Ultrasound-observed Tendon Abnormalities in Lateral Epicondylalgia: Exploring Associations With Neurosensory and Clinical Outcomes

By

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Abstract:

Background

Lateral epicondylalgia (LE) also known as tennis elbow is an overuse tendinopathy of the common extensor tendon at the lateral elbow causing persistent pain and disability. Current pathophysiological models have highlighted that local tendon structural abnormalities and sensory system changes are key factors associated with LE, however, the exact nature of the inter-relationship between these pathophysiological characteristics is largely unknown. In particular, there are notable knowledge gaps on the inter-relationship between local tendon pathology, sensory system changes and their relative contribution to pain and disability in LE. It is important to evaluate the inter-relationship between these pathophysiological factors to model the mechanisms underpinning the clinical presentation and recovery profile in people with LE. While the mechanism underlying the pathogenesis of persistent pain necessitates further exploration, it is equally important to determine the optimal treatment for improving tendon structure and sensory function in LE. Conservative treatments such as manual therapy/exercise and prolotherapy injections have been recognised as potentially effective treatment options for improving pain and function in LE. However, the effects of prolotherapy injections and manual therapy/exercise used, either singly or in combination, on improving tendon structural and sensory abnormalities are largely unknown. Furthermore, it is not clear whether the baseline presence of tendon abnormalities can influence the short- and long-term outcomes of prolotherapy injections and manual therapy/exercise in LE. The aims of
this dissertation were (i) to explore the inter-relationship between tendon structural abnormalities, sensory abnormalities and clinical outcomes over time; (ii) investigate the effectiveness of prolotherapy injections, manual therapy/exercise, both singly and in combination in improving tendon structural and sensory abnormalities over time; and (iii) examine the prognostic indicators of short- and long-term outcomes of these interventions for LE.

Methods
The sample for the thesis was 120 participants with a clinical diagnosis of lateral epicondylalgia, aged 18 to 70 years who enrolled in a single-blinded randomised clinical trial (RCT) of prolotherapy injections and manual therapy/exercise used singly and in combination with a 52-week follow-up. Ultrasound (US) examination, Quantitative Sensory Testing and clinical assessments (e.g., Patient-Reported Tennis Elbow Evaluation; PRTEE) were performed at baseline and at 6, 12, 26 and 52 weeks follow-up. The five studies of the current thesis studies include: 1) an inter-rater reliability study of scoring tendon structural abnormalities from static and dynamic US images by a non-radiologist using a composite scale score; 2) a cross-sectional study investigating the association between tendon structural abnormalities, sensory and clinical characteristics; 3) an RCT assessing the comparative effectiveness of prolotherapy injections and manual therapy/exercise in improving tendon structural and clinical outcomes over time; 4) an RCT investigating the effects of prolotherapy injections and manual therapy/exercise in improving sensory outcomes over time; and 5) a study investigating prognostic factors associated with short- and long-term clinical outcomes following prolotherapy injections and manual therapy/exercise in LE.
**Results**

The results of this thesis demonstrate that i) the composite US scoring method has good inter-and intra-rater reliability in grading tendon abnormalities in LE ii) US described tendon structural abnormalities has minimal association with sensory system changes iii) prolotherapy injections and manual therapy/exercise are effective in improving tendon structure, sensory and pain and function over time, with no significant differences between treatment conditions. Also, tendon structural abnormalities assessed using composite US score was significantly associated with pain and disability (PRTEE) at 6, 12, 26 and 52 weeks following interventions. iv) the baseline presence of tendon structural abnormalities was associated with PRTEE at 12 and 52 weeks.

**Discussion**

Findings for the US image rating scale used in the study support the reliability of non-experienced US observer for grading tendon abnormalities in LE. Given the poor vascular supply to the common extensor tendon, the presence of neovascularity can be considered a weak clinical indicator of cold hyperalgesia. Individuals exhibiting tendon thickness on the US images reported poor vibration detection threshold. Adding prolotherapy injections with manual therapy/exercises is beneficial in improving tendon and sensory abnormalities in LE. US evaluation of tendon abnormalities using a composite score can be a useful method for predicting treatment outcomes for LE.
Statement of Originality

This is to certify that to the best of my knowledge that the content of this thesis is my own work. This work has not previously been submitted for a degree or diploma at any university or another institute of tertiary education.

I do herewith declare that the material contained in this thesis is original work performed by me under the guidance and advice of faculty supervisors. Information derived from the published and unpublished work of others has been acknowledged in the text and a list of references is given in the bibliography.

Vijayakumar Palaniswamy

15 March 2018
Dedication

To my late father Palaniswamy, mother Saroja, brothers Saravanan Kumar and Jaya Kumar, wife Gayathri, daughter Harshitha, son Sidhaarthen, sister in laws Bharathi and Thenmozhi, mother in law Latha, nephew Ramana niece Sanskrithi whose love and support alongside guided me through the critical times of my life.
ACKNOWLEDGEMENTS

“When you come to the edge of all that you know, you must believe one of two things: There will be ground to stand. Or you will grow wings to fly.” --O.R. Melling

Indeed, this priceless quote from the famous novelist O. R Melling reflects my practical and philosophical approach towards the challenges of a PhD. I take this opportunity to thank everyone who helped me to stand my ground. First and foremost, I would like to express sincere gratitude to my supervisor team of Dr Leanne Bisset and Dr Shu-Kay Ng for their guidance, encouragement and constant support during my PhD. My sincere appreciation goes to my thesis external-supervisor Dr Michael Ryan and my research team involving Dr Michael Yelland, Dr David Rabago and Dr Nagarajan Manickaraj for their valuable contribution towards the study design, data collection, and manuscript review. I also wish to thank radiologists team Dr Craig Buchan, Dr Morgan McMeniman and ultrasonographer Ms Sian Pugh for their expert opinion, guidance and training with the development of the ultrasound scale and image analysis. Special thanks to my friends Pavan and Pramod and colleagues in the School of Allied Health Sciences (room 2.33) for providing their friendly support during the last four years. Very special thanks to Pavan for his compassionate attitude toward me and my family during the toughest times of my PhD. Above all, I would like to express the greatest thanks and appreciation to my wife Gayathri along with my daughter Harshitha and son Sidhaarthen for their countless sacrifices and hardships during my PhD. They have been the pillars of motivation to complete this thesis.
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## Abbreviations and Acronyms

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<tr>
<td>ANOVA</td>
<td>Analysis of Variances</td>
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<tr>
<td>CEO</td>
<td>Common Extensor tendon</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>Combined</td>
<td>Prolotherapy injections and manual therapy/exercise</td>
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<td>CPT</td>
<td>Cold pain threshold</td>
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<tr>
<td>DNIC</td>
<td>Diffuse Noxious Inhibitory Control</td>
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<tr>
<td>ECM</td>
<td>Extracellular matrix</td>
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<tr>
<td>ECRB</td>
<td>Extensor carpi radialis brevis muscle</td>
</tr>
<tr>
<td>ECRL</td>
<td>Extensor carpi radialis longus muscle</td>
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<tr>
<td>GEE</td>
<td>Generalised Estimated Equations</td>
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<td>HPT</td>
<td>Heat Pain threshold</td>
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<tr>
<td>ICC</td>
<td>Intra-class Correlation Coefficient</td>
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<td>LTT</td>
<td>Longitudinal tendon thickness</td>
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<td>LCL</td>
<td>Lateral collateral ligament</td>
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<tr>
<td>LUCL</td>
<td>Lateral Ulnar Collateral Ligament</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>PFG</td>
<td>Pain-free grip</td>
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<td>PG</td>
<td>Proteoglycans</td>
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<td>PPT</td>
<td>Pressure pain threshold</td>
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<tr>
<td>PRTEE</td>
<td>Patient-Rated Tennis Elbow Evaluation</td>
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<tr>
<td>QST</td>
<td>Quantitative Sensory Testing</td>
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<tr>
<td>SEM</td>
<td>Standard Error of Measurement</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>TUSS</td>
<td>Total Ultrasound Scale</td>
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<td>Transverse Tendon Thickness</td>
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<td>US</td>
<td>Ultrasound</td>
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<td>VAS</td>
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Chapter 1 General Introduction
1 Introduction

1.1 Introduction

Lateral epicondylalgia (LE), also known as “tennis elbow”, is considered as a chronic overuse–induced angiofibroblastic tendinopathy (Alvarez-Nemegyei et al., 2007). LE affects the common extensor tendon at the lateral elbow and is characterised by pain over the lateral humeral epicondyle that is aggravated by the resisted wrist and/or finger extension and gripping activities (Nirschl et al., 2003). LE is prevalent in 1-3% of the general population and 15% among industrial workers in occupations requiring repetitive gripping (Shiri, et al., 2006). LE is commonly associated with heavy economic burden due to higher treatment costs, work absence and productivity loss (Walker-Bone et al., 2012). Recovery by one year is the most commonly reported prognosis in the majority (89%) of people with LE with an average duration of a typical episode between six months and two years (Binder et al., 1983; Nirschl, 2015). Despite decades of research, it has become evident that severe LE is not self-limiting, and that a proportion of people suffering from this condition continue to experience chronic pain and disability that is unresponsive to treatment (Binder & Hazleman, 1983). Currently, a significant gap in the knowledge exists on its aetiopathogenesis, management and prognosis of LE (Bisset et al., 2015).

In contrast to its relatively simple clinical presentation, LE is characterised by complex pathophysiology encompassing three interacting components including progressive tendon structural changes, sensory system changes and motor impairments (Coombes, Bisset, et al., 2009). Despite its clinical significance and associated morbidity, the relationship between these pathophysiological factors over time is not clearly understood in LE. Coombes’ integrative pathological model (Figure 1) indicates that histological changes at the common extensor tendon are accompanied by alterations in the sensory system and
impairments in motor function (Alizadehkhaiyat et al., 2007; Bisset et al., 2006). Ultrasound (US) is a non-invasive, safe, and valid method of assessing tendon structure (Docking et al., 2012). Furthermore, US assessment of tendons has been shown to be reliable and repeatable when performed by a trained assessor, including by physiotherapists (Ingwersen et al., 2016; Poltawski et al., 2012). Multiple studies have shown the ability of ultrasound (US) to significantly detect these histological changes of common extensor tendon by visualising the echogenicity of the tendon (Clarke et al., 2010; Levin et al., 2005). The commonly reported US features of tendon abnormalities include tendon thickening, focal areas of hypoechogenicity, diffuse heterogeneity (areas of fibrillar disruption), neovascularity, and tendon microtears, calcification, bony abnormalities or enthesis changes (Connell et al., 2001a). Although evidence from cross-sectional studies (Chourasia et al., 2013; Coombes et al., 2015; Scott et al., 2013) suggest a lack of association between US detected tendon structural abnormalities and clinical symptoms. However, recent evidence suggests that the progression of structural changes and worsening of tendon pathology over time is a risk factor for the development of pain in tendinopathy (Cook et al., 2016). Therefore, it important to understand the relationship between these US observed tendon structural changes and clinical outcomes over time to gain more knowledge on the clinical course and prognosis, which will facilitate targeted interventions for LE.

Emerging evidence suggests that primary nociception (stimulation of the local nociceptors, including C- and A-delta fibres and their projections to the cortex through lateral spinothalamic tract) (Rio et al., 2014) occurs within the tendon tissue following overload (Cook et al., 2016; Rio et al., 2014). It is postulated that persistent nociception from tendon structural pathology (i.e., tendon pain) induces cellular and functional changes (i.e., sensitisation) within the nociceptive neuraxis (Rio et al., 2014; Wand et al., 2011). These
sensory system changes are clinically manifested as hyperalgesia and allodynia, where pain perception to normally innocuous stimuli is termed as allodynia and an increased pain perception to normally painful stimuli is described as hyperalgesia (Rio et al., 2014; Wand et al., 2011). In chronic pain states, it is recognised that individuals exhibiting hyperalgesic characteristics at the site of tissue injury (i.e., primary hyperalgesia) might also report hyperalgesic responses in remote locations (secondary hyperalgesia) of the body (Graven-Nielsen et al., 2010; Woolf et al., 2011). Hyperalgesia to mechanical and thermal stimuli are commonly reported in tendinopathy populations (Plinsinga et al., 2017; van Wilgen et al., 2013b). Individuals with chronic LE have reportedly demonstrated signs of local hyperalgesia (Woolf et al., 2011), and more widespread hyperalgesia (Fernandez-Carnero et al., 2009; Slater et al., 2005), including abnormal sympathetic noradrenergic processes of the nervous system (Smith et al., 1999).

Quantitative sensory testing (QST) is a psychophysical evaluation tool for large-and-small fibre function of the human somatosensory system (Chong et al., 2004; Zaslansky et al., 1998a). Multiple studies investigating the pain mechanism in LE using quantitative sensory testing (QST) have reported that individuals with LE exhibit wide variability in sensory impairments (Coombes et al., 2015; Fernandez-Carnero et al., 2009; Ruiz-Ruiz, et al., 2011). The spectrum of sensory impairments include heightened nociceptive withdrawal reflex (Lim et al., 2012), widespread mechanical hyperalgesia (i.e., bilateral deficits in pressure pain threshold) (Fernandez-Carnero et al., 2009), bilateral cold hyperalgesia (i.e., reduced threshold to cold pain) (Coombes et al., 2012), unilateral heat hyperalgesia (reduced heat pain threshold), and reduced vibration detection threshold (Fernandez-Carnero et al., 2009).
However, it is not yet known whether a causal relationship exists between US-observed tendon structural changes and sensory system changes. In particular, there is limited knowledge on the inter-relationship between tendon abnormalities, sensory system changes and clinical outcomes over time. To this end, we hypothesise that progressive tendon structural abnormalities are the underlying central driver of heterogeneous clinical presentations and sensory abnormalities in LE, and we also propose that there is an interactive relationship between the presence of US-observed tendon abnormalities, clinical symptoms and sensory system changes in LE (Figure 1). Understanding the relationship between the underlying pathophysiological factors is deemed critical in developing targeted interventions for LE.

Figure 1. The proposed interrelationship between tendon pathology, clinical and pain system changes.

Current literature on LE rehabilitation suggests that exercises, manual therapy and some combination of physiotherapy treatment were superior in improving pain and functional outcomes compared to placebo-treated or control groups in LE (Bisset et al., 2015; Bisset et al., 2006). Therapeutic exercise to the affected muscle and tendon is recognised as the core principle underpinning any given treatment for tendinopathy conditions including LE (Coombes et al., 2015). High-level evidence indicates that a combination of isometric,
isokinetic, concentric and eccentric exercises is more effective in improving pain and function compared to therapeutic US, placebo and friction massage (Bisset et al., 2015). Amidst several medical treatments proposed in the past, corticosteroid injection (CSI) is reported to be effective in providing short-term pain relief (Bisset et al., 2005; Coombes et al., 2013). However, strong evidence suggests that CSI produces deleterious effects on tendon healing in the long-term (Coombes et al., 2013; Gautam et al., 2015; Vicenzino et al., 2017) and not different to placebo injection at 6 months follow up (Claessen et al., 2016; Coombes et al., 2013). In recent years, several novel injection treatments including polidocanol (Zeisig et al., 2008), autologous blood injection (Connell et al., 2006; Connell et al., 2006b) platelet rich plasma injections (Calandruccio et al., 2017) and prolotherapy injections (Rabago, 2009) were proposed to treat LE.

Prolotherapy is an injection treatment of proliferating agents such as hypertonic glucose or sodium murrhuate solution (Rabago et al., 2010). It is delivered directly into the damaged tendon tissue to promote tendon healing by reversing the degenerative structural changes, and achieve pain reduction through a neurophysiological mechanism (Rabago et al., 2009; Rabago et al., 2017). Amidst the injection treatments, prolotherapy is showing potential in improving short-term and long-term pain, as well as improving biomechanical tendon characteristics in animal and human studies (Carayannopoulos et al., 2011; Dong et al., 2016; Rabago et al., 2009).

Physiotherapy treatment comprising exercise and manual therapy is recommended for managing LE, which is characterised by a range of heterogeneous presentations, including tendon matrix changes, sensory system changes and pain and functional impairments (Coombes et al., 2015). In particular, there is limited knowledge on the effectiveness of conservative treatment in improving tendon structure and sensory impairments over time.
The clinical effectiveness of physiotherapy, comprising Mulligan’s Mobilisations-with-Movements (MWM; manual therapy technique) and exercise, in significantly improving short- and long-term clinical outcomes is evidenced in LE (Bisset et al., 2015; Bisset et al., 2006; Vicenzino et al., 2001b). However, the effectiveness of this physiotherapy treatment and prolotherapy injections (either singly or combined) in improving tendon structural changes, sensory system changes and clinical symptoms over time in LE is largely unknown.

While previous studies have examined prognostic factors such as sociodemographic, sensory, physical and psychosocial characteristics associated with LE (Alvarez-Nemegyei et al., 2007; Coombes et al., 2015), there are still notable gaps in the knowledge of the influence of these characteristics on prognosis (Alvarez-Nemegyei et al., 2007; Bisset et al., 2015). In particular, the ability of baseline characteristics such as tendon structural abnormalities in influencing treatment outcomes in LE is largely unknown. Recent evidence suggests a significant association between sensory system changes and poor treatment outcomes in LE (Barratt et al., 2017; Coombes et al., 2012, 2015); however, the ability of US detected tendon abnormalities to predict long-term treatment outcomes is unclear.

In summary, the current state of knowledge on the relationship between tendon structural changes, sensory system changes and clinical outcomes is incomplete, and the effectiveness of prolotherapy injections and manual therapy/exercise in improving tendon structure and sensory system changes over time is still not clearly answered. A longitudinal study investigating the tendon structural changes over time, and its relationship with sensory and clinical outcomes following prolotherapy injections and physiotherapy treatment, are integral to clearly understand the reasons for heterogeneity in
clinical response following treatment and to develop new and effective treatment strategies for tendon injuries.

1.2 Research questions

In particular, this thesis will address the following questions:

1. What is the reliability of a non-radiologist US examiner compared to the “gold standard” (i.e., experienced radiologist) in performing grading of common extensor tendon abnormalities using a US image rating scale?

2. What is the relationship between tendon structural abnormalities, sensory system changes and clinical outcomes at baseline and over time in LE?

3. Does physiotherapy, prolotherapy injections or a combination of the two improve the tendon structural abnormalities and sensory changes in people with LE?

4. Does the level of tendon structural abnormalities at baseline predict clinical change over time?

1.3 Thesis aims

The aims of the thesis were to explore the short- and long-term relationship between tendon structural changes, sensory system changes and clinical outcomes following prolotherapy injections and physiotherapy treatment (single and combined) for people with LE. In particular, the aims were to:

1. To explore the inter and intrarater reliability in the evaluation of US-observed common extensor tendon abnormalities in people with LE;

2. To determine the association between US-observed structural abnormalities with sensory system changes, demographics, and clinical presentations at baseline in people with LE;
3. To determine the effectiveness of physiotherapy, prolotherapy injections, either singly or combined, in improving tendon structural abnormalities, sensory system changes and clinical characteristics over time;

4. To explore the prognostic capacity of baseline measures of US-observed tendon structural abnormalities on clinical outcomes following prolotherapy injections and/or physiotherapy at 1-year follow up in people with LE.
Chapter 2 Literature review

The primary aim of this thesis was to explore the relationship between common extensor tendon structural changes described by ultrasound, sensory characteristics and clinical characteristics over time in people with lateral epicondylalgia (LE). The following literature review is directed by the aims of this thesis.
2 Literature review

2.1 Definition

Lateral epicondylalgia (LE) is one of the most common overuse tendinopathy conditions, affecting the common extensor tendon at the lateral elbow (Nirschl et al., 1973). In particular, the extensor carpi radials brevis is considered the primary muscle involved in LE (Nirschl et al., 2003; Nirschl et al., 1979). It is characterised by localised pain with force loading (e.g., muscle contraction) and palpation over the tendon insertion at the lateral epicondyle, as well as functional impairments (Nirschl et al., 1974). Pain and/or weakness is usually aggravated by wrist extension, 3rd finger extension, forearm supination, gripping tasks and lifting heavy objects (Lucado et al., 2012).

2.2 Disease burden and epidemiology of lateral epicondylalgia

The annual incidence of LE in general practice is reported to be between 4 and 7 per 1000 participants, with a peak incidence in both men and women between 35 and 54 years of age (Smidt et al., 2006). Estimates of point prevalence suggest that LE commonly affects 1% to 3% of the population and up to 15% of manual workers in occupations that require repetitive wrist movements and gripping tasks (Shiri et al., 2006; Shiri et al., 2011). The frequency of elbow injuries such as LE in tennis players is highest among novice tennis players, purportedly because novice players exhibit greater eccentric loading of the forearm extensor muscles during the backhand stroke (Blackwell et al., 1994; Riek et al., 1999).

The clinical symptoms of LE may persist for several years and recurrence is common within 3 to 6 years after the initial diagnosis (Shiri et al., 2006). A high rate (12 weeks) of work absenteeism is reported in about 30% of individuals with LE (Mens et al., 1999) and
the direct costs of absenteeism in the workplace is reported to be approximately USD8099 per person (Silverstein et al., 2002). A recent study involving 85,318 people from the United States of America found that the proportion of new diagnoses in people aged less than 65 years was less than the proportion of diagnoses in people aged over 65 years (Degen et al., 2017). In addition, the proportion of people aged over 65 years who needed surgery was greater than their younger counterparts, and the average per-patient reimbursement was also significantly greater in this older population (Degen et al., 2017). In contrast to the above finding, Sander et al. (2015) reported a higher incidence in people under the age of 40 years (Sanders et al., 2015). The disparity is possibly attributed to the smaller biased sample of Sander et al and the findings might not completely represent a national trend. Further, the majority of the previous studies have reported incidence based on the single institution or smaller case series with smaller sample sizes (Degen et al., 2017).

2.3 Aetiological factors

The underlying aetiology is for LE includes repetitive work or overuse, resulting in degeneration of the common extensor tendon (Nirschl et al., 1974; Potter et al., 1995; Regan et al., 1992). There is also evidence to indicate that mechanosensitivity of the radial nerve may be a feature of LE (Lister et al., 1979; Yaxley et al., 1993). Additional factors that are identified to cause tennis elbow symptoms include playing racquet sports (Smidt et al., 2006), piano, handling tools weighing greater than 1 kg, frequent heavy loading activities (lifting >20 repetitions for >10 times in a day) and repetitive movements for more than 2 hours per day (van Rijn et al., 2009).
2.4 Evolution of pathophysiology paradigm of LE

Cyriax et al. (1936) reported that repeated pronation and supination movement in full elbow extension is a key predisposing factor for LE. In his seminal paper, he emphasised the lack of consensus on one specific pathology for LE. A grand list of 26 possible pathologies for LE was proposed. Some of the proposed pathologies included: joint pathologies (arthritis, synovitis, osteochondritis), ligament pathologies, muscle pathologies (periostitis, tears) or nerve pathologies (entrapment or neuritis of the radial or posterior interosseous nerve). In conclusions, tear between the tendinous origin of the extensor carpi radialis brevis and periosteum on the anterior surface of the lateral epicondyle was recognised as the most common pathoaeiology (Cyriax et al., 1936).

Goldie et al. (1964) performed a microscopic evaluation of muscle/tendon pathology using cadavers. They found evidence of hypervascularity, rupture of the normal architecture of collagen fibres, granulation tissue, oedema, cellular invasions and absence of true tendinous degenerative changes in the extensor aponeurosis (Goldie et al., 1964). Based on the surgical findings, Nirschl et al. (1999) suggested that acute inflammatory cells are primarily absent within the tendon. However, during the healing of partial tears, chronic inflammatory cells could be seen adjacent to the tendon tissue (Nirschl et al., 1992).

Kraushaar et al. (1999) demonstrated that LE is not an inflammatory condition rather it is fibroblastic vascular response known as angifibroblastic degeneration or tendinosis. Tendinosis is the commonly used term to refer the variable degenerative changes including collagen, disorientation, disorganisation, fibre separation and increased proteoglycans (PG), cellular activity, neovascularity and lack of inflammatory cells (Coonrad et al., 1973; Goldie et al., 1964; Kraushaar et al., 1999; Nirschl et al., 1973; Regan et al., 1992). Overall, early studies depicted LE as an inflammatory condition but later studies from Nirschl et al. (1979) and Kraushaar et al. (1999) described LE as a tendinosis,
characterised by degenerative changes of the common extensor tendon (Kraushaar et al., 1999; Nirschl et al., 1979).

### 2.4.1 Tendon structure

A fundamental knowledge of the tendon structure-function relationship is essential for understanding the pathogenesis that underlies tendinopathy conditions such as LE. Tendons are a special type of connective tissue that connects and transmit forces from muscle to bone (Benjamin et al., 2008; Kannus et al., 2000; Nourissat et al., 2015). Tendon has an organised structure of fibrillary arrangement (Figure 2.1). The triple-helical collagen molecules convene to form fibrils which in turn form fibres, fibre bundles that form the tendon unit (Kannus et al., 2000). The extracellular matrix (ECM) of the tendon comprises collagen (mostly Type 1), a small amount of elastin embedded in the hydrated proteoglycans (PG) matrix, glycoproteins and glycosaminoglycans (Benjamin et al., 2008). The tendon specific fibrillogenesis of Type 1 collagen is formed by the ECM components. Type 1 collagen and other ECM molecules are formed by tenocytes (tendon cells) that are located inside the collagen fibres and in the endotenon (Benjamin et al., 2008; Kannus et al., 2000). The tendon is capable of resisting compressive forces through the PGs which facilitate retention of water within the ECM (Kannus et al., 2000). The individual collagen fibril is the basic force-transmitting unit of the tendon, and it is suggested that failure or injury to these fibril triggers the onset of tendon injuries. This organisation of the ECM matrix at micrometre and nanometre levels is responsible for the physiological function and mechanical strength of tendon tissue (Nourissat et al., 2015).
2.4.2 Pathology of tendinopathy

Tendinopathy is a chronic painful condition occurring within tendons caused by mechanical, degenerative, and overuses disease (Weinreb et al., 2014). The pathology involves abnormalities to the organised hierarchical collagen structure, cellularity, and vascularity and it is clinically characterised by pain on loading, focal tendon tenderness, and reduced strength and movement on the affected side (Nourissat et al., 2015). It is considered a complicated and challenging condition that often responds poorly to treatment (Sharma et al., 2005).
A tendon’s ability to structurally respond to mechanical loading plays a significant role in tendon injuries (Sharma et al., 2005). Tendon is a mechanosensitive tissue that responds to excessive loading by changing its metabolism as well as its structural and mechanical properties (Sharma et al., 2005). However, repeated mechanical overloading can lead to micro-tearing of collagen fibrils, weakening the tendons and eventually leading to rupture (Ellenbecker et al., 2013). Tendinopathy may present with tendinosis, partial tears, incomplete full-thickness tears or complete full-thickness tears (Hodgson et al., 2012). Chronic tendinopathy results in chronic localised pain and mechanical weakness that may lead to spontaneous ruptures, which are observed as discontinuity of tendon fibres with or without retraction and a resultant tendon gap (van Schie et al., 2010). The gaps between the fibres may be filled with fluid (anechoic), fat and scar tissue (Hodgson et al., 2012).

Overuse, repetitive strain or mechanical overloads to tendons are thought to initiate the onset of symptomatic tendinopathy (Cook et al., 2009; Scott et al., 2013). It has been suggested that the pathogenesis of tendinopathy involves a 3-stage process that includes injury, failed healing and clinical presentation (Fu et al., 2010). Histopathological findings reveal variable degenerative changes including collagen, disorientation, disorganisation, fibre separation, increased proteoglycans (PG), cellular activity, neovascularity and lack of inflammatory cells (Kraushaar et al., 1999a). Imaging is required for recalcitrant cases to rule out other potential causes of this painful condition and to assess the broad spectrum of structural changes ranging from mild to severe tendinopathy (Sharma et al., 2005).

### 2.4.3 Continuum of tendon pathology

In the last decade, Cook et al. (2009) proposed a continuum of tendon pathology (Figure 2.2) which described the progression of pathological tendon structural changes into three stages: reactive tendinopathy, tendon disrepair (i.e., failed healing) and degenerative tendinopathy (Cook et al., 2009).
2.4.3.1 Reactive stage

According to the continuum model, during the first stage (i.e., reactive stage), non-inflammatory proliferative changes of the cell and tendon matrix occurs which manifests as transient adaptive, diffuse tendon thickening (Figure 2.2). These adaptive pathological tendon changes to compressive loading are different from the normal adaptive tendon changes to tensile loading. Therefore, little change in tendon thickness occurs in normal tendon and collagen integrity and neurovascular structures are largely preserved during this stage (Cook et al., 2009; Magnusson et al., 2008). These early adaptive changes in tendon structure during reactive stage are a precursor to subsequent long-term changes that possibly occur. The most common structural changes observed during this stage include thickening of the tendon, increased stiffness and reduced internal stress. At this stage, the tendon can potentially reverse back to the normal structure provided the overloading is reduced. Ultrasound (US) can be used to visualise tendon thickness and normal collagen structure during this stage (Cook et al., 2009a). The relative and absolute reliability of US in assessing tendon structure and measuring tendon size (cross-sectional area and thickness) are well documented in tendinopathy population including LE (Ingwersen et al., 2016; Krogh et al., 2013; McAuliffe et al., 2017). Clinical characteristics during this stage include the development of pain with acute overloading activities such as jumping and repeated landing (Cook et al., 2009).

2.4.3.2 Tendon disrepair

Tendon structural changes during this stage include increased cellularity, increased separation of collagen and disorganised appearance of the matrix. Greyscale and colour or power (Figure 2.2), Doppler US can be used to view the following features: discontinuity
of collagen fascicle, focal areas of hypoechogenicity and hypervascularity (Clarke et al., 2010).

### 2.4.3.3 Degenerative tendinopathy

Progressive tendon structural changes from the previous two changes reach the last and prominent stage of tendon pathology. During this stage, areas of cellular death due to apoptosis, trauma or exhaustion of cellular activity possibly occur at this stage. Large gaps created by the disorganisation of the tendon matrix are filled with blood vessels (Cook et al., 2009a). The presence of hypoechoic regions, hypervascular areas and diffuse heterogeneity associated with this stage can be visualised using US. The likelihood of a possible reversal or normalisation of tendon structure is remote. The presence of tendon swelling, focal nodular areas with or without diffuse thickening, and recurring pain episodes are common clinical characteristics of this stage. It is also possible that areas of degenerative changes presented in between areas demonstrating other stages of pathology and normal tendon tissue. Once the tendon pathology advances to degenerative phase, the capacity of the tendon to reverse the tendon structural changes is minimal (Cook et al., 2009). A surgical procedure such as ultrasonic percutaneous tenotomy may be recommended for targeted removal of degenerative diseased tissue to reduce pain and improve function (Barnes et al., 2015; Battista et al., 2017; Seng et al., 2016).
Figure 2.2 Continuum Model of tendon pathology (reproduced with permission from Cook et al., 2009)
2.4.3.4 Clinical application of the model

In accordance to the propositions of the model, it can be generally considered that older individuals showing thick nodular tendon may be more likely to reflect a degenerative tendinopathy, whereas fusiform shaped swelling of the tendon in young adults is more likely to develop reactive tendinopathy (Cook et al., 2009). Imaging methods such as US can provide essential information about the tendon changes when there are no explicit clinical manifestations. Ohberg et al. (2004) suggested that tendon thickening may persist for several years despite an improvement in tendons structure and pain (Ohberg et al., 2004). Also, it is indicated that pain can be experienced at any stage of tendinopathy, and thus can show association or dissociation with tendon pathological at a given time (Cook et al., 2009).

2.4.4 Integrative pathological model for LE

The integrative model by Coombes et al. (2009) proposed that tendon pathology in LE can be described as having three inter-related components namely i) local tendon structural changes ii) changes in sensory or pain system iii) impairments in the motor system. These model components may coexist in various proportions in an individual, causing heterogeneous clinical presentations (Coombes et al., 2009).

2.4.4.1 Tendon pathology of the common extensor tendon

Early histological studies of the extensor carpi radialis muscles (ECRB) using light and polarised microscope have reported the presence of tendon degenerative morphological changes such as disruption of collagen fibres, microtears, tendon thickening, increased cellularity, enthesis abnormalities (bony abnormalities), and intratendinous fibrocartilage formation (dystrophic calcification) neovascularisation with no evidence of inflammation in recalcitrant cases of LE (Kraushaar et al., 1999). Further evidence for the separation of
the lateral collateral ligaments, ECRB origin was also reported in people with LE (Walz et al., 2010). Notably, evidence for this histopathological imaging and surgical findings were observed in people with LE with duration of symptoms ranging from 6 to 48 months (Khan et al., 1999). In view of this, it is plausible to assume that a continuum of tendon structural changes might occur along the course of LE.

The common tendon pathological structural change in LE is consistent with Achilles and patellar tendinopathies, all of which reflect common underlying tendon pathology (Coombes et al., 2009; Maffulli et al., 2004). Angiofibroblastic hyperplasia is the common term given to describe the following four features of tendon pathology in LE: 1) increased cellularity and ground substance 2) neovascularity 3) increased density of neurochemicals 4) collagen disorganisation and presence of immature collagen (Fredberg et al., 2008; Nirschl, 1992; Regan et al., 1992). The most common location for the presence of pathological tendon structural changes is the deep and anterior fibres of the proximal insertion of the extensor carpi radialis brevis tendon (ECRB). The types of physical forces that cause or induce a pathological structural change in LE are usually tensile, compressive or shear forces (Coombes et al., 2009). The presence of neovascularity is been hypothesised to have an association with the pain experienced in LE (Coombes et al., 2009; Ljung et al., 2004; Ljung et al., 1999; Uchio et al., 2002).

2.5 Diagnosis of LE

In 1873, the first reporting of LE was made by Runge who described the condition as having tenderness over the lateral epicondyle which was aggravated by writing (Runge, et al., 1873). The diagnosis of LE is primarily based on clinical history and physical examination (Coonrad et al., 1973) with various diagnostic imaging methods used to provide a differential diagnosis to identify the location and extent of the injury and to
monitor the treatment response (Connell et al., 2001). Pain is usually experienced or aggravated by the contraction of the common extensor muscles during various activities.

2.6 Clinical examination

The most commonly used clinical tests to provoke pain symptoms of LE include resisted middle finger extension (Maudsley’s test) (Ahmad et al., 2013; Hsu et al., 2012), palpation over the insertion of the ECRB tendon (Ahmad et al., 2013), resisted wrist extension with elbow in full extension and pronation and lifting a chair in forearm pronation (Ahmad et al., 2013a; Gardner et al., 1970). In addition, diminished pain grip strength assessed by dynamometer is also considered a diagnostic test for LE (Shiri et al., 2006).

2.7 Imaging

Although a clinical diagnosis of tendinopathy is commonly based on tendon pain and thickening, the probability of misdiagnosis is higher in tendinopathy population (Scott et al., 2013a). Given the circumstances, US and MRI are commonly used to substantiate the clinical findings by visualising the location of tendon structural abnormalities (e.g., tendon thickening) and other relevant findings (Scott et al., 2013). Studies investigating the sensitivity and accuracy of imaging in detecting tendon abnormalities reported that US is more accurate than MRI when performed by an experienced examiner due to its greater spatial resolution (Warden et al., 2007), and anatomic details (Khan, Forster, et al., 2003; Rasmussen, 2000).

2.7.1 MRI

The most commonly reported MRI findings of the common extensor tendon abnormalities included increased signal of the tendon with possible focal thinning or thickening, abnormal separation between extensor tendons, partial and full thickness interstitial tears
(based on the extent of focal interruption), lateral collateral ligament (LCL) tears, focal chondral defects, muscle oedema, radiocapitellar widening, joint effusion and synovitis (Jeon et al., 2017; Potter et al., 1995). MRI is considered useful in distinguishing between severity levels of a condition which may help clinicians to predict clinical presentation and to determine suitable treatment options (Jeon et al., 2017). Specific MRI findings relative to common extensor tendon abnormalities in LE includes: tendon thickening with increased focal signal intensity, ganglion adjacent to the radial nerve (Aoki et al., 2005), presence of a lesion in the lateral ulnar collateral ligament injury (LUCL), LCL thickening or tear, increased signal in the anconeus muscle (Qi et al., 2013) and flexor-pronator strain indicated by high signal intensity in the flexor-pronator muscle bellies (Wenzke et al., 2013). However, MR imaging is considered as costly procedure and can only provide a global assessment of the region of interest whereas US can provide extended focus imaging of the area of pain or clinical suspicion of pathology (Docking et al., 2015).

2.7.2 US imaging of tendon structural changes in tendinopathy

Tendon structure and pathology can be visualised through the use of imaging such as (US) (Martinoli et al., 2002). US provides precise imaging of the alterations of both internal structures of tendon and peritendinous soft tissues. It provides support to the clinical diagnosis of several musculoskeletal conditions by visualising the tendon structural abnormalities (Bianchi et al., 2016; Connell et al., 2001). It is also well evidenced in tendinopathy population that US is a reliable tool to assess tendon structural abnormalities and measure mechanical properties of tendon (tendon thickness, stiffness, cross-sectional area) (Dones et al., 2014; Heales et al., 2014a; Krogh et al., 2013; Mc Auliffe et al., 2017).
In US, the echogenicity of the tendon is based on the density and arrangement of the collagen matrix and disintegration of tendon bundles leads to loss of echogenicity (van Schie et al., 2010). The fibrillar organisation of tendinous structure observed in the US reflects the histological organisation of collagen fibres (Martinoli et al, 1993). Normal tendons have a fibrillar pattern of parallel hyperechoic lines in the longitudinal plane and a hyperechoic round to ovoid image of bright clustered dots in the transverse plane. These brightly reflective fascicles within tendon are best seen when the US beam is perpendicular to the orientation of fascicles (Martinoli et al., 2002).

Tendinosis manifests as thickening, fragmentation, focal hypoechoic areas, diffuse heterogeneous areas, calcification and bony abnormalities leading to irregular patterns in the US echogenicity (Connell et al., 2001a). The progressive tendon structural changes from thickening to loss of fibrillar pattern observed by the US indicate the development of tendinopathy evidenced by pain and function limitation (Hodgson et al., 2012). Further, US imaging of partial thickness tendon tears is visualised as a hypoechoic area with a true defect or definite cleft within the intrasubstance area of the tendon (Bianchi et al., 2005). However, in the absence of true visualised cleft on both longitudinal and transverse plane US images, precise differentiation of tendinosis from partial thickness tear using US imaging can be a challenging task even for experienced US examiners. There is a possibility for both tendinosis and partial thickness tear to co-occur in some cases (Jacobson et al., 1999).

Assessing the structural changes can help track the natural history of tendinopathy and monitor the effects of treatment (Poltawski et al., 2012). The duration of tendon pain presence relates to the extent of changes taking place with tendon structure (Bashford et al., 2008). It is suggested that degenerative changes generally precede the development of
a macroscopic tendon tear, which may or may not is associated with symptoms. Partial or complete thickness tears, if left untreated, may lead to complete rupture of a tendon (Bashford et al., 2008).

Thickening of the tendon is recognised to be the early stage of tendon rupture (Kannus et al., 1991). Early detection of these structural changes by diagnostic imaging methods (US) is important to prevent the risk of potential tendon ruptures (Garcia et al., 2003). Variability in tendon thickness measurement according to the region of measurement has been reported in the literature (Toprak et al., 2012; Ustuner et al., 2013). Furthermore, the presence of partial-thickness tears within a tendon is thought to be associated with a failure to respond to conservative treatment (Hashefi, 2011). Research evidence has shown that patients with symptomatic tendinopathy (Achilles) and abnormal findings on the US had poorer treatment outcomes than those with normal US findings (Cook et al., 2002). Cook et al. (2009) proposed that reducing the load on a tendon may allow the pathological tendon structure to return to previous existing level (Cook et al., 2012; Cook et al., 2009). The treatment aims for the most common tendinopathy are based on the knowledge of the tendon matrix and its changes in health and disease (Riley et al., 2004). However, there is a limited knowledge of the progression of tendon structural changes over time.

While LE is considered an upper limb tendinopathy, it has been better characterised by complex pathophysiological presentation involving local tendon changes as well as deficits in the sensory and motor systems (Bisset et al., 2009a; Coombes et al., 2009; Fernandez-Carnero et al., 2009). Angiofibrablastic hyperplasia is the collective term that describes the key local tendon changes including increased cell numbers and ground substance, vascular hyperplasia, increased concentration of neurochemicals and
disorganised collagen structure (Nirschl, 1974). The ECRB tendon is recognised as the common site for these degenerative changes (Connell et al., 2001; Levin et al., 2005; Slater et al., 2005).

2.7.3 US imaging in LE

US is considered widely available non-invasive and cost-effective imaging technique for assessing structural changes in LE. Currently, there is no gold standard in imaging LE (Dones et al., 2014). However, US has provided convincing evidence for a broad spectrum of CEO structural and other associated abnormalities in LE representing mild to severe tendinosis (Clarke et al., 2010a; Lee et al., 2011; Levin et al., 2005a). The sensitivity and specificity of US in diagnosing LE ranges from 72-88% (Dones et al., 2014) and 36-100% respectively (du Toit et al., 2008; Heales et al., 2014; Khan et al., 2003). The US observable structural changes may include tendon thickening, focal hypoechoicinity, intratendinous tearing, neovessel infiltration, intratendinous calcification, and irregularities to bone cortex at the tendon insertion (Clarke et al., 2010; du Toit et al., 2008; Levin et al., 2005). Likewise, other structural abnormalities such as LCL thickening and tear injury to enthesis (bone) could also be visualised using US (Cohen, 2008; Sharma, 2005). LCL tear is represented as a disorganised echogenic band at the deep surface of ECRB tendon located between the radial head and capitellum (Connell et al., 2001b; Martinoli et al., 2002).

The most common US observed tendon structural abnormalities were focal hypoechoic area in the deeper portion of the tendon corresponding to the area of degeneration on either a normal background or characterised by decrease in echotexture with loss of fibrillar pattern and to some extent bone changes also noticed commonly noticed in US scans (Connell et al., 2001a). Hypoechoicinity of the CET origin has the best combination of diagnostic sensitivity and specificity (Dones et al., 2014). Previous studies have shown
that the presence of partial tears (anechoic foci), complete tears on a background of more diffuse tendinopathy changes (Clarke et al., 2010; Dones et al., 2014).

2.7.4 Pitfalls of US imaging

The musculoskeletal US is used to identify tendon abnormalities at a resolution of less than 1 mm and characterise by their echogenicity (Fornage et al., 1987). The normal tendon is hyperechoic in nature which is a bright echo of the tendon structure created with a significant difference in signal impedance at the interface between tissues and the reflected sound waves (McDonald et al., 2010b). The US probe is required to be aligned strictly perpendicular to the tendon axis and the beam (Fornage et al., 1987). Artifactual hypoechogenicity may result from improper positioning (i.e., obliquity) of the US probe in relation to the long axis of the tendon which leads to a false positive diagnosis of tendinosis (Fornage et al., 1987). US confirmation of the presence of tendon abnormality should be always obtained by evaluating both longitudinal and transverse images (Stivic et al., 2013). Structures appearing as black image produce no echo while weak or low echo display hypoechoic image (McDonald et al., 2010).

2.8 Sensory system changes in LE

2.8.1 Why we need to know about sensory changes in LE?

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Merskey et al., 1994; pain, 2018). The phenomenon of pain is as a physiological event in the body that requires a subjective awareness and it reflects the interplay of the physiology and psychosocial components (Merskey et al., 1994). The subjective experience of pain is influenced by three interacting components including sensory-discriminative, cognitive-
evaluative and motivational-effective (Casey et al., 1968; Jones et al., 1991). While the sensory component deals with the ability of the individual to evaluate the location, intensity, quality and behaviour of pain, the cognitive component is associated with effects of anticipation, attention suggestion and previous experience with pain (Auvray et al., 2010; Casey et al., 1968; Galea et al., 2002). The motivational-affective components describe the emotional factors (e.g., fear, anxiety) that affect the pain experienced (Casey et al., 1968; Galea et al., 2002).

