University of Kent | School of Sport and Exercise Sciences

The use of ultrasound imaging to evaluate the thoracolumbar fascia in people with and without lower back pain

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Kyra De Coninck

School of Sport and Exercise Sciences

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Abstract

Chronic lower back pain remains a poorly understood multi-factorial condition, associated with reduced quality of life and function. Traditionally, research in lower back pain has focused on vertebrae, trunk muscles, motor control and biopsychosocial factors. Despite this substantial body of research, chronic lower back pain remains a prevalent global issue affecting health and well-being. Recently, the thoracolumbar fascia has been recognised to play a role in the pathophysiology of chronic lower back pain. Currently, there are no standardised methods for imaging and analysis of the thoracolumbar fascia. This thesis seeks to advance methods of analysis as well as furthering our understanding of role thoracolumbar fascia plays in chronic lower back pain.

The study presented in Chapter 4 aims to assess the reliability of intra- and inter-image reliability of ultrasound images of the thoracolumbar fascia. One investigator acquired and measured ultrasound images of eleven participants. The morphology of the thoracolumbar fascia was measured using an adapted grey-scale MatLab script to measure the echogenicity and an on-screen cursor to measure the thickness of the dense connective tissue layers. The investigator measured the same series of images on day 1, and 2 days later. The investigator acquired a further set of images from the same participants 4 days later. Both sets of images were analysed 3 months after image acquisition. The intraclass correlation coefficient (ICC) for same image (intra-image) reliability was >0.94, which represents good reliability. The ICC for inter-image reliability of scans taken across 2 days of the same participants, ranged between >0.95 – 0.63, which represents good to moderate reliability. Inspection of

Bland Altman Plots revealed no systematic pattern of variability. It was concluded that ultrasound is a reliable method to evaluate the thoracolumbar fascia, when using one investigator.

The study presented in Chapter 5 used ultrasound to investigate the thickness and echogenicity of the thoracolumbar fascia in people with and without back pain. One hundred and forty-one participants took part in the study (74 with back pain, 67 without back pain). This study found that the echogenicity (brightness of pixels indicating presence of collagen) of the thoracolumbar fascia in people with lower back pain was 10% higher (p = 0.04), compared to people without lower back pain. Higher echogenicity suggests tissue fibrosis, as found in other pathological connective tissues.

The study reported in Chapter 6 was an investigation of the impact of a 4 week endurance training programme on the ultrasound outcomes of the thoracolumbar fascia. This study found no difference in either thickness or echogenicity in either the training group or the control group. This could be an indication that a longer training intervention is required in order to visualise changes in the thoracolumbar fascia, using ultrasound imaging.

The study presented in Chapter 7 was an inter-rater reliability study in which 30 medical practitioners rated the morphology of the thoracolumbar fascia of 30 ultrasound images of 30 individuals. The scans were rated on a Likert-type scale ranging from 5 being very disorganised, to 1 being very organised. Images were selected by a focus group and consisted of a representative range of thoracolumbar morphologies. This study found that medical practitioners can reliably rate scans, regardless of ultrasound experience (Cronbach's alpha – 0.98).

The conclusion of this thesis is that ultrasound is a reliable imaging method to evaluate the thoracolumbar fascia. Furthermore, higher echogenicity was found in images of people with lower back, which could be an indicator of fibrosis. Ultrasound is a viable and promising method to evaluate the thoracolumbar fascia, which has been associated with lower back pain.

These findings contribute to the emerging field of research into the pathophysiology of the human fascial system.

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Conference abstracts, posters and presentations

Third International Fascia Research Congress, 28-30 March 2012, Vancouver, BC, Canada:

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Oral presentation:

Why is fascia different in different people: An exploration of thoracolumbar fascia using ultrasound imaging.

Fifth International Fascia Research Congress, 14-15 November 2018, Berlin, Germany:

Oral presentation:

Ultrasound evaluation of the effect of an endurance programme on the thoracolumbar fascia of healthy adults.

Poster presentation:

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Ultrasound Training

Completed 12 months of training on a Musculoskeletal (MSK) Ultrasound course, at the Centre for Ultrasound Studies, Anglo-European Chiropractic College (AECC), University of Bournemouth. The course is accredited by the Consortium for Accreditation of Sonographic Education (CASE). This training involved ultrasound instruction and 250 hours of supervised MSK ultrasound scanning. All ultrasound protocols used in this thesis were verified by Dr Budgie Hussain, DMedImg, BMUS, DMU, DCR (R), Head of School of Medical Ultrasound (AECC).

Abbreviations

ANCOVA	analysis of covariance
ATP	adenosine triphosphate
CGRP	calcitone gene-related peptide
B-mode	Brightness mode
CNS	central nervous system
CT	Computational Tomography
CT-imaging	computational tomography imaging
BMI	Body Mass Index
CI	Confidence Interval
ECM	Extra Cellular Matrix
EMG	Electromyography
FNC	Fascia Nomenclature Committee
FCAT	Federative Committee on Anatomical Terminology
GAGs	Glycosaminoglycans
HA	Hyaluronan
Hz	Hertz
ICC	intraclass coefficient
LBP	lower back pain
MDC	Minimal Detectable Change
MHz	Megahertz
MRI	Magnetic Resonance Imaging

MSK	Musculoskeletal
µ	one millionth or 10^{-6}
No-LBP	no lower back pain
PAL	physical activity level
SCM	Spinal Control Model
SD	standard deviation
SEM	standard error measure
Substance P	a neuropeptide which acts as a neurostransmitter and neuromodulator
TGFβ-1	transforming growth factor beta 1 (a polypeptide protein and member of the cytokine family)
VAS	visual analogue scale
VO2Max	maximum rate of oxygen consumption

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Chapter 1 Introduction

1.1 General Introduction

Lower back pain is the largest cause of disability, affecting people's health and well-being world-wide (Global Burden of Disease, 2016). Early areas of research into the causes of lower back pain were focused on vertebral structures such as spinal joints and vertebral discs. However, these are now recognised to play a role in a small number of very specific cases of lower back pain, and are no longer considered to be part of the main cause of lower back (Hartvigsen, *et al.*, 2013). Lower back pain is now seen as a multi-factorial symptom with a considerable physical, psychological, social and economic impact on individuals and society (Buchbinder *et al.*, 2018). In pain research, trunk muscles are found to function differently in people with lower back pain (Hug *et al.*, 2014). Hodges and Tucker (2011) describe in great detail how people with lower back pain recruit trunk muscles in a different pattern. For example, people with lower back pain delay or adapt recruitment of the multifidus muscle in flexion (Danneels *et al.*, 2002; van Dieën *et al.,* 2003; Chapman *et al.*, 2009; Hodges and Smeets, 2015), the cross-sectional area of this group of spine stabilisers is reduced ranging from 5% to 10% in both young and older people with lower back pain (Hides *et al.*, 1995; Dickx *et al.*, 2010; Hides *et al.*, 2011; Sions *et al.*, 2016). Musculoskeletal differences in people with lower back pain are not just related to muscle firing patterns or morphology. Other authors find that symmetry, rather than asymmetry of abdominal muscles is associated with lower back pain (Gray *et al.*, 2015) The literature on the adaptations of muscles in lower back pain indicate there are significant and clinically relevant functional and structural differences in people with lower back pain, compared to healthy controls. However, a straightforward

comparison between findings is complicated due to the heterogeneous cohorts and use of different measurement tools and outcome measures in the lower back pain literature. For example, some trunk muscle studies have investigated the acute effects of experimentally induced pain on muscle adaptation in healthy individuals (Hodges *et al.*, 2003; Williams *et al*.,2010; Hug *et al.*, 2014) whereas other studies have focused on the effects of recurrent pain on activation and morphology of trunk muscles in clinical populations (Wallwork *et al.*, 2009; Whittaker *et al.*, 2013; Cai and Kong, 2015).

Advances in lower back pain research have been made due to the development of more precise measurement technology.

For example, innovations in electromyography (EMG) and the advent of high frequency real-time ultrasound imaging have meant that reliable and sensitive non-invasive measurements of muscles can be taken in-vivo in people with lower back pain. Technological advances in diagnostic ultrasound have meant that other soft tissue structures in the trunk, such as the thoracolumbar fascia can now be visualised and measured in different populations.

The thoracolumbar fascia has so far, largely been ignored in the medical literature. More recently however, a growing body of research into the human fascial system recognises the clinical relevance of fascial tissues (Findley, 2011; Klinger *et al.*, 2014; Dommerholt *et al.*, 2016). Some authors go even further and argue that research into the fascial tissues will not only help us to understand how we function as humans, but may hold the answers to the pathophysiology of many musculoskeletal conditions and the development of future treatments (Benjamin, 2009b; Vleeming,

2012). For instance, human movement is more than the recruitment of individual muscles in response to nerve impulses. All organs, bones and muscles are encased in fascia, forming a connective tissue network throughout the body. This fascial network used to be regarded as a passive wrapping material, but is now seen as a body-wide signalling system, which is responsible for the co-ordination of the motor system (Langevin and Sherman, 2007). Muscles move and adapt in relation to one another, the fascial tissues which wrap around muscles allow them to do this, by giving them form and allowing the correct amount of glide (Vinet and Zhedanov, 2011). Research into the fascial system, its composition, cellular responses and role in pathologies will allow us a more exact understanding of anatomy, physiology and the study of pain (Findley *et al.*, 2012a; Stecco *et al.*, 2013). Medical researchers require a more rigorous understanding of the function of fascial tissues in order to develop more effective treatments for conditions resulting from contractures, inflammation or fibrosis (Langevin and Agache, 2017).

This thesis is based on the in vivo ultrasound imaging of hundreds of human participants over the past 6 years. I performed these ultrasound scans myself, in order to obtain the most precise in-vivo observations of the morphology of living thoracolumbar fascia in a wide range of people with and without lower back pain. Ultrasound imaging has given me a unique vison into the human thoracolumbar fascia. Formerly, lower back pain was studied with a focus on muscles, vertebrae and joints. This suggested that fascia had no role to play in the pathophysiology of lower back pain, which, I argue in this thesis, is not the case.

Chapter 2 Literature review

2.1 Lower back pain

2.1.1 Impact of lower back pain

Lower back pain is a very common world-wide phenomenon, which occurs at all stages of life. In 2015, the Global Burden of Disease study estimated that 540 million people worldwide are affected by lower back pain at any time, an increase of 54% since 1990 (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Although this increase is partly due to population growth and ageing, rather than an increase in overall prevalence, lower back pain remains the number one cause of disability worldwide (Clark and Horton, 2018).

The literature on the socio-economic impact of lower back pain literature is extensive. This is evidenced by the World Health Organisation's International Clinical Trials Registry Platform which registered 2245 lower back pain clinical trials between 2007 and 2018 (World Health Organisation, 2018).

Around the world, lower back pain is associated with a sedentary life-style, obesity and a low socio-economic status (Hartvigsen *et al.*, 2018). Although lower back pain affects people of all ages, working-age people are most affected by lower back pain related disability. People in lower and middle income countries are affected more compared to higher income countries, as health-care systems in those countries tend to be less well organised (Hartvigsen *et al.*, 2018).

The economic impact of lower back pain differs between countries. For example, in the USA, 58 of 10,000 workers filed a back-related insurance claim, compared to

Japanese workers who submitted 1 of 10,000 claims in the same year (Volinn *et al.*, 2005). It has been estimated to cost around £1 billion to the NHS and an additional £565m to private healthcare providers (Maniadakis and Gray, 2000). The true costs of lower back pain however, are difficult to measure in direct economic and medical costs only (Maher, Underwood and Buchbinder, 2017). Since indirect costs, such as a decrease in earning capacity or absenteeism, can supersede the direct medical costs. It is important to note that most people with lower back pain do not seek medical care, but that lower back pain is associated with a range of different costs (Ferreira *et al.*, 2010). The National Office of Statistics reported that in the UK, between 2016 and 2017, 38% (194,000 cases) of all work-related musculoskeletal disorders, were back related. In addition, 3.2 million working days were lost between 2016 and 2017 due to work-related back conditions, with an average of 16.5 days lost per case (Health and Safety Executive, 2017).

The impact of psychosocial factors of lower back pain are well-recognised. Depression (Hoy *et al.*, 2010), catastrophizing (Lee *et al.*, 2015), diminished self-efficacy (van Erp *et al.*, 2015) and fear-avoidance beliefs (Smeets, van Geel and Verbunt, 2009) are seen as key predictors and can influence lower back pain disability. Repeated encounters with health care providers in high income countries can have an exacerbating effect on lower back pain. For instance if repeated visits to health-care providers do not resolve symptoms, these may result in frustration with the health-care system, social isolation and a further reduction in physical activity (Lee *et al.*, 2015).

Other psychosocial factors such as fears and concerns about the consequences of lower back pain, financial worries, and low self-esteem are common experiences for people living with lower back pain (Demyttenaere *et al.*, 2007; Tang *et al.*, 2008).

Due to the recurrent and fluctuating nature of lower back pain, it has been recommended that measures of pain severity ought be included in population, as these are already commonplace in clinical studies (Dionne *et al.*, 2011; Cuesta-Vargas and González-Sánchez, 2014; Macfarlane *et al.*, 2015). To address a lack of consistency in pain severity measurements, a group of international experts agreed on standard categorisations of lower back pain (Dionne *et al.*, 2008). Mild lower back pain was categorised as < 7/10 on a numeral rating score, and severe lower back pain as ≥ 7/10 (Dionne *et al.*, 2008). It is important to note that only 28% of cases worldwide (N = 151 million) are severe cases, however, these cases account for 77% of disability caused by lower back pain (Hartvigsen *et al.*, 2018). So, most people with lower back pain report and experience a mild to moderate pain severity and low levels of disability. However, for a small core of people living with severe lower back pain, this results in a very high impact on individual and societal wellbeing.

A detailed review of the socio-economic impact of lower back pain literature is beyond the scope of this thesis. Instead, this literature review will focus on the pathophysiology of lower back pain.

2.1.2 Pathogenesis of lower back pain

Lower back pain is a complex symptom, resulting from a range of different sources and conditions, rather than a disease caused by a single pathogen (Buchbinder *et al.*,

2018). Spinal structures such as vertebrae (Williams *et al.*, 2013), vertebral discs (Carragee *et al.*, 2004), facet joints (Dreyer and Dreyfuss, 1996) and ligaments (Panjabi, 2003) have all been extensively investigated, but to date, no conclusive spinal joint or bony structure has been identified to be the main source of lower back pain (Hartvigsen *et al.*, 2018). Degenerative changes in bony spinal structures or joint surfaces are no longer considered to be a source of lower back pain (Hartvigsen, Natvig and Ferreira, 2013), since signs of degeneration in vertebral endplates are visible on MRI scans in both people with and without lower back pain (McCullough *et al.*, 2012). Fundamentally, there are no widely accepted investigations which identify a disc problem, facet joints or vertebral endplates as the pathogenic source of lower back pain (Maher, Underwood and Buchbinder, 2017; Hartvigsen *et al.*, 2018). Most cases of lower back pain are not generated by the spinal structures listed above and are classified as non-specific lower back pain, since no specific anatomical structure can be identified to be the cause of lower back pain (Hartvigsen, Natvig and Ferreira, 2013).

Despite the lack of a single specific cause , lower back pain has been associated with altered movement patterns (Hodges and Tucker, 2011). In people with persistent lower back pain, changes in muscle recruitment patterns (Wallwork *et al.*, 2009; Hides *et al.*, 2011), motor control (O 'Sullivan and O'Sullivan, 2005; Hodges *et al.*, 2013), and muscle size and quality (Urquhart *et al.*, 2005; Teichtahl *et al.*, 2015; Goubert *et al.*, 2016; Sions *et al.*, 2016) have been demonstrated. For example, co-activation of trunk muscles is higher in people with lower back pain (Marras *et al.,* 2001; van Dieën *et al.*,2003). Muscle atrophy and a change in neuromuscular control of both trunk and abdominal muscles are also recognised as factors in lower back

pain (Danneels *et al.*, 2002; Vleeming *et al.*, 2014; Goubert *et al.*, 2016). Ultrasound imaging studies have found differences in muscle activity in transversus abdominis and multifidi, in both younger and older people with lower back pain (Hodges and Richardson, 1998; Hides *et al.*, 2011; Wilson *et al.*, 2016). Furthermore, trunk muscle activity is different in people with lower back pain, in both predictable and unpredictable perturbations (Hodges and Smeets, 2015). A delayed reflex control might be a predisposing factor, inaccurate information processing or poor position sense have all been suggested as possible explanations (Hodges and Tucker, 2011; Hodges *et al*., 2007). The spinal control model (SCM) proposes that people with lower back pain have motor control impairments that increase the noise in the electromyographic activity (Hodges and Tucker, 2011). Proponents of the SCM model suggest that these altered activation pattern may not a protective mechanism but instead a dysfunctional coping strategy (Hodges and Tucker, 2011; Hodges *et al.*, 2013). For example, experimental pain resulted in altered muscle recruitment, which continued after the pain had been removed (Hodges *et al.*, 2003; Moseley *et al.*, 2004). The SCM model proposes that through rehabilitation these dysfunctional patterns can be resetPanjabi's (2003) seminal hypothesis emphasized that spinal function relies not just on the trunk's musculature and neuromuscular system, but also includes the optimum function of the ligament structures. Subfailure of connective tissue structures such as interspinal ligaments, facet joint capsules and their associated mechanoreceptors have been hypothesized as factors in lower back pain and an altered recruitment pattern of muscles (Panjabi, 2006). In response to Panjabi's (2006) model, the inclusion of other connective tissue structures, such thoracolumbar fascia in the pathogenesis of lower back pain has been called for

(Schleip *et al.*, 2007). The literature and research evidence on the role of thoracolumbar fascia as a potential source of lower back pain will be reviewed in the subsequent sections of this literature review (Langevin, 2008; Benjamin, 2009b; Findley *et al.*, 2012b,Taguchi et al., 2009; Langevin *et al.*, 2011; Schilder *et al*., 2014b; Hoheisel and Mense, 2015; Zwambag *et al.*, 2018).

2.2 The thoracolumbar fascia

2. 2. 1 The fascial system and definitions of fascia

Historically, the anatomical view of fascia is that it is a packing material, which wraps around structures, with no particular function other than separating, containing, restraining and protecting structures such as muscles and organs. Its presence, as wrapping material or a connective sheet around muscles is clear in most anatomy books; its function is less well understood (Schultz and Feltis, 1996; Schleip, Findley, *et al.*, 2012). Early anatomists such as Vesalius (1543) observed and described the 'membrane muscolorum communis', a body-wide continuous membrane related to muscles (cited in Stecco, 2015). Centuries later, surgeons such as Camper (1801), Colles (1811) and Scarpa (1819) described subcutaneous fascial layers of the abdomen and pelvis when studying the formation of inguinal hernias (Lancerotto *et al.*, 2011). The anatomist Gerrish noted in 1899 the continuity of fibrous membranes, how deep fasciae surrounding muscles become

tendons, which in turn blend with the periosteum surrounding bones (cited in Benjamin, 2009). The 19th Century surgeon John Hilton, famous for this writings on rest and pain, wrote in 1863 *"Every fascia of the body has a muscle attached to it, and every fascia throughout the body must be considered as a muscle"* (cited in Gibson, 1955). Despite these early observations by anatomists and surgeons, fascia has been largely ignored in the medical literature. The reason for this has been two-fold, the lack of adequate measurement tools, and a continuing debate around nomenclature and definitions of both superficial and deep fascia (Schleip, Jäger and Klingler, 2012; Myers, Tozzi and Langevin, 2014; Schleip and Klingler, 2014; Stecco, 2014; Hedley, 2016). For example, both the thoracolumbar fascia and the fascia lata measure less than 2 millimetres in thickness. Fascia cannot be visualised with X-ray imaging, and is only partially visible in MRI scans. Any changes or increases in thickness are difficult to observe in gross dissection (Schleip and Baker, 2015). Advances in ultrasound measurements however, as well as biological tissue research, have resulted in an exponential increase in fascia research (Avila Gonzalez *et al.*, 2018).

The Federative Committee on Anatomical Terminology (FCAT, 1998), defined fascia as the dense connective tissue related to muscle, without including subcutaneous loose connective tissues. This attempt at classification largely failed, as many authors now consider the subcutaneous loose connective tissue inferior to the dermis to be part of the fascial system (Langevin and Huijing, 2009). A more comprehensive and functional definition of fascia is, that it is a connected network of loose and dense irregularly arranged connective tissue whose architecture is shaped by tensional loading. This definition excludes connective tissues such as bone or cartilage whose

morphologies are shaped by compression (Langevin and Huijing, 2009; Schleip, Jäger and Klingler, 2012).

Recently however, some have argued that classifying all fasciae as being part of the same tensional fascial web may hinder research and a deeper understanding. These authors call for a specific nomenclature of fascial tissue, based on histology, to improve clarity and avoid confusion in inter-disciplinary communication (Stecco, 2014). For instance, different layers and types of fascia are described using different terms, depending on the field of research. For example, a study into sensory innervation of fascial tissues uses the term 'specialised connective tissues' and included the loose subcutaneous tissue (Corey *et al.*, 2011), whereas a comparable investigation into the innervation of thoracolumbar fascia does not specify whether the subcutaneous tissue was included (Tesarz *et al.*, 2011) (both cited in Stecco, 2014).

Proponents of the all-inclusive categorisation, propose to include all dense tissue sheets, including joint and organ capsules, retinaculae, septa, as well as ligaments and tendons, which they term as densifications in the fascial tensional network (Schleip *et al.*, 2012). These authors propose to include the epimysium (wraps the whole muscle), perimysium (wraps bundles of muscle fibres) and endomysium (wraps each muscle fibre) of muscles in the fascial system. Langevin and Huijing (2009) acknowledge that ligaments and tendons blend with fascia, however, they do not recommend these structures are included in the term 'fascia'. Stecco (2015) favours an even narrower definition of fascia and excludes tendons, ligaments, aponeurosis and visceral capsules on the basis of their distinct fibre alignment and different function. Schleip *et al.* (2012) point out that excluding certain tissues misses

the concept of a body-wide tensional network. These authors propose a classification system on a continuum, which recognises the gradual transitions of tissues throughout the body. This classification system is based on fibre direction, tissue thickness and density (Schleip, Findley, *et al.*, 2012).

To summarise, all authors agree that not all connective tissue can simply be labelled as 'fascia' (Wendell-Smith, 1997; Langevin and Huijing, 2009; Kumka and Bonar, 2012; Schleip *et al.*, 2012; Adstrum *et al.*, 2017). An agreement to establish two different definitions was made in 2016 by the Fascia Nomenclature Committee (FNC). Guidelines propose that researchers focusing on the morphology and architecture of fascia are best suited to use a more narrow definition and are advised to use the term 'a fascia'. This permits the in vivo study of fascial layers and facilitates clear communication with and between medical and histological researchers. It also enables direct comparisons to be made between studies, using systematic reviews and meta-analyses. Whereas researchers who wish to investigate the functional aspects of fascia, such as force transmission or sensory capacities might find a wider definition more beneficial and, are advised to use the term 'the fascial system' (Langevin and Huijing, 2009; Stecco and Schleip, 2016; Adstrum *et al.*, 2017).

In the context of this thesis, the term *fascial system* will be used when discussing the fascial body-wide tensional network of fibrous collagenous tissues. The terms *fascia, fascial tissues* or *fasciae* will be used when discussing the morphology and histology of specific fascial tissues located between the skin and the muscle.

Most anatomists distinguish between the subcutaneous superficial fascia, as a layer of areolar connective and adipose tissues under the skin, and deep fascia,

a denser connective tissue forming a stocking around the muscles and tendons (Schleip *et al*.,2012).

The term 'ectoskeleton', was coined to capture the idea that fascia serves as a significant site of different muscle attachments, a soft tissue skeleton (Jones cites in Benjamin, 2009). For example, muscles such as gluteus maximus and latissimus dorsi attach mainly to fascial structures such as the thoracolumbar fascia. Other muscles such as the tensor fascia lata and tibialis anterior predominantly attach to fascia rather than bone (Stecco *et al.,* 2008). These anatomical connections indicate that fascial tissues are an integral part of the musculoskeletal system and are biomechanically functional tissues, rather than a passive packing or wrapping material. In this sense, some authors emphasize the importance of the continuity within the fascial system (Findley *et al.*, 2012b), and others wish to differentiate between the different specialised structures according to function such as compression and tension (Schleip and Klingler, 2014), and histological or cellular composition (Vinet and Zhedanov, 2011).

Scientific interest in fascia has been gaining momentum in terms of both basic and applied research. Four international fascia research congresses have taken place over the last ten years (Findley and Schleip, 2007; Huijing *et al.,* 2009; Chaitow *et al*., 2012, Wearing *et al.*, 2015). Equally, there has been a surge of publications over the last few decades from a very diverse range of disciplines ranging from histology (Yahia *et al*., 1992; Tesarz *et al*.,2011), to bio- engineering (Chen and Ingber, 1999), food science (Purslow, 2010), mathematical modeling (Benetazzo *et al.*, 2011) and biomechanics (Gracovetsky, 2008). In a review on the anatomy of fascia of the limbs and back, Benjamin (2009) concluded that fascia could hold many of the keys for

understanding muscle action and musculoskeletal pain as well as a wide range of therapies.

2.2.2 The anatomy of the thoracolumbar fascia

The thoracolumbar fascia forms a multi-layered dense and loose connective tissue complex connecting the latissimus dorsi with the contralateral gluteus maximus muscles, as well as connecting the paraspinal and anterior trunk muscles (Willard *et al.*, 2012) . Figure 2.1 shows the muscular attachments of the thoracolumbar fascia in a cadaver, with a drawing of the different fibre directions of the tissue layers found in the corresponding cadaver.

