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Effectiveness of single and combined treatments on biomechanical and clinical outcomes during walking in healthy individuals and individuals with knee osteoarthritis.

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Abstract

Knee osteoarthritis (OA) is considered a common chronic musculoskeletal disease affecting the medial compartment more than the lateral compartment and leading to disability and a reduction in activity level. Lateral wedge insoles (LWI) are a conservative treatment that aims to reduce the knee loading (External knee adduction moment (EKAM), which is increased in individuals with knee OA compared to healthy individuals. Although, LWI reduce EKAM in individuals with knee OA, no significant difference was seen in pain when compared to the control treatment (neutral insole). Patients and healthcare practitioners are driven by pain more than by mechanics. Therefore, reductions in pain and loading could be achieved with LWI if combined with other conservative treatments, such as a simple knee sleeve.

The overall aim of the thesis was to investigate the biomechanical and clinical effects of combining LWI with a knee sleeve, compared to each treatment used on its own. To accomplish this research, four studies were conducted. Firstly, a reliability study amongst healthy individuals was conducted. Secondly, a reliability study of individuals affected by knee OA was conducted. Both studies showed that most biomechanical and clinical outcomes have excellent reliability and low measurement error, which supports using them. Thirdly, a randomised crossover study was conducted among healthy individuals to investigate the immediate effects of the combined treatment and the single treatments. The results showed that a knee sleeve significantly reduced the knee joint frontal plane range of motion (ROM) but not the EKAM or muscle co-contraction. Furthermore, a significant reduction in the EKAM with use of LWI was noticed. The combined treatment showed both a reduction in the EKAM from LWI use and a reduction in frontal plane ROM, which supports the use of these treatments in individuals with knee OA.

In the fourth and main study, thirty-four participants with medial knee OA were enrolled and randomised into 3 groups (LWI, simple knee sleeve, LWI and simple knee sleeve). The immediate and six-week effect on biomechanical and clinical outcomes were measured and compared between and within groups. At baseline there was no significant difference between the groups. The results showed a significant reduction in the magnitude of change in EKAM for the combined group and the LWI group compared with the sleeve group. The magnitude of change in muscle co-contraction was higher in the sleeve group and the combined group compared to the LWI group.

The combined group (31.88%) showed greater reduction in pain than the LWI group (21.1%) and the sleeve group (11.16%); however, this was not statistically significant. Only the combined group and the LWI group showed improvement in balance and functional tests compared to their baseline. Finally, the pain pressure threshold did not change after treatment in all groups.

Overall, the findings of this thesis support combined treatment. A larger trial to investigate combined treatment and single treatments in a larger sample size is needed to make the findings more conclusive.

Chapter 1:   Introduction

1.1 Introduction

Osteoarthritis (OA) is considered to be one of the most common chronic musculoskeletal diseases. The knee is the joint most often affected by OA, and it is perhaps the most important site with regard to pain and disability, affecting some 30% to 40% of the population by the age of 60 years (Felson, 1990; van Saase, van Romunde, Cats, Vandenbroucke, & Valkenburg, 1989). A higher prevalence has been anticipated in the future due to rising levels obesity and an ageing population (Zhang & Jordan, 2010). In the United Kingdom (UK), 10% of individuals between 35 and 75 years old are affected by OA (Sangha, 2000). Furthermore, the cost of osteoarthritis is estimated to be 1% of the gross domestic product (GDP) in the UK, which shows the high impact of the disease and the need for effective treatment (National Institute for Health and Care Excellence (NICE), 2006). Recent research has shown that knee OA prevalence has increased two fold since the mid-20th century (Wallace et al., 2017). In 2016, the OsteoArthritis Research Society International (OARSI) announced that osteoarthritis is now considered as a serious disease.

OA is one of the most common secondary causes of death due to disability. Interestingly, disability caused by OA and severity of hip and knee OA has been found to significantly association with all-causes mortality and cardiovascular event (Hawker et al., 2014). Recent literature has shown that participants with knee OA are at a high risk of cardiovascular disease due to disability and inactivity (Nüesch et al., 2011). In Australia, OA is the third most common secondary cause of death, equal to asthma (4.8%) and exceeded only by dementia (5.6%) and depression (8.0%) (March & Bachmeier, 1997). It has been estimated that approximately 60,000 deaths occurred in 2000 as a result of OA disability (Mathers & Penm, 1999).

The typical symptoms of OA are pain, stiffness, crepitus, reduction in range of motion (ROM) and muscle spasm (Brandt, 1989). The risk factors which increase the prevalence and accelerate the progression of the disease have been divided into two groups (Heidari, 2011b). The first is the systemic group, which encompasses factors such as age, sex and race. The second group is the biomechanical group, which is determined by factors such as obesity, malalignment and muscle

weakness. Once the knee joint is affected with knee OA the mechanical progression is the leader (Felson, 2013).

The clinical and radiological changes related to knee OA are more commonly observed in the medial compartment than in the lateral compartment of the knee (Ahlbäck, 1968; Ledingham, Regan, Jones, & Doherty, 1993). This has been attributed to the higher load, which is transferred during walking, on the medial side than the lateral side (Mündermann, Dyrby, & Andriacchi, 2005). Another possible explanation for the higher load in the medial compartment of the knee is higher muscle co-contraction or co-activation, which can be defined as the synchronised activity of two muscles (agonist and antagonist) (T P Andriacchi, 1994; Sirin & Patla, 1987). Good muscle strength is required to bear these excessive loads; however, excessive muscle co-contraction might cause high loading Quadricep strength and activation were found to be decreased among individuals with knee OA (Fisher & Pendergast, 1997; Hurley, Scott, Rees, & Newham, 1997; O'Reilly, Jones, Muir, & Doherty, 1998; Wessel, 1996). Moreover, knee joint proprioception was shown to be impaired for people with knee OA (Hassan, Mockett, & Doherty, 2001; Hewitt, Refshauge, & Kilbreath, 2002; Hortobágyi et al., 2005).

The distribution of the load depends on the magnitude of the adduction/abduction moment and the forces of the ligaments and muscles balancing the moment at the knee joint. The ground reaction force (GRF) passes medially to the knee joint which increases the external adduction moment (EKAM) and therefore higher loading to the medial compartment (Johnson, Leitl, & Waugh, 1980; Schipplein & Andriacchi, 1991). EKAM can be measured by using a motion analysis system combined with force plate (Kim, Richards, Jones, & Hegab, 2004). EKAM is a common valid indirect surrogate measurement for medial contact force (Kutzner, Trepczynski, Heller, & Bergmann, 2013; Schipplein & Andriacchi, 1991). EKAM has been found to be higher in individuals with OA than healthy ones (Baliunas et al., 2002; Huang et al., 2008; Hurwitz et al., 2002; Kim et al., 2004; Mündermann, Dyrby, Hurwitz, Sharma, & Andriacchi, 2004; Rudolph, Schmitt, & Lewek, 2007; Thorp et al., 2006).

During walking, the EKAM and external knee adduction angular impulse (KAAI) have been linked to knee OA initiation (Amin et al., 2004; Andriacchi & Mündermann, 2006), severity (Kean et al., 2012; Sharma et al., 1998), progression (Chang et al., 2015; Foroughi et al., 2009; Miyazaki

et al., 2002) and symptoms (Bennell et al., 2011; Foroughi et al., 2009; Kim et al., 2004; Prodromos, Andriacchi, & Galante, 1985). Furthermore, EKAM and KAAI are associated with medial cartilage thickness loss in individuals with OA (Bennell et al., 2011; Chang et al., 2015). It has been anticipated that each 1% increase in the EKAM is associated with a 6.46 times increase in the risk of knee OA progression (Miyazaki et al., 2002). The EKAM has been identified as the single best predictor variable for proximal medial and lateral tibial bone density in situations of both knee OA (Thorp et al., 2006; Wada et al., 2001) and healthy knees (Hurwitz et al., 1998). The EKAM has been identified as the main determinate, not only for total load across the knee joint, but also for lateral-to-medial load distribution (Schipplein & Andriacchi, 1991; Zhao et al., 2007). EKAM has shown a good correlation with medial knee joint loading across subjects and activities (Trepczynski, Kutzner, Bergmann, Taylor, & Heller, 2014). However, a recent study highlighted the importance of considering the internal force (muscles) which cannot be measured by EKAM or KAAI (Trepczynski et al., 2014).

Surprisingly, higher muscle co-contraction in the medial side was correlated with the loss of medial cartilage in individuals with knee OA (Hodges et al., 2015). It is believed that increased muscle co-contraction comes at the expense of higher joint loading (Lloyd & Buchanan, 2001; Meyer et al., 2013; Schipplein & Andriacchi, 1991) and associated OA risk (Heiden, Lloyd, & Ackland, 2009; Wu, Burr, Boyd, & Radin, 1990; Zeni et al., 2010). Previous studies have demonstrated higher muscle co-contraction in individuals with knee OA than in healthy individuals (Hubley-Kozey, Hill, Rutherford, Dunbar, & Stanish, 2009; Zeni et al., 2010).

Balance is considered to be a complex neuromuscular process, which includes motor, sensory and integrated components (Hinman, Bennell, Metcalf, & Crossley, 2002). Balance can be defined as the ability to maintain (control) the centre of gravity provided by the feet. In the elderly population, poor mobility and the risk of falls are associated with lower balance (Campbell, Borrie, & Spears, 1989). Balance can be assessed in static or dynamic techniques (Patla, Frank, & Winter, 1990; Winter, Patla, & Frank, 1990). Both dynamic and static balance have been identified as being impaired in individuals with knee OA, with the former being more greatly affected (Hinman et al., 2002; Wegener, Kisner, & Nichols, 1997). Impairment in balance in individuals with knee OA can be associated with the ageing process, muscle weakness and/or proprioceptive deficit (Koceja, Allway, & Earles, 1999; Lin, Lin, Lin, & Jan, 2009; Slemenda et al., 1997). Although balance

deficits has not been found to correlate with radiological severity of knee OA (Jadelis, Miller, Ettinger, & Messier, 2001), treatment of knee OA is expected to improve balance to reduce the risk of poor mobility and falling.

Unfortunately, OA has no cure and management ranges from conservative to surgical modalities. Although surgical modalities have had high rates of success among individuals with knee OA, it is a great expense to the National Health Service (NHS) and has great influence on individual interim of functional independence and the recovery time. Additionally, surgery is not without the risk complication, which might not suit all patients (Bhatia, Bejarano, & Novo, 2013; Griffin et al., 2007; Lindenfeld, Hewett, & Andriacchi, 1997; Marks & Penton, 2004). Therefore, surgical management should not be at the forefront line and conservative treatment should be tried first. Pharmacological treatment, exercises and other modalities are available, however these only target the symptoms, such as pain, and might cause the disease to progress if not used wisely (Dieppe, 1995). Therefore, other treatment modalities which target biomechanical factors such as the EKAM and muscle co-contraction should be the primary focus if we are to find a way to delay the progression of knee OA and mitigate the impact on overall public health.

Conservative biomechanical treatments, referred in this thesis, are ones that aim to reduce the biomechanical factors which have been related to progression of knee OA. These include, gait modification, valgus knee braces, simple knee sleeves and functional foot orthoses. Gait modifications such as lateral trunk sway and altering foot angle have shown a reduction in EKAM (Hunt et al., 2008; Hunt, Wrigley, Hinman, & Bennell, 2010; Shull et al., 2013a, 2013b). However, higher trunk sway might increase the risk of falling, back pain and other associated back injuries (Rogers & Mille, 2003; Toriyama et al., 2011). Furthermore, this requires permanent adaptation which takes time and effort and might not be applicable by some individuals. Therefore, assistive device such as braces and insoles should be the focus.

The valgus knee brace is an effective treatment in pain reduction (Arazpour et al., 2013; Fu et al., 2015; Jones et al., 2013; Moyer et al., 2014), loading reduction (Laroche et al., 2014; Moyer et al., 2015; Toriyama et al., 2011). and muscle co-contraction (Fantini Pagani et al., 2013; Ramsey et al., 2007). The mechanism relies on providing three-point forces which place the knee in a valgus position to reduce the load on the medial side of the knee joint. Despite the good clinical and

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biomechanical effects, brace compliance is a major issue (Barnes, Cawley, & Hederman, 2002; Finger & Paulos, 2002; Van Raaij, Reijman, Brouwer, Bierma-Zeinstra, & Verhaar, 2010; Wilson, Rankin, & Barnes, 2011). Several reasons have been highlighted for the low compliance, such as skin irritation, mechanical problems, awkward shape, bulkiness and difficulty in putting on and taking off the brace (Barnes et al., 2002; Fu et al., 2015; Giori, 2004; Squyer, Stamper, Hamilton, Sabin, & Leopold, 2013; Van Raaij et al., 2010).

The lateral wedge insole is another modality which aims to reduce the loading of the medial side by targeting the EKAM. Previous studies have shown a significant reduction in EKAM and KAAI with lateral wedge insole use (Chapman, Parkes, Forsythe, Felson, & Jones, 2015; Duivenvoorden et al., 2014; Fu et al., 2015; Jones, Chapman, Forsythe, Parkes, & Felson, 2014). This is achieved by placing the foot in a more everted position which places the mechanical axis in a more upright position and creates higher ankle eversion moment. This will lead to shifting in the centre of pressure (COP) more laterally and therefore a reduction in EKAM throughout, reducing the moment arm (Jones et al., 2014; Kakihana, Akai, Yamasaki, Takashima, & Nakazawa, 2004; Levinger et al., 2010; Sasaki & Yasuda, 1987; Yasuda & Sasaki, 1987).

In a previous systematic review they included 12 studies which have shown a significant reduction in pain with lateral wedge insole use compared to the baseline (Parkes et al., 2013). Interestingly, when pain, while using the lateral wedge insole, is compared to that with a neutral insole, no significant difference was identified (Baker et al., 2007; Barrios et al., 2009; Bennell et al., 2011; Campos et al., 2015; Maillefert et al., 2001; Pham et al., 2004). One of the possible uses of a lateral wedge insole is in combination with another modality to achieve higher reduction in pain and maintain the effect of load reduction.

