrating that tendon pain does not necessarily equate with tissue damage. Furthermore, overuse tendon injury does not involve an inflammatory process with a clear end point that underpins most physiological pain. However, other aspects of tendinopathy fit more clearly into physiological pain - pain remains confined to the tendon and is closely linked temporally to tissue loading [16]. A clinical presentation that fails to be explained by either pain state classification is the rupture of a pathological yet pain free tendon, where nociceptive input would have been advantageous.

Local nociception

Tendon pathology results in cell activation and proliferation, matrix change (collagen disorganisation and increased large PG) and neovascularisation, in various combinations and severity [8, 17, 18] as well as changes to biochemical substances present. Change in collagen structure is the most obvious candidate for nociception because it is the load bearing structure in tendon, but loss of collagen integrity does not correlate with tendon pain [8].

There are few afferent nerves within tendon, and innervation patterns do not change with pathology [19, 20]. New vessels primarily bring autonomic vasomotor (and
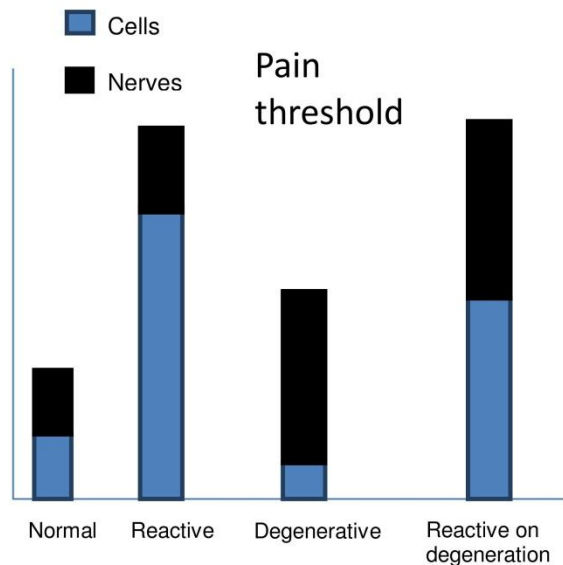
Figure 2. Tendon pain throughout different stages of the continuum of tendinopathy.

some sensory) nerves but neovascularisation is not present in every painful tendon. Neovascularisation (new vessels) has been associated with degenerative tendinopathy but is not a feature of early pathology [8]. Not all painful tendons have increased vascularity [8, 21] and vice versa [8], therefore the vessels or the nerves and receptors on vessel walls fail to explain tendon pain across all pathological presentations.

There are many biochemical changes in tendinopathy, none of which can fully explain tendon pain. Bioactive substances and their receptors may be important in pain behaviour. Neuropeptides and neurotransmitters, formerly attributed only to neurons, are now known to also be produced by tenocytes, however their actions and interactions are poorly understood. A key change is the increase in lactate [22], which decreases tissue pH and it is likely to alter cell activity, communication and ion channel expression of both tendons and nerves. Ion channels are important as they communicate the nociceptive message.

The cause of local source of nociception is currently unknown and pain is experienced across a range of clinical presentations. Theoretically, in reactive (early stage) tendinopathy (as described by Cook & Purdam 2009 [33]) there may be increased expression of nociceptive substances because of cell activation and proliferation, but no change in innervation. In degenerative tendinopathy (end stage) there may be little expression of nociceptive substances due to cell inactiva-

tion or death but greater innervation. At both ends of the spectrum pain is possible because the threshold is reached (Figure 2.). The painfree tendon may have substantial matrix disorganisation and cell compromise, but insufficient production of nociceptive substances and /or the neural network to reach a threshold to cause pain.

Central Nervous System

Tendon pain aims to protect the injured tendon from overload. Sustained peripheral nociceptive activity may lead to the development of central sensitisation [23]. Although central sensitisation accounts for widespread pain and hyperalgesia/allodynia in chronic pain patients, excessive pain response is not a clinical feature of tendon pain regardless of symptom chronicity. This may be explained by the on/off nature of tendon pain (that is, tendons rarely hurt at rest so the pain is not sustained in nature), reducing the likelihood of neural upregulation, or local saturation of the receptor that would then fail to stimulate the afferent nerve.

Few studies have examined if central pain processes are involved in tendon pain states [24, 25]. Tendinopathy pain would seem a unique chronic pain because pain generally occurs during loading, and although there is more pain with increasing load it disappears once the load is removed. Spreading of pain (for example secondary hyperalgesia) is not a common clinical feature of tendinopathy, especially in the lower limb. For example, pain in patellar tendinopathy, usually at the inferior pole, does not refer and is localised to this location regardless of the length of time of symptoms. However, developing symptoms on the other side is common and this mirroring is often attributed to bilateral loading patterns, although CNS neuroimmune mechanisms may be possible. A study by Årøen et al. (2004) [33] suggests that patients with an Achilles tendon rupture have increased risk of a contralateral tendon rupture, as well.

This may be due to high bilateral loads or genetic factors, but may also indicate central drivers to pathology and /or pain or systemic. Study on bilateral shoulder tendinopathy in both the pitching and unloaded limb of baseball pitchers also support this [26]. This view is further strengthened by data from an animal model where bilateral cell changes were observed in unilaterally loaded rabbits [27] and a unilateral chemically induced model of tendinopathy in horses [28].

Tendon pain has been associated with local sensory change such as increased mechanical sensitivity (pain
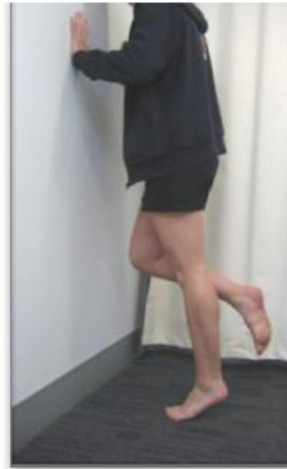
Figure 3. Isometric muscle contractions decrease tendon pain. Standing calf raise in inner range for Achilles tendon insertion.

with activity and tendon pressure) [29, 30], hyperalgesia and bilateral changes to pressure pain thresholds [31] and bilateral changes to thermal sensitivity [32]. However, another study in tendons demonstrated no differences in cold and heat pain, cold and warm detection thresholds [25].

Reducing tendon pain

An emerging area of interest for clinicians is the use of isometric exercise to reduce tendon pain. Research has shown that isometric contractions can reduce pressure pain thresholds in normal participants and have also been shown to reduce pain in patellofemoral pain syndrome and osteoarthritis. Isometric contractions reduce tendon pain immediately and for at least forty five minutes in patellar tendinopathy (Rio et al, 2013 [35]) and thus may have an important role in pain modulation to allow rehabilitation. Clinically, we have applied them to tendinopathy in the gluteus medius, patellar, Achilles, tendons of the elbow, hamstrings and the adductors. The aim is to build up the length of time of the contraction to greater than 45 seconds, using high loads without muscle fasciculation. Ideally they should be completed isolated muscle function in a range where the tendon is uncompressed, and should be repeated five times several times per day if necessary, depending upon the length of time of relief. An example for the Achilles tendon insertion is inner range calf raise holds (Figure 3).

Summary

The question of the pain of tendinopathy, physiological or pathophysiological, remains unanswered; however there is evidence for both; tendon based nociceptive contributions and extensive mechanisms within the periphery and the CNS that may up or down regulate

the experience of pain. It may be different for different tendons or vary depending upon the context around loading and the effect of this on the pain experience, for example work related elbow tendon pain versus sport related patellar tendon pain could have vastly different modulation. Importantly for clinicians, tendon pain is complex and requires thorough assessment of both musculoskeletal and neural contributors. The use of isometric exercise to reduce tendon pain is an easily accessible technique that is efficacious.

For a full discussion on this topic, please read *The Pain of Tendinopathy: Physiological or Pathophysiological?* Sports Medicine (September 2013) [35], available at: http://www.bodyinmind.org/wp-content/uploads/Rio2013.pdf

Ebonie Rio was awarded a post-graduate scholarship at the Australian Institute of Sport and has completed her Masters in Sports Physiotherapy. She is currently working with the Victorian Institute of Sport, Paralympic table tennis and wheelchair rugby teams whilst undertaking a PhD in tendon injuries.

Prof. Jill Cook is a Principal Research Fellow at the Faculty of Medicine, Nursing & Health Sciences at Monash University. Her research interests is in tendon injury, tendon pathology, sports injuries, and musculoskeletal injuries.

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feature article

Explaining ultrasound images of tendon pathology: A pathology model of load-induced tendinopathy

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Tendinopathy is used as an umbrella term for the clinical presentation of tendon pain, decreased exercise tolerance of the tendon and a reduction in function. Characteristic changes occur in tendon structure, resulting in a tendon that is less capable of sustaining repeated tensile load.

Tendinopathy can occur in the mid-tendon (e.g. the Achilles tendon); however, most tendon pathology and pain arises at the tendon attachment to bone (enthesis), such as the patellar tendon, medial and lateral elbow tendons and tendons of the groin. While the mid-tendon and the insertion are morphologically different in the normal state, the pathology is the same [1]. Traditionally, pathological tendons have been thought to fall into one of two categories: normal or degenerative tendinopathy with considerable cell and matrix changes. It is unreasonable to think that tendons transition from a normal to degenerative state quickly in one step and a better understanding of how tendon pathology originates and progresses is needed.

The model proposed by Cook & Purdam [2] hypothesises that there is a staged progression of pathology. Within the model, tendinopathy is considered a dynamic continuum with some potential for repair, and specific imaging features throughout the stages. In particular, ultrasound has been found to be valuable in staging tendon pathology and therefore directing appropriate intervention.

Existing tendon pathology concepts

Two terms have been used previously to describe tendon pathology: degenerative or failed healing. Degenerative tendinopathy is described variably; pathological terms such as hypoxic degeneration, hyaline degeneration and mucoid degeneration are used to describe structural change more evident in one key matrix component, all of which suggest non-reparative, end-stage pathology [3]. The key features of degenerative pathology are irreversible, degenerative cell changes and disintegration of the matrix.

Other authors have suggested that the injured tendon is in a healing phase with active cells and increased protein production, but with disorganisation of the matrix and neovascularisation. This has been called failed healing [4] (or angiofibroblastic hyperplasia) [5].

The Cook and Purdam model of pathology has included these stages as part of a continuum to provide a basis for the development of tendinopathy. It also provides evidence of transitioning between stages and identifies key clinical and imaging features of each stage.

The model of tendon pathology

The continuum model of tendon pathology has three stages: reactive tendinopathy, tendon dysrepair (Cormick, personal communication, 2007) (failed healing) and degenerative tendinopathy (fig 1). The model is described for convenience in three distinct stages; however, as a continuum there is continuity between stages.

Adding or removing load is the primary stimulus that drives the tendon forward or back along the continuum, especially in the early stages. Reducing load may allow the tendon to return to a previous level of structure and capacity within the continuum [6].

Pathological, imaging and clinical manifestations at each stage

1. Reactive tendinopathy
Reactive tendinopathy, a non-inflammatory, proliferative response in the cell and matrix, occurs with acute overload. The tendon becomes relatively and homogeneously thickened so as to reduce stress (force/unit area) by increasing cross-sectional area. If a normal tendon is overloaded slowly then proper adaptation occurs through tendon stiffening with little change in thickness [7].

In a reactive tendon the cells become more rounded, with capacity for increased protein production. The primary proteins made are large water-attracting proteoglycans (e.g. aggrecan) that result in some longitudinal separation of the collagen, with no change in neurovascular structures. The proteoglycans produced are in contrast to those in normal tendon tissue that consists mainly of small molecular weight proteoglycans (e.g. decorin).

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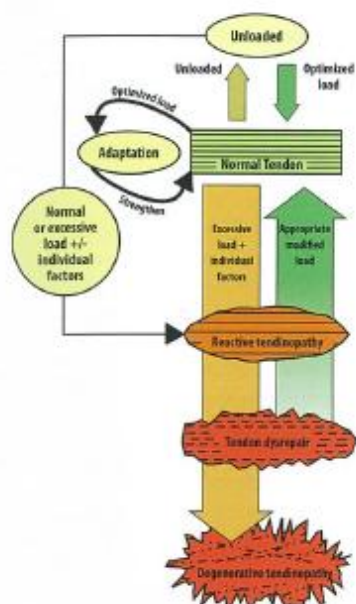
Fig 1. The Cook and Purdam model of tendinopathy courtesy *Clinical Journal of Sports Medicine*, Brukner and Khan. Chapter 5, 'Overuse Injuries' in Brukner and Khan's *Clinical Sports Medicine* (4th edition), Brukner et al. McGraw-Hill, Sydney, Australia, 2011. P000–000 (in press).

In summary, reactive response is a short-term adaptation to overload that thickens the tendon, reduces stress and increases stiffness. The tendon has the potential to revert to normal if the overload is reduced or if there is sufficient time between loading sessions.

Imaging Reactive tendons have diffuse fusiform swelling and no neovascular ingrowth. Tendon collagen integrity is mostly maintained but the diameter is increased on both magnetic resonance imaging (MRI) and ultrasound (US) scans. Ultrasound shows reflection from intact collagen fascicles, with no focal hypoechogenicity. Magnetic resonance imaging will show minimal or no increased signal at this stage. The change in imaging appearance is mainly derived from the increase in bound water within the larger proteoglycans (fig 2).

Clinical Clinically, reactive tendinopathy results from acute overload, usually a burst of unaccustomed physical activity. Reactive tendinopathy can also be seen clearly after a direct blow such as falling directly onto the patellar tendon [8].

Reactive tendinopathy is seen mainly in an acutely overloaded tendon and is more common in a younger person. For example, a young jumping athlete who dramatically increases the number of jumping/landing repetitions a week, may develop patellar tendon swelling and pain.

Unloaded tendons such as in the detrained athlete returning from illness or injury, or a sedentary person, may also be vulnerable to this stage of tendinopathy when load increases moderately.

2. Tendon dysrepair
Tendon dysrepair is similar to reactive tendinopathy but with greater matrix break down. Increased chondrocytic cells result in a marked increase in protein production (large proteoglycansand predominantly type 3 collagen). The increase in proteoglycans results in separation of the collagen that begins to disorganise the matrix. The changes are somewhat more focal, and matrix changes more varied than in the reactive stage. Those tendons toward the degenerative end of the dysrepair stage may have a mild increase in vascularity and associated neuronal ingrowth [9].

Imaging The imaging changes reflect increased matrix disorganisation. These tendons appear swollen but also have increasing evidence of collagen disorganisation as compared with a reactive tendon. On US there is some discontinuity of collagen fascicles and maybe small focal areas of hypoechogenicity. Mild increase in vascularity may be evident on colour or power Doppler and techniques to enhance vascularity (heat, exercise, hanging the limb) may show a greater number of vessels (Cormick, personal communication 2007). On MRI the tendon also appears swollen and there is mild increased signal within the tendon.

Clinical This pathology has been reported in chronically overloaded tendons in the young, but may appear across a spectrum of ages and loading environments. This stage may be hard to distinguish clinically. These tendons are thick, with more localised changes in one area of the tendon. Tendon dysrepair
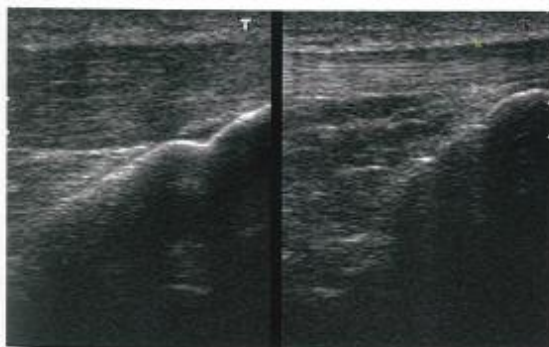
Fig 2. Ultrasound image of a reactive tendon (on left) showing diffuse thickening (note intact collagen fascicles) compared with normal tendon (right).
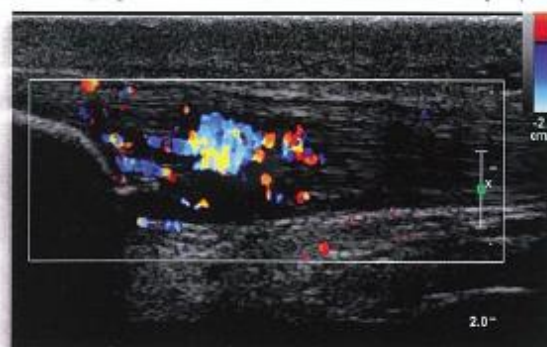
Fig 3. Ultrasound of a patella tendon demonstrating changes fitting with dysrepair/degeneration (note the vessels evident on power Doppler, hypoechoic areas and the tendon swelling).

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is best detected when imaging detects some focal structural changes without increased vascularity.

Some reversibility of the pathology is still possible with load management and exercise to stimulate matrix structure, especially if the matrix changes are mild [10]. The amount of vascularity may be a marker of degree of matrix disruption; the more vascularity the less reversibility overall, suggesting transition towards degenerative tendinopathy.

3. Degenerative tendinopathy

This stage demonstrates progression of both matrix and cell changes [5]. There may be areas of cell death due to apoptosis, trauma or tenocyte exhaustion [11] and areas of acellularity have also been described. Discrete areas of the matrix are disordered and filled with vessels, matrix break down products and a little collagen. There is much less capacity for reversibility of pathological changes at this stage. There is considerable heterogeneity of the matrix in these tendons, with islands of degenerative pathology interspersed between other stages of pathology and normal tendon. Partial tears in the degenerated region of the tendon matrix are also a feature in this stage [12].

Imaging The compromised matrix and the vascular changes can be extensive. On US, changes observed include hypoechoic regions due to fewer reflections from collagen fascicles (fig 3). There is a lack of organised, intact type I collagen bundles; instead they are replaced with thinner, less organised type III collagen. Larger proteoglycans that bind more water are present, cleaving apart collagen and causing further disorganisation. It is proposed that this allows areas for the vessel ingrowth, which is observed in this stage [13]. Vessels are numerous, large and easily visible on colour Doppler US. Magnetic resonance imaging demonstrates increased tendon size and intratendinous signal. The changes are more focal, rather than distributed throughout the tendon.

Clinical Older people have degenerative tendons, but it is also seen in a younger person with a chronically overloaded tendon. The classic presentation is a middle aged, recreational athlete with focal Achilles tendon swelling and pain. The tendon can have one or more focal nodular areas (correlating with small partial tears), with or without general thickening. Individuals with degenerative changes often have a history of repeated bouts of tendon pain, often resolving and returning as the tendon load changes. Degenerative tendinopathy, if extensive enough, or if the tendon is placed under high load, can lead to complete rupture [14], consistent with 97% of tendons that rupture having degenerative change [15].

It is possible to observe different changes within the one tendon reflecting different pathology. For example, reactive or degenerative tendons will demonstrate areas of the tendon with both features. Overall, the clinical presentation in this case will be a history of acute overload on the background of a degenerative tendon state.

Does imaging support this model?

Longitudinal imaging studies in humans demonstrate that some tendons transition up and down the proposed pathology model. Longitudinal imaging studies have consistently demonstrated that between 10% and 30% of tendons reported as abnormal at baseline became normal at follow up [16,17,18]. It is important to remember that a tendon can have a non-pathological response to load. Grigg, Wearing & Smeathers [19] showed that eccentric exercise of a normal Achilles tendon resulted in a decrease in diameter for 3 hours.

In contrast, in an abnormal Achilles tendon, an acute bout of exercise increased the MRI volume and signal after 30 minutes [20]. This suggests that the abnormal tendon rapidly increased its volume (as measured by circumference) and water content (either bound as part

of ground substance or in vessels) in response to load. This mimics a reactive response to load proposed in this model.

Transitioning from normal to reactive stage

The imaging appearance of tendons changes in both the short and long term. Nearly half of normal patellar tendons (with pain) became abnormal (mainly reactive tendinopathy) in the presence of ongoing load over a season of volleyball (high tendon load). A single tendon became hypoechoic, suggesting transition through a reactive tendinopathy to tendon dysrepair/degenerative tendinopathy [21,22].

Transitioning from reactive to dysrepair stage

Young athletes subject to tendon overload demonstrated microhypoechoic areas on US [17]. This may represent a transition from reactive to tendon dysrepair, where small islands of the tendon develop collagen disorganisation. The capacity to reverse pathology is limited, but some patellar tendons have become normal [22].