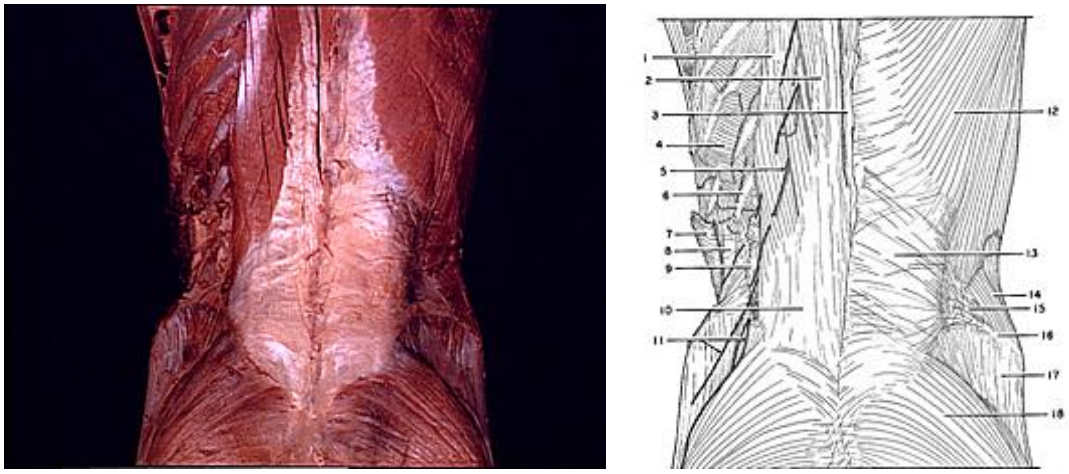


Figure 2.1 The thoracolumbar fascia

Cadaver dissection, skin and superficial fascia removed, exposing the dense connective tissue sheaths (left). Drawing of different fibres directions of adjacent fascial sheaths, corresponding with cadaver image (right) (Image from Stanford Medical History Centre - used with permission)

The dense connective tissue layers of the thoracolumbar fascia consists mainly of collagen type I fibre bundles, and some type III collagen (Stecco *et al.*, 2016). Type I collagen is the most prevalent type of collagen in the body. The fibrils form thick bundles of 2-10 µ in diameter and provide a strong resistance to force, tension and stretch, with a tensile strength of 500 -1000kg/cm^2. The main role of the

thoracolumbar fascia is to transmit forces (Barker *et al.,* 2004a), which explain the abundance of Type I collagen fibres. .

Type III fibers have a more narrow diameter, the fibers form a mesh-like structure and provide elasticity and a supporting framework for surrounding cells. These are the first to be secreted in scar tissue formation. (Lindsay and Robertson, 2008; Stecco, 2015). Loose connective tissue contains more collagen type III (Pavan *et al.*, 2014), which is also more present during repair and wound healing.

Recent studies found that the thoracolumbar fascia consists of layers of regular connective tissue, whereas previously it was thought fibres were arranged irregularly (Gatton *et al.*, 2010; Benetazzo *et al.*, 2011). Each dense layer consisting of mainly Type I collagen, is separated from the other by a thin layer of loose connective tissue, consisting of Type III collagen which permits sliding of one layer over another (Pavan *et al.*, 2014). The collagen fibres of adjacent layers are organised at specific angles of 75-80° which allow a shearing (Benetazzo *et al.*, 2011).

Traditionally, the distinction has been made simply between superficial (fascia superficialis) and deep fascia (fascia profunda) (see Figure 2.2).

[REDACTED]

Figure 2.2 Organisation of the superficial and deep fascia (Stecco model)
Image from: Stecco (2015) Functional Atlas of the Human Fascial System

Fascia superficialis was used as a term for the loose subcutaneous tissue, and fascia profunda described the dense connective tissue sheaths associated with muscles. This simplistic separation has been called into question (Huijing and Langevin, 2009; Schleip, 2013). In vivo ultrasound and MRI imaging suggests that the distinction between superficial and deep fascia is not always as clearly delineated as the early anatomical texts would make us believe (Langevin, 2009; Fourrie 2009). Cadaver studies have demonstrated that the loose connective tissue contains sheets of dense connective tissue in the upper limb (Stecco *et al*., 2006) (Figure 2.2). And conversely, thanks to the use of imaging techniques such as ultrasound, as well as blunt dissection we now have evidence of the presence of loose connective tissue between layers of dense fascia (Stecco, 2015).

To this date, the superficial fascia remains a subject for debate. Some anatomists classify the subcutaneous tissue as part of the skin structures (Wendell-Smith, 1997), others consider the subcutaneous tissue as being an integral part of the fasciae (Langevin *et al.*, 2009; Stecco, 2015). In this thesis, the latter view is taken, particularly as the areolar tissue contains dense connective tissue and has a close relationship with the thoracolumbar fascia.

The superficial fascia covering the thoracolumbar fascia is located directly under the skin and is continuous with the dermis. Langevin and Huijing (2009) describe it as a three dimensional meshwork of dense irregular connective tissue, membrane-like

sheets of tissue arranged in a honeycomb-like formation (Figure 2.2). Stecco (2015) refers to the superficial fascia as a sheet-like structure, connected to the skin via skin ligaments, the retinaculum cutis superficialis, and linked to the epimysium with retinaculae cutis profundis, very similar to the honey-comb structure described in the literature (Figure 2.2) (Langevin and Huijing, 2009). So where authors emphasise the existence of a body-wide membranous layer separating the subcutaneous tissue into two sub-layers (Stecco, 2015), others consider the presence of connective tissue in the subcutis as a continuous integral part of the fasciae (Langevin *et al.*, 2009; Corey *et al.*, 2011). For instance, ultrasound studies suggest that the histologic distinction between superficial, and underlying deep fascia is not always clear (Langevin and Huijing, 2009). Superficial fascia contains sheets of dense fascia, and conversely, layers of dense fascia, such as the thoracolumbar fascia, can be composed of multiple layers of dense connective tissue, interspersed with areolar connective tissue and fat (Langevin and Huijing, 2009). So, future studies may be prudent to include the superficial or loose connective tissue in investigations and evaluations of the thoracolumbar fascia of people with lower back pain.

This complex functional relationship between loose and dense fascia is exemplified by the infiltration of loose connective tissue and adipose tissue between dense connective tissue sheaths in the iliotibial tract as well as the thoracolumbar fascia (Figure 2.2)(Jelsing *et al.*, 2013; Szotek *et al.*, 2016).

Cadaver studies report that the thoracolumbar fascia consists of multiple laminae with each lamina containing fibres running in different directions (Figure 2.1) (Bogduk and Macintosh, 1984; Schuenke *et al.*, 2012; Willard *et al.*, 2012). More specifically, the collagen fibres of adjacent layers in the thoracolumbar fascia are

found to be orientated along specific angles of 75 - 80° (Benetazzo *et al.*, 2011; Chaudhry *et al.*, 2012). Traditionally the thoracolumbar fascia is classified as an irregular dense connective tissue. However, this is questioned as recent studies show that it consists of separate dense connective tissue layers with a specific regular collagen orientation. Collagen fibres in thoracolumbar fascia are not intertwined, and do not cross each other (Langevin and Huijing, 2009). In summary, in thoracolumbar fascia, densely packed collagen fibres are arranged at specific angles, enabling the thoracolumbar fascia to transfer mechanical forces in different directions (Chaudhry *et al.*, 2012), equally, it can resist stretch from many directions, due to its architecture.

More recently, two main models of thoracolumbar fascia have emerged, a two-layered structure (Stecco, 2015), and the three-layered model (Willard *et al.*, 2012). A comparison of both models is made in Table 2.1.

Table 2.1 Comparison of the three- and two-layered models of the thoracolumbar fascia

Three-layered model of the thoracolumbar fascia (Schuenke *et al.*, 2012; Willard *et al.*, 2012)	**Two-layered model of the thoracolumbar fascia** (Stecco, 2015)
Anterior layer: fascia passing anterior of the quadratus lumborum	Not considered to be part of thoracolumbar fascia
Middle layer : fibres attach to tips of transverse processes, then fan out between erector spinae and quadratus lumborum. It forms the aponeurosis of abdominal muscles (internal oblique and transversus abdominus)	= **Anterior layer**
Posterior layer : fibres attach to the thoracic and lumbar spinous processes. Surrounds posterior aspects of paraspinal muscles. Consists of superficial and deep laminae.	= **Posterior layer**

The main difference between the two models is that, the three-layered model includes an anterior layer, which is not included in the three-layered model. In the three-layered model, the anterior layer runs between the quadratus lumborum and the psoas (Fig 2.2). (Barker, Briggs and Bogeski, 2004b). Both models agree that the posterior layer, is formed by tissues surrounding the posterior aspect of the paraspinal muscles (Fig 2.3). In the literature, mean thickness of the posterior layer of the thoracolumbar fascia ranges from 0.52 millimetres measured with a micro meter using embalmed cadavers (Barker and Briggs, 1999) to 3.5 millimetres measured with ultrasound imaging in-vivo in healthy pain-free individuals and 4.2 millimetres in people with lower back pain (Langevin *et al.*, 2009). It is important to

note that the different measurement techniques may have given rise to the wide range of measurements. For example, the embalming process affects the fluid and fat content of tissues, which is a key component of the subcutaneous superficial fascia and the loose connective tissue found in between layers of the dense connective tissue sheaths of the thoracolumbar fascia.

An overview of mean, standard deviation and range measurements of the posterior layer of thoracolumbar fascia in the literature can be seen in Table 2.2).

Table 2.2 Overview of average thickness measurements of the thoracolumbar fascia in the current literature.					
Authors	**Anatomical location***	**Type of cohort**	**method of measurement**	**Mean thickness (mm) and SD**	**Range (mm)**
Barker and Briggs (1999)	Posterior layer L2 – L4	21 embalmed cadavers	manual micro meter	0.52	not reported
Barker *et al.* (2007)	Anterior layer L2- L4 (two-layer model)	18 embalmed cadavers	manual micro meter	0.55	0.11 – 1.34
Loukas *et al.*(2008)	Posterior layer, middle point	35 embalmed cadavers 5 fresh cadavers	Manual callipers	3 (± 0.5)	1 – 4
Langevin *et al.* (2009)	Posterior layer L2-L3	107 human subjects 60 LBP 47 control	Ultrasound imaging	LBP: 4.2 Control: 3.5	not reported
Whittaker, Warner and Stokes (2013)	Lateral to the anterior layer two-layer model)	50 human subjects 25 LBP & pelvic pain 25 control	Ultrasound imaging	LBP: 2.9 (±0.8) Control: 2.3 (±0.4)	LBP: 2.1 – 4.7 Control: 1.6 – 3.2

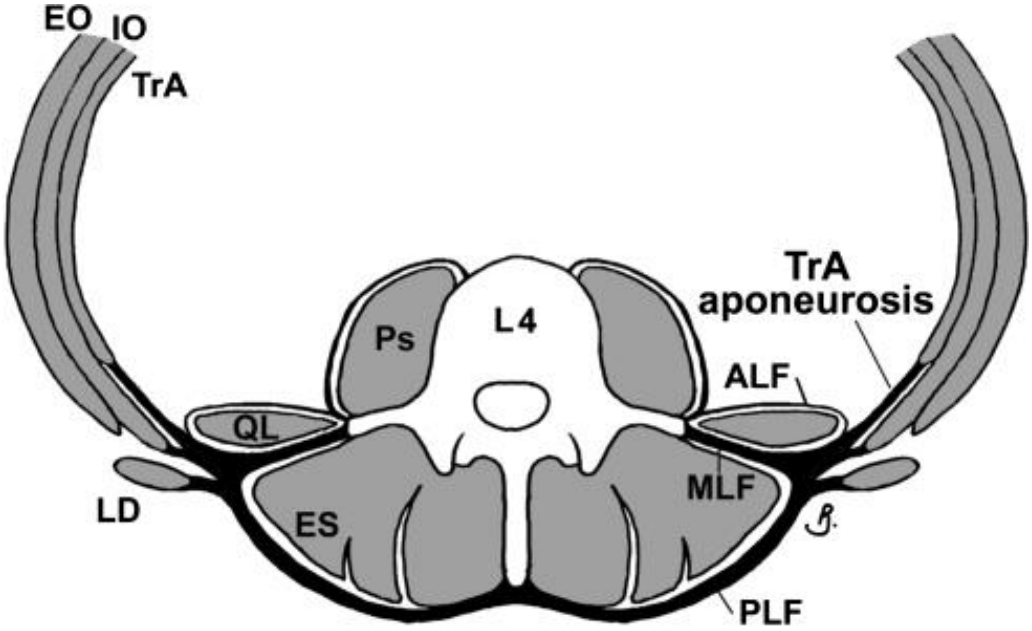


Figure 2.3 The three-layered model of the thoracolumbar fascia.
ALF: Anterior lumbar fascia ; EO: External Oblique; IO: Internal Oblique; TrA: Transversus Abdominus; MLF: middle lumbar fascia; PLF: posterior lumbar fascia (image from Barker *et al.*, 2007).

The outer lamina of the posterior layer of the thoracolumbar fascia connects the gluteus maximus and the contralateral latissimus dorsi muscle. These muscles conduct forces contralateral, through the thoracolumbar fascia, forming a pendulum during movements such as walking, running and swimming (Benjamin, 2009a). The inner lamina of the posterior layer fuses with the serrati posterior fascia and the erector spinae aponeurosis (van Wingerden *et al.*, 1993). Medially, the thoracolumbar fascia attaches to the supraspinal ligament and the spinous processes to the level of L4, the deeper layers form the epimysium of the erector spinae muscles (Figure 2.3) (Schuenke *et al.*, 2012; Willard *et al.*, 2012; Stecco, 2015). Distally, the posterior layer attaches to the posterior superior iliac spine, to the iliac crest, and the long dorsal sacroiliac ligament. Caudally to L4, the collagen fibres cross to the contralateral side and attach to the sacrum, the posterior superior iliac spine and iliac crest. This results in the thoracolumbar fascia being a large retinaculum

connecting the two halves of trunk with the upper and lower limbs, in effect an anatomical and functional junction box between all 4 quadrants of the body.

2.2.3 The load-bearing capacity of the thoracolumbar fascia

The first detailed studies of the load-bearing properties of the thoracolumbar fascia were by Bogduk and Macintosh (1984), this seminal study was based on cadaver dissections of the thoracolumbar fascia and biomechanical modelling. The authors found clear evidence of load transfer through the thoracolumbar fascia. Gracovetsky and Iacono (1987) similarly found that the thoracolumbar fascia had a load-bearing capacity during flexion in their study of the biomechanics of load transfer during lumbar flexion. A number of authors subsequently refined the biomechanical model of load transfer through the thoracolumbar fascia (Tesh *et al.*,1987; Barker *et al.*, 2004b).

Combined, these findings suggest that during trunk flexion in healthy subjects, forces are transferred through the thoracolumbar fascia from the trunk to the lower limbs. In patients with lower back pain however, the erector spinae muscles remain silent for longer, during flexion, demonstrating an absence of shift-loading in lower back pain (Shirado *et al.*, 1995). These findings suggest that the thoracolumbar fascia may have a reduced load-bearing capacity in people with lower back pain (Schleip, Zorn and Klingler, 2010).

Barker *et al*. (2007) demonstrated a further mechanical link between transversus abdominis and movement in the lower back, via the thoracolumbar fascia. They found that the transverse processes could be avulsed in embalmed cadavers by strong transversus abdominis contractions. Barker and colleagues argue that this anatomical link provides evidence for recommending submaximal contraction of

transversus abdominis in the treatment of certain forms of lower back pain. In addition, Barker *et al.* emphasize the strength and significance of the attachment of the middle layer to the transverse processes. They conclude that the thoracolumbar fascia is important in lumbar segmental control (Barker et al, 2004, 2007).

Recently, a review of myofascial force transmission studies (Krause *et al.*, 2016) reported three studies which demonstrated a force transfer between the latissimus dorsi and the contralateral gluteus maximus (Vleeming *et al.*, 1995; Barker, Briggs and Bogeski, 2004b; Carvalhais *et al.*, 2013).

Carvalhais *et al.* (2013) demonstrated that an active tensioning of latissimus dorsi in vivo, results in an increased passive tension of the contralateral gluteus maximus (p= < 0.004), supporting the existence of myofascial force transmission through the thoracolumbar fascia (Carvalhais *et al.*, 2013).

Authors of earlier cadaver based studies focused on the importance of the caudal connections of the thoracolumbar fascia with muscles such as the biceps femoris via the sacroiliac joint and the sacrotuberous ligament (Vleeming *et al.*, 1995; Schuenke *et al.*, 2012)

This anatomical connection demonstrates that the thoracolumbar fascia forms part of the lower back-pelvis-leg transfer of forces (Snijders *et al.*, 1993). In addition, studies have identified a force transfer between the hamstrings and the thoracolumbar fascia (Vleeming *et al.*, 1989; van Wingerden *et al.*, 1993; Vleeming *et al.*, 1995) Vleeming (2012) emphasises that the thoracolumbar fascia has a bracing effect on the lower lumbar spine and the sacroiliac joints, which is essential for an efficient load transfer between trunk and legs. Authors have proposed that some cases of lower back pain could be the result of a failed load transfer through the

thoracolumbar fascia from the trunk, to the pelvis and the legs (van Wingerden *et al.*, 1993; Pool-Goudzwaard *et al.*, 1998; Vleeming *et al.*, 2014).

Willard (2007) takes a different approach and emphasises the continuity of the thoracolumbar fascia with the supraspinous ligament, the facet joints and the deeper ligaments. In addition, the cadaver studies of Barker and Briggs (2007) highlight that the middle layer and the posterior layer are able to transmit tensile forces from the transversus abdominii muscles to the lumbar vertebrae. The authors argue that tension in the thoracolumbar fascia influences segmental control in the sagittal and transverse plane (Barker *et al.*, 2006). Reduced segmental control has been observed in people with lower back pain (Panjabi, 2003; Jemmett, MacDonald and Agur, 2004). Snijders *et al.* (1993) propose that a reduction in tension in the thoracolumbar fascia, as a result of an altered muscle recruitment pattern of the erector spinae and multifidii, may result in pelvic instability and lead to lower back pain. It is important to note that the type of force application or mechanical stimulation to the thoracolumbar fascia and the underlying muscles used in the literature varies widely, ranging from mechanically applied forces to manual traction. Even more importantly, force measurements vary from the use of an electronic strain gauge to visual inspection of photographs of the fascial area (Krause *et al.*, 2016). A number of earlier studies in the literature are cadaver based (Snijders, Vleeming and Stoeckart, 1993; van Wingerden *et al.*, 1993; Vleeming *et al.*, 1995; Pool-Goudzwaard *et al.*, 1998; Barker and Briggs, 1999), therefore any changes observed in fascial tissue properties could be affected by the embalming process (Barker *et al.,* 2004a). It has also been questioned whether traction, adequately mimics muscular contraction (Krause *et al.*, 2016).

Despite these methodological flaws, both ex vivo and in vivo results have yielded encouraging evidence which supports the notion that forces transmitted by the latissimus dorsi are transmitted via the thoracolumbar fascia to the contralateral gluteus maximus, and the hamstrings (Wilke *et al.*, 2016). The overall consensus is that through its different anatomical connections, the thoracolumbar fascia is a key factor in the biomechanics of the spine and pelvis. However, the mechanisms discussed above apply to the thoracolumbar fascia as a whole tissue, and do not include any changes or responses on a cellular level.

A different approach, is the study of fascia's morphology and cellular composition. These studies investigate not just the force transmission through the tissue as a whole, but recognises the importance of the different components in both the dense and the loose connective tissues which make up the thoracolumbar fascia.

2.2.4 Cellular responses in thoracolumbar fascia

The thoracolumbar fascia consists of multiple layers of dense connective tissue sheaths, interspersed with layers of loose connective tissue (Benetazzo *et al.*, 2011). Both loose and dense fascial layers consist of collagen fibres, elastin, glycosaminoglycan, and water albeit in different ratios. All of these components function collectively and give the tissue its viscoelastic properties (Stecco, 2015). Viscoelasticity means that fascial tissues respond immediately and over time to mechanical loading, some deformation is recovered, some isn't. The different components act together, for instance, the negatively charged glycosaminoglycans bind large amounts of water, whereas the collagen fibres counteract this and resist

tissue swelling through their strength and the way in which they are organised (Van Wingerden, 1995; Langevin, 2008). As discussed earlier, the thoracolumbar fascia has a load-bearing function. Excessive tensile forces, injury or severe tensile loading can induce temporary viscoelastic deformation or micro-tearing.

A major property of connective tissue is its ability to remodel in response to mechanical loading, which has been named mechanotransduction (Van Wingerden, 1995; Khan and Scott, 2009). Key components in this process are cells named fibroblasts, which secrete collagen and elastin, and respond to mechanical forces. The tissue response to mechanical loading is a complex process which involves several steps. Initially, cells sense and respond to mechanical load and elasticity of the extracellular matrix via integrin-mediated adhesion points. These adhesion or focal points, form a mechanical link between the cell's internal cytoskeleton and the surrounding extracellular matrix (Evans and Calderwood, 2007; Harburger and Calderwood, 2009). Integrin are proteins that function *mechanically*, by attaching the cell cytoskeleton to the extra cellular matrix (ECM) and *biochemically*, by sensing whether adhesion has occurred. This binding of integrin to the ECM supports cell adhesion and is crucial for tissue maintenance, repair and structural adaptations to loading (Harburger and Calderwood, 2009; Kjær *et al.*, 2009).

For instance, when fascia is stretched, fibroblasts respond within minutes by flattening and actively reorganizing their cytoskeleton (Langevin, Nedergaard and Howe, 2013). Animal studies also found that stretching of fascial tissues causes deformation of the cytoskeleton (Corey *et al.*, 2012).

During sustained stretching, chronic stimulation or wound healing, fibroblasts develop a contractility, and differentiate into smooth muscle-like cells called myofibroblasts (Hinz *et al.*, 2012). During wound healing, or chronic stimulation, the

fibroblasts increase the amount and type of collagen they secrete. These have a positive effect in wound-healing, however may also give rise to secretion of excessive collagen fibers and produce fibrosis.

In injured and non-injured tissues, these complex cellular responses have an important effect on the connective tissues' viscoelastic properties (Ingber, 2008). Conversely, changes in the viscoelasticity of connective tissue affects cellular deformation which happens when mechanical loading is applied to the tissue (Chen and Ingber, 1999). So fibroblasts play an active role in shaping the viscoelastic properties of connective tissues via reorganising its shape, its contractility, and modulating collagen secretion.

A further key component in fascia's extracellular matrix is a specific glycosaminoglycan called hyaluronan, which facilitates the gliding of the thoracolumbar fascia over adjacent muscles, and allows sliding of the individual fascial sheaths of the thoracolumbar fascia itself (Pavan *et al.*, 2014). A new category of fibroblasts has recently been discovered in the fascia lata. These fibroblasts have been named fasciacytes, and are found in small clusters at the border between the loose connective tissue and dense fascia (Stecco *et al.*, 2018). Here, they secrete hyaluronan which aids with the sliding of adjacent fascial sheaths (McCombe *et al.*, 2001). Fasciacytes are similar to synoviocytes, found in synovial capsules where they play a role in the secretion of synovial fluid, similarly stimulated by mechanical loading (Maffulli *et al.*, 2000; Magnusson *et al.*, 2010).

Pavan *et al. (*2014) propose that, as a result of a decrease in mechanical loading in chronic conditions such as lower back pain, the production of hyaluronan is altered. This may explain the densification of fascial layers and a reduction in the sliding ability of adjacent sheaths of the thoracolumbar fascia during flexion, in people with lower

back pain (Langevin *et al.*, 2011). For instance, the thoracolumbar fascia in people with lower back pain has been found to have 25% less shear strain during passive flexion, compared to people without lower back pain (Langevin *et al.*, 2011).

This complex cascade of cellular responses means that loading applied to the tissue causes a direct mechanical deformation of the cytoskeleton (Langevin, 2008). A flow chart of cellular responses found in the literature can be seen in Figure 2.4.

A reduction in mechanical loading can cause atrophy in the connective tissue, which tends to cause a decrease in collagen formation and water content in layers of dense fascia and has been named densification (Pavan *et al.*, 2014). This response has been differentiated from fibrosis which tends to result from an increase in collagen, an increase in interfibrillar crosslinking and restricted gliding of fibres against each other, resulting in disorganisation (Leask, Denton and Abraham, 2004; Reed, Lidén and Rubin, 2010). An increase in collagen cross-linking in endomysial, epimysial and perimysial connective tissue has been shown as a result of an increase in immobilisation (Williams and Goldspink, 1984; Järvinen *et al.*, 2002). Fascial tissue fibrosis may be due to a number of contributing factors, such as a decrease in physical activity as a result of fear of movement (Fritz *et al.*, 2004), or changes in muscle activation patterns (van Dieën, Selen and Cholewicki, 2003) (See Figure 2.4 for an overview).