Combining the lateral wedge insole and the valgus knee brace showed greater EKAM reduction (Al-Zahrani, Herrington, Liu, Hutchins, & Jones, 2013; Fu et al., 2015; Moyer et al., 2013) and a reduction of pain (Fu et al., 2015) compared to a single treatment. However, due to the low compliance with the valgus knee brace, the simple knee sleeve is an alternative to the valgus knee brace. The simple knee sleeve is a straightforward and inexpensive treatment (Bryk et al., 2011). Previous studies have shown a decrease in pain with sleeve use (Bryk et al., 2011; Cudejko et al., 2017, 2018a; Kirkley et al., 1999; Mazzuca, Page, Meldrum, Brandt, & Petty-Saphon, 2004;

Schween, Gehring, & Gollhofer, 2015). This decrease in the pain is proposed to be related to several causes such as a reduction in muscle co-contraction (Collins et al., 2011). Previous studies have showed contradicting results regarding the effect of knee sleeve on EKAM amongst individuals with knee OA (Collins et al., 2014; Schween et al., 2015) therefore, more studies are needed to show the effect of sleeve in EKAM. Encouraging results have showed a greater number of participants walked without knee pain on uneven ground with a combination of the lateral wedge insole and the simple knee sleeve compared to the lateral wedge insole alone (Keyaki & Toda, 2010). However, the biomechanical (EKAM, muscle co-contraction) effect, which is a key factor in terms of the progression of the disease, has not been investigated up to this point. It would be deemed that an ideal solution would have both positive clinical and positive biomechanical results and up to this point, this has not been established. Therefore, the aim of this thesis was to investigate the effect of combined treatment (lateral wedge insole and simple knee sleeve) on clinical and biomechanical outcomes and compare this treatment with that of each treatment individually.

1.2 Specific aims

In order to achieve the above aim, the following has to be established:

To investigate the reliability of different outcome measurements among healthy individuals (Chapter three).

To investigate the reliability of biomechanical and clinical outcomes in individuals with knee osteoarthritis (Chapter three)

To investigate the effect of combined treatment (simple knee sleeve and lateral wedge insole) on healthy individuals and additionally compare their effectiveness to the lateral wedge insole and simple knee sleeve on knee loading and muscle co-contraction during walking (Chapter four).

To investigate and compare the immediate clinical and biomechanical outcomes and the effect after six weeks of using single treatments (simple knee sleeve or lateral wedge insole) and combined treatments (simple knee sleeve and lateral wedge insole together) (Chapter five).

1.3 **Thesis structure**

The structure of the thesis is depicted in the below figure which gives an overview of the different chapters which are progressively built on in this thesis.

Chapter 1: Introduction

-Introduction

-Thesis aims

-Thesis structure

Chapter 2: Literature review

Chapter 3: Methodology

- General methodolgy

-Test– retest reliability for healthy individuals (study-1)

-Test– retest reliability for individuals affected with knee osteoarthritis (study-2)

Chapter 4:

The immediate effect of single and combined treatments on knee kinematics and kinetics on healthy during walking (study-3)

Chapter 5:

Effect of a lateral wedge insole and simple knee sleeve as a single and combined treatment in biomechanical and clinical outcomes in individuals with knee osteoarthritis (The IN-SLEEVE study) (study-4)

Chapter 6:

General conclusion and future studies

Chapter 2:   Literature review

2.1   Chapter overview

This chapter seeks to investigate the current literature in terms of conservative management of individuals with medial knee OA. The review covers all aspects of OA and a wide range of medial knee OA treatment. This was to develop the research question and hypothesis based on scientific research methods. This chapter starts with definitions of OA followed by prevalence and incidence focusing on medial knee OA. Risk and progression factors are then discussed following on with the biomechanical assessment of individuals with medial knee OA with focus on EKAM moment and muscle co-contraction. The link between the EKAM and muscle co-contraction and the progression of the disease was presented followed by how to modify them.

The second part of this chapter is focusing on current treatment available for individuals with knee OA. The orthotic management of individuals with medial knee OA was then reviewed and appraised. The chapter was then concluded with the aims and the hypotheses which look at investigating the effect of lateral wedge insole and simple knee sleeve as a combined treatment.

2.2   Osteoarthritis

Osteoarthritis (OA) is considered the most prevalent type of musculoskeletal disease, causing a reduction in quality of life with increasing disability (Lawrence et al., 2008). OA is considered a worldwide health problem. The prevalence of OA is expected to increase in the future due to obesity and the aging population (Zhang & Jordan, 2010). In 2017, Wallace et al, have found that the prevalence of the hip and knee OA has more than doubled since the mid-20th century (Wallace et al., 2017). A recent study showed that the diagnosis of symptomatic knee OA based on self-report questionnaire occurs relatively earlier in life (median 55 years), which suggests that prevention programmes should be offered earlier (Losina et al., 2013). OA can be defined as a heterogenous group of disorder which lead to symptoms and clinical signs combined with degeneration of the articular cartilage (Altman et al., 1986).

2.3 Etiopathogenesis of OA

The pathological features of OA include the loss of articular cartilage, abnormal remodelling and abrasion of subarticular bone, osteophyte formation and bone cysts (Iannone & Lapadula, 2003). Articular cartilage loss in OA may begin as a focal lesion and increasingly expand to engage specific joint compartments, thus leading to modifications in articulating surfaces (Lohmander, Lark, Dahlberg, Walakovits, & Roos, 1992) and causing the progressive loss of articular cartilage (Dieppe, Cushnaghan, Young, & Kirwan, 1993). The catabolism of the extracellular matrix exceeds its anabolism, which causes a net reduction in the quantity of the cartilage matrix that may lead to the complete erosion of the cartilage covering the bone on the joint surface (Sarzi-Puttini et al., 2005). Therefore, for a better understanding to the size of the problem and the proper planning to tackle the disease, the prevalence of OA must be considered.

2.4 Prevalence and global burden of OA

OA is considered a worldwide health problem affecting approximately 8% to 15% of the population (Rat et al., 2006). A recent report has shown that in the United Kingdom (UK), 1 out of every 3 (8.75 million) individuals over the age of 44 old is affected by OA (Arthritis Care, 2012). In the United States (US), arthritis and other rheumatic diseases cost $128 billion in 2003, equal to 1.2% of the gross domestic product (GDP), which was a 24% increase in from 1997 cost, according to the Centers for Diseases Control and Prevention (Yelin, 2007). Nevertheless, in the US, more than 27 million people suffer from OA, and the incidence of the disease is estimated to be about 3.1% annually (Blumenfeld et al., 2013; Lawrence et al., 2008).

In China, the prevalence of OA is estimated to be nearly 16% of the population (Jiang et al., 2012). In developing countries, studies on OA estimated the prevalence to range from 8% to 48% in India, Pakistan and Bangladesh (Haq et al., 2010). The cost of OA is estimated to be 1% of the GDP of the UK (NICE, 2006). In 2010, Arthritis Research UK estimated the cost of arthritis to the economy to be 8 billion pound a year. This shows the high impact of OA on the economy and emphasises the urgent need for effective treatments to reduce the cost.

2.5 Disability and co-morbidity from OA

OA is considered a common progression disease that has a major effect on an individual's function and ability. OA is one of the most common secondary causes of death due to disability and inactivity. Significant associations have been identified between the severity of disability caused by OA and all-causes mortality cardiovascular event (Hawker et al., 2014). The recent literature has shown that participants with knee OA are at high risk of cardiovascular disease due to disability and inactivity (Nüesch et al., 2011). In Australia, OA is the third leading secondary cause of death, equal to asthma (4.8%), and it is exceeded only by dementia (5.6%) and depression (8.0%) (March & Bachmeier, 1997). It has been estimated that approximately 60,000 deaths occurred in 2000 as a result of disability from OA (Mathers & Penm, 1999). Globally, OA has been ranked amongst the top 10 causes of disability (Lawrence al., 2008).

The impact of OA on disability is substantial, with the disability risk—defined as the need for assistance in walking and climbing stairs—being equal to that of cardiovascular disease and surpassing that of any other medical condition among the elderly population (Guccione et al., 1994). The dependence on others in performing daily living activities increases with the incidence of radiological OA, even in cases involving the non-appearance of symptoms (Guccione, Felson, & Anderson, 1990). In the presence of a chronic condition, the likelihood of disability increases even further (Ettinger, Davis, Neuhaus, & Mallon, 1994). However, the disability depends on the joints which are affected by OA. The clinical importance of focusing on disability is that disability is considered as risk factor for major diseases such as diabetes, obesity and cardiovascular disease (Warburton, Nicol, & Bredin, 2006). Furthermore, the low-activity level was associated with high loss of cartilage volume (Lin et al., 2013; Stehling et al., 2011). Therefore, it is hoped that when treating individuals with knee OA an improvement in physical activity is seen to reduce the risk for major disease.

2.6 Joints affected by OA

The joints most commonly affected by OA are the knees, hips and hands, although the disease occurs with a lower prevalence in other joints, such as the spine, feet, wrists, shoulders and ankles (Table 2-1) (Arthritis Care, 2012). OA of the hip and OA of the knee have the greatest impact on

the population, because the disease is more common in these joints than in others and because the resulting stiffness and pain significantly affect ability and morbidity. Symptomatic knee OA when defined by pain is more common than hip OA, which highlights the increasing importance of knee OA in disability and inactivity (Lawrence et al., 2008). Thus, there is a direct need to understand the role that knee OA has on the population.

Table 2-1 Estimated number of individual consulted the GP about OA in the UK (Arthritis Care, 2012).

Site	Age 45+
Knee Osteoarthritis	4.71 million
Hip Osteoarthritis	2.12 million
Hand/wrist Osteoarthritis	1.56 million
Foot/ankle Osteoarthritis	1.77 million
More than 1 joint	1.76 million
Other/unspecified	0.61 million

2.7 Prevalence and incidence of knee OA

The prevalence of OA differs depending on (1) the definition (e.g. clinical or radiological), (2) the studied population characteristics and (3) the studied joint. The prevalence of radiological knee OA in individuals over 44 years old was 19.2% in the Framingham study and 27.8% in the Johnston County project (Lawrence et al., 2008). A higher prevalence (approximately 37%) was observed in individuals aged 60 years and older in the third National Health and Nutrition survey (Lawrence et al., 2008). In the UK the number of individuals affected with knee OA over the age of 44 years old in 2010 was estimated to be 4.71 million. This number is estimated to increase up to 5.4 million in 2020 and will rise again to 6.4 million in 2035 (Arthritis Care, 2012).

In 1990, Ahlberg, Linder and Binhemd conducted a study to identify the prevalence of knee and hip OA in the population of the eastern province of the Kingdom of Saudi Arabia (KSA) and the prevalence of knee and hip OA was 3.5%. More recent study in KSA found in a house-to-house survey that the prevalence of clinical knee OA was 13%. This percentage was found to increase with age, reaching 60.6% of the population aged between 66 and 75 years old (Al-Arfaj et al., 2003).

There is a lack of meaningful data on the cumulative incidence of OA. The period over which OA risk is calculated is vital, but not always clearly defined or known. Furthermore, OA is a chronic condition occurring more commonly in the elderly, challenging risk, and death from other medical conditions makes it difficult to estimate the cumulative incidence of OA. The rate of the incidence of knee, hip and hand OA in USA was estimated to be 100/100,000 person-years, or 88,240 individuals in total (Oliveria, Felson, Reed, Cirillo, & Walker, 1995). This incidence rate increases sharply around the age of 50 and then stabilises around the age of 70, which is likely to be due to the reduction in physical activities, resulting in less joint damage and pain.

2.8 Financial impact of knee OA

In the UK, the national tariff for total knee replacements (TKR) due to OA was £5,198, resulting in an estimated cost of £426 million for primary TKR in 2010 (Chen, Gupte, Akhtar, Smith, & Cobb, 2012). However, this is only the hospital costs and not the associated costs, so the actual figure is much greater. In Canada, Gupta, Hawker, Laporte, Croxford and Coyte (2005) estimated that the indirect costs associated with hip and knee arthritis patients to be much higher than the direct annual cost. In 2016, 108,713 knee replacements were carried out in the UK which shows an increase of 3.8% compared to 2015 (Arthritis Research, 2018). Interestingly, 98% of the knee replacements in 2011 were due to the knee osteoarthritis (Arthritis Care, 2012). It has been estimated that the direct cost of osteoarthritis and rheumatoid arthritis on the healthcare system is £10.2 billion for 2018 (Arthritis Research, 2018). Osteoarthritis and rheumatoid arthritis were estimated to cost £2.58 billion due to working days lost and the figure expected to reach £3.43 billion in 2030 (Arthritis Research, 2018).

2.9 Classification of knee OA

Knee OA is classified by etiology into two types: primary (idiopathic) and secondary (i.e. trauma) (Lespasio et al., 2017). Idiopathic knee OA cause is unknown. This could have been attributed to abnormalities in body biomechanics, such as the many cases of hip OA that were considered primary because of an unrecognised deformity (Arden & Nevitt, 2006; Ganz, Leunig, Leunig-Ganz, & Harris, 2008). Many disorders have been documented to be causes of secondary OA, and they can be categorised into four groups (Table 2-2).

Table 2-2 Secondary causes of osteoarthritis

Types	Example
Anatomic	Epiphyseal dysplasias, Slipped femoral epiphysis, Legg–Perthes disease, Blount's disease
Traumatic	Joint fracture or osteonecrosis, surgery in joint (e.g. meniscectomy), Major joint trauma, Chronic injury (occupational arthropathies)
Metabolic	Acromegaly, Calcium crystal deposition, Ochronosis, Haemochromatosis
Inflammatory	Septic arthritis, whichever inflammatory arthropathy

Knee OA can also be divided based on the location of the affected side into three categories: medial (tibiofemoral) knee OA, lateral knee (tibiofemoral) OA and patellofemoral OA. It is possible to have isolated knee OA (i.e. medial) or combined knee OA (i.e. medial + patellofemoral).

2.10 **Diagnosis of knee OA**

Knee OA may be defined radiographically and clinically.