Transitioning from dysrepair to degenerative stage

Both these states are considered abnormal and not often identified as separate entities (fig 3). Imaging of highly loaded patellar tendons in jumping athletes demonstrates that they primarily transition towards abnormality and pain, an observation that is more apparent in adults [21] than in adolescents [23].

Clinical studies

The cumulative effect of load on a tendon has been clearly demonstrated when previously elite athletes showed a higher incidence of tendinopathy and rupture compared to age-matched controls

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[24]. As rupture represents end-stage degenerative tendinopathy [15], this supports the non-reversible nature of degenerative pathology, as these older ex-athletes had not spontaneously recovered tendon health.

The inability of a tendon to recover fully once it reaches the degenerative stage is supported by several studies that have shown that large hypoechoic areas do not change [25,26]. Similarly, tendons used for anterior cruciate ligament (ACL) graft replacements remain abnormal for years [27]. This lack of reversibility and inability of the tendon to repair is linked to the substantial disorganisation of the matrix as well as the changes to cells.

Placing pain in this model of tendinopathy

Pain can occur at any point in this pathological model, supporting the well-known dissociation between pain and pathology in tendinopathy. Even tendons that appear normal on imaging can be painful [21]. Conversely, two-thirds of tendons degenerative enough to rupture have been reported to be pain-free before rupture [15].

Neurovascular ingrowth [28], seen in this model at the late tendon dysrepair/degenerative phase has been associated with pain; however, this finding has not been substantiated in other cohorts. A supplementary cause of pain such as biochemical substances seems to be one possibility [18]. Production of substances such as catecholamines, acetylcholine and glutamate and their receptors by activated tendon cells [9] may explain pain in the cellularly active stages in this model: reactive and tendon dysrepair. Similarly, a reactive tendinopathy in the normal part of a degenerative tendon can also cause pain. At this stage of our understanding of this model it is reasonable to assume that there is an element of reactive tendinopathy when the tendon is acutely painful.

Discussion

This model of tendon pathology is consistent with the clinical presentations of tendinopathy. Although we have used the term 'load-induced tendinopathy', the relative contribution of tensile, compressive and combined loads may vary in different tendons, and at different areas of the tendon (such as the presence of bony protuberances).

It is highly probable that some tendons may have discrete regions that are in different stages at the one time. Examination of tissue in the latter stages of pathology reveals heterogeneous pathology in a single tendon [18]. It is possible that a tendon with degenerative change that is acutely overloaded may develop reactive change in previously normal parts of the tendon. This model explains most clinical presentations and most findings in the tendon literature. It can even encompass primary collagen tearing [29] and some form of inflammation underpinning the cell and matrix response. Emerging mechanisms for injury, complex interactions between the cell and matrix and systemic and local factors (growth factors, cytokines and treatments) will need to be built into this model. This model now requires scientific and clinical evaluation.

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feature article

Matching tendinopathy stage with efficacious intervention

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Introduction

Tendinopathy, the clinical syndrome of pain and dysfunction within a tendon, is a common, recalcitrant and disabling condition affecting both upper and lower limb tendons. Once a tendon becomes injured, changes that occur within the structure affect its ability to tolerate load. Commonly, people then try to avoid load or activity due to pain, fear of pain or advice to do so, which often results in further catabolism of the matrix and decreased load tolerance [1,2]. Conversely, some people with tendinopathy are prescribed inappropriate loading or interventions that contribute to ongoing pain and pathological progression.

In the June 2011 issue of **sound**effects, we introduced the concept of tendinopathy as a continuum of pathological change. Clinical presentation and imaging features unique to three stages were presented to support the model. In this article, the concepts are extended to include discussion about where common interventions may fit within the model to maximise positive outcomes for patients. The interventions discussed include those provided by many healthcare professions. This is intended as an overview for the purposes of education and discussion. Each patient requires specific assessment and intervention based on assessment findings. This article aims to provide a background to appropriate treatments for tendinopathy.

Brief review of stages

Reactive tendinopathy is a non-inflammatory response that leads to tendon thickening, reduces stress and increases stiffness. These changes appear to be cell-driven with an activation (rounding) and overall increase in the number of tendon cells (tenocytes). Protein production is increased, with larger proteoglycans (PGs) being manufactured by the tenocytes that bind more water (than the small PGs found in a normal tendon) and lead to separation of the collagen. Therefore, on ultrasound (US), these tendons demonstrate fusiform swelling with non-parallel tendon borders and reflection from intact collagen fascicles with diffuse hypoechogenicity occurring between intact collagen structures. Magnetic resonance imaging (MRI) also shows fusiform swelling with minimal or no increased signal at this stage. Importantly, there is no neovascularity.

Ongoing overload may result in progression to tendon dysrepair, a stage that describes a failed healing response. There is progressive matrix disorganisation within this stage, discontinuity of collagen fascicles and small areas of hypoechogenicity on US. On MRI, the tendon is swollen and shows increased signal within the tendon. There may be slightly increased vascularity visible on colour or power Doppler.

Degenerative tendinopathy, stage three of the continuum, is described as extensive matrix disorganisation that may have profuse neovascularity, matrix breakdown products and disordered collagen. There is little capacity for reversibility, unlike earlier stages of the continuum. Since tenocytes are responsible for manufacturing all of the components of the extracellular matrix, tenocyte death, trauma or exhaustion diminishes the ability to remodel. There is considerable variability within these tendons and may include areas of degenerative pathology as well as earlier stage pathology and even normal tendon. This variability within the tendon requires consideration before intervention. On US, hypoechoic regions with few reflections from collagen fascicles are common. Numerous and larger vessels are usually visible on Doppler US. MRI demonstrates increased tendon size and signal. Changes are more focal rather than spread throughout the tendon. There may be one or more focal nodular areas with or without general thickening. This stage is primarily seen in the older person, for example, the middle-aged, recreational runner with focal Achilles tendon swelling and pain, but this can also be seen in a chronically overloaded tendon e.g. young elite volleyball athlete with patellar tendinopathy. Typically, individuals with degenerative changes report a history of repeated bouts of tendon pain, often resolving but returning as the tendon load changes. Degenerative tendinopathy, if extensive enough, or if the tendon is placed under high load, can lead to rupture.

Clinically, tendinopathy can be separated into reactive/dysrepair and dysrepair/degenerative with the appearance of vessels delineating these two

presentations and assisting with the choice of interventions. Clearly, tendons without vessels that demonstrate early pathology (reactive/dysrepair) are not suitable for interventions aimed at vascularity. Therefore, the presence of vessels can assist with dividing patients into the two groups and more effectively targeting treatments.

Interventions

Common interventions and the evidence supporting or negating their use for the two clinical presentations are discussed.

Reactive tendinopathy/early dysrepair (no vessels)

The most effective intervention for acute reactive tendinopathy is load management. There are many exercises and activities that can be done at this stage that do not include very high loads, that is, energy storage and release in the tendon. Referral to a practitioner who is knowledgeable in tendon management is optimal. The practitioner will institute appropriate loading for the tendon. The tendon has the potential to revert to normal if the overload is sufficiently reduced or if there is sufficient time between loading sessions. Longitudinal imaging studies have consistently demonstrated that between 10% and 30% of tendons reported as abnormal at baseline become normal at follow-up [3-5]. Applying further overload in this stage, such as an eccentric program, would therefore exacerbate an up-regulated matrix and promote progression of matrix disorganisation and pathological change.

Non-steroidal anti-inflammatory medications (NSAIDs) have been reported to impair soft tissue healing in various tissues. Although pain may be reduced, they have a negative effect on tendon repair [6]. In reactive tendinopathy, this effect may be preferable to address tenocyte up-regulation and excess ground substance expression [7].

Ibuprofen (as well as indomethacin and naproxen sodium) has been shown to inhibit expression of key proteoglycans responsible for tendon swelling (aggrecan) in in-vitro tendon preparations [8]. Ibuprofen and celecoxib are reported to specifically down-regulate cellular response [9,10] and ibuprofen does not appear to have a detrimental effect on ultimate tendon repair [6]. Corticosteroids, primarily used to decrease pain, also decrease cell proliferation and protein production, therefore may be appropriate for an acutely reactive painful tendon. Peritendinous corticosteroid has been shown to reduce tendon diameter at 7 and 21 days after injection in tendons [11]. Although peritendinous injection is clinically accepted, it is not known whether peritendon injection induces cell and matrix change within the tendon. A recent review, which included a range of tendon sites, concluded corticosteroid injection may be beneficial in the short term but may be worse than other treatments in the intermediate and long terms [12].

In summary, load management is the most appropriate intervention for reactive/dysrepair tendinopathy as this has capacity to return to normal. There may be indication for interventions that address pain and some of the pathological change. Clearly, interventions that increase the load on the tendon at this stage would be inappropriate and detrimental to the tendon. These include but are not limited to: heavy loading (such as Alfredson Achilles eccentric heel drop program) and intratendinous injections or dry needling that can cause further reaction in the tendon.

Later dysrepair/degeneration

The aims for late tendon dysrepair/ degenerative stage treatments are to stimulate cell activity (if required), increase appropriate protein production (collagen or small proteoglycans) and maximise matrix restructure. Exercise interventions are again the key to improve

tendon structure and overall kinetic chain capacity (this is likely to include other muscle groups). A clinician who works effectively with tendinopathy patients will assess overall kinetic chain capacity and implement a plan to address any deficits or imbalances which may have increased susceptibility to tendon injury. Exercise, particularly eccentric exercise, has been shown to affect both tendon structure and pain. In terms of the effect on the matrix, eccentric exercise has been shown to increase collagen production in abnormal tendons but not in normal tendons [13] and improve tendon structure in both the short term [14] and the longer term [15] and decrease tendon vessels [16].

Adjunct therapies, such as extracorporeal shock wave therapy (ESWT), have been shown to have pain-relieving effects in a number of tendons although they have not been consistently shown to be superior to placebo treatment. Studies in animal tendons show variable morphological and mechanical benefits as well as detrimental effects from this modality. Ultrasound therapy has been shown to increase protein production at a tissue level [17] but is less effective than exercise [18].

Surgery for chronic painful (presumably degenerative) tendons has produced varied outcomes: 50–80% of athletes return to sport at their previous level [19-21]. Although surgical techniques vary considerably, their results are not dissimilar. Outcome after surgery was no better than eccentric exercise [22] or ESWT [23] for patellar tendinopathy. Surgery in nonathletic people produced poorer results than in active people [24], which also has important clinical implications. Despite these outcomes, surgery is considered a reasonable option in those who have failed appropriate and well designed conservative interventions.

In summary, load management with appropriate exercise prescription is

the key to rehabilitation and improving the capacity of the tendon to tolerate tensile load. There may be interventions that alleviate pain but these do not appear to be as effective as exercise for remodelling the matrix and would therefore not be appropriate in isolation to address tendinopathic change. Surgery, despite variable outcomes may be an option if conservative management has failed. It is worth noting that a long rehabilitation of appropriate exercises should follow surgical intervention.

Injection and topical therapies

All adjunct therapies, aside from those that slow cell activity and protein production (Table 1), are best limited to the late dysrepair/degenerative stage, as they will exacerbate a reactive tendinopathy. In a degenerative tendon the injection of various substances around or into the tendon (or the process of injection itself, such as dry needling) has been proposed to stimulate a healing response. Prolotherapy using glucose, autologous blood or platelet rich plasma (PRP) injections are proposed to stimulate tissue healing. Blood injection has been shown to stimulate cell proliferation, produce vascular endothelial growth factor [25] and induce matrix changes. However, in a randomised trial using PRP or saline injection in Achilles tendinopathy, there was no difference in clinical or ultrasound outcome between groups [26]. Injection itself, regardless of the substances injected, which includes dry needling, appears to have a stimulating effect on tendon structure, which can be a desired effect in the late stage dysrepair/degenerative tendon.

Injections of active vasoactive substances (sclerosing with polidocinol) and placebo (anaesthetic and adrenaline) substances have produced equivocal results. Compared with placebo injection,

polidocinol produced similar outcomes for the elbow tendon [27] but superior results for the Achilles [28]. Longitudinal studies have demonstrated that a good result (improvement in pain and function) was unrelated to structural change on US after two years in the elbow tendon [29]. Sclerosing therapy has repeatedly been shown to reduce pain and improve tendon structure in tendinopathy [30]. Interestingly, the effect on vessels appears to be delayed; vascularity increases in the short term after treatment, suggesting that the positive effect on pain may be through chemical neurolysis and not vascular change [31].

Aprotinin, a collagenase inhibitor, in a recent randomised placebo-controlled trial did not show benefits over placebo [32] although earlier, less rigorous studies have shown an effect on pain.

Glyceryl trinitrate applied topically has been shown to effectively reduce tendon pain in addition to the benefits of eccentric exercise in the short to mid term for the extensor tendon of the elbow [33] with no additional benefit compared with exercise alone at five years [34]. In the Achilles tendon, benefits were demonstrated in the short [35] and long term with improvements retained at three-year follow-up [36]. It is hypothesised to deliver increased amounts of nitric oxide (NO) to the injured tendon, leading to improvement in collagen synthesis. However, a recent study has not demonstrated increased tissue levels of NO, or benefit from the treatment [37].

Summary and other considerations

Individual factors, such as genes, age, sex, biomechanics and body composition may alter the progression of the tendinopathy forward or back in the continuum [38] and most are also likely to have an important role in the response to

treatment in tendinopathy. For example, some athletes appear resistant to tendinopathy despite high loads, and have never been shown to progress into reactive tendinopathy.

Improving the capacity to tolerate load is vital for tendon management. Whilst many interventions may mediate pain, which is important, failure to address tendon capacity and capacity of the kinetic chain (in terms of adequate strength, power, etc.) will likely result in recurrence of tendon pain. The issue of compressive loads inducing tendinopathy has not been covered in this article and may be an important consideration in tendon rehabilitation. It may also be appropriate to consider referral to a medical practitioner for suspected or present co-morbidity management e.g. diabetes or rheumatological disease that may affect tendon structure and load response. Some drugs, such as fluoroquinolones, also affect tendon structure [39-41]. Ultimately, there is no recipe treatment appropriate for all tendons and we hope this format assists with making sense of the available interventions. This article aims to encourage collaboration, open discussion, referral and, of course, improvements in outcomes.

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Table 1. Summary of stage-matched goals, interventions and considerations

Stage	Ultrasound appearance	Primary goals	Efficacious management	Adjunct therapies	Other considerations
Reactive/early tendon dysrepair	Fusiform swelling, non-parallel tendon borders, reflection from intact collagen fascicles, diffuse hypoechogenicity, minimal or no increased signal (MRI) No neovascularity	1. Dampen tenocyte response & impair production of large PGs 2. Prevent transition to further matrix breakdown	Physical load management may include reduction in frequency & intensity of tendon load (energy storage & release activities) Assessment of kinetic chain to address deficits as part of rehabilitation Pharmacological management may include tenocyte inhibitors (ibuprofen, celecoxib, corticosteroids) aggrecan inhibitors (ibuprofen, naproxen sodium, indomethacin)	Most adjunct (injection) therapies will worsen this stage of tendinopathy, except hydrocortisone	May require multiple team member involvement Popular 'heavy eccentric' loading will make these tendons worse Patient should discuss with their doctor all medications due to potential for drug-drug interactions.
Late tendon dysrepair/degeneration	Hypoechoic regions with few reflections from collagen fascicles Numerous & larger vessels (Doppler US) Increased tendon size & signal (MRI) Changes are more focal rather than spread throughout the tendon	1. Promote cell activity (if required), increase appropriate protein production (collagen or small proteoglycans) 2. Maximise matrix restructure	Physical management may require assessment of capacity of kinetic chain of affected & non-affected side to address deficits Exercise with eccentric component (see other considerations), ESWT, frictions, ultrasound	Medical management may include prolotherapy, blood injection therapies, Aprotinin, sclerosing therapy, topical glycerol trinitrate (is best used in conjunction with exercise)	Mixed pathologies (e.g. reactive on degenerative tendon) require careful assessment & appropriate load management e.g. may require a period of reduced load prior to starting exercise with eccentric component Important to have well designed program Older individuals are more likely to require investigations for co-morbidities Surgical referral if failed conservative management

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Appendix S. Book chapter: To hell and back: Achilles insertional tendinopathy

Ebonie Rio, Sean Docking, Jill Cook, Mark Jones

Subjective Assessment [1hd]

Demographics and social history [2hd]

Judy, a 55 year old post-menopausal woman, presented with a 13 month history of right-sided insertional Achilles tendon pain. She lived at home with her husband in a single storey house with three steps at the entrance. Judy enjoyed her employment as a full time medical receptionist and her usual work day primarily involved sitting, but she also got up and down frequently to photocopy and file. She was previously a teacher and enjoyed the change of occupation. Prior to her Achilles pain, Judy liked to walk every day for 3.5 km and 5-6 km each day on weekends. She described a very active social life and also enjoyed Pilates twice a week. She had been unable to exercise since having her Achilles pain and had gained about 15 kgs; she was unhappy about both her inability to exercise and the weight gain.

Pain presentation [2hd]

Judy presented wearing a removable rigid walking boot on her right foot that caused her to walk with a limp due to the leg length discrepancy. Her pain was confined to the Achilles insertion at the superolateral calcaneus; there was no spreading of pain and she was able to localize it with one finger (Figure x.1). She reported no sensation changes (no pins and needles or numbness). Judy also experienced occasional pain in the lumbar region that was eased with Pilates and did not radiate to her legs.

However, she had to cease Pilates as she felt her Achilles pain walking from the car to the fitness centre. She considered the lumbar pain was unrelated to her Achilles pain. Judy also reported right knee pain that had no impact on her walking and was not painful now. She further reported also having bilateral lateral hip pain that was mildly symptomatic and aggravated at night lying on her side. She was unsure if this preceded the Achilles pain.

Insert Figure x.1 here

Onset of pain [2hd]

Judy reported no change to her activity level preceding the onset of symptoms; no overload (e.g. increase in tendon load associated with change in activity) or relative overload after a period of time off. However, when questioned specifically about change in load before her symptoms started, she acknowledged that she had increased her walking around that time but thought the most significant change was the purchase of new shoes. She felt that the shoes rubbed on her heel in the area of her pain, but she persisted with wearing them as the podiatrist had prescribed them. When her symptoms were not improving the podiatrist changed her orthotics four times without any effect. Judy reported no previous history of Achilles symptoms in either tendon or any other tendon pain or rupture.

Behaviour of symptoms [2hd]

Judy described her pain as 'agony' after walking only a few minutes without the walking boot. Her pain was worse if she had to walk up an incline, longer distances or

faster. The Achilles pain was described as a grabbing pain that was highly irritable with pain rated as 9/10 on a numerical rating scale. Her pain was worse when walking in barefoot and flat shoes were more aggravating than shoes with a heel. She was unable to wear the shoes that she felt were linked to the onset of symptoms because of the pain. Pressure over the area was painful, especially with shoes that rubbed on her heel. The pain was worse during activity but ached afterwards depending upon how far or long she had walked, and it had started to bother her at work. There was a clear relationship between greater amounts of loading and increased pain. Judy reported that her symptoms were eased by the controlled ankle movement (CAM) walker boot and she now felt reliant on it.

Judy's morning pain and stiffness were severe; she reported crying with 10/10 pain in the morning and the pain taking hours to settle. She was now barely walking anywhere due to fear of pain and reported rarely leaving the house because her activity was so restricted, and this had helped ease her morning symptoms. When her symptoms were at their worst she experienced night pain but had none currently.

Rest eased the Achilles pain temporarily but it recurred once she returned to activity. During the past 13 months she had tried extended periods of rest and reduced activities (longest period was 7 weeks) but also took non-steroidal anti-inflammatory medication, so was unsure if it was the rest or medication that was helpful. She reported 8 weeks of complete pain relief from a glucocorticoid injection into the painful area, however the pain then returned to the same level.

Patient Perspectives: Expectations / goals / understanding of the problem [2hd]

Judy reported fear of pain that was now limiting her activity. She did not feel that she was ever going to get better and was concerned that her only option was surgery. Judy described her tendon as being weak and likely to snap. Her husband was a radiologist and she had had multiple ultrasounds of her tendon with the tendon reported as degenerative, abnormally thickened and having neovascularisation. She admitted to not knowing what all this meant but thought that 'it sounded bad' and these terms concerned her. She was also fearful of not being able to walk without the walker boot.