Although the pain experience is usually associated with tissue damage, it also can occur in the absence of tissue injury (Institute for Laboratory Animal et al., 2009). Acute pain is usually referred to as the output of sudden tissue damage which can resolve quickly before the tissue healing. In contrast, chronic pain is experienced beyond the normal healing time (Galea et al., 2002; Melzack et al., 1988). Once established, individuals with pain may also experience changes in the psychological (Unruh et al., 1996; Unruh et al., 1998), behavioural (Morris et al., 2007) responses to pain (Bushnell et al., 2015).

At this juncture, any physiological changes in the major pain processing systems including the peripheral and central nervous system can alter pain perception and maintain pain for a long time beyond the required for tissue healing. Evidence also suggests that there is an association between persistent tendon pain and central and peripheral nervous system changes (i.e., nervous system sensitisation) (Plinsinga et al., 2015). Although tendinopathy related pain is reported to have multiple sources, the presence of tendon structural changes is recognised as a key source of pain. In particular, the tendon of the ECRB muscle is identified as the common location for these pathological structural changes (Connell et al., 2001; Levin et al., 2005; Ruiz-Ruiz et al., 2011).
Occasionally, chronic pain can be also experienced at locations beyond the primary source of tissue damage which is not always associated with the tissue damage (Graven-Nielsen et al., 2010). In addition, there may be wide variation in pain experience between individuals with chronic pain. For example, people with minor tissue damage may report higher or less pain which may not equate to the extent of tissue damage (Graven-Nielsen et al., 2010). These findings suggest that there are specific sensory characteristics associated with pain which may be responsible for variations in the pain experienced (Casey, 1968; Galea, 2002; Strong, 2002). Therefore, relevant knowledge about the neuroanatomy and neurophysiological changes underlying the sensory system changes is paramount before exploring the sensory changes relative to the tendon structural changes in LE.

2.9 Neuroanatomy of the pain processing System

2.9.1 Nociceptors

Nociceptors are the primary sensory neurons that are activated by tissue-damaging stimuli (Figure 2.3). After converting the trauma stimulus into electrochemical energy, the nociceptors relay the electrochemical energy to the associated neuron (Adrian et al., 1931; Galea et al., 2002; Julius et al., 2001). These nociceptors have a characteristic threshold to noxious heat, intense pressure or irritant chemicals (Burgess et al., 1967; Julius et al., 2001). There are different types of nociceptors exist for various types of pain (Figure 2.3) (Julius et al., 2001). In tendons, the primary nociceptors are the three neuronal signalling pathways that innervate tendon connective tissue and blood vessels in the vicinity (Bjur et al., 2005; Danielson et al., 2006). The three neuronal pathways including autonomic, sensory and glutamatergic have been identified in the blood vessels and walls of the
tendon, peritendon and endotendon regions (Danielson et al., 2006, 2007; Lian et al., 2006).

2.9.2 Peripheral afferents

Different types of afferent fibres exist which relay different types of stimuli from nociceptor to the higher pain processing centres (Julius et al., 2001). The most common afferent fibres are i) Aδ-fibres is a small-diameter, thinly myelinated fibres that respond to both thermal (i.e., heat and cold pain) and mechanical stimuli. A high threshold stimulus is usually required for activation of Aδ-fibres ii) Aβ-fibres are large diameter fast-conducting fibres that respond to light touch. A low threshold stimulus is usually required for activation of Aβ-fibres iii) C-fibres are small unmyelinated fibres that respond to diffuse pain sensations (e.g., cold pain) (Julius et al., 2001; Konopka, 2012; Strong, 2002; Zaslansky et al., 1998).

![Types of Nociceptors](image-url)

**Figure 2.3** Types of Nociceptors (reproduced with permissions from Julius et al., 2001)
2.9.3 Cutaneous nociceptors

Mechanical nociceptors found on the skin have a high threshold for mechanical stimuli such as pressure, but usually do not respond to thermal stimuli, irritant chemicals or extreme old in the normal skin (Burgess et al., 1967). In addition to mechanical nociceptors, there are polymodal receptors found in the skin. As suggested by the name, these receptors respond to stimuli from heat, irritant chemicals and strong cooling sensation from the skin (Burgess et al., 1969). Type I and Type II AMH receptors are the alternative or abbreviated name given for A-fibre mechano-heat receptors. Type I AMH receptor have a high threshold for heat stimuli (>53°C). Type II AMH receptors have a low threshold for heat stimuli which usually signal the first pain sensation (Dubner et al., 1997). C-polymodal receptors are usually activated by several endogenous chemicals and injections such as intradermal and arterial injections. In usual circumstances, cold receptors respond strongly to persistent cooling but weakly to pressure stimuli (Strong, 2002; Weidner et al., 1999). Evidence suggests that cold pain is mediated by nociceptors found in the cutaneous veins (Strong et al., 2002; Weidner et al., 1999). A subgroup of Aδ-fibre and C-fibre nociceptors that are unresponsive to high threshold mechanically stimuli are described as mechanical-insensitive afferents (MIAs) (Julius et al., 2001; Strong, et al., 2002).

In summary, there are several types of nociceptors and variation in response to different types of stimuli (heat, mechanical, cold) is an inherent quality of these nociceptors. All these nociceptive and thermal stimuli synapse in the dorsal horn of the spinal cord (Mense, et al., 2001; Strong et al., 2002). At the level of the dorsal horn, enhancement or inhibition of nociceptive input is processed before a final summated pain signal projected to brain areas. In particular, second-order neurons from dorsal horns cells ascend to the brainstem
and thalamus through the spinal thalamic tract and finally project mainly to the primary contralateral somatosensory areas (SI) of the cerebral cortex (Brown, 1981; Ossipov et al., 2010). Some of the signals are carried by parabrachial tract which distributes to multiple brain regions including the limbic system, the anterior cerebral cortex, the prefrontal cortex, the amygdala and motor cortex through the basal ganglia (Brown et al., 1981; Cross et al., 1994). These regions are responsible for the discrete pain perception and motor response to the pain signals projected into the respective areas (Casey et al., 1968; Cross et al., 1994). The spinothalamic and parabrachial pathways are responsible for sensory-discriminative and affective-motivational aspects of pain experience respectively (Ab Aziz et al., 2006; Willis et al., 1991).

2.10 Pain modulation

Numerous theories on pain modulation in the musculoskeletal system exist in the current literature. A pain system comprised of nociceptors, spinal cord and brain and is usually considered robust, as strong intense stimuli are required to influence pain system changes in a normal situation (Woolf et al., 1996). However, following sensitisation, relatively harmless stimuli may be perceived as pain (Nijs et al., 2016). Hyperalgesia and allodynia (Figure 2.4) are considered as clinical characteristics of altered pain system (Woolf et al., 2011). Primary hyperalgesia is described as hyperalgesia observed in the regions of primary tissue injury, whereas secondary hyperalgesia is noted in areas at a distance from the site of primary tissue injury (Latremoliere et al., 2009; Rio et al., 2014; Woolf, 2011; Woolf et al., 2000). While the primary hyperalgesic region is characterised by a reduction in the threshold for mechanical or thermal stimuli, the secondary hyperalgesia areas exhibit an alteration in the threshold to mechanical stimuli alone (Raja et al., 1984). Increased pain perception to thermal and mechanical stimulation is described as thermal
and mechanical hyperalgesia (Konopka et al., 2012; Nijs et al., 2016; Zaslansky et al., 1998).

Figure 2.4 Hyperalgesia and Allodynia (reproduced with permissions from Woolf et al., 2011)

2.10.1 Peripheral sensitisation

Peripheral sensitisation has commonly referred to the sensitisation of the primary nociceptor involved (Ali et al., 1996; Mense et al., 1985). As most of the primary nociceptors are polymodal, stimuli of thermal, mechanical or chemical (e.g., endogenous neurotransmitters) nature can sensitise the nociceptor (Kumazawa et al., 1996). The primary nociceptors can exhibit variations in sensitisation processes by altering the response to each stimulus. Therefore, it can be inferred that a nociceptor showing sensitisation to one stimulus (e.g., thermal) can maintain a normal response to other stimuli (Kumazawa et al., 1998).

In addition to the above-described nociception, combinations of chemical mediators, altered levels of pH (Handwerker et al., 1991), silent mechanoreceptors (Schmelz et al.,
and inflammation-related changes in phenotypes of myelinated afferents (Woolf et al., 2011) can induce sensitisation in primary nociceptors.

2.10.2 Changes in central and peripheral nervous system (central sensitisation)

The process of central sensitisation is the result of changes that occur at the cellular level in the spinal cord and supraspinal centres in response to peripheral sensitisation (Buettner et al., 2005; Wright et al., 1999; Wright et al., 1994). Early studies assessing the neurophysiological changes in musculoskeletal conditions, such as LE, have reported that considerable changes occur within the nociceptive system in response to pain stimulus emanating from peripheral tissue injury (Cohen et al., 1992; Wright et al., 1994; Wright et al., 1992). The cascade of changes within the pain system include i) changes in the function of wide-dynamic-range cells (WDR); ii) increased excitability (wind-up) (Woolf, et al., 1989); iii) increase in the size of the reception field (Cook et al., 1987); iv) increased ability to respond to stimulus which was previously not sufficient to provoke a response (sensitisation); and v) increased somatic withdrawal reflexes (Woolf et al., 1984). All these changes usually contribute to increased responses to various sensory stimuli such as mechanical pressure, cold and heat (Nijs et al., 2010). These changes are commonly implicated in the transition from acute to chronic pain and early identification of these changes is deemed beneficial for predicting prognosis and to develop targeted interventions (Uddin et al., 2016).

2.10.3 Clinical manifestation of the sensory system or changes in the nociceptive system

The clinical manifestation of sensory system changes include i) development of mechanical hyperalgesia (Woolf et al., 1984); ii) widespread pain away from the primary source (Simons et al., 1983); iii) increased guarding and abnormal changes in skin
temperature (Diakow et al., 1988), and skin resistance (Riley et al., 1975). The presence of higher levels calcitonin gene-related peptide, substance-P, and NK1-R immunoreactions (Ljung et al., 2004) cause neurogenic inflammation in the tendon tissue which manifests as local and widespread hyperalgesia (Fredberg et al., 2008; Ljung et al., 2004b; Uchio et al., 2002).

2.11 Evidence of sensory changes in LE

Microdialysis of affected tendons has previously revealed increased presence of the pro-nociceptive neurotransmitters, glutamate (Alfredson et al., 2000), substance P and calcitonin gene-related peptide, and micro blood vessels in the proximal ECRB tendon; all of which may modulate pain perception (Coombes et al., 2009; Fredberg et al., 2008; Ljung et al., 2004a; Ljung et al., 1999; Uchio et al., 2002).

The clinical manifestations of central sensitisation in LE include the presence of bilateral sensory deficits such as mechanical and cold hyperalgesia (Fernandez-Carnero et al., 2009). The presence of hyperalgesia away from the site of local nociception has been associated with higher pain scores, greater decreased function and longer duration of symptoms in LE (Fernández-Carnero et al., 2009; Pienimaki et al., 2011; Ruiz-Ruiz et al., 2011b; Slater et al., 2005).

2.12 Assessment of sensory changes - Quantitative sensory testing (QST)

The experience of pain is facilitated through the integration of sensory information from various neuroanatomical structures including the peripheral nerves, spinal cord and brain (Hladnik et al., 2015). In the event of injury, the pain response serves as an essential protective mechanism in preventing further tissue damage (Kuner et al., 2010). QST is a non-invasive psychophysical method of assessing sensory nerve function (Chong et al.,
QST is a broader name for a battery of measures that assess sensory thresholds and pain perception and has been commonly used to investigate sensory function in different neuropathic and pain conditions, including LE (Chong et al., 2004; Rolke et al., 2006; Yarnitsky et al., 2004; Zaslansky et al., 1998). In particular, common sensory abnormalities such as hypo- and hyperalgesia, and allodynia can be quantified using QST (Rolke et al., 2006; Zaslansky et al., 1998).

### 2.12.1 Advantages of QST in assessing small fibre function

QST is useful in measuring small fibre nerve function, such as A-delta and C fibres, which are responsible for transmission of nociception (Rolke et al., 2006; Yarnitsky et al., 2004; Zaslansky et al., 1998). QST measures of small fibre function include pressure pain threshold (PPT), heat pain threshold (HPT), and cold pain threshold (CPT). QST allows us to quantify baseline sensory deficits and changes over time in different pain modalities (thermal, cold, mechanical) and provides a means by which we can differentiate pain pathways and mechanisms underpinning chronic musculoskeletal conditions such as LE (Chong et al., 2004; Yarnitsky et al., 2004; Zaslansky et al., 1998).

Assessment of thermal pain threshold is commonly employed QST (González-Duarte et al., 2016). In general, women were found to more sensitive to pain than men with lower thermal pain threshold reported in previous studies (Neziril et al., 2011; Rolke et al., 2006). However, the effects of gender pain hypersensitivity decrease with age (Neziril et al., 2011). Furthermore, there is substantial variation in pain perception between individuals (González-Duarte et al., 2016). Normative values of QST measured in a Latino population are lower (i.e., more sensitive to pain perception) than the normative values reported in a European population (González-Duarte et al., 2016; Rolke et al., 2006), suggesting that there may be differences in QST based on ethnicity (Diatchenko et al.,
Therefore, it can be inferred that individual factors such as age, gender and ethnicity have to be considered with QST measurements.

QST has been increasingly used to understand the pain mechanisms underlying chronic musculoskeletal conditions such as LE (Nijs et al., 2016; O'Leary et al., 2017; Zaslansky et al., 1998). The presence of cold hyperalgesia can be used to distinguish subgroups and predict poorer prognosis in people with LE presenting with severe pain and disability (Coombes et al., 2012a). The presence of these clinical characteristics signifies the complex pathophysiology involving peripheral sensitisation, central sensitisation and sympathetic mechanisms in conditions such as LE (Konopka et al., 2012; Nijs et al., 2016; Zaslansky et al., 1998). These somatosensory manifestations may exhibit resistance to tissue-based treatments (Rio et al., 2014) and contribute to poorer long-term outcomes in LE (Coombes et al., 2015).

QST is also used to measure the vibration sensation carried by the large myelinated Aβ fibres (Chong et al., 2004; Yarnitsky et al., 2004). Vibration sense is a distinct sensory pathway compared to the thermal and pain sensation and is transmitted through a dorsal column of the spinal cord (Gilman et al., 2002). Subcutaneous receptors such as Pacinian corpuscles and Merkel dis receptors are usually responsible for the detection of vibration sense and the threshold for detection of the vibration stimuli depend upon the activation of these two receptors (Gilman et al., 2002). People with sensory nerve disorder with large-fibre dysfunction usually show abnormalities in vibration detection, with higher threshold values commonly reported with “methods of limits” assessment (Meier et al., 2001; Yarnitsky et al., 2004). This detection threshold can be also influenced by systolic blood pressure (Maser et al., 1997), age (Lin et al., 2005), and psychological factors (Fagius et al., 1981). In LE, previous studies have shown decreased pressure pain and thermal pain.
threshold (Coombes et al., 2012; Fernández-Carnero et al., 2009; Ruiz-Ruiz et al., 2011; Slater et al., 2005) but elevated VDT (Fernández-Carnero et al., 2009) in the affected and unaffected side. An abnormal VDT reported being elevated in computer users, with symptoms in the hand and forearm (Jensen et al., 2002) as well as patient groups with various diagnoses including neuropathies or muscular- and connective-tissue disorders (Laursen et al., 2006) were reported in the literature. These findings of multisensory impairments including abnormalities in PPT, CPT, HPT and VDT indicate the alterations in the central nervous system processing of sensory information which is commonly implicated for multimodal sensory impairments in LE (Coombes et al., 2015; Nijs et al., 2016).

Moreover, it is not established whether these neurophysiological deficits recover or persist over time following treatment. There is a need to improve our understanding of the relationship between local tendon pathology and changes in the clinical characteristics, particularly deficits in the sensorimotor function so that people at risk of chronicity and/or failure to respond to treatment can be identified and more targeted and effective treatments may be developed.

Evidence on the impact of sex (men; women) on measures of PPT in pain-free population suggests that lower PPT were associated with women compared to men (Chesterton et al., 2003; Racine et al., 2012; Riley et al., 1998; Waller et al., 2016). However, there is also evidence for the absence of gender differences on PPT (Isselee et al., 1997; Sandrini et al., 1994). The disparity in pain threshold values between gender may be attributed to the influences of gonadal hormones (Riley et al., 1998) and differences in central pain modulation (i.e., women have less effective central inhibitory mechanism than men) (Martin, 2009) during the menstrual cycle phases (Tousignant-Laflamme et al., 2009).
2.13 Sensorimotor impairments in LE

The sensorimotor system is part of the motor control system which includes central integration and processing of sensory and motor components to provide stability with active movements (LePhart et al., 2000; Riemann et al., 2002). The sensorimotor system plays a vital role in joint position sense, the sensation of force and neuromuscular control using feedforward and feedback mechanisms (Riemann et al., 2002).

In addition to persistent pain, individuals with LE demonstrate a spectral of sensorimotor system abnormalities (Bisset et al., 2009; Coombes et al., 2009). The most commonly reported sensorimotor impairments include i) reduced rate of force development in the upper limb (Chourasia et al., 2012), ii) delayed reaction time and speed of movement of the upper limb (Bisset et al., 2009), iii) delayed timing of muscle activation (Heales et al., 2016; Manickaraj et al., 2016) and iv) altered contribution of individual muscles to an upper limb task between individuals with LE and healthy controls (Alizadehkhaiyat et al., 2007; Heales et al., 2015). These sensorimotor deficits can be found bilaterally in individuals diagnosed with unilateral LE (Heales et al., 2015). The presence of sensorimotor deficits such as delayed upper limb reaction time and slower speed of movement may persist despite improvement in clinical symptoms (Bisset et al., 2009).

2.13.1 Motor impairments

The most commonly reported motor impairments in LE include unilaterally and/or bilaterally reduced pain-free grip strength (PFG) (Pienimaki et al., 2002; Slater et al., 2005), flexor and extensor muscle strength imbalances (Alizadehkhaiyat et al., 2007), and morphological abnormalities in the ECRB muscle (Ljung et al., 1999).
2.13.2 Impairments in muscle strength and motor control

In particular, individuals with unilateral LE have demonstrated 43 to 64% lesser PFG compared to the unaffected side, contradictory findings of maximal grip strength (i.e., unilateral, bilateral and absence of weakness) (Alizadehkhaiyat et al., 2007; Bisset et al., 2006; Slater et al., 2005), weakness of flexor and extensor muscles (Alizadehkhaiyat et al., 2007), flexed wrist posture with gripping activities, bilateral impairments in reaction time and speed of movement with reaching tasks (Bisset, et al., 2006; Pienimaki et al., 1997), reduced electromyographic activity (EMG) in extensor carpi radialis muscles (ECR) in backhand tennis stroke (Kelley et al., 1994), isometric wrist extension (Rojas et al., 2007) and gripping tasks (Alizadehkhaiyat et al., 2007) and alterations in synergistic organisation of activation of forearm muscles were reported in people with LE compared to healthy pain free controls (Heales et al., 2016). In summary, the presence of unilateral and bilateral motor impairments in people with unilateral LE implies the role of the central nervous system in causing pain and disability (Heales et al., 2014).

2.14 Morphological changes

People with chronic LE have demonstrated distinctive morphological changes of muscles relative to the impairments in muscle strength. In particular, the presence of moth-eaten fibres, fibre necrosis, signs of muscle fibre regeneration as well as higher percentages of fast-twitch oxidative fibre type (Ljung, Lieber, et al., 1999) and greater duration and area – to-amplitude ratio of motor unit action potentials (Calder et al., 2008) were also reported in people with LE.
2.15 Influence of psychological, and behavioural factors on the pain experience

Psychological factors such as attitude, belief, appraisal and coping strategies can alter the perception of pain (Atlas et al., 2012; Bushnell et al., 2013; Hladnik et al., 2015; Unruh, 1996). These psychological factors can be influenced by the individual's age, gender, culture and family modelling about pain. The behaviours used by the individual to reduce pain perception are called coping strategies (Keefe et al., 2004). Anxiety is commonly associated with acute pain than chronic pain. Persistent or chronic pain commonly associated with substantial psychological distress and disability (Gamsa et al., 1994). The factors which elevate the anxiety levels in the individual experiencing pain include previous experience of pain, the uncertainty of the pain occurrence, and painful medical or health procedures (Keefe et al., 2004; Unruh et al., 1996). Behavioural response to pain is commonly reported during experience with acute sharp pain. On the other hand, pain behaviours are not pronounced during chronic pain, as excessive body movements may exaggerate pain experience. Thus, behaviours are usually reported to be restricted during chronic pain (Lindley et al., 2012; Unruh et al., 1996; Unruh et al., 1999; Unruh et al., 1998).

2.15.1 Impact of persistent pain on performance and quality of life

People with chronic musculoskeletal pain commonly report difficulty in performing daily activities of life (Henriksson et al., 1995). The pronounced difficulty is faced when performing the following tasks by people with LE: carrying bags, vacuum cleaning, peeling vegetables, stirring and holding tools (Henriksson et al., 1996; Henriksson et al., 2000). A low rating for quality of life is commonly reported by people with chronic pain (Henriksson et al., 1995; Unruh et al., 1999). In summary, psychological and behavioural
factors play a pivotal role in the experience of pain and these factors need to be assessed along with other clinical measures of LE.

2.16 Association between imaging findings and clinical Symptoms

Although clinical history and examination is the gold standard diagnosis for LE, imaging methods are considered a reliable method of histopathological evaluation of tendon abnormalities in structure (Bhabra et al., 2016). The association between histopathological and imaging findings (Khan et al., 1996; Potter et al., 1995) supports the role that imaging tendon structure may play in assessment and management of LE.

2.16.1 Relationship between tendon structural abnormalities and pain and function

Although several pathological models (e.g. inflammatory, continuum) (Nirschl et al., 1974; Cook et al., 2000) of tendinopathy implicate tendon structural abnormalities as the source of pain and functional impairments, the exact relationship between US-detected tendon structural abnormalities, pain and functional impairments is not clearly understood.

Clarke et al. (2010) reported a positive association between the size of intrasubstance tears within a tendon and poor clinical prognosis. Although neovascularity was implicated as a source of tendon pain in previous studies (Zeisig et al., 2006), the findings of Clarke and colleagues (2010) conclude that there is lack of association of between the presence of neovascularity and pain and functional impairments. Subjective scoring of tendon abnormalities has been considered a limitation of this study (Clarke et al., 2010). In addition, these studies (Clarke et al., 2010; Zeisig et al., 2006) failed to address the pain system changes such as hyperalgesia and its association with functional outcomes.

Chourasia et al. (2013) found a significant association between pain severity and functional measures (PRTEE) and biomechanical measures of grip strength and rate of force development, but no significant association between US findings and pain and
function. The presence of a mild form of tendon abnormalities on imaging, non-blinded assessors for group status, the subjective nature of the US scoring method, and the lack of a control group might have contributed to these non-significant results.

While the presence of neovascularity at the pathological tendon site was previously thought to not be associated with clinical symptoms (Zeisig et al., 2006), a 2-year follow-up study from the same authors indicated that a reduction in pain was associated with a reduction in neovascularity within the tendon (Zeisig et al., 2010). A lack of standard methodology to quantify neovascularity may be a reason for the contradictory study findings.

Croisier et al. (2007) reported normalised tendon structure following eccentric training, which is in contrast to Connell et al. (2007) that demonstrated residual structural abnormalities at 6 months follow up. Several studies in lower limb tendinopathy (Khan et al., 1997; Cook et al., 2000; Lian et al., 2005) have reported abnormalities in 59% of asymptomatic individuals, which implies an inexact relationship between tendon structure and pain.

Therefore, the overarching limitation of all these studies is that they are cross-sectional in design, which limits our ability to confirm a direct causal relationship between tendon pathology and clinical presentation. Surprisingly, despite the hypothesised association between tendon structural abnormalities and pain and function in several pathological models, no published study has investigated the association between tendon structure and clinical presentation over time. Understanding the interrelationship between local tissue pathology and clinical presentation over time would provide valuable insight into the mechanisms underpinning LE and assist with more targeted management strategies in this population.
2.17 Tendon abnormalities in asymptomatic individuals

Although several studies (Comin et al., 2012; Malliaras et al., 2006; Jhingan et al., 2011; McAuliffe et al., 2016; Clarke et al., 2010) in tendinopathy populations suggest that US detected tendon structural abnormalities at baseline is a risk factor for developing future symptoms, other evidence suggest a high incidence of tendon structural abnormalities on US imaging in asymptomatic healthy individuals (Cook et al., 1998; Fredberg et al., 2002; Jaen-Diaz et al., 2010; Khan et al., 2003; Malliaras et al., 2012; Cook et al., 2000). In particular, these US-observed tendinopathic abnormalities have been identified in the dominant arm of healthy individuals and may be attributed to increasing age of the asymptomatic individuals (Jaen-Diaz et al., 2010; Ustuner et al., 2013). However, there is also evidence to suggest that the majority of individuals with clinically diagnosed symptomatic Achilles and patellar tendinopathy do not exhibit any tendon abnormalities on US imaging (Fredberg et al., 2002). Although US imaging can be useful in confirming the absence or presence of tendinopathic changes in symptomatic elbows, the high incidence of tendon abnormalities in healthy individuals poses difficulty in diagnosis of LE by affecting the specificity of US imaging. This conflicting evidence in the current literature suggests a complex relationship between structure and development of symptoms which is not yet clearly understood.

While hypoechogenicity, neovascularity, and calcification and bony abnormalities within a pathological tendon are commonly detected on US imaging, hypoechogenicity (Dones et al., 2014) and intratendinous fibrillary disruption are more sensitive and specific to the clinical symptoms compared to other abnormalities (Dones et al., 2014; Heales et al., 2014). Furthermore, neovascularity, calcifications (Dones et al., 2014; Heales et al., 2015) and bony abnormalities were considered as inconsistent US observed abnormalities and
the role of these abnormalities in the diagnosis of LE is not clearly understood (Dones et al., 2014). On the other hand, evidence also suggests that the presence of tendinopathic changes in healthy populations may represent subclinical pathology rather than true intratendinous pathology or error in the examiner interpretation or accuracy of methods to detect tendon abnormalities (Heales et al., 2015). All these findings suggest that acknowledging the existence of these tendon abnormalities in asymptomatic elbows is essential for a good understanding of symptoms and signs in LE which in turn can provide guidance to health practitioners to make informed decision making in treating symptomatic LE population.

2.18 MRI findings in LE

Magnetic Resonance Imaging (MRI) is commonly used in recalcitrant cases of LE to visualise the extent of the local tissue pathology (LaBan et al., 2014). MRIs have demonstrated increased signal intensity in the affected tendon, tendon thickening, separation of the extensor tendon from the LCL (Aoki et al., 2005), intratendinous oedema, partial or complete tears LCL (Martin et al., 1998; Steinborn et al., 1999). The sensitivity and specificity of MRI in diagnosing tendinopathy compared to clinical examination are 0.95 and 0.50, respectively (McAuliffe et al., 2016).

2.18.1 Association between MRI findings and clinical symptoms

In line with the US, there is conflicting evidence regarding the association between structural changes identified on MRI and clinical symptoms. While there is evidence to indicate that the severity of MRI signal changes positively correlated with clinical symptoms (Pfahler et al., 1998; Qi et al., 2016), some previous studies have also indicated that MRI findings of pathological tendon structural changes might persist beyond the clinical improvement (Savnik et al., 2004) and signal changes in the ECRB tendon are
common findings in people without lateral elbow pain (Savnik et al., 2004; Steinborn et al., 1999; van Kollenburg et al., 2009). Similar to the US, the disparity between the clinical symptoms and MRI findings may be attributed to the i) short follow up period of individuals with LE (Savnik et al., 2004), ii) presence of MRI detected signal changes of ECRB tendon in almost all people with characteristics symptoms (Mackay et al., 2003; Pfahler et al., 1998) and varying methods of clinical measures (Qi et al., 2016).

2.19 MRI versus US

Overall conflicting evidence on the relationship between imaging and clinically significant symptoms exists in the current literature. Although both US and MRI have comparable accuracy in diagnosing LE (Khan et al., 2003), there is evidence that MRI should not be considered as an evaluation method to identify tendon structural abnormalities in LE (Bachta et al., 2017). Further, it is well documented known that normal adaptive or pathological tendon structural changes to loading are commonly reported using US imaging (Archambault et al., 1995). Currently, US is considered the best method to evaluate tendon mechanics as it is capable of providing real-time data with an extended field of view for tendon abnormalities at a low cost (Tardioli et al., 2012). Notwithstanding this, evidence from cross-sectional studies have reported the dissociation between US finding and symptoms (Chourasia et al., 2013; Scott et al., 2013), but yet, the temporal association between tendon structure, sensory function and pain have not been explored in a longitudinal study.

2.20 Management of LE

Most of the previous studies indicated that there is no real agreement regarding the most effective treatments for LE. In particular for the effective long-term outcomes for LE (Bisset et al., 2005; Chesterton et al., 2011; Riley, 2008). Several treatments for LE have
been suggested that include education, corticosteroid injections (CSI), orthotic devices, surgery and physiotherapeutic modalities such as exercises, US, laser, massage, electrotherapy and manipulations (Bisset et al., 2005; Bisset et al., 2015; Coombes et al., 2015b; Raman et al., 2012; Sayegh et al., 2015). Evidence from a systematic review suggests that there is a lack of evidence for the long-term benefit of any single treatment in LE (Bisset et al., 2015; Coombes et al., 2015). In that review, the effectiveness of a range of conservative treatments was synthesised, including acupuncture, exercise, manual therapy techniques, orthotics, taping, and electrotherapeutic devices (e.g., extracorporeal shock wave therapy (ESWT), US, laser). Positive short-term effects were reported for non-electrotherapeutic interventions such as manual therapy techniques, exercises and taping, with little or no benefit of electrotherapeutic devices (Bisset et al., 2005).

2.20.1 Corticosteroid injection for LE

Corticosteroid injection (CSI) is considered the most common medical treatment for LE. Previous authors have concluded that CSI therapy is effective in providing short-term pain relief (Coombes et al., 2013). It has been suggested that the short-term pain relief following CSI may be due to the analgesic effects of CSI on calcitonin gene-related peptide and substance P which is noted to be elevated in tendinopathy (Coombes et al., 2013; Fredberg et al., 2008). The long-term negative effects of CSI are attributed to the abnormal release of noxious chemicals and inhibition of collagen, extracellular matrix molecules and granulation tissue (Paavola et al., 2002). Furthermore, as the primary action of corticosteroid is thought to be anti-inflammatory in nature, the role of CSI in LE management is doubtful due to the absence of an inflammatory pathology (Khan et al., 2003; Khan et al., 1999; Riley, 2008).
2.21 Current evidence for management of LE

A single intervention may not be an effective treatment strategy for the management of all presentations of tendinopathy, due to the heterogeneity in clinical presentations (Cook et al., 2009; Coombes et al., 2015). Treatment planning for tendinopathy needs to consider the location of pathology, stages of tendon pathology (Cook et al., 2009), functional status, kinetic chain issues and comorbidities, to achieve treatment success (Scott et al., 2013).

A review by Bisset and Vicenzino (2015) indicated that physiotherapy treatment comprising of exercises and manual therapy techniques have superior short-term benefit for pain relief and improved function compared to other conservative interventions such as therapeutic US, friction massage and stretches. In that review, it was also documented that there were knowledge gaps in the following areas: i) the role of underlying pathophysiological characteristics in influencing treatment outcomes, ii) the role of prognostic factors in influencing treatment outcomes, and iii) the effectiveness of physiotherapy compared to other interventions in improving sensory changes (Bisset et al., 2015). A summary of exercise and manual therapy intervention studies provided in Table 2.1.
Table 2.1 Critical appraisal of common intervention studies for LE

<table>
<thead>
<tr>
<th>First Author</th>
<th>PEDro Score</th>
<th>Participants</th>
<th>Intervention (# sessions/weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise therapy</td>
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</tr>
<tr>
<td>Tyler 2010</td>
<td>6/10</td>
<td>n=21 (6M/5F) Mean age=47</td>
<td>Isolated Ecc exs (9) v Isotonic exs.(10); co-interventions of stretching, US+massage+ice</td>
<td>VAS; DASH</td>
<td>Ecc exs effective than isotonic in reducing pain and improving function</td>
<td>Small sample size; short follow up (7 weeks)</td>
</tr>
<tr>
<td>Viswas 2011</td>
<td>6/10</td>
<td>n=20 (10M/10F) Mean age=38</td>
<td>Ecc.exs (12) v friction massage with mills manipulation (10)</td>
<td>VAS, TEFS</td>
<td>Ecc exs better than friction massage with mills manipulation</td>
<td>No control group and follow up data</td>
</tr>
<tr>
<td>Soderberg 2011</td>
<td>6/10</td>
<td>n=42 (17M/24F) Mean age=48</td>
<td>Ecc exs (6 weeks) with band v band only (6 weeks)</td>
<td>VAS, PFG</td>
<td>Ecc exs with band better than band only in improving function</td>
<td>No effect on pain measures</td>
</tr>
<tr>
<td>Peterson 2014</td>
<td>6/10</td>
<td>n=120 (6M/5F) Mean age=47</td>
<td>Ecc exs (12 weeks) v Con exs (12 weeks)</td>
<td>VAS, wrist muscle strength, DASH, QOL</td>
<td>Ecc exs had faster recovery from pain than Con exs</td>
<td>No significant group difference</td>
</tr>
<tr>
<td>Pienimaki 1996</td>
<td>6/10</td>
<td>n=39 (14M/25F) Mean age=42</td>
<td>Iso, Con &amp; Ecc exs (4) v pulsed US</td>
<td>VAS, grip strength and isokinetic muscle function</td>
<td>Iso, Con &amp; Ecc exs better than the pulsed US for pain and grip strength</td>
<td>No healthy control group</td>
</tr>
<tr>
<td>Peterson 2011</td>
<td>7/10</td>
<td>n=81 (47M/34F) Mean age=48</td>
<td>Con + Ecc exs (3 weeks) v wait &amp; see (3 weeks)</td>
<td>VAS, DASH wrist ext muscle strength</td>
<td>Ecc exs is superior to wait and see in reducing pain</td>
<td>Non-blinded trial</td>
</tr>
<tr>
<td>Selvanettti 2003</td>
<td>5/10</td>
<td>n=62 (32M/28F) Mean age=41</td>
<td>Eccentric (4 weeks) v placebo US</td>
<td>Ko and Verhaar Scoring</td>
<td>Ecc exs effective than placebo in improving pain and function</td>
<td>No blind therapist and long-term effects observed</td>
</tr>
<tr>
<td>Coombes 2013</td>
<td>8/10</td>
<td>n=165 (102M/63F) Mean age=49</td>
<td>PT (Exs + MWM) (8 weeks) v CSI+ PT v placebo CSI injection</td>
<td>PRTEE, VAS, EuroQol, Tampa, PPT, PFG</td>
<td>PT + CSI did not show significant difference</td>
<td>Single CSI or placebo injection</td>
</tr>
<tr>
<td>Martinez- Silvestrini 2005</td>
<td>6/10</td>
<td>n=94 (50M/44F) Mean age=45</td>
<td>Stretching + Con (6 weeks) v Stretching + Ecc (6 weeks) v stretching (6 weeks)</td>
<td>PFG, DASH, VAS</td>
<td>No significant difference between groups</td>
<td>Unsupervised exs program, non-blinded assessor</td>
</tr>
<tr>
<td>Stasinopoulous 2017</td>
<td>6/10</td>
<td>n=34 (15M/19F) Mean age=43</td>
<td>Ecc exs (20) v Ecc +Con exs (20) v Ecc+Con+Iso exs (20)</td>
<td>VAS, PFG</td>
<td>Ecc+Con+Iso Exs was more superior than other groups in improving outcomes</td>
<td>Small sample size, Tendon structural changes not shown</td>
</tr>
<tr>
<td>Murtezani 2015</td>
<td>5/10</td>
<td>n=49 (28M/21F) Mean age=51</td>
<td>PT (US+Exs) (18) v CSI (2)</td>
<td>PRTEE, PFG, VAS</td>
<td>PT report greater improvement in measures compared to CSI</td>
<td>Small sample size and short follow-up</td>
</tr>
<tr>
<td>Park 2008</td>
<td>4/10</td>
<td>n=31 (12M/19F) Mean age=51</td>
<td>Immediate Iso.exs v delayed Iso exs</td>
<td>VAS, Modified Nirschl/Petrone core</td>
<td>Iso exs within 4 weeks produce significant improvement in outcomes</td>
<td>Non blinded assessor, small sample size</td>
</tr>
<tr>
<td>Bisset 2006</td>
<td>8/10</td>
<td>n=198 (128M/70F) Mean age=77</td>
<td>CSI (elbow) (2) v MWM+Exs (8) v wait</td>
<td>PFG, VAS, Global</td>
<td>MWM+Exs more effective</td>
<td>Pragmatic randomised</td>
</tr>
<tr>
<td>Study</td>
<td>Rating</td>
<td>n</td>
<td>Age</td>
<td>Intervention Details</td>
<td>Outcomes</td>
<td>Notes</td>
</tr>
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<tr>
<td>Struijs 2004</td>
<td>7/10</td>
<td>180</td>
<td>45</td>
<td>Exs + MT (9) brace + MT (9)</td>
<td>GIC, VAS, PFG</td>
<td>Conflicting results, no advantage of combined PT + Exs + MT over other groups</td>
</tr>
<tr>
<td>Smidt 2002</td>
<td>8/10</td>
<td>185</td>
<td>47</td>
<td>CSI (elbow) (3) Exs + US (9) wait and see</td>
<td>GIC, NPRS, PFG</td>
<td>Exs+US show superior treatment effect compared to other groups</td>
</tr>
<tr>
<td>Svernlov 2001</td>
<td>4/10</td>
<td>38</td>
<td>42</td>
<td>Ecc exs + band (12 weeks) + Contract-relax stretching + band (12 weeks)</td>
<td>VAS, PFG</td>
<td>Effects of the band not analysed</td>
</tr>
<tr>
<td>Olaussen 2015</td>
<td>7/10</td>
<td>177</td>
<td>47</td>
<td>PT (friction massage + MT + Ecc exs (12) + CSI (2) placebo injection + PT wait and see</td>
<td>GIC (success), VAS, PFG</td>
<td>Placebo injection + PT showed no added beneficial effect compared to other treatments</td>
</tr>
<tr>
<td>Wen 2001</td>
<td>3/10</td>
<td>28</td>
<td>48</td>
<td>Ecc exs (18) Stretching (12 weeks) + iontophoresis + pulsed US (1)</td>
<td>VAS, grip strength</td>
<td>No significant difference between treatment groups</td>
</tr>
</tbody>
</table>

### Manual therapy

<table>
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<tr>
<th>Study</th>
<th>Rating</th>
<th>n</th>
<th>Age</th>
<th>Intervention Details</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viswas 2011</td>
<td>6/10</td>
<td>20</td>
<td>38</td>
<td>Exs (12) friction massage with mills manipulation (10)</td>
<td>VAS, TEFS</td>
<td>Ecc exs better than friction massage with mills manipulation</td>
</tr>
<tr>
<td>Coombes 2013</td>
<td>8/10</td>
<td>165</td>
<td>49</td>
<td>PT (Exs + MWM) (8 weeks) CSI+ PT v placebo CSI injection</td>
<td>PRTEE, VAS, EuroQol, Tampa, PPT, PFG</td>
<td>PT + CSI did not show significant difference</td>
</tr>
<tr>
<td>Cleland 2005</td>
<td>5/10</td>
<td>10</td>
<td>40</td>
<td>PT (Ecc &amp; Con exs) + MT (elbow, wrist) (10) v PT +MT (cervical &amp; thoracic spine (10))</td>
<td>NPRS, DASH</td>
<td>PT + MT (Cervical + is effective than PT + MT (elbow, wrist) in improving outcomes</td>
</tr>
<tr>
<td>Carnero 2008</td>
<td>5/10</td>
<td>10</td>
<td>42</td>
<td>MT to cervical spine (2) v manual contract intervention (MCI)</td>
<td>PFG, PPT, HPT, CPT</td>
<td>Only immediate but not long-term effect of MT observed</td>
</tr>
<tr>
<td>Nourbaksh 2008</td>
<td>6/10</td>
<td>23</td>
<td>51</td>
<td>Oscillating energy manual therapy (OEMT) (6) vs placebo</td>
<td>NPRS, grip strength, OEMT showed greater improvement in pain and grip strength</td>
<td>Small sample size, only immediate but not long-term effect of MT observed</td>
</tr>
<tr>
<td>Paungmali 2003</td>
<td>8/10</td>
<td>24</td>
<td>48</td>
<td>MWM (elbow) (1) vs Placebo v Control</td>
<td>PPT, PFG, Thermal pain threshold</td>
<td>MWM more effective than other groups in improving PFG, PPT</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Rating</th>
<th>n (M/F)</th>
<th>Mean Age</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Struijs</td>
<td>2004</td>
<td>7/10</td>
<td>180 (151M/29F)</td>
<td>45</td>
<td>Exs +MT (9) v brace + Exs +MT (9)</td>
<td>GIC, VAS, PFG</td>
<td>Conflicting results, no advantage of combined PT +Exs+MT over other groups</td>
</tr>
<tr>
<td>Vicenzino</td>
<td>2001</td>
<td>5/10</td>
<td>24 (14M/10F)</td>
<td>46</td>
<td>MWM (elbow) (1) v Placebo v Control</td>
<td>PFG, PPT</td>
<td>Greater improvement in PFG &amp; PPT in MWM than other groups</td>
</tr>
<tr>
<td>Nagrale</td>
<td>2009</td>
<td>6/10</td>
<td>60 (17M/43F)</td>
<td>39</td>
<td>Cyriax (friction massage +Mills MT ) (12) v phonophoresis+Exs (12)</td>
<td>VAS, PFG, TEFS</td>
<td>Cyriax showed greater outcomes than phonophoresis+Exs</td>
</tr>
<tr>
<td>Hsu</td>
<td>2016</td>
<td>5/10</td>
<td>35 (9M/26F)</td>
<td>44</td>
<td>MT (4) V Acupuncture (4)</td>
<td>VAS, DASH</td>
<td>No significant difference between groups at 8 weeks</td>
</tr>
<tr>
<td>Olaussen</td>
<td>2015</td>
<td>7/10</td>
<td>177 (106M/71F)</td>
<td>47</td>
<td>PT (friction massage+MT+Ecc.exs (12)+CSI (2) v placebo injection+PT v wait and see</td>
<td>GIC (success), VAS, PFG</td>
<td>Placebo injection+PT showed no added beneficial effect compared to other treatments</td>
</tr>
<tr>
<td>Bisset</td>
<td>2006</td>
<td>8/10</td>
<td>198 (128M/70F)</td>
<td>47</td>
<td>CSI (elbow) (2) v MWM+Exs (8) v wait and see</td>
<td>PFG, VAS, Global improvement in change (GIC)</td>
<td>MWM+Exs more effective than other groups in improving PFG, PPT</td>
</tr>
</tbody>
</table>

**Prolotherapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Rating</th>
<th>n (M/F)</th>
<th>Mean Age</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarpone</td>
<td>2008</td>
<td>10/13</td>
<td>24 (14M/10F)</td>
<td>48</td>
<td>PrT injections (3) v Saline injection (3)</td>
<td>VAS, grip strength, isometric muscle strength</td>
<td>PrT is superior to saline in improving pain and function</td>
</tr>
<tr>
<td>Caraynnopoulos</td>
<td>2001</td>
<td>26 (13M/11F)</td>
<td>46</td>
<td>PrT (2) v CSI (2) exercises</td>
<td>VAS, DASH</td>
<td>No significant difference between groups at 6 months</td>
<td>Small sample size,</td>
</tr>
<tr>
<td>Rabago</td>
<td>2013</td>
<td>26 (17M/9W)</td>
<td>48</td>
<td>PrT with dextrose (3) v US-guided PrT (3)</td>
<td>PRTEE, PFG, MRI</td>
<td>Both injection groups effective than wait and see in improving outcomes</td>
<td>Small sample size,</td>
</tr>
</tbody>
</table>

Ecc = eccentric; Con = concentric; Iso = isometric; v = versus; exs = exercises; US = ultrasound; CSI = corticosteroid injection; PT = physiotherapy; MT = manual therapy; DASH = Disability of the Arm, Shoulder and Hand questionnaire, TEFS = Tennis Elbow Function Scale; PrT = prolotherapy injection; PRTEE = Patient-Rated Tennis Elbow Evaluation; NPRS = numeric pain rating scale; PFG = pain free grip strength’ VAS = visual analogue scale; US = ultrasound; PPT = pressure pain threshold; MWM = mobilisation with movement; HPT = heat pain threshold; CPT = cold pain threshold
2.21.1 Effects of physiotherapy on LE

Physiotherapy is commonly recommended for managing LE (Bisset et al., 2005; Bisset et al., 2015; Coombes et al., 2015; Vicenzino et al., 2009). A multimodal physiotherapy intervention combining exercise therapy and Mulligan’s Mobilisation-With-Movement (MWM) manual therapy technique has gained critical attention in the management for LE (Bisset et al., 2015; Coombes et al., 2015b; Sutton et al., 2016).