Radiographic:

There are many radiographic methods, and the most commonly used is the Kellgren–Lawrence (K/L) scoring and atlas grading scheme (Zhang & Jordan, 2010). This joint score grading system divides knee OA into five categories from 0 to 4, defining OA by the existence of explicit osteophytes (grade 2 or above). The more severe categories are characterised by the consecutive appearance of narrowing in the joint space, sclerosis, cysts and, finally, deformity (Bayramoglu, Toprak, & Sozay, 2007; Kellgren & Lawrence, 1963) (Table 2-3 and Figure 2-1).

Table 2-3 Kellgren–Lawrence OA Grading System (Kellgren & Lawrence, 1957)

Kellgren–Lawrence OA Grading System	Description
0 (normal)	No characteristics symptoms of OA
1 (Doubtful)	Narrowing of joint space is doubtful and probably osteophystic lipping
2 (Minimal)	Definite osteophytes and probable joint space narrowing
3 (Moderate)	Definite joint space narrowing and moderate osteophytes, some sclerosis and probable bone contour deformity
4 (Severe)	Severe joint space narrowing and sclerosis, large osteophytes and definitive bone contour deformity

Figure 2-1 Kellgren–Lawrence OA grading system (Link et al 2003): (A) grade 1, (B) grade 2, (C) grade 3, (D) grade 4.

However, population-based studies have revealed inconsistencies between radiological OA and symptomatic OA (Dieppe, Cushnaghan, Tucker, Browning, & Shepstone, 2000), defined as radiographic findings accompanied by pain or aching on most days (Dahaghin et al., 2005; Hannan, Felson, & Pincus, 2000). It has been proven that only half of radiological knee OA patients experienced knee pain (Hannan et al., 2000). Inconsistency between the radiological criteria and symptomatic OA are likely due to the limitations in radiological method to evaluate the tissue involved in the knee OA as synovium (Heidari, 2011b; Kinds et al., 2011). This shows the limitation in radiological criteria to diagnose this subgroup which stimulate the development of new methods of diagnosis of OA based on knee pain.

Clinical

The American College of Rheumatology (ACR) has developed several criteria to diagnose individuals with knee OA (Heidari, 2011a) via using a) history and a clinical examination; b) history, radiological findings and a clinical examination; or c) history, lab findings and a clinical examination.

History and clinical examination:

The patient is considered to have knee OA if knee pain was reported on the majority of the days of the previous month and accompanied by three out of the following: A) aged older than 50 years, B) 30 minutes of joint stiffness, C) bony enlargement, D) bony tenderness or E) crepitus.

History, radiological findings and clinical examination:

The patient will be considered to have knee OA if he or she complains of knee pain for the majority of the days in the prior month plus osteophytes and combined with one of the three following criteria: 1) aged older than 50 years, 2) more than 30 minutes of joint stiffness or 3) crepitus

History, laboratory findings and clinical examination:

The patient is considered to have knee OA if knee pain was reported on the majority of the days of the previous month and accompanied by five of the following eight criteria: A) aged older than 50 years, B) 30 minutes of joint stiffness, C) bony enlargement, D) crepitus E) erythrocyte sedimentation rate (ESR) higher than 45 mm/hour, F) synovial fluid signs of OA, G) no palpable warmth or H) rheumatoid factor higher than 1/40.

The key symptom of knee OA is pain, which occurs with joint movement and is relieved by joint rest, with the pain typically aching in nature and poorly located (Brandt, 1989). There is no strong correlation between joint symptoms and the degree or extent of radiographic or pathological change (Westacott, Webb, Warnock, Sims, & Elson, 1997). In severe and advanced knee OA, pain persists at rest and may cause a patient to awake from sleep due to a loss of defensive muscular joint guarding, which prevents painful movement during the day. Acute and sub-acute inflammations are sometimes associated with OA (Heidari, 2011b).

Morning stiffness is also a common complaint. Articular gelling, a temporary stiffness lasting only for several flexion-extension movements, is extremely common in elderly patients, especially in weight-bearing joints. Limitations in movement develop as the disease progresses as a result of joint-surface incongruity, capsular contracture, muscle spasm and contracture and mechanical block because of loose bodies or osteophytes. Crepitus, a grating or crackling sound as the affected joint is moved, may be due to joint surface irregularity and cartilage loss. Joint swelling may be caused by secondary synovitis or marginal thickness and changes in bone or cartilage (osteophytes). Advanced stages of the disease are associated with gross subluxation and deformity due to cartilage loss, subchondral bone collapse, bone cyst formation and overall bony overgrowth (Felson et al., 2000).

2.11 **Risk Factors for knee OA**

Studies of knee OA reveal that it has a multifactorial aetiology, and its onset risk factors can involve either systemic, local factors or their interplay (Heidari, 2011b). The importance of each factor may vary from one joint to another, depending on the stage of the disease and gender. Felson et al. (2000) suggested that risk factors for OA might even act in different ways according to individual radiographic characteristics, such as joint space narrowing and osteophytes. Individuals may have an inherited tendency to develop OA but will never develop the disease unless injured. Whether some of these variations are spurious or genuinely caused by different study populations, analytical methods or statistical powers, the definition of OA risk and risk factors are points of open debate.

2.11.1 Systemic risk factors

2.11.1.1 *Age*

Age is considered one of the strongest risk factors in knee OA and other joints (Blagojevic, Jinks, Jeffery, & Jordan, 2010; Felson, et al., 2000; Felson & Zhang, 1998; Lawrence et al., 2008). This increase in prevalence with age is likely due to the consequence of accumulative exposure to different risk factors and cellular changes that occur with increasing age, which makes a joint less capable of coping with adversity, such as muscle weakness, cartilage thinning and poor proprioception (Shane Anderson & Loeser, 2010). Interestingly, a recent study has shown that the higher prevalence's of knee OA since the mid-20 century were not explained by increased aging or BMI which highlights the need for more studies on the risk factors (Wallace et al., 2017).

2.11.1.2 *Race*

Ethnic variation in knee OA has been investigated in white Caucasians and African Americans, with the results conflicting. There appears a higher incidence of knee OA in African American women, which was highlighted in one large national study (Anderson & Felson, 1988). In contrast, in the Johnston County Osteoarthritis Project study, no variation in disease prevalence in the south rural area was found (Jordan, Linder, Renner, & Fryer, 1995). In studies assessing the difference between western and Asian populations, a Beijing OA study identified a higher prevalence of both

symptomatic and radiological knee OA than in the Framingham study (Zhang et al., 2001). In the middle east, the prevalence was identified as 53.3% in males and 60.9% in females, with the medial side more affected than the lateral side (96.6%) (Al-Arfaj & Al-Boukai, 2002). Interestingly, recent study showed that even pain and disability were worse in African American than non-Hispanic white individuals (Cruz-Almeida et al., 2014).

The relative contribution of socioeconomic, lifestyle and biological factors to ethnic variation are vague. Although body mass index differences in different ethnicities might explain some variation in the prevalence of radiological OA, the variation in radiological OA biomarkers suggests genetic and biological factors also play a role (Clark et al., 1999).

2.11.1.3 *Sex*

In studies that investigated gender differences, a higher prevalence of knee OA was highlighted in women after the age of 50 compared to men (Felson et al., 2000; Kohatsu & Schurman, 1990; Srikanth et al., 2005). Recent published data showed that estimated number of female sought treatment for knee OA to be higher than male (Arthritis Care, 2012). Moreover, the severity of the knee OA in females tends to be higher than in males (Srikanth et al., 2005a). In contrast, males do tend have a higher prevalence of knee OA under the age of 50 (Felson et al., 2000), which is likely due to hormonal factors.

2.11.1.4 *Nutritional factors*

Vitamin D deficiency was identified as a risk factor for developing knee OA through regulating the mineralisation in bone and cartilage (Misra et al., 2013). The continuous exposure to oxidants has been identified as a contributor to many age-related disorders involving OA (Frei, 1994). Nevertheless, a study that investigated the role of vitamin C highlighted the importance of this vitamin in OA. The risk of radiological knee OA was found to be reduced by threefold in individuals with a high and moderate intake of vitamin C compared to the low intake group (McAlindon et al., 1996). Vitamin C supplementation was found to reduce the risk of knee OA after controlling other confounding factors (Peregoy & Wilder, 2011).

2.11.1.5 *Genetics*

Several studies have shown that OA can be inherited and may differ from joint to joint (Osteoarthritis: National Clinical Guideline for Care and Management in Adults - NCBI, 2008; Zhang & Jordan, 2010). Family and twin studies have illustrated that the heritability component of OA is high in the hand and knee (35%–65%), hips (60%) and spine (70%) joints (Spector & MacGregor, 2004). Many genes are known for their interactions with OA, such as the receptor gene for vitamin D, which has an influence on bone density and is close to the location of type II collagen, gene factor I insulin-like growth and others (Felson et al., 1998; Spector, Cicuttini, Baker, Loughlin, & Hart, 1996).

2.11.1.6 *Bone density*

A higher bone mineral density is considered a risk factor for knee OA (Hannan, Anderson, Zhang, Levy, & Felson, 1993; Hardcastle, Dieppe, Gregson, Davey Smith, & Tobias, 2015; Nevitt et al., 1995). The mechanism by which bone mineral density increases the risk of knee OA remains elusive (Hardcastle et al., 2015). In contrast, once the disease has been initiated, a higher bone mineral density might protect against disease progression, as shown by the Framingham study (Zhang et al., 2000). Moreover, a reduction in bone mineral density in individuals with knee OA might accelerate the progression of the condition. These previous arguments show the complex and conflicting roles of bone density.

2.11.1.7 *Hormonal status*

Oestrogen is a factor that might affect bone mass density. Women with higher exposure to exogenous and endogenous oestrogen have higher bone mass density, which increases the risk of knee OA (Hannan et al., 1993; Hardcastle et al., 2015; Nevitt et al., 1995). On the other hand, oestrogen use might decrease the progression of the disease in individuals with knee OA (Felson et al., 2000).

These systemic risk factors for knee OA have been identified and the majority are non-modifiable; therefore, modifiable factors, local risk factors or biomechanical factors have also been proposed.

2.11.2 Local risk factors and biomechanical factors

Local factors that affect the risk of developing knee OA are thought to work through an abnormal joint mechanical loading that alters local forces across the joint. The following are factors that have been associated with a greater incidence and the progression of knee OA.

2.11.2.1 Obesity

Individuals who are overweight and obese have been identified as at a high risk for developing OA in the knee joint (Felson et al., 2000; Silverwood et al., 2015). In the Framingham study, women who lost 5 kg of mass showed a 50% risk reduction in developing symptomatic knee OA, which highlights the strong effect of mass on OA (Felson, Zhang, Anthony, Naimark, & Anderson, 1992). A weight loss of two units or more on the body mass index was also associated with a reduction in the risk of developing radiological knee OA by 50% (Felson et al., 1992) whilst a 5 unit increase was associated with 35% risk increase (Jiang, Tian, et al., 2012). The basic mechanism for the correlation of obesity and knee OA is likely to involve the effect of excessive weight on overloading of the knee and hip joints during activity and changes in body biomechanics during walking, leading to damage to the ligaments and the breakdown of cartilage and other support tissues (Messier, 2008).

The overall force across the knee joint during a single leg stance was suggested to increase by two to three pounds by each one pound increase in the mass of the individual (Bliddal, Leeds, & Christensen, 2014; Felson et al., 2000). Several studies have highlighted the successful effect of weight reduction as a conservative treatment solution for pain reduction and improvements in the disability of individuals with knee OA (Christensen, Bartels, Astrup, & Bliddal, 2006; Messier et al., 2004). Meta-analysis results concluded that weight loss reduction in obese individuals with knee OA by 5% in mass was associated with significant improvements in physical function (Christensen et al., 2006).

2.11.2.2 Knee malalignment

Robust evidence proposes that joint malalignment play an important role in knee OA progression (Tanamas et al., 2009). A study by Sharma et al. (2001) showed the importance of joint malalignment in individuals with knee OA. Abnormal limb alignment was strongly correlated with

knee OA progression in the deteriorated compartment (Felson et al., 2013; L Sharma et al., 2001). Individuals with a varus deformity had a fourfold risk of knee OA progression (medial compartment), while individuals with a valgus deformity have a fivefold increase in the risk of progression of lateral compartment knee OA. The link between malalignment and the incidence of knee OA is less clear, with one study showing an association (Brouwer et al., 2007) while others have not (David J Hunter et al., 2007). Varus knee alignment has been identified as one of the best indicators of a high knee adduction moment (Barrios, Higginson, Royer, & Davis, 2009), which has been proposed as a risk factor for the progression of medial knee OA.

2.11.2.3 *Acute joint injury and joint deformity*

Ligamentous and meniscus tears, articular surface fractures and dysplasia followed by the development of OA in the affected joint at a high percentage (Lohmander, Ostenberg, Englund, & Roos, 2004; Roos, Ostenberg, Roos, Ekdahl, & Lohmander, 2001; Silverwood et al., 2015). A study by Roos (2005) concluded that knee OA is more common in young adults after injury (Roos, 2005). In soccer players who have sustained an anterior cruciate ligament rupture, 51% of females showed radiological changes after 12 years (Lohmander et al., 2004), while 41% of men showed knee OA after 14 years (Von Porat, 2004). The prevalence of meniscal damage was much higher in individuals with radiological knee OA than in those with no OA (82% and 25%, respectively) in the Framingham study (Zhang & Jordan, 2010). The risk of TKR among individuals with knee OA was found to increase seven times with ACL injury and 15 times with meniscal injury which highlight the effect of such injuries on the development of end stage OA (Khan et al., 2018), hence the emerging and established work on the prevention of OA.