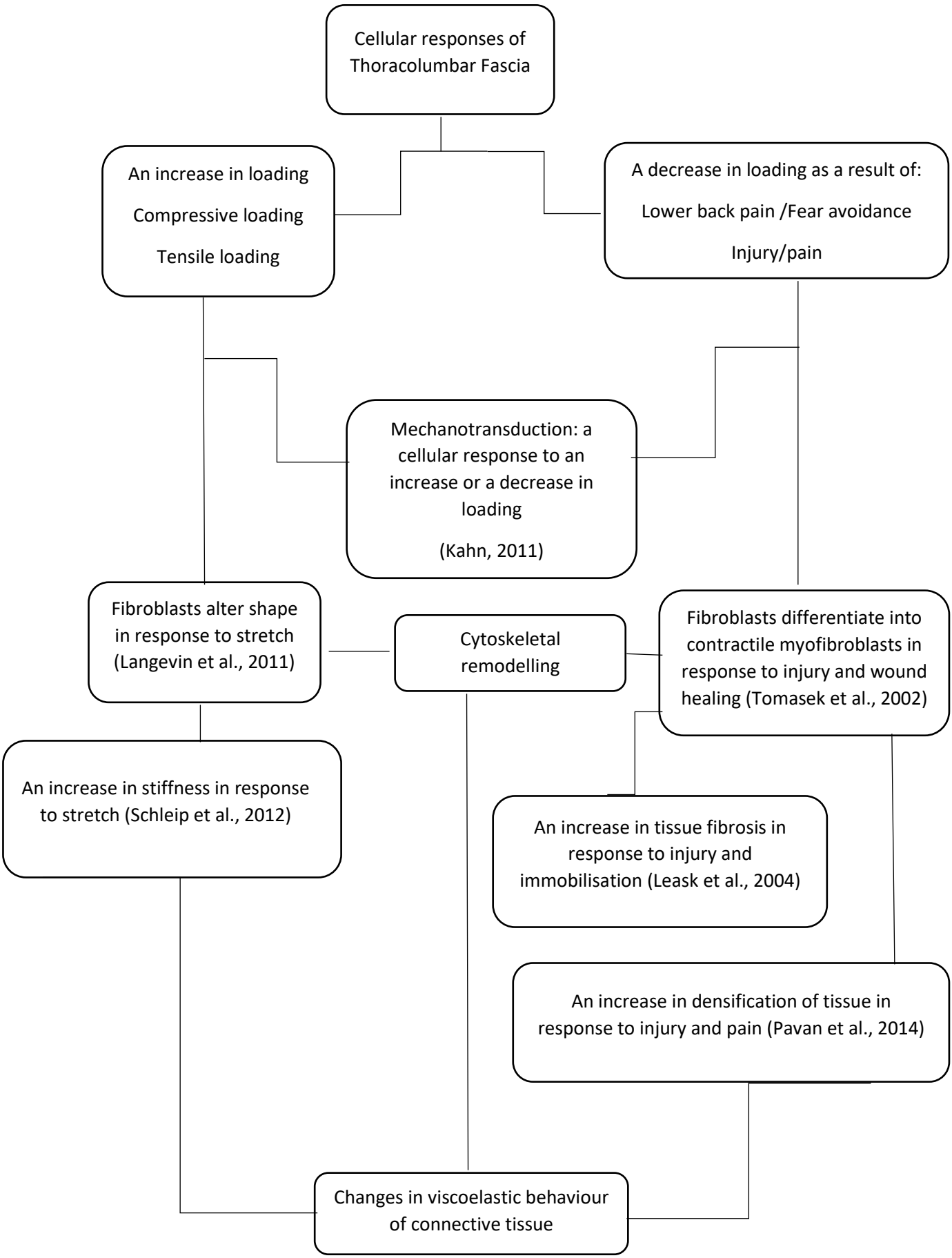


Figure 2.4 Cellular responses to mechanical loading in connective tissues

(Adapted from *Langevin and Sherman, 2007; Langevin, 2008; Wilke* et al.*, 2017)*

Whether tissue remodelling is adaptive or maladaptive depends on the duration and amount of increased or decreased mechanical stress, presence of inflammation and cytokines such as TGFβ-1 which stimulate fibrosis (Magnusson *et al.*, 2010; Kjaer, 2015). The importance of appropriate mechanical loading, in the form of exercise, physical activity or manual therapy, is increasingly recognised as an important factor for a successful recovery from injury (Khan, 2011). However, a fear of re-injury or causing tissue damage can reduce physical activity which can lead to further tissue remodelling. Studies have even shown that fear of pain in healthy individuals can cause a change in muscle activation patterns (Moseley, Nicholas and Hodges, 2004). A decrease in physical movement or activity is a potential major factor in the development of fascial tissue fibrosis and the further development of chronic pain (Pavan *et al.*, 2014). For instance, after trauma such as a sprain in ligaments, new collagen fibres will be produced, however if the patient is immobilised the collagen fibres will have an irregular disposition. This will cause restricted movement and prolonged recovery time. Only early movement permits the correct formation of collagen fibres along the functional lines of force (Kjaer *et al.*, 2009).

Sherman and Langevin (2007) propose a model in which an initial injury, leads to a decrease in physical activity, leading to connective tissue remodelling, and an increase in connective tissue stiffness and fibrosis.

Connective tissues clearly respond to mechanical loading, in either a functional adaptive way, or a dysfunctional maladaptive manner. Chronic degenerative conditions can result in either an increase in water binding hyaluronan, caused by a decreased collagen integrity and a reduced resistance to swelling (Woo *et al.*, 1975), or a decrease in hyaluronan and water content (Eckstein *et al.*,2006). A decrease in mechanical loading tends to result in atrophy and decreased collagen, hyaluronan

and water content, while fibrosis tends to cause an accumulation of collagen bundles, with disorganisation and a reduction in ability of fibres to glide over each other (Langevin, 2008). With a long duration of immobilisation, an increase in fibrillar crosslinks has been established (Donatelli and Owens-Burkhart, 1981). Connective tissue fibrosis is a key issue as it leads to increased stiffness and further movement impairment (Abbott *et al.*, 2013). Pavan *et al.* (2014) differentiate two different types of maladaptation of fascial tissues, damage to the loose connective tissue which affects the sliding between different layers, and damage to the dense connective tissue sheaths which affects force transmission. Pavan *et al.* (2014) suggest that an increase in thickness of the epimuscular fascia of the sternocleidomastoid in people with long-term neck pain is related to an increase in hyaluronan in the loose connective tissue, rather than an increase in the thickness of the dense connective tissue layers. It is currently not know whether this could also explain an increase in thickness of the thoracolumbar fascia of people with lower back pain (Langevin *et al.*, 2009). A further key component in understanding the function of the thoracolumbar fascia is the role of the nervous system, which will be discussed in the next section.

2.2.5 Innervation of fascia

Histological studies have found that the thoracolumbar fascia is richly innervated. Different types of nerve endings such as mechanoreceptors and free nerve endingshave been observed in both dense fascia and loose connective tissues (Yahia *et al.*, 1992; Tesarz *et al.*, 2011; Schilder *et al.*, 2014; Hoheisel and Mense, 2015), with Pacini and Ruffini mechanoreceptors, and free nerve endings being most common (Yahia *et al.*, 1992; Vinet and Zhedanov, 2011). The presence of

unmyelinated nerve endings in in the thoracolumbar fascia, which can be stimulated by stretching and mechanical stimulation (Corey *et al.*, 2011; Tesarz *et al.*, 2011) indicate a potential nociceptive functions. A review recently pointed out that presence of nociceptors is complex, some nerves may have nociceptive potential, as they stain positive for calcitone gene-related peptide CGRP, other nerves have a more definitive nociceptive role, as contain Substance P (Wilke *et al.*, 2017).

One study found that mechanical pinching of cat thoracolumbar fascia triggered spastic contraction of the back muscles, more so than when the back muscles were stimulated in the same manner (Pederson et al., 1956 cited in Wilke *et al.*, 2017). Other authors found that irritating the thoracolumbar fascia of rats with hypertonic saline activated a response in the dorsal horn (Taguchi, Tesarz and Mense, 2009). Since hypertonic saline is considered to stimulate afferent nociceptive nerves, the response in the dorsal horn was seen to indicate that irritated thoracolumbar fascia may be a source of pain. Furthermore, the same study saw a chronic induced inflammation of the back muscles resulting in a threefold increase of dorsal horn neurons (Taguchi *et al.,*2009). Gibson *et al.*(2009) found that hypertonic saline strongly increased pain ($p < 0.05$*)* when injected into the epimysium of a muscle exposed to Delayed Onset Muscle Soreness after eccentric exercise, compared to a much reduced response when injected into a similarly fatigued muscle or a control. Whether muscle fatigue can similarly provoke lower back pain is not yet confirmed.

A human study found that injection of hypertonic saline into the thoracolumbar fascia provoked more intense pain and longer lasting pain, 15 minutes compared to 10 minutes, when injected into the longissimus muscle (Schilder *et al*., 2014). It is important to note that both Schilder et al. (2014) and Gibson et al. (2009) may have caused inflammation in the subcutaneous connective tissue, rather than the dense

connective tissue itself as both studies were careful not to pierce the fascia and may have allowed the hypertonic saline to penetrate and stimulate nerve endings in the subcutaneous superficial fascia, rather than the dense fascia. Surgeons such as Dittrich (1963) and (Bednar (1995) examined the posterior layer of thoracolumbar fascia of patients with lower back pain, with histological staining, and found signs of injury, micro-tears, fatty tissue infiltration and inflammation. Bednar (1995) did not find any nerve fibres in the dense thoracolumbar fascia, however, small peripheral nerve bundles were found, which could be free nerve endings or could be associated with capillary bloodvessels. It is also important to note however that no age-matched controls were investigated, so it is not clear whether these findings also occur in the thoracolumbar fascia of healthy pain-free individuals.

Our understanding of fascial innervation is still incomplete and it is likely that there are regional differences of functional significance, as with ligaments. Hagert *et al.* (2007) distinguishes between ligaments at the wrist that are mechanically important yet poorly innervated, and ligaments with a key role in sensory perception that are richly innervated. For instance, dense connective tissue such as the thoracolumbar fascia adapts to mechanical loading, which is not conducive to having nerves and densely packed collagen fibres too close together. Whereas for instance, nerves tend to be located more abundantly in the loose connective tissues, such as the subcutaneous layers overlaying the thoracolumbar fascia, see Figure 2.5 (Tesarz *et al.*, 2011; Schilder *et al.,* 2014a).

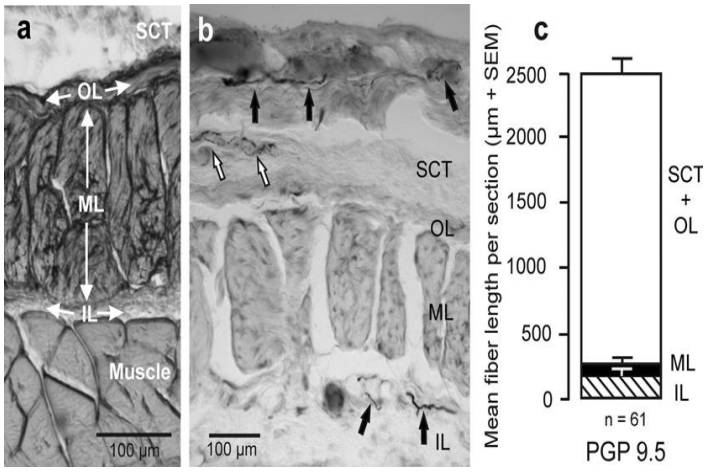


Figure 2.5 Innervation of the thoracolumbar fascia.

IL= inner layer. ML: middle layer. OL: outer layer .Black and open arrows= nerve tissue and nerve endings The majority of nerve fibres were located in the subcutaneous and outer layer ***(from Tesarz et al. 2011)***

Benjamin (2009) reminds us that it is sometimes difficult to ascertain from the literature whether it is the fascia itself which is innervated, whether the nerve fibres lie on the surface of the dense fascia, or in the adjacent loose connective tissue, and the type of nerve fibre or receptor.

A sensitisation in the peripheral and central nervous system is thought to contribute to tissue inflammation and alterations in connective tissue composition (Langevin, 2008). However, our understanding of fascial innervation is still incomplete and requires further research into the interactions between nerves innervating the dense and loose connective tissues, sensitisation and adaptations of fascial tissues.

In summary, the thoracolumbar fascia is a complex structure with connections to upper and lower body muscles. It is a load-bearing functional tissue, its multitude of layers slide over each other during muscle activation. On a cellular level, fascia alters its mechanical properties through specialist cells such as fibroblasts and fasciacytes. The thoracolumbar fascia tissue as a whole also adapts to mechanical loading. Whether a decrease in mechanical loading, due to lower back pain, can cause further

connective tissue atrophy, disorganisation or fibrosis is an important issue (Donatelli and Owens-Burkhart, 1981; Williams and Goldspink, 1984; Kannus *et al.*, 1997; Järvinen *et al.*, 2002; Bishop *et al.*, 2016). Investigations into the morphology of the thoracolumbar fascia with ultrasound imaging will be discussed in the last section of this literature review.

2.3 Diagnostic Ultrasound

Ultrasound imaging is a non-invasive method that allows visualisation of anatomical structures based on reflected sound waves. Ultrasound is now accepted as being of considerable diagnostic value. It was pioneered by the Glasgow obstetrician Ian Donald, and has been used in the diagnosis of musculoskeletal injuries since the 1970's. Ultrasound is a very high-pitched sound (> 20 000 Hertz (Hz) which is above the limits of human hearing. As a sound wave travels through tissues it causes compressions and rarefactions (relaxations), this is referred to as wave propagation (Whittaker *et al.*, 2007). Sound waves travel at different speeds through different tissues. When a sound wave hits a tissue it can be reflected (bounces back), or refracted (is absorbed). By identifying the returning sound wave, the echo, an image can be created. The amount of reflection is shown by the brightness of the pixels in the image, black for no echo (anechoic), and white for a strong echo (hyperechoic). The ultrasound scanner calculates the distance each echo is travelling back from and represents this as different depths on the image. The density of tissues and the smoothness of its surface determine the speed an ultrasound wave will travel through. The stiffer the tissue, the faster the sound wave will travel through it. Each tissue has a characteristic resistance to sound, called acoustic impedence. As a sound wave travels through different types of tissues, the sound wave will become weaker, this phenomenon is called attenuation. Ultrasonic waves in the frequency range of 1-20 MHz are used for medical diagnostic applications. Higher frequencies (7.5 – 18 MHz) are used to produce optimum quality images of superficial structures, lower frequencies (3.5 – 5 MHz) are more suitable for deeper structures (Reimers *et al.*, 1993; Ter Haar, 2010; Kremkau, 2011). The transducer or probe generates and

receives the ultrasound waves returning from the tissues, and converts these waves into electrical signals. Ultrasound waves are produced by piezoelectric crystals inside the transducer which produce a voltage when a sound wave is applied to them. The imaging system in the scanner processes the electrical signals and displays these as images on a screen (Hoskins *et al.*, 2003). The most common mode of image display is B-Mode, which is brightness mode. The brightness of each pixel indicates the strength of the returning signal, which represents the location and density of the tissues. B-mode can be used to investigate the morphology, density and thickness of tissues (Whittaker *et al.*, 2007). B-mode ultrasound images of a wide range of muscle morphologies have been validated through comparison to Magnetic Resolution Imaging (MRI). B-mode ultrasound has been used to investigate muscle atrophy and chronic dysfunction in people with lower back pain (Hebert *et al.*, 2009; Sions *et al.*, 2016). Chronic dysfunction leads to the decrease in water content and the increase in fibrous tissue, such as perymysial and endomysial fascia, this results in higher echogenicity. Whittaker *et al*. (2007), Langevin *et al.* (2009) and Hebert *et al.* (2009) have concluded that B-mode ultrasound is accurate for the measurement of trunk muscles and associated connective tissue structures of the lower back and abdomen.

There is no evidence that diagnostic ultrasound has produced any harm to patients in the four decades that it has been in use (BMUS, 2007, ter Haar & Duck, 2000). Modern ultrasound scanners, when used in accordance with guidelines published by British Medical Ultrasound Society, do not give rise to substantial concerns over safety (BMUS,2007). Exposure of embryonic tissues and foetal bone can result in secondary warming of adjacent soft tissues. However, these tissues do not form part of the proposed study. Additionally, some very high settings and long exposure times are capable of warming tissue to a level where adverse bio-effects may occur, particularly near lung tissue. Again, these tissues are not involved in this proposed study. The ultrasound settings and exposure times used in this study, are within the BMUS guidelines (BMUS, 2007). Further safety issues are discussed in more detail under methodology and risk factors.

Research has shown that ultrasound imaging can be used to quantitatively evaluate the structure of subcutaneous connective tissue in humans (Martin et al., 2001;

Langevin et al., 2007; Kremkau, 1998). The presence of collagen in fascia gives rise to slightly higher velocities than in other tissue.(ter Haar & Duck, 2000). This results in an increased echogenicity or brightness of fascia tissue in the ultrasound image, as compared to adjacent tissue such as dermis or muscle, with a much lower collagen content

2.3.1 Investigating the thoracolumbar fascia with ultrasound

Thoracolumbar fascia and other lumbar structures such as vertebrae, ligaments and muscles can be visualised by Magnetic Resonance Imaging (MRI) (Herlin *et al.*, 2015). For instance, the convex shape of the posterior layer in people with lower back pain has been differentiated from the more flat shape of the thoracolumbar fascia in people with lumbar kyphosis (p >0.01) (Kang *et al.*, 2007). In addition, Computational Tomography (CT) has been used to construct a three dimensional mathematical model to investigate the load-bearing capacity of the middle and posterior layers of the thoracolumbar fascia (Gatton *et al.*, 2010). However, MRI may not be the gold standard imaging modality for thoracolumbar fascia. An MRI study found that a radiologist's assessment of the thoracolumbar fascia (intact, incomplete disruptions, disruptions) of 42 pre-operative patients with an acute injury was in slight agreement with a subsequent assessment of the same patients by a surgeon during spinal surgery (Vaccaro *et al.*, 2009). The specificity was 53%, which is lower than previously reported in the literature. The authors conclude that MRI of the thoracolumbar fascia

and the posterior lumbar ligaments, should not be used to diagnose or determine treatment (Vaccaro *et al.*, 2009).

However, neither MRI nor CT imaging are able to visualise the detailed and complex relationship between the underlying muscle, the dense connective tissue layers of the thoracolumbar fascia interspersed with loose connective tissue, and the subcutaneous layers (Genu *et al.*, 2014a). . It has been shown that ultrasound imaging provides the highest measurement accuracy for thickness measurement of subcutaneous adipose tissue, which corresponds with the subcutaneous zone in this thesis (Störchle *et al.*, 2018) . A high resolution transducer (18 MHz) was used for all studies described in this thesis, which produces images with a pixel size of 0.058 millimetres. The pixel size in MRI is typically between 1.3 and 2 millimetres only.

Moreover, the body-wide dense connective sheath found in the subcutaneous superficial tissues cannot easily be visualised with MRI or CT (Stecco, 2015). Whereas ultrasound imaging can be used to quantitatively evaluate the detailed structure of subcutaneous connective tissue in humans (Martin et al., 2001; Langevin et al., 2007; Kremkau, 1998). McNally and Shetty (2010) found ultrasound to be superior to MRI for the diagnosis of fascial alterations in plantar fascia. In evaluating plantar fibromas using MRI, they were unable to diagnose fibromas, as the signals emitted were similar to those for normal fascia.

Moreover, ultrasound imaging is able to distinguish and differentiate between epimysial connective tissue wrapping muscles, the subcutaneous dense connective tissue sheaths and loose layers of connective tissues (Chandraratna *et al.*, 1997; Teyhen *et al.*, 2011; Whittaker *et al*., 2013). In ultrasound imaging, the presence of collagen in fascia gives rise to slightly higher velocities than in other tissue, compared to adjacent tissue such as dermis or muscle, with a much lower collagen content (Ter

Haar and Duck, 2000). This results in an increased echogenicity or brightness of fascial tissue in the ultrasound image.

An increasing number of medical disciplines use ultrasound to aid diagnosis, ranging from gastroenterology, gynaecology, rheumatology, orthopaedics and sports medicine (Kremkau, 2011). Ultrasound imaging is routinely used to aid the rehabilitation and treatment of lower back pain (Teyhen and Koppenhaver, 2011). In rehabilitation, it is used to evaluate muscle and soft tissue morphology and function. Here ultrasound is used to visualise small parts, detect malignancy, or diagnose fibrosis of connective tissues, and other pathologies (Kremkau, 2011).

To obtain high resolution images of fasciae it necessary to use linear probes with operating frequencies of 12-18 MHz (Stecco, 2015).

A pioneering ultrasound-based study by Langevin et al. (2009) found that, on average, subjects with lower back pain have 25% greater thickness and echogenicity compared to subjects without lower back pain, which could be a result of chronic inflammation, fibrosis or fatty tissue infiltration (Langevin et al., 2009). The studies presented in this thesis will further investigate these findings and evaluate the morphology of the thoracolumbar fascia with ultrasound imaging.

2.4 Conclusion

Lower back pain remains a global and poorly understood symptom. It has a considerable impact on individual people's lives and society as a whole. Despite extensive research into vertebral structures, as well as social and psychological causes of lower back pain, no definitive treatments have yet been found. Therefore,

many people continue to experience lower back pain as a recurrent phenomenon. It is however recognised that lumbar muscle size and recruitment patterns are altered in people with lower back pain. For many years, the connective tissues have been a neglected area in human physiology and rehabilitation research. However, the thoracolumbar fascia has been of particular interest as a potential source of lower back pain. Although research has been conducted into the anatomical connections, force transmission, cellular responses and innervation of the thoracolumbar fascia, there has been no extensive research on the evaluation of the thoracolumbar fascia using ultrasound.

A model for further investigations into the potential role of fascia in CLBP was proposed by Langevin & Sherman (2007), in which pain-related fear is thought to induce a cycle of decreased movement. In turn, it was proposed that an altered movement pattern may result in connective tissue remodelling of lumbar fascia, leading to inflammation, nervous tissue sensitisation and further decreased mobility. Other investigators have proposed that lumbar fascia, may have a role in lower back pain generation due to the tissue being prone to subfailure injuries (Schleip, Vleeming, Lehmann-Horn & Klingler, 2007). Another role of lumbar fascia which has been studied is its biomechanical properties. These studies indicate that lumbar fascia, via its anatomical connection to abdominal musculature, such as the multifidus muscle, and consequential force transmission, plays a role in lower back stability (Hodges et al., 2003; Barker et al. 2006). A plausible pathological mechanism is that ongoing local tissue inflammation combined with pain-related movement abnormalities may lead to connective tissue fibrosis, increased tissue stiffness and

further movement impairment which may contribute to CLBP (Langevin & Sherman, 2007)

2.5 Aims of the research

The aim of this thesis is two-fold. The first aim is establish whether ultrasound imaging is a viable method to investigate the thoracolumbar fascia in vivo in humans. The second aim is to demonstrate the clinical relevance of ultrasound based research into thoracolumbar fascia in people with lower back pain.

In order to address these aims, a number of research questions will be addressed in the remainder of this thesis.

2.6 Research questions

Research question 1:

Can an investigator reliably measure the thickness and echogenicity of the thoracolumbar fascia in ultrasound images?

Research question 2:

Can ultrasound detect structural differences in the thoracolumbar fascia of people with lower back pain and people without lower back pain?

2a. Is the thoracolumbar fascia thicker in people with lower back pain?

2b. Is the thoracolumbar fascia higher in echogenicity in people with lower back pain?

2c. Are pain frequency, pain severity and lower back pain disability scores associated with the thickness and echogenicity of the thoracolumbar fascia in ultrasound images?

2d. Is a sedentary lifestyle associated with the thickness and echogenicity of thoracolumbar fascia in people with lower back pain?

Research question 3:

Does a week endurance training programme affect the thickness and echogenicity of the thoracolumbar fascia in untrained individuals?

Research question 4:

Can human observers agree on the degree of organisation and disorganisation in ultrasound images of the thoracolumbar fascia?

Hypothesis:

Ultrasound imaging can be used to evaluate the morphology of the thoracolumbar fascia in people with and without lower back pain.

Chapter 3 General ultrasound methodology

3.1 Ultrasound image acquisition

Imaging studies were approved by the University of Kent's School of Sport and Exercise Research Advisory Group and were carried out in compliance with the Helsinki Declaration. All participants provided informed consent. Ultrasound procedures were performed by 1 trained investigator blind to the participants' condition in Chapter 5 (lower back pain vs no lower back pain), but not blind to group assignment in Chapter 6 (training group vs control group). Kyra De Coninck received 12 months of musculoskeletal ultrasound training at the Centre of Ultrasound Studies, Anglo-European Chiropractice College, University of Bournemouth (see page xvi for details). Kyra has detailed knowledge of musculoskeletal anatomy, having had 14 years of experience in teaching anatomy and sports massage.

The British Medical Ultrasound Society guidelines on safe use of diagnostic ultrasound equipment were adhered to (Ter Haar, 2010). Image acquisition took place in a sports clinic and a University teaching clinic. A semi-portable ultrasound scanner (MyLabGold 25; Easote, Rimini, Italy) with a linear array transducer (40 mm footprint, 6-18 MHz bandwidth; Easote LA435) was used to generate B-mode images. A frequency of 18MHz was set for all images, with a depth of 3 cm, in accordance with guidelines for optimum image quality for subcutaneous structures (Kremkau, 2006). The linear transducer allowed tissue penetration up to 90 mm, ensuring good quality image acquisition from participants with varying thicknesses of subcutaneous tissues, ranging between 5 mm to 90 mm.

The participants laid prone on a treatment couch, a pillow was placed under the hips to minimise lumbar lordosis, so that the lumbar fasciae would lie as horizontally as possible to the skin and the spine. The investigator was always positioned to the left

of the participants, in keeping with standardised protocols in radiology (Stokes et al., 2007). The location for image acquisition was an area 2 cm lateral from the intervertebral level between lumbar vertebrae 2 and 3, as fascial planes are the most parallel to the skin at this level. Lower levels, such as vertebrae 4 and 5 were not selected as the gluteal fat pad and lumbar spine curvature at this level causes more variability in the angle of transducer placement on the skin (Langevin et al., 2009).