2.21.2 Effectiveness of exercises therapy in LE

High-level evidence for the effectiveness of isometric, isokinetic, concentric and eccentric exercises in LE was primarily provided by RCTs (n = 10; Table 2.1). These studies included 1681 participants (1002 men, 678 women) with a mean age of 46 years. Overall, the results from these studies favoured exercise therapy in combination with other interventions such as orthotics (Selvanetti et al., 2003), MWM (Bisset et al., 2006), stretching (Tyler et al., 2010; Pienimaki et al., 1996; Silvestrini et al., 2005), or corticosteroid injection (Coombes et al., 2013). However, there is lack of high-quality evidence (i.e., consistent findings in multiple high-quality studies) (van Tulder et al., 2003) to support any single form of exercise over any other form of exercise or intervention for LE (Bisset et al., 2015).

Clinical measures of pain (e.g., PRTEE, VAS) (Bisset et al., 2006; Soderberg et al., 2012; Coombes et al., 2013; Peterson et al., 2014; Pienimaki et al., 1996) and function (e.g., pain-free grip strength) (Coombes et al., 2013; Soderberg et al., 2012) were primarily considered as treatment outcomes for most of the studies. Limited evidence from one study (Croisier et al., 2007) suggests that isokinetic exercise demonstrated significantly more reduction in tendon thickness and improvement of pain and function compared to a control group (TENS, ultrasound, deep friction massage and stretching) (Croisier et al.,
2007; Zeisig et al., 2010). However the study has a moderate risk of bias due to the following factors: lack of randomised treatment groups, no account of dropouts, short follow up period (9 weeks), lack of report on US operator reliability and lack of description of the standard US methods used in the assessment of intratendinous abnormalities and tendon thickness measurement.

In summary, most of these studies investigated the effects of the combination of therapies which renders difficulty in assessing the effects of individual treatment (Pienimaki et al., 1996). Furthermore, the contradictory findings in the current literature suggest that there is no consensus on the effectiveness of single best treatment for LE (Smidt et al., 2003). Previous studies investigating the effects of treatments have not provided knowledge on tendon structural changes following treatment, and it is unclear whether tendon structure changes in response to treatment.

2.21.3 Mechanisms of action of exercises

It is well documented that tendons are sensitive to mechanical forces, which induce adaptive changes in the mechanical, morphological and biomechanical properties of a normal tendon. Although, the extent of loading or loading history is said to be the decisive factor of remodelling of connective tissue such as tendons, loading beyond the threshold can predispose a tendon to injury (Archambault et al., 1995). The commonly reported physiological changes following a period of mechanical loading on a tendon include increased tendon stiffness, increased Young’s modulus, change in morphological properties, increased collagen synthesis and collagen linking, and changes in collagen fibril morphology (Bohm et al., 2015).
2.21.4 Effectiveness of manual therapy in LE

The most common manual therapy techniques for LE cited in the current literature includes cervical spine lateral glide oscillatory manipulation (Nourbakshsh et al., 2008), high velocity low-thrust cervical spine manipulation (Carnero et al., 2008), Mulligan’s MWM (Abbott et al., 2001; Slater et al., 2005; Vicenzino et al., 200; Paungmali et al., 2003), passive joint mobilisation (Cleland et al., 2005), Cyriax techniques and radial bone adjustment (Hsu et al., 2016).

Twelve RCTs have investigated the effectiveness of manual therapy in LE (Viswas et al., 2011; Cleland et al., 2005; Carnero et al., 2008; Nourbaksh et al., 2008; Paungmali et al., 2003; Struijs et al., 2003; Vicenzino et al., 2001; Nagrale et al., 2009; Coombes et al., 2013; Hsu et al., 2016; Olaussen et al., 2015; Bisset et al., 2006). The other study designs were case series (Iglesias et al., 2011), prospective cohort (Slater et al., 2005) and retrospective (Cleland et al., 2004). Immediate effects of a single treatment session or short-term effects of several sessions of manual therapy were assessed in most of these studies.

Evidence from two RCTs with a low risk of bias suggests that a immediate improvement in pain-free grip strength and PPT was significantly greater in MWM intervention compared to placebo (Paungmali et al., 2003; Vicenzino et al., 2001). MWM is also effective in immediately improving pain-free grip strength and sensory characteristics in LE (Paungmali et al., 2003; Slater et al., 2006; Vicenzino et al., 2007; Vicenzino et al., 2001). Furthermore, evidence from a case series (Iglesias et al, 2011) on rock climbers with LE suggest that a multimodal treatment comprised of cervical spine manipulations, MWM at the elbow and wrist, trigger point dry needling and Kinesio taping demonstrated significant improvement in pain, function and PPT.
Overall evidence from the current literature suggests that manual therapy techniques to the elbow, wrist and cervicothoracic spine may immediately reduce pain and increase pain-free grip strength following treatment (Bisset et al., 2015). In particular, Mulligan’s MWM has demonstrated superior short-term (6 weeks) and long-term (52 weeks) effects compared to wait-and-see approach and corticosteroid injections, respectively (Bisset et al., 2015; Vicenzino et al., 2009).

2.21.5 Mechanism of action of manual therapy

The mechanism of action for manual therapy is still hypothetical (Vicenzino et al., 2007). It is thought that manual therapy techniques produce pain relief via activation of the Diffuse Noxious Inhibitory Control (DNIC) system (Paungmali et al., 2003; Vicenzino et al., 2003; Vicenzino et al., 2007; Vicenzino et al., 1995). Alternatively, Mulligan proposed that the success of MWM is via correction of a positional fault in the underlying joint (Hing et al., 2015). Several studies have suggested that manual therapy techniques such as MWM modulate pain processes, as evidenced by an immediate increase in PPT following its application (Paungmali et al., 2003; Vicenzino et al., 2001; Vicenzino et al., 1996).

2.21.6 Effectiveness of prolotherapy injections in LE

Regenerative treatment such as prolotherapy injections has been proposed as an alternative treatment for chronic musculoskeletal conditions including tendinopathy, knee osteoarthritis and back pain (Rabago et al., 2010). The solution of hypertonic glucose with or without sodium murrhuate is commonly used as the proliferant solution for tissue healing (Goswami et al., 2012; Rabago et al., 2011). The benefits of prolotherapy injections in improving tissue repair in ligament, tendon, cartilage and bone has been investigated in several trials (Fullerton et al., 2010; Jensen et al., 2008; Reeves et al., 2016; Topol et al., 2016).
Overall there is limited evidence concerning the effectiveness of prolotherapy injection treatment in LE. In the current literature, only three RCTs (Table 2.1) have investigated the effectiveness of prolotherapy in LE, with limited evidence related to tendon structure or sensory outcomes. Scarpone et al. (2008), in a double-blinded RCT, reported significantly improved pain and grip strength at 8 and 16 weeks compared to control injections of saline in participants with chronic LE who had previously failed physiotherapy treatment. Exclusion of four randomised dropouts in the analysis, lack of formal assessment of assessor blinding and short follow-up time (16 weeks) were significant limitations to this study. Six-month follow-up results from another RCT (Caraynnopoulos et al., 2001) suggest that both prolotherapy and corticosteroid injection treatment produce significant improvement in pain and function at 3 and 6 months, but without significant differences observed between the treatments. Non-inclusion of results for 29% of study participants with inadequate follow-up, small sample size (N = 24) and a limited number of prolotherapy injections (N= 2) were considered as major limitations in this study (Carayannopoulos et al., 2001).

A pilot level single-blinded RCT assessing the effectiveness of prolotherapy injection in participants with chronic LE demonstrated significant improvement in elbow pain and function compared to baseline and wait-and-see control (Rabago et al., 2013). However, MRI findings from this study revealed minimal improvement in tendon structure over time with no significant difference between prolotherapy and a wait-and-see group (Rabago et al., 2013). Small sample size (N= 26), high variability in data, lack of a standardised rating scale for MRI, and a short follow-up time (16 weeks) suggests that the study findings be interpreted cautiously.
The conclusions drawn from previous systematic reviews (Sims et al., 2014; Krogh et al., 2013; Rabago et al., 2009; Coombes et al., 2010; Best et al., 2009; Dong et al., 2016) suggest that prolotherapy injection is clinically effective in improving pain and function, but there is still a lack of adequate evidence to recommend prolotherapy injection over other injections (e.g., corticosteroid) for treatment of LE and other tendinopathic conditions (Sanderson et al., 2015; Morath et al., 2013; C. Coombes et al., 2010). A recent Bayesian network meta-analysis indicated that prolotherapy may have superior intermediate treatment effects in treating LE (26 weeks) compared to other injection therapy such as botulinum toxin, platelet-rich-plasma and autologous blood, but it is recommended that more high-level evidence is required to confirm its superiority (Dong et al., 2016).

In summary, despite the limited evidence, results from three RCTs of moderate methodological quality suggest that prolotherapy injection with dextrose and sodium morrhuate solution is well tolerated in the LE population, and may reduce pain and improve functional outcomes in the short- to medium-term. However, most of the studies (N = 2) focussed only on pain and function outcomes with minimal findings related to tendon structural or sensory outcomes. In addition, the short- and long-term (52 weeks) effectiveness of prolotherapy in improving US-assessed tendon structure or sensory characteristics over time have not previously been investigated thoroughly. A RCT with longer follow-up and use of validated imaging scales is needed to provide high-quality evidence of the effectiveness of prolotherapy in the LE population.

2.21 7 Mechanism of action

The mode of action of prolotherapy injections is thought to involve stimulation of normal tissue repair (i.e., restoration of collagen fibre organisation) through induction of
inflammatory mechanisms relative to the amount and type of injection solution (Fullerton et al., 2010; Rabago et al., 2008). A recent study that investigated the immediate effects of dextrose on the human cultured tenocytes (Achilles tendon) reported that the initial cascade of the inflammatory response following cell death resulted in the release of chemotactic factors and inflammatory mediators to promote tissue healing (Banks et al., 1991; Ekwueme et al., 2017). In particular, it was hypothesised that the released inflammatory substances such as prostaglandins, thromboxanes and leukotrienes trigger the actions of inflammatory cells. The inflammatory cells, in turn, activate the fibroblasts to deposit new collagen at the injured site to indirectly strengthen the ligaments and tendon (Ekwueme et al., 2017). It is apparent from the evidence that the release of inflammatory mediators from the cell death predisposes tissue healing.

Although there is some evidence to indicate that prolotherapy is capable of improving tendon structural changes through an induced inflammatory mechanism (Banks et al., 1991; Rabago et al., 2017), the improvement in tendon structural changes did not always correspond with improvement in clinical symptoms. Maxwell et al. (2007) reported significant improvement in pain at rest as well as some improvement in tendon thickness, hypoechogenicity and neovascularity. However, 82% and 33% of Achilles’ tendons were reported to be unchanged in hypoechogenic area and neovascularity, respectively (Maxwell et al., 2007). Likewise, Ryan et al. (2010) demonstrated improvement in pain corresponding with improvements in some of the US-observed tendon structural abnormalities including tendon thickness, size of the hypoechogenic areas, neovascularisation and intratendinous tears (Ryan et al., 2010). However, the size of hypoechogenic regions and overall severity of hypoechogenicity remained unchanged following treatment (Ryan et al., 2010). The findings of disparity in the improvement of tendon structural changes and improvement in clinical symptoms may reflect the fact that longer time period is required for the tendon to
achieve normalise tendon structure and also, the current pain measures are inadequate to explain the improvement in tendon structural changes (Ryan et al., 2015).

2.22 Prognostic factors

Several socio-demographic, symptomatic, physical and psychosocial factors have previously been evaluated for their ability to predict changes in pain and functional impairments over time in people with LE (Coombes et al., 2015). Smidt et al. (2006) reported that a longer duration of symptoms, concomitant neck pain and more severe pain were associated with poorer treatment outcomes at 12 months (Smidt et al., 2006). There are multiple factors that may influence the severity of LE and thereby affect short- and long-term treatment outcomes (Knutsen et al., 2015). There is evidence that factors such as patient demographics (e.g. age, gender) (Knutsen et al., 2015), clinical history (e.g. duration of the condition), clinical presentations (e.g. severe baseline pain), presence of comorbidities such as neck and shoulder pain (Bisset et al., 2007; Coombes et al., 2014), and neurophysiological characteristics (hyperalgesia and allodynia) were reported to be associated with the severity of LE and poorer treatment outcomes (Coombes et al., 2012, 2015). However, the association between these demographic and clinical characteristics and observable tendon structural changes in LE has not been reported in the current literature.

2.23 Summary

The current evidence on the association between tendon structural changes and clinical symptoms is conflicting, with notable gaps in our knowledge remaining. Although numerous studies on lower limb tendons (Khan et al., 2003; Malliaras et al., 2012; Cook et al., 2000) have reported evidence of tendon structural changes in individuals with no history of symptoms, some studies (Malliaras et al., 2006; Comin et al., 2013) have shown
that the presence of tendon structural changes on imaging may increase the risk of developing pain. Consequently, the relationship between tendon structure and clinical symptoms is not yet completely understood (Docking et al., 2015). In addition, most of the studies reported in the current literature are based on lower limb tendinopathy (e.g., Achilles, patellar) which may not translate directly to upper limb tendinopathy such as common extensor tendon in LE. Differences in anatomy (e.g., morphology, site of pathology), biomechanics (loading patterns) and the heterogeneity between upper and lower limb tendinopathy may limit the reader’s ability to draw firm conclusions from the current literature.

While most cross-sectional studies on LE have reported a dissociation between the extent of tendon structural changes and clinical symptoms (Chourasia et al., 2013; Walton et al., 2011; Coombes et al., 2015), there is some conflicting evidence to suggest that the presence of structural changes may be risk factors for a poor prognosis in individuals with LE (Clarke et al., 2010). Furthermore, current research evidence also suggest that clinical characteristics (e.g. hyperalgesia, motor deficit) (Coombes et al., 2013l; Chourasia et al., 2013), severity of the condition, patient-specific demographics (age, gender, physical activity) and clinical history (e.g. loading history, previous treatment) may be also considered in addition to structural outcomes to explain more accurately the clinical effectiveness of interventions that aim to improve tendon structure (Coombes et al., 2012; Coombes et al., 2015; Chourasia et al., 2013). The current knowledge on the relationship between tendon structural, sensory and clinical changes are primarily based on cross-sectional studies which limit our understanding of the causal effects between this tendon structure, sensory changes, and clinical symptoms in LE.
While the cross-sectional study design of previous studies (Connell et al., 2001; Chourasia et al., 2013) limits our ability to understand whether tendon structural abnormalities on imaging precede and predict treatment outcomes, inconsistent evidence for the relationship between functional and structural changes following standard treatment (Exercise therapy) was reported in one systematic review (Drew et al., 2012). Also, the effectiveness of prolotherapy injections and physiotherapy in improving tendon structure and sensory function over time is unknown. The utility of US evaluation of tendon abnormalities in predicting the development of pain or functional impairments is largely unknown in LE. A review of findings from the current literature suggests that there is a lack of high-level evidence to provide a clear understanding on the relationship between tendon structural changes, clinical characteristics and treatment outcomes in people with LE. The knowledge of these fundamental factors affecting the tendon structural changes following injury and treatment is crucial to understand and develop new and effective treatment strategies for overuse or degenerative tendon injuries.

A longitudinal randomised clinical trial is required to investigate US-observed structural changes over time and their relationship with clinical and sensory characteristics. Investigating the relationship between tendon structure, sensory and clinical outcomes over time in a randomised clinical trial will provide high-level evidence to determine their interrelationship over time.
Chapter 3 Methods

This chapter provides the overview of the general methodologies used for the purpose of Chapter 4, 5, 6 7 and 8. The chapter begins by elaborating on the study design, protocols of the randomised clinical trial, data acquisition, identification of study variables, statistical analyses. Finally, ultrasound (US) operator training undertaken for image acquisition and image analysis, development of US image rating scale, quantitative sensory data processing prior to the onset of the study are described in this chapter.
3 Methods

3.1 Study design

This dissertation was part of the randomised single-blinded clinical trial conducted in the community setting on the Gold Coast, Australia. The overall aim of this RCT was to investigate the short- and long-term clinical effectiveness, and cost-effectiveness, of prolotherapy injections, physiotherapy (PT), and prolotherapy injections+PT (Combined) in improving clinical characteristics, US-observed tendon abnormalities, and sensory system changes in people with LE.

3.2 Recruitment

Over a 20-month period (between November 2012 and June 2014) period, 120 participants with a clinical diagnosis of unilateral LE were recruited from the general community through media releases (Gold Coast, Queensland, Australia).

3.2.1 Inclusion criteria

The participants were included based on the following criteria

- Aged between 18 and 70 years.
- History of pain over the lateral humeral epicondyle for more than 6 weeks.
- Elbow pain aggravated by palpation, resisted wrist/finger extension.
- A minimum score of 20/100 on the Patient-Rated Tennis Elbow Evaluation (PRTEE).
3.2.2 Exclusion criteria

Participants were excluded based on the following criteria:

- History of previous treatment for lateral elbow pain by any healthcare practitioner in the previous 3 months.
- Current pregnancy or breastfeeding.
- Presence of peripheral nerve involvement or cervical radiculopathy.
- Systemic inflammatory disorders including diabetes, rheumatoid arthritis or bleeding disorders.
- Malignancy.
- Any other neck or arm pain preventing daily work or recreation that required treatment within the preceding 3 months.
- Evidence of other primary sources of lateral elbow pain including osteoarthritis.
- History of upper limb dislocations, fractures or tendon ruptures within the preceding 10 years.
- History of corticosteroid injection to the affected elbow within the preceding 3 months.
- History of any medical condition or surgery that affected the delivery of the study treatments
- Unresolved litigations.

3.3 Ethics approval

This RCT was approved by the Griffith University Human Research Ethics Committee (PES/11/12/HREC) and written informed consent was obtained from all participants prior to enrolment (Appendix 2), in accordance with the Declaration of Helsinki. This trial was registered with Australia and New Zealand (ACTRN12612000993897).
3.4 Randomisation

All eligible participants were randomised to one of the three treatment groups by concealed allocation using a computer-generated random numbers table with a block size of six. The randomisation schedule was developed and held by the Griffith University Clinical Trials Centre, an independent off-site body. Information on allocation sequence was kept concealed from all study personnel involved in the treatment and assessment of participants. The randomisation schedule and appointments for treatments were managed by a trained research assistant who was not involved in data collection or analysis.

3.5 Blinding

Two blinded investigators not involved in the treatment screened the volunteers and collected the demographic data and all outcome measures at baseline, 6, 12, 26 and 52 weeks. US image data for each participant were collected by a single investigator over the course of the study (Figure 3.1). The primary endpoint was 52 weeks. Another blinded investigator (VJ) who was unaware of group allocation assessed the US images for tendon structural changes at baseline, 6, 12, 26 and 52 weeks (Figure 3.1).

3.6 Sample size

A sample of 105 participants, with 35 participants per group was initially estimated to determine a 13-points improvement in PRTEE ($\alpha=0.05$) (Poltawski et al., 2011) and to identify 20% difference between groups in the number of participants reporting “much better” or “completely recovered on the participant global impression of change (GIC) scale; assuming a success rate of 43% in the Combined group and a 23% rate in the physiotherapy group. However, after adjusting for conservative loss to follow up or drop-
out-rate of 10% and to achieve 80% power, a sample of 120 participants (40 participants per group) was required (Bisset et al., 2006).

3.7 Interventions

3.7.1 Prolotherapy injections

Participants assigned to the prolotherapy injections group received four injections of a solution made from 20% glucose and 0.4% lignocaine. The injections were delivered to the common extensor tendon as described by the protocol of Rabago et al. (2011). Injections were provided by two general medical practitioners of 15 years’ experience in prolotherapy injections treatment over the lateral epicondyle, supracondylar ridge, the radial head, the common extensor tendon and the lateral collateral and annular ligament. These areas were pre-identified as the injection sites by the tenderness to palpation method. Injections were provided at baseline, 6, 8 and 12 and 56 weeks.

3.7.2 Manual therapy/Exercise (PT)

Participants randomised to the PT group received four, 30-minute treatment sessions (one per week) of a standardised protocol described by Bisset et al. (Bisset et al., 2006, Coombes et al. 2013). The treatment sessions included education, manual therapy and therapeutic exercises as well as a home exercise program. Manual therapy techniques included MWM to the lateral elbow joint. The exercise program included (i) sensorimotor training for gripping and forearm movements and posture correction, (ii) progressive resistance exercises for wrist exercises for strength deficits, (iii) general arm strengthening exercises. Follow-up exercises were progressed upon the ability of the individual to avoid delayed onset muscle soreness and to facilitate optimal volume and loading of the tendon. Exercises diaries were maintained by the treating physiotherapists to monitor the progress and to enhance treatment adherence.
3.7.3 Prolotherapy injections+PT (Combined)

Participants in the Combined group received combined treatment protocol of prolotherapy injections and physiotherapy treatments as described above.
Fig 3.1 Flow diagram of participants through the study.
3.8 Study outcome measures

3.8.1 Clinical outcome measures

i. PRTEE was used to document pain and disability. PRTEE is a validated tool that quantifies self-reported pain and functional disability. The PRTEE is a 15-item questionnaire which evaluates pain (5 items) and functional disability domains (10 items) in LE using an 11-point Likert scale for each question, giving a total score ranging from 0-100. The PRTEE has excellent test-retest reliability (ICC = 0.93), and sensitivity (Rompe et al., 2007b). A change of 30-35% (8 to 12 points) of the baseline score following treatment is considered as a minimum clinically important difference (MCID) (Poltawski et al., 2011).

ii. Pain intensity at rest and the worst pain experienced in the preceding week was documented using a 100 mm visual analogue scale (VAS: 0 = no pain, 100 = worst pain imaginable). The VAS has a high test-retest reliability (r = 0.89) in the LE population and moderate correlation with pain-free grip (r = 0.47) (Sran et al., 2002). An individual with LE who reports a decrease in pain, following treatment, of 30 mm using a 100 mm scale is considered to have achieved a clinically important response (Lee et al, 2003). This MCID value is specific to VAS scores based on 0-100 mm scale and not 0-10 numeric rating scale (NRS) (Katz et al., 2015; Farrar et al., 2001).

iii. Pain-free grip (PFG) strength is well established as a highly reliable (ICC > 0.97) measure of motor impairment in LE. A Digital Analyser grip dynamometer (MIE Ltd, Leeds UK) was used to quantify PFG on the affected and unaffected sides. With the participant in a relaxed supine lying, the test arm was placed in elbow extension and pronation. Participants were instructed to gradually squeeze the dynamometer and to stop when the first sensation of pain was perceived. The PFG
in Newton (N) was measured at this point on the unaffected side first and repeated on the affected side. The measurement process was repeated three times with a 30-second rest interval, and the average of the three measures was recorded as PFG (Smidt et al., 2002; Stratford et al., 1989). Although no specific MCID values for PFG in LE available in the current literature, one study reported that a change of 19.5% from the baseline values can be considered as an MCID for PFG (Kim et al., 2014).

iv. The participant's perceived global improvement in their condition (GIC) is commonly measured using a 6-point Likert scale with response categories ranging from completely recovered, to much improved, improved, no change, worse and much worse (Bisset et al., 2006; Smidt et al., 2002; Coombes et al., 2009). Participants’ GIC were documented at 6, 12, 26 and 52 weeks. GIC is commonly used as the reference method for calculating the corresponding MCID values for continuous outcomes (e.g., PRTEE). A significant correlation between GIC and change scores in outcomes of interest (e.g., PRTEE) is essential to estimate MCID for the outcome measure of interest. (Poltawski et al., 2011). It is known that GIC and reduction in pain intensity are highly correlated (Farrar et al., 2000). In addition, a dichotomised measure of success was calculated using the GIC, with participants rating themselves as either completely recovered or much improved, deemed a ‘success’ (Bisset et al., 2006; Coombes et al., 2010).

v. Quality of life was assessed using the reliable (ICC = 0.87) EuroQol-5D (EQ-5D) (Rabin et al., 2001). EQ-5D is a standardised and validated (r =0.7) measure of the quality of life during a disease process and following an intervention. It consists of five dimensions of mobility, self-care, usual activities, and pain/discomfort (Marti et al., 2016). A change score of 0.05 for EQ-5D has been considered the MCID for
rheumatoid arthritis (Marra et al., 2005), however specific MCID values for EQ-5D usage in LE is not available in the current literature.

vi. In addition to the clinical measures, participant characteristics including age, gender, duration of the condition, smoking history, working status, type of work (manual or non-manual) and hand dominance were also documented.

3.8.2 US imaging of common extensor tendon abnormalities

US examination of the affected and unaffected elbows was performed by an experienced musculoskeletal US trained operator using SonixTouch (Ultrasonix, Richmond, BC, Canada) at baseline and 6, 12, 26 and 52 weeks (Figure 3.2). US is considered as the effective, reliable way for assessment of tendon abnormalities. It has a comparable accuracy as MRI in visualising the internal structures of the tendon (du Toit et al., 2008). US scanning was performed using a linear array transducer (7.5MHz) integrated and gain settings were fixed throughout all measurements at 50%. US appearance of the tendon with clear and homogenous hyperechoic and well defined hyperechoic appearance of the epitendon was determined as normal (Bianchi et al., 2016; Fornage et al., 1987; Griffith et al., 2015; Martinoli et al., 2002). The participants were instructed to be in a seated position with their elbow resting on a table at 90 degrees of flexion and their palms facing towards the table surface (pronated wrist position). Longitudinal still images were recorded in this position at the relative anterior, central and posterior regions of the common lateral extensor tendon using the head of the radius and contouring of the lateral epicondyle as anatomical reference guides (Radiology, 2018). A transverse still image was recorded at the thickest area of the LE tendon.
3.8.3 Ultrasound training

Evaluation of the tendon structure with the conventional US was the primary outcome measure in 3 studies of my thesis. Relevant US operator training was required for subjective and objective evaluation of tendon abnormalities as US is considered as highly operator dependent skills. Therefore, the primary investigator underwent US training over a 6-month period under the supervision of a senior radiologist at Gold Coast and Robina hospitals and a consultant ultrasonographer, Gold Coast, Australia. The various forms of training undertaken to improve the investigator skills include:

i. Self-directed learning of basic musculoskeletal US imaging principles and techniques using recommended texts (Bianchi et al., 2016; Griffith et al., 2015) and online education resources found on the website (Radiology, 2018) for European Society of Musculoskeletal Radiology (ESSR).

ii. One to one training to gain practical experience in scanning at the elbow, patient positioning, US transducer alignment, adjusting the US setting to optimise image resolution to detect blood flow, capture and save images and identification of tendon abnormalities in longitudinal and transverse scans of various cases of LE.
iii. Independent scanning of tendon structure in normal elbows of the volunteers from our department.

3.9 Inter- and intra-rater reliability for grading tendon abnormalities in LE

After US imaging acquisition and US training, the following study aims were established in order to develop a standardised tool to assess tendon structural abnormalities in LE.

I. To identify various tendon structural abnormalities seen on greyscale and Doppler US on the basis of literature findings and consensus from Dr Craig Buchan, Radiologist concerning the different abnormalities.

II. To develop a reliable US image rating scale to evaluate individual tendon abnormalities in LE.

III. To construct relevant US composite score for grade tendon abnormalities.

IV. To develop a valid and reliable method to quantify tendon thickness.

Therefore, appropriate literature was systematically searched and reviewed (Clarke et al., 2010; Connell et al., 2001; Krogh et al., 2013; Levin et al., 2005). We identified the following commonly reported tendon abnormalities to be included into the US image rating scale.

3.9.1 Summary of literature review findings

1) Greyscale US and Doppler US imaging are commonly used to identify tendon abnormalities including tendon hypoechogenicity, heterogeneity, tendon tears, tendon calcification, bony abnormalities and LCL abnormalities (Dones et al., 2014; du Toit et al., 2008; Heales et al., 2014; Jacobson et al., 2014; Krogh et al., 2013; Mc Auliffe et al., 2017; Poltawski et al., 2012).
2) Tendon hypoechogenicity in the presence of neovascularity is recognised as the significant predictor of pain (Cook et al., 1998; Heales et al., 2014; Jaen-Diaz et al., 2010; Malliaras et al., 2011; Malliaras et al., 2010). A 4-point ordinal rating scale is commonly used to grade both hypoechogenicity and neovascularity (Chourasia et al., 2013; Poltawski et al., 2012; Seng et al., 2016).

3) Neovascularity is commonly implicated in the onset of tendinopathy (Archambault et al., 1995).

4) Increased tendon thickness, bony abnormalities and calcification were usually detected in the affected elbows of individuals with LE (Jaen-Diaz et al., 2010; Krogh et al., 2013a; Teggeler et al., 2015).

5) The size of large intratendinous tear and presence of LCL abnormalities were identified as indicators of poor prognosis in LE (Clarke et al., 2010).

After identifying the specific tendon abnormalities based on the literature review and inputs from the radiologist, we constructed a 3 tier, global US image rating scale for LE (Appendix 10). The global ultrasound image rating scale comprised of both ordinal and dichotomous scales to assess tendon abnormalities including tendon hypoechogenicity, neovascularity, heterogeneity, tendon tears, calcification and bony irregularities. The 4-point ordinal (0-3) scales for assessing the severity levels of hypoechogenicity, neovascularity and heterogeneity were adapted from published studies (Poltawski et al., 2012; Seng et al., 2016). The dichotomous scale assessed the presence of hypoechogenicity, heterogeneity, neovascularity, calcifications, bony abnormalities Measurement of tendon thickness (mm) and size of the tendon tears (mm) on longitudinal and transverse scans were included as the quantitative components of the global US image rating scale. However, further investigation was necessitated to evaluate the US
examiners’ reliability in scoring the tendon abnormalities using the proposed 3-tier US image rating scale.

3.10 Intra- and inter-rater reliability of US image evaluation for grading common extensor tendon structural changes associated with LE: comparison between physiotherapists and a musculoskeletal radiologist

3.10.1 Background

Ultrasound (US) imaging is commonly used to visualise the internal structures of the tendon, confirm the diagnosis and monitor structural changes over time associated with tendinopathy (Clarke et al., 2010; Connell et al., 2001; Levin et al., 2005; Scott et al., 2013). For example, tendon pathological features such as thickening, focal hypoechoic, diffuse heterogeneous areas, partial intratendinous tears, calcification and enthesis irregularities can be identified using US imaging (Levin et al., 2005). However, previous research evidence from cross-sectional studies reported that pathological features identified using US imaging do not correlate well with clinical symptoms (Coombes et al., 2015; Scott et al., 2013). However, tracking changes in pathological features over time using US imaging may be helpful in understanding the local tissue response to treatments such as exercise, where the mechanism of loading is thought to influence tendon structural characteristics (Cook et al., 2012; Cook et al., 2009). US imaging is now increasingly used as a tool by non-radiologist clinicians such as physiotherapists’ in their clinical practice as well in research studies to characterise tendon pathology and monitor treatment effects over time (Potter et al., 2012).

The reliable use of US is often operator dependent and largely appears to correlate with the skill and experience of the operator (Bianchi, 2016). However, emerging evidence
suggests that non-experienced imager such as physiotherapists can use conventional greyscale (B-mode) US imaging to assess morphometric changes of muscles and tendons and also to make a conclusion based on the imaging findings (Ingwersen et al., 2016; Poltawski et al., 2012; Teggeler et al., 2015; Whittaker, 2006; Whittaker et al., 2007). While there is strong supportive evidence for physical therapist’s reliability in measuring thickness and cross-sectional areas of muscles, bladder (Whittaker et al., 2009) and peripheral vascular assessments (MacKinnon et al., 1983) using imaging (US and MRI) methods (Herrington et al., 2002). However, currently, there is limited evidence on the reliability of physiotherapists in the quantitative and qualitative evaluation of tendon abnormalities in LE.

Only two studies have previously reported the reliability of physical therapist’s reliability in grading tendon abnormalities using a subjective rating scale score (Poltawski et al., 2012) and quantitative measures of tendon thickness (Teggeler et al., 2015) respectively in LE. However, the reliability of identifying lateral collateral ligaments (LCL) and measuring tendon tear size was not reported in previous studies. It has been recommended that a combination of qualitative and quantitative evaluation of the tendon abnormalities will improve the diagnostic accuracy of US in LE (Toprak et al., 2012). To our knowledge, no previous studies have reported the inter-rater reliability between physiotherapists and musculoskeletal radiologists in evaluating US images for grading CET pathology using a combined quantitative and qualitative US image rating scale. Therefore the purpose of this study is to assess the intra- and inter-rater reliability in the grading tendon structural abnormalities using a 3-tier semi-quantitative US image grading system in people with tennis elbow.
3.10.2 Methods

An intra- and inter-rater reliability study design was utilised. Three raters (A, B and C), including one experienced (>8 years of experience) musculoskeletal radiologist (rater A) and two physiotherapists (raters B and C) independently assessed greyscale power Doppler images and cine-clips of participants (n= 20) that participated in the randomised clinical trial (RCT) for tennis elbow. Each rater quantified the severity of CET pathology using the 3-tier semi-quantitative US image rating scale (Appendix 10). Tier 1 comprised of qualitative evaluation of eight CET structural changes (tendon thickening, tears, eco-intensity, heterogeneity, neovascularity, calcification, enthesis and LCL irregularities). Tier 2 included the quantitative measurement (mm) of tendon thickness (longitudinal and transverse tendon thickness; LTT and TTT) and tear size (longitudinal and transverse tear size; LTS and TTS) on the recorded longitudinal and transverse US images. Tier 3 is a six-point ordinal scale for evaluating global tendon pathology of CET (Appendix 10). All the rating scores were aggregated to present global rating score of structural abnormality, on which all the raters have provided consensus prior to the study.

3.10.3 Raters and training

Three raters including, one musculoskeletal (MSK) radiologist (rater A) with 10 years’ clinical experience in MSK US, two physiotherapists (raters B and C) trained in acquiring and analysing US images of the common extensor tendon participated in the present study. Raters B and C (physiotherapist) were postgraduate (PhD in physiotherapy) students in our department. Rater B (NM) gained imaging experience specific to tendon abnormalities of LE, by working jointly with an experienced US operator in obtaining the US scans for the randomised clinical trial participants. Rater C (VJ) underwent US training over 6-months as described in the Methods chapter.
3.10.4 Participants

The present study utilised randomly selected lateral elbow image cases (n=20) from the US database pertaining to the RCT on LE. Ethics approval (PES/11/12/HREC) has been granted by Griffith University, Human Research and Ethics Committee. All the participants underwent US imaging of lateral elbows (healthy and affected) in a research laboratory at Griffith University, Gold Coast campus, Australia. The research adhered to the principles set forth in the Declaration of Helsinki.

3.10.5 Sample size calculation

The sample size for the present study was calculated using a method developed by Walter et al. (1998) where the sample size (k) is estimated based on the number of raters for each participant (n=3) and the required value of the intra-class correlation (ICC) coefficient (Walter et al., 1998). Thus, considering a minimum ICC of 0.4 for interrater reliability at a significance level of 0.05, we included 20 US image cases of elbows in this study.

3.10.6 Procedure

The acquired US images and cine-clips of CET were reviewed by OsiriX software version 7.0 on Mac OS computer (Rosset et al., 2004). OsiriX was equipped with an image processing tool that allowed raters to view the image dataset as presented. The study sample images cases were numbered and randomly assorted for all raters for reading purposes. The presence or absence of tendon structural abnormalities was confirmed by reviewing the longitudinal and transverse plane US images to avoid misinterpretation of US pitfalls and artefacts as structural abnormalities (Stevic et al., 2013). Consequently, randomly assorted longitudinal and transverse plane images of affected or unaffected lateral elbows from 20 random participants were presented to all raters by an investigator not involved in the rating procedure. The raters were unaware of the clinical status of the
elbows (i.e., US images) included in the study. Each rater used OsiriX software to perform their evaluation of CET on three separate occasions. Rater C (VJ) performed grading of tendon abnormalities on two separate occasions at least 2 weeks apart.

3.10.6.1 Image analysis

Qualitative and quantitative analysis of eight common structural abnormalities were performed using a 3-tier US image rating scale. The 3-tier rating scale used in our study is constructed upon on various rating scales reported in previous studies.

3.10.6.2 Qualitative evaluation of tendon abnormalities

Qualitative evaluation of static greyscale and Doppler images, cine-clips were performed by all raters. Raters were asked to independently identify and rate tendon thickening, intratendinous tears, eco-intensity, heterogeneity (fibrillar disruption), neovascularity, tendon calcification, enthesis and LCL abnormalities. The presence or absence of tendon thickening, tendon tears heterogeneity, calcification, entheses and LCL abnormalities were recorded using a “yes” (score=1) or “no” (score =0) categorical scale. In addition, a separate ordinal four-point (0-3) scale was used to identify and rate hypoechogenicity and neovascularity, where 0 = normal fibrillar pattern, 1 = < 30% of fibres affected, 2 = 30 to 50%, and 3 = > 50% fibres affected (Appendix 10).

3.10.6.3 Quantitative evaluation - tendon thickness measurement protocol

The longitudinal and transverse plane tendon thicknesses were quantified using a standardised measurement procedure recommended in the literature (Connell et al., 2001; Teggeler et al., 2015). Rater A manually measured longitudinal and transverse plane tendon thickness (in mm) of the tendon on US images using the length measurement tool of OsiriX V. 7.0 (MAC) (Rosset et al., 2004), while raters B and C used RadiAnt DICOM
Viewer software (Windows) V.3.4. 1 (Mediexant, Poznan, Poland) to measure LTT, TTT, LTS and TTS. LTT was quantified by measuring the perpendicular distance between the outer CET tendon surface and the bony edge of lateral epicondyle and using a 5 mm approximate distance from the mid-area of radiohumeral joint margin as the reference point (Fig 3.3 A) (Connell et al., 2001b; Teggeler et al., 2015). TTT was assessed by measuring the distance from a point on the humeral bone to the tendon surface (Fig.3.3 B). All measurements were performed independently by the three raters and the average of the measurement values was used for the statistical analysis.

![Image of US images showing LTT and TTT measurements](image)

**Figure 3.3. (A)** Lateral plane US image view demonstrating thickness measurement (mm) Of the common extensor tendon.**(B)** Transverse plane US view demonstrating (mm) Measurement of common extensor tendon from the top of humeral bone to the tendon surface.LE: lateral epicondyle, R: radius.

### 3.10.6.4 Measuring tendon tears

A partial intratendinous tear was defined as a focal hypoechoic defect within the substance of the tendon seen in both the longitudinal and transverse planes. A full-thickness tear was defined as a hypoechoic defect extending from the bursal to the articular surface planes (Connell et al., 2001; Levin et al., 2005). Most previous studies have agreed that
identification of partial tendon tears is difficult (Miller et al., 2002) and a definitive diagnosis of partial tears is heavily reliant on the experience level of the US operator (Cullen et al., 2007). Consequently, the experienced radiologist (rater A) was able to effectively identify and measure the size of intratendinous tears (mm) in longitudinal and transverse plane US images of each participant. However, considering the physiotherapist’s (rater B and C) inexperience and the reproducibility nature of the study, US images that were pre-identified by the MSK radiologist (rater A) were presented to the physiotherapists to perform tear size measurements. The numerical values of tears size measurement (mm) given by all the raters were used for statistical analysis.

3.10.6.5 Ultrasound Tennis Elbow Global Pathology Rating Scale (ULTEPRS)

ULTEPRS is a six-point descending (5-0) scoring system that assesses the different aspects of CET pathology by providing a rating score for the presence of various structural abnormalities on static greyscale US images. Each rating score correlates with the progressive nature (Continuum) of tendon pathology (i.e., mild, moderate and severe) observed on static US images. For example, a rating score of 5 indicates the presence of full-thickness intratendinous tear (severe) whereas rating scores from 1 to 4 suggest the presence of mild to moderate tendon pathological features such as diffuse heterogeneous fibrillar areas, mild hypoechoic areas (grade 1), large focal and well-defined hypoechogenicity (grade 3) RCL abnormalities and partial/incomplete intratendinous tear.

A rating score of zero indicates the normal fibrillar pattern of the tendon (Appendix 10).

The total US scale score was calculated as the sum of the qualitative evaluation (Tier 1) and ULTERPS (Tier 3) scores (Appendix 10) and ranged from 0 to a possible maximum of 16 (subjective rating score for the presence of tendon thickness confirmed on longitudinal and transverse images = 1; subjective rating score for the presence of intratendinous tear confirmed on longitudinal and transverse images = 1; presence of hypoechogenicity = 0-3;
presence of neovascularity = 0-3; presence of enthesis abnormalities = 1; presence of calcification present = 1; presence of RCL abnormalities = 1; ULTERPS = 0-5).

3.10.7 Statistical analysis

Raw agreement of the original estimates was assessed by calculating percentage agreement between the raters. However, percentage agreements do not take into account agreement that may have occurred due to chance. Therefore, intra- and inter-rater reliability was examined by intraclass correlations coefficients (ICC) (Krogh et al., 2013), Kendall’s coefficient of concordance (W) (Poltawski et al., 2012), generalised (Fleiss’ kappa; multiple raters) and Cohen kappa (k) (Landis et al., 1977). The standard error of measurement (SEM) and minimum detectable change (MDC) was computed from reliability measures to determine true changes in CET measurement scores (Poltawski et al., 2012).

In particular, the total US scale score for the 3-tier US image rating scale given by three raters were evaluated as continuous variables using ICC. We used ICC\(_{3,1}\) model (2-way mixed-effects, absolute agreement) model to determine the inter- and intra-rater reliability (absolute) for continuous scores of tendon thickness, intratendinous tear size and overall US image rating scale score. The standard error of measurement (SEM) and the minimum detectable change (MDC) was calculated for each of the US features using the ICC values obtained from intra-rater (test-retest) and inter-rater reliability study.

SEM was calculated using the formula (SEM = SD x √(1 – ICC)) and MDC at 95% is calculated using the value of f SEM is used to calculate MDC (Weir et al., 2005):

\[
MDC = 1.96 \times SEM \times \sqrt{2}
\] (Equation 1).
Generalised kappa (Fleiss kappa) and Kendall’s coefficient of concordance (W) were used to assess multiple-rater reliability for categorical scale estimates (heterogeneity, calcification, enthesis and LCL abnormalities) and ordinal scale scores (hypoechochogenicity, neovascularity and global pathology rating scale score). Common interpretation of multiple-rater reliability measured by Kendall’s W include: extremely strong agreement (0.71 to 9.0), strong agreement (0.51 to 0.70), moderate agreement (0.31 to 0.50), and weak agreement (0.11 to 0.30). In addition, pairwise (rater A vs rater B Vs rater C) and intra-rater (rater C) reliability analyses for categorical and ordinal scales were performed using Cohen kappa (k) and weighted Cohen kappa (K_w) coefficients with quadratic weights respectively. The strength of the inter-rater kappa agreement was interpreted according to the methods described by Landis and Koch. The agreement is considered slight (0.0 to 0.20), fair (0.2 to 0.4) moderate, (0.4–0.6), substantial (0.6 to–0.8), and almost perfect (0.81–1.00) based on the values of kappa coefficients (Landis et al., 1977).