2.11.2.4 *Occupational overuse*

Occupational activities that require the overworking of joints through repetitive task movement, leading to fatigued muscles, increases the risk of developing OA in the involved joints (Coggon et al., 2000; Cooper, McAlindon, Coggon, Egger, & Dieppe, 1994; Felson et al., 1991). The risk of developing OA was found to increase by more than twofold in men whose occupation required squatting/kneeling and carrying than in individuals whose jobs did not require such activities (Felson et al., 1991). The load across the knee joint is increased in a squatting or crouching position, and it is further increased by lifting weight, and turning in such a position further

increases torsional stress (Felson et al., 2000). A recent systematic review concluded that exposure to certain physical activities may be considered a risk factor for knee OA and pain (Silverwood et al., 2015)

2.11.2.5 *Physical activity/sports*

It has been demonstrated via epidemiological studies that the risk of developing knee OA increases with certain types of sporting activities (Cheng et al., 2000; Verweij, van Schoor, Deeg, Dekker, & Visser, 2009). Silverwood et al. (2015) concluded that habitual high physical activity appears to increase the risk of developing knee OA, whereas in individuals who participate in less intensive exercise do not appear to be at a high risk of developing knee OA. In a recent systematic review and meta-analysis which included 25 studies, they concluded that competitive runners have a higher risk of developing knee and hip OA than recreational runner (Alentorn-Geli et al., 2017). In contrast to the previous study Timmins, Leech, Batt and Edwards (2017) systematic review and meta-analysis concluded that it is not possible to determine the effect of running on the knee OA with current evidence.

2.11.2.6 *Muscle Weakness*

Longitudinal studies have shown that quadriceps weakness is a risk factor for knee OA (Brandt et al., 1999; Hootman, Fitzgerald, Macera, & Blair, 2004; Slemenda et al., 1998) and is common in individuals with knee OA (Alnahdi, Zeni, & Snyder-Mackler, 2012; Lewek, Rudolph, & Snyder-Mackler, 2004b). Furthermore, a recent study showed that quadriceps weakness is a predictor of symptomatic knee OA, but not radiological knee OA (Segal et al., 2009). It might be argued that muscle weakness may be due to disuse atrophy (Baker et al., 2004). However, individuals with radiological OA without knee pain or quadriceps mass loss have shown a reduction in the quadriceps muscle strength (Slemenda et al., 1997). A relatively small improvement in quadriceps strength (approximate mean of 25% for females and 20% for males) was estimated to cause a 20% to 30% decrease in the odds ratio of having knee OA (Slemenda et al., 1997). Moreover, recent systematic review supported that quadriceps weakness is a risk factor for developing knee OA (Øiestad, Juhl, Eitzen, & Thorlund, 2015).

The local biomechanical factors all predispose the individual to having a greater chance of developing OA, but when the disease is present, mechanical progression is the rule (Felson, 2013). Therefore, an understanding of the biomechanics of individuals with OA is necessary to determine which treatments for the individual are required.

2.12 Biomechanical changes in knee OA

Biomechanics as a word consists of two parts: 'bio' which refers to the living body, and 'mechanics' which refers to forces acting on objects and the consequence of this force in term of movement and equilibrium (Rau, Disselhorst-Klug, & Schmidt, 2000). Therefore, biomechanics as whole means the application of mechanics and its principles in the human body. Biomechanics of movement is the implementation of Newton's laws with regard to the neuromuscular system, which include the forces that cause movement and the inner forces that act within our body (Rau et al., 2000; Rose & Gamble. 2006). Before discussing the biomechanical gait changes that occur in individuals with knee osteoarthritis, typical biomechanical gait patterns will be discussed.

2.12.1 Walking gait cycle

As the human body moves forward, one of the lower limbs act to support the body, while the other advances itself forward to a new position, and then the limbs reverse their functions. This reciprocal event is repeated by each limb until the body reaches its final destination. A single sequence of these events (support time, forward movement time) is defined as a gait cycle (see Figure 2-2). The gait cycle is divided into two phases; stance phase, which starts as soon as the foot comes into contact with the ground, until the foot leaves the ground, and this consists 60% of the gait cycle; and swing phase, which represents the period when the foot is in the air, consisting 40% of the gait cycle (Kharb, Saini, Jain, & Dhiman, 2011).

The stance phase can be subdivided into three parts, starting with early-stance, mid-stance and finally late-stance. The three parts occur from 0% to 20%, 21% to 40% and 41% to 60% for the stance phases respectively. During the stance phase, five events occur respectively, which are the following heel strike (HS), foot flat (FF), mid-stance (MS), heel rise (HR) and finally toe-off (TO). During the swing phase, three events occur, which are initial-swing, mid-swing and terminal-swing respectively (Levine, Richards, & Whittle, 2012; Perry, Burnfield, & Cabico, 2010).

In each stance phase there are one period of single leg support and two periods of double leg support (10% each). However, the proportion of stance phase and swing phase varies with increases in speed. As the speed increases, the swing phase increases and the stance phase and double support period decreases. The stance and the swing phases can be divided into eight functional sub-phases; initial contact, loading response, mid-stance, terminal stance, pre-swing, initial-swing, mid-swing and terminal-swing (Levine, Richards, & Whittle, 2012; Perry, Burnfield, & Cabico, 2010). Each of the previously (eight) mentioned sub-phases has a functional goal, which is accomplished via a critical pattern of synergistic motion. The consecutive combination of the sub-phases also allows the limb to achieve three basic functions. The first one is weight acceptance (WA), which occurs in the first two sub-phases, the second one is single limb support (SLS) which happens in the next two sub-phases, and the third one is limb advancement (LA) which occurs in the last four sub-phases (Kharb et al., 2011; Perry, 1992, Perttunen, 2002).

At initial contact, the foot contact by the heel, the hip in flexed, the knee is extended while the ankle in dorsiflexion to neutral position. During the first 10% of the gait cycle (double limb support) the body mass is hold by hip flexion, knee flexion and ankle neutral position in order to absorb the shook. Then the body mass is progressively controlled in first period of single leg support (10-50%) by hip extension, knee extension and ankle dorsiflexion. In the second period of double support which starts from 50 % to 60%, the body weight starts to be transferred to the contralateral limb by hip and knee flexion and ankle plantarflexion. In the early swing phase (60% -75%), the hip and the knee reach the maximum flexion angle while the ankle is in planter flexion as the weight transferred to the other limb. In the mid swing (75%- 85%) the knee starts to extend and the ankle start to dorsiflex while the hip remains in extension until the tibia reach vertical position. Finally, in the terminal swing, the limb progression is completed by knee extension and the hip reached its earlier flexion and the ankle in dorsiflexion to neutral position (Kharb et al., 2011; Perry et al., 2010).

Each stride includes continuous changes in the alignment between the body and the supporting leg throughout stance, and the advancement of the leg throughout the swing phase, in order to deliver the required basic functions necessary for walking. These responses result in sequences of motion patterns being accomplished by each joint (hip, knee, ankle) (Kharb et al., 2011).
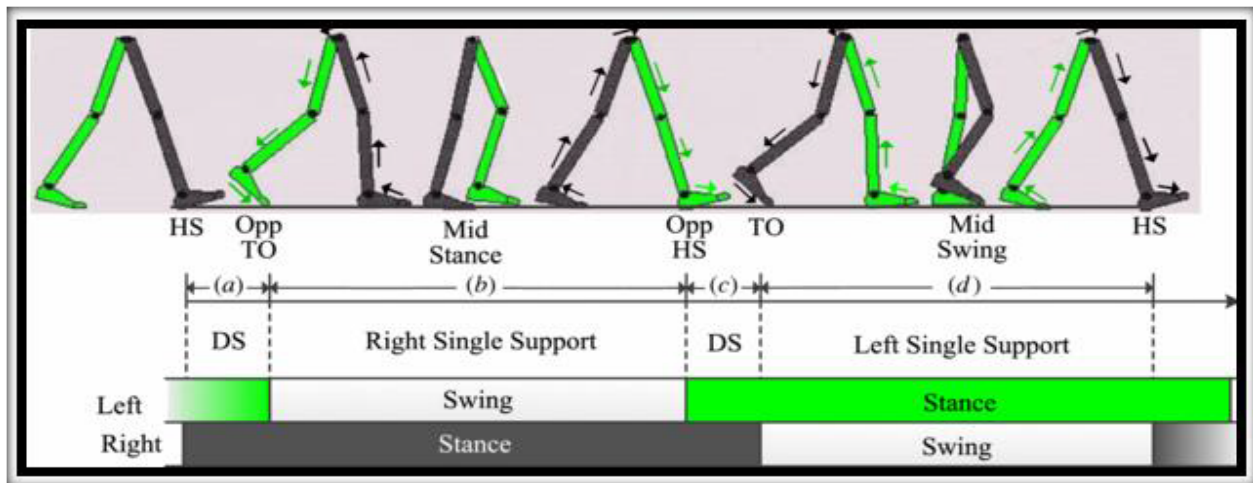
Figure 2-2 Walking gait cycle (Meng, Zhang, Sun, Wu, & Wong, 2012).

Several studies have investigated the impact of knee OA on gait characteristics and will be discussed in the following section.

2.12.2 Biomechanics of medial knee OA

2.12.2.1 Knee OA spatiotemporal, kinematics and kinetics

Studies into knee OA have shown that individuals with knee OA have shorter step lengths, slower walking speeds, longer double support periods, and a reduction in both knee and hip range of motion angle (Al-Zahrani & Bakheit, 2002; Andriacchi, Ogle, & Galante, 1977; Baliunas et al., 2002; Brinkmann & Perry, 1985; Kaufman, Hughes, Morrey, Morrey, & An, 2001b; Messier, Loeser, Hoover, Semble, & Wise, 1992; Messier et al., 2005).

Stance time has also been shown to increase (Al-Zahrani & Bakheit, 2002; Astephen, Deluzio, Caldwell, & Dunbar, 2008; Landry, McKean, Hubley-Kozey, Stanish, & Deluzio, 2007), whereas cadence and stride length were decreased compared to the control group (Al-Zahrani & Bakheit, 2002). Furthermore, individuals with knee OA have increased mid-stance external knee adduction moments as well as decreased peak knee flexion moments, peak hip adduction moments and peak hip extension moments compared to an age-matched control group (Astephen et al., 2008).

As proposed by Mündermann et al. (2005), reductions in walking speed in individuals with knee OA is probably in order to reduce knee load (Mündermann, Dyrby, & Andriacchi, 2005).

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Mündermann et al. (2005) states that the secondary gait changes noticed in individuals with knee OA reflect a possible technique used to shift the load quickly from the contralateral leg to the supported one. The study showed that individuals with medial knee OA landed in a more extended knee, had greater vertical GRF loading rate, had higher knee and hip abduction moment, indicating lateral shifting in the truck and rapid shifting in weight from contralateral limb to the supported limb. This strategy was successful in reducing the knee joint loading in individuals with less severe OA, but not the severe group. Mundermann et al. (2005) stated that increasing the loading rate in the knee, hip and ankle joints may increase progression of knee OA and lead to the onset of OA in the adjacent joints. Supporting evidence has also showed that 90% of individuals with medial knee OA had contralateral knee OA or went onto develop it within 10 years (Jones et al., 2013). In individuals with unilateral knee OA, the peak hip and knee flexion angle have been seen to reduce significantly compared to the non-affected side during early-stance during walking (Briem & Snyder-Mackler, 2009).

The knee joint plays an important role in absorbing the load generated when the leg comes in contact with the ground at early-stance at approximately 15 degrees of flexion. The faster the body moves, the higher the force, which requires the knee to move into more flexion to absorb the load (Winter, 1991). This increase in knee flexion depends on the eccentric contraction of the quadriceps muscles (Winter, 1983), which have been found to be weak in individuals with knee OA (Slemenda et al., 1997). Another mechanism that has been proposed to increase the compressive knee load is to increase the muscle co-contraction, which is found to increase in individuals with knee OA (Lewek, Rudolph, & Snyder-Mackler, 2004a). Additionally, higher walking speeds cause higher muscle co-contraction in individuals with knee OA (Zeni, Rudolph, & Higginson, 2010). Therefore, individuals with knee OA might additionally use this reduced speed strategy to reduce the knee joint load.

A reduction in maximum knee flexion angle (Astephen et al., 2008; Childs, Sparto, Fitzgerald, Bizzini, & Irrgang, 2004; Lewek et al., 2004; Schmitt & Rudolph, 2007) and knee external rotation moment (Landry et al., 2007) through the early-stance phase has also been identified in individuals with knee OA. Several reasons have been proposed as causes of such as pain (Kaufman et al., 2001), quadriceps weakness, landing on extra-flexed knee during initial contact (Childs et al., 2004), and knee instability stiffness strategy (Schmitt & Rudolph, 2007). Childs et al. (2004) stated

that a reduction in the sagittal plane range of motion (stiff knee) occurs when an individual lands on the more flexed knee, which leads to higher muscle co-contraction and, consequently, to higher loading as the contact area in the knee is smaller as well. A reduction in peak knee flexion moment during early and late-stance has also been identified (Astephen, Deluzio, Caldwell, Dunbar, & Hubley-Kozey, 2008; Baliunas et al., 2002; Kaufman et al., 2001b; Rudolph, Schmitt, & Lewek, 2007), which is believed to be a strategy used to reduce the knee joint load and therefore reduce pain during knee extension, as it demands less eccentric quadriceps contraction.

In individuals with medial knee OA, several biomechanical changes have been proposed to directly linked to increasing the medial compartment load or the progression of disease and this will be discussed in the following section.

2.12.2.2 *External knee adduction moment*

Previous literature has shown that the medial compartment is affected more than the lateral compartment (Bartel, 1992; Dearborn, Eakin, & Skinner, 1996; Hasan & Shuckett, 2010; Wise et al., 2012) by a factor of 4 to 10 times (Ahlbäck, 1968; Ledingham et al., 1993). One of the potential reason for the more common of medial compartment OA that the medial compartment bears higher loads during activities like walking and climbing stairs than the lateral compartment (Hurwitz, Ryals, Case, Block, & Andriacchi, 2002). The higher load on the medial compartment results from the way that the line of gravity passes through the medial compartment to the centre of the knee joint (Johnson, Leitl, & Waugh, 1980; Schipplein & Andriacchi, 1991). During walking, the medial compartment bears around 2.5 times higher load than the lateral compartment (Schipplein & Andriacchi, 1991).

The force distribution of the knee joint between the lateral and the medial compartments relies on two factors: the magnitude of the external abduction and adduction moments acting about the joint (Hurwitz et al., 1998; Schipplein & Andriacchi, 1991) and the contribution of the forces of the ligaments and muscles balancing the moment.