Firstly, the bony landmarks of the sacrum and the spinous processes of lumbar vertebrae were manually palpated. The spinous process of lumbar vertebra 5 was located, in most people, this is a deep, small, blunt point at the centre of the lumbosacral depression. Palpation then continued in a cranial direction where the spinous process of lumbar vertebra 4 was located, which has a larger spinous process. Subsequently, the spinous process at levels 3 and 2 were identified and were marked on the skin with a felt-tip pen. Early studies have recognised that the manual palpation of nominated spinous vertebra has a modest to good intra-therapist reliability for both clinical and research purposes (McKenzie and Taylor, 1997; Downey, Taylor and Niere, 1999). More recent studies however, have questioned the validity of manual palpation for lumbar vertebrae location (Robinson et al., 2009; Kilby, Heneghan and Maybury, 2012). Therefore, the manually located anatomical landmarks were subsequently verified with real-time ultrasound imaging in line with a standard protocol for lumbar ultrasound scanning (Stokes et al., 2007). When necessary, location marks on the skin were adjusted to reflect the verified spinous process landmarks. A footprint area of 40 x 5 mm, 2 cm lateral, to the left and the right of the marked spinous processes were subsequently outlined on the skin, to ensure accurate positioning of the transducer, see Figure 3.1 for transducer position.

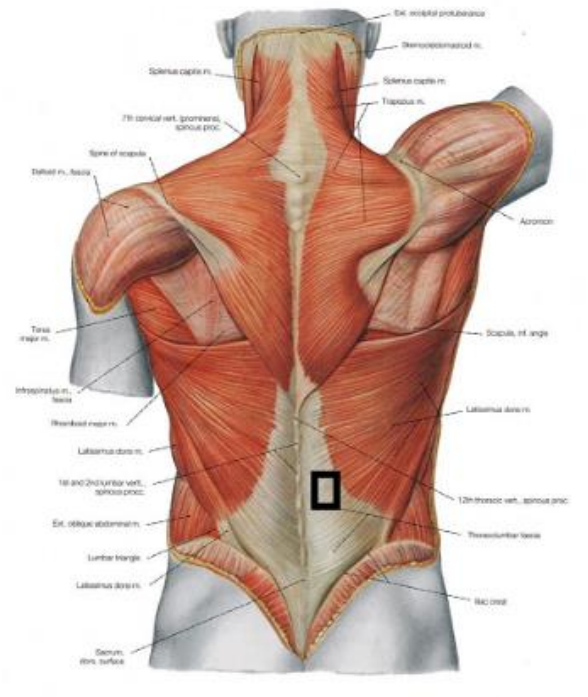


Figure 3-1 Position of transducer 2 cm lateral to the interspinous ligament between lumbar vertebrae 2 and 3. *Wikimedia Comms https://commons.wikimedia.org/wiki/File:Atlas_and_text-book_of_human_anatomy_(1914-)_(20351394431).jpg* [accessed 31.10.2017]

One focal region was set as close as possible to the thoracolumbar complex. Bi-lateral parasagittal (longitudinal) images were acquired from both left and right imaging sites. Great care was taken to avoid any pressure applied to the transducer in order to minimise compression of the subcutaneous and fascial tissues. See Figure 3.2 for anatomical orientation. This method of image acquisition is based on a validated protocol (Langevin *et al.*, 2009).

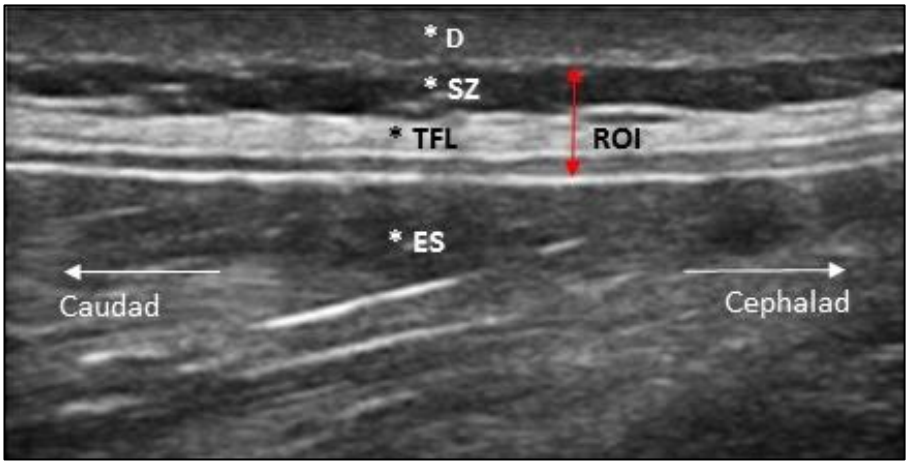


Figure 3.2 Anatomical orientation showing location of dermis

*(*D), subcutanous zone (*SZ), thoracolumbar fascia (*TFL) and erector spinae muscle (*ES). The area selected for data analysis is the region of interest (double red arrow, *ROI)*

3.2 Ultrasound image analysis

Images were measured offline using Matlab version R2012a (The Mathworks, Natick, MA). A measurement code for grey-scale image analysis automatically uploaded anonymised ultrasound scans from a directory. This code cropped the ultrasound image to a region of interest (ROI) which was a 1 cm wide region centred on the middle of the ultrasound image. Pixels were transferred to millimetres using the calculation in Hoskins *et al.* (2003). The total image was 512 pixels square, with an image depth of 30 millimeters. This means that each pixel represents 512^{th} of 30 millimeters (3: 512 = 0.0585 millimeters). Therefore, the pixel values were multiplied by 0.0585 to transform the values into millimetres.

The investigator plotted a reference point on a grey scale profile positioned next to the ultrasound scan, to mark the borders of the perimuscular and subcutaneous layers (Figure 3-3 example of image analysis).

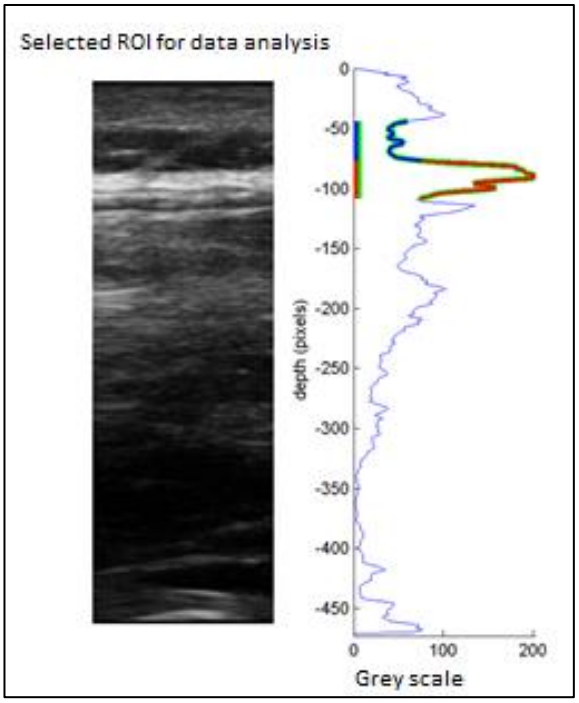


Figure 3.3 Ultrasound image analysis method showing region of interest. Thickness of combined zone (green), subcutanous zone (blue), perimuscular zone (red). The average grey scale profile corresponds to the ultrasound image. Grey scale was measured as arbitrary units between 0=black and 255=white.

All direct measurement values were concealed from the investigator during this process and prior to statistical analysis.

Combined subcutaneous and perimuscular zone thickness was measured as the distance between the deep border of the dermis and the superficial border of the muscle (Figure 3-3 green line) The perimuscular zone thickness was measured as the thickness of the echogenic layer closest to the muscle and separated from the nearest, more superficial echogenic layer by more than 2 mm (Figure 3.3 red line). Subcutaneous zone thickness was measured as the thickness of the zone between the dermis and the superficial border of the perimuscular zone (Figure 3.3 blue line). Thickness was calculated in pixels.

Echogenicity was measured as the average grey-scale value. Echogenicity for the combined subcutaneous and perimuscular zone was calculated as the area within the ROI. Echogenicity for individual subcutaneous and perimuscular zones was the area delineated by the respective thickness measurements (Figure 3.3).

Echogenicity and thickness were calculated for individual images on both the left and right sides, as well as averaged across sides within subjects.

Chapter 4: Reliability of measures of the thoracolumbar fascia

4.1 Introduction

In order to investigate the clinical utility of ultrasound imaging of the thoracolumbar fascia, it is critical to establish rater reliability. For this purpose, an intra-rater reliability study was conducted, as the acquisition and measurement of all images contained in this thesis were undertaken by a single investigator. Rater reliability of ultrasound imaging is well established for trunk muscles in older people (Wilson *et al.*, 2016), younger populations (Teyhen, 2011), healthy cohorts (Stokes *et al.*, 2007; Wallwork, Hides and Stanton, 2007) and people with lower back pain (Costa *et al.*, 2009; Sions *et al.*, 2016). Furthermore, the inter-rater reliability of ultrasound image measurements of the lateral raphe of thoracolumbar fascia in asymptomatic participants (Chen *et al.*, 2015) and in people with lower back pain has been confirmed (Whittaker, Warner and Stokes, 2013). The lateral raphe is located at the point where the tranversus abdominis attaches onto the posterior and middle layers of the thoracolumbar fascia (see figure 2.2). However, little attention has been paid to the rater reliability of the posterior layer of the thoracolumbar fascia located closer to the spine (marked PLF in figure 2.2).

In image reliability studies, the intra-image and inter- image analysis are key components, despite being regularly neglected in test re-test study design. (Hebert *et al.*, 2009; Cuellar *et al.*, 2017). The first component, intra-image reliability, is the extent of agreement between repeated measurements of the same image. In image reliability studies, agreement is defined as the extent to which measurements are identical (Kottner and Streiner, 2011). This type of agreement is important to ascertain repeatability of measurements of the same image. The second component

of image measurement reliability is the analysis of images taken at different times, called inter-image reliability. Inter-image reliability is defined as a measurement of two different images of the same participant, obtained and measured by the same investigator over a period of time. (Rousson, Gasser and Seifert, 2002; Hebert *et al.*, 2009). Inter-image reliability is a key factor in research and clinical practice as a patient's progress and tissue changes need to be reliably monitored over time. The risk for measurement error is greater in inter-image reliability, compared to re-measuring the same image, due to the repositioning of the transducer and error in repeated identification of anatomical landmarks (Whittaker *et al.*, 2007).

Choosing the appropriate statistical approach to analyse image and rater reliability has been the subject of debate for some time (Landis and Koch, 1977; Rankin and Stokes, 1998; Rousson, Gasser and Seifert, 2002; de Vet *et al.*, 2006; Kottner *et al.*, 2011; Berchtold, 2016; Koo and Li, 2016). A Pearson's correlation coefficient is used at times to measure agreement in both medical and social sciences, however, it is not considered to be a robust measurement of agreement and reliability as it merely points to a correlational relationship and cannot differentiate between systematic or random differences in measurements (Bland and Altman, 1986; Rankin and Stokes, 1998). A consensus on best practice of statistical analysis for image reliability studies is emerging (Kottner *et al.*, 2011; Berchtold, 2016). This approach recommends that agreement, meaning intra-image reliability, can be analysed with an appropriate intra-class coefficient, but that close attention needs to be paid to the standard error measurement in order to accurately evaluate absolute agreement (de Vet *et al.*, 2006). Reliability, meaning inter-image reliability, can be investigated with an appropriate intra-class coefficient combined with a visual inspection of Bland-Altman

plots, as neither test alone provides sufficient information to ascertain image reliability testing (Rankin and Stokes, 1998).

Establishing both the intra-image and inter-image reliability of the posterior layer of thoracolumbar fascia images is critical in order to ascertain both agreement and reliability of image analysis. This will enable further investigations into the variance of different morphologies, and whether these are clinically relevant in different populations, particularly in conditions such as lower back pain (Langevin *et al.*, 2009). The aim of this study is to determine the inter- and intra-image reliability of ultrasound images of the posterior layer of the thoracolumbar fascia, obtained by the same investigator.

4.2 Methods

4.2.1 Participants

Fourteen participants were recruited, 10 were drawn from a control group of a training study on the effect of a 4 week endurance training programme on the thoracolumbar fascia, and 4 were recruited independently. Two participants were withdrawn from the study, as the quality of the scans had been affected by a malfunction of the scanner probe. One further participant was withdrawn due to non-attendance of the second scan session. A total of 11 participants were included in the final analysis of data. Measurement of physical activity levels is described in Chapter 3: General Methods. Lower back pain was assessed as the presence of lower back pain in the previous 12 months. This study was approved by the University of Kent's School of Sport and Exercise Sciences Research Advisory Group (Prop 124-

2015-16). All participants gave written informed consent. Height was measured with a stadiometer, weight by calibrated scales.

4.2.2 Image acquisition and measurement

The ultrasound image acquisition and measurement protocols are described in detail in Chapter 3: General Ultrasound methodology.

Three zones were identified and analysed on all scans: the subcutaneous zone (*SZ in figure 4.1) between the inferior border of the dermis (*D in figure 4.1) and the superior border of the thoracolumbar fascia, the perimuscular zone between the superior border of the thoracolumbar fascia and the superior border of the muscle (*TFL in figure 4.1), and the combined zone between the inferior border of the dermis and the superior border of the muscle (ROI in figure 4.1).

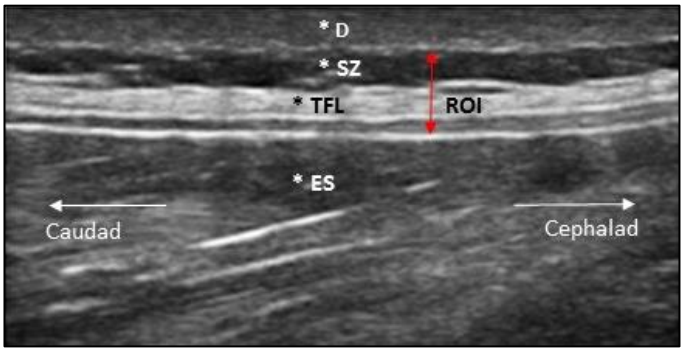


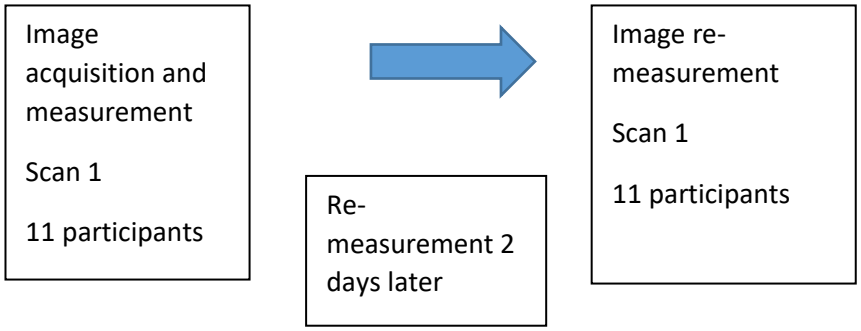
Figure 4.1 Anatomical orientation showing location of dermis

*(*D), subcutaneous zone (*SZ), thoracolumbar fascia (*TFL) and erector spinae muscle (*ES). The area selected for data analysis is the region of interest (double red arrow, *ROI)*

All scans were obtained by the same investigator, at the same time of day and were measured in a random order. During re-measurements, the investigator was blind to

any marks made on the skin made to locate bony landmarks for previous scans, any previous measurements or images on the ultrasound scanner's screen. The intra-image reliability was calculated by comparing 2 measurements of the same scan, 2 days apart. The inter-image reliability was calculated by comparing 3 measurements of 2 scans, with the second scan being obtained 4 days later. See figure 4.2 for a flow chart of image acquisition and analysis.

A. Intra-image reliability methodology: measurement of the same scan



B. Inter-image reliability methodology: analysis of two different scans

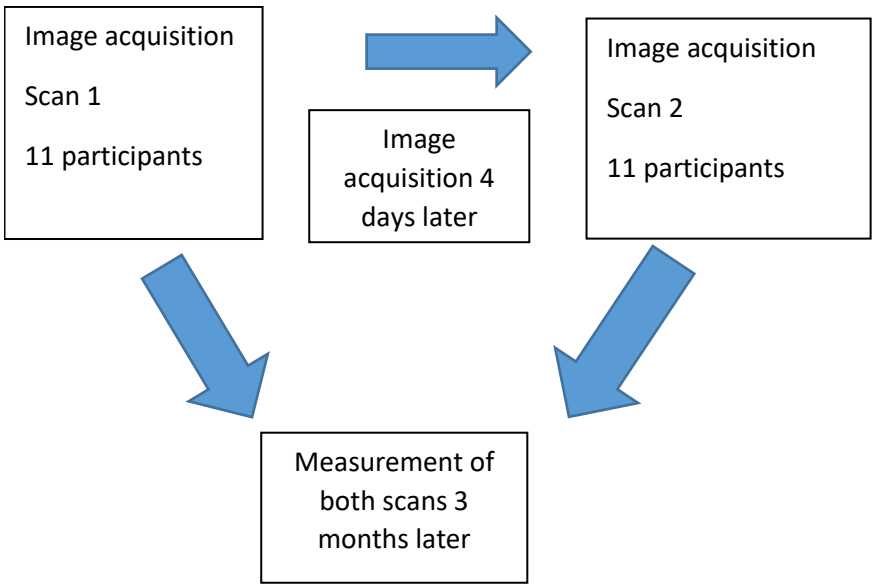


Figure 4.2 Flow chart of intra- and inter-image analysis

4.2.3 Data Analysis

Measurement reliability was assessed from the mean difference between pairs of measurements. Intraclass correlation coefficients (ICC) were used, using the (1,k) form where k represents the number of measurements, rather than the number of raters (Shrout and Fleiss 1979; Rankin and Stokes, 1998). To calculate intra-image reliability, the mean of 2 measurements was used in the calculation, hence ICC (1, 2) was used. Inter-image reliability was calculated comparing the mean of 3 image analysis measurements of scans from day one with the mean of 3 measurements of scans from day 2 using ICC (1, 3). ICCs were regarded as excellent if ICC were > 0.75, good if ICC were < 0.75, fair if ICC is > 0.4, poor if ICC were < 0.4 (Shrout and Fleiss, 1979).

The Standard Error Measurement (SEM) was calculated to assess error and therefore the level of imprecision, for both intra-image and inter-image reliability, using the formula $SEM = SD \times \sqrt{1} - ICC$ (de Vet *et al.*, 2006; Djordjevic and Konstantinovic, 2014). The minimal detectable change (MDC), which represents the minimum amount of change in thickness measurements that ensure the change is not the result of measurement error. MDC was calculated as $1.96 \times SEM \times \sqrt{2}$ (Whittaker et al., 2013). The establishment of minimal detectable change values could enable researchers to decide whether day-to-day variability is likely to be the result of measurement error.

The Bland and Altman method was used to inspect the inter-image reliability (Bland and Altman, 1986). The difference between the measurements of the 2 different

scans were plotted against the mean. Plots were inspected to identify any differences related to the measurements between the two different images (Bland and Altman, 1986). The limits of agreement were calculated as the mean bias plus or minus 1.96 times its standard deviation (SD) (Bland and Altman, 1986).

PASW Statistics 25 (SPSS, IBM Inc., Chicago, IL) was used to calculate ICCs with 95% confidence intervals to estimate reliability.

4.3 Results

The 11 participants (27% males) had a mean age of 25 years, mean body mass of 68 kg, 70% reported no lower back pain. See Table 4.1 for further demographic characteristics.

Table 4.1 Participant characteristics for training and control groups

	Participants (*N* = 11)
Gender Male / Female (%)	3 (27%) / 8 (73%)
Age (years)	25 ± 9
BMI (units)	23 ± 3
Body Mass (kg)	68 ± 16
Physical Activity level (%)	
Sedentary	0%
Moderate	84%
High	16%
Lower back pain (%)	
No lower back pain	70 %
Lower back pain	30 %

Values represent Mean ± Standard Deviation unless otherwise indicated. Physical activity was grouped into sedentary (less than 3 times a week, < 1 hour a week in total), moderate (physical activity >3 times a week, 1.5 to 3 hours) and high (> 4 times a week, > 3 hours).Section 4-3-1 Intra-image reliability

4.3.1 Intra-image reliability

Intra-image reliability for thickness of thoracolumbar fascia was excellent (Shrout and Fleiss, 1979), with ICCs >0.97 for both left and right subcutaneous and combined zones, and >0.94 for left and right perimuscular zone. See Table 4.2 for results.

4.3.2 Inter-image reliability

The ICC for inter-image reliability of thoracolumbar fascia thickness measurements was similarly excellent with ICCs of >0.95 for both left and right subcutaneous and combined zones. Those for the perimuscular zone were acceptable with an ICC of 0.63 for the left side, and 0.70 for the right side (Shrout and Fleiss, 1979). See Table 4.3 for results. The SEM and MDC indicate that inter-image reliability is consistently lower than intra-image reliability.

4.3.3 Inspection of Bland-Altman plots

Inspection of Bland and Altman plots of all inter-image thickness measurements revealed no systematic pattern of variability in measurement differences of all zones, across two scans acquired at different times (Bland and Altman, 1986). See Figures 4.3 and 4.4 for results.

Table 4.2 ICC and SEM results for intra-image reliability

Thoracolumbar Zone	N	Measure Mean (SD)	Re-measure Mean (SD)	Difference Mean (SD)	SEM	ICC (1,2)	MDC	95% CI
Left subcutaneous	11	4.40 (3.13)	4.52 (3.07)	-0.12 (0.06)	0.01	0.99	0.02	(0.97-0.99)
Right subcutaneous	11	4.66 (3.21)	4.73 (3.21)	-0.07 (0)	0.1	0.99	0.27	(0.98 – 0.99)
Left combined	11	6.78 (3.40)	6.92 (3.45)	-0.14 (0.05)	0.01	0.98	0.02	(0.94 – 0.99)
Right combined	11	6.94 (3.61)	6.9 (3.66)	0.04 (0.05)	0.01	0.99	0.02	(0.99 – 1.00)
Left perimuscular	11	2.23 (0.70)	2.18 (0.66)	0.05 (0.04)	0.01	0.96	0.02	(0.85 – 0.98)
Right perimuscular	11	2.27 (0.88)	2.16 (0.88)	0.11 (0)	0.2	0.95	0.55	(0.82 – 0.98)

Mean values, standard deviation values (SD) and Standard Error Measurements (SEM) are in millimetres Abbreviations: SEM: Standard Error Measurement. ICC: Intraclass Coefficient. minimal detectable change. CI: confidence interval.

Table 4.3 ICC and SEM results for inter-image reliability

Thoracolumbar Zone	N	Scan 1 measure Mean (SD)	Scan 2 measure Mean (SD)	Difference Mean (SD)	SEM	ICC (1,3)	MDC	95% CI
Left combined	11	6.74 (3.42)	6.65 (3.93)	0.09 (0.51)	0.1	0.95	0.27	(0.84-0.99)
Right combined	11	6.28 (3.90)	6.39 (3.82)	-0.11 (0.08)	0.01	0.95	0.02	(0.84 – 0.99)
Left subcutaneous	11	4.40 (3.10)	4.58 (3.51)	-0.18 (0.41)	0.08	0.95	0.22	(0.84-0.99)
Right subcutaneous	11	4.34 (3.46)	4.46 (3.46)	-0.12 (0)	0.17	0.97	0.47	(0.88 – 0.99)
Left perimuscular	11	2.34 (0.69)	2.07 (0.72)	0.27 (0.03)	0.02	0.63	0.05	(0.12-0.88)
Right perimuscular	11	1.94 (0.88)	1.92 (0.73)	0.02 (0.15)	0.08	0.70	0.22	(0.24 – 0.91)

Mean values, standard deviation values (SD) and Standard Error Measurements (SEM) are in millimetres. Abbreviations: SD: standard deviation. SEM: Standard Error Measurement. ICC: Intraclass Coefficient. MDC: Minimal Detectable Change. CI: Confidence Interval

Figure 4.*3* Bland and Altman plots for inter-image reliability of combined and subcutaneous zones.