General health [2hd]

Judy had several co-morbidities and was on medication for many of them (Table x.1), but these had been unchanged since the onset of the Achilles symptoms. She was really very keen to become active again, lose weight and try to reduce her medications. Judy had no red flags, for example, no recent loss of weight or cauda equina symptoms, nor did she have constant pain.

Insert Table x.1 here

Previous interventions [2hd]

Judy had tried multiple interventions delivered by several different practitioners. After the orthotic changes by the podiatrist had not helped she presented to her rheumatologist who managed her arthritis. The rheumatologist indicated a glucocorticoid injection would resolve the problem, and Judy had almost exactly 8

weeks of pain relief after injection before her pain returned. She then returned to the rheumatologist who tried a second glucocorticoid injection. This time Judy felt she had missed the spot and reported it felt like she couldn't get the injection in, and she had no symptom relief. She reported losing faith in this management and then saw a sports physician who told her not to have another cortisone injection under any circumstances as the tendon may rupture. The sports physician recommended a platelet rich plasma (PRP) injection and stated that 80% of patients get better with this treatment. Judy reported that the PRP injection was the most painful experience of her life and her pain was worse despite resting completely for two weeks after the injection.

Judy then sought treatment from a physiotherapist who gave her through-range eccentric exercises off a step. The exercises were very painful to perform and the tendon was not improving, but she was told to persist and ignore the pain as this was necessary for the tendon to recover. When the tendon pain did not settle, she was told it must be because she had poor core stability and was prescribed Pilates exercises. She was also told to try hydrotherapy but all these made no difference. The pain failed to improve after several months of physiotherapy.

Judy visited her rheumatologist three months before presenting. The rheumatologist expressed annoyance that she had seen anyone else as 'I manage you.' She was advised to have another cortisone injection. She declined as she was fearful of tendon rupture. Her rheumatologist decided that the tendon must be overloaded and put her in a rigid walker boot for 6 weeks. She was not given any advice of when or how to

remove the walker boot or resume activity, and 13 weeks had now passed. She was also referred to a surgeon for removal of her Haglund's morphology (the superolateral protruberance of the calcaneus). Judy saw the surgeon who advised recovery would take more than 1 year and thus she should have the operation soon.

Three weeks ago Judy thought she would try another physiotherapist. The assessment included hopping, jumping and lunging. These exercises were all painful and after attempting them three times she couldn't get out of bed for 3 days and so she didn't go back to the therapist. Judy acknowledged being nervous about what today's assessment would entail.

Start Box x.1 here

Reasoning question:

1. Based on your subjective examination, please discuss your 'diagnostic reasoning' regarding the most likely 'Source of Nociception and Associated Pathology' and your hypothesis about the dominant 'Pain Type' (i.e. nociceptive, peripheral neuropathic, maladaptive central nervous system sensitization), highlighting the clinical features supporting your hypotheses.

Answer to Reasoning Question:

The Achilles tendon insertion is the most likely source of nociception and tendinopathy is the most probable diagnosis/pathology. Morning pain and stiffness is a hallmark of Achilles tendinopathy. It is common for this to last up to 30 minutes; anything over 60 minutes may indicate a systemic contributor or cause of the tendon

pain (notably inflammatory diseases). There are two key clinical questions that support a diagnosis of Achilles tendinopathy:

Where is the pain?

Achilles tendon pain is localized and does not spread regardless of the length of time of the symptoms. In this case, Judy had pain at the lateral part of the insertion. Pain in the Achilles can also occur at the mid-substance, where patients commonly use two fingers to 'pinch' the area of pain.

What aggravates the pain?

Achilles tendon pain is aggravated by activities involving high tendon loads for the Achilles, especially energy storage loads. Low energy storage load activities include brisk walking, whereas high energy storage load activities involve running or change of direction. Activities such as cycling and swimming are low tendon load, and if these are the aggravating activities a clinician should have a high index of suspicion that the Achilles is not the source of nociception. Tendinopathy appears to be nociceptively driven as with Judy's presentation, and it is always intimately linked with loading. When a low tendon load activity is the aggravating factor there may be another pain source such as neural irritation or the Achilles peritendon structures. These presentations will usually have a more diffuse pain pattern than Achilles tendon pain.

In insertional Achilles tendinopathy, movement into dorsiflexion causes compressive loading where the tendon is compressed against the calcaneus; this can aggravate both pain and pathology (Cook and Purdam, 2012). Low load activities such as cycling can cause pain because of repeated compressive loads. Walking with low heeled shoes or

barefeet are typically more aggravating than with shoes with a higher heel. The Haglund prominence is an anatomical morphology, not a deformity, as it reduces load on the tendon insertion into the distal calcaneus by allowing compression of the Achilles tendon against the superior calcaneus (Benjamin et al., 2004). Removing this surgically exposes the insertion to greater load, increasing load on the tendon that has not adapted to full load on the insertion. Patients who display this morphology can have successful outcomes using rehabilitation without surgery (Fahlstrom et al., 2003, Jonsson et al., 2008).

Judy does not report any symptoms associated with maladaptive central nervous system sensitization, however it is well known that the experience of pain is modulated by conceptual and contextual factors. As such, education is critical so that language does not contribute to Judy's fear and pain experience. Therefore, increasing her understanding of tendinopathy and the rehabilitation process is likely to have a positive effect.

Posterior ankle pain has a number of differential diagnoses. The key differential diagnosis is posterior ankle impingement. Patients with impingement report pain in full passive and active plantar-flexion activities, including kicking in swimming (that would not typically aggravate the Achilles tendon). The retrocalcaneal bursa is part of the Achilles enthesis and should be managed as part of an insertional Achilles tendinopathy, and is therefore not considered in any separate diagnosis. Where there is local neural entrapment or pain referral, the pain location is generally more diffuse than with Achilles tendon pathology.

2. What is your interpretation of Judy's 'Perspectives on her Experience' (e.g. her understanding of her condition, fears, stress, coping, etc.)? Do you anticipate needing to address this in your management?

Answer to Reasoning Question:

Judy reported being concerned that her pain would not improve and she was fearful of the suggested surgery. She was extremely concerned about the loading aspect of the clinical assessment as removing the boot and being examined had previously made her pain worse. Overall she had very poor understanding of her condition and what was the best way to improve her symptoms.

3. Please discuss the potential 'Contributing Factors' (intrinsic and extrinsic) to the development of Judy's problem, and to her ongoing pain and disability.

Answer to Reasoning Question:

Reduction in oestrogen during menopause can contribute to tendon pathology and pain in older women. Information about her menopausal status and other, sometimes associated, general health issues will be important to ascertain.

The increase in Judy's weight has implications for both load on the Achilles and for circulating cytokines associated with visceral fat deposits that in turn are associated with tendinopathy (Gaida et al., 2008). The onset of Achilles tendon pain usually coincides with a change in load, in this case a mild change in activity and footwear that may have aggravated her tendon by direct compression on the site (rubbing) or through being too low in heel height. The presence of these other co-morbidities can

increase the risk of developing Achilles tendon pain, with an amplified response to changes in load.

4. Can you please highlight any aspects of Judy's presentation (e.g. pathology, clinical presentation, co-morbidities, medications, previous interventions) you feel signal the need for 'Precaution in the Physical Examination and Treatment'?

Answer to Reasoning Question:

This tendon has been under-loaded as Judy has been wearing a CAM walker boot for 13 weeks following several months of reduced activity. Physical tests that include high tendon load activities (such as hopping) are inappropriate for this tendon and indeed she had previously had a poor response to assessment that included high tendon load activities. Assessment should only continue as guided by individual patient responses. Tendon pain typically increases with tendon loading, however it is not necessary or recommended to complete all possible tests for each patient. Judy had no recent loss of weight or cauda equina symptoms, nor did she have constant pain. Her pain seemed to be of a mechanical origin as it was intimately linked with loading.

Clinical Reasoning Commentary:

Diagnostic reasoning regarding pain type, potential sources of nociception and associated pathologies, commences in the subjective examination and is continued throughout the physical examination and ongoing management, where diagnostic hypotheses are tested further. As discussed in Chapter 1, these diagnoses are formulated on the basis of established (research and experience based) clinical patterns. The specificity of musculoskeletal diagnoses varies with differing problems

and diagnostic tests. When the ability to identify specific sources of nociception and associated pathology is limited (e.g.non-specific low back pain), such as where overt pathology may not exist or clinical diagnostic tests lack validity to isolate sources of nociception, impairment based diagnoses (e.g. motion segment symptom provocation, mobility and control) become the focus. In contrast, problems such as insertional tendinopathy have clearer clinical patterns as discussed here that can be differentiated from other sources of nociception and pathology. While management will be largely guided by impairment based reasoning (i.e. patient's specific clinical presentation within the common clinical pattern), more accurate diagnostic classification enables more targeted research to identify effective management strategies that can then be tailored to the individual patient.

Judy's clinical presentation is judged as 'nociceptive dominant' and typical for tendinopathy that is intimately linked with loading. However despite this, conceptual and contextual influences on the modulation of patients' pain experiences (e.g. Judy's understanding of tendinopathy and associated fear) are highlighted and linked to management reasoning regarding education and care with language that may contribute to Judy's already expressed fears. This underscores the important reality discussed in Chapters 1 and 3 that unhelpful patient perspectives, commonly associated with maladaptive central nervous system sensitization, can present in any patient and with any dominant pain type and are therefore important to assess and manage to optimise clinical outcomes and potentially reduce the risk of progression to chronicity.

Contributing factors to the development and maintenance of patients' problems can be intrinsic or extrinsic and modifiable or non-modifiable. As discussed in Chapter 1, identification of contributing factors is important in management, both for reducing immediate symptoms and disability, and for minimizing the likelihood of recurrence. Consideration of contributing factors also informs judgments regarding the hypothesis category 'Prognosis'. This emphasizes the importance of undertaking medical/general health screening for co-morbidities and their management which may represent contributing factors that vary in the extent they are modifiable. Other factors such as patient weight, activity pattern and footwear are all modifiable and important to management reasoning, as are most physical impairments assessed in the physical examination (e.g. mobility, control/strength both locally and throughout the rest of the kinetic chain).

Similarly, the hypothesis category 'Precautions and contraindication to physical examination and treatment' should be based on co-morbidities and red flags screened, plus patients' individual clinical features, for example those related to constancy, severity and irritability of symptoms, as well as patient perspectives such as fear.

Stop Box x.1 here

Physical Assessment [1hd]

Observation [2hd]

Judy had a profound loss of muscle bulk of the right calf that was affecting both soleus and gastrocnemius. She had an obvious Haglund morphology on both calcanea, with increased swelling over the right insertion.

Gait [2hd]

Judy walked with a waddling gait and avoided pushing off on both feet. She had a reduced stride length and cadence.

Knee to wall lunge [2hd]

Right - 0cm and very painful at the end of range at Achilles insertion; Left 5 cm.

Functional assessment [2hd]

Judy had a lack of strength and power throughout the left leg when hopping; she had poor control, poor elevation and inability to hop with a consistent tempo. She was able to complete 16 heel raises on the left leg before fatiguing (Table x.2). The right side was only assessed with four double leg heel raises that produced pain (VAS 4/10) with an uneven weight distribution (more weight on the left leg). The pain was localized to the lateral heel that Judy could point to with one finger. The choice to limit her assessment was firstly, because the tendon had been unloaded in the boot and secondly, due to her fear of being over-assessed as she had been by the previous physiotherapist. She was unable to do a single leg heel raise on the right because of fear of pain.

Insert Table x.2 here

No assessment of her joints was undertaken at this point as the pain was clearly tendon mediated. If there was an equivocal response to initial treatment then further assessment of surrounding structures (such as the joints) would be undertaken.

Imaging [2hd]

While Judy had previous imaging of her Achilles, further investigation using Ultrasound Tissue Characterization (UTC) was suggested to quantify the structural integrity of the tendon. UTC is a novel imaging modality that utilizes conventional ultrasound by capturing 600 contiguous transverse images over a 12cm region. From this a 3-dimensional image is rendered where the stability of pixel brightness over the length of the tendon can be quantified into four echo-types (van Schie et al., 2010b). Previous research has validated these echo-types against equine histopathological specimens (van Schie et al., 2010b). It is an ideal tool to monitor tendon structure as it quantifies tendon structure and has a high degree of repeatability.

Judy's right Achilles tendon appeared focally thickened at the calcaneal insertion (Figure x.2) with the overall UTC echo-pattern compromised compared to the contralateral Achilles. A diffuse area of disorganization was observed within the tendon (Figure x.3) characterized by an increase in echo-type III (red pixels), indicating disorganized fibrillar structure, and echo-type IV (black pixels), representing amorphous matrix (Figure x.4). This area of disorganization was confined to a 1cm region at the calcaneal insertion, with the mean cross-sectional area (CSA) of the pathological lesion comprising approximately 40% of the transverse image. Her left Achilles did not appear thickened and the overall echo-pattern was within normal parameters.

Insert Figures x.2, x.3 and x.4 here

Despite an area of disorganization present within the tendon, the UTC results were explained to Judy with a focus on the volume and mean CSA on aligned fibrillar structure (Figure x.5). Despite the area of pathology and increased mean CSA of disorganized echo-types (echo-types III and IV), Judy's right Achilles also had an increased mean CSA of aligned fibrillar structure compared to the contralateral tendon and structurally normal tendons. Previous research has shown that this is a common feature of pathological tendons (40 of the 41 pathological Achilles tendons contained similar or an increased mean CSA of aligned fibrillar structure) (Docking et al., 2014). It appears the pathological tendon compensates for areas of disorganization by increasing its dimensions to ensure there is sufficient aligned fibrillar structure (Docking et al., 2014).

Previous imaging had a negative impact on Judy's perception of her tendon. She was referred for a UTC scan to provide reassurance her tendon could tolerate load. It was explained to Judy that she should not focus on the extent of disorganization as she had a sufficient amount of aligned fibrillar structure.

Insert Figure x.5 here

VISA-A Questionnaire [2hd]

The VISA-A score documents pain and function of the Achilles tendon (Robinson et al., 2001). It was developed for mid-Achilles problems but similarities allow its use in those involving the insertional Achilles tendon, although it may be less sensitive to change. One-hundred points is full pain-free function, 80 points suggests there is pain

sufficient to affect function, and 60 points indicates difficulty in function (Silbernagel et al., 2007a). Judy's VISA-A score was 23 points suggesting profound pain and functional deficits.

Start Box x.2 here

Reasoning Question:

5. In your Answer to Reasoning Question 1 you indicated Judy's subjective presentation was consistent with an Achilles tendinopathy. Would you please highlight the physical examination findings that support that clinical pattern and also whether the physical examination supported your previous hypothesis regarding the dominant Pain Type being nociceptive?

Answer to Reasoning Question:

Tendon pain frequently results in a loss of muscle bulk not only in the attached muscles (gastrocnemius and soleus) but often in other parts of the kinetic chain. In Judy's case this loss of bulk was likely to be exacerbated by the boot that completely unloaded the musculotendinous unit. Part of the rationale for strength training in rehabilitation is to address these muscle as well as tendon capacity.

The physical examination includes tendon loading tests where increasing pain is expected with increasing tendon load. However, it is not always appropriate (as it was not in this case) to complete all the examination and as such physical examination confirmation of tendinopathy was not possible, although the provocation of her localized pain with four double leg heel raises is consistent with a tendinopathy. Similarly, this specific reproduction of pain was consistent with her activity

restrictions described in the subjective examination and fit with the nociceptive dominant pain type that was hypothesized.

6. What is the relationship between UTC imaging and clinical symptoms and signs and how do you use the UTC findings to inform your management?

Answer to Reasoning Question:

While UTC quantifies tendon structure, it still does not correlate with clinical symptoms and pain. The disconnect between pain and structure within the tendon has been well documented in the literature (Cook et al., 2001a, Khan et al., 1996).

Education is a key part of imaging and its utilization. In low back pain, the inappropriate use of imaging has been linked to 'over-medicalization', a decrease in patients' self-perceptions of health, and a contribution to fear-avoidance behaviours (Flynn et al., 2011). Judy had a classic fear response to the negative words used in imaging reports.

The UTC's ability to quantify the volume of aligned fibrillar structure can help counter any negative understandings that the patient may have about their tendon. If the tendon contains similar or an increased amount of aligned fibrillar structure compared to normal the patient easily recognizes they have enough normal tendon structure to tolerate load and that load management strategies should be embraced.

Clinical Reasoning Commentary:

While provocation of Judy's localized pain with the double leg heel raises is considered consistent with tendinopathy, the reasoning evident in this answer highlights the value of the physical examination beyond diagnostic confirmation. In this example, the assessment is reduced to avoid aggravation of the problem and in consideration of Judy's expressed fears. A specific physical impairment is identified and measured (4 double leg heel raises) that will inform exercise dosage and enable outcome monitoring of progress.

The disconnect between pain and structure within the tendon reflects the broader disconnect between musculoskeletal pain and pathology generally. Despite this limitation, confirmed pathology should not be disregarded. Pathology must be considered with respect to precautions in examination and treatment (e.g. caution with applying excessive load to tendons demonstrating significant degeneration), and with respect to evidence supporting management and prognosis. Here the UTC is used in a novel educative way whereby the aligned fibrillar structure, rather that the pathology (e.g. areas of disorganization), is highlighted to give Judy confidence in her tendon and to enhance her motivation for exercise.

Stop Box x.2 here

Treatment [1hd]

Education [2hd]

Education for Judy focused on:

1. Debunking the myths and reducing fear around language

2. Understanding the importance of load

3. Teaching her when and how to 'listen' to her tendon.

Debunking the myths and reducing fear around language [3hd]

Terminology such as tear or degeneration can have a profound impact on an individual's perception of their injury and their capacity for improvement. The UTC was vital to address Judy's fear around rupturing the tendon. Education about load helps to reduce fear of movement and empower patients. It is important to understand that tendon pain is not inflammatory. Cytokines that are present in tendinopathy may have a role in cell signaling and the pathology itself, however their role is currently unknown. Clinically, it is important that patients and clinicians understand that the approach required is different to that for an injury with classic inflammation.

Understanding the importance of load [3hd]

It is vital to understand tendon load; both the loads that led the patient into trouble, and also that load is the most important factor in their rehabilitation. There are four types of load and each has a different effect on the tendon. Tensile load maintains fibrous tissue, compressive load can form or maintain cartilage, and a combination of these loads can form or maintain bone (Ingber, 2005).

High tensile tendon load is present in any activity that requires a tendon to store and release energy. For the Achilles tendon, this may include walking, running or hopping. However, when completing these activities, there are other loads on the tendon. For example, walking uphill will increase the compressive load on the Achilles insertion by increasing the amount of dorsiflexion.

When a patient understands that tendon pain increases with excessive tendon loading, you can explain how to modify loading to reduce symptoms. For example, Judy should avoid any dorsiflexion such as stretching and use shoes with a substantial heel to reduce compressive loads and increase low tensile tendon loads.

Conversely, tendon load is also the only intervention that can improve tendon pain and function, and the only stimulus shown to improve tendon mechanical properties (Kongsgaard et al., 2010). We often see patients who have been treated by practitioners who have an over-reliance on passive therapies that fail to address tendon or kinetic chain capacity. Tendons respond slowly to load, thus loading should be progressed in a very considered manner.

Teaching her when and how to 'listen' to her tendon [3hd]

Tendons may occasionally be uncomfortable during rehabilitation. It is important that Judy listens to her tendon's response to loading. That being said, we don't advocate painful rehabilitation as has been reported with eccentric protocols (Alfredson, 2003), and in fact early load such as isometric exercise should cause an immediate reduction in tendon pain. The tendon response in the 24 hours after activity is the most important gauge of progression. For the Achilles, it is possible to gauge progress using the length of time of morning pain or stiffness, or pain with a hop in athletes who present with a higher level of function.

Response to load can vary and it has implications for the loading program. If pain increases, the loading (or diagnosis) is wrong. If the pain response stays the same

while load is increased this is acceptable. For example, many athletes who place very high loads on their tendon in sport do not have a zero pain score the next day but are able to complete training and competition. If their pain is stable on a loading test, the tendon has not been aggravated by the load. The ideal scenario is reduction of pain with increasing load.