Therefore, evaluating the effects of biomechanical factors (i.e. loading) on knee OA progression are important. The gold standard method to measure the medial loading compartment loading during activity is to use the knee implantation; however, this method is impractical and invasive

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(Chang et al., 2015). The other method is to use indirect measurement of the medial compartment loading such as the External Knee adduction moment (EKAM) (Figure 2-3). EKAM can be defined as the turning moment (torque) acting on the shank due to a ground reaction force passing medially to the knee joint centre and it is argued that 60% to 80% of the knee compression load is distributed to the medial side of the knee joint by the knee adduction moment (Andriacchi, 1994).
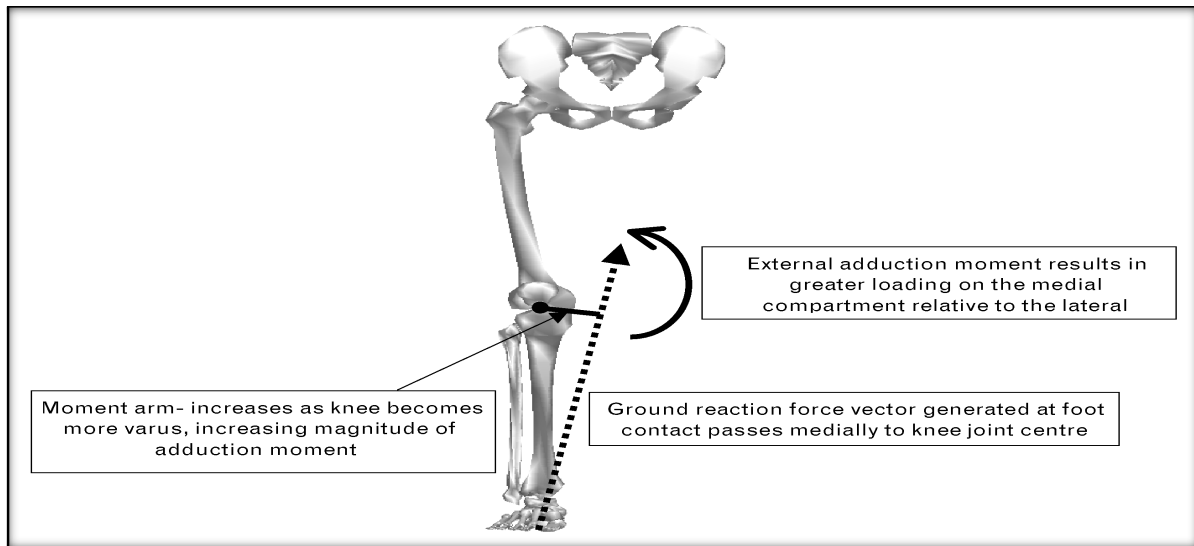
Figure 2-3 External knee adduction moment (Hinman & Bennell, 2009).

The perpendicular distance from the centre of the joint to the ground reaction force is called the moment arm. The product of multiplying the force by the moment arm is the adduction moment, which moves the knee inward (adduction). External forces, including the EKAM, can be measured by using a force plate to measure the ground reaction force accompanying the motion analysis system (Kim et al., 2004). The EKAM consists of two peaks and one trough (Figure 2-4). The first peak occurs during early-stance between 0-20% of the gait cycle, followed by the trough which occurs during mid-stance between 21-40% of the gait cycle, and the second peak takes place in the late-stance between 41-60% of the gait cycle (Hurwitz, Ryals, Case, Block, & Andriacchi, 2002; Newell, Hubley-Kozey, Stanish, & Deluzio, 2008).
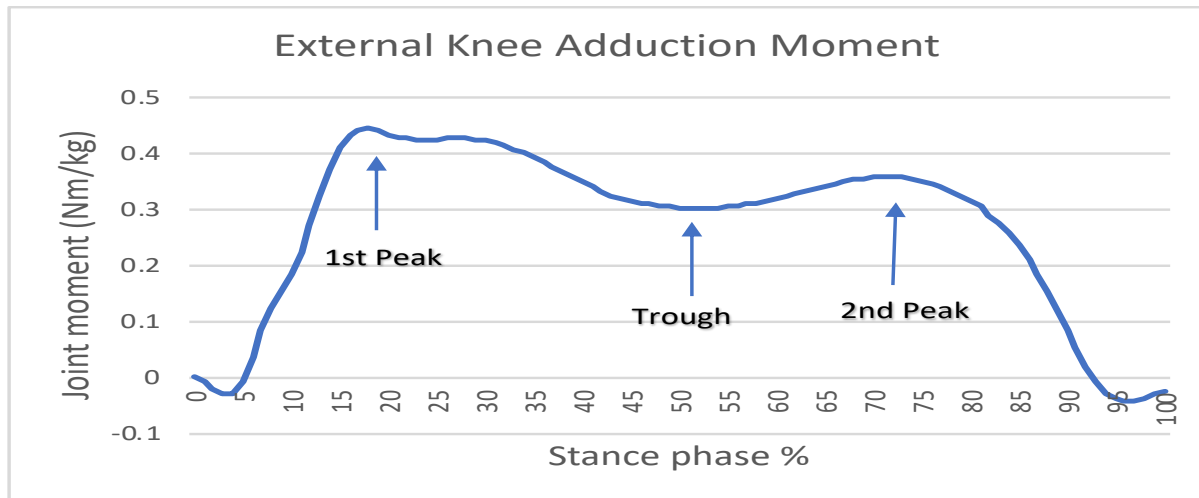
Figure 2-4 EKAM graph during walking.

Individuals with knee OA tend to walk with greater external knee adduction moments than individuals without knee OA; this adds an extra load to the medial side (Schipplein & Andriacchi, 1991; Sharma et al., 1998).

Several studies have investigated the difference in EKAM between individuals with knee OA and healthy which will be discussed next.

2.12.2.3 *Knee OA and EKAM*

Several characteristics of the EKAM outcome variables (1st peak, trough, 2nd peak, maximum) have been investigated in previous knee OA studies (Baliunas et al., 2002; Huang et al., 2008; Hurwitz et al., 2002; Kim et al., 2004; Mündermann, Dyrby, Hurwitz, Sharma, & Andriacchi, 2004; Rudolph, Schmitt, & Lewek, 2007; Thorp et al., 2006).

Baliunas et al. (2002) and Hurwitz et al. (2002) showed that the peak EKAM is higher in individuals with medial knee OA compared to healthy when matching for speed. Additionally, EKAM was found to be higher than three groups of healthy participants (young, middle, elderly) (Rudolph et al., 2007) with further research showing that individuals with mild and severe OA predominant in the medial compartment had higher peak EKAM across the stance and 1st peak EKAM than healthy (Thorp et al., 2006).

In the mid-stance phase, trough EKAM presented similar results to 1st peak EKAM showing higher value in individuals with severe (Huang et al., 2008) and mild to moderate (Landry et al., 2007) knee OA than healthy individuals. Furthermore, individuals with severe knee OA were found to walk with higher second-peak EKAM than healthy people did (Huang et al., 2008; Thorp et al., 2006). Kim et al. (2004) developed a new technique for assessing the EKAM in individuals with knee OA. The new method is called the single leg stance EKAM as a measurement for loading. The rationale for using this technique is that, during walking, EKAM can be affected by several factors, such as walking speed, the toes' outward angle, stride length and deviation of the trunk toward the effected limb. Using a single leg stance would eliminate the effect of compensatory mechanisms while allowing EKAM measurement. The results of the study showed that the maximum, minimum and average EKAM during single leg stance are higher in individuals with knee OA than the measurements are in healthy people. Interestingly, a previous study showed that individuals with more severe knee OA had more varus and higher maximum EKAM than less severely affected individuals did (Mündermann et al., 2004). Therefore, mid-stance EKAM (from 34% to 67% of the stance phase) and second-peak EKAM (from 68% to 100% of the stance phase) should also be considered when conducting a study.

Contradicting results to the previous studies showed that individuals with mild knee OA has no significant difference in maximum EKAM (Mündermann et al., 2004), trough (Huang et al., 2008) and 2nd peak (Huang et al., 2008; Thorp et al., 2006) than healthy. Moreover, individuals with more severe knee OA were found to has lower 2nd peak EKAM than healthy (Astephen, Deluzio, Caldwell, Dunbar, et al., 2008). A recent systematic review and meta-analysis investigated if individuals with medial knee OA exhibit gait changes including higher EKAM than healthy (Mills, Hunt, & Ferber, 2013). The study concluded that there is a lack in the evidence to support that individuals with knee OA show higher EKAM than healthy. The authors stated that gait modification adopted by some individuals with knee OA could be the cause for this.

The contradiction in previous literature regarding the difference between the individuals with knee OA and healthy in respect to the different characteristics of EKAM variable outcomes may be due to different reasons. Individuals with mild knee OA may adopted strategies to reduce the knee loading via truck lean or any other gait modification in order to reduce the EKAM and therefore it is important to separate individuals based on severity to see difference compared to healthy (Mills

et al., 2013; Mündermann et al., 2005). Walking speed is an important factor affecting EKAM as an increase the walking speed results in higher EKAM because EKAM is the product of GRF and moment arm (Mündermann et al., 2004). Therefore, self-selected speed and other confounder factors (age, MBI) should be controlled between the groups to see difference. Previous studies have showed that the statistical difference in trough EKAM between individuals with knee OA and healthy diminished after asking participants in both group to walking at faster speed (Landry et al., 2007). The variation in the selection criteria could be another potential factor as some studies used the ACR criteria and others have used radiological criteria specifying that only medial compartment participants included. Therefore, only individuals with medial compartment may show this high EKAM to healthy and not in individuals with patellofemoral compartment or OA in more than one compartment on radiograph.

Although the EKAM (first peak, trough, second peak) has been used often in previous studies, it represents joint loading at only a specific part of the stance phase and this may have been the reason why it has not been able to differentiate between individuals with severe and mild knee OA. Therefore, it is necessary to use an outcome that can reflect loading during the whole of the stance phase.

2.12.2.4 *External knee adduction angular impulse*

In 2006, a team of researchers were the first to adopt a new variable, used previously in running literature by Stefanyshyn, Stergiou, Lun, Meeuwisse and Worobets (2006) for characterising the EKAM in knee OA (Thorp et al., 2006). This variable is called the knee adduction angular impulse (KAAI), which represents both the duration and the magnitude of the EKAM during the stance phase (area under the curve in the positive side only) (see Figure 2-5). KAAI represents the adduction moment in the whole stance phase, and not at specific times, as first or second peak EKAM. KAAI has been identified as being a more sensitive variable for identifying the difference between moderate and mild radiological OA than EKAM. In contrast, peak EKAM during early-stance has not been able to identify the differences between mild and moderate knee OA groups (Kean et al., 2012; Thorp et al., 2006). This might be attributed to the slower walking speed as the disease progression correlated with speed with more severe knee OA showing lower speed. Therefore, once the speed is reduced the stance time is increased and the KAAI is increased.

Individuals with knee OA showed higher KAAI than healthy individuals in previous studies (Landry et al., 2007; Linley, Sled, Culham, & Deluzio, 2010; Newell et al., 2008). Furthermore, Thorp et al. (2007) found higher KAAI in symptomatic knee OA individuals compared to asymptomatic and healthy participants as well (Thorp, Sumner, Wimmer, & Block, 2007).
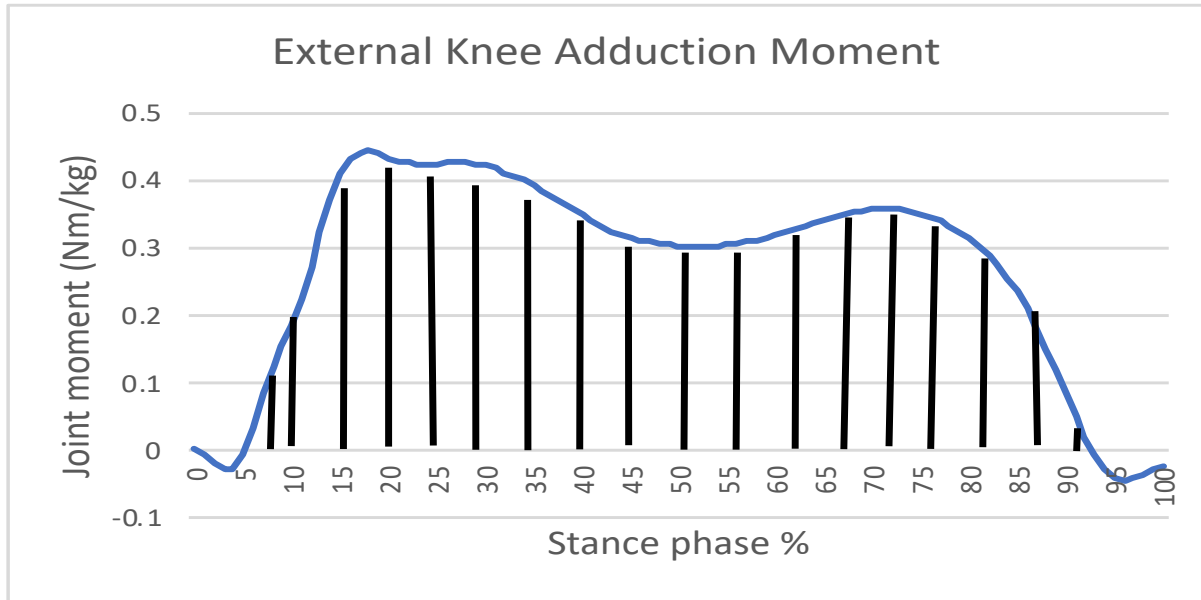
Figure 2-5 External knee adduction angular impulse (KAAI) graph. KAAI represented by the shaded area

Several studies have investigated the use of EKAM and KAAI as indirect measurements for loading and relationship between EKAM and symptoms and progression of the disease which will be discussed next.

2.12.2.5 *EKAM relationship with load*

Several studies attempt to investigate the relationship between the EKAM and the knee loading among healthy and individuals with knee OA. In 1991, Schipplein and Andriacchi used a musculoskeletal model to predict the knee loading in healthy and participant with knee varus deformity and OA. The study showed that in individuals with a varus deformity and OA had higher medial compartment loads than healthy individuals. This higher load tends to open the lateral compartment and EKAM was found to correlate with the lateral to medial load distribution. The study concluded that EKAM can be used to estimate the distribution of the force in the knee during walking.