3.10.8 Results

3.10.8.1 Clinical characteristics

Ultrasound images cases of 20 elbows from 14 participants with tennis elbow (mean age ± SD 56 ± 9.4 years) were assessed with qualitative and quantitative methods by three raters, of which, images cases of 4 participants (total 6 elbows) captured at multiple time points (follow-ups) of RCT trial were also included to sample image cases. Of these, 12 participants were right hand dominant and 85% of the sample participants were right side symptomatic. The results of the quantitative measurement of tendon thickness and tear size performed by all the raters are presented in Table 3.1. There was no significant difference between the raters for LTT and TTT. However, there was a significant difference between raters for LTS. A post hoc pairwise comparison with Tukey’s test
showed a significant difference between physiotherapist (raters B and C) for LTS. There was no significant difference between the radiologist and physiotherapists for LTS.

Table 3.1 Mean ± SD comparison between raters for tendon thickness and tear size

<table>
<thead>
<tr>
<th>US features</th>
<th>Rater A Mean ± SD</th>
<th>Rater B Mean ± SD</th>
<th>Rater C Mean ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTT (mm)</td>
<td>5.57±0.93</td>
<td>5.87±0.90</td>
<td>5.28±0.90</td>
<td>0.13</td>
</tr>
<tr>
<td>TTT (mm)</td>
<td>5.70±1.22</td>
<td>5.83±1.28</td>
<td>5.17±1.24</td>
<td>0.21</td>
</tr>
<tr>
<td>LTS (mm)</td>
<td>1.83±2.62</td>
<td>1.91±2.68</td>
<td>1.77±2.54</td>
<td>0.027*</td>
</tr>
<tr>
<td>TTS (mm)</td>
<td>1.3±2.03</td>
<td>1.17±1.97</td>
<td>1.25±2.98</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*significant P<0.05 (one-way ANOVA); LTT & TTT = longitudinal and transverse tendon thickness (mm); LTS & TTS = longitudinal and transverse tear size (mm).

Table 3.2 provides the results of the pairwise rater agreement analysis for the 3-tier US image rating scale features. For hypoechogenicity, a moderate inter-rater reliability (ICC = 0.4) and average percentage agreement (41%) observed was noted (Table 3.2). A substantial pairwise inter-rater reliability (ICC = 0.9) was recorded for hypervascularity and ordinal scores of USTERPS. However, there was poor pairwise inter-rater reliability and overall percentage agreement (56%) in detecting LCL abnormalities was noted mainly between raters A and B (Table 3.2). A perfect pairwise inter-rater reliability (ICC =1) and percentage agreement for heterogeneity (100%) were observed among all raters (Table 3.2).
Table 3.2 Pairwise inter-rater reliability: ICC and % inter-rater agreement on US scores

<table>
<thead>
<tr>
<th>US feature</th>
<th>Rater A vs Rater B</th>
<th>Rater B vs Rater C</th>
<th>Rater A vs Rater C</th>
<th>Average pairwise % agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total scale score</td>
<td>0.8^A (0.67-0.94)</td>
<td>0.8^A (0.66-0.95)</td>
<td>0.9^A (0.7-0.9)</td>
<td></td>
</tr>
<tr>
<td>Hypoechogenicity, 0-3</td>
<td>0.4^B (0.20-0.73)</td>
<td>0.6^B (0.40-0.91)</td>
<td>0.47^B (0.2-0.7)</td>
<td>41%</td>
</tr>
<tr>
<td>Hypervascularity, 0-3</td>
<td>0.9^B (0.90-1.00)</td>
<td>0.9^B (0.90-1.00)</td>
<td>1.00^B (1.0-1.0)</td>
<td>93%</td>
</tr>
<tr>
<td>USTERPS, 0-5</td>
<td>0.8^B (0.8-0.9)</td>
<td>0.8^B (0.80-1.00)</td>
<td>0.8^B (0.8-0.9)</td>
<td>63%</td>
</tr>
<tr>
<td>Heterogeneity, (yes/no)</td>
<td>1.00^C</td>
<td>1.00^C</td>
<td>1.00^C</td>
<td>100%</td>
</tr>
<tr>
<td>Calcification, (yes/no)</td>
<td>0.52^C</td>
<td>0.62^C</td>
<td>0.20^C</td>
<td>76%</td>
</tr>
<tr>
<td>Enthesis, (yes/no)</td>
<td>0.78^C</td>
<td>0.43^C</td>
<td>0.43^C</td>
<td>80%</td>
</tr>
<tr>
<td>LCL abnormalities, (yes/no)</td>
<td>0.15^C</td>
<td>0.11^C</td>
<td>0.48^C</td>
<td>56%</td>
</tr>
</tbody>
</table>

^A= ICC (95% CI); ^B = Weighted Cohen kappa coefficient (95% CI); ^C= Cohen kappa coefficient (95% CI); ^t indicates not applicable; USTERPS= ultrasound tennis elbow pathology rating scale score; LCL = lateral collateral ligament tear/abnormalities.

3.10.8.2 Inter-rater reliability

Table 3.3 presents the inter-rater reliability for the US scores given by all three raters. There was excellent (ICC > 0.9) inter-rater reliability for overall US scale scores, tendon thickness (LTT and TTT), tear size (LTS and TTS) and USTERPS. A moderate (0.4 to 0.5) inter-rater agreement was in identifying calcification and entheses abnormalities on US images were observed. In contrast, a poor inter-rater agreement was observed for LCL abnormalities (K= 0.06). Kappa coefficients were not calculated for heterogeneity as 100% agreement was found among all raters.
Table 3.3 Inter-rater reliability in scoring and measuring tendon abnormalities

<table>
<thead>
<tr>
<th>Feature</th>
<th>ICC (95% CI)</th>
<th>MDC</th>
<th>SEM</th>
<th>Cohen K</th>
<th>Weighted Cohen K (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall US scale score</td>
<td>0.97 (0.92 to 0.98)</td>
<td>2.91</td>
<td>8.06</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td>LTT (mm)</td>
<td>0.94 (0.8 to 0.97)</td>
<td>0.61</td>
<td>t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTT (mm)</td>
<td>0.95 (0.90-0.98)</td>
<td>0.76</td>
<td>2.12</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td>LTS (mm)</td>
<td>0.96 (0.93-0.98)</td>
<td>0.49</td>
<td>1.37</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td>TTS (mm)</td>
<td>0.96 (0.93-0.98)</td>
<td>1.02</td>
<td>2.83</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td>Hypoechochogenicity</td>
<td>0.80 (0.55-0.90)</td>
<td>t</td>
<td>t</td>
<td>0.72</td>
<td>t</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>0.99 (0.98-0.99)</td>
<td>t</td>
<td>t</td>
<td>0.99</td>
<td>-</td>
</tr>
<tr>
<td>Calcification</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>*</td>
<td>0.44 (0.191-0.69)</td>
</tr>
<tr>
<td>Enthesis abnormalities</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>*</td>
<td>0.55 (0.29 - 0.80)</td>
</tr>
<tr>
<td>LCL abnormalities</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>*</td>
<td>0.06 (-0.18-0.32)</td>
</tr>
<tr>
<td>USTERPS, 0-5</td>
<td>0.96 (0.93-0.98)</td>
<td>t</td>
<td>t</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*indicates not applicable for ICC or Cohen K. Dash (-) indicates kappa cannot be calculated (heterogeneity had 100% agreement among all raters; LTT & TTT = longitudinal and transverse tendon thickness (mm); LTS & TTS= longitudinal and transverse tear size (mm), MDC = minimum detectable change, USTERPS= ultrasound tennis elbow pathology rating scale; LCL = lateral collateral ligament tear/abnormalities.

3.10.8.3 Intra-rater reliability

Table 3.4 provides the intra-rater reliability data. There was excellent intra-rater reliability (ICC> 0.97), noted for overall scale scores tendon thickness (LTT & TT) tear size and ULTERPS. For enthesis abnormalities, moderate to substantial agreement was indicated for enthesis (k= 0.43), LCL (k=0.60) and calcification (k= 0.80). The SEM values for LTT and TTT ranged from 0.10 to 0.18 mm and the corresponding MDC values were 0.29 to 0.50 mm. For tendon tear size (LTS and TTS), the SEM values ranged from 0.27 to 0.29 mm with corresponding MDC value ranged from 0.77 to 0.82 mm (Table 3.4).
**Table 3.4** Intra-rater reliability in US evaluation of tendon abnormalities

<table>
<thead>
<tr>
<th>Feature</th>
<th>ICC (95% CI)</th>
<th>MDC</th>
<th>SEM</th>
<th>Cohen K (95% CI)</th>
<th>Weighted Cohen K (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall scale score</td>
<td>0.95(0.92-0.98)</td>
<td>3.62</td>
<td>1.30</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>LTT (mm)</td>
<td>0.94 (0.80-0.97)</td>
<td>0.29</td>
<td>0.10</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>TTT (mm)</td>
<td>0.95 (0.90-0.98)</td>
<td>0.50</td>
<td>0.18</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>LTS (mm)</td>
<td>0.96 (0.93-0.98)</td>
<td>0.82</td>
<td>0.29</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>TTS (mm)</td>
<td>0.96 (0.93-0.98)</td>
<td>0.77</td>
<td>0.27</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Hypoechochogenicity</td>
<td>T</td>
<td>t</td>
<td>t</td>
<td></td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>Neovascularity</td>
<td>T</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>1.00 (1.0-1.0)</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>T</td>
<td>t</td>
<td>t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcification</td>
<td>T</td>
<td>t</td>
<td>t</td>
<td>0.8 (0.63-1.0)</td>
<td>t</td>
</tr>
<tr>
<td>Enthesis abnormalities</td>
<td>T</td>
<td>t</td>
<td>t</td>
<td>0.4 (0.01-0.8)</td>
<td>t</td>
</tr>
<tr>
<td>LCL abnormalities</td>
<td>T</td>
<td>t</td>
<td>t</td>
<td>0.6 (0.1-1.0)</td>
<td>t</td>
</tr>
<tr>
<td>USTERPS</td>
<td>T</td>
<td>t</td>
<td>t</td>
<td></td>
<td>0.9 (0.9-1.0)</td>
</tr>
</tbody>
</table>

*T* indicates not applicable; Dash (-) indicates kappa cannot be calculated (heterogeneity had 100% agreement among all raters); MDC = minimum detectable change; USTERPS= ultrasound tennis elbow pathology rating scale score; LCL = lateral collateral ligament; LTT and TTT = longitudinal and transverse tendon thickness (mm); LTS & TTS= longitudinal and transverse tear size (mm); LCL = lateral collateral ligament tear/abnormalities

### 3.10.9 Discussion

The main aim of the current study is to investigate the inter-rater reliability of quantitative and qualitative evaluation of tennis elbow pathology using a 3-tier image rating scale. This is the first study that investigated individual and combined US indicators of tennis elbow pathology with additional levels of rating scales implemented. We noted that the inter-rater reliability estimates (Kendall’s w = 0.72) for hypoechochogenicity was consistent with a previous study (Poltawski et al., 2012). However, the overall inter-rater reliability indices for heterogeneity (i.e., fibrillar disruption), hypervascularity and enthesis abnormalities
obtained in the present study were greater than the values reported in previous studies (Krogh et al., 2013; Poltawski et al., 2012). The mean lateral and transverse plane tendon thickness (5.57 mm ±0.29; 5.56 mm ±0.34) of CET obtained from the quantitative evaluation of three raters are consistent with previous studies (Jaen-Diaz et al., 2010; Krogh et al., 2013; Teggeler et al., 2015; Toprak et al., 2012; Ustuner et al., 2013).

The MDC obtained for the total US scale score using the ICC values of inter-rater and intra-rater reliability procedure ranged from 2.9/16 (18%) (Table 3.3) to 3.6/16 (22.5%) (Table 3.4). Poltawski et al. (2011) determined an MDC of 2.0/12 (16%) for the aggregate US greyscale total score which is comparable to our study findings (MDC =18%). The MDC values obtained for the total US scale score is the smallest change in total US scale score which can be attributed to true change rather than measurement error alone (Stratford et al., 1996; Poltawski et al., 2011). Furthermore, the MDC values for overall tendon thickness from our study (ranged 0.29 to 0.50 mm) was comparable (0.39 to 0.50 mm) to Krogh et al. (2013) (Krogh et al., 2013). However, Teggeler et al. (2015) reported greater MDC values (0.50 to 0.78, mm) for overall tendon thickness compared to the MDC values from our study (0.29 to 0.50 mm). The higher MDC values for tendon thickness reported by Teggeler et al. (2015) suggest that their study participants demonstrated greater tendon thickness values compared to our study in their study cohort possibly due to differences in anthropometric profiles of the participants. Information regarding the MCID values of the total US scale score would help the clinicians and researchers to establish whether a particular treatment is beneficial or not. However, there are no known MCID values for US image rating scales in LE as considerable variability in US scoring method prevails currently in the literature.
We found that intra – and inter-rater reliability was excellent when measuring both lateral and transverse plane tendon thickness. Although results suggest that inter-rater reliability is excellent for tear size, the results need to be interpreted with caution as the physiotherapist assessed the tear size based on images classified by the radiologist as having tears. Notwithstanding this, our study findings suggest that relevant training in imaging and interpretation of the region of interest can improve the reliability indices of inexperienced US examiners such as non-radiologists.

Our results suggest that identifying the presence of calcification and LCL abnormalities in recorded US images were noted to be less reliable for physiotherapists compared to the experienced radiologist. We found inferior multiple-rater and pairwise kappa agreement (simple and weighted k-values) estimates for calcification and LCL abnormalities between raters B and C (i.e., physiotherapists). Further, the inter-rater kappa agreement values for calcification ($K = 0.44$) were comparatively lower than the values reported in previous studies (Krogh et al., 2013; Poltawski et al., 2012). Agreement scores for identifying the LCL abnormalities between physiotherapists (i.e., raters B and C) were found to lower compared to an agreement between radiologists and physiotherapists (i.e., raters A and B). These findings reflect the relative inexperience of physiotherapists (raters B and C) in grading the tendon abnormalities such as LCL abnormalities which may require greater hands-on experience with interpretation of US described musculoskeletal injuries.

While the strength of the study included blinding of the raters to the clinical status of the US image cases of elbows (i.e., symptomatic or non-symptomatic) and use of standardised US evaluation protocol, but the study was not without limitations. Firstly, only three raters participated in the study. Secondly, both quantitative and qualitative evaluations were performed on recorded images rather during live scanning of the elbow region. Finally, we
included tendon abnormalities such as intratendinous tears and LCL abnormalities that were not reported in any previous studies that investigated physical therapist’s reliability in the evaluation of tendon abnormalities US-based scoring (Krogh et al., 2013; Poltawski et al., 2012; Teggeler et al., 2015; Ustuner et al., 2013).

3.11 Summary of findings

i. First studies to implement a 3-tier semi-quantitative US image rating system to assess the tendon structural changes in LE.

ii. Inferior inter-rater reliability for the tendon abnormalities such as tendon tears, LCL and calcification.

iii. Superior ICC values for the overall image rating scale score obtained in the study indicated that non-radiologists such as physiotherapists with relevant training can perform a quantitative and qualitative evaluation of structural changes of CET.

3.11.1 Modification of total ultrasound image rating scale

In consideration of the findings of poor inter-rater reliability (ICC) estimates for assessing intratendinous tears, calcification and LCL abnormalities from the pilot study, the study aimed to develop a modified total US image rate scale (Appendix 11) and scoring method to corroborate all the currently described tendon structural abnormalities and after excluding the components (intratendinous tears, calcification and LCL) which yielded poor inter-reliability scores. Therefore, a composite US image rating scale was constructed excluding the criteria which were found to not be reliable to measure.

3.11.2 Total Ultrasound Image Scale Score (TUSS)

Based on the study finding, we developed a modified total US image rating scale (TUSS) to assess the four commonly reported US abnormalities including focal hypoechogenicity,
diffuse heterogeneous echotexture, neovascularity and insertion bony abnormalities (enthesis abnormalities). Among the four abnormalities, tendon hypoechochogenicity and neovascularity were graded as none, mild, moderate or severe (scored 0 to 3 respectively). In the event of a significantly uneven distribution of US grades for hypoechochogenicity and neovascularity, the 4-point scales were each dichotomised into a 2-point scale and used in the sub-grouping analyses. That is, hypoechochogenicity grades 0 to 2 were subgrouped into a ‘mild’ category with grade 2 labelled as a ‘severe’ category, and neovascularity grade 0 was labelled as an ‘absent’ category and grades 1 to 3 were labelled as ‘present’. The absence or presence (score 0 and 1 respectively) of diffuse heterogeneous areas and bony abnormalities were scored dichotomously. The sum of all features (excluding the dichotomised hypoechoic and hypervascular scores) gave a total US scale score (TUSS, maximal score = 8; Table 1) (Connell et al., 2001; du Toit et al., 2008; Heales et al., 2014; Ingwersen et al., 2016; Krogh et al., 2013).

3.11.3 Rater-agreement procedure

Following the development of the modified TUSS, rater-agreement exercises were carried out between the experienced ultrasonographer and the primary investigator during the training period. However, we did not perform another round of inter- and intra-rater reliability procedure for the modified TUSS scale as satisfactory to excellent inter-reliability was already established for criterion tendon abnormalities featured in the modified TUSS scale including, hypoechochogenicity, neovascularity, heterogeneity, bony abnormalities and tendon thickening. The MDC and MCID values for the modified TUSS was not estimated as there was no inter-rater or intra-rater reliability data for the modified TUSS scale.
Although the exclusion of tendon abnormalities such as tendon tears, RCL abnormalities and calcification from the modified TUSS is purely based on the poor reliability coefficients, an alternative approach or options such as inclusion of additional raters, substantial follow-up training with the experienced radiologist in scoring these tendon abnormalities followed with another round of inter-rater reliability procedure might have been useful to retain these abnormalities in the modified TUSS scale. However, the alternative option or approach was not available for us as the radiologist who assisted in our study withdrew from participating in the follow-up inter-rater reliability procedure due to work commitments. Therefore, for the purpose of the remaining studies, the modified TUSS scale in its present form (Appendix 11) was used to score tendon abnormalities on all recorded US images. Also, the good to excellent level of agreement between the ultrasonographer and the assessor in using the modified TUSS scale during the rater-agreement exercises was also useful in increasing the assessor’s confidence in using the modified TUSS scale.

3.12 Quantitative sensory testing

Quantitative sensory testing (QST) is a suite of non-invasive psychophysical tests used to investigate hyper-function of small diameter sensory fibres and hypo-function of large diameter sensory fibres (Zaslansky et al., 1998). Rolke et al. (2006) first published a series of papers which proposed the QST battery to assess somatosensory function in people with neuropathic pain (Rolke et al., 2006). A standardised QST protocol involving 13 different mechanical and thermal stimuli has been proposed by the German Research Network on Neuropathic pain (DFNS) (Rolke et al., 2006). The principles of QST measurement involve the determination of thresholds or stimulus-response curves for sensory processing under normal and pathological conditions (Yarnitsky et al., 2006; Zaslansky et al., 1998).
Evidence suggests that QST is useful in objectively measuring central pain processing and can quantify sensory dysfunction in pain pathways of the central nervous system. Musculoskeletal conditions may be complicated by the presence of sensory system changes which can be investigated using QST (Pavlokovic et al., 2010). In particular, QST is useful in the analysis of the pathogenesis, classification, differential diagnosis and prognosis of the chronic musculoskeletal pain. QST is reported to be useful in evaluating impairments of the sensory system in several musculoskeletal conditions such as whiplash injury, repetitive strain injury and knee osteoarthritis (Lautenbacher et al., 2005; Rolke et al., 2006). There is some evidence to suggest that altered nociceptive pain processing in the central nervous system may produce multisensory impairments in LE (Leffler et al., 2000; Nijs et al., 2016; Pavlaković et al., 2010; Rio et al., 2014), including reduced pressure, cold, and heat pain thresholds, and reduced vibration detection threshold (Coombes et al., 2012, 2014; Fernandez-Carnero et al., 2009; Ruiz-Ruiz et al., 2011; Slater et al., 2005; Wright et al., 1994; Zaslansky et al., 1998).

3.12.1 QST measurement protocol

The last 66 participants recruited into the RCT underwent QST for both affected and unaffected limbs at baseline and 6-months following interventions. Standardised QST was performed in a quiet department laboratory by a trained investigator who was blind to the participant’s group status (NM). The following sensory measures were recorded: pressure pain threshold (PPT), cold pain threshold (CPT), heat pain threshold (HPT) and vibration-detection threshold (VDT) (Pavlaković et al., 2010; Zaslansky et al., 1998).

3.12.2 Pressure Pain Threshold

PPT over the common extensor tendon of the elbow was measured using a digital pressure algometer (Somedic AB, Fasrsta, Sweden; Figure 3.4 (A)). All participants were tested in
supine lying, and the mechanical pressure was applied via a probe (area of 1 cm²) perpendicular to the skin at a constant rate of 40kPa/sec until the participant reported the first sensation of pain. PPT was defined as the amount of pressure (kPa) required for the first onset of pain, and the average of three consecutive PPT measurements was then used for further analyses. The intra-tester reliability for PPT using this digital algometer is ICC > 0.7, and a standard error of measurement of 7.08 kPa, for both healthy individuals and patient populations (Vicenzino et al., 2001; Coombes et al., 2013). The threshold value of 1.15kg/cm² (112.7 kPa) is considered as the minimum clinically important difference (MCID) for PPT (Calvo Lobo et al., 2017).

3.12.3 Thermal pain (Heat and Cold) thresholds

Thermal (Heat and Cold) pain thresholds (HPT, CPT) were tested using the Thermosensory Analyser (TSA-II, Medoc, Ramat-Yishai, Israel). Heat and cold stimuli were provided at a constant rate of 1°C/sec from a baseline temperature (32°C) via a Peltier 30 x 30 mm thermode to the skin over the lateral elbow (Figure 3.4 (B)). CPT and HPT were recorded as the minimum temperature (°C) used to evoke cold or heat pain perception using the method of limits. The average value of the three trials was then used for further analyses. High inter-rater reliability has been reported for both HPT (ICC 0.87) and CPT (ICC 0.89) (Paungmali et al., 2012).
3.12.4 Vibration Detection Threshold (VDT)

VDT of the distal phalanx of the middle finger was measured with the participant seated, using a vibrometer, which was attached to the TSA-II (VSA 3000, Medoc, Ramat-Yishai, Israel). VDT (µm) was recorded as the perception threshold where the participant first perceived the vibration. Five measures of VDT were averaged and used in further analyses. VDT has high test-retest reliability (ICC 0.86) (Felix et al., 2009).

3.12.5 Technical implications

Considerable attention to detail and focus from the participant is required during testing, as sensory perception may be altered by small changes to the testing procedure (Zaslansky et al., 1998). For example, a lack of attention from the participant during the pain threshold tests may result in an invalid response (Nothnagel et al., 2017). Evidence suggests that QST is prone to bias related to the attention, motivation, and cognitive processing ability of participants (Zaslanksy et al., 1998). A familiarisation procedure is
recommended, whereby the participant is orientated to the test stimuli in a non-painful range and on another body area, prior to the baseline measurement, to reduce anxiety levels in participants associated with the QST procedures (Cathcart et al., 2006).

### 3.12.6 QST findings in LE

Wright and colleagues first identified widespread changes in sensory/pain perception in people with unilateral LE, providing evidence for the presence of secondary hyperalgesia in this population (Wright et al., 1994). Later studies have provided further evidence of local and widespread sensory abnormalities in chronic LE, including bilateral cold pain hyperalgesia, unilateral heat pain hyperalgesia and vibration stimulus detection abnormalities (Leffler et al., 2000; Carnero et al., 2009; Lim et al., 2012; Coombes et al., 2012, 2015). Furthermore, Coombes and colleagues performed a post hoc analysis of randomised clinical trial data and reported that the presence of bilateral cold hyperalgesia was a risk factor for a poorer prognosis in LE (Coombes et al., 2012).

There is limited evidence for the effectiveness of physiotherapy treatment including manual therapy and exercises therapy in improving QST assessed sensory abnormalities in LE. A series of randomised double-blinded placebo-controlled studies from Vicenzino et al. documented that specific manual therapy skills (Mulligans MWM) to the cervical spine (C5/6) and elbow produced mechanical hypoalgesia (increased threshold to PPT) and improved PFG via activation of the endogenous descending pain inhibitory system (Vicenzino et al., 1998, 2001; Paungmali et al., 2003; Carnero et al., 2011). The hypoalgesic effect induced by manipulation is also considered as a multifaceted process involving the joints, peripheral nociceptors, segmental inhibitory mechanisms and psychological factors (Wright et al., 1995). In addition, Slater et al. reported significant bilateral hyperalgesia in response to saline-induced muscle pain in LE compared to
healthy controls, which further supports the hypothesis of central nervous system changes in this population (Slater et al., 2005).

In contrast, the effects of prolotherapy, a non-operative emerging injection-based treatment that introduce hypertonic irritant solution of glucose with lignocaine directly into the injured tissues, are thought to involve direct stimulation of local tissue healing (Rabago et al., 2009, 2013; Scarpone, et al., 2008; Krogh et al., 2013; Rabago et al., 2014; Carayannopoulos et al., 2011). Currently, there is no high-level evidence for the effectiveness of prolotherapy in improving sensory abnormalities in LE.

3.13 Statistics

Generalised estimated equations (GEE) is a commonly used statistical method to fit a marginal model for longitudinal/cluster data of clinical trials and biomedical studies (Gibbons et al., 2010; Wang et al., 2016). GEE models are considered as an extension to the existing generalised linear models (GLM) which are primarily used for analysis of continuous and categorical correlated outcomes based on quasi-likelihood estimation. A working correlation structure link function assumed distribution needs to be specified for analysing the correlated data. GEE models are also called as a marginal model as they provide the estimated marginal means of the parameters and adjusted standard errors for factors, interactions and covariates. It is also considered a robust method for missing data. Missing data are assumed as missing completely at random (MCAR) (Gibbons et al., 2010; Paradis et al., 2002).
Chapter 4 Relationship between ultrasound-detected tendon abnormalities and sensory and clinical characteristics in people with chronic lateral epicondylalgia.

Acknowledgement of Co-authorship

I have made a substantial contribution to data processing, image analysis, data analysis and interpretation of the results of the study. I have drafted and critically edited the final manuscript.

The following made significant contributions to this study: Dr Leanne Bisset, Dr Shu-kay Ng, Dr Michael Ryan, Dr Michael Yelland, Dr Nagarajan Manickaraj, and Dr David Rabago.
4 Relationship between ultrasound-detected tendon abnormalities and sensory and clinical characteristics in people with chronic lateral epicondylalgia

4.1 Introduction

Lateral epicondylalgia (LE), also known as tennis elbow, is a chronic tendinopathy involving the common extensor tendon. It is characterised by lateral elbow pain on the resisted wrist and finger extension, focal tenderness on palpation and functional decline (Binder et al., 1983; Nirschl et al., 1992; Shiri et al., 2006). Estimates of prevalence suggest that 1 - 3% of working adults aged between 34 to 64 years, 50% of tennis players (Gruchow et al., 1979) smokers, manual workers are affected by LE, with equal risk in both men and women (Binder et al., 1983; Shiri et al. 2006). LE is recognised as a challenging condition to treat (Nirschl et al., 1992) and is commonly associated with a heavy economic burden due to high treatment costs, work absence and productivity loss (Sanders et al., 2015).

Historically, it was believed that the clinical presentation of chronic pain in tendinopathic conditions such as LE was associated with local tendon structural changes (Khan et al., 2003). Greyscale and colour Doppler US imaging are common methods used for assessing tendon structural changes including thickening, hypoechogeticity, fibrillar echotexture, neovascularity and bony abnormalities at the tendon insertion (Connell et al., 2001; du Toit et al., 2008; Heales et al., 2014). However, recent pathophysiological models on tendinopathy populations suggest altered sensory processing may play a role in
Recent evidence suggests discordance between tendon structural changes identified on imaging (e.g., US, magnetic resonance), and pain and functional impairments (Scott et al., 2013b). This discordance between structure and clinical severity may be explained by sensory system changes that lead to widespread hyperalgesia (Fernández-Carnero et al., 2009; Graven-Nielsen et al., 2010; Nijs et al., 2010). Widespread hyperalgesia, measured using quantitative sensory testing (QST), has been associated with increased clinical severity (Fernández-Carnero et al., 2009). Several studies have identified sensory changes, in LE including mechanical (pressure pain threshold, PPT) and thermal (heat and cold pain threshold,) hyperalgesia (Fernández-Carnero et al., 2009), impaired vibration detection threshold (Fernández-Carnero et al., 2009). and heightened nociceptive withdrawal reflex (Lim et al., 2012). However, there is variability in the anatomical distribution of mechanical (i.e., local vs widespread reduction in PPT) (Coombes et al., 2012; Fernández-Carnero et al., 2009; Wright et al., 1992) and thermal hyperalgesia (i.e., unilateral vs bilateral increase in cold pain threshold, CPT) (Coombes et al., 2012; Wright et al., 1992) reported in previous studies. As such, the role peripheral and/or central mechanisms may play in differentiating the clinical severity of LE has not yet been fully elucidated.

Currently, there is no conclusive model explaining the transition from localised to widespread sensory changes in LE. It has been proposed that evaluation of the local pathological structural changes (location of primary nociceptors) is paramount to understanding the transition from local to widespread hyperalgesia in individuals with varying musculoskeletal pain severity (e.g., mild, moderate and severe) (Graven-Nielsen et al., 2010; Rio et al., 2014). In LE, the tendon of the extensor carpi radialis brevis muscle
is generally considered as the primary source of nociception, (Ljung et al., 2004b; Ruiz-Ruiz et al., 2011) and it can be hypothesised that increased nociceptive stimulation from the progressive pathological tendon structural changes results in upregulation of the neuronal input leading to widespread hyperalgesia (Graven-Nielsen et al., 2010). However, there is currently no evidence for the association between pathological tendon structural and sensory changes to support the hypothesis.

Therefore, the primary aim of this study was to examine the association between tendon structural and sensory characteristics in people with chronic LE. A secondary aim was to determine the interrelationship between structural, sensory, pain and functional measures. We hypothesised that tendon structural changes would be related to sensory changes in LE and that a combination of sensory and structural characteristics will explain the heterogeneity of clinical severity in LE.

4.2 Materials and methods

4.2.1 Participants

This cross-sectional study investigates the association between several dependent and independent variables. Sixty-six individuals with a clinical diagnosis of LE (25 women aged 48.7 ± 7.7 years and 41 men aged 51.6 ± 7.4 years) were recruited between September 2013 and June 2014 from the general community. Inclusion criteria were participants aged between 18 to 75 years with a clinical diagnosis of LE (Bisset et al., 2006a), based on lateral elbow pain present for a minimum of six weeks that was aggravated by palpation, gripping, and resisted wrist/finger extension. In addition, a minimum score of 20/100 on the Patient-Rated Tennis Elbow Evaluation (PRTEE) was also required. Exclusion criteria comprised of current pregnancy or breast feeding,
presence of peripheral nerve involvement or cervical radiculopathy, systemic disorders including diabetes or rheumatoid arthritis, concomitant neck or other arm pain preventing usual work or recreation or required treatment within the past three months, evidence of other primary sources of lateral elbow pain such as osteoarthritis, sensory disturbance in the affected hand confirmed, history of upper limb dislocations, fractures or tendon ruptures within the preceding 10 years, history of corticosteroid injection to the affected elbow within the previous three months, or history of elbow surgery or malignancy. The study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants prior to their participation. Ethical approval was obtained from the Griffith University Human Research Ethics Committee.

4.2.2 Sample size calculation

A priori analysis using the G* Power 3.1 statistical software was performed to calculate the required sample size based on the following parameters: multiple linear regression fixed model ($R^2$ deviation from zero) with 13 predictors, statistical significance level of 0.05, large effect size (0.35) and 80% power (Faul et al., 2009). The results of the a priori analysis revealed that a sample size of $N = 64$ was required for the study.

4.2.3 Outcome measures

4.2.3.1 Clinical measures

The clinical measures identified for the purpose of the study include PRTEE, pain visual analogue scale (PVAS) and pain-free grip (PFG) of affected and unaffected sides. In addition to the clinical measures, participant’s characteristics including age, gender, occupation, smoking habit, duration of symptoms and hand dominance were also included in the study.
4.2.3.2 Quantitative Sensory Testing (QST)

A trained investigator recorded the pressure pain threshold (PPT), cold pain threshold (CPT), heat pain threshold (HPT), and vibration detection threshold (VDT) (Pavlaković et al., 2010; Zaslansky et al., 1998) of the study participants as described in the methods chapter (Chapter 3).

4.2.3.3 Pressure Pain Threshold

PPT was measured over the common extensor tendon insertion on both affected and unaffected elbows using a digital pressure algometer (Somedic AB, Fasrsta, Sweden) and a standardised testing protocol consistent with previous studies (Lautenbacher et al., 2005). The assessor applied pressure at a constant rate (40kPa/sec), with the probe (area of 1 cm²) perpendicular to the skin (Lautenbacher et al., 2005). The amount of force (kPa) required to evoke the first sensation of pain, distinct from pressure, was recorded, and three consecutive measurements with a rest time of 30 seconds between trials were averaged and used in further analyses. High reliability was established in a previous study using this equipment (ICC 0.99) (Paungmali et al., 2012).

4.2.3.4 Heat and Cold Pain Thresholds

HPT and CPT were measured bilaterally over the lateral elbow using the method of limits in accordance with the German Network of Neuropathic Pain guidelines (Rolke et al., 2006). All participants were tested in a quiet room at a standard temperature (24°C) using the Thermosensory Analyser (TSA-II, Medoc, Ramat-Yishai, Israel). A thermode (30 x 30 mm), placed over the lateral elbow, delivered either a cold or heat stimulus at a constant rate of 1°C/sec from a baseline temperature (32°C) until a pain sensation was first perceived by the participant or when the upper limit of 50°C or lower limit of 0°C is reached. The participants were asked to press a response button when they first perceived
a painful heat or cold sensation. The temperature corresponding to the point of termination was documented as HPT or CPT, and the average of three recorded HPT and CPT pain threshold measurements were used in further analyses. High inter-rater reliability has been reported for both HPT (ICC 0.87) and CPT (ICC 0.89) using this equipment (Paungmali et al., 2012).

4.2.3.5 Vibration Detection Threshold (VDT)

Each participant was seated comfortably with the test hand supported on a table. A computer-controlled Vibratory Sensory Analyser VSA-3000 (Medoc Ltd, Ramat Yishai, Israel) with a stimulating area of 1.2 cm² was utilised to measure VDT of the distal phalanx of the middle finger. The vibration stimulus was progressively increased at a constant rate from 0.1 to 130 µ/s, until the participant pressed the response button as soon they first perceived the vibration. Five measurements were made on each hand, and the mean was used in further analyses. A previous study observed high reliability for measuring vibration sensation (ICC = 0.86) (Felix et al., 2009).

4.2.3.6 Ultrasound imaging of tendon abnormalities

All US imaging on bilateral elbows were performed immediately following the clinical examination, by an experienced examiner with five years of musculoskeletal US experience in tendinopathy populations. US imaging was performed using SonixTouch US equipment (Ultrasonix, Richmond, BC, Canada) (Obst et al., 2014), with a high frequency 38 mm linear transducer (L14–5W/60) and a frequency range of 14-5 MHz. Firstly, greyscale US with standardised B-mode image settings (depth 2cm, gain 55%, dynamic range 68DB, map 4, power 0) was performed over the common extensor tendon, with participants in a seated position and the arm resting on the table in approximately 70° shoulder abduction, 90° elbow flexion and pronated forearm (Clarke et al., 2010; Connell
et al., 2001; Krogh et al., 2013). Following the greyscale US imaging, the presence of neovascularity within the same region was evaluated by standardised power Doppler US settings (pulse repetition frequency of 500 Hz, wall filter 40 Hz, gain range of 55-90%) with minimal probe pressure and adjusted sensitivity to detect low flow and minimal noise level. Longitudinal and transverse plane static images of the common extensor tendon were obtained with the transducer positioned parallel to the long axis of the tendon with the head of the radius and contour of the lateral epicondyle as anatomical reference guides. All the captured images were stored with a unique identifier in a re-identifiable format, in a password-protected storage drive.

**4.2.3.7 Ultrasound assessment of tendon thickness**

Tendon thickness measurement of the longitudinal and transverse images demonstrating optimal anatomical details was performed using the length measuring tool of the RadiAnt DICOM Viewer Version.3.4.1 (Mediexant, Poznan, Poland) (Ingwersen et al., 2016). Utilising a 5 mm distance from the radiohumeral joint margin as the standard reference point, longitudinal image tendon thickness was measured as the perpendicular distance between the tendon surface and the cortical bony interface of lateral epicondyle (Figure 3.3A) (Connell et al., 2001; Krogh et al., 2013; Teggeler et al., 2015). Transverse image tendon thickness was assessed by measuring the distance from a point on the humeral bone to the tendon surface (Figure 3.3 B, Chapter 3). High reliability (ICC > 0.7) for measuring common extensor tendon thickness on captured images has been reported in previous studies (Krogh et al., 2013; Teggeler et al., 2015).

**4.2.3.8 Image analysis**

All the captured US images were evaluated by a single assessor (VP) who was blind to clinical and sensory outcomes, as well as to the affected side. The assessor underwent
targeted training for six months from an experienced (>10 yrs.) musculoskeletal ultrasonographer in the acquisition, grading and measurement of US images. Following the training phase, the assessor and the ultrasonographer practised the US image grading procedure on 15 de-identified elbow images to establish a minimum of 80% overall agreement in using the US scoring system. Previous studies have reported acceptable test-retest reliability (ICC > 0.7) for grading greyscale and colour Doppler findings by non-radiologists using the semi-quantitative scoring method (Krogh et al., 2013; Poltawski et al., 2012).

**4.2.3.9 Ultrasound assessment of tendon structure**

Tendon echotexture and vascularity on the captured US images of bilateral elbows were graded with respect to focal areas of hypoechogenicity, diffuse heterogeneous areas, neovascularity and insertional bony abnormalities. Hypoechogenicity and neovascularity were graded as none, mild, moderate or severe (scored 0 to 3 respectively). In the event of a significantly uneven distribution of ultrasound grades for hypoechogenicity and neovascularity, the 4-point scales were each dichotomised into a 2-point scale and used in the sub-grouping analyses. That is, hypoechogenicity grades 0 to 2 were sub grouped into a ‘mild’ category with grade 2 labelled as a ‘severe’ category, and neovascularity grade 0 was labelled as an ‘absent’ category and grades 1 to 3 were labelled as ‘present’. The absence or presence (score 0 and 1 respectively) of diffuse heterogeneous areas and bony abnormalities were scored dichotomously. The sum of all features (excluding the dichotomised hypoechoic and hypervascular scores) gave a total ultrasound scale score (TUSS, maximal score = 8; Table 1) (Connell et al., 2001; du Toit et al., 2008; Heales et al., 2014; Ingwersen et al., 2016).
4.2.4 Statistical analysis

All statistical analyses were performed using SPSS Statistics version 24 (IBM, Chicago, IL, USA). Descriptive statistics for continuous data were expressed as means ± standard deviations while categorical data were reported as frequencies (percentages). Normality assumptions of all continuous variables were assessed using Shapiro-wilk test statistics. In order to assess differences between affected and unaffected sides, paired samples t-test, Wilcoxon signed rank, McNemar’s test, and Friedman’s statistics were used for normally distributed continuous variables, non-normally distributed continuous variables, dichotomous and ordinal variables respectively. Participants who reported bilateral symptoms were excluded from analyses comparing affected and unaffected sides.

To assess differences in clinical and sensory measures for grades of hypoechogenicity, neovascularity and bony abnormalities, one-way analyses of variance (ANOVA) were used. Univariate and multivariate linear regression analyses were then used to examine the relationship between tendon structural and sensory measures for both affected and unaffected elbows in a two-stage procedure as described in a previous study (Coombes et al., 2014b). In addition to sensory and structural characteristics, demographic characteristics of age, gender, and duration of condition were also assessed as factors in the regression analyses, due to their known predictive value for pain and disability (PRTEE) (Coombes et al., 2012, 2014) and PFG. In order to provide meaningful and important predictors for consideration in the final multiple regression analysis models, purposeful selection of predictor variables with univariate linear regression analysis initially performed for each of the potential predictor variables at a statistical significance of $P < 0.15$ (Bursac et al., 2008). The significant predictor variables ($P < 0.15$) from the univariate analyses were then examined in a final multivariate regression analysis model using backwards elimination approach to determine the most parsimonious model that
described the relationship among variables (Bursac et al., 2008). To ensure the validity of results, additional analyses were performed to substantiate the findings from the multivariate regression analyses; 1) forward stepwise regression tests were performed to ascertain whether the final model predictors obtained were similar to the “backward” stepwise regression method, and 2) separate correlation analyses were performed to determine whether collinearity or multicollinearity existed between predictor variables. Further, ordinal predictor variables (hypoechogenicity, hypervasculaarity) were treated as numerical variables for both univariate and multivariate regression analyses. Secondary analysis included a similar statistical approach to determine the significant structural and sensory predictors of PRTEE and PFG measures of affected elbows and PFG measures of unaffected elbows respectively. The significance level was set at 5% with two-tailed hypothesis test for all analyses except univariate linear regression analyses.

4.3 RESULTS

4.3.1 Participant characteristics

Descriptive statistics for the demographic, tendon structural, sensory and clinical measures of participants are presented in Table 4.1. Bilateral symptoms were reported by 10 (15.2%) participants. Ultrasound imaging was not performed on the unaffected elbow for one participant who reported unilateral LE symptoms. Nine participants (13.6%) had a previous corticosteroid injection greater than six months ago. In the affected elbows, the presence of grade 3 (72.7%) hypoechogenicity, absence of neovascularity (81.8%) and presence of insertional bony abnormalities (74.2%) were the most prevalent US findings, whereas the presence of grade 2 and 3 (44.6% each) and absence of neovascularity (87.5%) were the most common US findings in the unaffected elbows of our LE participants.
Table 4.1 Demographic, clinical, tendon structural and sensory measures for the affected (N = 66) and unaffected elbows (N =56)

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Mean ±SD; n (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.5 ± 7.6</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.7 ± 3.9</td>
<td></td>
</tr>
<tr>
<td>Occupation, N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>29 (43.9%)</td>
<td></td>
</tr>
<tr>
<td>Non-manual</td>
<td>32 (48.5%)</td>
<td></td>
</tr>
<tr>
<td>Not working</td>
<td>5 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Male, N</td>
<td>41 (62.1%)</td>
<td></td>
</tr>
<tr>
<td>Dominant side affected, N</td>
<td>43 (65.2%)</td>
<td></td>
</tr>
<tr>
<td>Right side dominant, N</td>
<td>60 (90.9%)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Clinical measures</th>
<th>Affected side</th>
<th>Unaffected side</th>
<th>Affected vs Unaffected mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms, weeks</td>
<td>50.8 ± 2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous injection treatment &gt;3 months, N</td>
<td>14.1 (11.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRTEE total score, /100</td>
<td>30.8 ±10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRTEE pain, /50</td>
<td>22.6 ± 6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRTEE function, /50</td>
<td>15.2 ± 8.3</td>
<td></td>
<td></td>
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<tr>
<td>Rest pain, mm</td>
<td>17.1 ±16.2</td>
<td></td>
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<tr>
<td>Worst pain, mm</td>
<td>67.1 ± 22.8</td>
<td></td>
<td></td>
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<tr>
<td>EuroQol -5D, /100</td>
<td>82.3 ±13.7</td>
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</tr>
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<table>
<thead>
<tr>
<th>Pain-free grip strength, Newtons</th>
<th>Affected side</th>
<th>Unaffected side</th>
<th>Affected vs Unaffected mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>151.0 ± 97.9</td>
<td>263.1 ± 105.3*</td>
<td>-106.6 (-135.3, -77.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tendon structural measures</th>
<th>Affected side</th>
<th>Unaffected side</th>
<th>Affected vs Unaffected mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal tendon thickness, mm</td>
<td>6.1 ± 0.8</td>
<td>5.5 ± 0.7*</td>
<td>0.5 (0.3, 0.7)</td>
</tr>
<tr>
<td>Transverse tendon thickness, mm</td>
<td>5.5 ± 0.6</td>
<td>4.8 ±1.4*</td>
<td>0.7 (0.2, 1.2)</td>
</tr>
<tr>
<td>Hypoechogenicity, N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (3.0 %)</td>
<td>6 (10.7%)*</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>16 (24.2 %)</td>
<td>25 (44.6%)*</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>48 (72.7%)</td>
<td>25 (44.6%)*</td>
<td></td>
</tr>
<tr>
<td>Neovascularity, N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>54 (81.8 %)</td>
<td>49 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>12 (18.2 %)</td>
<td>9 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
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</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of bony abnormalities, N</td>
<td>48 (72.7%)</td>
<td>29 (51.8%)*</td>
<td></td>
</tr>
<tr>
<td>TUSS 0-8</td>
<td>4.6 ± 0.9</td>
<td>3.9 ±1.1*</td>
<td>0.6 (0.4, 0.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensory measures</th>
<th>Affected side (n = 66)</th>
<th>Unaffected side (n = 56)</th>
<th>Affected vs Unaffected mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT, kPa</td>
<td>254.8 ±107.2</td>
<td>371.7 ± 136.7*</td>
<td>-113.3 (-144.8, -81.9)</td>
</tr>
<tr>
<td>CPT, °C</td>
<td>9.3 ± 10.9</td>
<td>7.4 ± 9.3*</td>
<td>2.2 (0.3, 4.1)</td>
</tr>
<tr>
<td>HPT, °C</td>
<td>46.6 ± 3.4</td>
<td>47.5 ± 2.1*</td>
<td>-0.8 (-1.5, -0.09)</td>
</tr>
<tr>
<td>VDT, µ/s</td>
<td>1.8 ±1.1</td>
<td>1.7 ± 1.5</td>
<td>0.1 (-0.2, 0.4)</td>
</tr>
</tbody>
</table>

*significant differences between affected vs unaffected elbows P<0.05; PPT = pressure pain threshold; HPT = heat pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; TUSS = total ultrasound scale score; PRTEE = Patient-Rated Tennis Elbow Evaluation; EQ-5D = EuroQol - 5D: quality of life questionnaire.
4.3.2 Within-subject differences

The affected side exhibited significantly higher TUSS scores, greater tendon thickness, a greater number of severe hypoechogenicity and reduced PFG PPT, HPT and greater CPT compared to the unaffected side (Table 4.1). Neovascularity and VDT did not differ between the affected and unaffected sides. The presence of heterogeneous fibrillar echotexture was observed in 100% of affected elbows. As such, this outcome was unable to be included in further statistical analyses as it was observed to be a constant variable (i.e., has just one value: the presence of heterogeneous echotexture = 1).