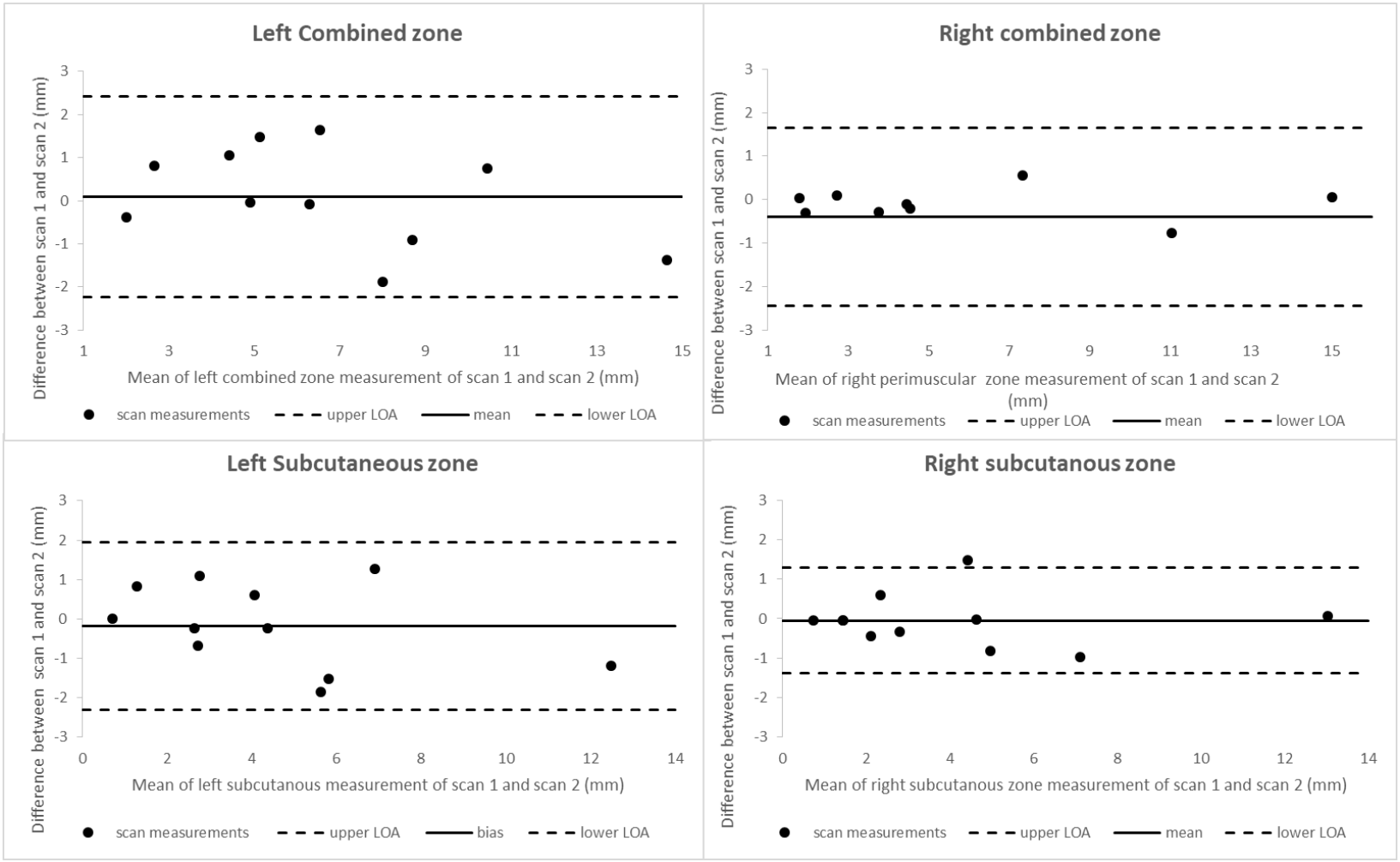


Figure 4.3. LOA: Limits of Agreement, calculated as the mean bias plus or minus 1.96 times its standard deviation.

Figure 4.4 Bland and Altman plots for inter-image reliability of the perimuscular zones

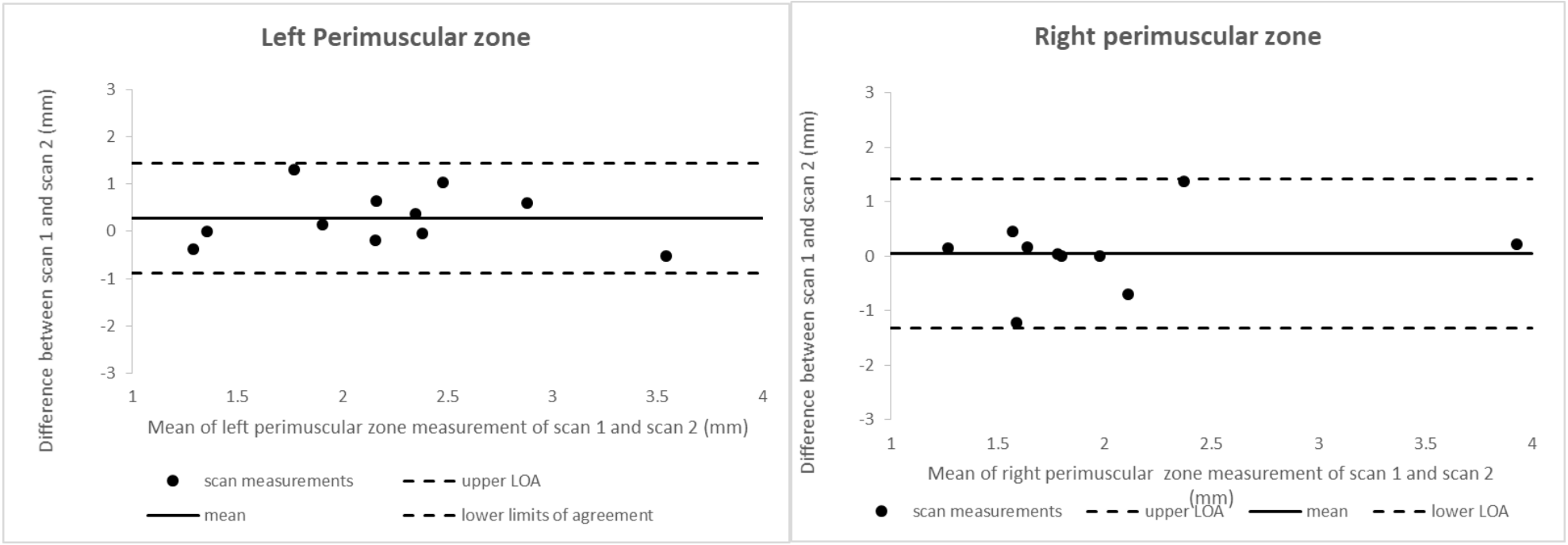


Figure 4.4. LOA: Limits of Agreement, calculated as the mean bias plus or minus 1.96 times its standard deviation.

4.4 Discussion

Results from this study show excellent intra-image reliability of measurements of the posterior layer of the thoracolumbar fascia with ICCs ranging from 0.95 to 0.99 and small SEMs ranging between 0.01 and 0.2 mm. All measurements were below the minimal detectable change, indicating 95% of measurements were not due to error.

In subcutaneous tissues, the speed of ultrasound waves is 145 ms^{-1} (Störchle *et al.*, 2018), any error due to speed sound would be 0.04 mm in a combined zone of subcutaneous and perimuscular tissue of 6 millimetres thickness, which is within the measurement error determined by image resolution (Störchle *et al.*, 2018).

Inter-image reliability was good to excellent with ICCs ranging from 0.63 to 0.97, and SEMs from 0.08 to 0.17 mm. All measurements were below the minimal detectable change, indicating that 95% of measurements were not due to error. ICC values are often described using descriptors such as 'excellent', 'good' or 'poor' (Landis and Koch, 1977; Shrout and Fleiss, 1979). Hebert et al. (2009) support an alternative interpretation of ICC values. This approach classifies ICC values greater than 0.70 as sufficient for comparisons between groups and ICC values greater than 0.90 to be appropriate for individual level comparisons (Hebert *et al.*, 2009). This interpretation suggests that the intra-image and inter-image reliability results are appropriate for individual comparisons.

Even though there were slightly lower values for the measurements of 2 different images (inter-image) of the perimuscular zone (ICC = 0.63 – 0.70, SEM = 0.02 – 0.08 mm), as opposed to the measurement of the same image of the subcutaneous zone

(ICC = 0.99, SEM = 0.01 – 0.1 mm), the overall ICC results indicate a stability comparable with systematic reviews of ultrasound rater reliability studies (Hebert *et al.*, 2009; Koppenhaver *et al.*, 2009). For instance, Wallwork and colleagues examined the intra-image reliability of the multifidus muscle thickness at rest in healthy participants and found ICCs ranging from 0.88 to 0.95 with SEMs between 0.06 and 0.11 mm (Wallwork, Hides and Stanton, 2007). It is important to note that even though the ICCs in Wallwork et al.'s study are slightly lower, the SEMs are also small, comparable to this present study. Similarly, Koppenhaver's team found an ICC of 0.97 for intra-image reliability of the multifidus muscle, with a comparable small SEM of 0.01 mm (Koppenhaver *et al.*, 2009). As highlighted in the introduction of this chapter, a key factor in intra-image reliability is agreement. And for agreement to be confirmed, a small SEM is required (de Vet *et al.*, 2006; Berchtold, 2016). Thus demonstrating that one rater can reliably measure the same image of the posterior layers of thoracolumbar fascia. The reliability of intra-image measurements (ICC = 0.95-0.99) is excellent, whereas the measurements of 2 different images (inter-image) had slightly lower ICCs in the present study (ICC = 0.63 -0.97). Inter-image reliability is less stable, due to potentially more variability introduced in image acquisition.

This is in contrast to a reliability study of the lateral raphe of the thoracolumbar fascia, which found a slightly higher excellent inter-image reliability ICC of 0.98, with an SEM of 0.16 mm (Chen *et al.*, 2015) (see figure 4.1 for anatomical orientation). This might be due to the fact that, Chen and colleagues compared two different images, which were acquired only half hour apart, whereas the present study

compared two images acquired 4 days apart. It has been pointed out that where measurements are taken with a short time interval, this can potentially lead to recall bias (Djordjevic, Djordjevic and Konstantinovic, 2014), which could explain the slightly higher ICC reported by Chen *et al.* (2015).

In a similar study, Whittaker and colleagues (Whittaker, Warner and Stokes, 2013) included the lateral raphe of the thoracolumbar fascia in an inter-image reliability study of the abdominal muscles. Even though the authors did not report specific inter-image ICCs for this particular muscle-fascia junction, they found excellent ICCs for the abdominal wall muscles attached to this lateral raphe of the thoracolumbar fascia (tranversus abdomini, rectus abdominis and internal and external obliquus) ranging between 0.92 and 0.99, with SEMs ranging from 0.1 to 0.9 mm. Images were acquired 1 to 7 days apart, it is not clear whether recall bias was a confounding factor. Whitaker *et al.* (2013) did not report specific ICCs for the fascial tissues which limits a direct comparison with the current study.

An important consideration in reliability studies, is the use of the average of multiple measurements, rather than a single measurement. Some authors report that using an average of 3 measurements reduces SEM by 50%, compared to a single measurement of the multifidus muscle (Hebert *et al.*, 2009; Koppenhaver *et al.*, 2009), whereas others only report modest improvements, compared to single measurements (Djordjevic, Djordjevic and Konstantinovic, 2014). An average of 3 measures was used for the inter-image calculations in this present study, however in a clinical setting, time may not permit three measurements of an image.

There are currently no known ultrasound-based studies investigating the reliability of measurements of the posterior layer of the thoracolumbar fascia. There are however, a few studies testing the validity of using ultrasound for thoracolumbar fascia measurements. Imaging layers of the thoracolumbar fascia is particularly challenging due to the multiple hyper-echoic layers of dense irregular connective tissue interspersed with hypo-echoic layers of loose connective tissue, adipose tissue and fluid. These different layers can appear in clearly defined striated layers in some people and have a more irregular or disorganised morphology in others (Langevin and Sherman, 2007; Stecco, 2015). A pioneering study comparing ultrasound images of thoracolumbar fascia with 3-D renditions, and a histological analysis of the same tissue, demonstrated high positive correlations for both parallel ($r=0.79$, $p< 0.001$) and perpendicular ($r= 0.63$, $p<0.001$) orientations to the surface of the skin (Langevin *et al.*, 2007). Similarly, an animal ultrasound study of equine pelvic anatomy, concluded that ante-mortem ultrasound images of the thoracolumbar fascia correlated with gross post-mortem anatomic findings, both in terms of thickness and cross-sectional area measurements (Engeli *et al.*, 2006). These studies demonstrate that ultrasound is a valid method to investigate thoracolumbar fascia. Furthermore, this present study establishes that intra-image reliability of the thoracolumbar fascia is excellent, and inter-image is good to excellent.

4.5 Limitations

Ultrasound imaging is limited by nature, it cannot specify the exact type of tissue being imaged, slight changes in position of the transducer affect image quality, and acquisition of images are operator dependent (Whittaker and Stokes, 2011; Sions *et al.*, 2015). However, with training, clinicians may be able to reliably perform ultrasound images of the thoracolumbar fascia. It has been demonstrated for example, that trained novice examiners are able to achieve good to excellent reliability for measurements of multifidus in both young and older populations (Sions *et al.*, 2014).

A limitation of this present study is that only intra-rater measurements were involved. Inter-rater and multi-rater studies are required to further establish the reliability of ultrasound imaging of the thoracolumbar fascial tissues.

Participants in this present study were relatively young, mean age 25, ±9. Age related changes such as fibrosis, fatty tissue infiltration could potentially increase thoracolumbar fascia thickness, a decrease in water content can decrease the ultrasound image echogenicity, which could affect reliability of measurements (Stokes *et al.*, 2007; Wilson *et al.*, 2016; Cuellar *et al.*, 2017). This suggests that further studies with an older population are required.

Lower back pain has been associated with increased fibrosis, increased thickness and/or disorganisation of thoracolumbar fascia, which would influence ultrasound analysis of the thoracolumbar fascia (Langevin *et al.*, 2009; Whittaker, Warner and Stokes, 2013). Therefore, further research is required to determine whether lower

back pain may affect thickness and echogenicity of the thoracolumbar fascia, which will be investigated in the next chapter.

4.6 Conclusion

This study has demonstrated that intra-image and inter-image reliability of ultrasound measurements by one examiner are good to excellent for the assessment of the posterior layer of thoracolumbar fascia. These findings are comparable to reliability calculations of the lateral raphe of the thoracolumbar fascia and lumbar and abdominal muscles, meaning that ultrasound imaging can reliably be used for an in vivo assessment of the specialised connective tissues in the lower back. Given the proposed role of the thoracolumbar fascia in spinal stabilisation and lower back pain, the next study in this thesis will compare the ultrasound features in the posterior layer of the thoracolumbar fascia of people with and without lower back pain.

Chapter 5: An ultrasound evaluation of the thoracolumbar fascia in people with and without lower back pain

5.1 Introduction

In the previous chapter, intra-rater ultrasound measurements of the thoracolumbar fascia were shown to have good to excellent reliability, indicating that these lumbar fascial tissues can be reliably measured by the same investigator. In order to further examine the utility of using ultrasound to analyse the thoracolumbar fascia in lower back pain, this chapter presents an ultrasound-based study which measures and compares, not only the thickness, but also the brightness, or echogenicity, of the thoracolumbar fascia in people with and without lower back pain.

Lower back pain (LBP) remains a poorly understood condition, and is associated with substantially reduced health-related quality of life and function (Buchbinder *et al.*, 2018). Traditionally, research studies into the causes of chronic lower back pain in adults focus on the structural pathology of the vertebrae (Bogduk and Engel, 1984), the ligaments (Panjabi, 2006), associated lumbar and abdominal muscles (van Dieën, Selen and Cholewicki, 2003), dysfunctional motor control (Hodges and Tucker, 2011) and biopsychosocial factors (Deyo, 2015). However, over the last 20 years, the clinical significance of the thoracolumbar fascia has increasingly been recognised (Langevin, 2008; Klinger *et al.*, 2014). Earlier case study reports by surgeons, of herniation and fat infiltration in the thoracolumbar fascia were thought to only represent a small minority of LBP patients (Bonner and Kasdon, 1945; Herz, 1945; Faille, 1978; Lawdahl, Moss and Van Dyke, 1986). However, detailed histological studies (Dittrich, 1963; Bednar, Orr and Simon, 1995) and more recent MRI-based investigations report subcutaneous oedema and fat infiltration in lumbar subcutaneous tissues of people

with lower back pain (Sevick and Wallace, 1999; Genu *et al.*, 2014b). For instance, an MRI-based study reports subcutaneous oedema and fat infiltration in the lumbar region in 39% of 307 lower back pain patients, this increased to 60% in patients with lower back pain, weighing more than 85 kilogrammes in body mass. MRI signals related to oedema and fat infiltration were found at lumbar vertebral level 3 and 4 in 54% of the cohort (Shi *et al.*, 2003). The focus of this study was on subcutaneous oedema, how the presence of oedema and fat infiltration may affect the structure and function of the thoracolumbar fascia was not mentioned. It is not known whether similar findings could be observed in a matched control group. A different approach was taken in an ultrasound-based study, in which Langevin *et al.* (2009) compared the thickness and echogenicity of the thoracolumbar fascia including the subcutaneous tissues of people with lower back pain, compared to a matched control group. The lower back pain group exhibited 25% thicker connective tissue, with significantly greater echogenicity, despite the LBP group consisting of reasonably active people with relatively mild pain symptoms. Reviews have similarly confirmed the presence of significant morphological differences in the thoracolumbar fascia of people with lower back pain (Taguchi, Tesarz and Mense, 2009; Willard *et al.*, 2012; Wilke *et al.*, 2017). What remains unknown is whether these differences could be observed in a more sedentary population with LBP.

The aim of the study presented in this chapter, was to investigate the thickness and echogenicity of the thoracolumbar fascia in sedentary and physically active people with lower back pain, compared to a healthy control group without lower back pain. The first hypothesis was that, in people with lower back pain, the thickness and

echogenicity of the thoracolumbar fascia will significantly differ, compared to a control group. The second hypothesis was, that thickness and echogenicity would significantly differ in sedentary people with lower back pain, compared to physically active people with lower back pain. These differences could potentially be the result of connective tissue fibrosis, subcutaneous oedema, or fatty tissue infiltration as a result of chronic inflammation, or changes in the organisation of thoracolumbar fascia could be a result of movement adaptation due to chronic pain.

5.2 Methods

5.2.1 Participants

This study was approved by the University of Kent, School of Sport and Exercise Sciences Research Advisory Group (Prop 79-2010-2011).

Inclusion criteria for the control or no lower back pain group (NLBP) were the absence of lower back pain or any other chronic pain which limited or had limited activities of daily living. For example pain as a result of any injuries or conditions such as adhesive capsulitis, patellofemoral pain or hip related pain, or similar conditions.

The inclusion criteria for the non-specific lower back pain group (LBP) was a history of self-disclosed recurrent or chronic lower back pain for at least 12 months as defined by Von Korff (1994). Recurrent lower back pain was defined as being present or occurring in multiple episodes over less than half the days in a 12 month period.

For example, pain every 2 or 3 months or less. Chronic lower back pain was defined as being present on at least half the days in a single episode in a 12 month period. For example, pain lasting at least 6 months of the year.

Further exclusion criteria based on self-reporting for both groups were: incidences of severe back or lower limb injury or surgery, major spinal deformity, ankylosing spondylitis or rheumatoid arthritis, spinal fracture, tumour or infection, clinical neurological deficit suggestion nerve root compression (as defined by Waddell (2004), neurological or psychiatric conditions, bleeding disorders, corticosteroid medication or corticosteroid injection at the L2-3 level, pregnancy, C-section in the previous 4 years, acute systemic infection.

Participants who rated their current pain intensity as less than 2 cm on the VAS score, choose less than 3 words on the McGill Pain questionnaire, or scored less than 14% on the modified Oswestry Low Back Pain questionnaire, an internationally-known measure of low back pain-related disability with established reliability and validity (Calmels *et al.*, 2005; Vianen, 2008) were excluded from the back pain group to increase the likelihood that participants would be representative of persons with significant chronic lower back pain related disability who might seek outpatient services (Sions *et al.*, 2015).

The LBP group completed the Short Form McGill Pain questionnaire (Melzack, 1987) (Appendix A), the Oswestry lower back disability Scale questionnaire (Fairbank, Couper, Davies & O'Brien, 1980) (Appendix B). Studies have shown that the Short Form McGill Pain questionnaire is as sensitive and specific as the original longer questionnaire, but has the benefit of being less time-consuming to complete

(Schmidt *et al.*, 2006). In addition, both groups completed a customised pre-scan health questionnaire (Appendix C). Physical activity was grouped into sedentary (less than 3 times a week, < 1 hour a week in total), moderate (physical activity >3 times a week, 1.5 to 3 hours) and high (> 4 times a week, > 3 hours). Intensity was not specified.

178 participants were initially recruited. All of whom initially met the inclusion criteria. 24 participants were excluded as a number of exclusion criteria were disclosed post-scanning, as the reported back pain levels were likely to be related to the condition or intervention listed in Table 5.1. 154 participants met the initial inclusion criteria.

Table 5.1 Rationale for the exclusion of 24 participants post-scanning

Number of participants affected	**Reason for exclusion**
2	Facet joint pain
2	Radicular pain
1	Spina bifida occulta
2	Fibromyalgia
4	Spinal surgery
2	Lymphedema
1	Dislocated T8 rib
1	Osteoporosis
2	Scoliosis
1	Discectomy L4-5 / L5-S1
1	Spondylolisthesis
1	Kidney removed
1	Epidural
2	Caesarean section
Total: 24	

Abbreviations: T8= Eighth thoracic rib. L4-5 = intervertebral space between lumbar fourth and fifth vertebra. L5-S1 = intervertebral space between the fifth lumbar vertebra and the sacrum.

A further 13 participants were excluded as they had circled fewer than 3 items on the Short-Form McGill Pain Scale rating index, or scored less than 14% on the Oswestry Low Back Pain Disability questionnaire. These low scores are not considered to represent low back pain, as defined by an expert panel consensus statement (Dionne *et al.*, 2008)

This resulted in a total of 141 participants included in the study presented in this chapter.

5.2.2 Ultrasound data acquisition and image analysis

The data acquisition and image analysis procedures are described in Chapter 3 General Methods. To briefly summarise, participants would lie prone on a treatment couch. Anatomical landmarks were located using ultrasound image scanning. The precise location was marked on the skin, which was 2 cm lateral of the interspinous ligament between L2 and L3. Bi-lateral longitudinal ultrasound images were acquired.

To ensure probe movement was not a potential factor, inter-image reliability tests were carried out. Inter-image reliability for the measurement of the thickness of the combined connective tissues of the thoracolumbar fascia was excellent ($ICC_{(1, 3)} \geq 0.95$), reliability for the perimuscular connective tissue layer was good ($ICC_{(1, 3)} < 0.63$), as analysed and reported in chapter 4.

5.2.3 Data analysis

T-tests (Mann-Whitney U Test) and chi-square tests were used to compare LBP and No-LBP groups for demographic characteristics. Correlations between BMI, Thickness and Echogenicity were performed using the Spearman's rho test. The subcutaneous thickness measurement was used as a measure of body composition (Störchle *et al.*, 2018). The correlation between subcutaneous thickness and perimuscular thickness and echogenicity was analysed with the Spearman's rank test.

Analysis of covariance (ANCOVA) using BMI and subcutaneous thickness as a covariate, were performed to compare connective tissue thickness and echogenicity of the LBP and No-LBP groups.

Additionally, bivariate correlation analyses based on Pearson's r were used to examine the relationship between measurements of symptom severity (numbers of words circled on Short Form McGill questionnaire), pain intensity (VAS 0-10 scale), pain frequency (yearly, monthly, weekly or daily) and degree of disability (Oswestry Disability Scale) and ultrasound outcomes within participants with LBP.

Statistical analyses were performed using SPSS (IBM Corp. released 2016. IBM Statistics for Windows, Version 24.0. Armonk, NY: USA)

The outcome measures presented are the averages of right and lift sides for thickness, echogenicity and normalised echogenicity in all three zones, because no

findings were found to be side-specific, as analysed with a Wilcoxon-Signed Rank Test. Significance levels were determined based on $\alpha = 0.05$.

5.3 Results

Participant characteristics for LBP and No-LBP groups are shown in Table 5.2 There were no significant differences between groups in age (p = .32), mean BMI (p = .52), and weight (p = .80). There were however, significant differences between the groups in gender (p = 0.03) and physical activity (p = .02).

Table 5.2 Participant characteristics

	Total	**No LBP**	**LBP**	**P value**
	N= 141	N= 67 (46%)	N = 74 (54%)	
Age	33 (± 11)	32 (± 11)	34 (± 10)	0.32
Gender (% m/f)	42% / 58%	52% / 48%	34% / 66%	0.03*
Body mass (kg)	74 (± 13)	74 (± 13)	74 (± 13)	0.8
BMI	25 (± 5)	25 (± 5)	25 (± 4)	0.52
Physical Activity Level				0.02*
(n / %)				
sedentary	51 / 36%	16 / 24%	34 / 47%	
moderate	59 / 42%	33 / 50%	26 / 35%	
high	31 / 22%	17 / 26%	14 / 18%	

*Physical Activity levels are based on participants that completed the survey (No-LBP = 66, LBP = 74) * = significant at alpha level set at 0.05*

5.3.1 BMI and subcutaneous thickness as covariants

BMI was moderately correlated with the combined connective tissue thickness (r = 0.53, $p < 0.001$,). Similarly, the subcutaneous and perimuscular connective tissues were moderately associated with BMI (r = 0.43, $p < 0.001$, r = 0.40, $p < 0.001$ respectively).

BMI was weakly correlated with subcutaneous, combined and perimuscular echogenicity (r = - 0.17, $p = 0.002$, r = -0.17, $p = 0.003$, r = -0.14, $p = 0.016$ respectively)

The normalised echogenicity of the subcutaneous and combined zones were also weakly correlated with BMI (r = - 0.18, $p = 0.001$, r = 0.19, $p = 0.001$ respectively). The normalised echogenicity of the perimuscular connective tissue was not correlated with BMI (r = 0.09, $p = 0.105$).

Despite the relationship between BMI and ultrasound measures, BMI could not be used as covariate since it didn't meet the of the assumptions required for subsequent analysis of covariance, no linearity, homogeneity of regression slopes, nor normality of residuals were found.

Therefore, measurements of the subcutaneous connective tissues, were used as the covariant, as these tissues are a gross measurement of adipose tissue, and were subsequently used to investigate the relationship between body fat and ultrasound measures.

There was a moderate correlation between thickness of the subcutaneous layer and the thickness of the perimuscular connective tissues (rho = 0.35, p = 0.001). However, there was no relationship between subcutaneous tissue thickness and perimuscular echogenicity (rho = 0.27, p = 0.36 respectively). All assumptions required for using the subcutaneous layer as a covariant were met, therefore this layer was used as the covariant, as a more direct measure of subcutaneous fat, rather than BMI.

Therefore, analyses of covariance (one-way ANCOVA) were performed to assess differences in these outcome measures between LBP and No-LBP groups while adjusting for the thickness of subcutaneous zone.