Instruction in home exercise [2hd]

Judy was prescribed double leg calf raise holds with body weight in plantar-flexion. She was too fearful to start with just a single leg. This was tested in the clinic and prescribed as five isometric holds of 45 seconds each (with two minutes rest between each isometric hold) as this was manageable without any muscle fasciculation. On immediate reassessment after the isometric exercise, Judy was able to perform twenty-five double leg raises with a pain score of 0/10 (previously four raises at 4/10). Judy was instructed to complete these throughout the day at work as no equipment was required. Judy was also given single leg seated calf raises twice a day and she chose to hire a seated calf raise machine (Figure x.6) so that she could complete these easily at home.

Insert Figure x.6 here

Start Box x.3 here

Reasoning Question:

8. Judy had received a variety of treatments in the past without success. Would you provide a brief overview of the research evidence for the efficacy of the more common therapeutic interventions and discuss your reasoning for the specific exercises and dosage you selected for Judy?

Answer to Reasoning Question:

Judy had predominantly had passive treatments in the past that failed to address strength or improve capacity in the muscle-tendon unit and the kinetic chain. The standard eccentric exercise program was inappropriate as she had an insertional Achilles problem (Cook and Purdam, 2012). Eccentric exercises over a step have been shown to not be beneficial for insertional Achilles tendinopathy due to the compression against the calcaneus in dorsiflexion (Cook and Purdam, 2012, Jonsson et al., 2008). Judy's presentation was also too painful for the modified eccentric exercise program for insertional Achilles tendinopathy (Jonsson et al., 2008). Appropriate load exercises such as isometric load out of compression has been found to be clinically beneficial for tendon pain, and has been shown to reduce pain instantly and for at least 45 minutes in a patellar tendon study (Rio et al., 2015). Clinical experience supports that isometric load is also beneficial for other tendon pains. It is important that the load is appropriate for the individual. Seated calf raises using a machine are a good way of starting below body weight in some patients and building up. At the other extreme, some high level athletes require the addition of external load such as using a Smith machine whilst doing calf raises.

Glucocorticoid injections reduce tendon cell proliferation and activity (Scutt et al., 2006) and offer pain relief. However, they should never be used in isolation and

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without load management and tendon rehabilitation. Some studies have shown poorer outcomes when they are included in treatment but data for the Achilles is limited (Coombes et al., 2010).

PRP is no more effective than placebo (de Vos et al., 2010) and should not be presented as a gold standard of treatment for tendinopathy.

Clinical Reasoning Commentary:

As evident here, clinical reasoning about 'Management' should be evidence-informed, tailored to patients' individual presentations (e.g. with respect to mode of exercise and dosage), and monitored (reassessed) to determine effect and guide progression.

Stop Box x.3 here

Between treatments [2hd]

Judy was encouraged to contact the therapist with any questions or if she had any problems between appointments. Part of the education about tendon load also included information about how to use load (isometrics) to reduce pain if there was a flare-up. The morning pain score is used to indicate how the tendon responded to the loading of the day before. The decision was made by the therapist and Judy to continue in the boot for the first week and then slowly wean her off the boot by increasing walking (firstly only around the house) without it. Due to the long period of time in the boot, removing it entirely would have resulted in a large increase in tendon load to which the tendon was unaccustomed.

Second Appointment (two months after initial assessment) [1hd]

Subjective Assessment [2hd]

Judy reported much less fear of her tendon and was no longer wearing the boot. Judy had only taken two weeks to completely cease using the boot, which was faster than anticipated. However, she used the morning score to confirm that her tendon was tolerating her gradual reintroduction of walking in shoes. Her Achilles was no longer bothering her at work. She had no morning pain or stiffness. She was still bothered by walking with barefeet or when wearing flat shoes, or shoes that rubbed on her heel (these scenarios gave her morning pain and stiffness of 4-6/10 depending upon the length of time). She had been walking pain-free every 3 days for approximately 2-3 km providing she wore her tennis shoes. This had been built up according to her education, that is specific distances were not provided; instead Judy was encouraged to 'listen' to her tendon and modify or increase her load accordingly. In terms of general health, Judy had been in hospital recently for a routine colonoscopy where her heart had gone into atrial fibrillation that didn't settle so she was admitted overnight.

Goals: Judy had planned a trip to the mountain range of the Kimberley region in northwestern Australia in 3 months time and wanted to be able to walk every day and enjoy her holiday without pain. Her new goal was also to be pain-free and to be able to walk downstairs normally.

Physical Assessment [2hd]

On observation Judy was in normal shoes. There was no redness of her calcaneus and her muscle bulk had improved but still was not as large as the contralateral side. On

her knee to wall test she recorded 9cms on the left side and 5 cm on the right, again an improvement from the first visit. Her gait had also improved; she was not limping and was pushing off both feet. Functionally Judy could perform 18 calf raises on the left side, but on the right side she was still afraid to initiate a single leg calf raise. However she could take full body weight once in plantar-flexion (during a double leg raise with weight shifted to the right side). She was able to do more than 25 double leg raises.

Imaging [3hd]

Judy was referred for a follow-up UTC scan on her right Achilles. The overall echo-pattern for the right Achilles tendon had improved in comparison to the previous scan (Figure x.7). While the percentage of normal tendon fascicles (echo-type I) was similar, a significant decrease in the percentage of echo-type III and IV was observed. The diffuse pathological area at the calcaneal insertion was still apparent, however a reduction in the mean CSA (from approximately 40% to approximately 10%) was observed with the length remaining unchanged (Figure x.8). A decrease in the mean CSA of disorganized tissue was observed with the mean CSA of aligned fibrillar structure remaining similar (Figure x.9).

Insert Figures x.7, x.8, x.9 here

VISA-A [3hd]

Her VISA–A score had increased to 63 out of 100, still indicating substantial pain and dysfunction but considerably improved from the previous time.

Treatment [2hd]

Education [3hd]

We continued the discussion around footwear to avoid compression at the insertion by utilizing a shoe with a substantial heel raise and to slowly increase walking load and be consistent with shoes and activity. Tendons respond poorly to change so consistency in rehabilitation and walking load is important. Judy was reminded the most important time to 'listen' to the tendon was the morning after a walk. A return to walking plan was developed together according to tendon loading principles.

Exercise [2hd]

Judy's rehabilitation was progressed. She was to complete the isometric holds one day, followed by a double leg raise with weight shift to the right leg the next. She also completed left leg raises for a cross-over strengthening effect (Hendy et al., 2012a, Kidgell et al., 2011). If Judy had walked too much and experienced an increase in morning symptoms, she was to increase the frequency of completing the isometric holds during the day. Judy was taught how to progress these between now and the next appointment. She also started sit to stand exercises for general quadriceps and gluteal muscle function. Based on assessment of the number of repetitions Judy could perform with good control through the full kinetic chain, she was started with four sets of six repetitions and given information about progressing to encourage a strength and endurance focus.

Third Appointment (7 months later, 9 months after initial assessment) [1hd]

Subjective Assessment [2hd]

Judy reported that she had had a wonderful holiday and walked at least 3 km per day and felt no pain. She avoided barefoot walking and was adherent with her exercises and walking before her holiday. Since she had returned, she had been less diligent with her exercises and reported having occasional walking pain. There was no change in her general health, and a recent check-up with her rheumatologist found everything was stable. Judy reported occasional pain at the top of the double calf raise home exercise. Footwear choice was still important as her boots which were very flat aggravated her pain. She remained fearful of flat shoes and had purchased new wedged sandals for summer that had an external heel to ensure there was no compression from excessive dorsiflexion nor did they rub on the insertion. Her current activity consisted of walking 2.5 km per day and one session of Pilates per week.

Physical Assessment [2hd]

Judy had no swelling or redness over the calcaneus and her other assessment tests were similar to the previous assessment. She was able to single leg heel raise ten times, however assessment of her technique revealed that she was supinating at the top of range. This decreases the load on the calf and is a 'cheat movement'. Judy was instructed on the correct way to perform calf raises and was only able to complete six repetitions with the correct technique.

Imaging [2hd]

The overall echo-pattern for the right Achilles was stable in comparison to the first follow-up scan (Figure x.10). All four echo-types were similar with little variation observed over the length of the tendon. The diffuse area of disorganization was still apparent and the size and length of the area of pathology had remained unchanged.

Insert Figure x.10 here

Goals and expectations [2hd]

Judy expected now to return to her pre-injury level of walking and two Pilates sessions per week. She also expressed that she now expected the tendon would get better and that she would be able to return to full activity.

Treatment [2hd]

Re-education of her calf raise technique (Figure x.11) was undertaken to ensure appropriate alignment and calf activation to avoid posterior ankle pain. This included taking a video for Judy to watch. A trial of soft tissue work on her calf to increase knee to wall distance effected no change on her range of movement.

Insert Figure x.11 here

Judy's home exercises were progressed to increase her strength on both sides by (1) changing her double leg calf raise with weight shift to the right, (2) adding single right leg calf raises with isometric holds, and (3) continuing to increase her walking distance.

All the education previously delivered to Judy was reiterated and she was again told how to avoid exacerbations and what to do if one occurred. She clarified her future self-management and was happy to continue to monitor and manage her tendon.

Reasoning Question:

9. Earlier you indicated that UTC imaging does not correlate with symptoms and

    signs. Would you discuss the value of using imaging as an outcome measure of

    clinical improvement?

Answer to Reasoning Question:

If repeat imaging is utilized, it is critical that the patient's expectations are managed.

A number of studies have shown that clinical improvement is not mediated by

improvements in tendon structure (Drew et al., 2014). Importantly, the patient should

be educated that their tendon is likely to remain abnormal / pathological even if their

pain has improved. When repeat scanning with UTC, the ideal scenario is to hopefully

see improvements in tendon structure coinciding with a decrease in pain and increase

in tendon load. However, an equally suitable outcome is that the tendon's structure

remains stable coinciding with a decrease in pain and increase in tendon load.

Explaining to the patient that the tendon's ability to return to normal is limited and

that the tendon will find a state of equilibrium is of critical importance in minimizing

negative psychological outcomes with imaging.

Clinical Reasoning Commentary:

The value of imaging as an outcome measure is clarified and its value as a resource

for education is re-emphasized. 'Reasoning about Teaching', a 'Clinical Reasoning

Strategy' (i.e. focus) discussed in Chapter 1, emphasizes that teaching, like all

management tools, needs to be tailored to the individual patient and reassessed to

evaluate the patient's understanding (learning) and other effects (e.g. altered fear and behavior).

Stop Box x.4 here

No further appointments were made and Judy was advised to continue to increase her exercises as able with the ongoing goal of being able to complete 20 single leg calf raises at least three times a week.

Appendix T. Book chapter: Managing tendinopathies

CHAPTER 10

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TENDON AND TENDINOPATHY

sc0010 CHAPTER **10.1** ■ TENDON AND TENDON PATHOLOGY

1

Hazel Rosemary Corinna Screen

s0010 ## INTRODUCTION AND TENDON FUNCTION

p0010 Tendons perform the primary role of connecting muscle to bone to facilitate motion. At first glance, these passive, collagen-rich tissues appear to be very simple rope-like structures. However, as we delve further into their mechanobiology, we discover that this view is far too simplistic. Structure and material properties are not universal across tendons, but are optimized to enable different types of tendons to effectively perform their varied functional roles within the musculoskeletal system.[1] As a clinician, it may therefore not be appropriate to treat all tendons in the same manner, and knowledge of how tendon structure and function are optimized becomes critical to understanding and treating injuries and diseases effectively. As our understanding of the differences between tendons evolves, we can begin looking for opportunities to target treatment modalities towards specific types of tendon or even types of injury, based on an understanding of the basic science of these conditions.

p0015 In connecting muscle and bone, tendons provide a passive linkage to ensure that active muscle contraction results in joint movement. Including a tendon in the muscle-to-bone connection is vital for a number of reasons. Firstly, muscle is compliant whereas bone is very stiff. Tendon provides a gradated change in materials characteristics between these extremes, minimizing the development of areas of stress concentration where failure is likely to occur.[2] Secondly, to provide active contraction, muscles are often quite bulky, particularly when they must generate significant power. The role of the tendon in this instance is to move the muscle belly away from its point of action.[3] This creates space, but also allows the tendon to work like a lever arm, moving the point of action away from the centre of rotation, thereby reducing the forces required for movement, much like a spanner does when manipulating a nut.

p0020 Beyond these universal functions, specific tendons, aided by their individual material properties, assist movement in different ways. Tendons such as the flexor and extensor tendons in our hands are subjected to low stresses and strains, but must modulate muscle contraction with extreme precision to allow us to perform intricate activities such as writing. They must be reasonably inextensible, so muscle contraction is transferred fully and precisely to the fingers, yet must provide a degree of damping in the system so our movements are not jerky but finely controlled.[4] This functional role contrasts heavily with that of a tendon such as the Achilles. The Achilles must withstand multiples of body weight when we walk or run, and act as part of the locomotory system to help propel us forward. It must act like a spring, stretching when it is loaded before recoiling to return energy to the system as we push off, thereby improving locomotory efficiency.[5] While tendons, such as the Achilles, must be sufficiently stiff to enable efficient force transfer to the skeleton, they must also incorporate a degree of elasticity to enable them to stretch and store energy.[6,7]

p0025 Tendons such as the Achilles and patellar are termed energy-storing tendons, whereas those in the hand are referred to as positional tendons. While the hand tendons and Achilles provide examples of extreme functional requirements, many tendons require a combination of these properties, and must find an appropriate balance between energy storage and stiffness for efficient force transfer. Creating these opposing functional requirements necessitates subtle structural and compositional differences between tendons to provide appropriate mechanical behaviour;[8] such differences may also result in differences in the mechanisms of damage or injury between these tendons.

COMPOSITION AND STRUCTURE s0015

p0030 It is staggering to appreciate that the tendon extracellular matrix, as in all biological materials, is made entirely from the tissue's resident cells. The cellular component only constitutes approximately 10% of the dry weight in mature tendon, with the predominant cell type termed

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the tenocyte.[9] While tenocyte phenotype remains poorly understood, it is known that tenocytes are sensitive to the mechanical loading environment they perceive during tendon use, and control tendon structure, composition and health at least partly in response to these stimuli.[10] Understanding the important chemical and mechanical stimuli that govern tenocyte metabolism, and harnessing these to promote healthy matrix production or repair, is subsequently a key area of interest in tendon basic science research.

p0035   The general structure of tendon extracellular matrix (ECM) was first described in the late 1970s in the seminal work of Kastelic and co-workers.[11] Tendon ECM is typically 60–90% type I collagen, arranged in a series of hierarchical levels. The smallest structural unit is the nanoscale individual collagen molecule and these cross-link together to build collagen fibrils, in the order of 50–500 nm diameter. Collagen fibrils aggregate into fibres, then fascicles, and finally the whole tendon, with the collagen at each of these hierarchical levels interspersed with a proteoglycan-rich matrix (Fig. 10-1A). The highly aligned, hierarchical organization of collagen is responsible for the exceptional tensile strength of tendon. Tendon also contains approximately 0.5–3%

elastin, 2–5% proteoglycans and small amounts of a range of other types of collagens[12,13] (Fig. 10-1B). While these proteins are far less abundant than collagen type I, they may still play important roles, with elastin known to provide high elasticity and proteoglycans responsible for imbibing water and resisting compressive strains or providing lubrication. A range of other glycoproteins have been reported in different tendons in varying amounts, but no clear structural roles have been identified for most of these additional proteins to date.

From a materials science perspective, the tendon p0040 ECM may be described as a fibre-composite material. A fibre composite is a material that is made by combining two distinct materials together, where each material is known as a phase; the fibre material makes the 'fibre' phase, and the secondary material surrounding them makes another phase known as the 'matrix' phase. The 'fibres' of a fibre composite are strong under tension and reinforce the material, whereas the surrounding 'matrix' is usually more ductile, holding the 'fibres' together and helping them to share or distribute the applied loads.[14] Fibre-composite materials are in common use, examples include; steel-reinforced concrete and carbon fibre. They provide a number of advantages over
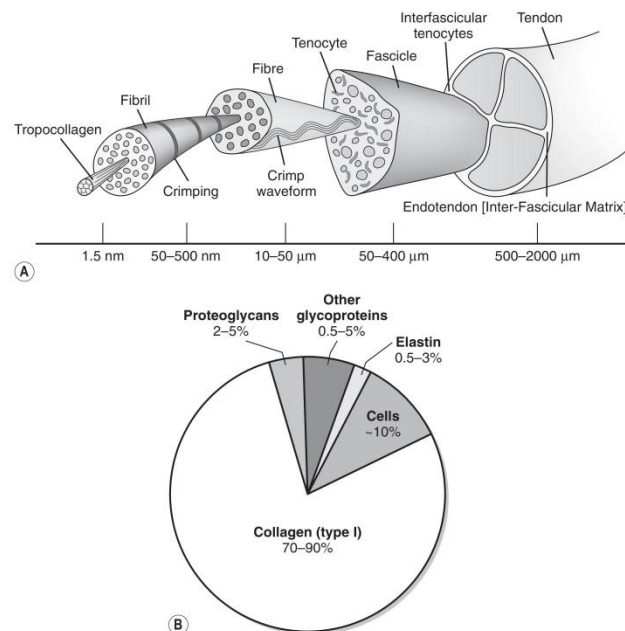
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FIGURE 10-1 ■ (**A**) Schematic depicting the hierarchical structure of tendon, in which collagen units are bound together by either crosslinks or non-collagenous matrix at multiple hierarchical levels, to make a fibre-composite material with outstanding tensile strength. (**B**) Tendon composition varies according to the functional role of the tendon, but the composition of the majority of tendons is within the ranges outlined in the pie chart.

single-phase materials, as they combine the properties of both constituent parts, allowing material to both be light weight and strong. They also have good fatigue resistance, as damage in one area cannot easily propagate through the whole material because the 'fibres' of the composite are all separate entities.

p0045   When considering tendon from a materials science perspective as a fibre composite, the aligned collagen units constitute the 'fibres' and the surrounding proteoglycan-rich phase the 'matrix'. As such, tendon is effectively a multilevel fibre-composite material, as there is a fibre-composite arrangement (collagen units surrounded by matrix) at every level of its hierarchical structure. It is easy to get confused with the terminology as, from a biological perspective, the term fibre is also used to describe a single level of the tendon hierarchy. Indeed, to add to the confusion, different terms are also regularly used by different research groups to describe each level of the tendon collagen hierarchy, so care must be taken when reviewing the literature to be clear to what the text is referring. In this text, quotation marks around the word fibre denotes the more generic materials science use of the word.

MECHANICAL BEHAVIOUR   s0020

There have been numerous investigations into the p0050 mechanical properties of tendons. Typically a tendon is pulled to failure, recording how much force is required to stretch the tissue, and how much it stretches before it breaks. This is shown graphically in a force-extension curve (Fig. 10-2A), and the stiffness can be found from the slope of the curve, where a steeper curve denotes a stiffer tendon. While these data are useful, they are not only dependent on the properties of the tendon, but also the size of the piece of tendon tested (intuitively, it takes more force to break a thicker sample, simply because it is thicker), so data is usually normalized and presented as a stress-strain curve, which specifically describes the properties of the tissue itself (Fig. 10-2B). The term modulus is then used for the gradient of the curve, so modulus is simply a normalized stiffness measure, taking into account dimensions of the test sample.

The three-stage shape to the tendon stress–strain p0055 curve is typical of the mechanical behaviour of many of our soft tissues, although compared to other tissues such
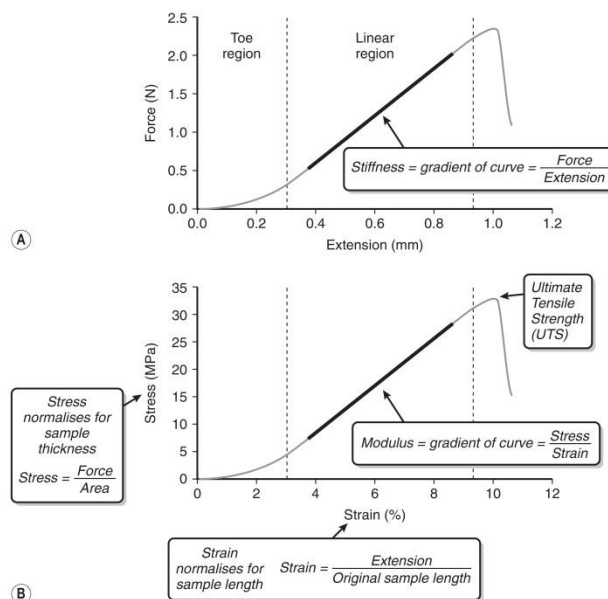
FIGURE 10-2 ■ (**A**) Schematic depicting a typical force–extension curve for a tendon pulled apart to failure. The data shows how much force is required to stretch the tendon until it breaks. The gradient of the force–extension curves denotes the stiffness of the sample. A steeper gradient would denote a stiffer sample, where more force was required to extend the sample. (**B**) The force–extension data can be normalized for sample dimensions and shown as a stress–strain curve. The stress–strain characteristics of a material are thus independent of the test sample size, so the stress–strain curve describes the generic material behaviour. The gradient of the stress-strain curve is referred to as the modulus.