4.3.3 Comparison of sensory and clinical findings between US Grades for structural abnormalities

Sensory and clinical characteristics for sub-groups of participants based on grades for each US measure are reported in Table 4.2. CPT was significantly superior in individuals identified with neovascularity in the affected elbows, compared to those with none or minimal signs of neovascularity. In contrast, rest pain (mm) was worse among participants identified with insertional bony abnormalities compared to participants with no bony abnormalities in the affected elbows (Table 4.2) (Poltawski et al., 2011). For the unaffected elbows, VDT was significantly worse in individuals with insertional bony abnormalities compared to participants categorised with no insertional bony abnormalities (Table 4.2).
Table 4.2 Mean ±SD of clinical and sensory measures for dichotomised greyscale US outcomes for the affected (N = 66) and unaffected side (N = 56)

<table>
<thead>
<tr>
<th>US parameter</th>
<th>Duration of condition, weeks</th>
<th>PRTEE, /100</th>
<th>Resting pain, /100</th>
<th>Worst pain, /100</th>
<th>PFG, Newtons</th>
<th>EQ-5D, /100</th>
<th>PPT, kPa</th>
<th>HPT, °C</th>
<th>CPT, °C</th>
<th>VDT, µm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoechochogenicity</td>
<td></td>
<td></td>
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<tr>
<td>Mild</td>
<td>AF, n = 18</td>
<td>52.0 ± 61.8</td>
<td>30.6 ± 8.3</td>
<td>13.3 ± 15.7</td>
<td>67.7 ± 21.2</td>
<td>135.2 ± 83.2</td>
<td>81.1 ± 10.6</td>
<td>270.8 ± 104.8</td>
<td>46.0 ± 3.3</td>
<td>11.7 ±11.0</td>
</tr>
<tr>
<td></td>
<td>UAF, n = 30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>239 ± 97.9</td>
<td>-</td>
<td>364.5 ± 126.2</td>
<td>47.3 ±3.4</td>
<td>6.6 ±9.4</td>
</tr>
<tr>
<td>Severe</td>
<td>AF, n = 48</td>
<td>35.8 ± 45.9</td>
<td>30.9 ± 10.2</td>
<td>18.5 ±16.3</td>
<td>66.8 ± 23.6</td>
<td>157.0 ±103.1</td>
<td>82.8 ±14.3</td>
<td>248.2 ±108.7</td>
<td>46.8 ±3.4</td>
<td>8.4 ±10.9</td>
</tr>
<tr>
<td></td>
<td>UAF, n = 25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>291.3 ±108.8</td>
<td>-</td>
<td>380.4 ±150.7</td>
<td>47.7 ±2.4</td>
<td>8.1 ±9.2</td>
</tr>
<tr>
<td>Neovascularity</td>
<td></td>
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<tr>
<td>Absent</td>
<td>AF, n = 54</td>
<td>40.3 ± 54.0</td>
<td>31.1 ±10.6</td>
<td>17.4 ±15.6</td>
<td>67.4 ±20.1</td>
<td>141.6 ±95.2</td>
<td>80.9 ±13.9</td>
<td>252.8 ±108.8</td>
<td>46.3 ±3.6</td>
<td>10.8 ±11.4</td>
</tr>
<tr>
<td></td>
<td>UAF, n = 48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>255.6 ±101.4</td>
<td>-</td>
<td>383.8 ±141.5</td>
<td>47.5 ±2.1</td>
<td>7.1 ±8.9</td>
</tr>
<tr>
<td>Present</td>
<td>AF, n = 12</td>
<td>39.5 ± 34.5</td>
<td>29.7 ± 7.1</td>
<td>15.8 ±19.2</td>
<td>65.8 ±29.9</td>
<td>192.5 ±103.2</td>
<td>89.0 ± 7.8</td>
<td>264.2 ±104.0</td>
<td>48.1 ±1.8</td>
<td>2.4 ±3.9</td>
</tr>
<tr>
<td></td>
<td>UAF, n = 7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>314.4 ±124.9</td>
<td>-</td>
<td>292.1 ±57.8</td>
<td>47.4 ±2.6</td>
<td>8.6 ±12.4</td>
</tr>
<tr>
<td>Insertional bony abnormalities</td>
<td></td>
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</tr>
<tr>
<td>Absent</td>
<td>AF, n = 18</td>
<td>37.2 ± 44.7</td>
<td>27.5 ± 7.4</td>
<td>8.8 ±14.0</td>
<td>64.4 ±21.2</td>
<td>162.9 ±93.9</td>
<td>78.8 ±11.5</td>
<td>248.9 ±117.3</td>
<td>46.4 ±3.4</td>
<td>8.8 ±10</td>
</tr>
<tr>
<td></td>
<td>UAF, n = 27</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>234.9 ±101.3</td>
<td>-</td>
<td>354.0 ±126.6</td>
<td>47.1 ±2.0</td>
<td>7.0 ±9.6</td>
</tr>
<tr>
<td>Present</td>
<td>AF, n = 48</td>
<td>41.3 ± 53.2</td>
<td>32.1 ± 10.2</td>
<td>20.2 ± 16.0*</td>
<td>68.1 ±23.5</td>
<td>146.4 ±99.3</td>
<td>83.7 ±13.9</td>
<td>257.2 ±104.1</td>
<td>46.7 ±3.4</td>
<td>9.5 ±11.2</td>
</tr>
<tr>
<td></td>
<td>UAF, n = 29</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>288.4 ±104.0</td>
<td>-</td>
<td>390.0 ±146.6</td>
<td>47.9 ±2.1</td>
<td>7.5 ±9.0</td>
</tr>
</tbody>
</table>

* Significant difference between US sub-groups; P<0.05; US = ultrasound; PRTEE = Patient-Rated Tennis Elbow Evaluation; PFG = pain-free grip strength; EQ-5D: EuroQol EQ-5D quality of life questionnaire; PPT = pressure pain threshold; HPT = heat pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; AF = affected side; UAF = unaffected side.
4.3.4 Relationship between demographic, structural and sensory measures

The association between demographic, structural and sensory measures in affected and unaffected elbows are reported in Tables 4.3 and 4.4 respectively. Neovascularity on the affected side was the only variable to show a significant association with HPT \( (P = 0.08) \) at the univariate level, so no subsequent multivariate regression analysis was required. Similarly, gender and neovascularity were the only significant univariate predictors of PPT on the affected \( (P = 0.11) \) and unaffected side \( (P = 0.09) \) respectively (Table 4.3 and 4.4), so no further analyses were performed.

The final multivariable models included predictors for CPT (neovascularity, TUSS) and VDT (age, gender, duration of the condition, LTT, TTT) on the affected side, and HPT (gender, bony abnormalities, LTT, TUSS) and VDT (age, gender, hypoechogenicity, bony abnormalities, TTT, TUSS) on the unaffected side. The only significant predictor of CPT on the affected side in the final multivariable regression model was neovascularity, which explained 7.5% of the variance in CPT (Table 4.3). For VDT, women were more likely to have a lower threshold (women mean \( 1.1 \pm 0.5 \) \( \mu \text{m/s} \) versus men \( 1.9 \pm 1.3 \) \( \mu \text{m/s} \)) to vibration detection (Table 4.3). The adjusted \( R^2 \) values from the final model revealed that female gender and TTT explained 22.5% of the variance in VDT on the affected side (Table 4.3). For the unaffected side, female gender was the only significant predictor of HPT in the final multivariate model, which explained 9.4% of the variance (Table 4.4). Further, TUSS significantly predicted VDT in the final model, explaining 12.7% of the variance (Table 4.4).
Table 4.3 Univariate and multivariate regression analyses examining predictors of sensory measures for the affected side.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HPT, °C Univariate</th>
<th>PPT, kPa Univariate</th>
<th>CPT, °C Univariate</th>
<th>CPT, °C Multivariate</th>
<th>VDT, µm/s Univariate</th>
<th>VDT, µm/s Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI) P †</td>
<td>β (95% CI) P †</td>
<td>β (95% CI) P †</td>
<td>β (95% CI) P †</td>
<td>β (95% CI) P †</td>
<td>β (95% CI) P †</td>
</tr>
<tr>
<td>Intercept</td>
<td>10.8 (8.0 to 13.7) &lt;0.001</td>
<td>2.8 (-0.2 to 7.6) 0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>-0.02 (-0.1, 0.08) 0.60</td>
<td>0.1 (-3.5, 3.8) 0.94</td>
<td>0.05 (-0.3, 0.4) 0.77</td>
<td>0.03 (-0.02, 0.09) 0.06 †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.7 (-2.4, 0.9) 0.39</td>
<td>-44.5 (-99.7, 10.7) 0.11 †</td>
<td>1.6 (-3.9, 7.3) 0.54</td>
<td>-0.7 (-1.3, -0.1) 0.01 †</td>
<td>-0.6 (-1.3, -0.02) 0.04 *</td>
<td></td>
</tr>
<tr>
<td>Duration, weeks</td>
<td>0.0 (-0.01, 0.01) 1.0</td>
<td>-0.2 (-0.8, 0.2) 0.31</td>
<td>-0.01 (-0.05, 0.03) 0.61</td>
<td>-0.005 (-0.01, 0.001) 0.08 †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoechogenicity</td>
<td>0.5 (-1.1, 2.1) 0.49</td>
<td>-24.7 (-76.0, 26.4) 0.33</td>
<td>-2.6 (-7.8, 2.5) 0.31</td>
<td>0.02 (-0.5, 0.6) 0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neovascularity</td>
<td>1.6 (-0.2, 3.3) 0.08 †</td>
<td>-11.4 (-60.4, 83.2) 0.75</td>
<td>-8.4 (-15.1, -1.6) 0.01 †</td>
<td>-8.4 (-15.1 to -1.6) 0.015 *</td>
<td>0.1 (-0.6, 0.9) 0.67</td>
<td></td>
</tr>
<tr>
<td>Bony abnormalities</td>
<td>0.2 (-1.6, 2.2) 0.76</td>
<td>8.2 (-52.1, 68.7) 0.78</td>
<td>0.7 (-5.4, 6.9) 0.82</td>
<td>0.2 (-0.5, 0.8) 0.59</td>
<td></td>
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</tr>
<tr>
<td>LTT, mm</td>
<td>0.4 (-0.5, 1.4) 0.40</td>
<td>-4.6 (-36.9, 27.6) 0.77</td>
<td>-1.4 (-4.6, 1.7) 0.37</td>
<td>0.3 (-0.6, 0.6) 0.11 †</td>
<td></td>
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</tr>
<tr>
<td>TTT, mm</td>
<td>0.3 (-1.2, 1.8) 0.69</td>
<td>-28.9 (-79.1, 21.1) 0.25</td>
<td>-1.0 (-5.6, 3.6) 0.67</td>
<td>0.8 (0.3, 1.3) &lt;0.001 †</td>
<td>0.6 (0.1 to 1.2) 0.01 *</td>
<td></td>
</tr>
<tr>
<td>TUSS, 0-8</td>
<td>0.5 (-0.3, 1.4) 0.20</td>
<td>-4.3 (-34.5, 25.8) 0.77</td>
<td>-2.2 (-5.2 to 0.72) 0.13 †</td>
<td>0.08 (-0.2, 0.4) 0.61</td>
<td></td>
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</tr>
<tr>
<td>Adjusted R²</td>
<td>0.075</td>
<td></td>
<td></td>
<td></td>
<td>0.225</td>
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</tr>
</tbody>
</table>

β = Unstandardised regression coefficients; *statistically significant P < 0.05, CI = confidence interval; † P significance ≤ 0.15; HPT = heat pain threshold; PPT = pressure pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; TUSS = total ultrasound scale score.
### Table 4.4: Univariate and Multivariate regression analysis examining predictors of sensory and PFG measures of the unaffected side for unilateral LE participants (N = 56)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate HPT, °C β (95% CI)</th>
<th>P</th>
<th>Multivariate HPT, °C β (95% CI)</th>
<th>P</th>
<th>Univariate CPT, °C β (95% CI)</th>
<th>P</th>
<th>Multivariate CPT, °C β (95% CI)</th>
<th>P</th>
<th>Univariate VDT, µ/s β (95% CI)</th>
<th>P</th>
<th>Multivariate VDT, µ/s β (95% CI)</th>
<th>P</th>
<th>Univariate PPT, kPa β (95% CI)</th>
<th>P</th>
<th>Multivariate PPT, kPa β (95% CI)</th>
<th>P</th>
<th>Univariate PFG, Newtons β (95% CI)</th>
<th>P</th>
<th>Multivariate PFG, Newtons β (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>49.6 (47.9, 51.2)</td>
<td>0.001</td>
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<tr>
<td>Age</td>
<td>0.02 (-0.05, 0.09)</td>
<td>0.52</td>
<td>0.09 (-0.2, 0.4)</td>
<td>0.07</td>
<td>0.04 (-0.01, 0.08)</td>
<td>0.01</td>
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<tr>
<td>Female gender</td>
<td>-1.4 (-2.5, 0.3)</td>
<td>0.01*</td>
<td>-1.4 (-2.5, 0.3)</td>
<td>0.01</td>
<td>-0.5 (-1.1, 0.07)</td>
<td>0.04</td>
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<tr>
<td>Hypoechoogenicity</td>
<td>0.05 (-0.8, 0.9)</td>
<td>0.09</td>
<td>1.4 (-2.2, 5.2)</td>
<td>0.92</td>
<td>0.3 (-0.1, 0.8)</td>
<td>0.08</td>
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<tr>
<td>Neovascularity</td>
<td>-0.11 (-1.8, 1.6)</td>
<td>0.09</td>
<td>1.5 (-6.0, 9.1)</td>
<td>0.92</td>
<td>-0.1 (-1.0, 0.8)</td>
<td>0.09</td>
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<tr>
<td>Bony abnormalities</td>
<td>0.8 (-0.3, 1.9)</td>
<td>0.15</td>
<td>0.5 (-4.5, 5.5)</td>
<td>0.83</td>
<td>0.6 (-0.05, 1.12)</td>
<td>0.03</td>
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<tr>
<td>LTT, mm</td>
<td>0.61 (-0.2, 1.4)</td>
<td>0.13</td>
<td>-0.7 (-4.3, 2.7)</td>
<td>0.65</td>
<td>0.03 (-0.4, 0.5)</td>
<td>0.87</td>
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<tr>
<td>TTT, mm</td>
<td>-0.05 (-0.5, 0.4)</td>
<td>0.81</td>
<td>0.6 (-1.6, 2.9)</td>
<td>0.57</td>
<td>0.2 (-0.1, 0.6)</td>
<td>0.12</td>
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</tr>
<tr>
<td>TUSS, 0-8</td>
<td>0.4 (-0.1, 1.0)</td>
<td>0.10</td>
<td>-0.04 (-2.4, 2.2)</td>
<td>0.97</td>
<td>0.3 (0.01, 0.6)</td>
<td>0.04</td>
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</tr>
<tr>
<td>Adjusted R²</td>
<td>0.094</td>
<td>0.127</td>
<td>0.312</td>
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</tbody>
</table>

\( \beta \) = Unstandardised regression coefficients; *statistically significant \( P < 0.05 \), CI: confidence interval, †\( P \) significance ≤ 0.15, HPT = heat pain threshold; PPT = pressure pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; PFG = pain-free grip strength; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; TUSS: total ultrasound scale score
4.3.5 Relationship between structural, sensory and clinical measures

The association between structural and sensory characteristics with clinical measures of pain and function are reported in Tables 4.4 and 4.5. Potential predictor variables were identified for PRTEE (bony abnormalities, HPT, CPT and VDT) and PFG (gender, neovascularity, LTT and VDT) in the affected side, and subsequently included in the multivariate regression analyses (Table 4.5). Higher HPT (i.e., less hyperalgesic) was the only significant predictor of higher PRTEE scores (more severe pain and disability) in the final model, explaining 10.4% of the variance in the affected elbows, while female gender was associated with lower pain-free grip strength, explaining 21.9% of the variability of pain-free grip strength on the affected side (Table 4.5). For the unaffected side, female gender, hypoechogenicity, bony abnormalities, LTT and TUSS were included in the final multivariable regression model for PFG. The final model analysis revealed that women recorded lower pain-free grip strength, which was similar to the affected side, explaining 31.2% of the total variance (Table 4.4).
Table 4.5. Univariate and Multivariate regression analyses examining clinical predictors of PRTEE and PFG in the affected side (N = 66)

<table>
<thead>
<tr>
<th>Variables</th>
<th>PRTEE /100</th>
<th>PRTEE /100</th>
<th>PFG, Newtons</th>
<th>PFG, Newtons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>P</td>
<td>β (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>PFG, Newtons</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.1 (-0.2, 0.4) 0.44</td>
<td>0.6 (-2.5, 3.8) 0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.6 (-4.3, 5.6) 0.80</td>
<td>-94.6 (-139.3, -49.8) &lt;0.01</td>
<td>-96.6 (-142.1, -1.2) &lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>-0.01 (-0.05, 0.03) 0.72</td>
<td>-0.2 (-0.6, 0.3) 0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendon structural measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoechochogenicity</td>
<td>0.3 (-4.2, 4.9) 0.87</td>
<td>29.0 (-17.2, 74.9) 0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neovascularity</td>
<td>-1.3 (-7.6, 4.8) 0.66</td>
<td>50.5 (-11.1, 112.3) .10†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bony abnormalities</td>
<td>4.5 (0.7, 9.8) 0.08†</td>
<td>-16.4 (-70.9, 38.0) 0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTT, mm</td>
<td>0.5 (-2.3, 3.3) 0.73</td>
<td>28.7 (0.4, 57.0) 0. 04†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTT, mm</td>
<td>2.2 (-1.9, 6.3) 0.30</td>
<td>22.1 (-17.9, 62.3) 0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUSS, 0-8</td>
<td>1.1 (-0.8, 3.1) 0.26</td>
<td>14.8 (-11.8, 41.5 ) 0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPT °C</td>
<td>1.0 (0.3, 1.6) &lt;0.01†</td>
<td>1.03 (.32,1.74) &lt;0.01*</td>
<td>0.1 (-7.7, 8.1) 0.96</td>
<td></td>
</tr>
<tr>
<td>CPT °C</td>
<td>-0.2 (-0.4, 0.05) 0.13†</td>
<td>-0.7 (-3.0, 1.4) 0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDT, µ/s</td>
<td>1.8 (-0.2, 4.0) 0.07†</td>
<td>17.2 (-4.0, 38.5) 0.11†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT, kPa</td>
<td>-0.003 (-0.02, 0.03) 0.78</td>
<td>-0.1 (-0.3, 0.1) 0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>0.104</td>
<td>0.219</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

β = Unstandardised regression coefficients; *statistically significant P < 0.05; CI = confidence interval; †P≤0.15; PRTEE = Patient-Rated Tennis Elbow Evaluation; PFG = pain-free grip strength; HPT = heat pain threshold; PPT = pressure pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; TUSS = total ultrasound scale score
4.4 Discussion

Structural changes in the load bearing tendon were previously conceptualised as the mechanism for pain in LE (Öhberg et al., 2001; Scott et al., 2013). However, the contemporary literature suggests that structural changes in the affected tendon, such as hypoechoic and heterogeneous regions, bony abnormalities at the insertion, and neovascularity, do not correlate with the severity of clinical presentation (Coombes, et al., 2009; Coombes et al., 2015; Scott et al., 2013). While the non-association between tendon structure and clinical presentation has been well documented, the relationship between tendon structure and sensory characteristics, and clinical presentation is less clear. The present cross-sectional study of 66 participants with a clinical diagnosis of LE provides unique insight into the interrelationship between US-observed structural changes, QST-measured sensory system changes, and clinical measures of pain and function. The results demonstrate that few tendon structural characteristics are related to sensory system changes, and in many cases the relationship is conflicting. For example, in the final model for VDT on the affected side, 22.5% of the variance could be explained by a combination of transverse tendon thickness and gender, with greater TTT and female gender associated with poorer VDT. Similarly, there was a significant inverse association between the absence of neovessels and higher (i.e. worse) CPT. Of the few structural or sensory characteristics that predicted clinical severity, greater HPT was the only significant predictor of higher pain and disability (PRTEE) on the affected side, explaining 10.4% of the variance. For the unaffected side, only female gender predicted lower PFG, but greater TUSS predicted more impaired VDT.

The inverse relationships identified in this study, as reflected by more severe clinical symptoms associated with less severe structural and sensory characteristics, may be
explained by Cook’s continuum model of pathology (Cook et al., 2016). Pain in
tendinopathy may be derived from the increased expression of nociceptive substances,
stimulating the nociceptors near, or in, the peritendon. This nociceptive stimulation from
the peritendon may occur due to increased tendon thickness, or via a reactive process in
the healthy load-bearing portion of the tendon in response to the inability of the
degenerative tendon portion to transmit tensile load (Cook et al., 2016). This reactive-on-
degenerative model may explain the lack of association between structural tendon changes
and sensory and clinical characteristics in LE, as the size and severity of the degenerative
tendon portion are not responsible for the magnitude of nociception in this model. This
hypothesis requires further validation and may continue to evolve over time with the
development of more sensitive imaging modalities.

Of interest is the significant side-to-side differences in sensory measures (PPT, CPT and
HPT) in our LE population. Without a control group for comparison, we are unable to
confirm the presence or absence of bilateral hyperalgesia. However, data extracted from
Coombes et al. (2012) suggests that CPT and HPT on the unaffected side in our LE cohort
are not different to previously published control data (7.1 ± 4.6°C and 44.3 ± 2.5°C,
respectively) (Coombes et al., 2012). As such, the unilateral mechanical and thermal (HPT
and CPT) hyperalgesia in our population suggests a local peripheral pain state rather than
a centrally-driven pain state. This is consistent with a recent study that found patellar, and
Achilles tendinopathies exhibited only local, rather than widespread, sensory changes
(Plinsinga et al., 2017). This lack of bilateral hyperalgesia contrasts the findings reported
by Coombes et al. (2012) (Coombes et al., 2012) who found widespread cold hyperalgesia
only in a severe subgroup of people with LE. A less severe clinical presentation in our
cohort (PRTEE 30.8 compared to 40.1 in Coombes et al. (2012)) may explain the lack of
widespread changes identified in our study (Coombes et al., 2012). We found that HPT
was the only significant predictor of PRTEE, with higher HPT (i.e., less hyperalgesic) associated with higher pain and disability. This suggests that patients presenting to the clinic with high levels of pain and disability are likely to exhibit normal HPT, suggesting that the relevance of HPT in directing treatment is limited. Further, we observed that female gender was the only significant predictor of lower heat pain threshold, which is consistent with Rolke et al. (2006) (Rolke et al., 2006).

Participants showing increased transverse tendon thickness of the common extensor tendon in the affected elbows were more likely to have poorer vibration detection threshold (higher values indicates less sensitive VDT). The mean VDT (1.8 µm/sec) for affected elbows in our study was higher (i.e., poor detection of vibration) than age-matched normative values (ranging from 1.0 to 1.7 µm/sec) previously reported (González-Duarte et al., 2016; Rolke et al., 2006). It may be that poorer VDT in the affected limb may occur through compression of the radial nerve via the larger cross-sectional area of the affected common extensor tendon. Recently, Gurcay et al. (2017) (Gürçay et al., 2017) reported the presence of increased thickness of the common extensor tendon with an increased cross-sectional area of the radial nerve on the affected side compared to the unaffected side in 44 LE participants. Importantly, there was no loss of electrophysiological function on the affected side in this cohort, suggesting a subclinical picture of radial nerve entrapment at the supinator may exist in some people with chronic LE (Kotnis et al., 2012). While our participants were screened for any neurological impairment, the elevated VDT may reflect a feature of subclinical impairment in a sensory function that is not perceived by the individual. Elevated VDT (1.8 µ/sec) on the affected side in LE has previously been reported (Fernández-Carnero et al., 2009). However, the difference in VDT in this previous study was not statistically significant when compared to a healthy control group, possibly due to the small sample size (LE group N = 11,
Neovascularity on the affected side was identified in only a small subgroup within our LE cohort (12/66). We found a negative association between the presence of neovessels and CPT, with the presence of neovascularity in the affected tendon associated with lower (i.e., less sensitive) CPT. That is, the absence of neovessels was associated with increased cold hyperalgesia on the affected side, which is consistent with previous work, which found the absence of neovessels was associated with a facilitated temporal summation of pain, lower pressure pain tolerance and higher habitual pain intensity (Jespersen et al., 2013). Jespersen et al. (2013) propose that the presence of neovessels may reflect inflammatory activity associated with an early reactive overloading stage of LE, such as that described by Cook et al. (2016) (Cook et al., 2016). This hypothesis assumes that neovessels disappear or reduce with chronicity of tendinopathy, a concept which has not yet been confirmed.

4.5 CONCLUSION

In this observational cross-sectional study, structural and sensory measures were weakly associated with clinical characteristics in participants with chronic LE, reflecting a disconnect between structure, sensory and clinical presentation in LE. Notwithstanding this, increased transverse tendon thickness may be related to sensory system impairment in LE.
Chapter 5 Effects of prolotherapy injections, physiotherapy or combination on tendon structural changes in people with chronic lateral epicondylalgia.
5 Effects of prolotherapy injections, physiotherapy or combination on tendon structural changes in people with chronic lateral epicondylalgia

5.1 Background

Lateral epicondylalgia (LE), commonly known as tennis elbow, is an overuse musculoskeletal injury involving the common extensor tendon (CET) at the lateral elbow (Nirschl, 1992). LE involves a complex pathophysiological interplay between local tendon pathology, and sensory and motor system impairments (Coombes et al., 2009). Structural changes within the CET include increased cellularity, disorganisation of collagen fibres, increased vascularity (blood flow) and increased presence of immature collagen (Nirschl et al., 1992). There is a well-documented lack of correlation between the severity of structural changes within the CET and the severity of clinical characteristics in LE (Coombes et al., 2009; Coombes et al., 2015). However, this conclusion is based on cross-sectional studies that have compared participants with LE to healthy controls at a single point in time (Chourasia et al., 2013; Scott et al., 2013). The longitudinal time course of changes in tendon structure in response to changes in clinical severity is not well explored. While a multimodal treatment approach targeting the multi-dimensional pathophysiology and heterogeneous clinical presentation have been recommended (Coombes et al., 2015), there is currently no consensus on any single treatment for LE. There is high-level evidence which suggests that physiotherapy (PT) treatment comprising manual therapy and exercise is more effective than a wait-and-see or placebo injection in providing pain relief and functional improvements in the short-term (6 to 8 weeks) (Bisset et al., 2015) and superior to corticosteroid injection in the medium-term (12-26 weeks) (Bisset et al., 2006; Coombes et al., 2013). The effects of physiotherapy treatment on tendon structure
are less clear. Only one study has investigated the effects of physiotherapy on structural changes over time in participants with LE (Croisier et al., 2007a). This study evaluated the short-term (9 weeks) effects of eccentric exercise on tendon structure and found no significant change compared to a control group.

Prolotherapy injections is a regenerative treatment that introduces a small volume of an irritant solution of dextrose and local anaesthetic directly into the painful or damaged tendon and ligament tissues, to promote cellular and tissue healing through inflammatory (>10% dextrose concentration) or non-inflammatory (<10% dextrose concentration) mechanism of action (Rabago et al., 2017; Reeves et al., 2016). Although preliminary research findings indicate that prolotherapy injections provide significant therapeutic benefits in people with LE, evidence of the regenerative effects of prolotherapy injections on local tissue structure over time are still lacking (Dong et al., 2015; Rabago et al., 2013; Scarpone et al., 2008). Furthermore, the comparative effectiveness of prolotherapy injections and physiotherapy in improving tendon structure over time has not been documented.

Although evidence from cross-section studies in tendinopathy population suggest an apparent disconnect between the US appearance of tendon structural changes and the symptoms (Coombes et al., 2009; Coombes et al., 2015; Scott et al., 2013) but it remains unknown if improvement in tendon structural changes is associated with improvement in pain and function following treatment in LE.

The primary objectives of this study were two-fold: 1) to evaluate the tendon structural changes over time in LE, and 2) to determine to compare the short- and long-term effectiveness of prolotherapy injections and PT, used both singly and in combination. The
null hypothesis was that there would be no difference over time or between groups in tendon structure.

5.2 Methods

5.2.1 Study Design

This prospective longitudinal study is part of a single-blinded RCT that investigated the clinical efficacy, pathophysiological tendon structural abnormalities and sensory system changes of prolotherapy injections, physiotherapy and combined in people with chronic LE. The complete protocol of the single-blinded RCT is described in Chapter 3.

5.2.2 Participants

For the purpose of this study, the data of all the participants in the RCT who had US and clinical assessment at baseline, 6, 12, 26 and 52 weeks, were evaluated. The flow of participants for this study is reported in (Figure 3.1; Chapter 3). One hundred and twenty participants were included in the analyses (Figure 3.1; Chapter 3), with >85% follow-up rates across all groups (Fig 3.1; Chapter 3).

5.2.3 Outcome measures

5.2.3.1 Primary outcome measures

Evaluation of tendon structural abnormalities on static US images using the composite TUSS scores and measurement of tendon thickness on longitudinal and transverse scans were performed at baseline, 6, 12, 26 and 52 weeks. The complete description of US measures is provided in methods chapter (Chapter 3). The assessor for US image analyses was blinded to the intervention group and assessment time.
5.2.3.2 Secondary outcomes

Demographic data including age, gender, occupational status, duration of the condition and affected side were recorded. In addition, self-reported measures including the Patient-Rated Tennis Elbow Evaluation (PRTEE), Quality of life (EuroQOL-5D) and global rating change score (GIC) were recorded at baseline and at all follow-up time points (i.e., 6, 12, 26 and 52 weeks) were considered as secondary outcomes for the purpose of the study.

5.2.4 Statistical analysis

All statistical tests were performed using SPSS Statistics version 24.0 (IBM, Chicago, IL, USA), on an intention-to-treat basis, by an investigator (VP) who was blind to group allocation. Descriptive statistics were used to describe participant demographics and tendon structural characteristics. For continuous variables, means and standard deviations were reported, whereas, for categorical variables, frequency and percentages are reported. Chi-square statistics and one-way analysis of variance (ANOVA) were used to describe the baseline group differences for categorical and continuous measures respectively. Generalised estimating equation (GEE) method (Hardin et al., 2000) was used to estimate the marginal means over the time for tendon structural measures obtained at baseline, 6, 12, 26 and 52. A first-order autoregressive relationship AR (1) was considered as the \textit{a priori} working correlation matrix structure to account for the within-subject correlation for repeated tendon structural measures. Wald $\chi^2$ test statistics and normal distribution with identity link within GEE model were utilised to evaluate the treatment effects of all continuous repeated tendon structural measures. GEE analysis utilises all data including the missing data of all participants to provide the estimated marginal mean difference between groups. All missing data were assumed to be missing completely at random (MCAR). Each outcome measure (TUSS, LTT, TTT & PRTEE) was included as a
separate response variable and group (Prolotherapy, PT and Combined) and time included as predictors in the GEE model to determine the Treatment and Treatment x Time effect. Participant demographics and baseline tendon structural values were entered into the model as covariates to determine whether they significantly influenced variations in the tendon structural measures over time in all GEE analyses. The threshold for statistical significance was set at $P < 0.05$ (95% CI). A post hoc analysis with the least significant difference method within GEE was performed to determine the pairwise group differences in estimated marginal mean change score relative to baseline at 6, 12, 26 and 52 weeks. Univariate regression analysis was performed to determine the linear association between TUSS and PRTEE over time. All statistical tests were two-tailed with a significance level of $< 0.05$.

5.3 RESULTS

5.3.1 Participants

The flow of participants through the clinical trial is shown in Figure 3.1. The study observed the a priori-defined compliance of participants, i.e., a minimum of 75% attendance at treatment sessions. The demographics and US characteristics of 120 participants are presented in Table 3.1. The groups were comparable at baseline for all demographic and tendon structural characteristics, although the PT and Prolotherapy injections groups had a higher number of participants with right side affected, whereas the Combined group had an equal ratio of participants with left and right elbows affected. One hundred and twenty participants were included in the analysis (Figure 3.1), with >85% follow-up rates across all groups. All groups had an equal number (n = 40) at baseline. The number of study participants for each group at 6, 12, 26 and 52 weeks is reported in the flow chart (Figure 3.1).
Table 5.1 Baseline characteristics for prolotherapy injections, COMB (Prolotherapy + PT) and physiotherapy groups. Values are Mean ± SD / n (%); (n = 120) where applicable

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 120)</th>
<th>Prolotherapy (n = 40)</th>
<th>COMB (n = 40)</th>
<th>Physiotherapy (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.7 ± 7.7</td>
<td>48.7 ± 7.1</td>
<td>47.1 ± 6.8</td>
<td>50.5 ± 9.0</td>
</tr>
<tr>
<td>Duration of pain (weeks)</td>
<td>42.7 ± 63.5</td>
<td>45.8 ± 71.7</td>
<td>42.0 ± 64.4</td>
<td>40.5 ± 54.7</td>
</tr>
<tr>
<td>Gender, Women</td>
<td>52 (43)</td>
<td>18 (45)</td>
<td>18 (45)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Employment, Manual work</td>
<td>45 (37.5)</td>
<td>11 (27.)</td>
<td>15 (37.5)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Non-Manual work</td>
<td>59 (49.2)</td>
<td>25 (62.5)</td>
<td>19 (47.5)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Not working</td>
<td>16 (13.3)</td>
<td>4 (10)</td>
<td>6 (15)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Previous episode of LE, N (%)</td>
<td>40 (33.6)</td>
<td>12 (30)</td>
<td>15 (37.5)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Affected side, Right</td>
<td>71 (59.2)</td>
<td>28 (70)</td>
<td>24 (60)</td>
<td>19 (75)</td>
</tr>
<tr>
<td>Left</td>
<td>30 (25)</td>
<td>6 (15)</td>
<td>18 (45)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>19 (15.8)</td>
<td>6 (15)</td>
<td>10 (25)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Dominant side affected, Right</td>
<td>86 (78.2)</td>
<td>32 (88.9)</td>
<td>22 (57.9)</td>
<td>32 (88.9)</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of pain (weeks)</td>
<td>42.7 ± 63.5</td>
<td>45.8 ± 71.7</td>
<td>42.0 ± 64.4</td>
<td>40.5 ± 54.7</td>
</tr>
<tr>
<td>Tendon structural measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoechogenicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (1.7)</td>
<td>2 (1.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Grade 2</td>
<td>25 (20.8)</td>
<td>10 (25)</td>
<td>11 (27.5)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>93 (77.5)</td>
<td>28 (70)</td>
<td>29 (72.5)</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Neovascularity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>102 (85.8)</td>
<td>34 (85)</td>
<td>37 (92.5)</td>
<td>31 (77.5)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>15 (12.5)</td>
<td>5 (12.5)</td>
<td>3 (7.5)</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (0.8)</td>
<td>1 (2.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Presence of bony abnormalities</td>
<td>89 (74.2)</td>
<td>27 (67.5)</td>
<td>28 (70.0)</td>
<td>34 (85.0)</td>
</tr>
<tr>
<td>TUSSE, 0-8</td>
<td>4.6 ± 0.9</td>
<td>4.5 ± 1.0</td>
<td>4.5 ± 0.8</td>
<td>5.0 ± 0.8</td>
</tr>
<tr>
<td>LTT, mm</td>
<td>6.1 ± 0.8</td>
<td>5.9 ± 0.8</td>
<td>6.0 ± 0.7</td>
<td>6.4 ± 0.8</td>
</tr>
<tr>
<td>TTT, mm</td>
<td>5.6 ± 0.7</td>
<td>5.6 ± 0.8</td>
<td>5.4 ± 0.7</td>
<td>5.8 ± 0.7</td>
</tr>
</tbody>
</table>

PT = physiotherapy; Combined = prolotherapy injections+PT; COMB (prolotherapy injections+PT) = prolotherapy injections and physiotherapy; TUSSE = total ultrasound scale score; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; PRTEE = Patient-Rated Tennis Elbow Evaluation
5.3.2 Effect of treatment

5.3.2.1 Total ultrasound scale score

Figure 5.1 and Table 5.2 show the mean TUSS scores and changes over time for each group. Significant improvements ($P<0.05$) in tendon structural abnormalities were observed for all groups at every follow-up time point (Table 5.2). There were no significant differences between the groups throughout the 1-year follow-up (Table 5.2). However, at 6-weeks, a significantly ($P<0.05$) higher reduction in mean TUSS was observed in PT (mean difference from baseline -1.9, 95% CI: -1.5 to -0.3) and Combined groups (-0.6, 95% CI: -1.1 to -0.1) compared to the prolotherapy injections (Table 5.2; Figure 5.1).

![Graph showing change in estimated mean total ultrasound scale score (TUSS) for all groups. Error bars denote standard errors.](image)

**Figure 5.1** Change in estimated mean total ultrasound scale score (TUSS) for all groups. Error bars denote standard errors.
Table 5.2 Effects of prolotherapy injections, physiotherapy, and combined treatments on tendon structural and clinical outcomes on the affected side at all time points over a one-year follow-up.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Prolotherapy</th>
<th>Combined</th>
<th>PT</th>
<th>Prolotherapy vs PT</th>
<th>Prolotherapy vs Combined</th>
<th>PT vs Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TUSS, /8</strong></td>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 weeks</td>
<td>4.5 (1.01)</td>
<td>4.5 (0.8)</td>
<td>5.0 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>4.7 (0.9)</td>
<td>4.03 (0.8)</td>
<td>4.2 (1.1)</td>
<td>-1.9 (-1.5 to -0.3)*</td>
<td>-0.6 (-1.1 to -0.1)*</td>
<td>0.2 (-0.2 to 0.8)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>4.3 (1.0)</td>
<td>4.0 (1.1)</td>
<td>4.6 (1.1)</td>
<td>-0.2 (-0.9 to 0.4)</td>
<td>-0.3 (-0.9 to 0.2)</td>
<td>-0.1 (-0.6 to 0.5)</td>
</tr>
<tr>
<td>26 weeks</td>
<td>3.7 (1.5)</td>
<td>3.7 (1.5)</td>
<td>4.0 (1.5)</td>
<td>-0.2 (-1.0 to 0.5)</td>
<td>-0.1 (-0.9 to 0.6)</td>
<td>0.1 (-0.7 to 0.8)</td>
</tr>
<tr>
<td>52 weeks</td>
<td>3.7 (1.0)</td>
<td>3.4 (1.0)</td>
<td>3.6 (1.5)</td>
<td>-0.5 (-1.2 to 0.1)</td>
<td>-0.1 (-0.8 to 0.4)</td>
<td>0.4 (-0.3 to 1.1)</td>
</tr>
<tr>
<td><strong>Longitudinal tendon thickness, mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 weeks</td>
<td>5.9 (0.8)</td>
<td>6.0 (0.7)</td>
<td>6.4 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>5.5 (1.3)</td>
<td>5.2 (1.2)</td>
<td>5.6 (0.9)</td>
<td>-0.2 (-0.8 to 0.3)</td>
<td>-0.4 (-1.0 to 0.2)</td>
<td>-0.2 (-0.7 to 0.4)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>5.8 (0.6)</td>
<td>5.4 (0.7)</td>
<td>5.9 (0.8)</td>
<td>-0.3 (-0.7 to 0.1)</td>
<td>-0.4 (-0.8 to -0.07)*</td>
<td>-0.1 (-0.5 to 0.2)</td>
</tr>
<tr>
<td>26 weeks</td>
<td>4.9 (1.0)</td>
<td>5.1 (0.5)</td>
<td>5.1 (0.9)</td>
<td>-0.2 (-0.8, to 0.4)</td>
<td>0.1 (-0.4 to 0.5)</td>
<td>0.3 (-0.1 to 0.7)</td>
</tr>
<tr>
<td>52 weeks</td>
<td>5.1 (0.7)</td>
<td>4.8 (0.6)</td>
<td>5.1 (0.7)</td>
<td>-0.5 (-0.9 to 0.02)*</td>
<td>-0.4 (-0.8 to 0.05)</td>
<td>0.1 (-0.3 to 0.5)</td>
</tr>
<tr>
<td><strong>Transverse tendon thickness, mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 weeks</td>
<td>5.6 (0.8)</td>
<td>5.4 (0.7)</td>
<td>5.8 (0.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>3.9 (2.2)</td>
<td>3.6 (2.2)</td>
<td>4.7 (1.6)</td>
<td>0.4 (-0.6 to 1.4)</td>
<td>0.03 (-1.1 to 1.1)</td>
<td>-0.4 (-1.4 to 0.7)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>4.2 (2.0)</td>
<td>3.9 (2.0)</td>
<td>4.4 (2.1)</td>
<td>-0.1 (-1.1 to 0.9)</td>
<td>-0.2 (-1.1 to 0.8)</td>
<td>-0.1 (-1.1, 1.0)</td>
</tr>
<tr>
<td>26 weeks</td>
<td>4.1 (1.4)</td>
<td>3.2 (1.9)</td>
<td>3.5 (2.0)</td>
<td>-0.8 (-1.7 to 0.1)</td>
<td>-0.7 (-1.6 to 0.2)</td>
<td>0.1 (-1.0 to 1.1)</td>
</tr>
<tr>
<td>52 weeks</td>
<td>4.4 (0.5)</td>
<td>4.3 (0.5)</td>
<td>4.6 (0.6)</td>
<td>-0.1 (-0.6 to 0.5)</td>
<td>-0.1 (-0.6, 0.4)</td>
<td>-0.04 (-0.5 to 0.4)</td>
</tr>
<tr>
<td><strong>PRTEE, /100</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 weeks</td>
<td>41.3 (14.2)</td>
<td>37.1 (12.1)</td>
<td>41.7 (15.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>24.5 (14.6)</td>
<td>18.3 (12.2)</td>
<td>19.7 (14.3)</td>
<td>-6.3 (-13.4 to 0.8)</td>
<td>-5.3 (-12.4 to 1.7)</td>
<td>0.9 (-6.2 to 8.1)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>18.2 (13.5)</td>
<td>12.4 (10.1)</td>
<td>12.2 (12.4)</td>
<td>-7.4 (-13.3 to -1.5)*</td>
<td>-5.2 (-11.4 to 1.0)</td>
<td>2.2 (-4.2 to 8.7)</td>
</tr>
<tr>
<td>26 weeks</td>
<td>8.9 (8.2)</td>
<td>8.2 (10.5)</td>
<td>10.3 (10.4)</td>
<td>-1.0 (-6.5 to 4.5)</td>
<td>0.03 (-6.0 to 6.1)</td>
<td>1.1 (-4.9 to 7.2)</td>
</tr>
<tr>
<td>52 weeks</td>
<td>4.9 (7.4)</td>
<td>3.9 (5.5)</td>
<td>4.4 (7.0)</td>
<td>-2.0 (-7.4 to 3.2)</td>
<td>-0.6 (-5.7 to 4.6)</td>
<td>1.7 (-2.9 to 6.4)</td>
</tr>
</tbody>
</table>

Combined = prolotherapy injections + PT; PT = physiotherapy; TUSS = total ultrasound scale score; * P<0.05; † between-group data from GEE analyses (adjusted for demographic and baseline data) with positive results in favour of the first group; PRTEE = Patient-Rated Tennis Elbow Evaluation; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness.
5.3.2.2 Longitudinal and transverse tendon Thickness

Figures 5.2, 5.3 and Table 5.2 shows the temporal changes in the LTT and TTT for all treatment groups. All groups showed a significant reduction in LTT and TTT over time ($P<0.01$; Table 5.2), but there was no significant difference between groups. A significantly higher reduction in LTT was demonstrated in the Combined (mean difference from baseline -0.4, 95% CI: -0.8 to -0.07) and PT groups (-0.5 95% CI: -0.9 to -0.02) compared to the prolotherapy injections group at 12 weeks ($P = 0.02$) and 52 weeks ($P = 0.04$) follow-up, respectively.