5.3.2 Covariance between No-LBP and LBP groups.

Echogenicity of the combined connective tissue layers was significantly greater in the LBP group compared with the non-LBP group (ANCOVA F (1,138) = 3.86, $p < 0.05$). These differences were primarily driven by a significantly higher echogenicity in tissues closer to the muscle, the perimuscular tissues (ANCOVA, F (1, 138) = 4.34 p = 0.04), rather than the subcutaneous tissues (ANCOVA, F (1,138) = 0.66, p = 0.41).

Normalised echogenicity was not statistically significantly different in LBP group compared to the non-LBP group.

Thickness for the perimuscular and combined connective tissues were not significantly greater in the LBP group compared to the non-LBP group (ANCOVA

perimuscular: F (1,139) = 0.70, *p*= 0.40 and combined: F (1,139) = 0.028, *p* = 0.86) See Table 5.3 for unadjusted mean values and their standard deviation.

Table 5.3 Unadjusted means and standard deviation values of connective tissues in the lower back.

	Total unadjusted (mm) Mean (±SD)	**No Pain (N67) (mm) Mean (±SD)**	**Pain (74) (mm) Mean (±SD)**
Av Thick Comb	6.57 (±3.55)	6.21 ± 3.47	6.89 ± 3.61
Av Thick Peri	2.80 (± 1.80)	2.75 ±2.05	2.84 ± 1.56
Av Echo Sub	40.46 (± 18.64)	38.34 (± 21.43)	42.38 (± 15.58)
Av Echo Comb	70.56 (± 23.72)	67.93 (± 25.63)	72.94 (±21.74)
Av Echo Peri	114.04 (± 29.86)	108.75 (± 29.88)	118.83 (± 29.23)

Av Thick Comb = average thickness combined. Av Thick Peri = average thickness perimuscular. Av Echo Sub = average echogenicity subcutaneous. Av Echo comb = average echogenicity combined. Av Echo Peri = average echogenicity perimuscular. Thickness is in millimetres, Echogenicity is in grey scale (range 0=black – 255 = white) Data are unadjusted mean, ± standard deviation, unless otherwise stated. Thickness/ Echo was greater in the pain group (M, SD), compared to the no pain group (M, SD).

Pain characteristics of the LBP group are shown in Table 5.4. There were no significant correlations between ultrasound outcome measures of the perimuscular connective tissues and responses to the McGill pain questionnaire, current pain intensity (VAS 1-10 scale) (Thickness r = 0.20 , *p* = 0.31, Echogenicity r = 0.07, *p*= 0.67), pain frequency (Thickness τ_b= 0.05, *p* = 0.69, Echogenicity $\tau_{b=}$ 0.13 *p* = 0.13), the Oswestry disability scale (Thickness τ_b= 0.02, *p* = 0.85, Echogenicity $\tau_{b=}$ 0.10 *p* =

0.22), or physical activity levels (Thickness τ_b= -0.15, *p* = 0.10, Echogenicity τ_b < -0.01 *p* = 0.98).

However, pain severity (number of words circled) was weakly correlated in a negative direction with perimuscular thickness (τ_b= - 0.17, *p* = 0.047). Pain severity was weakly correlated in a positive direction with echogenicity ($\tau b_=$ 0.24, *p* = 0.005) among the LBP group. Furthermore, a moderate correlation between physical activity levels and thickness was found in the no pain group, in a negative direction (τ_b= -0.32, *p* = 0.001).

Table 5.4 Indices of symptom severity and disability in participants with LBP

McGill Pain rating score (# of words circled) (N=74)	4 (± 3)
MCGill Pain rating index (N = 74)	8 (± 7)
Current pain intensity (N = 27)	
VAS (0-10 scale)	3 (± 1.8)
Pain frequency (N= 74)	
Yearly	10 /14%
Monthly	35 / 47%
Weekly	14 / 19%
Daily	15 / 20%
Von Korff's lower back pain classification	
Pain group N=74	
chronic pain (n / %)	45 / 58%
recurrent pain (n / %)	28 / 37%
single occurrence pain (n/ %)	4 / 5%
Oswestry disability scale (N=73)	
No disability 0%	8%
Mild (0-20% disability)	63%
Moderate (20-40% disability)	28%
Severe (40-60% disability)	1%

VAS = visual analogue scale

5.4 Discussion

This study found a significant difference in the echogenicity of the thoracolumbar fascia in adults with lower back pain, compared to a matched control group. No difference was found in the thickness of thoracolumbar fascia between pain and no pain groups.

5.4.1 Echogenicity of thoracolumbar fascia

In this study, the echogenicity of the thoracolumbar fascia was found to be brighter in a lower back pain cohort, compared to a control group ($p = 0.04$). There was also a moderate positive association between echogenicity and perceived pain severity. These findings are consistent with those of Langevin *et al.* (2009), the only comparable study found in the literature. Langevin and colleagues also found greater echogenicity in the thoracolumbar fascia ($p < 0.01$), of a lower back pain cohort, in tissues measured at the same anatomical location as the present study (Langevin *et al.*, 2009). An explanation for these differences can be found in a pioneering hypothesis which proposed that the collagen fibres in specialised connective tissues, such as the thoracolumbar fascia, may remodel and alter, as the result of pain-related altered movement patterns (Langevin and Sherman, 2007). An extension of this model proposes that chronic pain and trauma can cause fibrosis of the collagen sheaths in perimuscular fasciae which could further explain the brighter echogenicity seen in the present study (Pavan *et al.*, 2014). Further evidence of changes in

ultrasound features of thoracolumbar fascia were found in an animal study, which reported that thoracolumbar fascia in pigs, remained altered after an 8 week period of movement restriction combined with a local injury to fascia (Bishop *et al.*, 2016). An important finding in the Bishop *et al.* (2016) study was, that changes observed in the fascia were not accompanied by spinal cord neuroplastic changes. These were measured by no changes in spinal cord dorsal horn substance P or calcitonin gene-related peptide (CGRP). These findings suggest that chronic pain did not affect the changes observed in the thoracolumbar fascia. The authors suggest that restricted fascia mobility may cause altered movement patterns and therefore could still be a contributing factor to lower back pain without being the direct source of pain. In the future, studies could be conducted on injured thoracolumbar fascia in humans. This may clarify the role of injury, reduced mobility and pain factors, on the structure and function of the lumbar fasciae.

An increase in echogenicity has been found in connective tissues such as tendons, when put under tension in vitro (Duenwald *et al.*, 2011). At present it is not clear whether the increase in echogenicity in the present study, could be the result of an increase in tension in the lumbar fascial tissues in people with lower back pain. Conversely, in vitro and in vivo studies in tendons have shown a decrease in echogenicity, correlated to tendon damage (Malliaras *et al.*, 2008; Duenwald-Kuehl, Lakes and Vanderby, 2012). There are important differences between tendons and dense connective tissue sheaths such as the thoracolumbar fascia. The mechanical stress-strain behaviour of a tendon is linear (Magnusson *et al.*, 2008), whereas the response to forces of dense connective tissues such as the thoracolumbar fascia is

non-linear (Wong *et al.*, 2012; Kjaer, 2015). This is due to the multi-layered structure of dense connective tissue sheaths, with collagen fibres arranged at specific angles in adjacent layers (Benetazzo *et al.*, 2011; Pavan *et al.*, 2014).

These different findings suggest that the relationship between an increase in echogenicity and the mechanical behaviour of multi-layered connective tissues such as the thoracolumbar fascia is complex, and still not fully understood. The present study indicates that further investigations into the relationship between changes in echogenicity and the stress-strain behaviour of the thoracolumbar fascia in different populations are warranted.

5.4.2 Thickness of thoracolumbar fascia

The present study found no significant difference in the thickness of thoracolumbar fascia in people with lower back pain, compared to a control group. This does not support previous ultrasound evaluations of the thoracolumbar fascia. Langevin *et al.*, (2009) found an increase of 25%, and Whittaker et al. (2013) reported an increase in thickness of lumbar fascia of 22% in people with lower back pain. The ultrasound settings and anatomical positioning of the transducer in the study presented in this chapter were identical to the Langevin *et al.* (2009) study. However, Langevin and colleagues included layers of oedema when visible between the thoracolumbar fascia and the muscle (personal communication), whereas the study presented in this chapter did not consider oedema to be part of the thoracolumbar fascia. Presence of oedema between the posterior layer of the thoracolumbar fascia and the underlying

erector spinae muscle in people with lower back pain has been reported in MRI studies of people with and without lower back pain (Genu *et al.*, 2014b; Herlin *et al.*, 2015). The decision not to include oedema in the thoracolumbar fascia measurements, may explain why the study in this chapter did not find a significant increase in thickness.

Whittaker and colleagues, found an increase of 22% in the thickness of perimuscular abdominal connective tissues in cohorts with lower back pain (Whittaker, Warner and Stokes, 2013). The anatomical site of image acquisition in the Whittaker study was the lateral raphe of the thoracolumbar fascia, which is situated more lateral and closer to the anterior trunk. In the study presented in this chapter and the Langevin et al. (2009) study, the measurements were taken 3 cm lateral of the spinous processes on the posterior side of the trunk . The abdominal fascial tissues are recognised to be an extension of the thoracolumbar fascia, and connect directly into the anterior and posterior layers of the thoracolumbar fascia (see figure 4.1 for anatomical orientation).

The present study found an average perimuscular thickness of 2.84 millimetres in the pain group and 2.75 millimetres in the no pain group, a difference of 0.09 millimetres. The difference found in the previous chapter, in intra-image variability for average perimuscular thickness was 0.08 millimetres, with an SEM 0.2 and an MDC of 0.55. The day-to-day or inter-image difference was 0.15 millimetres, with an SEM of 0.08 and an MDC of 0.22.This indicates that the level of difference between the pain and no-pain groups is not large enough to be able to detect a meaningful difference between populations.

The Whittaker *et al.* (2013) study found an average thickness of 2.9 millimetres (SD 0.4) in the lower back pain cohort, and 2.3 millimetres (SD 0.4) in the control group, which amounts to a difference of 0.6 millimetres, which is large enough to be able to detect a meaningful change. The Langevin *et al.* (2009) study, found an overall thicker average perimuscular fascia (estimated from a figure) measuring 4.2 millimetres in the pain group and, 3.5 millimetres in the control group, which is a difference of 0.7 millimetres, equally large enoughto detect a meaningful change.

A further explanation of the differences in findings between the study presented here and the Langevin and Whittaker studies, could be the different levels of physical activity of participants. Unfortunately, no intensity or duration of physical activity was reported in either the Langevin or Whittaker studies. The lower back pain participants in the Langevin *et al*. (2009) study consisted of 62% of participants taking part in high levels of physical activity, compared to 29% in the study presented in this chapter. Moderate levels of physical activity were more similar, 29% in the Langevin *et al.* (2009) study, and 35% in the study presented in this chapter. As discussed in the literature review, connective tissues adapt to mechanical loading. Therefore, higher levels of physical activity may have resulted in larger muscle size and consequently a thicker thoracolumbar fascia. This proposed association requires further research, particularly as neither study found an association between physical activity and ultrasound outcome measures in the lower back pain groups. It is also important to note that the actual differences in thickness between the cohorts in the

Langevin *et al.* (2009) study and the study presented in this chapter is 1.36 millimetre, as illustrated in Table 5.5.

See Table 5.5 for an overview of all average thickness measurements of lumbar fasciae found in the literature, including the present study. Currently, no normative values exist for lumbar fasciae. Some measurements in the literature (Barker and Briggs, 1999; Barker *et al.*, 2010) are taken from cadaver specimen, and measured with a micro meter, whereas others are measurements taken by ultrasound in vivo. It has been suggested that measurements taken from cadaver tissue may be affected by shrinkage as a result of the embalming process (Barker *et al.*, 2010). Therefore, direct comparisons between cadaver and in vivo measurement should be made with caution. Measurements of lumbar fascial tissues taken by MRI do not exist at present. As seen in table 5.5, the present study's average measurements are comparable to other ultrasound-based measurements in the literature, however, it is important to note that the range in the present study is wider than in previously published studies.

In addition, Pavan *et al.*, (2014) suggested that reporting an increase in ultrasound-based thickness measurements in fascia may be misleading. Pavan *et al.* (2014) found an increase in the fascia of the sternocleidomastoid muscle in people with neck pain. The authors report that further analysis of images demonstrated that the increase in thickness was the result of an increase in the loose connective tissue layers containing hyaluronan in between the dense connective tissue sheaths, rather than an increase in the dense connective tissue layers themselves. This phenomenon has not yet been investigated in the thoracolumbar fascia, however Pavan's *et al.* (2014) findings warrant further research.

Table 5.5 Overview of average thickness measurements of thoracolumbar fascia in the current literature

Authors	**Anatomical location***	**Type of cohort**	**method of measurement**	**Mean thickness (mm) and SD**	**Range (mm)**
Barker and Briggs (1999)	Posterior layer L2 – L4	21 embalmed cadavers	manual micro meter	0.52	not reported
Barker *et al.* (2007)	Anterior layer* L2- L4	18 embalmed cadavers	manual micro meter	0.55	0.11 – 1.34
Loukas *et al.*(2008)	Posterior layer, middle point	35 embalmed cadavers 5 fresh cadavers	Manual callipers	3 (± 0.5)	1 – 4
Langevin *et al.* (2009)	Posterior layer L2-L3	107 human subjects 60 LBP 47 control	Ultrasound imaging	LBP: 4.2 Control: 3.5	not reported
Whittaker, Warner and Stokes (2013)	Lateral to the anterior layer*	50 human subjects 25 LBP & pelvic pain 25 control	Ultrasound imaging	LBP: 2.9 (±0.8) Control: 2.3 (±0.4)	LBP: 2.1 – 4.7 Control: 1.6 – 3.2
Study presented in this thesis (Chapter 5)	Posterior layer L2-3	141 human subject 74 LBP 67 control	measurements of ultrasound images by investigator	LBP: 2.84 (±1.56) Control: 2.75 (±2.05)	LBP: 1.23 – 10.20 Control: 1.20 – 12.93

**according to the 2 layer model* (Stecco, 2015).*Abbreviations: mm = millimetres. n/a = not available. LBP = lower back pain*

5.4.3 Pain symptoms of cohorts in thoracolumbar fascia studies

In the present study, pain intensity, as measured on a 10 point scale, was 3. These findings were comparable with both the Langevin *et al.* (2009) and Whittaker *et al.* (2013) studies, who reported pain intensity values of 3 and 3.9 respectively. A pain intensity value of < 7/10 is considered to be mild (Dionne *et al.*, 2008). Future studies may wish to select participants with severe pain of ≥7/10 to further analyse ultrasound features of the thoracolumbar fascia, as suggested by Langevin *et al.* (2009).

Other factors in the present study, such as symptom severity, measured by numbers of words circled on the McGill pain scale, were different compared to the literature. Symptom severity in the present study was 4, compared to 8 in the Langevin et al. study. There was a weak positive correlation in the present study between echogenicity and pain symptom severity. This is despite pain severity being less in this study compared to Langevin *et al.* (2009) who found no correlation between ultrasound measures and symptom severity. In the present study, 47% of the pain group experienced pain monthly, compared to 29% in the Langevin study. Both studies reported similar levels of mild disability on the Oswestry disability scale, 63% in the present study, and 67% in the Langevin *et al.* (2009) study.

Defining and measuring lower back pain is a complex issue. The use of pain severity and pain frequency measurements have been highlighted as good practice in lower

back pain research (van Tulder, Koes and Bombardier, 2002; Fritz, Beneciuk and George, 2011; Axén and Leboeuf-Yde, 2013). It has been highlighted however, that measuring pain symptoms using a one year recall period, as suggested by Von Korff *et al.* (1990) and used in the Langevin *et al.* (2009) and the present study, may not be an optimal time frame. Instead, a recall period of 4 weeks has been recommended (Dionne *et al.*, 2008).

5.4.4 Demographics of cohorts in thoracolumbar fascia studies

An a priori power calculation revealed that a total of 128 subjects would be required, with a minimum of 64 subjects in each group to reveal a significant difference, with the adoption of alpha at 0.05, a power of 0.8 and an effect size of 0.5 (Faul *et al.*, 2007). Post-hoc power calculations were carried with a lower effect size of 0.25, power of 0.8 and alpha at 0.05, this calculation revealed that 269 participants would be required. The study was conducted with 141 participants, which means it could be underpowered. A post-hoc analysis revealed that 141 participants result in a power of 0.44, with an effect size of 0.25.

In the present study, the gender balance was different between the groups, the pain group consisted of 66% women, compared to 48% in the control group. Globally lower back pain is more common in women than in men (Hoy *et al.*, 2012). It is also thought that women are more likely to seek medical help when experiencing lower back pain (Fillingim *et al.*, 2003). However a review on gender and lower back pain

studies found no evidence to demonstrate that women consult doctors more than men (Hunt *et al.*, 2011).

Average age was not different between groups, although it is worthy to note that this study consisted of a slightly younger demographic (33 ±11), compared to Langevin *et al.* (2009) (38.5 ±13.6). This difference in age is not thought to be important, as ultrasound studies find degenerative changes in the muscle and connective tissues in the lower back a factor only in patients of more than 60 years old (Sions *et al.*, 2016).

Even though the mean BMI of all participants in the present study and the Langevin *et al.* (2009) study was exactly 25 units, and 23 in the Whittaker *et al.* (2013) study, the standard deviation for all participants in the present study was 5, compared to a much lower 0.7 in the Langevin *et al.* (2009) study. It is important to note that the range of BMI units in the present study ranged from 18 to 33, similar to the Whittaker *et al.* (2013) values. This range of BMI units reflects the range found in the general pain-free population as well as the lower back pain population (Vos *et al.*, 2016). However, despite the fact that a wide range of BMI values is representative of the population at large, future studies may wish to exclude participants with very low or extremely high BMI values, to avoid unduly skewing the profile of the cohort.

Physical activity levels of cohorts are another important factor to consider. It is widely recognised that an increased or decreased amount of loading affects tissues such as bone (Skerry, 2008), ligament (Loghmani and Warden, 2013) and tendons (P Magnusson *et al.*, 2010). It is known that mechanical loading affects the thoracolumbar fascia. Whether loading and physical activity affects fascial tissues differently or similarly compared to other connective tissues, such as tendon or

ligaments is not known (Khan, 2011). In the present study, 47% of the lower back pain group were sedentary, compared to 24% of the control group (see table 5.2). No association was found between physical activity levels and the pain group, but a moderate negative association was found between physical activity levels and the control group. The direction of this relationship suggests that the thoracolumbar fascia was thinner in people with higher levels of physical activity. This suggests there is an inverse relationship between physical activity and thickness in the control group.

In the present study, 26% of the control group and 18% of the LBP group took part in high levels of physical activity (greater than 5 times per week > 3 hours). The Langevin *et al.* (2009) study consisted of 67% of high level activity in the control group, and 62% in the LBP group. By contrast, the Whittaker *et al.* (2013) study excluded participants who self-reported high levels of activity, consistent with those of an athlete. At the other end of the spectrum, the present study consisted of 47% sedentary people in the pain group and 24% in the control group. In contrast, the Langevin study consisted of 9% sedentary people in the pain group, and 8% in the control group. Physical activity levels were not reported in the Whittaker study (Whittaker, Warner and Stokes, 2013).

5.4.5 Methodological considerations

To ensure movement generated by the ribcage or thorax was not an issue in the present study, great care was taken to ensure scanning was consistently performed

with the participant lying prone, breathing at a normal rate. During data collection, it was observed that the slightest movement, such as an increase in breathing would affect image acquisition, particularly in slim built participants. When detecting movement, the ultrasound scanner automatically switches to video capture, which was a useful movement detector. When movement was detected, imaging continued until a still image was acquired. Movement caused by breathing occurred in less than 10% of all participants. Future studies may consider image acquisition at the end of a normal expiration, as described in Whittaker et al. (2013) in order to make image acquisition more consistent in relation to respiration.

5.5 Conclusion

The present study found that the echogenicity of thoracolumbar fascia in ultrasound images was significantly brighter in people with lower back pain. Furthermore, echogenicity was moderately correlated with pain severity, in a positive direction, despite a low level of pain severity. In addition, the present study found that in a cohort without lower back pain, thoracolumbar fascia was moderately thinner in those people engaged in higher levels of physical activity.

Future studies should therefore investigate whether an increase in physical activity levels and loading, results in adaptations of the thoracolumbar fascia, and whether these changes can be measured by ultrasound. This will be further investigated in the next chapter, a study on the effect of an endurance training programme on the echogenicity and thickness of thoracolumbar fascia in untrained people.

Chapter 6: An ultrasound evaluation of the effect of an endurance training programme on the thoracolumbar fascia of untrained individuals

6.1 Introduction

As discussed in Chapter 2, one of the key properties of connective tissue is its mutability, plasticity and remodelling in response to varying levels of mechanical stimuli. Studies demonstrate that an increase in loading results in improved size and strength of tendons (Kannus *et al.*, 1997; Magnusson *et al.*, 2010), ligaments (Van Dommelen *et al.*, 2006), bone (Skerry, 2008) and cartilage (Eckstein, Hudelmaier and Putz, 2006). It is recognised that the thoracolumbar fascia responds to contractions of latissimus dorsi and gluteus maximus by increasing its tension (Nikolai Bogduk and Macintosh, 1984; Loukas *et al.*, 2008). Moreover, biomechanical studies have reported that the tension in the thoracolumbar fascia offloads the erector spinae muscles after around 45 degrees of lumbar flexion. (Gracovetsky and Iacono, 1987). In flexion, the erector spinae muscles relax, even while holding significant loads. This relaxation is possible as the increased tension in the thoracolumbar fascia takes on the forces transmitted from the legs to the upper extremities. When the trunk returns to an upright position, the thoracolumbar fascia begins to slacken, forcing the erector spinae to engage (Gracovetsky and Iacono, 1987; Macintosh, Bogduk and Gracovetsky, 1987; Gracovetsky *et al.*, 1990; Gracovetsky, 2008). Little is known however about the effect of prolonged bouts of flexion, and therefore tension, on the structure of the thoracolumbar fascia. Cycling is an interesting model to study this effect, due to the flexed position of the rider.

During cycling, the quadriceps and the crural muscles are the main agonists, however, both the gluteus maximus and latissimus dorsi contract and are active

throughout (So, Ng and Ng, 2005). Moreover, increasing the pedalling rate is associated with increased activity in the gluteus maximus (Wozniak Timmer, 1991; Fonda and Sarabon, 2010). However, whether gluteus maximus activation during cycling has an effect on force transmission or collagen synthesis of the thoracolumbar fascia is yet unknown.

Understanding whether a cycling training programme has an effect on the thoracolumbar fascia will be useful for developing specific and effective training for lower back rehabilitation programmes. Cycling is a popular recreational and sporting activity that has many therapeutic qualities, for instance stationary cycling is commonly used in post knee surgery rehabilitation, as it is non-weight-bearing on knee ligaments (So, Ng and Ng, 2005; Oja *et al.*, 2011).

Chapter 3 in this thesis demonstrated that ultrasound is a reliable modality to evaluate the thoracolumbar fascia. Furthermore, a recent study concluded that ultrasound is a reliable method for visualising fascial tissues, including changes in fascial thickness following physiotherapy treatments (Stecco *et al.*, 2014). Moreover, ultrasound has been demonstrated to be a valid and reliability technique to assess changes in thickness and echogenicity of the thoracolumbar fascia (Langevin *et al.*, 2009)..

The purpose of this study is to investigate the acute effects of a 4 week endurance cycling training programme on the thickness and echogenicity of thoracolumbar fascia.

6.2 Method

6.2.1 Participant recruitment and selection criteria

The study was approved by the School of Sport and Exercise Sciences ethics committee (Prop 79-2010-11, 124-2015-16). This was a quasi-experimental study design, the participants in the training group were recruited from a pre-existing training study cohort (Coakley and Passfield, 2014). The participants in the control group were recruited separately using opportunistic sampling. All participants volunteered and provided informed consent. Six participants withdrew from the training group, and four withdrew from the control group, these participants failed to attend the follow-up scanning session 4 weeks after the base-line scan, and did not respond to reminders. This resulted in the training study comprising of fifteen participants, and the control group of fourteen (Table 6.1). Exclusion criteria consisted of: previous severe back or lower limb injury or surgery, major structural spinal deformity (scoliosis, kyphosis, stenosis); ankylosing spondylitis or rheumatoid arthritis; spinal fracture, tumour or infection; nerve root compression, bleeding disorders, corticosteroid medication or corticosteroid injection at lumbar vertebrae 2 and 3 level of the back; pregnancy; smoking; and acute systemic infection. Participants in both groups completed a physical activity level questionnaire in which physical activity levels were categorised into sedentary (physical activity less than 3 times a week <1 hour cumulative time), moderate (physical activity 3-5 times a week 1.5 to 3 hours) and high levels (greater than 5 times a week > 3hours). On entry into

the study all participants reported to be engaged in no more than 3 hours of exercise per week in the three months before the study.

6.2.2 Training protocol

The training group participants completed four weeks of supervised endurance cycling training four times a week on a stationary cycling ergometer (Lode Excalibur Sport, Lode, Groningen, The Netherlands). Participants trained four times a week, for four weeks, alternating between 60% and 100% of their peak aerobic power completed in a pre-training, time-to-exhaustion test. The 60% effort training sessions were divided into 5 minute blocks separated by 1 minute rest until the target training duration was reached. The 100% effort training sessions were split into 2 min blocks, followed by 2 minutes of active rest at 25% effort and 1 minute passive rest. Participants in this group were asked to complete as many repetitions as possible in the first training session, which set the baseline for subsequent training session. An increase in intensity was achieved by encouraging participants to either complete an extra 5 minute block or one extra repetition after every two training sessions. The mean total training time ranged between 8 and 16 hours, with a large inter-individual variability. The training protocol is a standard training method in endurance training (Hopker *et al.*, 2009; Coakley and Passfield, 2014).