The study showed that EKAM as the main determinate not only for total load across the knee joint, but also for lateral-to-medial load distribution. To test the validity of prediction of the knee dynamic load based on gait characteristics Hurwitz et al. (1988) conducted a study. The study measured the gait characteristics and bone density dual energy x-ray absorptiometry to 28 healthy participants. The result showed that peak EKAM is the best predictor variable for medial to lateral knee load distribution ratio (R^2 =0.31) which lead the authors to concluded EKAM is a valid outcome to predict the medial to lateral force distribution. Others studies showed similar results regarding the EKAM and showing that EKAM is the single best predictor for proximal medial and lateral tibial bone density in individuals with knee OA (Thorp et al., 2006; Wada et al., 2001).

In one participant with an implanted knee tray two studies investigated the relationship between EKAM and the knee load (Mündermann, Dyrby, D'Lima, Colwell, & Andriacchi, 2008; Zhao et al., 2007). Both studies used similar method in which the tray only measure the total load and therefore dynamic contact model was needed to investigate the distribution of the load between the knee compartments. Zhao et al, (2007) found that at 20% of the gait cycle, a high proportion of the load (70%) is transmitted by the medial compartment. Furthermore, a significant strong correlation was identified between the peak EKAM and the medial contact force ($R^2 = 0.77$) and medial to total force ($R^2 = 0.69$) across the gait cycle. Mundermann et al. (2008) stated that in most activities (walking, squatting, stair ascending, stair descending, golf swings, sit to stand, stand to sit) greater load is placed in the medial compartment. Interestingly, the medial to lateral knee load ratio in peak compressive force was found to be 1.7 during walking (Mündermann et al., 2008). More recently, a study investigated the relationship between EKAM and medial loading across 9 subjects and 10 activities (Trepczynski et al., 2014). All subject had an implant tray and the results showed significant strong correlation across subjects and activities with R^2 equal to 0.88. All previous study supports that EKAM is valid surrogate measurement to measure the dynamic loading in medial compartment. Zhao et al. (2007) stated that the load distribution between the medial and the lateral knee compartments is likely to depend on the limb alignment and other characteristic which influence EKAM.

2.12.2.6 *EKAM and relationship with clinical symptoms*

If loading is greater on the knee joint, one may infer that the pain would also be greater. A recent study investigated the effect of EKAM on pain and found that individuals with bilateral medial knee OA had higher pain in the limb with the higher EKAM. The odds ratio of pain after walking was found to increase by 3.05 with between limb EKAM difference higher or equal to 1.0 %BW*Ht (Marriott et al., 2017). Interestingly, in a study which included 132 elderlies, individuals who developed knee pain after 3 to 4 years had higher baseline peak EKAM by 8% to 39% than the individuals who did not develop knee pain (Amin et al., 2004). In individuals with medial knee OA the first peak EKAM also showed a significant correlation with the total WOMAC with an R equal to 0.33 (Hurwitz et al., 2002). In similar population (medial knee OA) Miyazaki et al. (2002) also showed a significant relationship between pain and EKAM (R=0.33). However, both of these studies did show weak correlations. Stronger correlations were found between WOMAC pain (R=0.63), WOMAC function (R=0.66), total WOMAC (R=0.63) and mean single leg EKAM in individuals with medial knee OA (Kim et al., 2004). Further, Thorp et al. (2007). showed that symptomatic individuals with knee OA grade 2 had higher peak EKAM and KAAI than asymptomatic individuals with knee OA grade 2 or healthy individuals.

Interestingly, EKAM was identified to be a predictor of clinical outcomes of high tibial osteotomy (Prodromos, Andriacchi, & Galante, 1985). Follow up (3 to 8.9 years) with the same groups of patients revealed that 9 of the 14 patients in the high adduction moment group and 3 of the 14 in the low adduction moment group had a varus deformity on the back before surgery (Wang, Kuo, Andriacchi, & Galante, 1990).

All previous studies support that notion that increase pain is correlated to an increase in the EKAM and this could be due the higher load. The previous claim is supported by studies which showed that using intra-articular pain relief in individuals with knee OA lead to further increases in the knee loading (EKAM) (Henriksen et al., 2006; Paoloni et al., 2012; Schnitzer, Popovich, Andersson, & Andriacchi, 1993). In 2009, a systematic review included 14 studies concluded that the 1st peak EKAM is correlated with WOMAC total score and WOMAC pain score is correlated with the mean EKAM in individual with medial knee OA (Foroughi et al., 2009).

2.12.2.7 *EKAM and OA progression*

One of the earlier studies which aimed to investigate the relationship between EKAM and knee OA progression was Miyazaki et al., (2002), who assessed the EKAM for 106 participants with medial knee OA at baseline. Of those 106, 76 participants were reassessed after 6 years. The results showed a significant negative correlation between the EKAM and knee joint space widths and positive correlation between EKAM and the mechanical axis (varus alignment) after 6 years. Furthermore, the risk of the knee OA progression was found to increase by 6.46 times with a 1 unit increase in the EKAM. In 12 healthy participants. Koo and Andriacchi (2007) showed that the peak adduction moment correlated significantly with the ratio of medial to lateral cartilage in the tibial (R^2=0.32) and femur (R^2=0.43). Furthermore, a significant correlation was found between loss of knee cartilage volume over 12 months and the KAAI (Bennell et al., 2011). Since EKAM and associated variables have been shown to be an indicator of the knee OA progression, the reduction in these variables must be achieved if one is aiming to reduce the progression of the disease.

However, Walter et al, (2010) stated that the reduction of the EKAM alone does not always guarantee the reduction in medial joint loading and this is likely to be due to the increase in knee flexion moment (KFM) which might reduce the benefit of reducing the EKAM. However, this study only included one participant with an implanted knee plate tray, and with the knee in neutral alignment, which likely reduces the generalisability of the result. Furthermore, individuals with medial knee OA has varus alignment (Sharma et al., 2001) and this might cause different results. In 2014, a study showed that both peak EKAM and the KFM has an effect of knee joint progression (R^2=0.60), however this was in two different anatomical sites. The study found that KFM has an effect of the tibial cartilage while EKAM has an effect on femoral cartilage (Chehab, Favre, Erhart-Hledik, & Andriacchi, 2014). The previous studies highlight the importance of considering the change in the KFM when investigating the effect of any treatment in EKAM

In contrast to the previous studies (Chehab et al., 2014; Walter, D'Lima, Colwell, & Fregly, 2010) recent studies investigated the relationship between the knee OA progression and other biomechanical factors (KAAI, EKAM, KFM) over two year (Chang et al., 2015). This large (212 knee OA) longitudinal cohort study with participant recruited from community allowed for

adjustment for confounder factors which increase the generalisability of the study. The result showed that peak EKAM and KAAI at baseline were significantly correlated with disease progression. However, peak KFM did not showed any significant correlation with joint space narrowing, cartilage damage, medial or lateral tibial surface damage.

In summary and based on the previous studies EKAM is an important measurement for the load distribution, the knee OA progression, and symptoms. Therefore, in order to reduce the progression of the knee OA and reduced the symptoms EKAM should be targeted (reduced). Furthermore, KFM does have less evidence supporting it but this should not be neglected in clinical trials. Additionally, Trepczynski et al. (2014) highlighted that estimating the change in medial contact force depending solely on the EKAM may be less accurate in presence of muscle co-contraction. The higher levels of intersegment force could also be due to higher muscle co-contraction, even in cases of the same external moment and joint forces, as calculated by the inverse dynamics theory (Lu, Taylor, O'Connor, & Walker, 1997). Therefore, it is important to understand the role of internal forces (muscles) in the knee loading and the change in co-contraction with treatment.

2.13 Muscular response

Several studies have identified neuromuscular alterations in individuals with knee OA. These alterations include prolonged activity duration in vastus lateralis (VL), medial hamstrings (MH), medial gastrocnemius (MG) and tibialis anterior (TA) (Childs et al., 2004) and increased co-contraction between VL/MH, TA/MG (Childs et al., 2004), vastus medialis (VM)/MG (Lewek et al., 2004a) VL/lateral hamstring (LH), VM/MG (Ramsey, Snyder-Mackler, Lewek, Newcomb, & Rudolph, 2007). This emphasises the importance of considering the role of internal forces in producing joint loading especially when assessing biomechanical treatments to reduce joint loading.

2.13.1 Muscle co-contraction

Muscle co-contraction refers to the concurrent recruitment of synergic muscles (Sirin & Patla, 1987), where the term "synergic muscle" refers to all muscles around the joint that contribute towards generating a moment of force during dynamic activities (Nigg, MacIntosh, & Mester, 2000). Increased medial muscle co-contraction has been correlated with medial cartilage volume

loss rates in individuals with knee OA and varus alignment (Hodges et al., 2015). It is believed that increased muscle co-contraction comes at the expense of higher joint loading (Hubley-Kozey, Hatfield, & Stanish, 2013; Lloyd & Buchanan, 2001; Meyer et al., 2013; Schipplein & Andriacchi, 1991) and associated OA risk (Heiden, Lloyd, & Ackland, 2009; Wu, Burr, Boyd, & Radin, 1990; Zeni et al., 2010). Recent studies have concluded that a careful selection of muscle co-contractions (VM/MG) can be used to represent medial joint loading (Winby, Gerus, Kirk, & Lloyd, 2013).

Three justifications for altered neuromuscular responses in OA have been identified; Firstly, higher lateral muscle co-contraction to oppose the high medial joint loading (Andriacchi, 1994); secondly, higher medial joint muscle co-contraction in response to greater joint space narrowing (laxity) (Lewek et al., 2004a); thirdly, higher medial joint muscle co-contraction in response to instability concomitant with medial joint space narrowing (Childs et al., 2004).

There are two types of muscle co-contraction; the first one is generalised co-contraction, while the second one is directed co-contraction (Lloyd & Buchanan, 2001). In the former, all agonist and antagonist knee activities are equal, whereas in the latter the lateral agonist and antagonist co-contract to support the external knee adduction moment. Direct co-contraction is thought to be important in supporting the external knee adduction moment to prevent lateral condyle lift off and reduce the force concentration on the medial side (Schipplein & Andriacchi, 1991). The generalised co-contraction can have the same effect as direct co-contraction, but due to the non-directionality, it is less effective in preventing condyle lift off and may excessively increase the articular loading (Andriacchi, Andersson, Ortengren, & Mikosz, 1984; Lloyd & Buchanan, 2001; Zhang, Xu, Wang, & Hendrix, 2001). Co-contraction has been noticed during crossover cutting and sidestepping (Besier, Lloyd, & Ackland, 2003a; Besier, Sturnieks, Alderson, & Lloyd, 2003b), when individuals support isometric abduction/adduction moment (Lloyd & Buchanan, 2001; Zhang et al., 2001). Direct co-contraction has been identified as resisting adduction/abduction perturbations at the knee in ligamento-muscular reflexes (Buchanan, Kim, & Lloyd, 1996). Nevertheless, voluntary direct co-contraction has been revealed to support static knee abduction/adduction moment (Andriacchi et al., 1984; Zhang et al., 2001), and during side stepping it supports abduction moments (Besier et al., 2003a, 2003b).

Several studies have investigated the muscle activities and co-contraction in individuals with knee OA. These studies show higher co-contraction in individuals with OA in the medial side and lateral side of the knee joint compared to the control group. The lateral co-contraction occurs between the following muscles: lateral quadriceps (LQ)/semimembranosus (SM) (Zeni et al., 2010), VL/MH (Childs et al., 2004), TA/MG (Childs et al., 2004), biceps femoris (BF)/VL (Hortobágyi et al., 2005), lateral gastrocnemius (LG)/TA (Hortobágyi et al., 2005), VL/LH (Hubley-Kozey, Hill, Rutherford, Dunbar, & Stanish, 2009; Ramsey et al., 2007), VL/LG (Hubley-Kozey et al., 2009), LQ/LH (Schmitt & Rudolph, 2007); while the medial co-contraction is between the following pairs: medial quadriceps (MQ)/MG (Rudolph et al., 2007; Schmitt & Rudolph, 2007), VM/MG (Lewek, Ramsey, Snyder-Mackler, & Rudolph, 2005; Lewek et al., 2004a), VM/MH (Hubley-Kozey et al., 2009), and MQ/MH (Schmitt & Rudolph, 2007).

Other studies have shown no significant differences between the OA group and control group regarding muscle co-contraction. This is between the following muscles: VL/SM (Collins, Richardson, & Higginson, 2014), BF/VM (Liikavainio, Bragge, Hakkarainen, Karjalainen, & Arokoski, 2010), VM/MH and VL/LG (Lewek et al., 2004, 2006; Ramsey. et al., 2007), VL/LH (Lewek et al., 2004, 2006), and LQ/LG, LQ/LH, MQ/MG, MQ/MG (Rudolph et al., 2007). This contradiction between the results might be due to different factors, such as differences in age, disease severity, muscle weakness, knee alignment, and walking speed.

Muscle co-contraction has been found to increase with age. Greater disease severity has shown higher co-contraction between VL/LH, VL/LG , VM/VM , VM/MG compared to controls, while the less severe group only showed VL/LH higher than the control group (Hubley-Kozey et al., 2009). Child et al. (2004) have shown that co-contraction increases significantly between self-selected and fast walking speeds. Quadriceps weakness is correlated with higher VM/MG and VM/MH co-contraction before the knee malalignment correction, but not afterwards (Ramsey et al., 2007). Nevertheless, other factors such as knee laxity show correlations with VM/MG and EKAM (Lewek et al., 2004a). Self-reported instability in individuals with OA, which affects their activities of daily living (ADL), showed higher medial co-contraction than individuals with no or with instability not affecting ADL (Lewek et al., 2005).