![Figure 5.2](image)

**Figure 5.2** Change in estimated mean longitudinal tendon thickness (LTT) for all groups. Error bars denote standard errors.

5.3.2.3 Pain and function (PRTEE)

Significant improvement in pain and function over time for all treatment groups ($P<0.001$) was observed. However, the GEE analysis results show that there were no significant between-group differences in PRTEE. At 12-week follow-up, a significantly higher
reduction in PRTEE in favour of PT ($P = 0.01$) compared to prolotherapy injections was observed (Table 5.2).

### 5.3.2.4 Association between tendon structural changes and PRTEE over time

Univariate regression analysis shows a significant association between tendon structural outcomes (TUSS, LTT and TTT) and PRTEE over time (Figure 5.4 to Figure 5.6). For TUSS, a significant change in estimated mean PRTEE score from 32.1 at baseline to 4.3 at 52 weeks ($P<0.001$, Table 5.2) is significantly associated ($P<0.05$, Figure 5.4) with a significant change in estimated mean TUSS from 4.6 at baseline to 3.6 at 52-weeks weeks ($P<0.001$). Likewise, a change in mean LTT (mm) and TTT (mm) from 6.1 and 5.5 at baseline to 5.0 and 4.4 respectively at 52 weeks was significantly ($P<0.001$; Figure 5.5 and Figure 5.6) related to change in mean PRTEE score over time (Figures 5.5; 5.6; Table 5.2).

![Figure 5.3](image-url)  
**Figure 5.3** Change in estimated mean (SD) transverse tendon thickness (TTT) for all groups. Error bars denote standard errors.
**Figure 5.4** Change in mean Patient-Rated Tennis Elbow Evaluation score (PRTEE) and in mean total ultrasound scale score (TUSS). Data presented as mean (standard error).

**Figure 5.5** Change in mean Patient-Rated Tennis Elbow Evaluation score (PRTEE) and in Longitudinal Tendon Thickness (LTT) over time. Data presented as mean (standard error).
Figure 5.6 Change in mean Patient-Rated Tennis Elbow Evaluation score (PRTEE) and in Transverse Tendon Thickness (TTT). Data presented as mean (standard error).

5.4 Discussion

The purpose of this single-blinded RCT study was to provide insights on tendon structural changes over time and to evaluate the comparative effectiveness of prolotherapy injections and physiotherapy treatment on tendon structure in people with LE. We found that tendon structure was consistently improved over time for all groups with greater reduction in TUSS observed for the combined and PT groups at 6 and 12 weeks’ follow-up in comparison with prolotherapy injections, thereby rejecting the null hypothesis. For the secondary outcome measures at 12 weeks and 52 weeks follow-up, there was a greater reduction in LTT for the Combined and PT groups compared to the Prolotherapy injections group, which showed non-significant changes in all US measures at all follow-up time points. Further, improvement in tendon structural measures was observed to be significantly related to improvement in pain and function following prolotherapy injections and physiotherapy interventions.
US evaluation of common extensor tendon at 52 weeks using TUSS showed improvement in tendon structural abnormalities including reduced hypoechochogenicity, improved fibrillary pattern, reduced neovascularity and bony abnormalities for all groups with significant association with PRTEE over time. The mean reduction in TUSS scores at 52 weeks compared with those at baseline for all the groups ranged from 1 to 1.4 points using 8-point TUSS. In the absence of published MCID values, the results of other trials using the same outcome measures can be compared (Katz et al., 2015). The effect size for TUSS exceeds that of other studies using a similar outcome measure (i.e., aggregate US rating scale) (Poltawski et al., 2012; Connell et al., 2009). Furthermore, the mean reduction in longitudinal and transverse tendon thickness at 52 weeks for all groups compared to baseline ranged from a mean 0.8 mm to 1.4 mm and 1.1 to 1.2 mm respectively. In particular, PT and prolotherapy injection groups respectively demonstrated a greater mean reduction in longitudinal (1.4 mm) and transverse tendon thickness (1.2) compared to Combined groups at 52 weeks. The large effect size for tendon thickness in our trial exceeds that of other studies (Connell et al., 2009, 2006) and the calculated MDC values (Table 3.3) for longitudinal (0.61 mm) and transverse tendon thickness (0.76 mm) in our trail. Consequently, the present study findings provide evidence of the clinical value of US assessed tendon abnormalities and tendon thickness which could contribute to the diagnosis of LE and evaluation of targeted treatment for tendon tissue. However, the lack of a significant difference between treatment groups limits our ability to determine the superiority of one treatment over other.

The pattern of difference in PRTEE scores from baseline was consistent with TUSS. A minimal clinically important difference (MCID) of 8-13 points or 37% of baseline score for PRTEE scale of 100 (0= no disability) has been considered as the minimal clinically important difference (Poltawksi et al., 2011). We set a decrease of 13 points in the PRTEE
as the criterion for success of treatment. While at 12 weeks, prolotherapy injection achieved an MCID in PRTEE of approximately 23 points compared to other groups, all participants irrespective of treatment gained an MCID in PRTEE of approximately 28 points at 52 weeks follow-up. In summary, both prolotherapy injection and PT treatments are an effective way in which to treat individuals with chronic lateral epicondylalgia, as demonstrated by a significant decrease in tendon structural and pain and function measures over the short- and long-term.

This is the first randomised clinical trial to demonstrate both short- and significant long-term improvement in common extensor tendon structure. Zeisig et al. (2008) have reported persistent structural abnormalities including grey scale changes on US at 2-year follow up in a small sample of 30 participants with LE who received an intra-tendinous injection of polidocanol and lignocaine (Zeisig et al., 2008). The contradictory study findings of Zeisig et al. (2008) may relate to the following factors: small sample size, not considering extratendinous treatments to facilitate remodelling of structural changes such as physiotherapy, US follow-up measures were performed only at just two-time points (i.e., baseline and 2-year) in a 2-year follow-up study and finally evaluation of structural abnormalities with subjective measures alone. Although not directly comparable, the insignificant MRI based tendon structural outcomes following prolotherapy injections treatment in Rabago et al. (2013) possibly highlights the importance of considering the US rather than MRI for visualising the internal architecture of tendon and monitoring the progressive tendon structural changes, mainly the tendon fibrillar alignment and vascularity (Docking et al., 2015). Further, the findings from three Korean studies in fact demonstrated the utility of US as an sensitive outcome measure in assessing treatment response and also as a significant prognostic indicator of outcomes following prolotherapy injections injection (Shin J et al., 2002; Park J et al., 2003; Kang S et al., 2003).
2004); though all the three studies were published in Korean language (Fullerton et al., 2010). Therefore, the positive findings of our study may relate to the following factors: i) inclusion of both intratendinous (i.e., prolotherapy injections) and extratendinous (i.e., physiotherapy) treatment which might have mediated significant remodelling of the tendon structure, ii) US evaluation of tendon structural abnormalities using both quantitative (i.e., TUSS) and qualitative measures (tendon thickness), iii) serial US follow-up of tendon structural changes to demonstrate longitudinal tendon structural changes over time and finally iv) blinded (clinical and group status) assessment of tendon structural changes using previously validated US image rating scale.

However, the significant short and long-term improvement in tendon structure (TUSS) demonstrated in both PT and combined groups compared to prolotherapy injections group reinforces that it was PT treatment indeed played a vital role in effectively improving tendon structure by enhancing the tensile capacity of the tendon. Evidence suggests that improvement in tensile strength achieved through loading is positively correlated with production of “normal collagen (Type I) in opposition to abnormal collagen (Type III) usually found in tendinosis (Riley et al., 2008). Likewise, the significant short and long-term improvement in tendon thickness (LTT) exhibited by the participants in both PT and Combined groups compared to prolotherapy injections suggestive of the beneficial effects of PT (manual therapy and exercise) which might have established significant change in mechanistic properties (example, thickness, volume) of the tendon through fluid exudation mechanism (Nuri et al., 2017). Therefore, the above findings suggest that combined treatments of prolotherapy injections and physiotherapy provided no additional benefit over the single treatments of prolotherapy injections or PT.
Evidence suggests that structural changes of the common extensor tendon accrue over time and reason to be related to clinical outcomes in LE (Ryan et al., 2015). However there is no evidence to support the hypothesis the author’s best of knowledge, this is the first study to demonstrate a significant association between improvement in tendon structure and pain and function over time in LE. The present study findings may provide evidence to the propositions that improvement in tendon structure facilitates clinical improvement in pain and function after prolotherapy injections and physiotherapy treatment. The present study findings are in contrast to the established evidence from cross-sectional studies (Chourasia et al., 2013; Coombes et al., 2015; Scott et al., 2013), which suggest that there is a discord between imaging (i.e., US) observed tendon structural abnormalities and clinical symptoms; though this conclusion was based on outcome measures taken at a single time point. However, the findings from this study need to be interpreted with caution as the effects could be mediated by treatment factors and the relationship between imaging and clinical symptoms were not investigated along the natural course of LE.

5.4.1 Limitations of the study

There are several limitations of this study. Firstly, the subjective evaluation of 3-dimensional tendon structural changes using 2-dimensional US images; however the quantitative assessment of tendon thickness in our study improved this limitation by providing robust and meaningful findings on tendon structure in LE. Secondly a lack of true healthy control group to compare the natural time course of tendon structural changes with those following treatment. Thirdly, a formal evaluation of US image assessor blinding was not performed, though the group status was blinded and the assessor (VJ) was not consciously aware of group clinical data. Future studies should include more 3-dimensional US imaging to accurately locate and evaluate the tendon structural changes.
over time. Strengths include 1-year follow-up RCT study design, quantitative and qualitative assessments of tendon structural changes, minimal missing US images data and significant time and treatment x time effect for TUSS and LTT for all treatment groups.
Chapter 6 Comparative effectiveness of prolotherapy injections, physiotherapy or combinations in improving sensory characteristics in people with chronic lateral epicondylalgia.
6 Comparative effectiveness of prolotherapy injections, physiotherapy or combinations in improving sensory characteristics in people with chronic lateral epicondylalgia

6.1 Background

Lateral epicondylalgia (LE) is recognised as a common musculoskeletal condition of the lateral elbow; characterised by complex pathophysiology, recurring symptoms and variable prognosis (Bhabra et al., 2016; Coombes et al., 2015; Nirschl, 1992). Approximately, 1-3% of the general population, 15% of workers and 50% of tennis players (Shiri et al., 2006) are commonly affected by LE. The pathophysiology of LE considered a multi-dimensional construct, as has been conceptualised as the interaction between local tendon pathology, sensory system or pain perception changes and motor impairments (Coombes et al., 2009). Evidence suggest that in particular the subgroups of individuals displaying multisensory impairments (Coombes et al., 2015; Fernandez-Carnero et al., 2009; Slater et al., 2006) are more likely to be associated with poorer treatment outcomes in LE (Coombes et al., 2012, 2015; Fernandez-Carnero, et al., 2009). It is therefore important to determine the optimal treatment to improve sensory impairments in LE. However, currently, there is no consensus on the effectiveness of any single treatment in improving sensory impairments in LE.

Whilst there is evidence for multisensory impairments, but the focus of previous intervention studies was only limited to evaluating the hypoalgesic effects of manual therapy techniques on mechanical hyperalgesia (i.e. reduced PPT) in LE. High level evidence suggest that prolotherapy injections injection treatment and physiotherapy (PT) treatment program comprising of Mulligan's MWM and exercise therapy possibly achieve
significant pain reduction by affecting (sensorineural effect) the underlying neurophysiological mechanism (Croisier et al., 2007; Kjaer et al., 2009; Rabago et al., 2017). However, it is currently unknown whether the combined prolotherapy injections and PT treatment can influence significant effect in individuals characterised by varying proportions of sensory and clinical characteristics of LE.

Evidence suggests that centralised component of the sensory system or pain perception changes independent of specific pain condition or location (central or peripheral) can cause abnormal responses in multiple sensory modalities in chronic pain conditions including LE (Latremoliere et al., 2009; Woolf, 2011). It is well documented that individuals with LE can be sub-grouped based on varying degrees of sensory impairments including lowered pressure, cold and heat pain threshold (PPT, CPT and HPT) and vibration detection threshold (Coombes et al., 2015; Jespersen et al., 2013). In particular, the baseline assessment of pressure pain threshold and cold pain threshold in a subgroup of individuals is a useful method to predict the development of pain and function (Coombes et al., 2015; Jespersen et al., 2013; Vicenzino et al., 1998). Thus, based on the findings, we hypothesise that mechanical and cold pain hyperalgesia if present in a subgroup of individuals can mediate treatment responses. However, there is no evidence to support this hypothesis.

Therefore, the purpose of the current study was 1) to evaluate the sensory and clinical response to single and combined treatment of prolotherapy injections and PT (exercise therapy & MWM) for LE; and 2) to determine whether subgroups of individuals displaying reduced PPT and CPT demonstrate differences in treatment response. We hypothesised that there would be no difference between the treatment groups/subgroups concerning the sensory and clinical changes.
6.2 Methods

6.2.1 Study design

The complete description of the methodology is provided in Chapter 3 (Methods). In this planned post hoc analysis, the subset of participants who had QST and clinical assessment at 25 were included in the study (Figure 6.1). The study was performed in accordance with the Declaration of Helsinki and ethical approval was granted by The Griffith University Human Research Committee.

6.2.3 Sample size

As described in Chapter 3, sample size calculations were based on a power of 0.80 to determine between-group differences of 13 points improvement on Patient-Rated Tennis Elbow Evaluation (PRTEE) (Poltawski et al., 2011) from baseline, with a dropout rate of 10% and $\alpha = 0.05$ were considered. Accordingly, a sample of 120 participants (40 per group) was recruited for the original RCT study (Bisset et al., 2006). However, not all participants were able to undergo QST at baseline ($N = 66$) and 26 weeks ($N = 38$) (Figure 6.1). We performed a post-hoc power analysis using G* Power 3.1 statistical software (Faul et al., 2009) based on the following parameters: ANOVA (fixed effects, special main effects and interaction) with achieved sample size $N = 38$, the statistical significance of $\alpha=0.05$, and a large effect size (0.75). The analysis revealed that the QST data had 81.4% power to detect a significant difference ($P<0.05$).
Figure 6.1 Flow of participants through the study.
6.2.4 Outcome measures

6.2.4.1 Primary outcomes

Sensory measures of pressure pain threshold (PPT), cold pain threshold (CPT), heat pain threshold (HPT) and vibration-detection threshold (VDT) were collected. The detailed QST methodology is described in Chapter 3.

6.2.4.2 Secondary outcomes

Clinical measures of PRTEE (Rompe et al., 2007), pain-free grip strength (PFG) in Newtons (N) (Smidt et al., 2002; Stratford et al., 1989), and global impression of change (GIC) scale scores were evaluated. For the purpose of the study, participants who responded as either “much improved” or “completely recovered” and responses “much worse”, “worse”, “no change”, or “improved” were classified as “success” and “non-success”, respectively.

6.2.5 Statistical analysis

All statistical analyses were performed using SPSS Statistics version 24.0 (IBM, Chicago, IL, USA) and Prism version 3.1 (GraphPad Software, Inc, La, Jilla, CA, USA) with an intention-to-treat approach. Continuous data are reported as mean ±SD whereas categorical data are presented as frequencies and percentages. Change in sensory and clinical status was first calculated by subtracting the baseline scores from the post-intervention score (i.e., 26-weeks) scores. Shapiro-Wilk statistics test showed that changes scores of all sensory and clinical variables were normally distributed. The treatment groups were compared for baseline normal and non-normal distributed demographic, clinical, US and sensory measures using One-way ANOVA and non-parametric Kruskal-Wallis tests as required. Further, within-group comparison of change scores of sensory and
clinical measures was performed using the Wilcoxon signed-rank test and paired t-tests respectively. We performed a two-way analysis of variance (ANOVA) to determine the main effect for treatment and side (i.e., dominant versus non-dominant side affected) on change scores of sensory and clinical outcomes (PRTEE and PFG). Group (treatment) and side (dominant versus non-dominant) were considered as fixed effects in the model. Further, baseline values of sensory and clinical outcomes were included into the model as covariates. Interaction terms for group x side, group x baseline values of outcome measures were included in the model to assess their interaction effects on treatment outcomes. Significant main effects were followed up with the appropriate post-hoc test (i.e., Least Square Differences) to test our null hypothesis. All $P$ values were obtained using two-tailed tests with a significance level set at $P<0.05$. $P$ values are presented without adjustment for multiple testing.

For the purpose of answering the secondary aim, we first assessed the significant interaction between treatment groups and subgroup characteristics (i.e., baseline PPT and CPT). After observing a significant interaction between treatment x subgroup characteristics, we then defined PPT and CPT subgroups in our sample. For PPT subgroups, we first calculated the minimum detectable change value (MDC) using the equation. $1.96 \times \sqrt{2} \times SEM$, where the standard error of measurement (SEM) is based on the three repeated scores of baseline PPT (Walton et al., 2011). The estimated MDC (101.8 kPa) was used as a criterion to delineate participants into three subgroups: improved (>MDC), no change (-108.1 to 108.1) and worse (<108.1). Likewise, the median split of change scores of CPT was used to classify participants as improved CPT (< median) and worse CPT (> median). To investigate whether the treatment effect differs in PPT and CPT subgroups, the absolute change scores of sensory (PPT, HPT, CPT and VDT), clinical (PRTEE, PFG) and success outcomes were compared using univariate ANCOVA and
independent t-test respectively. Post hoc Bonferroni tests were performed for pairwise comparisons of the subgroups.

6.3 Results

6.3.1 Participants

All individuals in our sample (N = 66) had their clinical, tendon structural and sensory assessment at baseline. At 26 weeks, however, only 38 participants completed the QST (HPT, CPT, VDT). There were no significant baseline differences in demographics, clinical, tendon structural and sensory characteristics between the groups with the exception of age, which was significantly different between groups (Table 6.1). There was a greater number of participants with their dominant side affected side (65.2%) in all groups but no significant differences between groups. Therefore, the influence of side (dominant versus non-dominant) and age on post-treatment sensory outcomes were also investigated in the two-way ANCOVA.
Table 6.1 Baseline characteristics for prolotherapy injections, COMB (Prolotherapy + PT) and physiotherapy (PT) groups. Values are mean ±SD; n (%), (N = 66)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 66)</th>
<th>Prolotherapy (n = 22)</th>
<th>Combined (n = 24)</th>
<th>PT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.5 ± 7.6</td>
<td>48.0 ± 7.2</td>
<td>48.9 ± 6.6</td>
<td>55.2 ± 7.2</td>
</tr>
<tr>
<td>Gender, Women</td>
<td>25 (37.9)</td>
<td>8 (36.3)</td>
<td>11 (45.8)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Employment</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Manual work</td>
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<td>8 (27.5)</td>
<td>11 (38.0)</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>Non-Manual work</td>
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<td>12 (37.5)</td>
<td>12 (37.5)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Not working</td>
<td>5 (7.6)</td>
<td>2 (40)</td>
<td>1 (20)</td>
<td>2 (40)</td>
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<td>Affected side</td>
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<tr>
<td>Right</td>
<td>39 (59.2)</td>
<td>14 (57.1)</td>
<td>12 (30.7)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Left</td>
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<td>4 (28.6)</td>
<td>10 (21.7)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>10 (15.1)</td>
<td>4 (40)</td>
<td>2 (20)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Dominant side affected, yes</td>
<td>43 (65.2)</td>
<td>15 (35)</td>
<td>14 (32.5)</td>
<td>14 (32.5)</td>
</tr>
</tbody>
</table>

## Tendon Structural Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All (n = 66)</th>
<th>Prolotherapy (n = 22)</th>
<th>Combined (n = 24)</th>
<th>PT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUSS, 0-8</td>
<td>4.6 ± 0.9</td>
<td>4.4 ± 1.0</td>
<td>4.5 ± 0.9</td>
<td>4.9 ± 0.9</td>
</tr>
<tr>
<td>LTT, mm</td>
<td>6.1 ± 0.8</td>
<td>6.0 ± 0.7</td>
<td>6.1 ± 0.7</td>
<td>6.3 ± 0.9</td>
</tr>
<tr>
<td>TTT, mm</td>
<td>5.5 ± 0.6</td>
<td>5.4 ± 0.6</td>
<td>5.5 ± 0.7</td>
<td>5.6 ± 0.6</td>
</tr>
</tbody>
</table>

## Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>All (n = 66)</th>
<th>Prolotherapy (n = 22)</th>
<th>Combined (n = 24)</th>
<th>PT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pain, weeks</td>
<td>40.2 ± 50.8</td>
<td>32.8 ± 43.0</td>
<td>34.4 ± 55.3</td>
<td>55.3 ± 66.1</td>
</tr>
<tr>
<td>PRTEE, 0-100</td>
<td>29.5 ± 8.8</td>
<td>30.8 ± 11.2</td>
<td>31.2 ± 9.6</td>
<td>29.5 ± 8.8</td>
</tr>
<tr>
<td>GIC, 1-6</td>
<td>4.2 ± 0.7</td>
<td>4.3 ± 0.9</td>
<td>4.1 ± 0.5</td>
<td>4.2 ± 0.9</td>
</tr>
<tr>
<td>PFG, Newtons</td>
<td>136.5 ± 97.9</td>
<td>136.5 ± 77.2</td>
<td>140.3 ± 68.1</td>
<td>163.7 ± 126.3</td>
</tr>
</tbody>
</table>

## Sensory outcomes

<table>
<thead>
<tr>
<th></th>
<th>All (n = 120)</th>
<th>Prolotherapy (n = 22)</th>
<th>Combined (n = 24)</th>
<th>PT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT, kPa (N = 120)</td>
<td>272.7 ± 108.8</td>
<td>257.3 ± 130.2</td>
<td>222.9 ± 113.0</td>
<td>272.7 ± 108.8</td>
</tr>
<tr>
<td>CPT, °C</td>
<td>9.3 ± 10.9</td>
<td>10.0 ± 13.3</td>
<td>11.2 ± 11.1</td>
<td>9.7 ± 10.7</td>
</tr>
<tr>
<td>HPT, °C</td>
<td>46.6 ± 3.4</td>
<td>47.0 ± 2.9</td>
<td>45.1 ± 4.7</td>
<td>46.1 ± 3.6</td>
</tr>
<tr>
<td>VDT, µ/s</td>
<td>1.8 ± 1.8</td>
<td>1.3 ± 0.4</td>
<td>2.1 ± 1.7</td>
<td>1.7 ± 1.3</td>
</tr>
</tbody>
</table>

PT = physiotherapy; Combined = prolotherapy injections + PT; COMB (prolotherapy injections + PT) = prolotherapy injections and physiotherapy; TUSS = total ultrasound scale score; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; PRTEE = Patient-Rated Tennis Elbow Evaluation; PFG = pain free grip strength; GIC = global impression of change scale; PPT = pressure pain threshold; CPT = cold pain threshold; HPT = heat pain threshold; VDT = vibration detection threshold.

### 6.3.2 Within-group differences

Wilcoxon signed-rank test revealed significant improvement in all sensory and clinical measures from baseline with the exception of CPT. Combined and the prolotherapy injection group had a greater number of sensory and clinical measures significantly (P < 0.05) improved from baseline compared to PT (Table 6.2). Participants in PT group demonstrated significant improvement in CPT (negative change score; -2.6 ± 9.4) from baseline compared to prolotherapy and Combined group that showed worsening of CPT.
(positive change scores, 4.2 ± 11.8 and 2.8 ± 9.1). Also, PT demonstrated greater improvement in PPT (change score: 135.4 ± 136.4) compared to prolotherapy injections (change score: 57.7 ± 149.8) and Combined (change score: 100.1 ± 115.5); although insignificant group differences observed (Table 6.2).

Table 6.2 Comparison of change scores of sensory and clinical outcomes between/within treatment groups. Values are Mean ± SD / n (%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Prolotherapy (n =22)</th>
<th>Combined (n = 24)</th>
<th>PT (n = 20)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPT °C</td>
<td>Baseline</td>
<td>47.0 ± 2.9</td>
<td>45.1 ± 4.7</td>
<td>46.1 ± 3.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>48.2 ± 2.5</td>
<td>46.9 ± 3.6</td>
<td>47.1 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>Change score</td>
<td>1.5. ± 1.7†</td>
<td>1.8 ± 3.4†</td>
<td>1.0 ± 3.3</td>
<td>0.773</td>
<td></td>
</tr>
<tr>
<td>CPT °C</td>
<td>Baseline</td>
<td>10.0 ± 13.3</td>
<td>11.2 ± 11.1</td>
<td>9.7 ± 10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>14.2 ± 11.8</td>
<td>14.0 ± 9.1</td>
<td>7.1 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>Change score</td>
<td>4.2 ± 5.4†</td>
<td>2.8 ± 9.8</td>
<td>-2.6 ± 9.4</td>
<td>0.140</td>
<td></td>
</tr>
<tr>
<td>VDT µ/s</td>
<td>Baseline</td>
<td>1.3 ± 0.4</td>
<td>2.1 ± 1.7</td>
<td>1.7 ± 1.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>1.3 ± 0.6</td>
<td>1.4 ± 0.7</td>
<td>1.7 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Change score</td>
<td>- 0.03 ± 0.5</td>
<td>-0.7 ± 1.3†</td>
<td>-0.06 ± 0.6</td>
<td>0.276</td>
<td></td>
</tr>
<tr>
<td>PPT kPa</td>
<td>Baseline</td>
<td>272.7 ± 108.8</td>
<td>257.3 ± 130.2</td>
<td>222.9 ± 113.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>330.5 ± 117.9</td>
<td>357.5 ± 77.8</td>
<td>357.9 ± 122.0</td>
<td></td>
</tr>
<tr>
<td>Change score</td>
<td>57.7 ± 149.8</td>
<td>100.1 ± 115.5†</td>
<td>135.4 ± 136.4†</td>
<td>0.295</td>
<td></td>
</tr>
<tr>
<td>PRTEE 0-00</td>
<td>Baseline</td>
<td>29.5 ± 8.8</td>
<td>30.8 ± 11.2</td>
<td>31.2 ± 9.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>9.2 ± 8.8</td>
<td>7.6 ± 11.4</td>
<td>7.7 ± 7.7</td>
<td></td>
</tr>
<tr>
<td>Change score</td>
<td>-20.3 ± 12.4</td>
<td>-23.1 ± 14.5†</td>
<td>-23.4 ± 11.4†</td>
<td>0.293</td>
<td></td>
</tr>
<tr>
<td>PFG Newtons</td>
<td>Baseline</td>
<td>136.5 ± 77.2</td>
<td>140.3 ± 68.1</td>
<td>163.7 ± 126.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>271.7 ± 148.5</td>
<td>238.9 ± 122.2</td>
<td>296.2 ± 145.0</td>
<td></td>
</tr>
<tr>
<td>Change score</td>
<td>135.1 ± 158.4</td>
<td>98.5 ± 121.2†</td>
<td>132.5 ± 180.0†</td>
<td>0.743</td>
<td></td>
</tr>
</tbody>
</table>

*significant between-group comparisons (ANCOVA); †significant within-group difference (Wilcoxon signed rank) (P<0.05); PT = physiotherapy; combined = prolotherapy injections+PT; HPT = heat pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; PPT = pressure pain threshold. Data were calculated with the following covariates: age, baseline

6.3.3 Between-group differences

A non-significant treatment effect was noted (Table 6.2). A significant main effect for Side (dominant vs non-dominant) was evident in PPT and VDT measures. There was no significant interaction effect of Group x Side for all outcome measures (Table 6.2).
6.3.4 Comparison of sensory, clinical and success outcomes between treatment groups, PPT and CPT subgroups

Subgroup analyses revealed significant differences in PFG ($P < 0.01$) and PPT ($P = 0.02$) between PPT subgroups (Table 6.3). Compared to baseline, significantly greater improvement in PFG (348.4 ± 139.5) was observed in individuals identified with improved PPT (Table 6.3) than those individuals with worse or no change in PPT (Table 6.3). However, the relative success at 26 weeks following treatment was noted in 7.5% of individuals identified with improvement in PPT compared to 48.1% and 44.4% of individuals that demonstrated worse and no change in PPT respectively (Table 6.3).

The sensory measures of PPT and HPT were significantly improved from baseline for CPT subgroups. In particular, individuals identified with improvement in CPT following intervention (N =19; Table 6.3) demonstrated significantly lesser improvement in PPT (-134.6 ± 10.6; Table 6.3) compared to individuals a worse CPT (N =19; Table 6.3) that demonstrated greater improvement in PPT (-9.2 ± 109.2; Table 6.3).
Table 6.3 Subgroup Analyses: mean ± SD comparison of change scores of sensory, clinical and success outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
<th>PRTEE /100</th>
<th>PFG N</th>
<th>Success</th>
<th>Non-success</th>
<th>PPT kPa</th>
<th>CPT °C</th>
<th>HPT °C</th>
<th>VDT µ/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT, kPa</td>
<td></td>
<td>n = 27</td>
<td>n = 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse, N = 24</td>
<td>&gt;101.8,</td>
<td>-22.7 ± 15.6</td>
<td>85.7 ± 154.4</td>
<td>12 (44.4%)</td>
<td>5 (71.4%)</td>
<td>204.7 ± 80.7</td>
<td>-2.2 ± 3.5</td>
<td>3.2 ± 4.8</td>
<td>-0.8 ± 1.3</td>
</tr>
<tr>
<td>No change 20</td>
<td>-101.8 to 101.8</td>
<td>-19.8 ± 10.1</td>
<td>129.0 ± 127.4</td>
<td>13 (48.1%)</td>
<td>1 (14.3%)</td>
<td>-7.3 ± 51.1</td>
<td>4.1 ± 8.0</td>
<td>0.8 ± 1.2</td>
<td>-0.1 ± 0.7</td>
</tr>
<tr>
<td>Improved, N = 3</td>
<td>&lt; -101.8</td>
<td>-23.4 ± 14.9</td>
<td>348.4 ± 139.5*</td>
<td>2 (7.5%)</td>
<td>1 (14.3%)</td>
<td>156.0 ± 39.3*</td>
<td>8.4 ± 8.0</td>
<td>0.1 ± 0.4</td>
<td>-0.09 ± 0.04</td>
</tr>
<tr>
<td>CPT, °C</td>
<td></td>
<td>n = 22</td>
<td>n = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved, N = 19</td>
<td>&lt; 1.6</td>
<td>-20.2 ± 13.9</td>
<td>155.9 ±178.4</td>
<td>8 (36.4%)</td>
<td>4 (80%)</td>
<td>-134.6 ±10.6</td>
<td>-4.3 ± 7.0</td>
<td>2.6 ± 3.3</td>
<td>-0.4 ± 1.2</td>
</tr>
<tr>
<td>Worse, N = 19</td>
<td>&gt;1.6</td>
<td>-25.0 ± 11.1</td>
<td>143.6 ±143.5</td>
<td>14 (63.6%)</td>
<td>1 (20%)</td>
<td>-9.2 ± 109.2†</td>
<td>7.3 ± 6.5†</td>
<td>0.3 ± 2.0†</td>
<td>-0.6 ± 2.2</td>
</tr>
</tbody>
</table>

* significant difference between PPT sub-groups (ANOVA) \( P<0.05 \); † significant difference between CPT sub-groups (Student t-tests) \( P<0.05 \); PRTEE = Patient-Rated Tennis Elbow Evaluation; PFG = pain-free grip strength; EQ-5D = EuroQol quality of life questionnaire; PPT = pressure pain threshold; HPT = heat pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; AF = affected side; UAF = unaffected side. A negative change score for PRTEE measures indicates improvement and positive change score of PFG indicates improvement.
In contrast, individuals identified with improvement with CPT had greater improvement in HPT (2.6 ± 3.3) compared to and individuals with worse CPT that exhibited lesser improvement in HPT (0.3 ± 2.0; Table 6.3). Further, the relative success was reported by lesser percentage (36.4%) of individuals identified with improved CPT whereas, a greater percentage (63.6%) of individuals exhibited worse CPT reported success at 26 weeks (N = 24; Table 6.3).

The mean difference (95% CI) in change scores of sensory, clinical and success outcomes between treatment groups and subgroups are reported in Table 6.4. As can be seen in Table 6.4, differences in treatment response were observed between treatment groups and subgroups at 26 weeks. There were no significant mean differences (95% CI) between treatment groups for all outcome measures, but significant mean differences (P<0.05) in PPT, HPT and PFG noted for CPT and PPT subgroups respectively at 26 weeks. For CPT subgroups there was a significant improvement in VDT for individuals identified with worse CPT with at 26 weeks Combined and with a significant benefit of Combined and PT over the prolotherapy injections treatment. Although the two-way ANOVA found no significant group differences for CPT, post hoc pairwise comparison using LSD revealed a greater change (i.e. higher CPT) in CPT at 26-weeks with no significant treatment effect of PT over Combined (mean difference -5.3; 95% CI -12.1 to 1.4; Table 6.4) or prolotherapy injections (mean difference -8.0; 95% CI -14.7 to -1.2; Table 6.4).
Table 6.4. Results of ANOVA to determine differences in change scores of sensory, clinical and success outcomes between treatment groups and subgroups at 26 weeks (N = 38).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subgroups</th>
<th>Prolotherapy Mean</th>
<th>SD</th>
<th>Combined Mean</th>
<th>SD</th>
<th>PT Mean</th>
<th>SD</th>
<th>Mean differences (95% CI)</th>
<th>PT vs Prolotherapy</th>
<th>PT vs Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRTEE 0-100</td>
<td>Overall</td>
<td>-24.3</td>
<td>9.7</td>
<td>-21.3</td>
<td>14.5</td>
<td>-17.4</td>
<td>13.6</td>
<td>2.9 (-5.4 to 11.4)*</td>
<td>6.9 (-1.0 to 12.2)</td>
<td>3.9 (-4.3 to 12.2)</td>
</tr>
<tr>
<td></td>
<td>PPT</td>
<td>Worse</td>
<td>-28.0</td>
<td>7.9</td>
<td>-25.7</td>
<td>15.5</td>
<td>-14.7</td>
<td>18.4</td>
<td>2.2 (-15.8 to 20.3)</td>
<td>13.0 (-6.8 to 33.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No change</td>
<td>-21.4</td>
<td>10.2</td>
<td>-19.4</td>
<td>12.6</td>
<td>-19.8</td>
<td>10.1</td>
<td>3.7 (-12.5 to 20.1)</td>
<td>-2.3 (-20.3 to 15.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved</td>
<td>-23.4</td>
<td>14.9</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>CPT</td>
<td>Improved</td>
<td>-25.7</td>
<td>10.5</td>
<td>-17.2</td>
<td>16.9</td>
<td>-21.5</td>
<td>12.0</td>
<td>10.9 (-13.1 to 35.0)</td>
<td>5.0 (-18.0 to 28.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Worse</td>
<td>-23.6</td>
<td>12.9</td>
<td>-26.0</td>
<td>11.9</td>
<td>10.8</td>
<td>4.8</td>
<td>-2.4 (-18.8 to 13.9)</td>
<td>-1.5 (-18.6 to 15.5)</td>
</tr>
<tr>
<td>PFG Newtons</td>
<td>Overall</td>
<td>135.1</td>
<td>158.4</td>
<td>98.5</td>
<td>121.2</td>
<td>132.4</td>
<td>180.0</td>
<td>-33.6 (-130.7 to 63.4)</td>
<td>18.1 (-80.9 to 117.2)</td>
<td>51.7 (-42.7 to 146.2)</td>
</tr>
<tr>
<td></td>
<td>PPT</td>
<td>Worse</td>
<td>94.3</td>
<td>149.1</td>
<td>73.8</td>
<td>137.5</td>
<td>95.3</td>
<td>221.5</td>
<td>-28.2 (-196.2 to 139.7)</td>
<td>50.0 (-136.6 to 236.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No change</td>
<td>73.9</td>
<td>83.6</td>
<td>129.8</td>
<td>111.7</td>
<td>162.9</td>
<td>159.2</td>
<td>54.6 (-98.2 to 207.5)</td>
<td>59.8 (-87.2 to 207.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved</td>
<td>348.4</td>
<td>139.5</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>HPT °C</td>
<td>Overall</td>
<td>158.1</td>
<td>159.0</td>
<td>116.8</td>
<td>64.3</td>
<td>194.1</td>
<td>270.7</td>
<td>15.4 (-190.6 to 221.5)</td>
<td>36.9 (-167.2 to 241.1)</td>
<td>21.5 (-135.2 to 178.2)</td>
</tr>
<tr>
<td></td>
<td>PPT</td>
<td>Worse</td>
<td>0.8</td>
<td>2.5</td>
<td>3.3</td>
<td>5.6</td>
<td>4.6</td>
<td>5.2</td>
<td>-2.8 (-10.1 to 4.4)</td>
<td>-0.5 (-8.0 to 6.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No change</td>
<td>0.8</td>
<td>1.5</td>
<td>0.8</td>
<td>1.3</td>
<td>0.6</td>
<td>1.3</td>
<td>-0.2 (-2.6 to 2.2)</td>
<td>-0.4 (-3.0 to 2.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved</td>
<td>0.1</td>
<td>0.4</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>VDT μ/s</td>
<td>Overall</td>
<td>-0.03</td>
<td>0.5</td>
<td>-0.7</td>
<td>1.4</td>
<td>-0.06</td>
<td>0.6</td>
<td>-0.2 (-0.9 to 0.4)</td>
<td>0.1 (-0.6 to 0.8)</td>
<td>0.3 (-0.1 to 0.8)</td>
</tr>
<tr>
<td></td>
<td>PPT</td>
<td>Worse</td>
<td>-0.4</td>
<td>0.0</td>
<td>-0.6</td>
<td>0.8</td>
<td>-0.04</td>
<td>0.4</td>
<td>0.4 (-1.0 to 1.2)</td>
<td>0.4 (-1.0 to 1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No change</td>
<td>0.5</td>
<td>0.5</td>
<td>-0.5</td>
<td>0.4</td>
<td>-0.2</td>
<td>0.7</td>
<td>-0.9 (-1.9 to 0.6)</td>
<td>-0.7 (-1.6 to 0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved†</td>
<td>-0.09</td>
<td>0.04</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>CPT</td>
<td>Overall</td>
<td>Overall</td>
<td>Overall</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>-0.3</td>
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<tr>
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<td>5.0</td>
<td>-9.2</td>
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<td>-0.07</td>
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<td>-11.4 to 0.3</td>
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</table>

*significant difference between subgroups (ANCOVA) P<0.05; † parameters cannot be constructed as group factor has one level; PRTEE = Patient-Rated Tennis Elbow Evaluation; PFG = pain-free grip strength; EQ-5D = EuroQol quality of life questionnaire; PPT = pressure pain threshold; HPT = heat pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; AF = affected side; UAF = unaffected side; A negative change score for PRTEE; pain measures indicates improvement and positive change score of PFG indicates improvement.
For PPT subgroups, individuals identified with worse PPT demonstrated a greater change in CPT at 26 weeks with the significant treatment benefit of Combined and PT over the prolotherapy injections (Table 6.4).

6.3.5 Associations between change scores of sensory and clinical outcomes

A separate correlation analysis using Pearson correlation tests revealed significant correlations between sensory and clinical measures following interventions: Change scores of CPT was significantly negatively and positively related to change scores of HPT and change scores of PPT respectively (Table 6.5) and change scores of PPT was positively related to PFG and CPT (Table 6.5).

<table>
<thead>
<tr>
<th>Variables</th>
<th>CPT change score Correlation coefficient</th>
<th>PPT change score Correlation coefficient</th>
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</thead>
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<td>PFG, Newtons</td>
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<tr>
<td>HPT 0°C</td>
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<td>PPT, kPa</td>
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</table>

*P<0.05; PRTEE = Patient-Rated Tennis Elbow Evaluation; PFG = pain-free grip; HPT = heat pain threshold; CPT = cold pain threshold; VDT = vibration detection threshold; PPT = pressure pain threshold.
6.4 Discussion

This is the first randomised clinical trial to evaluate the overall and subgroup effect of prolotherapy injections and physiotherapy on sensory and clinical measures in individuals with chronic LE. We found improvement in all sensory (PPT, HPT and VDT) and clinical measures (PRTEE and PFG) following all interventions, with the exception of CPT. The study observed that participants receiving physiotherapy showed clinically meaningful improvement in cold hyperalgesia, although not statistically significant. However, participants receiving prolotherapy and Combined treatment exhibited worsening of cold hyperalgesia following the intervention. Although there was no statistically significant difference between study groups, a secondary analysis showed that Combined and physiotherapy (manual therapy/exercises) groups demonstrated statistically significant differences in treatment effect for subgroups of individuals characterised by worse mechanical and cold hyperalgesia in comparison to prolotherapy injections. Subgroup analyses with post hoc pairwise comparisons suggested that physiotherapy and Combined groups demonstrated significantly greater improvement in VDT and CPT respectively compared to prolotherapy at 26 weeks. Therefore the study demonstrated that while there may be benefits in adding physiotherapy treatment to prolotherapy injections for improving pain, function and sensory abnormalities, the effects of the combined treatments is not superior to physiotherapy alone. In particular, the study findings substantiated that the presence of sensory abnormalities in a subgroup of individuals might influence the treatment responses. However, these significant treatment effects for subgroups cannot be generalisable to all individuals with LE as the significant subgroup differences for PFG, PPT CPT and HPT are incongruent with the overall treatment comparison.
Prolotherapy is an injection-based treatment that commonly uses a combination of hypertonic dextrose solution (usually 15-25%) and lidocaine (1%) solution in to reduce pain and stimulate tissue repair via a pro-inflammatory process (Banks et al., 1991; Rabago et al., 2013). Evidence suggests that prolotherapy injections treatment may involve multifactorial mechanisms, including needle and tissue displacement effects, injection solution-related effects and tissue-specific effects to achieve pain reduction (Rabago et al., 2017). Although evidence from animal and human studies (Banks et al., 1991; Rabago et al., 2017; Ekwueme et al., 2017) suggests that sensory nerves around a painful tendon might be directly influenced by prolotherapy injections (dextrose), there is no evidence for the effectiveness of prolotherapy injections in improving sensory abnormalities assessed by QST. Our study is the first to demonstrate a significant improvement in sensory and clinical measure measures in both prolotherapy injections and Combined groups.