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t0010   **TABLE 10-1   The mechanical properties of a range of different tendons**

Tendon Type	Modulus (MPa)	Ultimate Tensile Strength (MPa)	Authors	Ref
Ovine plantaris tendon (energy storing)	1650 ± 290	90 ± 12	Bennett et al. (1986)	17
Wallaby tail tendon (positional)	1662 ± 105	107 ± 19	Bennett et al. (1986)	17
Equine superficial digital flexor tendon (energy storing)	614 ± 115	115 ± 24	Thorpe et al. (2011)	18
Equine common digital extensor tendon (positional)	1012 ± 154	157 ± 34	Thorpe et al. (2011)	18
Rat tail tendon (positional)	663 ± 167	47 ± 8.4	Screen et al. (2004)	15
Rat Achilles tendon (energy storing)	400 ± 50	40 ± 6	Netti et al. (1996)	19
Human Achilles tendon (energy storing)	816 ± 218	71 ± 17	Wren et al. (2001)	20
Human hamstring tendon (energy storing)	362 ± 21	87 ± 13	Butler et al. (1984), Schechtman et al. (2000)	21,22

The modulus and ultimate tensile strength are reported in MPa (as described in Fig.10-2).

as skin, tendon has a high failure stress and modulus (Table 10-1). The low stiffness behaviour we can see during the toe region results from the alignment and organization of collagen in the loading direction, in addition to straightening of the collagen fibres, which display a periodic crimp pattern in the unstressed state.[15,16] With further applied strain, the stiffness of the tendon increases rapidly, in what is commonly referred to as the linear region. With all the collagen straightened and aligned in the loading direction, the large increase in stiffness in this region reflects the direct loading of the tendon structure. The stress–strain behaviour of the tendon is then reasonably linear until close to failure, at which point material microrupture leads to a steady drop in stiffness, as the fibres pull apart and the sample fails.[2]

p0060   Modulus or stiffness values for tendon are generally reported from the linear region, and most tendons probably operate within this region during physiological loading. Positional tendons, which experience very small loads in use, are stiffer (high moduli), but probably only just encounter sufficient load to operate in the linear region, whereas energy-storing tendons are more extensible and are often loaded to values close to the absolute failure stress of the tissue, explaining their significantly high risk of injury[23,24] (Fig. 10-3). In order to facilitate these different load requirements and mechanical characteristics, the mechanisms by which positional and energy-storing tendons extend during the linear region also differ. Tendons with a more positional function appear to stretch predominantly through sliding between collagen fibrils and fibres.[25] This sliding is governed by the proteoglycan-rich matrix between these collagen units, which creates the more viscoelastic and damped behaviour required in positional tendons such as the digital extensor and flexor tendons of the hand, and possibly the rotator cuff. By contrast, recent data indicate that there is very little viscous sliding behaviour between fibres and fibrils in energy-storing tendons such as the Achilles and patella. Instead, the fascicles are helically
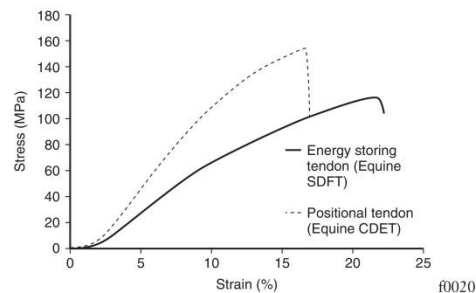
FIGURE 10-3 ■ Typical stress–strain curves, contrasting the mechanical behaviour of the energy-storing equine superior digital extensor tendon (SDFT) and the positional equine common digital extensor tendon (CDET). The high failure strain and reduced stiffness of the energy-storing tendon is important to facilitate its energy-storing role.

arranged like individual springs, and when the tendon is stretched, the springs can stretch to store energy and recoil very effectively.[26] In energy-storing tendons, sliding occurs predominantly between fascicles and is more elastic in nature, with recent data indicating that fascicle sliding maybe critical for energy-storing function[18] (Fig. 10-4). While these data are very recent, and further work is necessary to fully understand the important structural differences between tendon types, they do highlight the importance of taking a tendon-specific, or at least tendon function specific, approach to considering an injury. Some data suggest that the specific high-strain mechanisms in energy-storing tendons (both fascicle sliding and helical arrangement) reduce in efficacy as tendon ages, coinciding with an increased injury risk.[27,28] If factors such as reduced fascicle sliding are implicated in increased tendon injury risk, it may be possible to
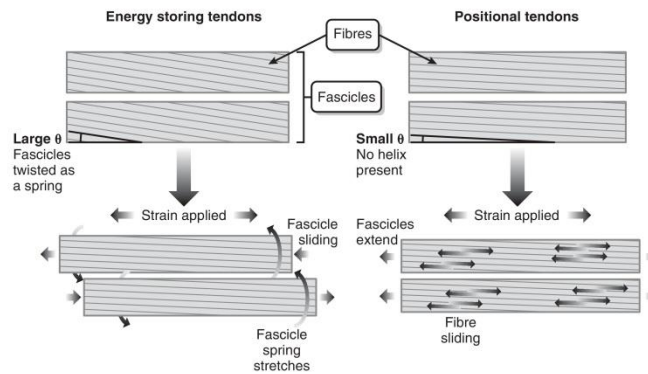
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FIGURE 10-4 ■ Energy-storing and positional tendons meet their different mechanical requirements though differences in their structure and how it responds to applied strain. Energy-storing tendons extend through stretching or unwinding of the helical organization in their fascicles, so the fascicles act like springs (see the large θ, denoting a larger twist to the resting fibre arrangement). The fascicles also slide past one another to enable the high strains seen in these tendons. By contrast, positional tendons have little twist in the resting configuration (small θ) and instead extend through sliding between adjacent collagen fibres within fascicles.

develop more targeted treatments to directly treat these mechanical and structural changes.

s0025 ## TENDON INJURIES AND REPAIR

p0065 Despite our increased understanding of normal tendon structure and function, there remains a surprising dearth of knowledge concerning tendon pathophysiology. This lack of knowledge reflects not just the complexities associated with tendon diseases, but also the difficulties in exploring these during the early stages of disease development. We do not know if the pain signals alerting a patient to tendon damage are delayed relative to injury onset, and it is rare to perform any immediate invasive protocol to assess injury post diagnosis.

p0070   There is a suggestion that the processes leading to sudden tendon rupture are different to those involved in the development of tendinopathic conditions,[29] but it is also quite possible that the development of tendinopathy differs between tendon types. Sudden tendon ruptures tend to occur in people who have been largely pain free in the lead up to injury, whereas tendinopathic patients present with significant, often debilitating pain, but the condition rarely progresses to rupture.[30] Understanding of pain mechanisms is currently very limited and it is uncertain if the different presentation of these conditions indicates different underlying pathophysiologies, or if the pain associated with tendinopathy simply prevents additional overuse and damage accumulation in this condition. For a tendon to rupture it must already be structurally compromised; however, these injuries have only ever been viewed post rupture, so the nature of early tendon deterioration and structural compromise remains unknown. In tendinopathic tendon, classic reports of the condition describe a highly disordered tendon matrix containing increased levels of collagen type III,

proteoglycans and water, with increased vasculature but no signs of inflammation[29,31,32] (Fig. 10-5 compares healthy and tendinopathic tendon sections). However, while these findings have led to a strong leaning towards diagnoses of tendinosis, this perspective has been derived from the analysis of tendons months after the initiation of the disease, and provides little insight into the early development of the condition.

It seems highly likely that tendon pathogenesis will p0075 involve interplay between localized overuse matrix damage, and a cell mediated response to the loading conditions. Various animal models have been adopted to investigate the interplay of these factors in early tendinopathy.[34] These generally report that cyclic overuse of tendon results in disruption of the tendon matrix, and an increase in cell number and a rounding of the cells, alongside an up-regulation of various catabolic proteinases.[35-38] However, the order in which these processes are initiated and how they progress to the aetiology reported in long-term degenerate tendinopathy remains unknown, and significantly more work is necessary if the aetiology of tendinopathy is to be established. Current theories suggest that the up-regulation of various matrix proteases in early tendinopathy may be accompanied by an inflammatory response, a cellular attempt to turnover and repair the tendon.[39-42] The increase in cell number is additionally thought to occur as a result of infiltration of inflammatory cells to the injured site.[41] Such a repair response fits with the concept that tendon pathology is a continuum in which early stage reactive tendinopathy may correlate with minimal local damage that can be effectively repaired by the cells, whereas excess overload can imbalance any repair attempts and lead to an inappropriate cell metabolic response and more significant matrix breakdown.[43]

Fibre-composite theory indicates that tendon damage p0080 will initiate in the non-collagenous matrix components,[44]

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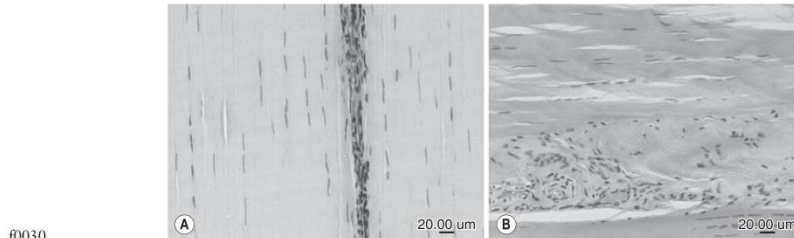
FIGURE 10-5 ■ Histological sections, viewed with a Nikon Eclipse 80i, from the energy-storing equine superior digital extensor tendon. Images compare (**A**) a healthy tendon and (**B**) a tendinopathic tendon. Note the aligned and ordered matrix in the healthy tendon, and clearly differentiated interfascicular matrix. By contrast, the tendinopathic sample shows the disordered matrix, rounded cells and increased cellularity. For colour version see plate section. (Photographs taken in Professor Peter Clegg's laboratory, University of Liverpool.[33])

hence the fraying of collagen seen in late-stage chronic tendinopathy is likely a later phenomenon, quite possibly cell mediated in nature. Indeed, the turnover of non-collagenous matrix is substantially faster than that of collagenous matrix in tendon,[45] with some studies indicating that the half-life of tendon collagen is hundreds of years, so is barely altered in normal healthy mature tendon.[46] Furthermore, the turnover of non-collagenous matrix is faster in more highly loaded energy-storing tendons, suggesting it may provide an important mechanism by which tendons can manage and repair injuries before they propagate.[45] With fascicle sliding currently proposed as a key mechanism facilitating tendon extension in energy-storing tendons, the non-collagenous matrix between fascicles is an interesting target for further study.

p0085   With such limited understanding of the initiation and development of tendinopathic conditions, it is perhaps unsurprising that so many treatment options for tendon conditions have been proposed. However, as we begin to identify the structural and functional differences between tendons in health, it becomes less surprising that a one-size-fits-all approach is ineffective in treating tendinopathies.[47] All of the intrinsic and extrinsic factors which may lead to tendinopathy must be considered, with epigenetics and ageing also currently of prominent interest in establishing disease risk.[47] Studies are now focusing on tendon overload or fatigue damage development in different types of tendon, and how ageing alters matrix structure and increases injury risk. Hopefully new opportunities for targeting treatments will soon be forthcoming.

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sc0015 # CHAPTER 10.2 ■ MANAGING TENDINOPATHIES

Jill L Cook • Ebonie Rio • Jeremy Lewis

s0030 ## INTRODUCTION

p0090 Tendinopathy is the term given to the combination of pain and loss of function originating from tendon. It is a common clinical presentation and occurs in upper and lower limb tendons. Tendinopathy is typically associated with changes in tendon structure, but not all changes result in symptoms and a loss of function. This is confusing for patients and clinicians, and as such, clinical examination currently remains the cornerstone of assessment. Changes in tendon-loading behaviour typically precede the onset of symptomatic tendinopathy and load management currently underpins the treatment for tendinopathies.

p0095 Prevalence of tendinopathy generally increases with ageing tissue and cumulative load increase susceptibility.[1] Lateral epicondylopathy has a reported prevalence of 1.3% in the general population,[2] but may be as high as 40% in tennis players,[3] and it is most common in the fourth and fifth decades.[2,4] An episode of lateral epicondylopathy may be prolonged and associated with episodes of recurrence.[2] Patellar tendinopathy is common in sports that involve jumping (energy storage and release) and quick changes in direction, such as occur in basketball. It is more common in younger populations, with prevalence rates reported as high as 40% in jumping athletes.[5,6]

p0100 Tendinopathy can be persistent and recalcitrant to treatment and symptoms may continue for more than 15 years.[7] Although ongoing research has resulted in a better understanding of tendinopathy management, substantial deficits in the knowledge required to treat this common musculoskeletal problem exist and managing tendinopathies remains a challenge. Chapter 10A highlighted differences in tendons and their function and it is clear that clinically a 'one-size-fits-all' approach is not appropriate and treatment must be individualized. A holistic approach that appreciates the individual's aspirations, and a consideration of other relevant factors such as; age, previous injuries, co-morbidities, hormonal status and lifestyle factors (e.g. smoking) need to be factored in to treatment planning.[8]

TENDON PATHOLOGY   s0035

p0105 Tendon structure is complex and the process that leads to tendon pathology is controversial. Chapter 10A has comprehensively covered normal tendon and tendon pathology; however, additional clinical and imaging factors need to be considered. Firstly, as described in Chapter 10A, tendon pathology may not be uniform and there may be discrete regions of pathology within a tendon that are surrounded by normal tendon. Secondly, there are pathological variations between different tendons, for example, patellar tendinopathy tends to develop well-defined areas of pathology, whereas the Achilles may demonstrate quite diffuse pathology. Thirdly, and as mentioned, pathological changes observed within tendons do not always correlate with symptoms.

p0110   Pure tendinopathy (within the body of the tendon) occurs most commonly in the mid-Achilles tendon region. Tensile overload is the key driver of tendon pathology, and energy storage (rapid tendon lengthening) and release loads are particularly stressful for tendon.[9] The use of a tendon like a spring (stretch and release) occurs in many vocational and athletic activities to reduce the metabolic demand of high speed movement. This is exemplified in the Achilles during activities involving sprinting and jumping. Normally, tendon structure can sustain these loads, and Chapter 10A describes the sliding between helically arranged fascicles during energy storage.

p0115   Most other tendons develop pathology at the complex bone–tendon junction, excess tensile, compressive or shear loads (and combinations) can induce pathology. The bone–tendon junction is designed to transition mechanical load between the more flexible tendon and stiffer bone. This complex structure is called the enthesis organ[10] where compression of the tendon against the bone proximal to the insertion protects the insertion and improves the mechanical advantage of the tendon.[11] The compression is ameliorated by fibrocartilage within the tendon and on the bone, and bursae are typically present between the tendon and bone.[12]

p0120   Excessive compressive load at the insertion causes change within the enthesis organ, increasing pathology in the tendon and possible inflammation in the bursa. It is a clinical homily that symptomatic bursitis is part of compressive insertional tendinopathy and should be managed as a tendinopathy and not as an isolated bursitis. For example, trochanteric and subacromial bursal injections should not be seen as a standalone treatment but should be considered as part of the staged management of rotator cuff and gluteal tendinopathy.[13,14]

p0125   Tendons where compressive loads have a role in tendinopathy include the Achilles insertion, hamstring origin, gluteal medius and minimus, tibialis posterior, peroneals and adductor tendons. In the upper limb the rotator cuff tendons are susceptible to compressive tendinopathy. It is important to note that the site of compression can be immediately before the insertion or quite distant from it, as is the case with the peroneal tendon and tibialis posterior. During extremes of shoulder movement, compression may occur within the structurally independent parallel fascicles of the rotator cuff tendons.[15] The compression proximal to the tendon insertion is not true of all tendons; patellar and elbow tendinopathy do not have an obvious compressive site. The tip of the patella[16] and the fat pad[17] have been proposed as potential compressive structures in the patellar tendon, but their involvement is not confirmed.

s0040 ## Pathoaetiology

p0130   The transition from structurally normal tendon to structurally degenerate tendon is well described in animal models, with a cell-initiated process that affects the ECM.[18] Uncertainty exists if this process is identical in humans and remains the subject of ongoing debate due in part to the differences between small animal and human tendons. Small animals have different anatomical architecture, different metabolic rates and different capacity to repair tendon. There is also the challenge of translating knowledge from large quadrapedal animal models such as equine tendon to bipedal humans.

p0135   There are several hypothetical models to describe the transition from normal tendon to pathology. The models can be divided into: (a) the cell models, where the cell is the first response to overload; and (b) collagen-tearing models, where the initial injury occurs in the ECM. The cell model was first proposed by Leadbetter[19] and developed further in the continuum model.[20] The continuum model proposes that the cells detect overload and respond by increased proteoglycan production that progressively separates and then disrupts the collagen matrix, leaving potential for vessel ingrowth. Tendon pain has not been fully integrated into this pathology model but is likely to occur in the early reactive phase or in a reactive on degenerative presentation where the remaining normal part of the tendon that is loadbearing is overloaded as the area of the pathology fails to absorb and transfer load.

p0140   Conversely, the collagen-tearing models propose a variable response after collagen tearing, including inflammation,[21] pain, failed healing[22] and degeneration. Pain is integrated into these models, however the link to common clinical presentation is not always obvious, and the cause of pain in tendons throughout the various stages of pathology has not yet been identified.

p0145   Definitive evidence of an inflammatory process, in the traditional sense, is lacking at any stage of tendon pathology. There has been recent interest in inflammation having a role in tendon pathology[23] and the literature and evidence in this complicated area remains uncertain and incomplete. One area of confusion is semantics, particularly the definition of inflammation, and the presence of what substances, cells or processes indicate inflammation. It is important to note that tendon pain is not consistent with a triphasic inflammatory process, so clinicians should consider avoiding therapies such as absolute rest, ice and anti-inflammatory medications as definitive treatments for tendinopathy.

p0150   It is important to emphasize that current understanding of the structural, cellular and chemical changes that occur in pain-free and painful tendons is poor. Most importantly, how pathology and pain are linked is not clear.

s0045 ## Source of Tendon Pain

p0155   Pain is the primary reason people with tendinopathy present to clinicians. This is true for the young athlete experiencing tendinopathy for the first time or for someone with a long history of tendon symptoms. Both seek resolution of pain but we currently know little about the origin of the pain, and if it differs in these clinical examples and in different tendons.

p0160   Pain is an output from the central nervous system (CNS), which may or may not be associated with a physiological nociceptive input caused by tissue disruption. Persistent symptoms often indicate that there are changes within the CNS which are contributing to a chronic pain state. The clinical features of tendinopathy include tenderness to palpation (primary hyperalgesia), well-localized pain, impaired function but no spreading of pain (secondary hyperalgesia) regardless of the length

of time of symptoms and variable evidence of local and more distant sensory change. This indicates that physiological (tissue protecting) and pathophysiological (functional changes within the nervous system) pain are present in tendinopathy.

p0165   The evidence for local nociceptive input is strong as tendon pain typically has a transient on/off nature closely linked with loading. It appears that tendon pain serves to protect the injured tendon. However, many features of tendon pain, such as its tendency for chronicity and the fact that pain during rehabilitation is sometimes encouraged[24] and may not be deleterious,[25] demonstrate that it is more complex than local tissue damage. To add to this complexity, there may be differences in upper and lower limb tendons, as well as between energy storage and positional tendons.