As the OA progresses, the medial compartment degenerates and the space between the two medial condyle reduces, which can lead to laxity in the medial soft tissue, reducing its contribution to joint stability (Lewek et al., 2004; Sharma et al., 1999). This impairment to passive stabilisation increases the demand on active stabilisation (muscle co-contraction) to compensate for the lack of stabilisation. The inability of the active stabiliser to perform this mission has been hypothesised to lead to frequent episodes of joint instability and additional degeneration changes (Lewek et al., 2004; Sharma et al., 1999). Studies on knee OA with laxity has been reported to increase the medial thigh and shank muscles' co-contraction. This highlights the importance of laxity as one of the main causes of increased muscles co-contraction (Lewek et al., 2004a; Rudolph et al., 2007).

A recent study was conducted to investigate the correlation between joint loading, muscle co-activation and joint moment, using an electromyography-driven model. The results show that only the sum of the activation measurements for the medial hamstring and gastrocnemius muscles correlate significantly with medial joint loading. On the lateral side, the sum of both EMG measurements (quadriceps/hamstring), lateral quadriceps/lateral hamstring, lateral quadriceps/lateral gastrocnemius) and activation measurements (lateral quadriceps/lateral hamstring, lateral quadriceps/lateral gastrocnemius) were correlated with loading. Other outcomes (first peak EKAM, peak flexion moment) were correlated with medial and lateral loading, with higher correlation for the former (Winby et al., 2013).

Two peaks have been identified in knee joint contact force during walking (Harrington, 1976; Hurwitz et al., 1998; Morrison, 1970a). The first one occurs at contralateral toes-off, which corresponds to quadriceps muscle action, while the second one, at contralateral initial contact, corresponds to gastrocnemius action. The quadriceps and gastrocnemius muscles are the dominant muscles in resisting the knee external adduction moment. Nevertheless, the quadriceps and gastrocnemius were found to be the main contributors to the joint contact force. Therefore, the previous mentioned explanation of the muscle co-contraction studies should be included as an outcome in intervention studies aiming to reduce medially directed loads.

Muscle weakness is well documented in individuals affected with knee OA in addition to high muscle co-contraction (Alnahdi et al., 2012; Palmieri-Smith, Thomas, Karvonen-Gutierrez, & Sowers, 2010). However, previous studies have showed no correlation between muscle strength

and EKAM (Lim, Hinman, Wrigley, Sharma, & Bennell, 2008). Furthermore, a recent study showed that individualised muscle strength exercises do not reduce the knee loading (EKAM) in individuals with knee OA (Henriksen et al., 2017). However, one of the area's that can be affected by muscle weakness and knee laxity is dynamic balance. Individuals with knee OA suffer from progressive loss in lower extremity tasks, such as walking, and ascending and descending stairs (Guccione et al., 1994). The impact of knee OA on balance may be a possible explanation for the disability in these individuals as balance is a fundamental component of these daily activities and the risk of falling increases with impaired balance (Chuang et al., 2007; Dionyssiotis, 2012; Muir, Berg, Chesworth, Klar, & Speechley, 2010).

2.14 **Balance**

Balance is considered a complex neuromuscular process, which includes motor, sensory and integrated components (Hinman, Bennell, Metcalf, & Crossley, 2002). Balance can be defined as the ability to maintain (control) the centre of gravity provided by the feet. In the elderly population, poor mobility and the risk of falling are associated with reduced balance (Dionyssiotis, 2012; Muir et al., 2010). Balance can be assessed statistically or dynamically. Assessing dynamic balance is more important, since it mimics the demands of physical activities better than using static assessments (Gribble, Hertel, & Plisky, 2012).

Both static and dynamic balance deficits have been identified in individuals affected by knee OA, but dynamic balance deteriorates more (Hinman et al., 2002; Wegener, Kisner, & Nichols, 1997). Balance defects could be related to the ageing process, muscle weakness and/or proprioceptive impairment (Koceja et al., 1999; Lin et al., 2009; Muir et al., 2010; Slemenda et al., 1997; Stevens, Lang, Guralnik, & Melzer, 2008). Although no relationship has been found between balance and progression of knee OA (Jadelis et al., 2001), balance impairment increases the risk of falling and disability in the elderly, and therefore should be assessed (Dionyssiotis, 2012) especially when a new intervention is introduced.

Previous studies have assessed balance by using expensive (force platform) (Hassan et al., 2001; Hurley, Scott, Rees, & Newham, 1997a; Wegener et al., 1997) and non-expensive (step test) measures (Hinman et al., 2002; Lim, Hinman, Wrigley, Sharma, & Bennell, 2008). In the step test the participant is asked to balance on single leg and try to step up and down 15cm step high as fast

as possible for 15 second. The number of times with which the participant is able take the contralateral limb up and down the step is the outcome of the test (K. D. Hill, Bernhardt, McGann, Maltese, & Berkovits, 1996). Previous studies have showed significantly lower number of steps in individuals with knee OA (12 steps) compared to healthy individuals (17 steps) (Hinman et al., 2002). However, the step test is dynamic standing test with two major limitation. Firstly, the step test measures the dynamic balance in one direction (anterior) and secondly the step test neglect the distance between the standing base and the step which might play an important role in balance. Therefore, other methods of measuring dynamic balance is advocated to be used

The Star Excursion Balance Test (SEBT) is an inexpensive and quick method used to assess balance. SEBT is used in laborites and clinics to measure the effect of treatment intervention or to investigate if one returned to normal condition (Gribble et al., 2012). In the SEBT the participant is asked to stand on one leg and using the contralateral leg to reach as far as possible in 8 directions (anterior, medial, lateral, posterior, anterolateral, anteromedial, posteromedial, posterolateral) (Olmsted, Carcia, Hertel, & Shultz, 2002). The distance at which contralateral leg reaches is the outcome of the test. The SEBT might be considered as a challenging test for individuals with knee OA as they are more likely to be elderly and have a balance deficit. SEBT might be more challenging on the neuromuscular system than step test and be considered as true dynamic test. However, one of limitation for SEBT is the length of the testing session if it were tested in all directions (Munro & Herrington, 2010; Robinson & Gribble, 2008).

One of the methods to overcome this problem is to focus on certain direction which focus more on specific muscles (Earl & Hertel, 2001; Herrington, Hatcher, Hatcher, & McNicholas, 2009; Olmsted et al., 2002). In the presence of chronic ankle instability SEBT is recommended to be tested in the medial, posteromedial and anteromedial directions snice these directions were the most affected compared to healthy (Hertel, Braham, Hale, & Olmsted-Kramer, 2006). In individuals following an ACL tear, SEBT is recommended to be tested in anterior, medial, lateral and posteromedial directions as these directions were significantly affect compared to healthy (Herrington et al., 2009). However, in knee OA performing SEBT in anterior and medial directions are the most relevant to this population and proposed to be used in this thesis for two reasons. Present of muscle quadriceps and gluteus muscle weakness in individual with knee OA (Alnahdi,

Zeni, & Snyder-Mackler, 2012; Hinman et al., 2010; Slemenda et al., 1997) and to reduce the risk of falling from performing the test in all directions.

SEBT has shown good reliability in its studies which supports the use of this method (Hertel, Miller, & Denegar, 2000; Kinzey & Armstrong, 1998). SEBT has been used in individuals with knee OA to assess the effect of exercise and valgus knee braces (Al-khlaifat, 2012; Al-Zahrani, 2014), however it has not been used to assess other conservative approaches in knee OA patients.

2.15 Physical function tests

The ability to perform daily activity (physical function) is considered one of the main outcomes for individuals with knee and hip osteoarthritis (Bellamy et al., 1997). Physical activities are concerned with ability to move around and perform the daily activities. Assessing physical function test using performance–based tests are often assessed by measuring the time, distance or repetitions methods and are assessor observed (Stratford, Kennedy, Pagura, & Gollish, 2003; Wright, Hegedus, Baxter, & Abbott, 2011). They assess what each individual can do rather than how precise he/she can do, which is measured by using the patients reported outcomes (Terwee, Mokkink, Steultjens, & Dekker, 2006). Patient performance test is recognised to measures different construct component of physical function than patient reported outcome (Stratford & Kennedy, 2006; Terwee et al., 2006) and the former may be better in differentiating between function and pain than using patient report outcome (Faucher et al., 2002; Stratford, Kennedy, & Woodhouse, 2006; Thumboo, Chew, & Soh, 2001). Undestanding the effect of disease on functional impairment is impotent to better understanding the functional ability of the patients.

The Osteoarthritis Research Society International (OARSI) in 2013 developed a recommended set of physical function tests for testing the physical ability of the individuals with knee osteoarthritis individuals (Dobson et al., 2013). The minimal number of core set of tests which should be used in any knee OA study are three (40-metre fast-paced walk test, 30-second chair-stand test, a stair-climb test). 30-second chair-stand test, 40-metre fast paced walk test and stair-climb test have been used in previous studies to test the effect of the treatment in individual with knee osteoarthritis (Dobson et al., 2013). The reliability for such outcome measurement were encouraging (Gill & McBurney, 2008; Kennedy, Stratford, Wessel, Gollish, & Penney, 2005; Wright, Cook, Baxter, Dockerty, & Abbott, 2011). 30 second chair test showed high Intra-class Correlation Coefficient

(ICC) ranging between ICC=0.93 to 0.98 (Gill & McBurney, 2008). While stair-climb test showed 0.90 ICC and identified to be able to detect deterioration and improvement in individual with knee OA underjoining TKR (Kennedy et al., 2005).

2.16 **Pain**

Pain is the primary reason individuals seek medical treatment (Dubois, Gallagher, & Lippe, 2009). Pain is defined by The International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Neogi, 2013). Pain is a complex and subjective phenomenon, which makes it difficult to study. Each individual has his or her own perception of pain, and several factors, including biological, social and psychological ones, can interact with pain (Institute of Medicine, 2011) (see Figure 2-6).

The way in which the central nervous system (CNS) transmits and processes pain information is affected by several genetic factors. In general, these factors affect an individual's sensitivity to pain by either decreasing or increasing the transmission of signals. The body's ability to release hormones as adrenaline (the pain starving effect) is dependent on genetic factors, which may impact the survival rate of neurons and therefore affect the strength of the nociceptive afferents (Institute of Medicine, 2011). Furthermore, response to pain (emotional, physical and cognitive) is generally learned during childhood. Hence, these learned responses are critical to how adults cope with pain. For example, previous studies have shown that children with an unhealthy response (somatic and emotional) to recurrent pain are more likely to develop chronic pain later in life (Macfarlane, 2010; Walker, Garber, Van Slyke, & Greene, 1995). These may underlie the theory that the body's cumulative efforts to adjust to acute stress may eventually harm various tissues, organs and body systems (Institute of Medicine, 2011).

Under normal circumstances, a pain signal is a warning signal that indicates something is wrong, such as when injuring a ligament or touching hot material. In these situations, pain plays a protective role, signalling to individuals to rest or to withdraw from danger (Neogi, 2013).
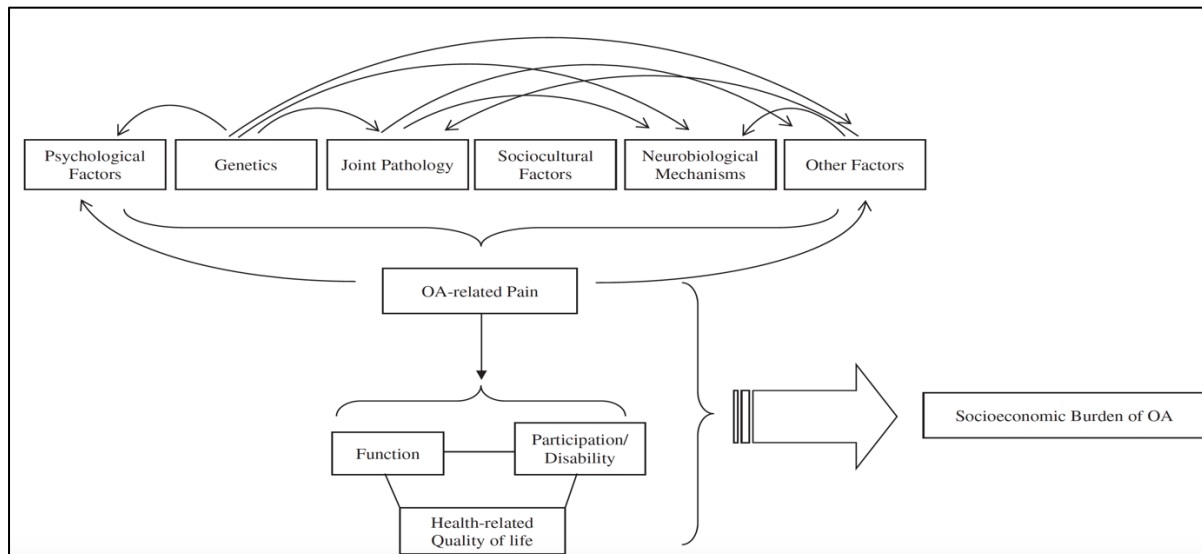
Figure 2-6 Diagram illustrate the multifactorial nature of the pain (Neogi, 2013).

2.16.1 Knee OA and pain

Knee pain is a critical symptom in knee OA. Interestingly, more than half of individuals affected with knee OA have stated that knee pain is their worst problem (NICE, 2014). Furthermore, pain is a risk factor for disability and total knee replacement (Hochberg, 1996; Lee et al., 2013; Maly, Costigan, & Olney, 2006). Previous prospective studies showed that knee pain at baseline represents a risk for both disability and radiological progression (Creamer, Lethbridge-Cejku, & Hochberg, 1998; Hassan, Doherty, Mockett, & Doherty, 2002). This highlights the importance of treating pain in individuals with knee OA.

Knee pain in the early stage of OA occurs and is aggravated during activities such as walking and further increases with long periods of weight bearing (Dieppe & Lohmander, 2005). In advanced cases of knee OA, the pain intensity increases and may persist at rest and at night (Hafez, Alenazi, Kachanathu, Alroumi, & Mohamed, 2014; Roach & Tilley, 2007). This pain leads to avoidance of moving the painful joint and therefore to impaired functional activity (Dandy and Edwards, 2009). Knee OA pain normally occurs in the area of the knee or around the knee and in some situations in the upper leg or above the joint (Peter et al., 2011). The knee pain is described as aching or throbbing during rest and as sharp stabbing pain during activity (Kidd, 2006). Unlike any other conditions that resolve or heal with time, knee OA pain is a disease which does not heal (Neogi, 2013).