A clinically important difference is identified as the meaningful and worthwhile change in treatment outcome reported by the patient. It is known that a minimum clinically important difference (MCID) is the threshold value for such a change and should be at least as large as the observed MDC (Beaton et al., 2000; Copay et al., 2007). Also, a threshold value of 2.4 kg/cm² (i.e., 235 kPa) is reported as MCID in LE (Carnero et al., 2007). Our study findings of improved threshold values for PPT at 26 weeks following intervention in all treatment groups (ranging from 330 kPa to 357 kPa) exceeded the published MCID (235 kPa) and estimated MDC (101.8 kPa) which reflects the true change in PPT measures facilitated by the significant pain inhibition effects of prolotherapy injections and physiotherapy treatment. However, clinicians need to be aware that a statistically significant improvement was observed only in the Combined and PT groups and not with the prolotherapy injection alone. The lack of statistically significant
improvement for PPT in the prolotherapy injection group suggests that PT treatment might have exerted a major effect in improving PPT in the Combined group. In the absence of published MCID values for CPT for LE, we used a decrease or increase of 15-20% of the baseline score as MCID (Wright et al., 2017; Moss et al., 2016). The change in CPT scores following the intervention compared to baseline exceeded the MCID values in all groups, with a mean increase of 43% in prolotherapy, mean decrease of 25% in Combined and mean decrease 26% reduction in the PT group. However, a statistically significant within-group difference was only observed in prolotherapy compared to other groups. Although prolotherapy demonstrated a significant change in CPT compared to baseline and exceeded the MCID following intervention, the direction of change (i.e. increase in CPT 10 to 14) was not deemed clinically meaningful. Evidence suggests that a threshold value greater than 13°C can increase the risk for future pain and disability by 26 fold in individuals with whiplash (Sterling et al., 2003, 2005).

In regard to pain and function measures, a threshold value of 13-15 (37%) points using the PRTEE scale (Poltawski et al., 2011) and 6.5 kg/m² (i.e., 63.7 N or 19.5%) (Kim et al., 2014) for grip strength were considered as MCID for these outcomes. Our study findings of significant improvement in PRTEE and PFG exceeded the established MCID values at 26 weeks in all groups. The mean decrease in PRTEE at 26 weeks was 9.2 points for prolotherapy, 7.6 for Combined and 7.7 for the PT group. Likewise, the mean increase in PFG at 26 weeks was 271.7 N for prolotherapy injection group, 238.9 N for Combined and 296.2 N for PT groups. The clinical meaningful improvements in pain-free grip strength and self-reported pain and function (i.e., PRTEE) in all groups suggest that both exercise and manual therapy treatment has produced both significant hypoalgesic and sympathoexcitatory effects operating through the descending pain modulation mechanism (Paungmali et al., 2003; Vicenzino et al., 2003; Vicenzino et al., 2007; Vicenzino et al., 2007).
1995). It is also well documented that improvement in pain and pain-free grip occurs following the application of sustained glide force by a physiotherapist and active osteokinematic movement (Mulligan et al., 2010; Paungmali et al., 2003; Slater et al., 2006; Vicenzino et al., 2007; Vicenzino et al., 2001), possibly related to the activation of descending inhibitory pathways in the central nervous system. In addition to manual therapy, the progressive resistance exercise program possibly contributed to the post-interventional hypoalgesic effect by activating multiple interacting pain mechanisms, including the endogenous opiate system and spinal or supraspinal inhibitory mechanisms (Ellingson et al., 2014; Koltyn et al., 2014; Slater et al., 2010; Solomon et al., 2002). Thus, the current study findings provide further supportive evidence for the effectiveness of exercise therapy and MWM in significantly improving pain and pain-free grip strength in LE, and it is consistent with the results from previous studies (Bisset et al., 2006; Paungmali et al., 2003; Slater et al., 2006; Vicenzino et al., 2001).

On the contrary, the worsening of cold pain threshold (i.e., cold hyperalgesia) seen in the prolotherapy and Combined groups may be explained by a number of possible theories. Firstly, the application of prolotherapy injections might have induced increased sympathetic activity, resulting in increased sensitivity to cold stimuli attributed to altered sensory responses in cutaneous areas supplied by the radial nerve (Banks et al., 1991; Smith et al., 1999; Willis et al., 1992). Evidence suggests that cold hyperalgesia is associated with peripheral sensitisation and central disinhibition of nociceptive pathways or maintenance of afferent activity in nociceptive neurons by the sympathetic activity such as release of nor-adrenaline release and sympathetic vasoconstrictor reflex (SVR) (Coombes et al., 2012; Smith et al., 1999; Willis et al., 1992). Recent evidence from an in vitro study suggests that prolotherapy induces an inflammatory response in human tenocytes which involves the release of inflammatory mediators such as prostaglandins,
thromboxanes and leukotrienes following cell death or necrosis (Ekwueme et al., 2017). In particular, it is known that chemotactic chemicals such as prostaglandins and thromboxane promote vasoconstriction and swelling within the injured areas (Banks et al., 1991). Secondly, the application of a local anaesthetic solution of lidocaine (0.4%) along with dextrose (proliferant) might possibly have contributed to local vasoconstriction leading to persistent cold hyperalgesia. There is evidence to suggest that local anaesthetic solutions such as lidocaine might induce vasoconstriction depending upon the vascularity of the injection site (Liu et al., 1995; Sung et al., 2012). To this end, we hypothesise that the vasoconstrictive effects following abnormal sympathetic activity may lead to increased sensitivity to cold stimuli or cold hyperalgesia in people receiving prolotherapy injections for LE.

The significant improvement in pressure pain threshold seen in Combined and physiotherapy groups compared to prolotherapy support the hypothesis that physiotherapy treatment comprising of exercise therapy and MWM produce significant hypoalgesic effects (Paungmali et al., 2003; Slater et al., 2006; Vicenzino et al., 2007; Vicenzino et al., 2001). The results suggest that exercise and manual therapy may activate the periaqueductal gray and descending pain modulation systems (Paungmali et al., 2003; Vicenzino et al., 1998). In particular, the results provided supportive evidence for the effectiveness of progressive resistance exercises (i.e., isometric, concentric, eccentric) in decreasing mechanical hyperalgesia. The findings are consistent with several previous studies in LE (Bisset et al., 2006; Coombes et al., 2013; Martinez-Silvestrini et al., 2005; Slater et al., 2010; Stasinopoulos et al., 2004) and other tendinopathy conditions (Ingwersen et al., 2017). It could be inferred that persistent improvement in mechanical hyperalgesia, observed at 26 weeks, reflects the tissue-specific mechanical adaptions in
response to the progressive resistance exercises protocol used in our study (Bohm et al., 2015; Kjaer et al., 2009; Slater et al., 2010).

We found significant differences in the response to treatment for subgroups of individuals based on changes in pressure pain threshold and cold pain threshold. Although individuals identified with worsening of pressure pain threshold demonstrated a poor change in pain and function (i.e., poor PRTEE change score), and pain-free grip strength, a positive response was observed in CPT (improvement in CPT), HPT (i.e., improved HPT) and VDT (reduced VDT). In contrast, individuals identified with worsening of CPT demonstrated show poorer treatment response in terms of pain-free grip strength, heat pain threshold and vibration perception; although significant improvement in PRTEE was noted. These findings are agreement with a previous study (Coombes et al., 2015), which found that the presence of bilateral cold pain hyperalgesia is a significant predictor of poor treatment outcomes.

Further, the findings of the current study are more likely to be explained by the findings of Coombes et al. (Coombes et al., 2015) which suggest that the presence of multisensory hyperalgesia implicates a complex interaction of neurophysiological mechanism which results in poor treatment outcomes in LE. Therefore, based on study findings we suggest that improvement in mechanical or cold pain hyperalgesia may not necessarily be accompanied by an improvement in clinical or sensory measures, as the treatments were not tailored to the specific neural mechanism of each sensory measure or treatment are not effective in inducing centralised changes in order to improve the sensory function. However, the study findings need to be interpreted with caution as the subgroups might lack the sufficient statistical power to detect the differences in treatment effect.
In a comparison of treatment success between subgroups, we found that the relative treatment success at 26 weeks was reported by a greater percentage of individuals identified with no changes (48.1%) compared to individuals identified with worse (44.4%) and improved pressure pain threshold. On the other hand, very few individuals (20%) reported non-success as opposed to success at 26 weeks which was reported by 80% of individuals with CPT subgroups (Table 6.3). A similar pattern was observed for CPT subgroup, although equal subgroups noted. These findings suggest that presence of worse sensory changes in these individuals is of subclinical findings and possibly not adequately pronounced to be able to perceive as a failure (non-success) of treatment.
Chapter 7 Exploring the prognostic value of ultrasound observed tendon abnormalities in people with chronic lateral epicondylalgia
Exploring the prognostic value of ultrasound observed tendon abnormalities in people with chronic lateral epicondylalgia

7.1 Background

Lateral epicondylalgia (LE) also known as tennis elbow is a chronic overuse injury of the common extensor tendon causing persistent lateral elbow pain and functional impairments (Nirschl et al., 1992). LE is a challenging and expensive condition to treat due to its complex pathophysiology, heterogeneous clinical presentation and variable prognosis (Coombes et al., 2015). Previously, it was reported that 83-90% of individuals with LE demonstrate improvement in symptoms with wait-and-see treatment approach (Bisset et al., 2007; Smidt, Lewis, et al., 2006) but recent findings suggest about 20% of individuals report persisting symptoms irrespective of treatment even after 3 to 5 years from initial diagnosis (Coombes et al., 2013). Given the poor outcomes in LE, several prognostic factors were identified including demographic, clinical, physical and psychological, but yet it remains unclear which individuals affected with LE likely to have a poor response for any particular treatment (Vicenzino et al., 2009).

Ultrasound (US) evaluation of tendon abnormalities such hypoechogenicity, heterogeneity, neovascularity and bony abnormalities using a semi-quantitative scoring is a commonly used method in clinical trials of tendinopathy conditions including LE (Clarke et al., 2010; Connell et al., 2001; Jhingan et al., 2011; Maxwell et al., 2007; Poltawski et al., 2011; Ryan et al., 2011). Although evidence from several cross-sectional studies indicate the apparent disconnect between these US described tendon abnormalities and clinical symptoms (Coombes et al., 2015), yet it recognised as essential prognostic indicators following the intervention (Clarke et al., 2010). However, one previous study (Clarke et
al., 2010) reported that the size of intratendinous tears and presence of LCL tear influenced the short-term outcomes of physiotherapy treatment of eccentric exercises; though the findings were based only on the subjective evaluation of tendon abnormalities. Currently, there is limited knowledge on the ability of both composite US score for assessing tendon structural abnormalities and quantitative measures of tendon thickness to predict short and long-term clinical outcomes following the intervention.

Recent evidence suggests that prolotherapy injections and physiotherapy program of exercise and Mulligan's MWM is effective in improving pain and function in LE. Conflicting evidence exists regarding the effectiveness of physiotherapy and prolotherapy injections treatment on treatment outcomes, as the effects of treatment may vary in individuals with specific characteristics of LE (Bisset et al., 2007). Likewise, recent trials on the efficacy of prolotherapy injections injection in LE have reported inconsistent results. Despite positive outcomes of pain and function, insignificant MRI based tendon structural outcomes following prolotherapy injections were reported in a pilot-level randomised clinical trial (RCT) (Rabago et al., 2017). Currently, it is not clear whether the presence of baseline tendon structural abnormalities described by US could predict short-term and long-term treatment outcomes of prolotherapy injections and physiotherapy in LE.

Therefore, the purpose of this study was to evaluate the clinical utility of baseline tendon structural characteristics in predicting short- and long-term treatment outcomes in a 1-year follow-up of a randomised clinical trial comparing prolotherapy injections, physiotherapy treatment, or a combination of both in LE. We hypothesised that the severity of US tendon structural abnormalities assessed at baseline will not influence short- or long-term outcomes in LE.
7.2 Materials and methods

7.2.1 Study design

This is a prospective longitudinal study utilising data from the original single-blinded RCT of participants receiving treatment for LE. The study methodology has been reported previously in Chapter 3. Briefly, a total of 120 participants with a clinical diagnosis of LE were randomised to receive either prolotherapy injections, physiotherapy or a combination of prolotherapy + physiotherapy. Demographic, clinical, sensory and US evaluation of affected and unaffected elbows were performed at baseline and 6, 12, 26 and 52 weeks follow-up. The study was approved by the Griffith University Research Ethics committee and all 120 participants provided written informed consent prior to enrolment into the study.

7.2.1 Clinical outcomes and predictor variables

Clinical outcomes of interest for the purpose of the study were the Patient-Rated Tennis Elbow Evaluation (PRTEE) scores, pain-free grip strength (PFG) measured by Digital Analyser grip dynamometer (MIE Ltd, Leeds UK) and the participant perceived improvement reported on a six-point Likert scale (Global Impression of Change (GIC): 1 = much worse to 6 = completely improved) at 12 (short-term), and 52 weeks (long-term) were considered as the primary clinical outcomes in this current study. US outcomes including total ultrasound rating scale score (TUSS), longitudinal tendon thickness (LTT), and transverse tendon thickness (TTT) obtained at baseline were considered as the potential predictor variables for answering the aims of the study. Demographic variables such as age, gender and duration of condition were also included a priori as previous studies have recognised them as significant predictors of treatment outcomes in LE (Coombes et al., 2012 & 2015; Knutsen et al., 2015; Shiri et al., 2007).
7.2.3 Statistical analysis

All statistical analyses were performed using SPSS Statistics version 24.0 (IBM, Chicago, IL, USA) and Prism version 3.1 (GraphPad Software, Inc, La, Jilla, CA, USA). Normality of the continuous variables was checked using Kolmogorov-Smirnov test statistics. Comparison of baseline categorical variables between the group was performed using chi-square tests and those of continuous variables were performed using one-way ANOVA. Univariate and multivariate linear regression analyses were performed to examine the association of each tendon structure measure with pain and function. All the potential predictor variables regardless of univariate significance were included into the final multivariate linear regression model to determine the significant PRTEE, and PFG assessed at 12 weeks (short-term) and 52 weeks (long-term) using a backward stepwise linear method as described in a previous study (Coombes et al., 2015). Treatment outcomes assessed at short-term of 12 weeks and long-term follow up at 52 weeks were used for the analyses. A binary logistic regression model analysis was performed to determine the predictor of treatment success at 12 and 52 weeks. Age, gender and duration of condition were included in all univariate and multivariate regression analyses due to their known predictive capacity on pain and function in LE (Coombes et al., 2012; Knutsen et al., 2015). In addition to the backward stepwise approach, a forward stepwise regression method was also performed to ensure the validity of the findings.

For the purpose of the current study, the six-point GIC scores were dichotomised into two groups, where participants who perceived themselves to be either “completely recovered” or “much-improved” were categorised as a “success”, with all other responses (i.e., “much worse”, “worse”, “no-change” and “improve”) as a “non-success”. Univariate analyses using independent sample t-tests and chi-square analysis were performed on the two groups (success vs non-success) comparing them for demographic, tendon structural
outcomes assessed at 12, 26 and 52 weeks. Variables from the univariate analyses with a significance level of $P<0.15$ were identified as potential predictor variables and included in subsequent multivariate logistic regressions to determine the final model predictors of success at 12, 26 and 52 weeks.

7.3 Results

7.3.1 Participants

All 120 participants had demographic, clinical and US evaluation at baseline and > 85% follow-up rates were documented. The mean duration of symptoms reported by the study participants at baseline was 42.7 weeks. Baseline demographic, clinical, tendon structural and sensory characteristics were matched for all treatment groups (Table 7.1). Fourteen participants (11.2%) had a history of corticosteroid injection more than 3 months prior to the screening for study enrollment.

Regardless of the treatment group, success was observed in 50 (52.6%) and 91 (89.2%) participants at 12 and 52 weeks follow-up respectively (Figure 7.1). Of the 45% documented non-successes at 12 weeks, 40% of participants reported themselves to be “improved”, with “no change” in recovery status reported by 7.4% participants. At 52 weeks, 10.8% participants reported themselves to be “improved”.

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Table 7.1 Baseline characteristics for prolotherapy injections, COMB (Prolotherapy + PT) and physiotherapy (PT) groups. Values are mean ± SD ± n (%).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 120)</th>
<th>Prolotherapy (n = 40)</th>
<th>COMB (n = 40)</th>
<th>PT (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.7 ± 7.7</td>
<td>48.7 ± 7.1</td>
<td>47.1 ± 6.8</td>
<td>50.5 ± 9.0</td>
</tr>
<tr>
<td>Gender, Women</td>
<td>52 (43)</td>
<td>18 (45)</td>
<td>18 (45)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Employment, Manual work</td>
<td>45 (37.5)</td>
<td>11 (27.)</td>
<td>15 (37.5)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Not working</td>
<td>16 (13.3)</td>
<td>4 (10)</td>
<td>6 (15)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Previous episode of LE, N (%)</td>
<td>40 (33.6)</td>
<td>12 (30)</td>
<td>15 (37.5)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Right</td>
<td>71 (59.2)</td>
<td>28 (70)</td>
<td>24 (60)</td>
<td>19 (75)</td>
</tr>
<tr>
<td>Left</td>
<td>30 (25)</td>
<td>6 (15)</td>
<td>18 (45)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>19 (15.8)</td>
<td>6 (15)</td>
<td>10 (25)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Dominant side affected, Right</td>
<td>86 (78.2)</td>
<td>32 (88.9)</td>
<td>22 (57.9)</td>
<td>32 (88.9)</td>
</tr>
<tr>
<td>Dominant side affected, Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical outcomes

| Duration of pain, weeks                | 42.7 ± 63.5   | 45.8 ± 71.7           | 42.0 ± 64.4   | 40.5 ± 54.7 |
| PRTEE, 0-100                          | 40.0 ± 14.1   | 41.2 ± 14.2           | 37.1 ± 10.8   | 41.7 ± 15.6 |
| GIC 1-6                               | 4.03 ± 0.8    | 3.7 ± 0.8             | 4.2 ± 0.7     | 4.9 ± 0.9   |
| PFG, kPa                              | 148.5 ± 95.4  | 160.2 ± 109.8         | 135.3 ± 64.2  | 147.8 ± 107.2 |
| EuroQol EQ-5D, /100                   | 82.3 ± 13.7   | 83.1 ± 11.2           | 80.4 ± 16.9   | 82.1 ± 13.7 |

Tendon structural outcomes

| TUSS,0-8                              | 4.5 ± 0.9     | 4.5 ± 1.0             | 4.5 ± 0.8     | 5.0 ± 0.8   |
| LTT, mm                               | 6.1 ± 0.8     | 5.9 ± 1.3             | 6.0 ± 0.7     | 6.4 ± 0.8   |
| TTT, mm                               | 5.6 ± 0.7     | 5.6 ± 0.8             | 5.4 ± 0.7     | 5.8 ± 0.7   |

Sensory outcomes

| PPT (kPa)                             | 245.1 ±100.8  | 247.8 ±83.7           | 248.8 ±105.6  | 243.5 ±114.3 |
| CPT (°C)                              | 9.3 ±10.6     | 9.9 ±12.3             | 10.1 ±10.4    | 7.6 ±10.4   |
| HPT °C                                | 46.6 ±3.4     | 47.0 ±2.9             | 46.0 ±4.0     | 46.9 ±3.1   |
| VDT (µ/s)                             | 1.8 ±1.8      | 2.0 ±2.4              | 1.8 ±1.5      | 1.7 ±1.1   |

PT = physiotherapy; COMB = prolotherapy injections+PT; TUSS = total ultrasound scale score; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; PRTEE = Patient-Rated Tennis Elbow Evaluation; PFG = pain-free grip; EuroQol EQ-5D: quality of life questionnaire; GIC = global impression of change scale.

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7.3.2 Predictors of clinical outcomes

Regression analyses assessing the relationship between identified predictors and PRTEE 12 and 52 weeks are reported in Table 7.2. Greater TUSS at baseline was the only variable to demonstrate a significant positive association with PRTEE ($P = 0.07$) assessed at 12 and 52 weeks at the univariate level. At 52 weeks, the final multivariate regression model showed there was no significant association between any of the other identified potential predictors and PRTEE, with the exception of TUSS (Table 7.2).
<table>
<thead>
<tr>
<th>Variables</th>
<th>PRTEE 12 weeks Univariate</th>
<th>PRTEE 12 weeks Multivariate</th>
<th>PRTEE 52 weeks Univariate</th>
<th>PRTEE 52 weeks Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta ) (95% CI) ( P )</td>
<td>( \beta ) (95% CI) ( P )</td>
<td>( \beta ) (95% CI) ( P )</td>
<td>( \beta ) (95% CI) ( P )</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.7 (-10.8, 14.3)</td>
<td>0.78</td>
<td>2.2 (-11.5, 16.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Age, years</td>
<td>-0.1 (-0.4, 0.1)</td>
<td>0.24</td>
<td>0.2 (-0.1, 0.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Women, N</td>
<td>-0.7 (-5.6, 4.1)</td>
<td>0.75</td>
<td>2.4 (-7.9, 2.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration, weeks</td>
<td>-0.01 (-0.01, 0.5)</td>
<td>0.31</td>
<td>-0.04 (-0.001, 0.09)</td>
<td>0.04*</td>
</tr>
<tr>
<td>TUSS, 0-8</td>
<td>2.5 (-0.02, 5.1)</td>
<td>0.04*</td>
<td>3.1 (0.4, 5.8)</td>
<td>0.02*</td>
</tr>
<tr>
<td>LTT, mm</td>
<td>-0.3 (-3.3, 2.6)</td>
<td>0.96</td>
<td>0.3 (-3.3, 3.4)</td>
<td>0.985</td>
</tr>
<tr>
<td>TTT, mm</td>
<td>-0.3 (-3.8, 3.1)</td>
<td>0.84</td>
<td>-0.1 (-4.0, 3.7)</td>
<td>0.94</td>
</tr>
<tr>
<td>Adjusted ( R^2 )</td>
<td>0.052</td>
<td></td>
<td>0.091</td>
<td></td>
</tr>
</tbody>
</table>

*\( P < 0.05 \); \( \beta \) = Unstandardised regression coefficients; *statistically significant \( P < 0.05 \); CI = confidence interval; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; TUSS = total ultrasound scale score; PRTEE = Patient-Rated Tennis Elbow Evaluation.
For PFG, gender, LTT and TTT at baseline were significantly associated \( (P<0.01) \) with greater PFG at 12 weeks at the univariate level (Table 7.3). However, the final multivariate model regression analysis indicated that baseline TTT was the only significant predictor of PFG (Table 7.3), which explained 28.6% of the variance in PFG. At 52 weeks, gender was found to be the only significant \( (P<0.01) \) predictor of PFG in the multivariate regression model analysis. The adjusted \( R^2 \) values from the final multivariate regression model indicated that gender was negatively associated with PFG, explaining 23.4% of the variance (Table 7.3).

**Table 7.3** Examining potential predictors of PFG at 12 and 52 weeks follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>PFG</th>
<th>PFG</th>
<th>PFG</th>
<th>PFG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 weeks</td>
<td>52 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>( \beta ) (95% CI)</td>
<td>( P^a )</td>
<td>( \beta ) (95% CI)</td>
<td>( P^a )</td>
</tr>
<tr>
<td>Intercept</td>
<td>233.9 (47.7, 420.2)</td>
<td>0.01</td>
<td>681.8 (536.4 to 827.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, Years</td>
<td>-1.7 (-4.7, 1.3)</td>
<td>0.26</td>
<td>-4.0 (-7.1, -0.8)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Women,</td>
<td>-131.6 (-171.7, -1.4)</td>
<td>&lt;0.001*</td>
<td>-121.5 (-167.6, -75.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Duration, weeks</td>
<td>-0.1 (-0.4, 0.2)</td>
<td>0.52</td>
<td>0.1 (-0.2, 0.4)</td>
<td>0.55</td>
</tr>
<tr>
<td>TUSS, 0-8</td>
<td>8.0 (-17.8, 33.8)</td>
<td>0.53</td>
<td>18.8 (-8.4, 46.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>LTT, mm</td>
<td>39.6 (13.8, 65.8)</td>
<td>&lt;0.001*</td>
<td>14.9 (-13.1, 43.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>TTT, mm</td>
<td>44.1 (13.5, 74.6)</td>
<td>&lt;0.001*</td>
<td>29.4 (0.9, 57.9)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Adjusted ( R^2 )</td>
<td>0.286</td>
<td>0.390</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*\( P<0.05 \); \( \beta \) = Unstandardised regression coefficients; \*statistically significant \( P<0.05 \); CI = confidence interval; LTT = longitudinal tendon thickness; TTT = transverse tendon thickness; TUSS = total ultrasound scale score; PFG = pain free grip strength.
7.3.3 Predictors of response

Binary logistic regression analyses revealed that none of the tendon structural outcomes predicted treatment success or non-success at 12 and 52 weeks.

7.4 Discussion

LE is commonly described as an overuse tendinopathy. The presence of local tendon pathology and sensory system changes are usually implicated for the heterogeneous clinical presentations and poor treatment response in LE (Bisset et al., 2015; Coombes et al., 2009; Coombes et al., 2015; Vicenzino et al., 2009). Although the clinical examination is currently considered the gold standard for diagnosing LE (Potter et al., 1995), US evaluation of the common extensor tendon is usually performed to describe the extent of the structural changes and to monitor the treatment response. Currently, there is limited evidence on the prognostic value of tendon abnormalities detected by subjective and objective US evaluation in LE. This study demonstrated that US scoring of tendon structural abnormalities at baseline is a consistent predictor of both short- and long-term pain and disability, whereas increased transverse tendon thickness was found to be a significant predictor of pain-free grip strength in the short-term (12 weeks). At 52 weeks, 39% of the variance in pain-free grip strength could be explained by a combination of the baseline demographics of age, gender and duration of the condition.

Our study findings of a significant association between increased tendon thickness and improved pain-free grip strength assessed at 12 weeks is an interesting finding for a debate. It has been suggested that tendons with increased tendon thickness and tendon hypoechogenicity represent different phases of tendon pathology (i.e., continuum) (Cook et al., 2009a). Malliaras et al. (2010) determined that the transition of the tendon with
normal echotexture on US imaging to diffuse tendon thickening is more likely than to a hypoechoic region (Malliaras et al., 2010). It is also been suggested that individuals displaying tendon hypoechogenicity are more likely to develop pain over time (Malliaras et al., 2010). In conclusion, we could postulate that the presence of tendon thickness at baseline will not influence changes/improvement in function measures such as pain-free grip strength attributed to interventions.

At one year, female gender was found be the only significant predictor of pain-free grip strength. Separate subgroup analysis comparing the mean difference (95% CI) between gender indicated that female participants (mean difference 148 N, 95% CI 87.4 to 209.5 N) reported lower pain-free grip strength compared to male participants. These findings are consistent with previous studies (Coombes et al., 2015; Smidt, Van der Windt et al., 2002; Stratford et al., 1989).
Chapter 8 General discussion
8 Discussion

The primary purpose of this thesis was to explore the relationship between US detected tendon structural abnormalities, sensory changes and clinical outcomes over time in lateral epicondylalgia (LE). Chapter 4 explored the relationship between the US, sensory and clinical characteristics of LE at a single point in time. It was observed that there was a minimal association between tendon structural and sensory changes. In several cases, a conflicting relationship between tendon structure and sensory measures was demonstrated. Secondary analyses demonstrated that most of the sensory characteristics were not related to pain measures, with the exception of heat pain threshold. Although greater heat pain threshold was found to be an only significant predictor of greater pain and poorer function (i.e., Patient-Rated Tennis Elbow Evaluation; PRTEE) in the affected elbows, the findings were not clinically significant.

The comparative effects of single and combination of prolotherapy injections and physiotherapy (exercise and manual therapy) in improving tendon structure and sensory measures were primarily assessed in Chapters 5 and 6. The results of the randomised clinical trial demonstrated that both tendon structure and sensory function improved for all treatment groups. We found in Chapter 5 that both subjective US scores for tendon abnormalities and quantitative measures of tendon thickness significantly improved at all time points (6, 12, 26 and 52 weeks) compared to baseline. Secondary analyses showed that progressive improvement in tendon structural abnormalities was significantly associated with progressive improvement in pain and function in LE. Sensory measures of pressure, cold and heat pain threshold (PPT, CPT and HPT) and vibration detection threshold (VDT) were found to be significantly improved following all interventions.
Although there was no statistically significant difference between treatment groups, subgroup analyses indicated that combined and physiotherapy treatments produced significant improvement in vibration detection threshold and cold pain threshold in a subgroup of individuals characterised by worse cold pain threshold.

In Chapter 7, we evaluated whether tendon structural abnormalities and quantitative measures of tendon thickness can be used to predict pain and disability in LE. The results indicated that the presence of abnormal tendon structure at baseline was related to both short and long-term pain and disability reported by the participants. Also, increased tendon thickness was noted to be significantly associated with improved pain-free grip strength at 12 weeks’ follow-up. Gender was found to be significantly associated with pain-free grip strength at 52 weeks; a pattern was observed that female gender was consistently associated with lower pain-free grip at baseline (Chapter 4) and 52 weeks. In the following texts, the results of the different studies of the thesis are revisited and discussed in a broader perspective.

8.1 Inter-rater reliability between physiotherapists and experienced musculoskeletal radiologist in grading the tendon structural abnormalities using a 3-tier US image rating scale

This study demonstrated good reliability in grading the tendon abnormalities such as hypoechogenicity, heterogeneity, neovascularity and bony abnormalities using 3-tier short US rating scale and excellent measuring tendon thickness on the recorded US images. The minimum detectable change values for tendon thickness measurement were calculated for tendon thickness which can be useful to determine which can be used to determine whether we could be 90% confident of the improvement in tendon thickness following the intervention. We established reliability in using the US scale prior to the onset of the
subsequent studies which was paramount for the purpose of different studies of this thesis including cross-sectional and longitudinal studies (Chapters 4, 5 and 7). The total US scale score included multiple levels to grade the severity of both hypoechogenicity and neovascularity (0-4), which is consistent with many previous studies that investigated the reliability of US evaluation in LE (Poltawski et al., 2012). Evidence suggested that US scales with more levels of rating can be more sensitive in detecting the minimum detectable change (true change) or predicting the treatment response (Poltawski et al., 2012).

However, the results have to be interpreted with caution as there was a small number of participants (raters) which might have influenced the agreement coefficients (Lee et al., 2012; Portney et al., 2010). Although we tested the reliability of measuring tear size, the measurements were performed on the US images that were pre-identified with the presence of tears by the radiologist. As such, this measure explains the higher reliability values. However, based on the finding from this study, we removed the components (size of tears, calcification and LCL abnormalities) from the modified total US image rating scale (TUSS) as they were found to be less reliable between raters.

8.2 Relationship between US-observed tendon abnormalities and sensory system changes

We observed a significant difference in both tendon and sensory measures between the affected and unaffected elbows. In particular, the significant differences in sensory measures of pressure, cold and heat pain threshold between the sides (affected vs unaffected) is consistent with previous studies (Coombes et al., 2012; Fernandez-Carnero et al., 2009; Ruiz-Ruiz et al., 2011). However, we cannot suggest that our individuals
demonstrated widespread pressure, cold or heat hyperalgesia as there was clear lack of normal controls and the study did not assess threshold measures at multiple regions of the body.

Although we observed a minimal association between tendon structural changes and sensory changes, some of the findings provide newer insights into the relationship between pathophysiological factors as indicated in the integrative pathological model for LE (Coombes et al., 2009). In particular, the novel finding of a significant negative association between the absence of neovascularity and cold pain hyperalgesia may be useful information for clinicians involved in the rehabilitation of overuse tendon injuries such as LE. The fact that the absence of neovascularity associated with cold hyperalgesia suggest that there might be a significant reduction in vascularity as tendon pathology reaches the most pronounced stage (i.e., greater degeneration of tendon pathology (Cook et al., 2016). The tendon is commonly recognised as a relatively hypovascular structure and perhaps the degenerative tendon structural changes could have occurred at the hypovascular (i.e., absence of neovessels) regions of the tendon. Also, evidence suggests that colour Doppler imaging is less reliable in detecting the blood vessels tendinopathy; although the findings are based on the patellar tendon (Docking et al., 2015). The findings of considerable presence of neovascularity in the unaffected side with no significant difference between sides reflect the fact that neovascularity may not be a good indicator of pain (Cook et al., 2004). On the other hand, the lack of significant association between tendon structural abnormalities and clinical symptoms observed at a single point in time suggests that a longitudinal study is required to investigate the temporal association between tendon structure, sensory and clinical outcomes.
The results of the study must be considered in the light of some limitations. Firstly, the total US image rating scale (TUSS) used in this RCT study was, in fact, a modified version of a 3-tier total image rating which was pilot-tested for inter-rater and intra-rater reliability using the gold standard experienced radiologist (Chapter 3; Methods). Secondly, the quality of imaging, interpretation and scoring could have been higher if performed by an experienced radiologist instead of by a non-radiologist who was trained in performing the US scan (Poltawski et al., 2012). However, good reliability for scoring the commonly observed tendon abnormalities such as hypoechogenicity, heterogeneity, neovascularity and bony abnormalities was already demonstrated for the assessor trained specifically for tendinopathy imaging.

Other limitations of this study include the are cross-sectional study design and the subjective nature of the US scale used for grading tendon abnormalities. We presume that the cross-sectional study design is indeed limited in establishing the causal relationship between variables which are known to be in transition or of progressive nature. For example, pathological changes in tendon structural may progress to the next stage of the continuum of pathology or reverse to the normal stage depending upon the capacity of the tendon tissue and staging of the tendon (Cook et al., 2016). Likewise, the progressive nature of sensory changes in the persistent pain states can be inferred by the presence of bilateral deficits in mechanical (i.e., PPT) and cold pain threshold (CPT) (Lim et al., 2012). Therefore on account of these findings, it is reasonable to believe that the current cross-sectional study design has limitations in determining the causal relationship between tendon structural and sensory outcomes. Another reason for the minimal association between tendon structural and sensory measures is that the subjective scale US scale score may not reflect the true extent of structural abnormalities.
8.3 Effects of prolotherapy injections and manual therapy/exercises on tendon structure

This longitudinal randomised clinical trial provided empirical evidence for the comparative effectiveness of single and Combined treatment of physiotherapy and prolotherapy injections on US detected tendon abnormalities over time. Significant improvement in tendon structure at all time points was observed for all treatment conditions. At 6 weeks, Combined and physiotherapy treatment produced significantly greater improvement in tendon abnormalities compared to prolotherapy injections. The study also demonstrated that Combined and physiotherapy had a significantly greater reduction in tendon thickness at 12 and 52 weeks respectively compared to prolotherapy injections. Overall, the novel findings from the study are that physiotherapy showed additional benefit when combined with prolotherapy injections in improving tendon structure and tendon thickness over time.

Significantly greater improvement in tendon abnormalities for the physiotherapy and Combined group at 6 weeks provides empirical evidence for the positive tissue remodelling effects of prolotherapy injections and physiotherapy. In particular, the significant improvement in tendon abnormalities such as hypoechogenicity, heterogeneity and neovascularity reflect that physiotherapy treatment has indeed evoked positive biochemical responses such as increased type 1 collagen turnover, new collagen synthesis. Further, optimal positive remodelling of tendon structure may possibly be influenced by the optimal loading imparted in the tendon through exercises (Archambault et al., 1995; Bohm et al., 2015) compared to prolotherapy injections at 12 and 52 weeks.
The significant improvement in longitudinal tendon thickness over time for all groups suggest that both physiotherapy and prolotherapy injections treatment have induced improvement in the mechanical strength of tendon which has resulted in a reduction in tendon thickness (Archambault et al., 1995; Tardioli et al., 2012). It is safe to state that physiotherapy comprising of exercise therapy has indeed provided the required muscle strength to allow normal mechanical loading on pathological tendon structure which has to lead to normal tendon homeostasis and a reduction in tendon thickness. Cook et al. (2009) suggested that a pathological tendon has the ability to revert reactive tendon under optimal or reduced loading conditions (Cook et al., 2009). Likewise, the cascade of cellular changes following the induced inflammatory response to prolotherapy injections of growth factors accelerate the extracellular matrix repair and strengthens the tendon tissue over time (Banks, 1991).

8.4 Longitudinal relationship between changes in tendon structural and clinical measures of pain and function

Secondary analyses of the randomised clinical trial (Chapter 5) provided strong evidence that improvement reduction in tendon structural abnormalities and tendon thickness were significantly associated improvement in pain and function (PRTEE) over time. Although the cross-sectional study (Chapter 4) demonstrated no significant association between tendon structural abnormalities and clinical outcomes in the affected elbows, the longitudinal study showed a significant association between them. This disparity between the findings reflects the fact the association between the presence of US observable pathological tendon abnormalities and relative clinical symptoms could possibly affect by the different stages of tendon pathology explained by Cook’s continuum model of pathology (Cook et al., 2016). As such, it is conceptualised that the presence of tendon structural abnormalities at a single point of time might not be directly related to the pain
and dysfunction (PRTEE), however, progression and worsening of tendon pathology might be a risk factor for the development of pain (Cook et al., 2016). Therefore a longitudinal study is warranted to evaluate the association between changes in structure and pain over time.

Accordingly, the results of our study provided empirical evidence in support of the above-stated hypothesis. The study findings on the significant temporal association between tendon abnormalities and clinical symptoms relationship is consistent with one previous study on LE (Croisier et al., 2007) and several previous studies on other tendinopathic conditions (de Vos et al., 2011; de Vos et al., 2010; Kongsgaard et al., 2009; Torstensen et al., 1994). Although de Vos et al. (2012) observed no significant association between improved tendon structure and function over time, he reported a significant association between neovascularity and symptoms at follow-up (de Vos et al., 2012). The disparity in the findings possibly resulted from the selective US imaging used in the study. In his thesis, he used the conventional US to measure neovascularity, but tendon abnormalities were evaluated by US tissue characterisation (UTC) (de Vos et al., 2011; van Schie et al., 2010). However, the current thesis used a composite US score to evaluate tendon abnormalities including neovascularity which was found to be effective compared to the UTC.

8.5 Effects of prolotherapy injections and physiotherapy on sensory function

This randomised clinical trial comparing the effects of prolotherapy injections and physiotherapy found that all sensory measures significantly improved at 26 weeks follow-up. In participants, who received prolotherapy injections and Combined treatment resulted in a significant reduction from baseline for the greater number of sensory measures compared to physiotherapy. Although the overall treatment effect was similar between
treatment groups, we observed the statistically significant difference in treatment effect for both pre-identified subgroups (i.e., PPT and CPT). In particular, we found that combined treatment comprising of physiotherapy and prolotherapy injections produced greater improvement in vibration detection threshold in a subgroup of individuals identified with worsening of cold pain threshold (i.e., cold hyperalgesia) at 26 weeks. In particular, secondary analyses provided novel evidence that a subgroup of individuals identified with improved pressure pain threshold demonstrated greater improvement in pain-free grip strength compared to individuals with worsening of pressure pain threshold following interventions. Furthermore, individuals with improved cold hyperalgesia exhibited improvement in heat pain threshold at 26 weeks following interventions. We found a significant association between changes in pressure pain and cold pain threshold at 26 weeks following interventions. Similarly, the changes in pressure and cold pain threshold were significantly associated with changes in pain-free grip strength and heat pain threshold respectively at 26 weeks.

Therefore the overall findings suggest that sensory measures of pressure pain and cold pain threshold showed were responsive to prolotherapy injections and physiotherapy treatment at the individual patient level. It can be suggested that individuals showing improvement in pressure pain threshold and cold pain threshold are more likely to show improvement in pain-free grip strength and heat pain threshold respectively. To the end, we hypothesise that changes in cold pain threshold reflects the central change in the pain system and could affect the threshold of multiple sensory modalities at the local and multiple locations. All of these study findings provide support to the established perspective that LE is indeed a disorder of central pain modulation.
The study findings do have limitations. We did not evaluate psychological factors in LE cohort. It is possible that behavioural changes, fear, anxiety or depression could have affected the threshold measures as previous studies have found that psychosocial factors may significantly influence treatment effects (Alizadehkhaiyat et al., 2007; Coombes et al., 2014). Further, the findings of differences in treatment effects within subgroups in the present study could have resulted due to QST’s high sensitivity in detecting the distinct response of each individual to the different stimuli and not necessarily reflect the true treatment effect (Rolke et al., 2006).

8.6 US-observed tendon structural abnormalities: predictors of short-term and long-term outcomes in LE

This is the first study that identified specific baseline US findings as significant prognostic indicators of both short-term and long-term pain and functional outcomes in lateral epicondylalgia. The presence of baseline tendon structural abnormalities assessed by composite US scale score is significantly associated with poor pain and disability outcomes at 12 weeks and 52 weeks. Further individuals demonstrated increased measures of tendon thickness on US images were significantly associated with increased pain-free grip strength at 12 weeks.

The novel study findings on the significant temporal association between tendon abnormalities and pain and disability provide empirical support to the integrative pathophysiological model for LE. As such, the continuum of tendon structural abnormalities has been conceptualised as the significant contributor to the pathogenesis of chronic LE (Coombes et al., 2009a). Although evidence from cross-sectional studies on tendinopathy reflect the disassociation between imaging findings and clinical presentations observed at single point of time (Chourasia et al., 2013; Coombes et al., 2015; Scott et al.,
2013), but recent evidence from Cook et al. (2016) (Cook et al., 2016) suggest that individuals exhibiting worsening of tendon structural abnormalities over time might be at greater risk for developing pain and disability in the future. Our study finding provides strong empirical evidence towards this current understanding of current knowledge on tendinopathy from Cook et al. (2016).

The significant association between baseline tendon thickness and improved pain-free grip strength at 26 weeks following treatment is an interesting finding for debate. Current opinions on the evidence from the 2016 update continuum model suggest that tendon pathological structural abnormalities and function loss (e.g. worsening or improvement of pain-free grip strength) can coexist without the influence of pain. Further, it is suggested that structural changes during the reactive stage can get worse or reversed depending upon the loading pattern of the tendon. Thus, the current evidence of improvement in pain-free grip following our exercise therapy treatment (combination of isometric, eccentric and concentric exercises) is consistent with several previous studies (Croisier et al., 2007; Stasinopoulos et al., 2017) and also provides support to the continuum of tendon pathology which proposed that tendon will adapt and strengthen under optimal loading conditions.

In summary, the significant association between the baseline tendon thickness and improved pain-free grip strength at 26 weeks could be considered as the significant effects of treatment conditions, whereas the increased tendon thickness at the baseline is possibly an adaptive thickening of the tendon in response to abnormal loading. The strong evidence provided in this study is consistent with a recent systematic review of Achilles and patellar tendinopathy (McAuliffe et al., 2016).
8.7 Limitations

In this thesis, the US scoring of tendon abnormalities for all the studies was performed by a single assessor which may be considered as problematic. The longitudinal nature of analysis of the US images suggests that there is a possibility the intra-rater reliability for the single assessor might fluctuate over time due to rater fatigue or differential accuracy over time (Wolfe et al., 2001). As such, variability in the interpretation and scoring of the tendon abnormalities may have varied over time. In order to minimise this potential variability, a random selection of images was re-scored after the full dataset had been scored and checked for consistency. However, no formal test-retest reliability was conducted and may be considered a limitation.

In the two comparative treatment studies of this thesis (Chapters 5 and 6), the lack of a placebo or healthy control group may limit the conclusions drawn. The inclusion of healthy control participants is deemed beneficial for comparing the pathological tendon structural changes in individuals with LE and the normal adaptive structural changes in age- and/or activity-matched asymptomatic controls (de Jonge et al., 2015). Further, the inclusion of an asymptomatic control or placebo group in the study design could have given more insights about the effects of the single treatments of prolotherapy injections or physiotherapy on sensory outcomes compared to a control. However, we decided against the inclusion of a control (no treatment) group, as we were concerned that it would compromise the recruitment process of participants into the RCT. In addition, the RCT was designed as a pragmatic clinical trial by which we could directly compare the clinical effectiveness of a new treatment (prolotherapy) against a physiotherapy treatment which is well known to be superior to a control (no intervention) in improving clinical outcomes in the short-term (Bisset et al., 2006; Coombes et al., 2010).
Although the QST method used in this thesis is a valid method to quantify sensory abnormalities for various stimuli, the study findings support the established evidence that QST demonstrates variation in response to the different types of stimuli. In particular, variation in response was more likely due to the subjective nature of testing where participants full co-operation and attention during the procedure is paramount (Chong et al., 2004; Yarnitsky et al., 2004; Zaslansky et al., 1998). Other factors that might influence the results include the make of the device, room temperature, test location, size and location of the test site, stimulus velocity and participants' characteristics such as age, gender, motivation, vigilance and attention (Zaslansky et al., 1998). Furthermore, interpretation of sensory abnormalities was challenging due to the following factors 1) lack of minimum meaningful difference between ipsilateral and contralateral side 2) presence of local and widespread sensory abnormalities cause interaction between nociceptive and other sensory systems (Hansson et al., 2007), 3) lack of a Z scores of the thresholds (Rolke et al., 2006), 4) high between-participant variability for some of QST measures (e.g., VDT ranged from 0.1 to 6.9; CPT range from 0.0 to 29.8) (González-Duarte et al., 2016), and 5) high percentage of lost sensory data due to equipment failure during the data collection phase.