p0170   Furthermore, the source of pain in tendons cannot currently be seen on tendon imaging, as there is an inconsistent relationship between pain and pathological changes identified on imaging. Tendons demonstrating little tissue disruption on imaging may still be associated with pain.[26] Neither ECM change[27] nor neovascularization[28,29] has been consistently linked to pain. Similarly, severe pathology that progresses to tendon rupture may never have caused symptoms.[30] Lastly recovery, defined by improvement in the experience of pain and return to activity, also correlates poorly with imaging.[31]

p0175   The source of local nociception may include changes in tendon biochemistry, the tendon cell or nerve. Early stage tendinopathy may have profound biochemical and cell changes but little neural ingrowth; conversely, degenerative tendons may have areas of acellularity and less biochemical involvement but an increase in the nerve supply.[32] Furthermore, the nerve supply is not uniform throughout tendon, and in fact there appears to be few neural structures within tendon even when it is pathological.[33] Most of the nerve supply appears to be peritendinous so it is possible that pathology may occur within the tendon, without the CNS receiving any nociceptive input, potentially explaining asymptomatic tendinopathy.

p0180   There is some evidence for CNS modulation in tendinopathy; multiple studies have demonstrated alterations in sensory response both at the site of tendon pain and at other body sites.[34,35] Changes to brain and spinal cord excitability and cortical reorganization may occur with tendon pain.[36] This may explain the poor correlation between local tendon imaging changes and symptoms.[37] Modulation of neural activity may occur at the spinal cord and cortical levels; input (nociception) may be either up-regulated or down-regulated to produce variable outputs (motor/muscle activation and pain). Ongoing research into the contribution from, and the changes to, the CNS in tendon pain are required.

s0050 What Causes Tendon to Become Painful?

p0185   Unusual or unaccustomed load on tendon is associated with onset of pain, but why change in load results in pain or where the pain is coming from remains unknown. However, many people place high loads on tendons and never experience symptoms, even in the presence of tendon pathology. This reinforces the fact that tendon injury and tendon pain are a result of a complex interaction of intrinsic and extrinsic factors, as well as biopsychosocial factors. The experience of pain is unique for each individual and is based around the context of the experience, alterations to sensory integration and motor changes.[38]

ASSESSMENT   s0055

p0190   A thorough history is mandatory when assessing someone with tendinopathy. The priority is to identify recent tendon overload and current aggravating activities. Changes in loading may be very subtle, especially in athletes where a simple change in running shoe may bring on Achilles tendon symptoms. Similarly, a change in working height, speed of activity, weight or resistance of equipment may provoke rotator cuff and lateral elbow tendinopathy. It is important to identify previous episodes of tendon pain, their cause, what treatments were received and the response to treatment.

p0195   Assessment should enquire about pain and pain behaviour. Tendon pain commonly is reported as being maximal 24 hours after the aggravating activity. However, each tendon has its own classic pain behaviour, for example Achilles tendinopathy will be associated with morning stiffness and pain, patellar and hamstring tendinopathy with pain on sitting. In the upper limb, pain associated with lateral epicondylopathy commonly increases with wrist extension and the rotator cuff (especially the supraspinatus and infraspinatus) is typically painful in shoulder external rotation (often with shoulder elevation). Due to difficulties in achieving a definitive diagnosis, other causes of pain in these regions need to be considered.

p0200   Questioning is required pertaining to risk factors that may heighten the tendon's response to load, or contribute to a low baseline capacity of the tendon, making it more vulnerable to loading. Factors such as gender, age, obesity and systemic conditions (such as diabetes and menopause) may also influence the response to treatment. These conditions may sometimes be undiagnosed and in many cases require referral for investigation. Lifestyle factors such as smoking behaviour need to be identified.

p0205   The level of the clinical examination will be determined by the responses gained in the interview, as the history will indicate tendon irritability and capacity. Someone who is older and generally inactive presenting with substantial pain when the tendon is first loaded, will not be examined to the same level or in the same way as a younger athlete with mild pain, experienced after extreme activity. Clinical reasoning skills will determine the appropriate level of examination for the individual patient.

p0210   Key features of physical examination include determining the area of pain. Typically, tendon pain should be localized and require no more than two fingers to demonstrate the area. Bursal involvement in some tendinopathies, such as in rotator cuff and gluteus medius tendinopathies, may have a more extensive pain distribution. However, extensive pain distribution that does not change with increasing load, should trigger suspicion for an alternate or coexisting condition.

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p0215   Examination may reveal muscle wasting in the affected muscle–tendon unit and this may extend to regions above and below the affected tendon. In the lower limb, it is necessary to assess how the person absorbs and transfers load in both single leg and bilateral activities. In the upper limb it is important to determine how load is transferred from the lower limb to the upper limb, especially in explosive activities such as pitching in baseball and serving in tennis. Local tendon assessment involves graded loading of the involved tendon and examination is complete when sufficient information about tendon pain and capacity has been obtained. Although commonly used clinically, tendon palpation may not be informative[39] and more research is needed.

p0220   Imaging is frequently used as a diagnostic tool in tendinopathy, and will demonstrate the extent of the pathology and determine if there are any associated structural abnormalities such as peritendinopathy or bursal thickening. Its application in clinical reasoning currently remains limited due to the poor relationship between structural pathology and pain. Recent advances in ultrasound imaging such as ultrasound tissue characterization that can produce relative quantities of four echotypes that have been correlated with tendon pathology may improve the utility of imaging in clinical diagnosis.[40] Ruling the tendon in or out as the source of symptoms should still be primarily based on the patients history and clinical examination.

s0060 MANAGEMENT OF TENDINOPATHY

p0225 The management of tendinopathy is primarily determined by the clinical presentation, the risk factor profile of the individual and an appreciation of, but limited reliance on, any imaging findings. Tendon rehabilitation should always be specific to the person and their functional level.

p0230   Patient education and appropriate loading strategies are essential in successful management. Patient education should include explanation that while excessive load is the likely initiating factor it is also load that will reduce pain and improve function. Therapeutic load must be administered carefully and in a graduated and controlled fashion. Education must reinforce that treating a tendinopathy demands the same respect as fracture healing. No-one would consider serving in tennis with a broken humerus, or running on a fractured tibia. Equally, tendon rehabilitation must be given time and be carefully planned.

p0235   The key to rehabilitation is a graduated exercise-loading programme. Initially consider isometric contractions as this type of muscle contraction may reduce tendon pain. This may be followed by muscle strengthening involving heavy slow-resistance training (considering all relevant muscles within the kinetic chain).[41] The next stage involves increasing load on the tendon by incrementally introducing speed and finally energy storage loads. When designing a rehabilitation programme, time between exercise sessions should be considered, and the 24 hour pain response following loading will guide progression. Three to four days between sessions may

initially be important when introducing increases in speed, especially in substantially deconditioned tendon.

Endurance and compression loads should be included p0240 as tolerated but usually not in the initial stages of management as they can be provocative. Eccentric loading is inherent in all these stages, but the authors do not use it as an isolated treatment.

Lifestyle management is a critical component of p0245 tendon rehabilitation, as many people with tendon pain are unable to exercise effectively. Excess weight, insulin resistance or diabetes, high cholesterol, poor diet and smoking can all affect the recovery of a tendon and treatment should include discussion and education of these important issues.

Treatments such as massage of the muscle, electro- p0250 therapy and taping or bracing may be considered as adjuncts to a load-based rehabilitation, but they should not be the main focus of management. Frictions over the tendon, heavy stretching and excessive loading will all be detrimental to a tendon especially in the early stages of rehabilitation.

There is no quick fix solution and adequate time and p0255 care must be given to restore the tendon to the optimal level.

CONCLUSION   s0065

Tendinopathy is a common yet complex musculoskeletal p0260 problem. Assessment requires a thorough history to ascertain the loading and individual factors that contributed to symptoms and a detailed physical evaluation to guide load-based rehabilitation. Patient education is an essential component of tendon rehabilitation.

The presence of tendon pain 24 hours after loading p0265 should guide rehabilitation as opposed to pain on palpation or pain during exercise. The role of the CNS in the modulation of tendon pain is gaining increasing interest and assessment of the contribution of the CNS may be an important consideration.

Rehabilitation must be graded, commencing with p0270 isometric loads to reduce tendon pain, followed by progression through strength, power and sports and activity-specific function. However, the progression needs to be adjusted to reflect the goals of the specific individual and the capacity of the tendon.

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S

Appendix U. Details pertaining to optimising reliability of transcranial magnetic stimulation method

Selection of representative muscle from the quadriceps group

The tendon fibres of the rectus femoris muscle are the only tendon fibres of the quadriceps muscle group that continue over the anterior surface of the patellar to form the patellar tendon (Reider et al., 1981). The tendon fibres of the vasti muscles (vastus medialis, vastus intermedialis and vastus lateralis) insert mainly at the margins of the patella or blend with the retinacular of the knee (Reider et al., 1981). There are no data to support preferential wasting of particular quadriceps muscles in other anterior knee pain (AKP) such as patellofemoral pain (PFP) (Giles et al., 2013), thus the rectus femoris muscle was chosen as the representative muscle of the quadriceps in all studies. Surface electromyography was applied to the rectus femoris muscle (Figure U1) and this process is detailed in the methods of all papers.
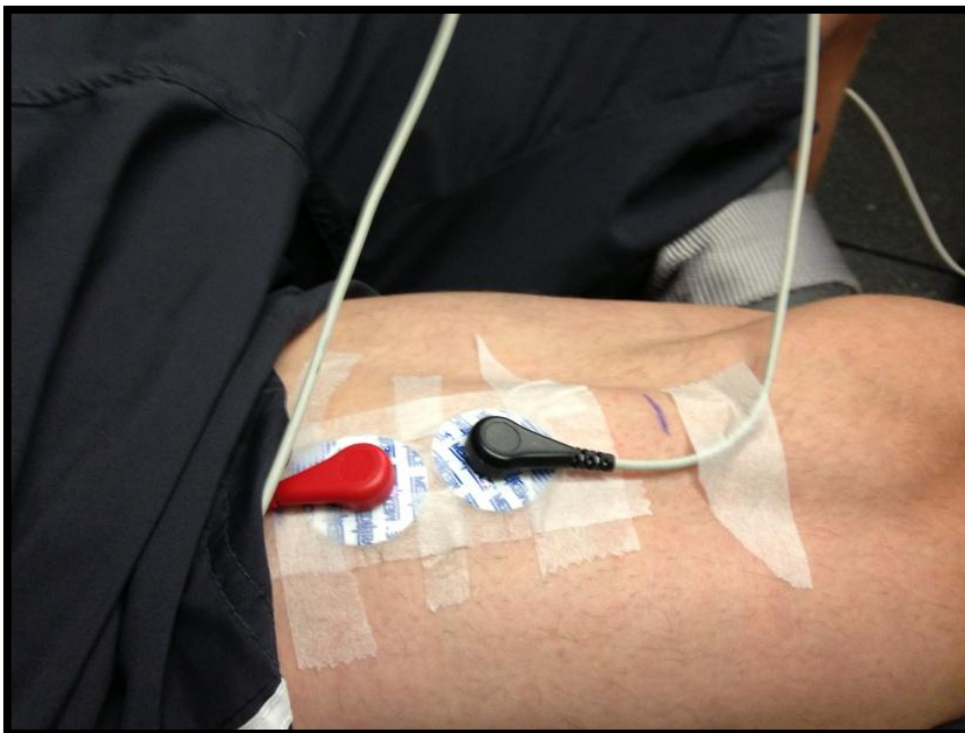
Figure U1 Surface electrode placement on the rectus femoris muscle

Transcranial magnetic stimulation technique

The following pertains to the method for maximising the reliability of the TMS

techniques used in this thesis. The skin where the surface electrodes were to be

placed was prepared to reduce impedance by shaving, abrading and cleaning with

70% isopropyl alcohol. Bipolar gel Ag-AgCl electrodes were placed over the rectus

femoris muscle (Figure U1) and the grounding electrode was placed over the patella

and subsequently used as a common reference for all electrodes. These electrodes

were placed on the rectus femoris with an inter-electrode distance (centre to centre) of

20mm. The exact area of placement was three fifths of the distance between the

anterior superior iliac spine (ASIS) and the upper border of the patella, with the

reference (ground) electrode being placed on the patella to ensure no muscle activity

was recorded. All cables were fastened with tape to prevent movement artefact.

sEMG signals were amplified (1000x), bandpass filtered (high pass at 13 Hz, low pass

at 1000 Hz), digitized online at 2 kHz for 500 ms, recorded and analysed using

PowerLab 4/35 (ADInstruments, Bella Vista, Australia).

The participants' skull was measured from nasion-inion and intra-aural anatomical

landmarks to assist with estimating the location of the M1 (Figure U2).

Nasion: superior to the bridge of the nose

Inion: the most prominent projection of the occipital bone
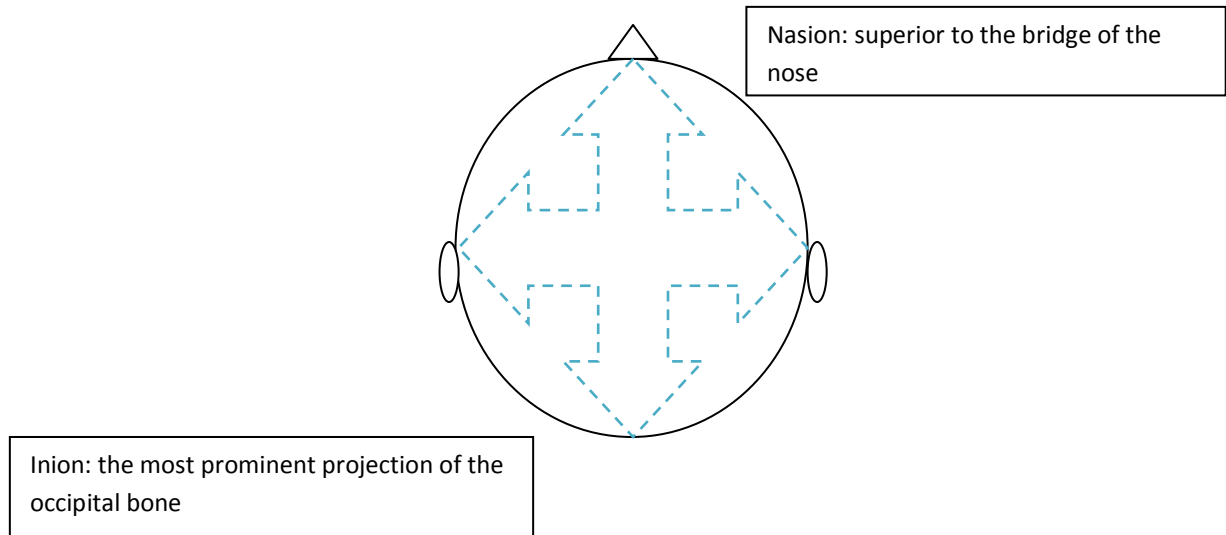
Figure U2 Landmarks used to approximate the location of the M1.

The TMS coil was placed over the contralateral M1 in the region estimated to represent the quadriceps (rectus femoris) muscle group based on human topography (Figure U3).

Primary motor cortex
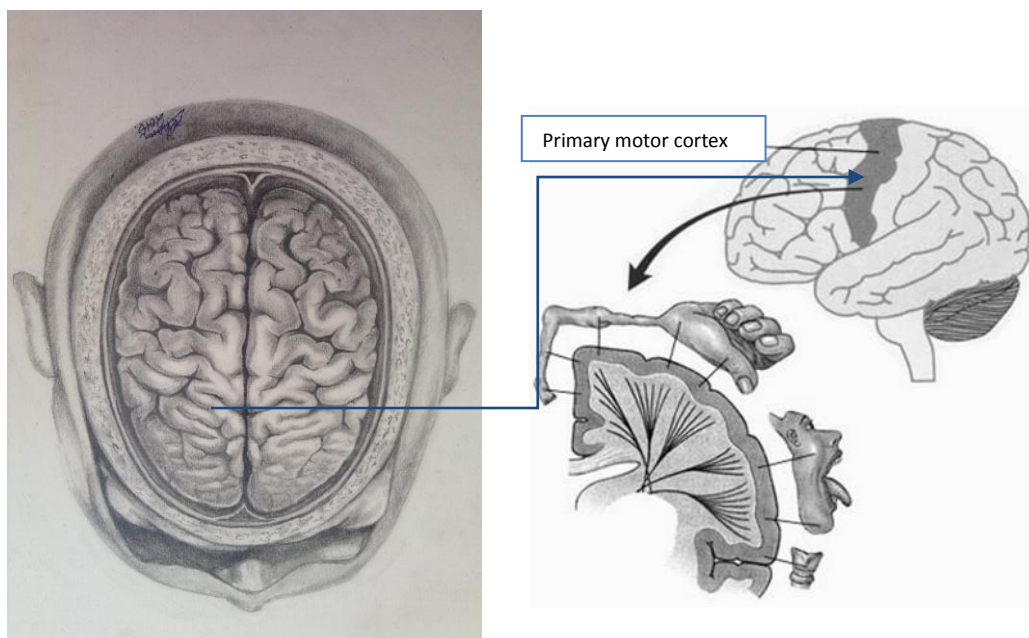
Figure U3 Indication of the location of the primary motor cortex and representation of muscles (art work by Shan Shan Zhan used with permission)

Transcranial magnetic stimulation was applied to the skull via a double cone coil

(Figure U4) held tangentially to the skull in the anterior-posterior direction with the

patient seated (Figure U5). Sites were explored in the estimated motor region of the

quadriceps to ascertain the optimal site or 'hot spot': the site at which the largest MEP

response was recorded. Optimisation of the hot spot reduces the variability and

number of MEPs that need to be recorded (Brasil-Neto et al., 1992).

Figure U4 The double cone coil was used in this work to deliver the stimulus
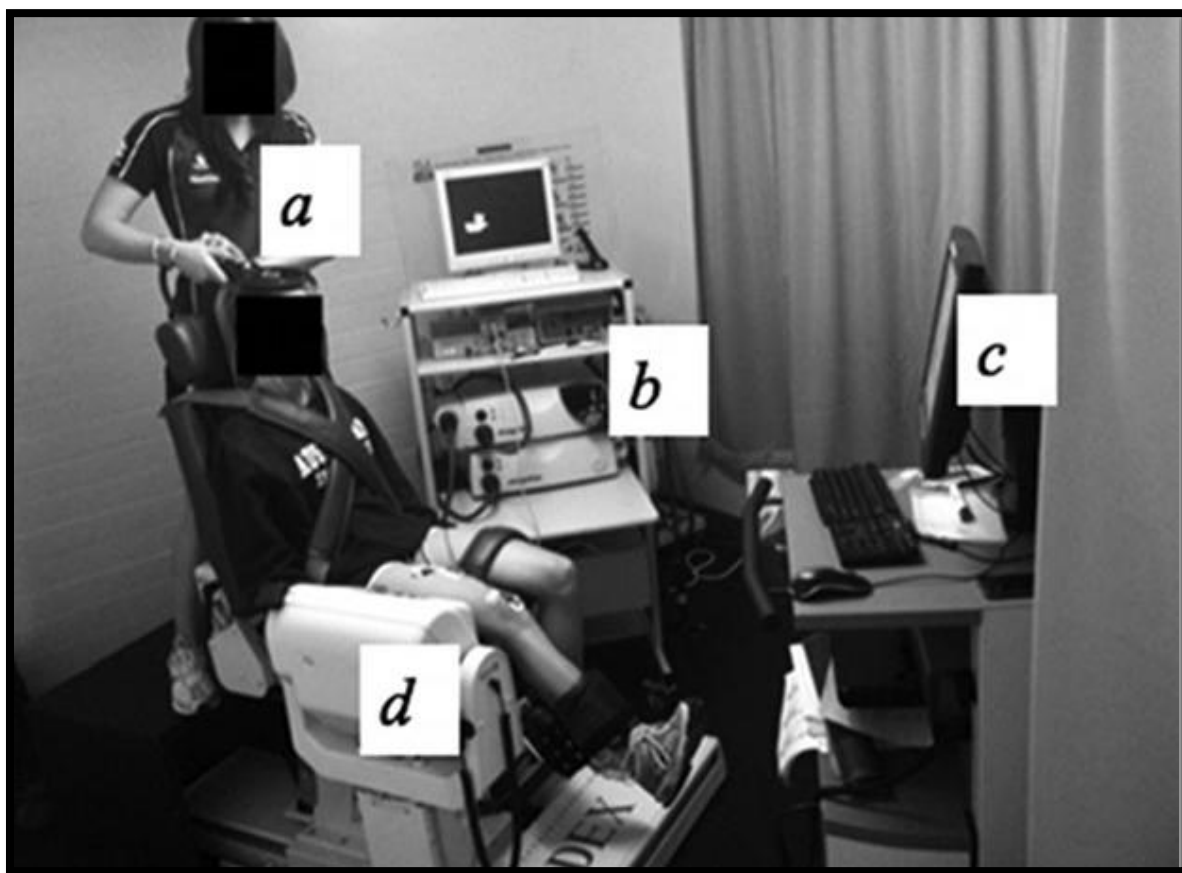
Figure U5 Participant set up for Transcranial magnetic stimulation

   a) TMS coil over the participant skull (the picture on the right denotes the direction of current for

       the circular coil held in the anterior posterior direction).

   b) TMS stimulator (a BiStim unit, to two Magstim 2002 stimulators (Magstim, Dyfed, UK)).

   c) Visual feedback of torque for participant

   d) Isokinetic equipment providing strength

(Source: Deakin University Laboratory and http://www.med.upenn.edu/lcns/noninv.shtml)

The stimulus intensities used to establish the TMS stimulus response curves were determined

for each individual according to their AMT and individual hot spot. Participants were asked

to maintain a 10% MVIC using visual feedback from a computer display (Figure U6).