The control group continued their usual physical activity pattern without increasing or decreasing usual physical activity patterns. Physical activity levels were self-reported at base-line and verbally verified at the 4 week follow-up visit.

6.2.3 Ultrasound protocol

Ultrasound images were taken of all participants at baseline and 4 weeks later. The ultrasound image acquisition protocol and image measurement protocol are described in Chapter 3: General Ultrasound methodology.

6.2.4 Statistical Analysis

Prior to analysis, each variable was examined separately for missing values. T-tests and chi-square tests were used to compare the training and control groups for participant characteristics.

The main outcome measures were thickness and echogenicity of the thoracolumbar fascia. Thoracolumbar thickness was analysed with a two-way (time by group) repeated measures analyses of variance (ANOVA). Since normalised echogenicity did not meet the assumption for an ANOVA, an analysis of covariance (ANCOVA) was used.

The primary purpose of this study was to understand if there was an interaction between the trained and control groups (the independent variables) and baseline and post-4 weeks data (the dependent variables).

Thickness and normalised echogenicity were analysed for 3 different layers: the subcutaneous layer, the perimuscular layer and the combined subcutaneous and perimuscular layer. The anatomical orientation and delineation of these layers are described in Chapter 3: General ultrasound methodology.

Normalisation of echogenicity is an amplitude scaling calculation that accounts for the gain changes due to depth. Data were scaled to compensate for depth dependent changes in gain by applying the normalisation factor provided by Esaote, the ultrasound manufacturer.

6.3 Results

No participant had missing data. Participant characteristics are reported in Table 6.1.

Table 6.1 Participant characteristics for training and control groups

	Training group (*n* = 15)	**Control group (*n*= 14)**	**P value**
Gender Male / Female (%)	13 (87%) / 2 (13%)	3 (21 %) / 11 (79%)	<0.01*
Age (years)	26 ± 7.5	22 ± 2	0.04*
BMI (units)	24.09 ±2.3	22.57 ±2.6	0.10
Body Mass (kg)	78.61 ±10.10	64.50 ±6.60	0.31
Physical Activity level (%)			0.43
Sedentary	27%	7%	
Moderate	40%	50%	
High	33%	43%	
Lower back pain (%)			0.73
No lower back pain	80 %	71%	
Lower back pain	20 %	29%	

Values represent Mean. ±Standard Deviation unless otherwise indicated.

Skewness of all variables was assessed by inspection of histograms and calculation of z-scores from skewness scores. All variables were found to be skewed, consequently, all data were log10 transformed prior to analysis. , which resulted in a normal or near-normal distribution. Consequently, normal distribution was assessed by examination of Normal Q-Q Plots, which resulted in a normal or near-normal distribution.

All data were assessed for outliers, by examination of studentised residuals for values greater than ±3. One outlier was found for subcutaneous thickness, with a studentised residual value of 3.52. This was not deemed to be the result of data entry error or measurement error. This value was replaced with the highest valid value, as suggested in Dancy, Reidy and Rowe (2012) as the outlier represented a genuinely unusual measurement.

No significant differences were found between left and right scans, so side-average measurements were used in all statistical analyses. Mean and standard deviations of all thickness measurements are reported in Table 6.1.

6.3.1 Thickness measurements

When testing assumptions required for the ANOVA analysis of thickness measurements, homogeneity of covariance was found, as assessed by Box's test of equality of covariance matrices (combined thickness p=0.145; subcutaneous thickness p=0.029; perimuscular thickness p=0.140). There was no homogeneity of

variances, as assessed by Levene's test of homogeneity. It was decided however to ignore this violation, and proceed with the analysis, using transformed data.

6.3.1.1 Combined thickness layer:

There was no relationship between the combined thoracolumbar fascial thickness layers, the training group and the control group and time, F(1,27) = 0.52, p=0.47, partial η^2 = 0.01. No difference was found after 4 weeks, F (1,27) = 1.76, p=.19, partial η^2 = 0.06. Lastly, there was no difference between the groups, F (1, 27) = 1.54, p= 0.22, partial η^2 = 0.05.

6.3.1.2 Subcutaneous thickness layer

There was no relationship between the subcutaneous thoracolumbar fascial thickness layers, the training group and the control group and time, F (1, 27) = 3.96, p = 0.65, partial η^2 = 0.120.

No difference was found after 4 weeks, F (1, 27) = 4.15, p= 0. 051, partial η^2 = 0.133

Lastly, there was no difference between the groups, F (1, 27) = 0.08, p= 0.78, partial η^2 = 0.003.

6.3.1.3 Perimuscular Thickness layer

There was no relationship between the perimuscular thoracolumbar fascial thickness layers, the training group and the control group and time $F(1,27) = 1.299$, $p=0.26$, partial $\eta^2 = 0.046$.

No difference was found after 4 weeks, $F(1,27) = .003$, $p=0.97$, partial $\eta^2 = .0005$.

Lastly, there was no difference between the groups, $F(1, 27) = 4.676$, $p=0.040$, partial $\eta^2 = 0.148$.

Table 6.2 Means and variability measurements of baseline and post 4 weeks training thickness measurements in mm

	Baseline thickness (±SD)	**SE**	**95 % CI**	**Post 4 weeks thickness (±SD)**	**SE**	**95 % CI**	**p-value**
Combined layer							0.47
Training	5.87 (± 1.81)	.47	(4.86 – 6.87)	5.74 (**±** 1.84)	.48	(4.72 – 6.76)	
Control	8.45 (± 4.90)	1.31	(5.62 – 11.28)	7.98 (**±** 5.10)	1.36	(5.03 – 10.92)	
Subcutaneous layer							0.65
Training	3.17 (**±** 1.23)	.52	(2.08 – 4.25)	3.13 (**±** 1.08)	.56	(1.97 – 4.28)	
Control	3.92 (**±** 2.65)	.54	(2.80 -5.04)	3.44 (**±** 2.93)	.58	(2.25 – 4.64)	
Perimuscular layer							0.26
Training	2.70 (**±** 0.87)	.22	(2.22 – 3.18)	2.61 (**±** 3.04)	.29	(1.97 – 3.25)	
Control	4.27 (**±** 2.94)	.79	(2.57 – 5.97)	4.53 (**±** 3.04)	.81	(2.77 – 6.30)	

All measurements are in millimetres, unless stated otherwise. SD = Standard Deviation. SE = Standard Error. CI = Confidence Interval

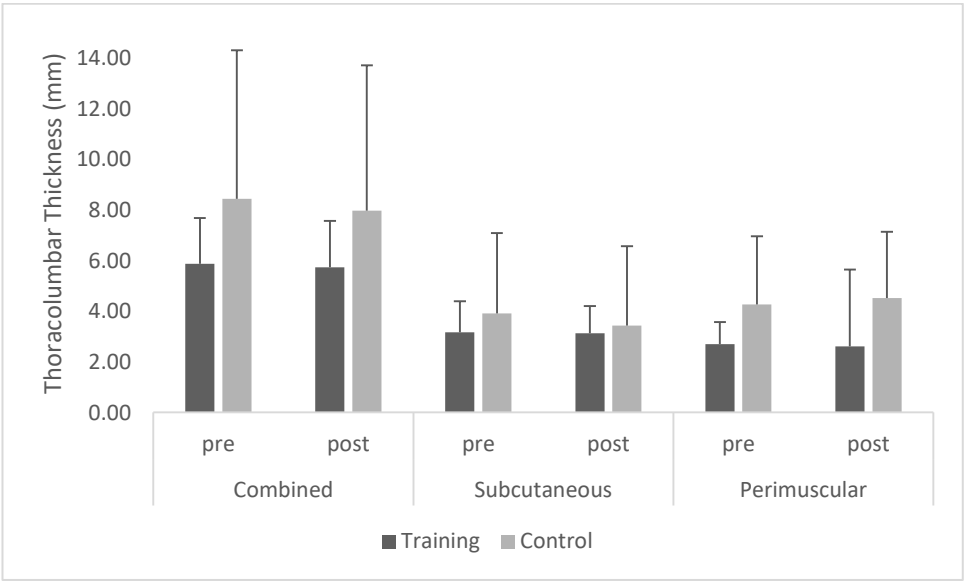


Figure 6.1: Mean and standard deviation of thoracolumbar fascia thickness in millimetres (mm)

6.3.2 Normalised Echogenicity

As statistically significant differences were found at baseline between both groups for normalised echogenicity, and since this violates the assumption for a repeated measures ANOVA, the ANCOVA test was used to analyse normalised echogenicity.

There was a linear relationship between pre and post-intervention normalised combined echogenicity for both the training and the control groups, as assessed by visual inspection of a scatterplot. There was no linear relationship between pre and post-intervention of echogenicity of the subcutaneous nor perimuscular echogenicity for both the training and the control groups, as assessed by visual inspection of a scatterplot. As an ANCOVA is considered to be robust against non-linearity, the analyses was conducted using untransformed data.

There was a homogeneity of regression slopes as the interaction terms were not statistically significant. Echogenicity of combined layer:, $F(1,25) = 0.006$, $p = 0.941$., subcutaneous layer: $F(1,25) = 0.614$, $p = 0.441$., Perimuscular layer: $F(1,25) = 0.269$, $p = 0.609$.

Standardized residuals of combined echogenicity for the training and control groups were normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$) ($p=0.143$, $p=.164$ respectively). For the subcutaneous layer this resulted in: Standardized residuals for the training group were normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$) ($p=0.635$, but were not normally distributed for the control group ($p=.045$).

For the perimuscular layer, this resulted in standardized residuals for the training and control groups were normally distributed, as assessed by Shapiro-Wilk's test (p> .05) (p= 0.471 , p =.211 respectively).

Homoscedasticity was found for all layers, as assessed by visual inspection of the standardized residuals plotted against the predicted values.

In the combined and perimuscular layers, the assumption of homogeneity of variances was violated, as assessed by Levene's test for equality of variances (p=0.15 and p=0.10 respectively*).* This violation was ignored, as ANCOVA is considered to be sufficiently robust against this violation (Dancey, Reidy and Rowe, 2012).

6. 3. 2. 1 Normalised Combined Echogenicity

There was no difference in normalised combined echogenicity between training and control groups, $F(1,26) = 2.209$, $p = .149$, partial $\eta^2 = .078$.

Table 6.3 Normalised Echogenicity of the combined thoracolumbar connective tissue layers

		baseline		***post 4 weeks***	
	N	*Mean*	*SD*	*Mean*	*SD*
Training	15	0.44	0.07	0.41	0.08
Control	14	0.36	0.13	0.41	0.14

SD = standard deviation. All values are normalised echogenicity unless stated otherwise.

6.3.2.2 Normalised Subcutaneous Echogenicity

There was no difference in normalised subcutaneous echogenicity between training and control groups, $F(1,26) = 1.571$, $p = .221$, partial $\eta^2 = .057$.

Table 6.4 Normalised Echogenicity of the subcutaneous thoracolumbar connective tissue layers

		baseline		***Post 4 weeks***	
	N	*Mean*	*SD*	*Mean*	*SD*
Training	15	.24	.06	.22	.06
Control	14	.19	.10	.23	.13

SD = standard deviation. All values are normalised echogenicity unless stated otherwise

6.3.2.3 Normalised Perimuscular Echogenicity

There was no difference in normalised perimuscular echogenicity between training and control groups, $F(1,26) = .347$, $p = .561$, partial $\eta^2 = .013$.

Table 6.5 Normalised Echogenicity of the perimuscular thoracolumbar connective tissue layers

		baseline		***post 4 weeks***	
	N	*Mean*	*SD*	*Mean*	*SD*
Training	15	0.68	0.07	0.66	0.07
Control	14	0.55	0.15	0.58	0.15

SD = standard deviation. All values are normalised echogenicity unless stated otherwise

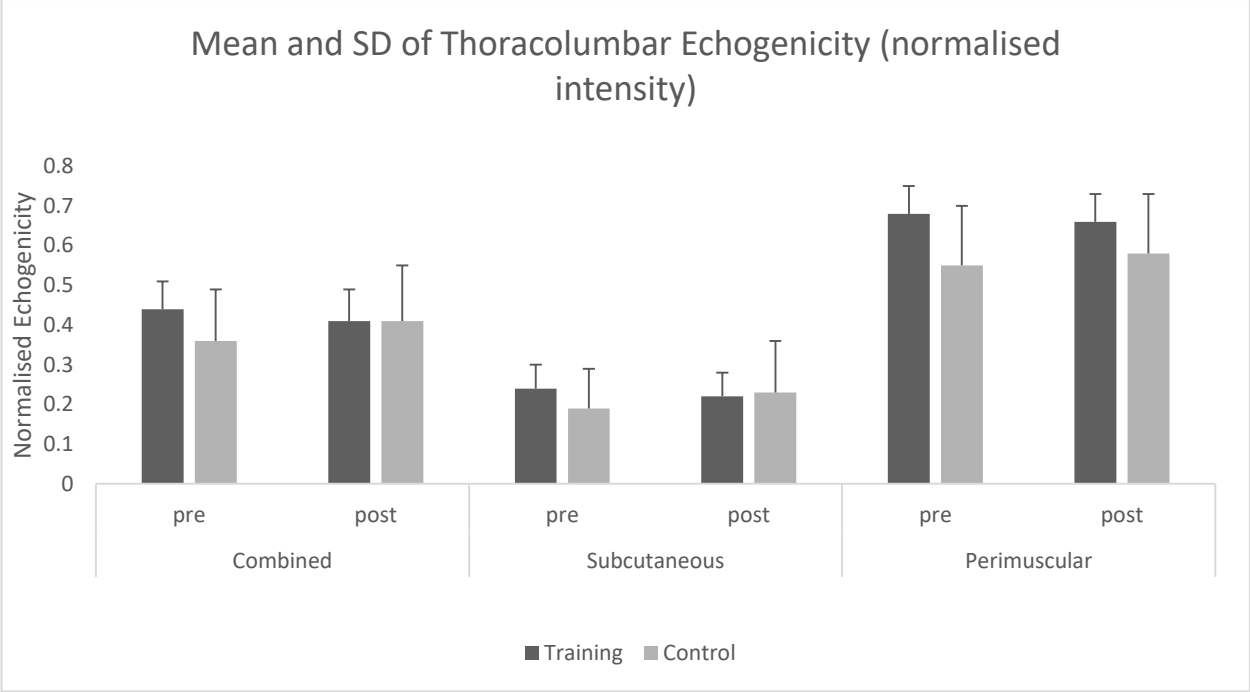


Figure 6.2 Mean and standard deviation of normalised echogenicity (0 = black, 1= white)

6.4 Discussion

This study found that a 4 week endurance training programme had no significant effect on the thickness or echogenicity of the thoracolumbar fascia. This is the first study evaluating the effect of an endurance cycling training programme on the thoracolumbar fascia.

The results of the study presented in this Chapter suggest that 4 weeks of cycling may not be a sufficient period for adaptations in the thoracolumbar fascia to be observed, or that endurance training has no effect on the morphology of the posterior layer of the thoracolumbar fascia. Future studies could investigate the effect of a training programme on the thoracolumbar fascia over a longer period or choose an activity with a different type of mechanical loading.

It is important to note that a large inter-individual difference has been found in myofascial force transmission through the thoracolumbar fascia, from the gluteus maximus to the latissimus dorsi (Carvalhais *et al.*, 2013). Force transfer from biceps femoris, a major contributor in muscle recruitment during cycling, to the sacrotuberous ligament varied between 7 and 69% with a high inter-individual variance between cadaver specimen (van Wingerden *et al.*, 1993). An inter-individual difference may have affected load transfer and consequently the results in the study presented in this Chapter, as 50% of the participants in the training group increased in perimuscular thoracolumbar fascia thickness, the other half of participants decreased. However, statistically this was not significant.

Furthermore, the training sessions involved sub maximal training including a range between 8 and 16 hours of training, some sessions will have induced fatigue. Studies have reported that muscle fatigue in the lower body alters the muscle activation pattern during cycling (So, Ng and Ng, 2005). This may have affected the force transmission through the thoracolumbar fascia. In healthy pain-free individuals this may have no impact, however, it is not known whether this may have an impact on people with lower back pain.

A further factor affecting the thoracolumbar fascia during mechanical loading, could be tissue hydration (Schleip, Duerselen, *et al.*, 2012), as well as temperature (Sapin *et al.*, 2009). Changes in tissue hydration and temperature have been shown to alter the sliding ability of the thoracolumbar fascia, and may consequently affect the force transfer through the lumbar connective tissues. Ultrasound imaging however is not able to evaluate outcome measures such as tissue hydration and temperature.

Studies have postulated that intramuscular fascia does not alter its collagen content as a result of training, but rather may alter its fibril arrangement or synthesis of other molecules such as cross-links (Järvinen *et al.*, 2002; Kjaer, 2015). It is currently not known whether a similar phenomenon could be observed in the thoracolumbar fascia as a result of mechanical loading.

Although the participants are reported as untrained, the initial physical activity survey revealed that most were already habitually active, albeit for less than 3 hours a week. The pre-training VO2 Max scores (Coakley and Passfield, 2014) reinforces this notion. Therefore, future studies evaluating the effect of a training programme on the thoracolumbar fascia of sedentary individuals would be warranted.

6.5 Conclusion

This study found no significant differences in the thickness or echogenicity of the thoracolumbar fascia after a 4 week cycling training programme, compared to an independent control group. Future studies could focus on a longer intervention period and a different type of loading such as for instance, resistance training.

Chapter 7: An intra-rater reliability study of thoracolumbar fascia morphology in ultrasound images.

7.1 Introduction

Studies presented in this thesis so far, have evaluated the thickness and echogenicity measurements of the thoracolumbar fascia. Over the course of these studies, a pattern of a disorganised appearance of the perimuscular connective tissues, and the irregular distribution of hyperechoic areas in the subcutaneous connective tissues in some participants. A more organised architecture of connective tissues was found in others. In some images, it was difficult to distinguish the perimuscular layers from the epimysium of the muscle. Differentiating the subcutaneous zone was equally problematic in some images: blurry distinctions, flaky, cloudy images interspersed with connective tissue.

Outcome measures such as thickness or echogenicity are not able to capture these observed differences in morphology. Therefore, a further study was conducted to qualitatively evaluate the morphology of the thoracolumbar fascia.

A growing body of evidence supports the notion that the thoracolumbar fascia, an anatomical structure consisting of layers of dense connective tissue in the lumbar area of the trunk, is clinically important in people with chronic lower back pain (Yahia *et al.*, 1992; Langevin and Sherman, 2007; Langevin *et al.*, 2009; Taguchi, Tesarz and Mense, 2009; Helene M Langevin, Fox, Koptiuch, Badger, Greenan-Naumann, N. a Bouffard, *et al.*, 2011; Hoheisel *et al.*, 2011; Tesarz *et al.*, 2011; Willard *et al.*, 2012). The thoracolumbar fascia has been shown to play an important role in force transmission between lower limbs and trunk in both ex-vivo cadaver studies (Macintosh, Bogduk and Gracovetsky, 1987; Barker *et al.*, 2014) and in-vivo research

during walking (Vleeming *et al.*, 1995; Carvalhais *et al.*, 2013). Subcutaneous fascial bands have been found to mechanically link the skin, subcutaneous layers and deeper muscles. The differences in morphological characteristics of subcutaneous fascial planes may reflect how mechanical forces are distributed across various tissues (Li *et al.*, 2011) . However, what is not clear, is whether medical practitioners are able to agree on these different morphological features in ultrasound images of thoracolumbar fascia.

The architecture of the thoracolumbar fascia is complex, it consists of layers of dense collagenous connective tissue, interspersed with loose connective tissue which allows the dense layers to slide and hence play a role in trunk mobility. The thoracolumbar fascia is continuous with the aponeuroses of major trunk muscles which are instrumental in movement and vertebral control (Willard *et al.*, 2012; Barker *et al.*, 2014). It has been hypothesised that fibrosis, densification and thickening in the thoracolumbar fascia may be the result of an inflammatory response or soft tissue injury (Langevin and Sherman, 2007; Corey *et al.*, 2012; Pavan *et al.*, 2014; Schilder, Hoheisel, Magerl, Benrath, Klein and R.-D. D. Treede, 2014; Diviti *et al.*, 2017). For instance, a recent animal study demonstrated that an induced soft tissue injury in the lumbar region, when combined with movement restriction, led to fibrosis, and significant thickening of thoracolumbar fascia (Bishop *et al.*, 2016). An earlier pioneering ultrasound based human study concluded that the thoracolumbar fascia in people with chronic lower back pain demonstrated 25% greater thickness compared to a matched control group (Langevin *et al.*, 2009). A follow-up investigation found that thoracolumbar fascia shear strain during passive trunk flexion, was reduced in people with chronic lower back pain by 56% (Helene M

Langevin, Fox, Koptiuch, Badger, Greenan- Naumann, N. A. Bouffard, *et al.*, 2011). In both aforementioned studies, Langevin's research team found significant differences not only in fascial thickness and echogenicity, but also in disorganisation of the architecture of the connective tissues of people with chronic lower back pain. Even though the clinical relevance of fascial tissues has been established (Klinger *et al.*, 2014), to date no classification of thoracolumbar fascia has been developed. In order to develop a classification system, a level of inter-observer reliability of the different types of architecture of thoracolumbar fascia needs to be established.

The aim of this study was to determine the inter-rater reliability for the rating of morphological characteristics of thoracolumbar fascia in ultrasound images, on Likert-type scale, by a range of clinicians.

7.2 Methods

7.2.1 Participants

The study was approved by the University of Kent's Ethics Committee and conducted in compliance with the Helsinki Declaration. Informed consent was obtained from all participants.

The inclusion criteria for participants were: medical professionals in the orthopaedic, sports medicine or sport rehabilitation field, with or without ultrasound experience or training. Twenty raters were recruited at a European Sports Medicine symposium

to rate the scans independently, in a group setting. Subsequently, a further 10 participants were recruited through opportunistic sampling (see Table 1 for characteristics).

Table 7.1: Characteristics of raters

Clinical training	**N=30**
MD	21 (70%)
Physiotherapists	7 (23%)
Radiologists	2 (6%)
Years of clinical experience	13.03 (± SD 9.6)
USI training & experience	**N=30**
Trained & experienced	12 (40%)
Untrained & unexperienced	17 (57%)
not known	1 (3%)
Frequency of USI usage	**n=12 (40%)**
daily	4 (33%)
weekly	4 (33%)
monthly	4 (33%)

USI = ultrasound imaging

This group viewed the scans individually on a standard size desktop PC computer (screen size 50 x28 cm). These participants received the same presentation on thoracolumbar fascia. All scans were anonymised and displayed in randomised order. All participants viewed all 30 scans. Participants were asked about clinical

training, years of clinical experience, musculoskeletal ultrasound training, and frequency of ultrasound image usage for diagnostic purposes in clinical practice.

7.2.2 Ultrasound image data acquisition

Images were taken at the intervertebral level 2-3, as fascial planes are the most parallel to the skin at this level (Langevin *et al.*, 2009). The interspinous ligament between lumbar vertebrae 2 and 3, and the superficial border of posterior paraspinal muscles were identified using a validated protocol (Stokes *et al.*, 2007). One focal region was set as close as possible to the thoracolumbar complex. Bi-lateral parasagittal (longitudinal) images were taken 2 cm lateral of the intervertebral disc space between lumbar vertebrae 2 and 3. The image acquisition was based on a validated protocol (Langevin *et al.*, 2009). All images presented to raters were obtained using uniform settings, a frequency of 18MHz was used, with a depth of 3 cm, which allow optimum image quality for subcutaneous structures (Kremkau, 2006). See Figure 3.2 for example of ultrasound image and anatomical orientation.

Each ultrasound image was obtained using B-Mode imaging, with a MyLabGold25 semi-portable ultrasound scanner (Easote, Rimini, Italy). A 4 cm, 18MHz linear array transducer (Easote LA435) was used for all images.

7.2.3 Selection of ultrasound images for reliability study

Initially, a single investigator selected 40 scans from a data-base of 308 bi-lateral scans of 154 male and female subjects with and without lower back pain from a larger prior study. A focus group then viewed the 40 images and selected 30 scans. Both the individual investigator and the focus group were instructed to select scans which, in their opinion, represented both 'organised' perimuscular fascia and 'disorganised' perimuscular fascia, with a range in between. 'Organised' was defined as 'being able to draw a rectangular box' around the hyperechoic zone, 'disorganised' was described as 'not being able to draw a rectangular box' around the hyperechoic zone. All raters were blind to any pathology or background information related to the scans. These 30 scans were deemed to represent the range of morphologies from very disorganised to very organised and a range of scans in between (Figure 7.1).