8.8 Clinical implications

The different studies of this thesis have significantly contributed new knowledge to the existing body of literature on the pathophysiology, treatment and prognosis of LE. Firstly, the minimum detectable changes calculated for US-based tendon thickness measurements and MCID values for PRTEE are useful quantities for interpretation of our RCT data. Our concurrent collection of TUSS, tendon thickness, QST assessed sensory measures and GIC ratings allow an estimate of the MCIC for the TUSS, tendon thickness and sensory measures in LE. The empirical evidence for the significant association between tendon
structure and sensory function can be used for informed decision making concerning the assessment and monitor the individuals receiving treatment. In particular, the findings of a significant association between greater tendon thickness and higher vibration detection threshold provide novel insights about the subclinical findings of possible sensory loss (i.e., higher threshold for vibration detection) due to possible radial nerve entrapment caused by an increase in tendon thickness. Keeping up with the above evidence, a US imaging study has reported the swelling of the radial nerve and tendon thickness in the affected elbows of people individuals with LE (Gurcay et al., 2017). Therefore, this finding should be carefully considered by clinicians and researchers when developing specific assessment methods and targeted interventions for people with LE.

The current multimodal intervention involving physiotherapy and prolotherapy injections protocol which resulted in improvement in tendon structure and tendon thickness should be implemented in rehabilitation programs for tendon overuse injuries. The results from chapters 5 and 6 provide high-level evidence for the efficacy of prolotherapy in improving multifaceted pathology of LE, including tendon structural and sensory abnormalities and pain and functional impairments. However, more robust prospective longitudinal studies are required as cross-sectional studies cannot determine the causality between tendon structural, sensory and clinical characteristics of LE. findings.

Given that LE is prevalent in approximately 50% of tennis players (Gruchow et al., 1979), identification of athletes who may be at risk of developing LE, using screening tools such as US and QST, may help healthcare providers to implement preventive or optimal loading programmes. The evidence to support the baseline assessment of pressure and cold pain threshold in LE is promising. The findings that the presence of baseline characteristics such mechanical and cold hyperalgesia are known to be associated with the
risk for worsening or improvement of clinical and sensory outcomes, can help clinicians and researchers to implement treatment options on the basis of the underlying specific neurophysiological mechanism for each of sensory characteristics.

8.9 Recommendations for future research

Firstly, future studies should aim to implement greater objective US measures of tendon abnormalities to precisely evaluate the causal association between tendon structural abnormalities and sensory changes occurs at one point in time. In particular, the relationship between US detected tendon abnormalities observed at different stages of a continuum of tendon pathology and sensory system changes observed in various regions of the body should be investigated in future studies.

Finding from the Chapter 3 studies encourage future studies to involve in exploring the interventions in LE and other musculoskeletal conditions using the established tendon-structural and clinical paradigm. Results from Chapters 5 to 7 suggest that more epidemiological research studies are required to assess the natural course of these tendon structural, sensory and clinical characteristics in other relevant chronic musculoskeletal conditions.

We also recommend multidimensional chronic pain studies which could potentially utilise our Chapters 5 and 6 findings on the longitudinal tendon structural, sensory and clinical changes to develop diagnostic tools which could facilitate mechanism-based classification of pain and treatment strategies. The next step would be to perform clinical treatment trials in these subgroups of patients with distinct somatosensory patterns to substantiate the mechanism-based treatment concept. Further research to identify specific somatosensory profile or sensory pattern associated with other chronic musculoskeletal conditions can be
useful for clinicians to perform a reliable clinical evaluation of musculoskeletal pain conditions (Rolke et al., 2006; Uddin et al., 2016).

In addition, integrating other emerging objective US methods such as sonoeastography (Klauser et al., 2017), colour variance elastography, Doppler waveforms can be useful to validate the conventional 2-D data with other objective imaging methods. Secondly, the effects of single treatment of physiotherapy or in combination should be evaluated using the complete QST battery of sensory measures involving seven tests for measuring 12 parameters (Rolke et al., 2006).

8.10 Conclusion

The results from the thesis suggest that US-observed tendon structural abnormalities are associated with few sensory abnormalities at a single point in time and longitudinally related to pain and disability in people with LE. It can be inferred that the variability in the severity of tendon structural changes, sensory system changes and clinical changes at a single point in time might have influenced the measures of association between these interacting factors. Physiotherapy and prolotherapy treatments are noted as effective in improving tendon structure, sensory and clinical outcomes over time.
References


Coombes, B., Bisset, L., Brooks, P., Khan, A., & Vicenzino, B. (2013a). Effect of Corticosteroid Injection, Physiotherapy, or Both on Clinical Outcomes in Patients With Unilateral Lateral Epicondylalgia A Randomized Controlled Trial Sign In to


Tendinopathy: Primary Results From the Double-Blind Randomized Controlled RoCTEx Trial. *Orthopedic Journal of Sports Medicine, 5*(8), 2325967117723292.


assessed with sonoelastography: histologic correlation. European Radiology, 27(8), 3460-3466.


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APPENDICES

APPENDIX 1  Ethical Approval
APPENDIX 2  Information Sheet & Consent Form
APPENDIX 3  Clinical Screening Questionnaire
APPENDIX 4  EuroQOL-5D, EQ-5D Questionnaire
APPENDIX 5  Exercise Compliance Questionnaire
APPENDIX 6  GIC and VAS Questionnaire
APPENDIX 7  Physiotherapy Exercises
APPENDIX 8  Physiotherapy Advice Brochure
APPENDIX 9  Prolotherapy injections Advice Brochure
APPENDIX 10  3-Tier Ultrasound Image Rating Scale
APPENDIX 11  Modified Total Ultrasound Image Rating scale
APPENDIX 12  Copyright: Permissions and licensing agreement Forms
Dear Dr Ryan,

I write further to the additional information provided in relation to the provisional approval granted to your application for ethical clearance for your project "Full Review - Randomised Clinical Trial of Prolotherapy Injections and an Exercise Program Used Singly and in Combination for Refractory Tennis Elbow" (GU Ref No: PES/11/12/HREC).

The additional information was considered by Office for Research.

This is to confirm that this response has addressed the comments and concerns of the HREC.

Please advise when Roshanak is enrolled into HDR so that we are able to add her to the research team.

Consequently, you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.

Regards

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At this time all researchers are reminded that the Griffith University Code for the Responsible Conduct of Research provides guidance to researchers in areas such as conflict of interest, authorship, storage of data, & the training of research students. You can find further information, resources and a link to the University’s Code by visiting http://www62.gu.edu.au/policylibrary.nsf/xupdatemonth/e7852d226231d2b44a2875c00624e77?opendocument

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Information Sheet & Consent Form

Randomised Clinical Trial of Prolotherapy injections Injections and an Exercise Program Used Singly and in Combination for Refractory Tennis Elbow

INFORMATION SHEET

Who is conducting the research

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| m.yelland@griffith.edu.au |
| Leanne Bisset MPhty, PhD |
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| Griffith University |
| Angus Ng PhD |
| School of Medicine |
| Griffith University |
| David Rabago MD |
| Department of Family Practice |
| University of Wisconsin-Madison |

Why is the research being conducted?

Tennis elbow is a common painful condition that can make it much harder to perform activities at work and in the home. There is not a standard treatment for tennis elbow and uncertainty remains as to what is the best treatment for this condition.

Exercise is a common, practical and inexpensive treatment. Under the guidance of a physiotherapist, exercise-based treatments are commonly thought to be effective.

Prolotherapy injections is the injection of a solution that will help the body begin healing through a process that creates inflammation, healing and strengthening of weakened tendons and ligaments. There is some evidence that prolotherapy injections is effective for healing tendon injuries at other parts of the body, such as the ankle, foot, and even the elbow. However, prolotherapy injections has never been compared to exercise in a clinical trial on tennis elbow before.

The following study is being carried out to test how well physiotherapy directed exercises can reduce pain and improve symptoms of tennis elbow compared to prolotherapy injections. This study will also find out whether doing both treatments is better than doing either treatment alone.

Description of Treatments Used in this Study

This study requires participants to attend a clinic or clinics for treatment. Depending on which group you are assigned to, participants are asked to attend either 4 or 8 of these treatment sessions that will take place on the Gold Coast or in the Brisbane area. Each treatment session will last 15 to 30 minutes.

Prolotherapy injections Injections
Participants who are assigned to the prolotherapy injections group will be offered four injection treatments spaced 4 weeks apart. At each treatment the affected elbow ligaments and tendons will be injected with a
solution of concentrated glucose and local anaesthetic to encourage inflammation and healing. Sodium morrhuate (from cod liver oil) may be added to the solution in the last 2 treatments to increase the effect if there has been insufficient improvement by this stage. As the injections are meant to cause some inflammation, the injection site may be sore for 2 to 7 days after treatment before symptoms improve.

**Physiotherapy and Therapeutic Exercise**

Four physiotherapy sessions lasting 30 minutes will be provided by a post-graduate qualified physiotherapist over a 4-week period. The physiotherapy-based treatment in this study will involve 3 components: education, a manual therapy technique called Mobilisation with Movement (MwM), and a therapeutic exercise program. For the education component, the participant will be informed on why tennis elbow occurs and how the participant can compensate certain tasks in the home and at the workplace to minimize the symptoms of tennis elbow. The MwM technique, which involves moving the elbow joint through a movement while applying pressure to specific locations around the elbow, is the second component of the physiotherapy treatment and will be done by the physiotherapist at each of your treatment visits. Lastly, therapeutic exercises will serve as an important foundation for the physiotherapy treatment and are divided into 3 main groups: 1) retraining of gripping and forearm movements, 2) addressing forearm muscle weakness with wrist extension, and 3) general arm strengthening. Each of the exercises will be reviewed in the in-person treatment visit with the participant then performing the exercises at home on daily basis. Physiotherapists will prescribe exercises based on the participant's capabilities at any given session to allow for optimal exercise volume and load setting without exacerbating pain. The overriding rule for all exercise is that pain should not be provoked during or after exercise, including avoidance of delayed onset muscle soreness.

**Combined Treatment Arm**

The combined protocol involves 4 prolotherapy injections injection treatments at 4 weekly intervals and 4 visits to the physiotherapist for Physiotherapy and Therapeutic Exercise protocol described above, but timed for 1, 2, 3 and 5 weeks after the first prolotherapy injections treatment to allow recovery from any post-injection soreness.

**Can I Use Other Treatments In This Study**

If you consent to be in the study, you will be requested to stay in your treatment group for the duration of the study, i.e. three months from the start of treatment. If you need extra pain relief during the study period, pain relief medication may be used. Brand names for these medications include Panamax, Codalgin, Panadeine, Panadeine Forte, Dige Sic, Capadex and Paradex. For more significant pain after injections, you will be provided with a script for Endone (oxycodone) tablets at the first treatment visit. In those receiving prolotherapy injections injections, no aspirin or other anti-inflammatory medication (such as Voltaren, Brufen, Nurofen, Naprosyn, Mobic or Celebrex) should be used for pain relief following injections as they will prevent the inflammatory process that is part of the treatment. If you are already taking an anti-inflammatory medication for reasons other than tennis elbow, they can be stopped temporarily around the time of treatment. Liniments should also not be used. The restrictions on pain medications do not apply after treatment is completed. Finally, any other injection or exercise treatments should be avoided as they may interfere with the effect of the treatments given in the study. If you do use any other treatments during the study, you will need to tell the researchers so they can document this.

**What participants will be asked to do**

This study requires participants to attend a clinic or clinics for treatment. Depending on which group you are assigned to, participants are asked to attend either 4 or 8 of these treatment sessions that will take place on the Gold Coast or in the Brisbane area. Each treatment session will last 15 to 30 minutes.

As this is a clinical trial, we are interested in closely watching whether a person’s symptoms change over time. We are asking participants to attend 5 in-person monitoring appointments: 1 at the beginning of the study and 4 follow-up appointments at 1.5, 3, 6 and 12 months after the start of the study. Each of these monitoring appointments will last approximately 60 minutes.
We are also asking participants to complete a 2-minute online survey to update the study team on how alternative treatment usage and whether there has been any recurrence of pain. This survey will be sent out every month for the duration of the 52 weeks.

The basis by which participants will be selected or screened

Individuals eligible to take part in this clinical trial must be adults aged between 18 and 70 years who have been experiencing pain over the outside of their elbow for at least 6 weeks.

Individuals are initially screened through a phone call to inquire about the location and duration of their pain, treatments used in the past 3 months, allergies, surgeries performed on the affected elbow, and whether or not they are pregnant or breastfeeding. Eligible individuals will then have an appointment with a study team member to confirm the location and severity of elbow symptoms, find out whether there is weakness in handgrip on the affected side, as well as rule out certain other factors such as elbow pain that does not come from the tendon, some types of neck pain and medication use that may interfere with the treatments used in this study.

The expected benefits of the research

All of the treatment groups in this study are active, which means it is expected that most people will feel some improvement in their elbow pain but the amount of pain reduction may vary between individuals and between treatment groups. There is also no guarantee that every participant will experience reduced elbow pain. Participants who attend all in-person monitoring appointments will have their name entered in a draw to win a $1000 travel voucher.

Risks to participants

The main side effect of the prolotherapy injections injections is a mild to moderate flare in tendon pain and stiffness sometime between two to seven days after the injections. This occurs in about half of the patients having this treatment. The mild to moderate flare in tendon pain and stiffness is temporary and usually well controlled with medication or local heat. It is due to the inflammation deliberately caused by the injections to help the healing process. It is less frequent later in the series of injections and is very rarely bad enough for patients to want to stop treatment.

Participants are advised to contact their Health Insurers such that they are aware of any implications that participation in this trial may have on their current insurance.

Cost Reimbursement

All treatments in the study are provided to participants at no cost to them. Participants will need to find their own way to the treatment and assessment centres but will receive a $40 petrol voucher to help offset the costs associated with travel incurred while taken part in this research. Vouchers will be given-out to participants at the 12 month in-person monitoring appointment.

Confidentiality

Information about participants will be collected during the study; however, it will be coded so that it will not be identifiable. Participant information will be stored in a locked cabinet in the office of the study coordinator Michael Ryan during and after the research project. Dr. Ryan's office is itself located inside a key card locked building. The subject ID key linking participants’ subject code with their name will also be stored in this locked cabinet. All data from participants will be entered into spread-sheets using this subject code that will not contain any personally identifiable information (such as name, date of birth, etc.).

Participation is voluntary

Involvement in this study is entirely voluntary. Participants may choose to withdraw from this study at any time without penalty and without any impact on the future care of their condition, whatever treatment(s) they have already received.

Questions / further information

For additional questions about this research study please contact the Study Coordinator, Michael Ryan, at any time by phone: 07-5552-7443, or email: Michael.ryan@griffith.edu.au.
The ethical conduct of this research

Griffith University conducts research in accordance with the National Statement on Ethical Conduct in Human Research. If you have any concerns or complaints about the ethical conduct of this research project you should contact the Manager, Research Ethics on 3735 5585 or research-ethics@griffith.edu.au.

Feedback to participants

After this study is completed, we would be happy to share with participants a summary of this study’s findings before we submit our results for formal publication. Please indicate to the research team at any point in your involvement with the study that you would like a copy of the study findings and one will be made available to you.

The research involves access to, collection or generation of identified personal information, and there is no plan to disclose identified information to third parties

The conduct of this research involves the collection, access and / or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without participant’s consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded. For further information consult the University’s Privacy Plan at http://www.griffith.edu.au/about-griffith/plans-publications/griffith-university-privacy-plan or telephone (07) 3735 5585.

Terms and Conditions of Entry of Prize Draw for Travel Voucher worth AU$1000

1. When you enter the competition, you accept these terms and conditions of entry.

2. Employees of Griffith University (“the University”) are eligible to enter; however, members of the research team and their immediate family are not eligible to enter.

3. Entry into the competition is by:

giving a completed consent to undertake research form to the Research Officer (Marnie Ryan) in Room 1.10 of building G02.

4. The first random drawn entry will receive a travel gift voucher worth AU$1000 to be redeemed at STA Travel.

5. The decision of the University is final and no correspondence will be entered into.

6. The prize is not transferable and cannot be redeemed for cash. The prize is not refundable.

7. The winner releases the University from any and all causes of action, losses, liability, damage, expense (including legal expenses) cost or charge suffered, sustained or in any way incurred by the winner as a result of any loss or damage to any physical property of the winner, or any injury to or death of any person arising out of, or related to or in any way connected with the University or the prize.

8. Any winner drawn for the prize who is unable to fulfil all of these terms and conditions will forfeit the prize and another winner will be drawn.

9. The winner will be notified by email and phone by no later than October 31st, 2014, or corresponding to the completion of follow-up testing on the final enrolled participant.

10. The competition opens to entries at October 10th, 2012 and the competition closes at October 1st, 2014 or corresponding to the completion of follow-up testing on the final enrolled participant. The competition is drawn at October 2nd, 2014 or corresponding to the day after the completion of follow-up testing on the final enrolled participant.
11. The prize will be available for collection by the winner at Griffith University Gold Coast Campus immediately after the draw.

Randomised Clinical Trial of Prolotherapy injections and an Exercise Program Used Singly and in Combination for Refractory Tennis Elbow

CONSENT FORM

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Research Team
Leanne Bisset MPhty, PhD (Griffith University)
Michael Ryan PhD (Griffith University)
David Rabago MD (University of Wisconsin-Madison)
Jennifer Whitty PhD (Griffith University)
Angus Ng (Griffith University)

By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that my involvement in this research will include up to 8 treatment sessions, 5 in-person monitoring appointments and a series of online survey responses;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand that with participation in this research project I will receive a $40 petrol voucher help offset any travel expenses incurred at the 12 month monitoring appointment. I will also be entered to win a $1000 travel voucher once I complete the final 12 month follow-up appointment;
- I understand that my participation in this research is voluntary;
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without comment or penalty, and that my withdrawal will not affect any treatments that were initiated;
- I understand that I can contact the Manager, Research Ethics, at Griffith University Human Research Ethics Committee on 3735 5585 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

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Clinical Screening Form

**Baseline Information**

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**Body Chart**

- Anterior shoulder
- Anterior upper arm
- Anterior elbow
- Anterior forearm
- Anterior wrist and hand

- Cervical spine
- Thoracic spine
- Posterior shoulder
- Posterior upper arm
- Posterior elbow
- Posterior forearm
- Posterior wrist and hand

Other
# Medical History

**Conditions:**

**Investigations:**

**Medication:**

**Weight change:**

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# Recreational/Sport Activity

Do you regularly participate in any sport over the past 7 days? Did you regularly participate in any sport prior to the start of your lateral elbow pain?

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</tr>
</tbody>
</table>

Have you had to alter, reduce or altogether stop participating in a sport/activity as a result of your elbow pain? If yes, which activity(s)?

**Posture:**

**Cervical spine ROM (AM):**

**Cervical palpation (PAVMS, PPVMS):**

**ANTERIOR**

**Sperling’s Test**
# Shoulder ROM

<table>
<thead>
<tr>
<th>Flexion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HBB</td>
<td></td>
</tr>
<tr>
<td>ER</td>
<td></td>
</tr>
<tr>
<td>Abduction</td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td></td>
</tr>
</tbody>
</table>

# Elbow ROM (with OP)

<table>
<thead>
<tr>
<th>F</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S (0°)</td>
<td></td>
</tr>
<tr>
<td>P (0°)</td>
<td></td>
</tr>
<tr>
<td>F/AB</td>
<td></td>
</tr>
<tr>
<td>E/AB</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
</tr>
<tr>
<td>S (90°)</td>
<td></td>
</tr>
<tr>
<td>P (90°)</td>
<td></td>
</tr>
<tr>
<td>F/AD</td>
<td></td>
</tr>
<tr>
<td>E/AD</td>
<td></td>
</tr>
</tbody>
</table>

# Muscle

<table>
<thead>
<tr>
<th>Stretch</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist Extension</td>
<td></td>
</tr>
<tr>
<td>3rd Finger Extension</td>
<td></td>
</tr>
<tr>
<td>2nd Finger Extension</td>
<td></td>
</tr>
</tbody>
</table>

## Palpation:
(Nominate position of arm and orientation of the direction of palpation)

## Neurological:
Sideglide +/- Neural provocation test 2b (Note: UL position)

## Pain Free Grip Strength

<table>
<thead>
<tr>
<th>RIGHT ARM</th>
<th>LEFT ARM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>Trial 2</td>
</tr>
</tbody>
</table>

Eligibility |  |
Reason for ineligibility? |  |
**EuroQOL-5D, EQ-5D Questionnaire**

**EQ-5D-5L Descriptive Scale**
*Under each heading, please tick the ONE box that best describes your health TODAY*

**Mobility**
- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**Personal Care**
- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** (e.g. work, study, housework, family or leisure activities)
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed
EQ-5D-5L Visual Analog Scale

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below

YOUR HEALTH TODAY =
Exercise Compliance Questionnaire

Exercise Program Compliance

The following questions will ask you about your compliance with the recommended therapeutic exercises that the physiotherapist had given you to complete. Please tick the box that BEST represents your response for that question.

Exercise Frequency

The therapeutic exercises used in this study are designed to be performed EVERY DAY for optimum recovery. Over the past 2-weeks how OFTEN would you say you have done the exercises?

- I haven’t done any exercises at all
- I hardly do any exercises, maybe once every couple weeks
- I do my exercises about once a week
- I do my exercises a couple times a week
- I do my exercises almost every day
- I do my exercises as recommended daily

Exercise Type

There are several types of exercises recommended that you perform during an exercise session to ensure all areas of arm weakness are addressed and to stimulate recovery of the tendon. On a given exercise that you have performed over the past 2-weeks, HOW MANY DIFFERENT TYPES of exercises have you performed?

- I haven’t done any exercise types in a given session
- I would do about half of the exercise types in a given session
- I would do almost all of the exercise types in a given session
- I would do all the recommended exercise types in a given session

□ □ □ □ □
GIC and VAS Questionnaire

Self-reported Measures

General Improvement
Rate the change in your arm pain since the beginning of this study by circling the category which best describes this change.

1 much worse  2 worse  3 no change  4 improved  5 much improved  6 completely recovered

Resting Pain Intensity Score (mm):
Mark this scale to indicate the level of pain you currently experience at rest, where 0 is ‘no pain’ and 100 is ‘worst pain imaginable’.

No Pain 0  Worst Imaginable Pain 100

Worst Pain Intensity Score (mm):
Mark this scale to indicate the worst level of pain you experienced during the past week, where 0 is ‘no pain’ and 100 is ‘worst pain imaginable’.

No Pain 0  Worst Imaginable Pain 100
PHYSIOTHERAPY EXERCISE

PHYSIOTHERAPY EXERCISE PROGRAM

The goals of physiotherapy are to:

1. Reduce pain
2. Improve function
3. Reduce recurrence rates

What can I do?

The following advice is widely regarded to be very important for tennis elbow sufferers.

♦ Activities that increase your elbow pain, especially those that increase pain for longer than a few minutes should be avoided.

♦ Avoid lifting objects in your hand with your palm down.

♦ Take regular breaks from repetitive gripping or manipulation of objects eg tools use, typing or mouse use.

♦ Over-the-counter medication, hot or cold packs or forearm braces may be used for pain as needed.

Motor Control Exercises:

*The following exercises are aimed at improving the control and awareness of movements of your forearm.*

*Perform 10 repetitions of each exercise, at least twice per day. Each exercise is done slowly over a count of 8 seconds.*

**Palm Slides** –

Place your forearm flat on the table with your palm facing down. Ensure your hand is in line with your forearm. Keeping your fingers straight, slowly slide your finder tips along the table toward your wrist then return to the starting (flat) position. You will feel your knuckles lift making a peaked shape then flatten. Do not let your wrist tilt sideways or let your fingers curl under (bend).

**Forearm Rotation** –

Start with your elbow bent and resting on a desk with your wrist and hand free. Make a light fist with all fingers except your little finger. Imagine an **axis** running through your **little finger** toward your elbow. Slowly turn your palm up and down over a count of 8 seconds, such that the rotation occurs around this axis. The tip of your little finger should spin on the same point in space. Perform 10 repetitions slowly, aiming for full range in each direction. Do not force your elbow into any positions that are painful.

You should not feel any elbow pain when doing these exercises. If you are experiencing any pain during or following any exercise or have any questions, please contact your physiotherapist immediately.

**Grip Posture Retraining** –
Gripping of objects is commonly painful in tennis elbow, especially if the palm faces down. Research has shown that people with tennis elbow adopt a different wrist posture when gripping to those without pain.

With your elbow bent by your side, hold the plastic pipe in your hand with your thumb facing up (A). Position your wrist slightly cocked back (towards the back of your hand). This is the most efficient position for gripping. Slowly grip the pipe and release over a count of 8 seconds. Grip only to the point of onset of discomfort but do not provoke sharp elbow pain. This may be combined with a glide to your elbow.

Progress this exercise as tolerated by changing the starting position to place the palm facing down (B) and stretch the arm in front of the body with elbow straight (C). Your Physiotherapist will advise you when you are ready to progress.

**Strengthening Exercises:**

**Supination**

Rest your forearm on a table with your palm down and allow your wrist to sit over the edge. Grasp the Theraband in your affected hand such that the loose end sticks out on the thumb side. Wrap the band over the top of your hand and secure the other end with your other hand. Slowly turn your palm up against resistance then release over a count of 8 seconds.

**Pronation**

Rest your forearm on a table with your palm up and allow your wrist to sit over the edge. Grasp the Theraband in your affected hand such that the loose end sticks out on the little finger side. Wrap the band around your hand and secure the other end with your other hand. Slowly turn your palm down against resistance and release over a count of 8 seconds.

*** Note that the band is wrapped around the hand in opposite directions for the above exercises. Arrow points to end of band (on thumb side for supination or little finger side for pronation).

**Alternative Exercise:**

**Supination and Pronation**

Rest your forearm on a table and allow your wrist to sit over the edge. Hold a hammer or weight in your affected hand with the heavy end pointing upwards. Slowly turn your palm up then down over a count of 8 seconds, such that the weight alternately lowers to each side. Progress by holding the hammer closer to its end.

**Wrist Extension Strengthening Exercises:**
The below exercises are aimed at improving forearm strength and provide stimulation for tendon remodelling. Each exercise is done slowly over a count of 8 seconds. Perform 2-3 sets of 10 repetitions with a rest period of 2-5 minutes between sets. These exercises should be repeated twice each day. These exercises must be progressively increased to gradually load the muscles and tendons at the elbow.

Starting Position:

Sitting, with your forearm resting palm down on a table (or on your thigh), with your wrist over the edge. Hold the Theraband handle in your affected hand and secure the other end underneath your foot. Try to maintain good posture. Slowly lift and then lower the wrist against resistance through a comfortable range over a count of 8 seconds.

Progressions:

Resistance should be progressed so that it is ‘somewhat difficult’ to perform 10 repetitions without aggravation of pain. This can be achieved by shortening the band in 1cm increments or by changing the Theraband colour. Marking the band helps monitor your progress.

Prescribed Theraband colour: ____________________

Comments:

You should not feel any elbow pain when doing these exercises. If you are experiencing any pain during or following any exercise or have any questions, please contact your physiotherapist immediately.

Exercise Progression:

Once wrist strengthening with the Theraband is comfortable, progress to more extended elbow positions.

Wrist extension with arm outstretched –

Position your arm in front of your body with your elbow straight. Hold the Theraband handle in your affected hand with your palm down. Secure the other end underneath with your other hand below. Slowly lift and then lower the wrist against resistance over a count of 8 seconds.

Elbow Glides

The following exercises are aimed at decreasing the pain you experience when gripping and moving your arm. Perform 1 set of 10 repetitions, at least twice per day. These glides can be combined with other exercises to allow them to be pain-free. Your physiotherapist will direct you to perform ONE of the following of glides.

LATERAL ELBOW Glide with Grip –

Start with your elbow bent at your side. It may be helpful to lean your upper arm against a wall. Hold an object in your hand with your palm facing up. Locate the bony point on the inside of your elbow. Place the
web space of your unaffected hand just below this bony point. Your thumb and fingers will wrap around the
elbow, but should not press strongly. Slowly apply an outward glide (force directed away from your body)
with your web space. While maintaining the glide, slowly grip then release over a count of 8 seconds. Adjust
the glide as shown by the physiotherapist so you do not experience any pain.

**Glide with Movement –**
As above, locate the bony point on the inside of your elbow. Apply a gentle outward glide (force directed
away from your body) with your web space. Sustain this glide while you slowly bend and straighten the
elbow through full range 3-6 times. Adjust the glide as shown by the physiotherapist so you do not
experience any pain.

You should not feel any elbow pain when doing these exercises. If you are experiencing any pain during or
following any exercise or have any questions, please contact your physiotherapist immediately.

**RADIAL HEAD Glide with Grip –**
With your elbow bent by your side, hold an object in your hand with your thumb facing up. Locate the most-
tender point on the outside of your elbow with your finger tips. Slide your finger tips approximately 2cm
below this point so that you are on a round bony ridge. By turning your palm up and down you should be
able to feel this bony ridge bone rotate under your fingers. Apply a gentle glide with your fingers (force
directed towards your body). While maintaining the glide, gently grip the pipe over a count of 8 seconds and
then relax.

**Glide with Movement –**
As above, locate the bony radial head with your finger tips. Apply a gentle glide (force
directed toward the body) with your fingertips. Sustain this glide while you slowly bend and straighten your
elbow through full range. Be sure to adjust the glide as shown by the physiotherapist so you do not
experience any pain.

**Comments**

**OTHER GLIDE—**

**Forearm Stretches:**
*These exercises are aimed at stretching the muscles and tendons at the elbow. Perform 2-3 repetitions of
each stretch before and after exercise sessions and strenuous activities.*

**Wrist flexors –**
With your elbow straight and palm down, use your unaffected hand to gently pull your affected hand up until
you feel a pull on the front of your forearm and hold the stretch for 30 seconds.
**Wrist extensors**

With your elbow straight and palm down, use your unaffected hand to gently pull your affected hand down until you feel a pull on the back of your forearm and hold the stretch for 30 seconds.

**Posture Correction Exercise:**

*Poor posture may place increased strain on the elbow. Perform the following corrections, holding for 15 seconds x 4 repeats, regularly throughout the day and while exercising.*

- Start by adjusting your pelvis such that it rolls forward to allow a small inward curve in your low back.
- Lengthen your spine upwards as if you are growing taller.
- Gently lift the base of your skull of the top of your neck, making a gentle chin tuck.
- Gently draw your shoulder blades downward and inward in a ‘V’ shape.

**All adjustments should be gentle and comfortable.**

**General Arm Exercises:**

*People with tennis elbow are generally weaker in their whole upper limb and this may place increased strain on the elbow. The below exercises are aimed at improving the strength and endurance of your upper body.*

*Perform 2-3 sets of 10 repetitions each, once per day, slowly and smoothly.*

**Biceps curls**

Stand with your elbow straight and your arm hanging at your side. Holding the weight in your hand (with your palm up), slowly bend your elbow to bring the weight towards your shoulder and then slowly lower.

**Triceps curls**

Lie on your back with your arm pointing towards the ceiling and bend your elbow so your hand is near your shoulder. Use your opposite hand to support below the elbow if needed. Holding the weight in your hand, slowly straighten your elbow towards the ceiling, and then slowly lower.

**Bent over rows**

Lean forward supporting yourself on a table top with your affected arm hanging towards the ground. Be sure to bend your knees slightly and keep your back straight. Holding the weight in hand, bend your arm up keeping your elbow pointing toward the ceiling.

**Bench press**

Lie on your back with your knees bent and your elbows bent so your hands are resting beside your chest. Holding the weight in hand, slowly straighten your elbow to lift the weight towards the ceiling, and then slowly lower.

**Alternative Exercise:**
The following exercise does not require any equipment and MUST be performed if the previous ones are not.

Wall push-ups –

Lean against a wall with your hands shoulder width apart and your elbows bent. Slowly push your body away from the wall by straightening your elbows while keeping your palms flat against the wall, and then slowly return to the starting position. You should not feel any elbow pain when doing these exercises. If you are experiencing any pain during or following any exercise or have any questions, please contact your physiotherapist immediately.
**Physiotherapy Advice Brochure**

**TENNIS ELBOW TREATMENT STUDY**

**PHYSIOTHERAPY ADVICE BROCHURE**

GRiffith University is conducting research to answer important questions about tennis elbow.

The clinical trial you are enrolled in will determine which of these two treatments, physiotherapy or prolotherapy injections, works best. Also, it will help us understand how these treatments affect your elbow, particularly the damaged tendon at your elbow.

**WHAT IS TENNIS ELBOW?**

Tennis elbow, also called lateral epicondylitis or lateral epicondylalgia, is pain on the outside of your elbow that is made worse with gripping and direct pressure over the area. Most people that get tennis elbow do not play tennis but tennis players often experience it, so that’s where the name comes from.

Tennis elbow is thought to be caused by micro-trauma to tendons that attach the forearm muscles to the outside of your elbow. These muscles are generally responsible for keeping your wrist stable during hand activities such as gripping. Tennis elbow may be caused by repetitive use of these muscles but some people get it without being able to recall any excessive arm activity.

**THE HEALING PROCESS**

There are many treatments currently being used to treat people with tennis elbow. The current best available evidence tells us that pain-free movements are beneficial to the healing process for tennis elbow, so use your arm within the limits of pain.

Remember, do not do any activity that increases your elbow pain. Avoid lifting, holding or carrying objects in your hand with your palm facing down, as this places more stress on the injured muscles and tendons.

Use over-the-counter medication for pain relief, such as paracetamol, as needed. The application of a hot or cold pack over the outside of the elbow for 15 minutes may help to decrease pain. Be careful not to burn your skin by ensuring the pack is not too hot or too cold, and that it is wrapped in a cloth or towel.
You may find that a forearm brace available from your local pharmacy, will decrease your elbow pain during activity. You are able to use this if it provides relief.

Above all, avoid or modify as best you can, any activities that increases your elbow pain, especially those that increase your pain for longer than a few minutes.

**PHYSIOTHERAPY TREATMENT OF TENNIS ELBOW**

Physiotherapy treatment aims to reduce pain and promote healing and strengthening of the muscles and tendons around the elbow and arm, and involves 4 treatment sessions at weekly intervals. The treatment will consist of some manual therapy techniques and exercises which will be taught to you, re-examined, and progressed as appropriate, at each session.

**ARE THERE ANY SIDE EFFECTS TO PHYSIOTHERAPY?**

The main aim of the physiotherapy treatment is to reduce your elbow pain so you can exercise and strengthen the affected muscles in a pain-free manner. Despite this, there are some occasions when you might experience a temporary and mild increase in elbow pain. Attempts should be made to minimise this increased pain through the use of taping, braces and over-the-counter medication which can be used between treatment sessions.

For the findings of the study to be worthwhile, you must keep to the treatment to which you have been allocated.

If you have any concerns or questions about the trial, please contact the chief investigator, Associate Professor Michael Yelland at Griffith University on:

0404 072 209 or m.yelland@griffith.edu.au
Prolotherapy injections injections are a treatment that aims to reduce chronic tendon and ligament pain by injecting weakened tendons and ligaments with solutions that create inflammation followed by healing and strengthening of these structures. It involves the repeated injections of a strong solution of glucose and local anaesthetic with the addition of sodium morrhuate, if the response is slow. In the case of tennis elbow, injections are performed at 4 weekly intervals for a total of 4 treatments.

WHAT SHOULD I DO BEFORE INJECTION TREATMENTS?

No injection treatment is totally painfree, but a lot can be done to reduce the pain of injections. Before injecting the ligaments, the skin overlying the ligaments is numbed with a bleb of local anaesthetic. Although these blebs sting like an antbite, they reduce the overall level of discomfort with this treatment, and may even make the treatment work better. Taking a painkiller at least half an hour before each treatment is also helpful. Keeping your mind off the pain by talking to the doctor about something interesting during the injections is very helpful. A heat pack may be applied to the treated area after the injections to sooth any discomfort that may occur.

WHAT ARE THE SIDE EFFECTS OF INJECTIONS AND HOW SHOULD I DEAL WITH THEM?

Side effects are minimised by using careful injection techniques, however minor side effects are still common. The main side effects of prolotherapy injections injections are a mild to moderate flare in the pain and stiffness sometime on days two to day seven after the injections. It is temporary and usually well controlled with medication or local heat. If you need extra pain relief following injections paracetamol, codeine or tramadol may be used initially. Brand names for these medications include Panamax, Codalgin, Panadeine, Panadeine Forte and Tramal. For more significant pain after injections, you will be provided with a script for Endone (oxycodone) tablets at the first treatment visit. One Endone tablet can be taken with two paracetamol tablets up to four times daily as required. If you are still concerned you should call your treating doctor to arrange review of the problem.

No aspirin or other anti-inflammatory medication (such as Voltaren, Brufen, Nurofen, Naprosyn, Mobic or Celebrex) should be used for pain relief following injections as they will prevent the inflammatory process that is part of the treatment. If you are already taking an anti-inflammatory medication for reasons other than tennis elbow, it should be stopped 2 days before each injection treatment and can be resumed 4 days afterwards after the inflammation from the injections has settled.

A very rare side effect, possibly 1 in 500, is an acute allergic reaction to sodium morrhuate (from cod liver oil), which is included in the injection solution on the third and fourth treatments in those who are slow to respond to treatment. The chances of this are minimised by excluding people who are allergic to seafood, but as a precaution,
participants are asked to stay at the surgery for 15 minutes after injections including sodium morrhuate, so that any allergic reaction can be detected and immediately treated.

Another very rare side effect following injections is wrist drop, a temporary weakness in the muscles that raise the hand at the wrist joint. This is caused by local anaesthetic blocking the nerve to the muscles that raise the hand and is avoided by using injection techniques that avoid this nerve. In the rare event that this happens, you will be reassured that this side effect will last no more than about 30 minutes and that full function of the hand and wrist will return after this time.

HOW SHOULD I USE MY AFFECTED ARM AFTER INJECTIONS?

In the first week after injection treatments, you should reduce the use of the injected elbow while the inflammation is present, particularly if there is an increase in the pain during this period. As the pain settles, you can gradually return to your usual activities.

Activities that do not provoke pain can be safely continued. Activities that cause a minor temporary increase in pain for less than 30 minutes can also be continued, but if the pain lasts longer than this, then the activity should not be repeated until your overall level of symptoms reduces.

WHAT CAN I DO TO AVOID AGGRAVATIONS OF MY ELBOW PAIN?

Aggravations of elbow pain can be avoided with the following simple measures:

- Avoid lifting, holding or carrying objects in your hand with your palm down.
- Take regular breaks from repetitive gripping or manipulation of objects eg: tools use, typing or mouse use
- The application of a hot or cold pack over the outside of the elbow for 15 minutes may help to decrease pain. Be careful not to burn your skin by ensuring that the pack is not too hot or too cold.
- Forearm braces and wraps available at your pharmacy may decrease elbow pain with activity. Use them if they help relieve pain.

If you have any concerns or questions about the trial, please contact the chief investigator, Assoc Prof Michael Yelland on phone 0404 072 209 or email m.yelland@griffith.edu.au
3-Tier Ultrasound Image Rating Scale

1. **CEO thickness**: Does any region of the tendon appear thickened in longitudinal and transverse plane? Measure the longitudinal tendon thickness (LTT) approximately 5mm from the point that divides radial head and humerus. Measure the transverse tendon thickness (TrTT) from a point on humeral bone.

2. **Heterogeneity of CEO**: Does any region of the tendon in longitudinal plane appear significantly heterogeneous (non-uniform) in fibrillar structure relative to the expectation of normal.

3. **Echo-intensity of CEO**: Does any region of the tendon appear significantly hypoechoic? Please select the appropriate grade of hypoechogenicity.

<table>
<thead>
<tr>
<th>Hypoechoic Area</th>
<th>Grade</th>
<th>✓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&lt;30 %</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>30 – 50 %</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt; 50 %</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
4. **Intratendinous Tear**: Does any region of the tendon in longitudinal or transverse plane have well-defined anechoic cleft suggesting an intrasubstance tear? Measure the longitudinal tear size (LTS) and transverse tear size (TrTS) in millimeter.

![Images of ultrasonography showing intratendinous tear](le_r.png)

Enter LTS [ ] Enter TrTS [ ]

5. **CEO Enthesis**: Does any region of the tendon in longitudinal plane have significant irregularity at its attachment to the Lateral epicondyle?

![Images of ultrasonography showing CEO Enthesis](le_r.png)

Yes [ ] No [ ]

6. **RCL Abnormality**: Does any region of the radial collateral ligament (RCL) appear significantly abnormal (hypoechoic, heterogeneous, tear, etc.) relative to your expectation of normal?

![Images of ultrasonography showing RCL Abnormality](le_r.png)

Yes [ ] No [ ]

7. **Intratendinous Calcification**: Does any region of the tendon have hyperechoic mass within any region that suggests calcification?

![Images of ultrasonography showing Intratendinous Calcification](le_r.png)

Yes [ ] No [ ]
## Ultrasound Tennis Elbow Pathology Rating Scale (ULTEPRS)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ultrasound findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>normal fibrillar pattern and echogenicity</td>
</tr>
<tr>
<td>1</td>
<td>presence of heterogeneity &amp; grade 1 hypoechogenicity</td>
</tr>
<tr>
<td>2</td>
<td>presence of heterogeneity &amp; grade 2 hypoechogenicity (diffuse)</td>
</tr>
<tr>
<td>3</td>
<td>presence of grade 3 hypoechogenicity (focal, well-defined), cortical irregularities, enthesis abnormalities, calcification, RCL abnormalities</td>
</tr>
<tr>
<td>4</td>
<td>partial/incomplete intratendinous tear (anechoic)</td>
</tr>
<tr>
<td>5</td>
<td>complete full thickness intratendinous tear</td>
</tr>
</tbody>
</table>

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**End of Questionnaire**
## Modified Total Ultrasound Image Rating scale

<table>
<thead>
<tr>
<th>Ultrasound feature</th>
<th>Description</th>
<th>Grading range</th>
<th>Grading criteria</th>
<th>Possible Maximum score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoechogenicity</td>
<td>Ordinal</td>
<td>0 to 3</td>
<td>0 = normal ibrillar &amp; hypoechoic structure</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 = hypoechoic lesions affecting less than 30% of whole section of the tendon.</td>
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<tr>
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<td></td>
<td>2 = hypoechoic lesions affecting more than 30% and less than 50% of the whole section of the tendon.</td>
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<td></td>
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<td></td>
<td>3 = single large or multiple hypoechoic lesions affecting more than 50% of the whole section of the tendon / high-grade tendinosis.</td>
<td></td>
</tr>
<tr>
<td>Neovascularity</td>
<td>Ordinal</td>
<td>0 to 3</td>
<td>0 = no detectable neovessels</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 = neovessels detected in less than 30% of the whole section of the tendon</td>
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<td></td>
<td>2 = neovessels detected in more than 30% but less than 50% of the whole section of the tendon</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 = neovessels detected in more than 50% of the whole section of the tendon</td>
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17.1 In the event that any provision of this Agreement is held to be invalid, the remainder of the provisions shall continue in full force and effect.

17.2 There shall be no right whatsoever for any third party to enforce the terms and conditions of this Agreement. The Parties hereby expressly wish to exclude the operation of the Contracts (Rights of Third Parties) Act 1999 and any other legislation which has this effect and is binding on this agreement.

17.3 To the fullest extent permitted by law, this Licence will be governed by the laws of England and shall be governed and construed in accordance with the laws of England. Any action arising out of or relating to this agreement shall be brought in courts situated in England save where it is necessary for BMJ Group for enforcement of remote proceedings to bring an action in an alternative jurisdiction.