Figure U6 Visual display of 10% maximal voluntary isometric contraction that was to be maintained during delivery of each stimulus

The top horizontal line was the target. The researcher delivering the stimulus could visualise this screen also thus ensure stimuli were applied during the appropriate level of contraction. The rise in red line demonstrates the participant increasing force until the target, then once stable the stimulus was applied to the M1 and is observed on the screen as a spike. Participants were then given a rest prior to the next stimuli.

At each stimulus intensity, 10 stimuli were applied over the contralateral M1, with the percentage of stimulator output delivered in a progressive fashion commencing at 10% below AMT and increasing in 5% increments of stimulator intensity until plateau of MEP amplitude was observed (MEP$_{MAX}$). Each stimulus was delivered in random intervals every 10 to 12 sec to avoid stimulus anticipation, and a minimum of 60 seconds rest was provided between each set of stimuli to reduce the possibility of muscle fatigue (Carroll et al., 2001b). Sets of peak to peak MEP amplitudes were averaged for each trial as recommended to reduce variability (Carroll et al., 2001a, Ridding and Flavel, 2006. Peak to peak MEP amplitudes increase with stimulus intensity until saturation (MEPMAX) {Chen, 2000 #8781). The stimulus response

curve was constructed by plotting mean MEP amplitude, normalised to the

participants M_{MAX} against stimulus intensity (Kidgell and Pearce, 2011).

Paired-pulse TMS was used to explore SICI. This delivers a sub-threshold stimulus

(70% AMT) and a supra-threshold stimulus (120% AMT) at an interstimulus interval

of 3ms.

In order to calculate SICI, MEP amplitude was calculated as a ratio by applying the

following equation (Weier et al., 2012a).

$$SICI = \frac{MEPpp}{MEPsp} \times 100$$

Where;

- MEPpp represents the average MEP amplitude from the paired-pulse stimuli.

- MEPsp represents the average MEP amplitude from the single-pulse stimuli.

Maximal voluntary isometric torque: The maximum voluntary isometric

contraction (MVIC) torque of all participants was determined by three attempts at

1RM of isometric leg extension at a knee ankle of 60° using an Isokinetic

dynamometer (Biodex system 4 Pro, 1 Biodex Medical 2 Systems, Shirley USA)

(Figure U7). Participants were placed in a seated position of 90 degrees hip flexion

and the axis of the dynamometer was then aligned with the anatomical axis of the

knee joint, using the joint line as a landmark. The leg was held to the dynamometer

lever arm using a padded strap positioned 5 cm superior to the malleoli of the ankle.

The participant was asked to contract their quadriceps maximally three times for five

seconds with 90 seconds rest between efforts and identical instructions and

encouragement was provided through all testing sessions to achieve MVIC torque.

The highest peak torque of the three trials was recorded as their MVIC torque.

Figure U7 Biodex (Biodex system 4 Pro, 1 Biodex Medical 2 Systems, Shirley USA)

equipment. The participant is seated and testing leg strapped to lever, shown here for left leg set up.

The screen provides visual feedback of the torque level, which is pre-set to 10% of their MVIC.

(Source: http://biomechanics.uoregon.edu/MAL/clinical.html)

Once MVIC was obtained, 10% MVIC was calculated as all TMS testing was

conducted during 10% MVIC quadriceps contraction. The MVIC root mean square

EMG (rmsEMG) activity was also recorded. The rmsEMG reflects the mean power

of the signal and is the preferred recommendation for smoothing (Wren et al., 2006).

During testing, to maintain 10% MVIC, visual feedback was provided, however any

trials where rmsEMG was too high or too low were discarded and retested. Testing

during 10% MVIC enables lower stimulus intensities to be used (Carroll et al., 2001b)

and reduces the variability of MEPs (Kiers et al., 1993, Thickbroom et al., 1999a,

Thickbroom et al., 1999b).

Maximal compound wave (M_{MAX}): The maximal compound wave is the direct

motor response obtainable by electrically stimulating the peripheral nerve. The MEP

can be normalised to the maximal compound wave for each individual as this makes

the size of the MEP relative to that individuals own motor neuron pool. The maximal

compound wave was obtained for studies in the quadriceps from the femoral nerve of

the side of the muscle being tested. Participants were supine on a plinth with the limb

being tested hanging freely over the edge (Figure U8).

Figure U8 Participant testing position to obtain M_{MAX}

Patient lies supine with leg that is being tested hanging freely off the plinth and femoral triangle

exposed

The femoral nerve is accessible in the femoral triangle, which is bounded by the inguinal ligament superiorly, the medial border of the adductor longus muscle medially and the medial border of the sartorius muscle laterally (Figure U9). Its floor is formed by the pectineus, adductor longus and iliacus muscles and roof is fascial. Within the femoral triangle from lateral to medial are the femoral nerve, femoral artery, femoral vein and a canal containing lymphatic vessels. The femoral artery is easily located by palpation (strong pulse felt with the finger tips) and the femoral nerve is immediately lateral to this.
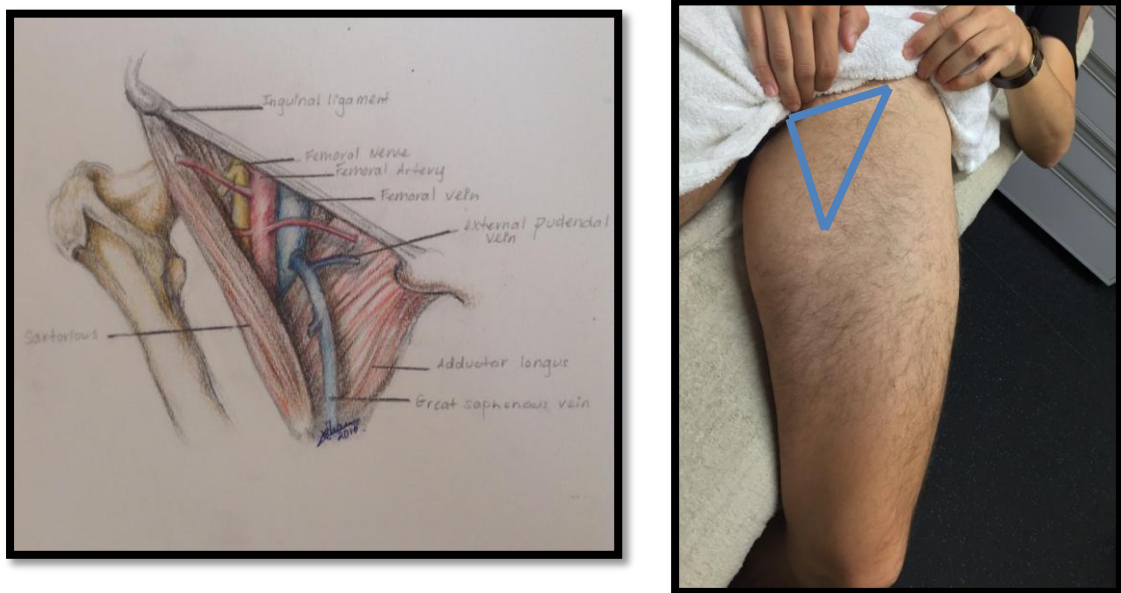
Figure U9 The femoral triangle (left image for right leg and photograph mirror image for left leg) (artwork by Shan Shan Zhan used with permission)

The M-wave was obtained by direct supra-maximal electrical stimulation (pulse duration 1 ms) under resting conditions. A high-voltage constant current stimulator (DS7, Digitimer®, Hertfordshire, UK) was used to deliver each electrical pulse. Stimulation was delivered by positioning bipolar electrodes over the femoral triangle. An increase in current strength was applied until there is no further increase in sEMG

amplitude (M_{MAX}). To ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} obtained from five stimuli will be delivered and recorded at 0.2 Hz.

Appendix V. The use of ultrasound to determine the presence of pathology in the patellar tendon

Ultrasound (US) images of the patellar tendon were captured using ultrasound tissue characterisation (UTC), which consists of an ultrasound probe (SmartProbe 10L5, Terason 2000; Teratech) mounted in a tracking device (UTC Tracker, UTC Imaging). This set up standardises the transducer tilt angle in relation to the tendon. The tracker device moves the ultrasound probe automatically at a constant speed perpendicular to the long axis of the patellar tendon from the inferior pole of the patella distally. An ultrasound image of the transverse plane of the tendon is captured every 0.2 mm over the length of the patellar tendon. The UTC software (UTC 2010, UTC Imaging) constructs the sagittal and coronal planes from the transverse images creating a 3D ultrasound data-block (van Schie et al., 2010a).

Most commonly, grey scale US is used to identify three main features that indicate tendon abnormality; hypoechoic area and anterior/posterior (AP) diameter. These features reflect alterations in the tendons acoustic impendence and size due to increased ground substance (Cook et al., 2004a) and collagen fibril separation (Jozsa et al., 1990). These pathological changes appear to be staged (Cook and Purdam, 2009) and the presence of any or all of them indicate abnormal tendon structure.

A single researcher conducted the ultrasound and analysed the images for the presence of pathology indicating tendon abnormality (yes/no) according to a pre-determined algorithm based on previous imaging studies (Figure V1).
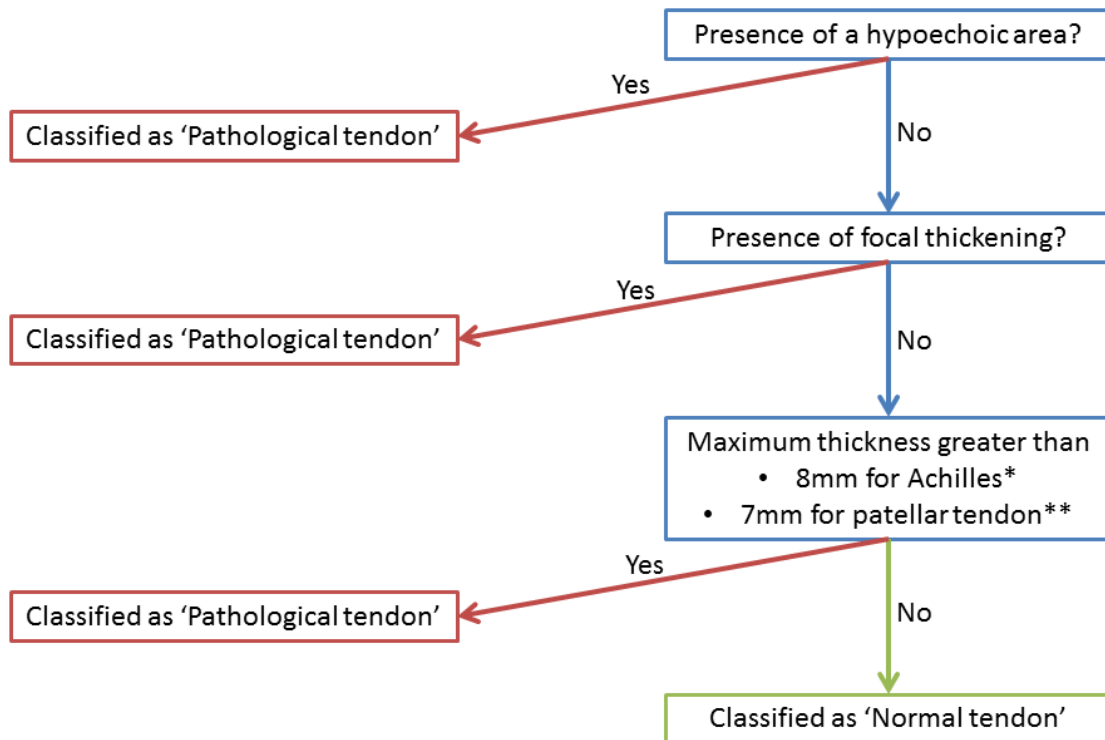
*Astrom et al (1996) Imaging in chronic achilles tendinopathy: a comparison of ultrasonography, magnetic resonance imaging and surgical findings in 27 histologically verified cases. Skeletal Radiology
**Schmid et al (2002). Is impingement the cause of jumper's knee? Dynamic and static magnetic resonance imaging of patellar tendinitis in an open-configuration system. Am J Sports Med

Figure V1 Algorithm to determine the presence of tendon pathology in the patellar tendon for studies in this thesis (Docking SI, used with permission)

Appendix W. VISA-P questionnaire

VICTORIAN INSTITUTE OF SPORT

ASSESSMENT SCALE

1. For how many minutes can you sit pain free?

   0 mins [| | | | | | | | |] 100 mins

2. Do you have pain walking downstairs with a normal gait cycle?

   strong severe pain [| | | | | | | | | |] no pain

3. Do you have pain at the knee with full active nonweightbearing knee extension?

   strong severe pain [| | | | | | | | | |] no pain

4. Do you have pain when doing a full weight bearing lunge?

   strong severe pain [| | | | | | | |] no pain

5. Do you have problems squatting?

   unable [| | | | | | | | |] no problems

6. Do you have pain during or immediately after doing 10 single leg hops?

   strong severe pain/unable [| | | | | | | | |] no pain

7. Are you currently undertaking sport or other physical activity?

   ☐ Not at all

   ☐ Modified training ± modified competition

   ☐ Full training ± competition but not at same level as when symptoms began

   ☐ Competing at the same or higher level as when symptoms began

8. Please complete **EITHER A, B or C** in this question.

- If you have **no pain** while undertaking sport please complete **Q8a only**.

- If you have **pain while undertaking sport but it does not stop you** from completing the activity, please complete **Q8b only**.

- If you have **pain that stops you from completing sporting activities**, please complete **Q8c only**.

8a. If you have **no pain** while undertaking sport, for how long can you train/practise?

NIL	1-5 mins	6-10 mins	7-15 mins	>15 mins
☐	☐	☐	☐	☐

OR

8b. If you have some pain while undertaking sport, but it does not stop you from completing your training/practice for how long can you train/practise?

NIL   1-5 mins   6-10 mins   7-15 mins   >15 mins

OR

8c. If you have **pain which stops you** from completing your training/practice for how long can you train/practise?

NIL   1-5 mins   6-10 mins   7-15 mins   >15 mins

Appendix X. Overview of the neural control of skeletal muscle including the primary motor cortex and corticospinal tract

The pre-central gyrus contains the M1, located in the frontal lobe and is responsible for planning and executing voluntary skeletal muscle movement (Stippich et al., 2002). A number of regions have projections that are involved in muscle activation that highlight that motor activation is an integrated response. These include the supplementary motor area, pre-motor area, somatosensory cortex, parietal lobe and cingulate gyrus, whose roles are vast and integrate a number of systems in planning, utilisation of visual, auditory and spatial information as well as emotion formation, memory and learning (Table X1).

Table X1 Functions of the cortex areas whose fibres contribute to the corticospinal tract (Nathan et al., 1990)

Region	Function
Primary motor cortex	Plan and execute movement (approximately 31% of the fibres of the tract originate from the M1)
Supplementary motor area	Precise function yet to be determined but may have roles that include postural stabilisation, the coordination of both sides of the body, internally generated movement – not triggered by sensory events, and the control of sequences of movements. However, it is also active during non-sequential, uni-manual, and stimulus-cued movements demonstrating the integration of many areas in movement.

Pre-motor area	Functions not entirely understood, may play a role in planning movement, in the spatial and sensory guidance of movement, in understanding the actions of others, and in using abstract rules to perform specific tasks
Somatosensory cortex	Receive and react to sensory input and communicate to motor areas if motor response is required
Parietal lobe	Primary role in producing planned movements – receives input from the three sensory systems that localise the body and external objects in space (visual system, auditory system, and the somatosensory system).
Cingulate gyrus	Receives inputs from the thalamus and the neocortex and is a part of the limbic system, which is involved with emotion formation and processing, learning, and memory. Also involved in pre-motor functions,

Impulses that are generated in the M1, modulated by both excitatory and inhibitory synapses, descend the spinal cord after having passed through the internal capsule, brainstem and medulla oblongata, via the axons of the largest pyramidal cells known as Betz cells, thus termed the pyramindal tract or corticospinal tract/pathway, and synapse on the motor neuron pool to effect muscle activation (Schieber, 2001). Stellate cells are interneurons as they are confined to the cortex and are involved in inter and intra hemispheric communication (Schultz and McCormick, 1994). The

neurons of the M1 innervate particular muscle groups and are therefore arranged somatotopically, termed the motor homunculus however there is considerable overlap and plasticity associated with use or insult (Sanes and Donoghue, 2000, Carroll et al., 2001a).

Upper motor neurons (UMN) originate in the motor cortex and synapse with lower motor neurons in the ventral horn via the release of the neurotransmitter glutamate (Schieber, 2001). The UMN that causes skeletal muscle activation is termed a Betz cell and are located within the fifth layer of the grey matter in the primary motor cortex (Schieber, 2001). The corticospinal tract, consists of the lateral and anterior tracts. Most fibres of the lateral corticospinal tract decussate in the medulla oblongata, thus the contralateral hemisphere controls limb movement (Schieber, 2001).

Lower motor neurons (LMN) innervate skeletal muscle fibres and are located in either the ventral horn of the spinal cord and anterior nerve roots (spinal lower motor neurons) or the cranial nerve nuclei of the brainstem and cranial nerves with motor function (cranial nerve lower motor neurons) (Burke, 2007). They are classified based upon the type of muscle fibre they innervate; alpha motor neurons (α-MNs) innervate extrafusal muscle fibres and are responsible for muscle contraction, and gamma motor neurons (γ-MNs) innervate intrafusal muscle fibres involved in afferent input (as part of the muscle spindle) (Burke, 2007).

The α-MN and the extrafusal muscle fibre it innervates are termed a motor unit and the connection between them is termed neuromuscular junction (for overview of this topic see (Stifani, 2014)). It is at this site, the synapse, that the action potential is transduced to the muscle fibre via voltage-dependent calcium channels that open,

allowing calcium to enter the neuron resulting in acetylcholine (Ach) release (Fambrough, 1979). This neurotransmitter diffuses through the synapse and binds nicotinic acetylcholine receptors (nAChRs) on the plasma membrane of the muscle fibre. The binding of ACh to the receptor can depolarize the muscle fibre, causing a cascade that eventually results in muscle contraction (Stifani, 2014).

All of the motor units comprise the motor pool and contractions are controlled in part by the number of motor units that are activated (Heckman and Enoka, 2004). Recruitment is dependent upon the task and described by the Henneman's size principle that indicates that motor units are recruited from smallest to largest based on the size of the load (Latash, 1998). For smaller loads requiring less force, slow twitch, low-force, fatigue-resistant muscle fibres are activated prior to the recruitment of the fast twitch, high-force, less fatigue-resistant muscle fibres. The CNS has two systems to control muscle force through motor unit recruitment; spatial recruitment (the activation of more motor units to produce a greater force) and rate coding (describes the frequency of activation of muscle fibre contractions) (Armstrong and Taylor, 1982). Consecutive stimuli on the motor unit from the α motor neuron causes the fusion of muscle twitches and produces a greater force than a single contraction (Armstrong and Taylor, 1982). Decreasing the inter-stimulus enables the muscle to produce greater force with the same amount of motor units (Heckman and Enoka, 2004). As stated, further modulation of muscle recruitment occurs in the brain via the inhibitory and excitatory neurons that synapse onto the motor cortex prior to activation of the LMN and was the topic of interest in this work.