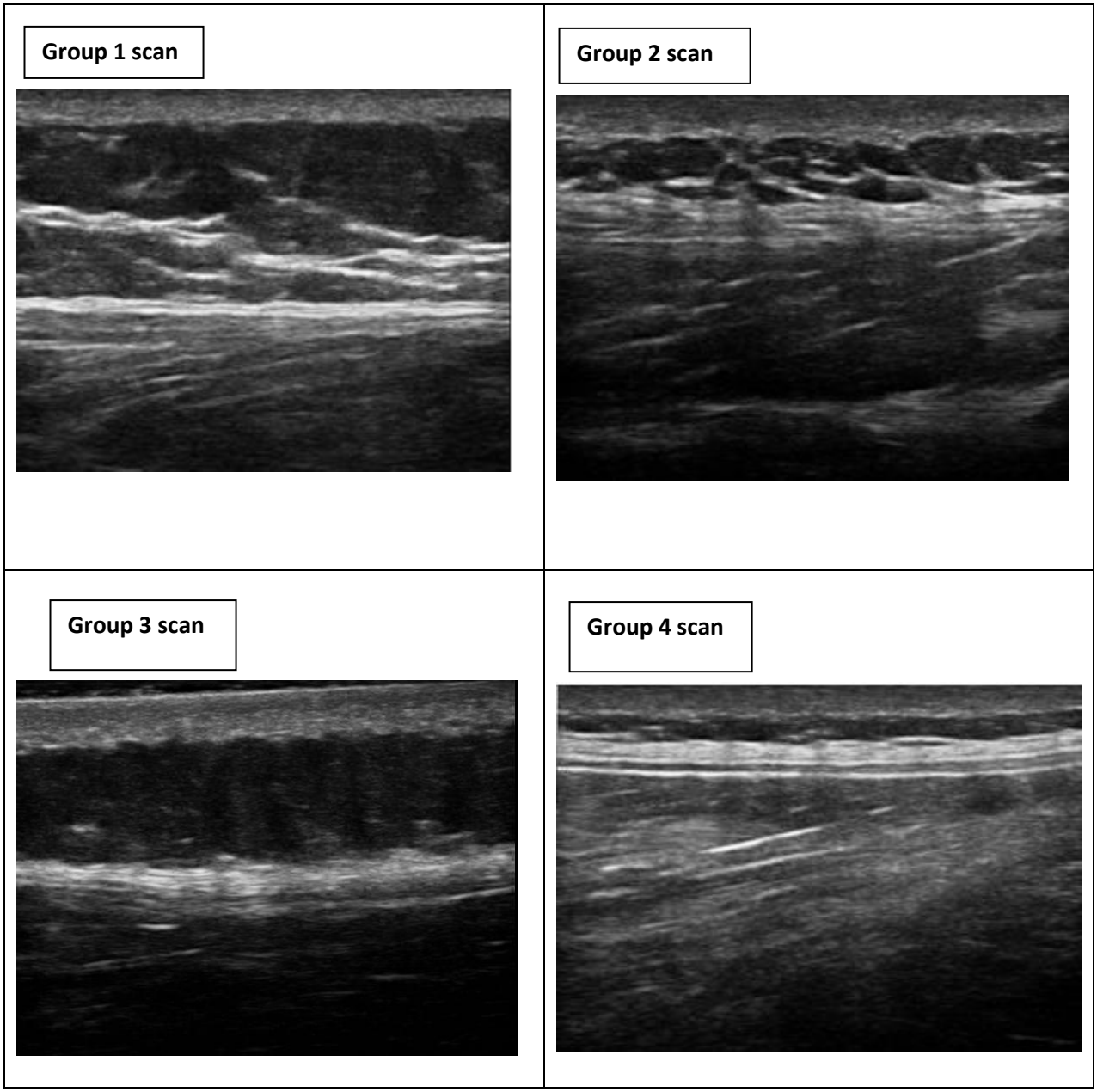


Figure 7.1. Sub-groups of different TLF morphologies.

Group 1 =example of 'very disorganised', Group 2= 'somewhat disorganised' Group 3= 'somewhat organised', Group 4= 'very organised' . The sub-grouping was based on the median scores for each scan.

7.2.4 Inter-observer reliability rating protocol

In inter-observer reliability studies, it is vital that raters apply coding to data they understand (Krippendorff, 2004). For this reason, a 20 min presentation about the thoracolumbar fascia was delivered, this facilitated anatomical orientation and exposed the participants to a representative range of ultrasound images prior to rating. Participants were not given examples of actual ratings, only of the range of images they would be rating, to avoid bias. (See Figure 1 for anatomical orientation and region of interest). Scans were projected on a standard sized screen (133 x 100 cm).

Table 1 shows that 57% had no training or experience in ultrasound imaging, 40% had experience ranging from monthly to daily evaluations of ultrasound imaging, 1 participant did not respond to this question, no observers had experience in evaluating ultrasound images of thoracolumbar fascia.

Participants were instructed to rank the region of interest (ROI in Figure 3.2) which included the thoracolumbar fascia (* thoracolumbar fascia in Figure 3.2) and the subcutaneous zone (*SZ in Figure 3.2) on a Likert-type scale. A Likert scale with rating points from 1 to 10 was used, point 1 was labelled as ‘very disorganised’ and point 10 as ‘very organised’, the intermediate points were numbered but remained unlabelled. Participants were familiarised to the definition of thoracolumbar fascia organisation and disorganisation. For instance, ‘very organised’ was defined as ‘to be able to draw a rectangular shaped box around the hyperechoic area of thoracolumbar fascia.

Participants viewed scans sequentially in a time frame of 30 seconds to 1 minute. They were able to modify responses, request to re-assess a scan, and make written comments about their decisions. Participants could not discuss ratings with each other, in order to avoid bias. All responses were anonymised prior to analysis.

7.2.5 Data analysis

Inter-rater reliability was assessed from the total raw scores of all 899 decisions, and the raw scores divided into 4 sub-groups using Cronbach's alpha, to assess internal consistency among observers (Cronbach and Shavelson, 2004; Tavakol Mohsen, 2011). The Cronbach's alpha coefficient was calculated using SPSS (version 21) statistical software. Standard error of measurement (SEM) was calculated as the square root of error variance in accordance with de Vet's guidelines (de Vet *et al.*, 2006). The Krippendorff's alpha for ordinal measures was used to assess inter-observer agreement (Krippendorff, 2004; Hayes A F, 2007) and was calculated using a custom-designed online calculator (Freelon, 2013). As Likert scales are an ordinal measurement, the median and interquartile range for the total of scans was calculated, as well as for each scan individually (Jamieson, 2004; Norman, 2010).

Participant ratings of scans were categorised into four groups (LaValley and Felson, 2002; Norman, 2010; Hallgren, 2012). Group 1 (very disorganised) consisted of all

scans with a median rating of 1 to 3. Group 2 (somewhat disorganised) consisted of all median ratings from 4 to 5. Group 3 (somewhat organised) consisted of all median ratings from 6 to 7. Group 4 (very organised) consisted of all median ratings from 8 to 10 (Figure 2). The Cronbach's alpha and Krippendorf's alpha were calculated using the original raw scores from individual raters for each scan.

7.3 Results

The median (m= 5) and interquartile range (IQR=4) of the total ratings were calculated (range = 1-10), as well as for each group (Table 7.2 and Figure 7.2).

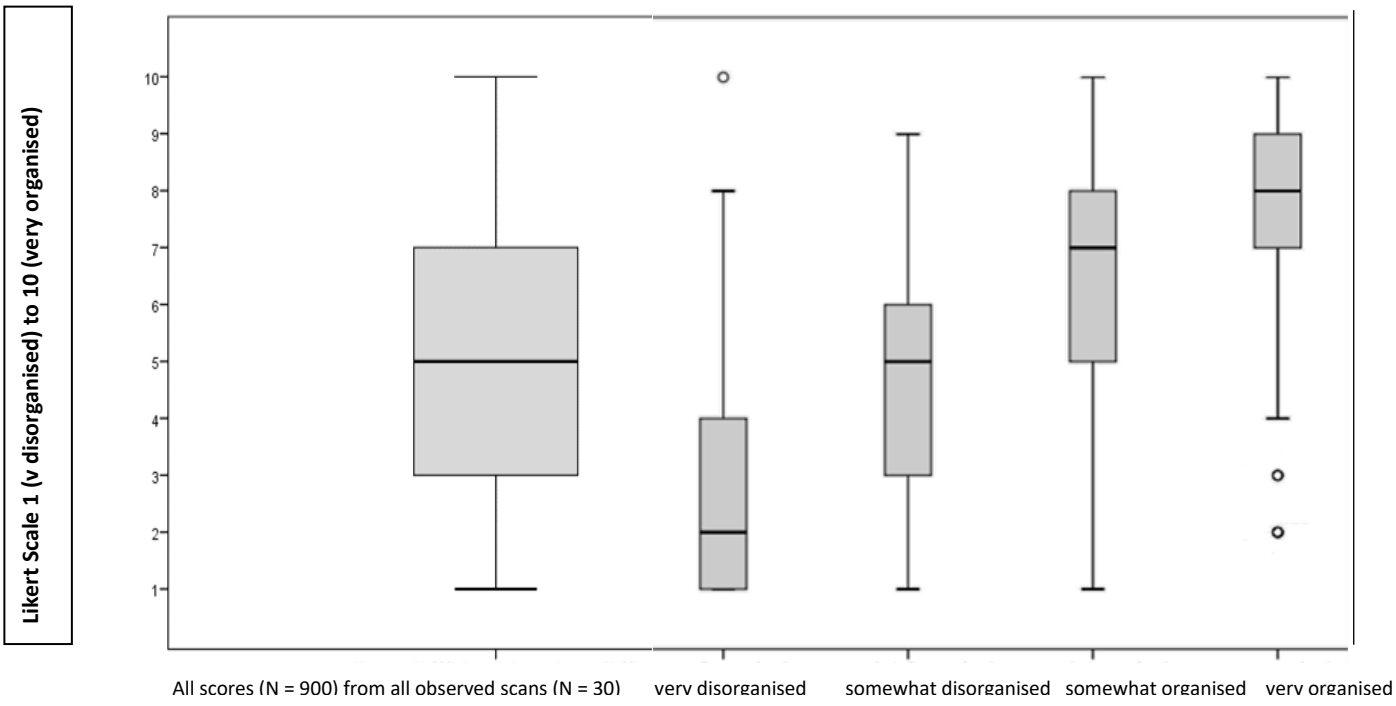


Figure 7.2 . Boxplots for total scores of the ratings (899 decisions) and ratings for each sub-group. Central tendency is the median, distribution is the interquartile range.

All participants assessed all scans, except one participant who did not complete one rating. The Cronbach's alpha was 0.98, which is considered excellent according to the Landis and Koch criteria (Landis and Koch, 1977). Observers without ultrasound imaging experience scored a Cronbach's alpha = 0.96, observers with ultrasound imaging experience scored a Cronbach's alpha = 0.95, both in the excellent range. Scores between 4 sub-groups are reported in Table 2. The Krippendorff's alpha for ordinal measures was .61, with an error variance of 0.63, indicating a modest degree of agreement.

Table 7.2: Inter-rater reliability scores for all data and sub-groups

Group	Decisions (%)	Median (IQR)	Cronbach's alpha	Landis and Koch criteria	SEM
All data	899	5 (4)	.98	excellent	0.10
Group 1	300 (32.8%)	2 (3)	.70	excellent	0.40
Group 2	209 (22.6%)	5 (3)	.68	good	0.17
Group 3	150 (20.3%)	7 (3)	.47	moderate	0.56
Group 4	240 (24.2%)	8 (2)	.56	moderate	0.50

SEM = standard error of measurement. Group 1 = very disorganised. Group 2 = somewhat disorganised. Group 3 = somewhat organised. Group 4 = very organised.

7.4 Discussion

In this study we found that medical practitioners agree on different morphological features in ultrasound images of thoracolumbar fascia such as levels of organisation and disorganisation. This agreement is independent of experience in ultrasound image rating. We found that the knowledge gap between musculoskeletal (MSK)-trained radiologists, MSK-trained medical doctors and physiotherapists on the one hand, and clinicians untrained and inexperienced in MSK ultrasound, did not affect the inter-observer agreement.

It is important to establish internal consistency before images can be used for research or clinical evaluation to ensure validity (Tavakol Mohsen, 2011). The measurement error was smaller in both groups of disorganised scans, and higher in the more organised groups. This could be an indication that it may be easier to interpret disorganisation or irregular shapes rather than organisation or regular shapes. The modest Krippendorf's alpha for the ratings suggests that a minimal amount of measurement error was introduced by the independent observers, and therefore statistical power for subsequent analyses is not substantially reduced.

In this cohort, the differences in ultrasound experience do not appear to impact on consistency. We did not observe any raters who systematically under- or over-rated the images. Novice raters have demonstrated good to excellent reliability in measuring abdominal and lumbar muscle thickness obtained by ultrasound scans (Teyhen *et al.*, 2011; Wilson *et al.*, 2016). However, a straightforward comparison

between quantitative measures of lumbar and abdominal muscle tissue, commonly found in the literature on rehabilitation of lower back pain, and this study's qualitative ratings of subcutaneous connective tissue requires caution. Substantial observer variability can occur, even at the expert level of image interpretation (Bankier *et al.*, 2010). Interestingly, in this study, experienced radiologists agreed with the interpretation of clinicians relatively inexperienced in the reading of ultrasound images. The American College of Radiology Imaging Network (ACRIN) has highlighted that in order to improve the research in interpretation of medical images, observers in reliability studies should ideally reflect a broad range of experience to provide a sufficient level of generalisability (Obuchowski, 2004).

In multi-reader medical image interpretation, the phenomenon of 'groupthink', has been identified, where the opinion of novice raters might be influenced by senior or experienced raters (Bankier *et al.*, 2010). In order to avoid a situation of potential pseudo-consensus, all raters viewed the scans independently without discussing decisions with each other.

This study has a number of limitations. First, it involved a small cohort size of both observers and scans. The results are encouraging and should be validated in a larger cohort (Obuchowski, 2004). Secondly, the study relied on static ultrasound images. Future studies may consider functional and dynamic measurements. Finally, we did not determine the frequency in which raters interpret the same image differently. This needs to be taken into account for future studies.

7.5 Conclusion

Medical practitioners agree on morphological features such as levels of organisation and disorganisation in ultrasound images of thoracolumbar fascia, regardless of experience. These findings will be useful for the establishment of a clinical diagnostic scale and the further development of using ultrasound as a decision-making tool for researchers and clinicians

Chapter 8: General Discussion

8.1 General discussion

Studies conducted in this thesis found that ultrasound images of the thoracolumbar fascia can reliably be measured by the same investigator, the most reliable were the combined layers, the perimuscular layer was moderately reliable (ICC range = 0.99 – 0.63) (Chapter 4). In a subsequent cross-sectional study (Chapter 5), I found that the thoracolumbar fascia in people with lower back pain is higher in echogenicity (p = 0.04), but no difference was found in thickness. An intervention in the form of a 4 week endurance training programme did not alter the thickness or echogenicity of thoracolumbar fascia, compared to a control group (Chapter 6). The last study in this thesis found that the morphology of thoracolumbar fascia can reliably be rated by a range of experienced and inexperienced medical practitioners (Chapter 7).

Studies evaluating the thoracolumbar fascia with ultrasound is growing, and findings about the morphology of thoracolumbar fascia are inconclusive (Langevin *et al.*, 2009; Langevin *et al.*, 2011; Murakami, Sakuraba and Nagai, 2011; Whittaker, Warner and Stokes, 2013; Bishop *et al.*, 2016; Wong *et al.*, 2017; Langevin *et al.*, 2018). The findings of Chapter 4 however, have established that the mean reliability measurements are similar to comparable reliability of muscle and associated connective tissue measurements with ICCs ranging from 0.98 to 0.58 (Koppenhaver *et al.*, 2009; Whittaker, Warner and Stokes, 2013; Sions *et al.*, 2014). This is fundamental, as test re-test reliability is a key aspect when evaluating soft tissue characteristics (Hebert *et al.*, 2009). Additionally, it lays the foundations for further ultrasound-based investigations into the morphology of thoracolumbar fascia.

The higher levels of echogenicity found in the study presented in Chapter 5 and the Langevin *et al.* (2009) study may be an indication of fibrosis of the collagen fibres in the thoracolumbar fascia of people with lower back pain. Fibrosis has been found in other connective tissues such as tendons (Goodier *et al.*, 2016), ligaments (Liu *et al.*, 2016) and joint capsules (Lindenhovius and Jupiter, 2007) as a response to chronic immobilisation and tissue repair. Furthermore, the study in Chapter 5 found that the thoracolumbar fascia of people with lower back pain had a 10% increase in echogenicity compared to that of people without lower back pain (p = 0.04). A comparable study by Langevin *et al.* (2009) found an increase in echogenicity of 20% (p < 0.001) in people with lower back pain. Studies found that high frequency ultrasound transducers (600 MHz) and lower frequency transducers (5 and 10 MHz) are able to detect an increase in echogenicity in echocardiograms of fibrotic myocardial fascia (Chandraratna *et al.*, 1997a; Tabel *et al.*, 2006). The authors found the increase in echogenicity was associated with thicker collagen fibres and more mature fibrotic fascial tissues in both rat myocardial and human myocardial tissues. This means that the higher echogenicity found in the study presented in Chapter 5 and the Langevin et al. (2009) study could be related to the presence of larger collagen fibres. Whether this means fibrotic tissues is also found in the thoracolumbar fascia of people with lower back pain requires further histological investigations. The use of ultrasound imaging to determine the relationship between relative higher levels of echogenicity in people with lower back pain compared to a control group, combined with histological research of evidence of thickened collagen fibres and fibrosis of thoracolumbar fascia in both animal and humans with chronic pain should be further explored. The next step in this field would be to investigate

whether these findings are reversible. A promising future direction for research would be to ascertain whether echogenicity in thoracolumbar fascia changes or reduces as a result of, for example, an exercise intervention over a period of several months.

It is important to note that the study conducted by Langevin *et al.* (2009) consisted of 62% highly physically active individuals with lower back pain, whereas the study presented in Chapter 5 consists of 14% highly physically active in the lower back pain group. In contrast, the Langevin et al. (2009) study consisted of 9% sedentary individuals, whereas the study presented in Chapter 5 consisted of 47% of sedentary people in the lower back pain group. It could be argued that a sedentary cohort is more representative of a lower back pain population, as people with lower back pain tend to be less physically active (Hartvigsen *et al.*, 2018). In addition, a sedentary lifestyle has been shown to be a key factor in the prevalence and exacerbation of lower back pain (Buchbinder, Pransky and Hayden, 2010). The study presented in Chapter 5 found a moderate negative correlation between physical activity levels and thickness in the no pain group (τ_b= -0.32, p = 0.001). It can be presumed that being more physically active, would result in more mechanical loading of the thoracolumbar fascia, possibly resulting in an absence of fibrosis, compared to a lower back pain population. The implications are that the relationship between physical activity and the architecture of the thoracolumbar fascia of people with lower back pain requires further investigation. The literature on mechanotransduction (Khan and Scott, 2009; Kjaer *et al.*, 2009; Khan, 2011) offers an understanding into the effects of mechanical loading on changes of collagen at a cellular level. The few ultrasound-based studies on thoracolumbar fascia and the

findings in Chapter 5 do not yet provide compelling evidence of a straightforward relationship between physical activity and the architecture of thoracolumbar fascia. This calls into question, whether physical activity status is an effective model to measure mechanical loading and any effect on the architecture of the thoracolumbar fascia. Whereas investigating the long-term effect of an increase in active weight-bearing exercise in a sedentary population with lower back pain might be a more promising model to study the effect of mechanical loading on the connective tissues of the lower back.

Consequently, Langevin and Sherman's (2007) pathophysiological model, which proposes that the thoracolumbar fascia may adapt to mechanical loading requires further investigation. The study presented in Chapter 6 evaluates the impact of an increase in physical activity, as an in vivo form of mechanical loading, on the ultrasound-based measurements of the thoracolumbar fascia. This study found that a four week cycling endurance training program had no effect on the thickness or echogenicity of the thoracolumbar fascia in untrained individuals with and without lower back pain. The findings suggest that despite the thinner fascia found in physically active people in Chapter 5, the thoracolumbar fascia may require a different exercise type, intensity and dosage of training in order to adapt to mechanical loading. Nevertheless, the findings from Chapter 4 and 5 demonstrate that ultrasound is a reliable method to investigate thoracolumbar fascia, and that the thoracolumbar fascia of sedentary people with lower back pain is higher in echogenicity in people compared to a healthy control group.

The main aim of Chapter 6 was to evaluate whether ultrasound imaging could measure the impact of an increase in mechanical loading on the thoracolumbar fascia. The findings in Chapter 6 demonstrate that 4 week endurance training programme does not affect the thickness or echogenicity of the thoracolumbar fascia in young untrained individuals with and without lower back pain. This demonstrates that further research into measuring the impact of mechanical loading on thoracolumbar fascia is required.

The focus on echogenicity and thickness measurements in thoracolumbar fascia cannot explain the irregular morphology observed in ultrasound images. In order to develop a future diagnostic scale for thoracolumbar fascia, it is important to develop an appropriate lexicon or terminology to describe the architecture of thoracolumbar fascia The principle aim of the study presented in Chapter 7 was to rank the different morphologies of thoracolumbar fascia through observation, as a preliminary investigation. This study investigated whether medical practitioners could reliably rank the organisation of the thoracolumbar fascia on a Likert-type scale from very disorganised to very organised. This study demonstrated good to moderate reliability of ranking ultrasound images on a scale of very disorganised to very organised was shown to be excellent. Moreover, this reliability was independent of ultrasound image acquirement or assessment experience. This is the first time that images of the thoracolumbar fascia has been ranked in this manner. The results of the study presented in Chapter 7 could lay the foundation for the further development of classification criteria of the morphology of the thoracolumbar fascia.

This thesis aimed to assess the utility of ultrasound imaging in evaluating adaptations of the thoracolumbar fascia in people with and without lower back pain. A pathophysiological model proposed by Langevin and Sherman (2007), states that pain, injury, stretching and movement patterns result in a cellular response and consequently fascial tissue remodelling and adaptation. Observations of maladaptation such fibrosis and densification have been reported in fascial tissues (Barker and Briggs, 1999; Langevin *et al.*, 2009; Ercole *et al.*, 2010; Pavan *et al.*, 2014)The studies in this thesis aimed to further our understanding of how and whether these adaptations can be detected in the thoracolumbar fascia using ultrasound imaging. As ultrasound imaging is regularly used in lower back pain rehabilitation, an evaluation of fascial adaptation and maladaptation may be able to become part of future clinical practice.

8.2 General limitations

As highlighted in this thesis, there are a number of considerations and constraints when using in vivo ultrasound imaging of human tissues in investigations. Ultrasound cannot visualise the cellular structure of the thoracolumbar fascia. However recently, high frequency ultrasound studies have been able to differentiate thicker collagen fibres in myocardial tissues affected by chronic fibrosis (Chandraratna *et al.*, 1997b; Seo *et al.*, 2005; Mercado *et al.*, 2015). Using high frequency ultrasound to evaluate thoracolumbar fascia may provide a clearer insight into the increase in echogenicity found in people with lower back pain.

A further limitation is that all images were acquired at rest in a prone position. It is not known whether weight bearing, standing upright for example or lumbar flexion would alter any ultrasound findings.

Furthermore, future studies may wish to set a cut-off point for high BMI. A large subcutaneous layer, as a result of a high, means that settings for a more average BMI range are not appropriate and may result in less than optimum scan quality.

8.3 Future directions

The findings from this thesis contribute to the literature surrounding ultrasound evaluations of the thoracolumbar fascia, as well as our broader understanding of the structure and function of the human fascial system. However, the studies presented in this thesis also highlight areas which warrant further investigations. The findings in Chapter 5 highlight that further research into the composition and structure of thoracolumbar fascia in people with lower back pain is warranted. Moreover, due to the known reduced capacity in muscle recruitment in people with lower back pain, future investigations could consider the relationship between the size and quality of muscles such as longissimus or multifidus and the thickness and echogenicity of the thoracolumbar fascia in people with and without lower back pain. All these structures can be visualised and measured reliably with ultrasound. This would hopefully provide insights into any differences and associations between muscles and overlying connective tissues. The results in Chapter 5 suggested that

tissue fibrosis might the cause of an increase in echogenicity in people with lower back pain. Ultrasound elastography is a emerging specialist technique used to evaluate tissue stiffness in liver tissue (Hudert *et al.*, 2018) and myocardial tissue (Tabel *et al.*, 2006), in order to diagnose tissue fibrosis. Evaluating the degree of stiffness in thoracolumbar fascia and any association with echogenicity would provide a clearer insight into the structure of the lumbar connective tissues in people with and without lower back pain.

High frequency ultrasound studies have been able to visual thicker collagen fibres in fibrotic myocardial tissue. Further investigations of thoracolumbar fascia using high frequency ultrasound may provide further insights into the composition and structure of the tissue. This non-invasive technique may allow us to research whether specific interventions are able to reverse fibrosis in the thoracolumbar fascia.

Since the findings in Chapter 6 were not significant, future research should evaluate the effect of an increase in mechanical loading over a longer period of time.

The participants used in the study in Chapter 6 were all under 30 years of age. It is unclear whether the thoracolumbar fascia of older participants may have responded differently to a 4 week training programme. Future research should assess the effect of training or loading on older individuals, from both healthy and clinical populations.

Finally, the findings in Chapter 7 warrant further investigations into the development of a classification scale for thoracolumbar fascia. This would enable

researcher and clinicians alike to evaluate the structure of the thoracolumbar fascia against a set of criteria.

8.4 General Conclusion

This thesis built on and contributes to work in the field of the role of fascia in lower back pain. Although a number of studies have examined fascia, there has not been a strong focus on the in vivo imaging of thoracolumbar fascia using ultrasound. As such, the studies presented in this thesis provide additional insights about the morphology and adaptations of thoracolumbar fascia. The investigations presented here differ from previous studies by identifying the increased echogenicity in a sedentary population with lower back pain and by investigating the impact of a 4 week endurance training programme. Furthermore, the studies presented here demonstrate the reliability of quantitative test re-test measurements, and the reliability of qualitative ratings of thoracolumbar fascia imaging.

In doing so, the research studies presented here draw strongly on the work by Langevin and Sherman (2009) and Stecco *et al.* (2011) who propose a pathophysiological model to explain adaptations and maladaptation of the human fascial system.

The studies presented in this thesis contribute to the development of methodologies to further investigate the role of thoracolumbar fascia in lower back pain, a poorly understood world-wide condition.

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