Appendix Y. Pilot data

Pilot study to investigate the potential relevance of jumping load on the corticospinal excitability

While habitual activity has been shown to effect the M1, no study was identified that specifically considered the type of activity and the influence on the M1 and motor drive. Thirteen physically active, healthy participants were recruited (Table Y1.) All participants completed at least three sessions per week of structured activity and included a mix of elite, sub-elite and recreational athletes. Athletes nominated their dominant leg for testing and the contralateral corticospinal excitability was tested using single-pulse TMS as described in Chapter 3.

Table Y1 Characteristics of participants in the pilot study that investigated the influence of jumping on corticospinal excitability

Characteristics	Description
N (men)	13 (9)
Age years (median+range)	26 (21-37)
BMI (mean±SD)	23.9±2.6
Weekly activity	Australian football, swimming, touch football, running, martial arts, volleyball and badminton

BMI, body mass index

Following TMS testing, participants were grouped according to activity type (jumping yes/no). Data were coded and all data were analysed blinded to group activity type (Table Y2). Stimulus response curves were constructed (normalised to M_{MAX}) and

the slope was calculated using GraphPad Prism in the same manner as the other studies in this thesis. Data for M_{MAX}, active motor threshold (AMT) and MVIC are presented as median and range. In order to be conservative, non-parametric analyses (Mann Whitney U) were conducted on all comparisons, as the sample size was small and groups were an uneven number. Physically active people who did not participate in sports that have a jumping requirement exhibited lower corticospinal excitability, evidenced by a decrease in the slope of the stimulus response curve (higher number indicates decrease in slope) (Table Y2).

Table Y2 Corticospinal responses, peripheral measures and descriptions of each group

Group by activity (jumping yes / no)	Characteristics	M_{MAX}	AMT	MVIC	Slope (AU)
N=8 jumping participants (median+range)	6 men Australian football Martial arts Volleyball Badminton	24.61 (21.84-27.68)	42 (31-50)	172.5 (152-274)	5.91 (4.08-7.90)
N=5 non-jumping participants (median+range)	3 men Swimming Touch football Running	21.51 (18.7-27.46)	35 (31-50)	168 (105-183)	14.04* (9.66-17.69)

AMT, active motor threshold; MVIC, Maximum voluntary isometric contraction; AU, arbitrary units * denotes p=0.002

These data suggest that jumping has a profound effect on the CSE and that it is therefore important that any comparisons made between controls, those with other AKP or PT participate in jumping sports. Data were checked for the potential effect of gender and found to be non-significant ($p = 0.26$). There were no differences between groups for M_{MAX}, AMT or MVIC ($p < 0.05$).

Based upon these data, the decision was made to recruit both men and women but only include athletes that played / trained at least three times per week in jumping sports in all studies.

Pilot testing for developing intervention protocols

There were no data on the potential effect of load on immediate analgesia in PT. Pilot testing was conducted to attempt to identify some of the parameters that may be important (high or low load, shorter or longer time under tension) and to match isotonic and isometric protocols for rating of perceived exertion (RPE). It was by no means exhaustive and the exact dosage for tendon pain warrants further investigation. The process for developing the protocols used in Chapter 4 is outlined (Figure Y1).

Step 1
- Compare the effect of different loads (% MVIC) on the numerical rating scale (NRS) of the single leg decline squat test (SLDS) in a subgroup with PT (n = 7) (Table Y3).
- The isometric condition was chosen as this could be easily quantified as a percentage of maximum voluntary isometric contraction (MVIC) using the Biodex pro (figure).
- Compare the effect of different time under tension on SLDS (table 2).

Step 2
- Match isometric protocol and isotonic protocol (on a leg extension machine) for rating of perceived exertion in a healthy active in-season population (n = 4).
- Test the feasibility in a healthy active population (ability to complete full repetitions and sets protocols without delayed onset muscle soreness, n = 4).

Step 3
- Repeat step two based upon feedback until protocols were matched and achievable (testing completed over two month period).

Figure Y1 Process for developing the parameters used in Chapter 4

The order of testing was chosen to examine the testing conditions within the study and to observe whether the outcome measures themselves (or TMS testing) influenced SLDS. First, maximal MVIC with short duration was trialled as this was part of the TMS testing to obtain MVIC, therefore, it had to be determined whether this outcome measure influenced SLDS outside of any intervention. Secondly, participants were required to sustain low levels of MVIC during TMS testing, so 10-20% MVIC was trailed to ensure that sustained low level contractions (as part of TMS testing) did not influence pain on SLDS. Third, higher load MVIC was trialled with combinations of time under tension.

Table Y3 Combinations of load and time under tension that were trialled

Percentage of MVIC	Protocol^	Mean change score in SLDS
100	3 x 3 seconds	0
	3 x 5 seconds	0
	Outcome and reasoning for next trial: This outcome measure could be tested without influencing SLDS in the study. It also indicated short duration maximum holds did not induce analgesia. Longer holds were not able to be sustained at 100% MVIC so load was decreased and time under tension was increased to trial if longer time under tension was effective	
10- 20	3 x 30 seconds	0
	5 x 1 minute	0
	3 x 2 minutes	0
	5 x 2 minutes	0
	Outcome and reasoning for next trial: TMS testing could be completed at low levels of MVIC without influencing SLDS. Low load, longer time under tension made no change to SLDS so the decision was made to trial a heavy load (but less than 100% MVIC) for longer time under tension (as short duration had been ineffective). 70%	

	was selected.	
70	5 x 45 seconds	7±0.38
	Outcome and reasoning for selecting this protocol: this combination of load and time under tension provided significant pain relief as well as a time under tension that could be easily matched with an isotonic protocol relevant to tendon loading (4 sets x 8 repetitions)^.	
>85	5 x 45 (participants were unable to sustain time without muscle shaking)	Incomplete trial

^ Increased tensile load in the posterior region of the proximal patellar tendon during leg extension is greatest near full extension (Dillon 2008) this is a painful position for people with PT, therefore isometric loading was completed away from this position. Isotonic repetitions were completed in a comfortable range (that clinically usually does not include the final 10 degrees of extension.)

The subgroup of athletes used in this pilot was not included in the cross over study nor were they recruited from the same population as the study participants that completed any of the intervention studies to avoid bias or contamination. Furthermore, a baseline session (week one) without any intervention was included in the final cross over study design also, to validate and replicate these results and again check if any of the outcome measures themselves influenced SLDS.

Rating of perceived exertion was recorded for the isometric protocol and trials were performed to match the isotonic protocol. This was calculated based on matching for time under tension: -

Isometric protocol

5 x 45 seconds = 225 seconds total

Isotonic protocol

4 x 8 @ three seconds concentric phase, four seconds eccentric phase = 224 seconds

total.

100% of 8RM provided a comparable RPE to the isometric protocol.

Appendix Z. Equipment list

Table Z1 Equipment used in this work

Components	Equipment	Purpose	Personnel
Current and past injury history	Questionnaire developed specifically for the study	Information about current length of time of symptoms, past tendon injury and general health status	Self-reported, interview by researcher if further clarification required
Presence of patellar tendon pathology	UTC : Diagnostic ultrasound machine (Appendix V)	Assessment of patellar tendon pathology	Specially trained researcher
Diagnosis of patellar tendinopathy	Single leg decline squat board (Figure 2.2)	Provocative test for presence or absence of patellar tendon pain	Researcher to demonstrate, participant to complete for left and right legs and provide numerical rating scale (NRS) 0-10
Tool for PT pain and function	VISA – P Questionnaire (Appendix W)	Assessment of the severity of patellar tendon symptoms	Self-completion
Location of electrode placement, positioning and skin preparation	Tape measure (Lufkin©) Marker pen (Sharpie©)	Measure the distance (cm) from anterior superior iliac spine to superior patella and mark distance on anterior thigh of 2/3 of this distance Skin preparation of	Researcher

	Shaver	rectus femoris muscle	Researcher
	Abrasive pad	and patella (for ground	
	Single use 70%	electrode)	
	isopropyl alcohol swab		
		Record signal from	
	Two surface electrodes	rectus femoris muscle	
	(bipolar Ag-AgCl	(Figure U1)	
	electrodes[b]) and one		
	ground electrode		
	Skin tape	Fix electrodes to the	
		skin over rectus femoris	
		muscle and clavicle	
Participant positioning	Patient plinth	Maintain a comfortable	
	Pillow for head	and consistent testing	
		position for M_{WAVE}	
		(Figure U8)	
Stimulation and signal recording	M wave stimulator	Direct muscle response	
	PowerLab 8[a]	and recording	
	Laboratory analogue-digital interface		
Signal analysis	Computer		Researcher
Transcranial magnetic stimulation	BiStim unit, Magstim 2002 stimulators (Magstim, Dyfed, UK) Double cone coil	Magnetic stimulation to induce electrical current in cortical areas	Researcher
M wave	Electrical stimulator	Direct stimulation of the femoral nerve	Researcher

Maximal voluntary isometric contraction	Biodex system 4 Pro, 1 (Biodex Medical 2 Systems, Shirley USA) (Figure U7)	Isokinetic dynamometer to record contraction & provide resistance during testing protocol)	Researcher
		Height (cm), weight (kg), waist and hip circumference (cm)	
Anthropometric measurements	Stadiometer , electronic scales to record body weight	To calculate BMI	Researcher

[a]ADinstruments, Australia; [b]Nihon Koden, Japan); SLDS, single leg decline squat; BMI, body mass index

Appendix AA. Supplementary file for Chapter 6

This supplementary file accompanies the publication contained in Chapter 6 that has been submitted to the British Journal of Sports Medicine.

Method

Preliminary data contained in this supplementary file were collected using the method described below. Participants were recruited from sub-elite and elite basketball and volleyball populations and were aged over 18 years and all playing / training three times per week. If they were not able to participate in games and trainings three times per week for any reason including PT, they were not included because of the potential for activity to modify the primary motor cortex and motor control.

Note that the larger randomised clinical trial (RCT) (Rio et al., unpublished data and van Ark et al., unpublished data) included participants aged over 16 years however, only participants aged over 18 years were offered transcranial magnetic stimulation (TMS) testing.

Athletes were asked to complete a VISA-P, a questionnaire about patellar tendon pain and function that is scored between 0 and 100 with 100 being maximal pain free function (Visentini et al., 1998). Height in centimetres (cm) using a stadiometer and weight in kilograms (kg) without footware were recorded and this has been described previously (Rio et al., 2015).

Clinical diagnosis of patellar tendinopathy

Patellar tendinopathy (PT) in all studies was diagnosed as localised pain at the inferior pole of the patella during jumping and landing as well as during the single leg decline squat (SLDS), a reliable patellar tendon pain provocation test (Purdam et al., 2003).

Grey scale ultrasound (US) was used to confirm the diagnosis by applying the following where at least one criterion had to be satisfied; presence of a hypoechoic area, increased thickness of the anterior/posterior diameter greater than six millimetres (mm) or the presence of vessels. Athletes with bilateral symptoms were asked to nominate their most painful knee on the SLDS using a numerical rating scale (NRS) 0-10 and measures of quadriceps torque were taken from this side only and the contralateral hemisphere was tested with TMS.

Inter-person data

Jumping athletes were recruited and offered bilateral TMS testing. Following testing, they were assessed clinically and using US to determine the presence of tendon pain (NRS pain on SLDS) and tendon pathology (US) for sub-grouping into unilateral or bilateral tendon pain or pathology.

Inseason intervention study - Tendon neuroplastic training

Concealed randomisation was achieved by asking the athlete to draw an opaque sealed envelope with no external markings (Schulz and Grimes, 2002a). The envelope contained a number (either one = isometric or two = isotonic) produced by random number generation (Excel 2007©).

Data were collected as part of a RCT with two intervention arms completed over four weeks during a competitive season. The intervention was completed four times per week. There were two active intervention arms, either externally paced isometric or isotonic muscle contractions and no sham group. Protocols were matched for time under load and rest between sets (set at two minutes to allow muscle recovery) (Table AA1) (Ahtiainen et al., 2003). Repetition maximum (for the isotonic group) and MVIC (for the isometric group) were determined to calculate starting loads. As

muscle work during isometric exercise and isotonic exercise cannot be directly measured, protocols were matched for rating of perceived exertion on the basis of pilot studies and to specifically avoid delayed onset muscle soreness as this was an in season study) and muscle pain may negatively affect compliance or sporting participation). Furthermore, the protocol were matched for time under tension and based upon data supporting the use of external pacing to modulate corticospinal excitability and inhibition.

Auditory cues have been shown to be beneficial on the induction of neuroplasticity (Goodwill et al., 2012, Hendy et al., 2012b, Kidgell and Pearce, 2010, Kidgell et al., 2011, Latella et al., 2012a, Weier et al., 2012b). Therefore both groups received an auditory file to play on their smart phone device during their exercise sessions that provided verbal instructions and paced the muscle contractions. The aims of this were to try to ensure timing was adhered to, provide auditory stimulation and avoid self pacing so that the only difference between groups was muscle contraction type.

Table AA1 Protocol used in the randomised clinical trial

	Isometric group	Isotonic group
Time under tension	5 x 45 seconds = 225 seconds	4 x 8 3 seconds concentric and 4 seconds eccentric phase = 224 seconds
Starting load	80% MVIC	80% 8RM
Progression	2.5% as able	2.5% as able
External pacing and cues	Metronome and verbal instructions	Metronome and verbal instructions

| Equipment | Leg extension machine | Leg extension machine |
| Range | 60 degrees | Comfortable range 10 degrees – 100 degrees |

Note: the protocol was modified from (Rio et al., 2015) to prevent delayed onset muscle soreness.

Transcranial magnetic stimulation

Single-pulse TMS was used to obtain stimulus response curves and paired-pulse TMS technique was used to quantify SICI and these methods have been published elsewhere (Rio et al., 2015).

Outcome measures and statistical tests

For the inter-person study, outcome measures were active motor threshold, CSE and SICI. For the RCT, outcome measures were short-interval intra-cortical inhibition (SICI) and VISA-P. Non-parametric tests were chosen due to small sample size.

Results of the inter-person study

Bilateral data was obtained for 16 athletes (32 hemispheres). Of these, four were control participants recruited to compare SICI against the published physiological normal range for the quadriceps (50-70%) (Weier et al., 2012a) as it was unknown if SICI may be altered in jumping athletes. The median SICI ratio for both sides of control athletes was 56.81 (range 50.86-58.81) and there were no differences between hemispheres in control participants (p=0.49). There were no differences between sides in control participants for the slope of the stimulus response curve, left = 7.28, n=4, right = 9.55, n=4, p=0.83. This supported data obtained in previous studies of control participants (Rio et al., 2015 accepted) and previously published physiological ranges (Weier et al., 2012a). Two athletes for whom bilateral data was obtained were excluded (one swimmer and one rock climber). This was because significant differences were found in corticospinal excitability of athletes that regularly jumped

and those that did not despite the same number of structured physical activity sessions in a week, in a pilot study of 13 athletes (p=0.002). Therefore, fourteen athletes were included in the data provided in the paper, n=4 controls and n=10 with tendinopathy.

The following sub-groups emerged: -

Unilateral tendinopathy (unilateral pain with unilateral pathology) n=3

Bilateral tendinopathy (bilateral pain and pathology) n=2

Unilateral tendinopathy (unilateral pain with bilateral pathology) n=5.

Therefore, the question posed was - what is the effect of unilateral pain on the other side (n=8)?

Results from randomised clinical trial – tendon neuroplastic training

Nine athletes (seven men and two women) with either unilateral (n=5) or bilateral (n=4) PT who were taking no medication were included in the study (Table AA2). This was part of a larger trial of 29 people, who were all offered inclusion in the TMS component. Nine athletes completed the study, four in the isotonic group and five in the isometric group.

Table AA2 Baseline characteristics and testing

	intervention	LOT sx	height	weight	BMI	KTW L	KTW R	VISA	Leg	SLDS	MVC	AMT	M wave	curve	V50	SICI
									Baseline							
M	isotonic	84	181.5	74	22.4	11	7	69	R	8	202	26	26.52	0.10	1.70	41.87
M	isometric	24	185	81	23.7	13	8	13	R	7	113	28	18.64	0.22	1.45	33.82
F	isometric	1	178	65.3	20.6	12	11	65.5	R	5	177	33	15.48	0.24	1.68	56.3
F	isotonic	24	170.5	100.9	34.7	12	9	46	L	7	220	29	18.38	0.15	1.48	24.65
M	isometric	36	188	81.1	23.0	12	11	76	R	7	165	36	22.35	0.13	1.41	41.12
M	isotonic	4	183	79.7	23.8	17	16	65	L	5	263	25	17.47	0.12	1.39	79.74
M	isometric	36	182.6	84.1	25.2	7	8	63	L	7	152	35	24.29	0.12	1.45	28.61
M	isotonic	120	194	96.5	25.6	17	17	65	R	9	221	38	22.82	0.12	1.44	20.17
GROUP		30	182.8	81.05	23.7	12	10	65		7	189.5	31	18.64	0.13	1.454	41.12

M, male; F, female; LOT sx, length of time of symptoms (months); BMI, body mass index; KTW, knee to wall (cm); SLDS, single leg decline squat; MVC, maximal voluntary isometric contraction; AMT, active motor threshold; Mwave, maximal compound wave; SICI, short-interval intra-cortical inhibition

The individual data is provided (Table AA3, AA4) including calculated change scores for the outcome measures – VISA-P, SLDS, SICI. Median and mean are provided, though non-parametric tests were chosen due to small sample size.

Table AA3 Individual post intervention data

	VISA	SLDS	MVC	AMT	M wave	Curve slope (AU)	V50	SICI
Isotonic	67	3	268	23	25.39	0.05	1.79	91.37
	59	4	228	27	21.99	0.23	1.74	71.26
	84	1	244	25	19.03	0.11	1.4	72.99
	73	3	280	30	24.73	0.07	1.53	82.98
Median	70	3	256	26	23.35	0.10	1.64	77.98
Mean	70.75	2.75	255	26.25	22.79	0.12	1.63	79.65
Isometric	41	4	165	26	20.78	0.23	3.48	99.45
	97.5	2	188	33	16.67	0.33	1.93	81.56
	84	4	229	33	19.98	0.15	1.41	72.12
	72	2	264	35	21.25	0.25	1.48	75.79
	78	3	210	33	20.42	0.25	1.71	52.45
Median	78	3	208.5	33	20.38	0.24	1.71	75.79
Mean	73.625	3	211.5	31.75	19.67	0.24	2.08	76.27

MVC, maximal voluntary isometric contraction; AMT, active motor threshold; Mwave, maximal compound wave; SICI, short-interval intra-cortical inhibition; AU, Arbitrary units

Table AA4 Change scores pre and post intervention

	VISA	SLDS	MVC	% MVC change	AMT	M wave	curve	V50	SICI
Isotonic	-2	5	66	32.67	-3	-1.13	-0.05	0.09	49.50
	13	3	8	3.64	-2	3.60	0.08	0.27	46.61
	19	4	67.82	25.79	0	1.56	-0.01	0.06	-4.32
	8	6	59	26.70	-8	1.90	-0.05	0.09	62.8
Median	10.5	4.5	62.5	26.24	-2.5	1.73	-0.02	0.09	46.61
Isometric	28	3	52	46.01	-2	2.14	0.01	2.03	65.63
	32	3	11	6.21	0	1.19	0.09	0.254	25.25
	8	3	64	38.79	-3	-2.37	0.02	-0.007	40.00
	9	5	28	13.79	-2.5	1.67	0.02	1.14	56.12
	15	4	30	16.67	0	-0.16	0.07	0.25	23.84
Median	18.5	3	40	26.29	-2.25	1.43	0.02	0.70	43.56

The individual SICI data following the RCT is provided (Table AA5).

Table AA5 Individual pre and post cortical inhibition

	Pre (%)	Post (%)	Change (%)
Isometric	33.82	99.45	65.63
1			
	56.30	81.56	25.25
2			
3	41.12	72.12	31.00
4	24.26	75.79	56.12
5			
	28.61	52.45	23.84
Group median	33.82	75.79	43.56^
Isotonic	41.87	91.37	49.50
1			
	24.65	71.27	46.62
2			
3	77.31	72.99	-4.32
4	20.17	83.00	62.81
Group median	33.26	77.98	46.62#

^ p=0.06, # p=0.25

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