2.16.2 Source of knee OA pain

The mechanism of knee OA pain is complex and is not fully understood to date (Hunter, Guermazi, Roemer, Zhang, & Neogi, 2013; NICE, 2014). Knee cartilage has no blood supply or nerve supply, which makes it incapable of generating pain directly. However, other tissues around the joint, such as the synovium, subchondral bone, joint capsules and ligaments, are rich with pain receptors, which makes them a source of pain (Dieppe & Lohmander, 2005; Felson, 2005). As previously mentioned, knee OA is a disease of the whole joint and not the cartilage, which highlights the importance of the surrounding tissue in pain production. Previous magnetic resonance imaging (MRI) studies showed a correlation between pain and subchondral bone change and synovitis (Hill et al., 2001, 2007; Roemer et al., 2009; Torres et al., 2006), which suggests that these tissues could be a source of the pain in knee OA.

Mechanical pain is one important source of knee pain in knee OA (Trouvin & Perrot, 2018). Interestingly, a weak correlation has been identified between the radiological severity of knee OA and knee pain (Dieppe, 2005; Hannan, Felson, & Pincus, 2000). Several reasons can be attributed to the previous weak correlation. As described earlier in this section, knee pain is a subjective measurement, and other confounding factors may affect the severity of the pain or contribute to the pain. These factors include but may not be limited analgesic treatments, expectation, mood and coping strategies (Bradley, 2004; Colloca & Benedetti, 2006; Gamsa, 1990; Villemure, Slotnick, & Bushnell, 2003; Wager, 2005; Zubieta et al., 2001). In addition, impaired joint proprioception has been associated with pain progression and functional limitation (Felson et al., 2009). In a situation where tissue injury occurs, inflammatory mediators like bradykinin are released, which leads to nociceptor nerve fibre sensitisation. Subsequently, the release of inflammatory agents leads to increased sensitivity around the injured tissue, a phenomenon known as hyperalgesia (primary sensitisation). As a result of repeated depolarisation of the primary afferent, central sensitisation occurs by the continuous release of neurotransmitters (Enohumah & Imarengiaye, 2008).

Central sensitisation, which is abnormal pain processing of signalling from the CNS, is a common mechanism in chronic OA. In central sensitisation, pain is perceived as stronger due to increased firing of spinal neurons, with or without peripheral stimulation (Staud, Robinson, Weyl, & Price,

2010). These changes explain the increased sensitivity to painful stimuli (hyperalgesia) and the increased perception of mild stimuli as very painful (allodynia) (Crombez, 1993). Recently, psychosocial factors (anxiety, depression, mood and stress) have been identified as sources of pain in central sensitisation (Arendt-Nielsen et al., 2010; Graven-Nielsen & Arendt-Nielsen, 2002). Thus, pain perception is a sum of multiple factors that are necessarily to quantify.

Without controlling the factors that lead to variations in individual pain, the correlation will be confounded (Marriott et al., 2017). Without doubt, some of the confounding factors cannot feasibly be measured or gathered in most studies. By using a within-subject study design to control for these factors throughout, a strong correlation have been found between radiological severity and the incidence (new pain), presence and severity of pain (Neogi et al., 2009; Niu, Jingbo, Felson, David T., Neogi, Tuhina, Zhang, 2012). Furthermore, a strong correlation has been found between loading and pain (Marriott et al., 2017). Such studies highlight the importance of loading and other factors in the knee pain.

Therefore, modification of any of the factors that affect pain could results in a reduction in pain. Previous studies have shown that higher EKAM is correlated with higher loading (Trepczynski et al., 2014). Interestingly, modelling studies showed that alterations in muscle patterns, which is a feature of individuals with knee OA, may lead to increased joint loading while walking (Brandon, Miller, Thelen, & Deluzio, 2014; Sritharan et al., 2017). Furthermore, a previous study showed a correlation between higher muscle activity and knee pain (Wilson, Deluzio, Dunbar, Caldwell, & Hubley-Kozey, 2011). An increase in muscle co-contraction may lead to an increase in joint loading and therefore to greater pain. There is also some evidence that higher loading could be linked to bone marrow lesions (Alliston, Hernandez, Findlay, Felson, & Kennedy, 2018; Felson et al., 2003), which might be due to higher stress on the bone. Therefore, targeting loading by reducing EKAM and muscle co-contraction is a sensible option to reduce pain and the progression of knee OA. Laxity and patients' confidence in their knees could be factors that contribute to higher loading through increased muscle co-contraction and muscle activity. As has been mentioned previously, proprioception has been correlated with pain severity, so improving proprioception may lead to pain reduction.

2.16.3 Measuring the knee pain

In studies and cohort trials on knee OA several methods are typically used to measure pain. For assessing knee pain, the most common methods are a numeric rating scale (NRS) or a visual analogue scale (VAS), which assess pain via single questions about a specific period of time or by using subscales such as the Knee injury and Osteoarthritis Outcome Score (KOOS) or the Western Ontario and McMaster Universities Arthritis Index (WOMAC). In the latter (subscales), the pain is assessed for a specific activity such as walking or ascending and descending stairs (Neogi, 2013). More recently, pain assessment has integrated a more comprehensive approach, such as quantitative sensory testing (Trouvin & Perrot, 2018), which will be discussed in the following section.

2.16.4 Pain pressure threshold

The knee pain in individuals with knee OA considered a key symptom (Dieppe & Lohmander, 2005). Knee pain pathophysiology is complex and local contributors probably involve raised mechanical stress on intra-articular and pre-articular tendons and ligaments, intra-osseous pressure and synovial inflammation (Brandt et al., 2008; Dieppe & Lohmander, 2005; Kidd, 2006). In addition to the previous local mechanisms, quantitative sensory testing studies supported that the neurogenic responses in osteoarthritis pain (Arendt-Nielsen et al., 2010; Imamura et al., 2008; Kosek & Ordeberg, 2000). This change in pain modulation was identified to contribute to the pain severity in individuals with OA (Lundblad, Kreicbergs, & Jansson, 2008).

Quantitative sensory testing technique (QSTT) is one method which has been used to evaluate the mechanism of OA pain. QSTT involves assessing the somatosensory response to the applied external stimulus (Pavlaković & Petzke, 2010). The QSTT can be applied at the affected side to identify the localised somatosensory changes or to distal part to identify the widely spread somatosensory (Arendt-Nielsen & Yarnitsky, 2009). Pain on the affected side suggests a local sensitisation while to distal part suggest a combined central and local sensitisation (Graven-Nielsen & Arendt-Nielsen, 2002).

Previous studies have shown that individuals with knee OA have lower pain pressure threshold than the control group (Arendt-Nielsen et al., 2010; Imamura et al., 2008; Wessel, 1995).

Furthermore, high ICC ranging from 0.93 to 0.98 was identified by a previous study for using such measurement which indicated the importance of using it (Mutlu & Ozdincler, 2015). Mutlu & Ozdincler (2015) concluded that pain pressure threshold was sensitive to detect the change caused by a treatment. Another study found that the reliability of pressure pain threshold increased from (ICC=0.53-0.87) to (ICC=0.84-0.91) in knee OA individuals when using an average of two trials instead on one trial (Søren Thorgaard Skou, Simonsen, & Rasmussen, 2015). Therefore, to quantify the pain pressure threshold might be an important factor to understand the contribution of it to pain severity and to investigate the treatment effect on pain pressure threshold.

In summary, mechanical factors are indicated as some of the primary factors that are related to progression of the disease in individuals with knee OA. The previous sections have identified increased EKAM and higher muscle co-contractions along with greater disease progression. This is associated with clinical changes and also balance impairments. Therefore, reducing EKAM and muscle co-contraction appear to be important aspect and one would postulate that treatments intended to reduce these variables will help to reduce pain, improve physical function and reduce the effect of the disease on public health. The following sections will review the different management approaches in the treatment of medial knee OA.

2.17 Management of medial knee osteoarthritis

Although, currently, there is no cure for OA, treatments are aimed at preserving and/or improving the individuals' joint mobility, decrease pain and limit disability (Zhang et al., 2010). The management of OA ranges from surgical to conservative approaches which will be discussed in the following sections.

2.17.1 Surgical treatment

Surgical approaches such as arthroscopy, osteotomy and knee arthroplasty are used as treatments for knee OA. Surgical interventions are generally considered to be suitable treatments for OA when all other approaches have failed to treat or relieve the symptoms (Dieppe & Lohmander, 2005; Rönn, Reischl, Gautier, & Jacobi, 2011).

Khan, Evaniew, Bedi, Ayeni and Bhandari (2014) conducted a systematic review and meta-analysis which investigated the effect the effect of arthroscopic surgery in individuals with knee OA including debridement, partial meniscectomy or both by comparing it to sham or exercise or medical treatment. The review included 9 trials and concluded that arthroscopic intervention has a small effect on pain compared to control 2.4mm in 100mm visual analogue scale. The study stated that the effect of arthroscopic intervention is limited in time up to 6 months and showed absence of effect after one and two years. Furthermore, arthroscopic intervention showed no effect on functional improvement and associated with harms (Khan et al., 2014). This conclusion was supported by a more recent systematic review which showed that arthroscopic surgery had a small effect on pain and function compared to conservative approach in short term for individuals with knee OA. The study stated that the long term effect (2 years) for the arthroscopic surgery on pain and function is very small or no effect (Brignardello-Petersen et al., 2017).

High tibial osteotomy is another surgical procedure used to transfer the mechanical axis from medial to slightly lateral to the midline of the knee to decrease the load which has the potential to enhance the clinical symptoms and delay the course of the OA process. Based on 13 studies, a coherent systematic review identified strong evidence for supporting the use of osteotomy to improve pain and function outcomes (Brouwer et al., 2007). The study concluded that there is no evidence to compare high tibial osteotomy to conservative approach. The same authors updated the review in 2014 and stated although the review included more studies, the conclusion of the study was the same as in 2007 study (Brouwer et al., 2014). Significant improvements have been observed with high tibial osteotomy in knee instability, laxity, muscle co-contraction (VL / MG) and EKAM after six months, which increases later on (Ramsey, Snyder-Mackler, Lewek, Newcomb, & Rudolph, 2007). However, successful outcomes rely on the stage of the OA, proper patient selection, and the achievement of adequate correction.

Under- or over-correction of the alignment might lead to speeding up the progression of knee OA (Briem, Ramsey, Newcomb, Rudolph, & Snyder-Mackler, 2007) and that the degree of correction was among the factors that affect the post-operative results in 10 year longitudinal study (Schuster et al., 2018). Furthermore, individuals with a high body mass index are associated with poor outcome results in osteotomy (El-Azab et al., 2011). Quadriceps weakness and flexion contracture may persist after the alignment correction, even with knee function improvement, which suggests

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that the movement strategy continues the joint destruction and hinders long term improvement. Quadriceps and hamstring intensive exercise preoperatively have been shown to improve post-surgical outcomes, which highlights the importance of pre-surgical rehabilitation (Kean, Birmingham, Garland, Bryant, & Giffin, 2011). Prodromos et al., 1981 showed that only 50% of individuals with high EKAM pre-operatively had good to excellent results 2.3 years postoperatively compared to 100% in individuals whom had a low EKAM. Furthermore, recurrent varus deformity was significant in individuals with high EKAM which led to failure to reduce the loading in such group. Unfortunately the next step from this point would be a joint replacement / arthroplasty.

The effect of various techniques for joint arthroplasty, which involve changing the articulating surface of a joint, is well documented in the literature (Altman et al., 2005; Zhang et al., 2005). Various studies and systematic reviews have acknowledged arthroplasty as being an effective procedure and have reported a reduction in pain, improvement in function, increasing tolerance for the performance of activities of daily life, and improving health related quality of life (Aujla & Esler, 2017; da Silva, Santos, de Sampaio Carvalho Júnior, & Matos, 2014; Shan, Shan, Suzuki, Nouh, & Saxena, 2015; Skou et al., 2015).

Uni-compartmental knee arthroplasty (UKA) preserves proprioception, and evidence shows a higher range of motion than TKR arthroplasty (Lonner, 2009). For some individuals with knee OA, UKA is the step taken before a TKR becomes necessary (Lonner, 2009). Systematic reviews which have compared total TKR and UKA showed similar outcomes after five years regarding pain and function. Survival of the prosthesis is higher in TKR at 10 years, whereas deep vein thrombosis is lower in UKA than TKR (Griffin et al., 2007; Health Quality Ontario, 2005). In a recent randomised clinical trial which included 528 participants this showed that TKR is not superior to UKA in participants with medial knee OA. UKA showed 1.9 points higher in oxford knee score, lower complications and lower failure rate than TKR after one year (Beard et al., 2017).

Individuals with knee OA treated with UKA revealed cadence, step and speed improvements, and also the single leg support period increased, which reflects a more symmetrical gait (Weidenhielm, Olsson, Broström, Börjesson-Hederström, & Mattsson, 1993). Moreover, the double support period decreased, which supports quicker weight transfer during walking. Despite the vast

evidence that highlights the improvement in function and reduction in pain from using arthroplasty, evidence regarding time and indication of surgery could not be found. However, surgeon and non-surgeon related factors including technical skill are really important in the survival rate and achieve better outcome for UKR (Campi, Tibrewal, Cuthbert, & Tibrewal, 2018). Study showed that malalignment of prothesis with after UKR by 2 degree my predispose implant failure (Lonner, 2009).

Although surgical interventions have had good success (Briem et al., 2007; El-Azab et al., 2011; Ramsey et al., 2007), they represent great expense for the National Health Service (NHS), and have a significant impact on affected individuals in terms of recovery time and functional independence. There may also be some individuals for whom for surgery is not appropriate (e.g. too young) or who do not want surgery (Bhatia et al., 2013; Marks & Penton, 2004). Another important aspect to be seen after TKR and other surgery is the patient satisfaction. Patients tend to be less satisfied than surgeon and pre-operative expectation was among the factors that has an effect on patients satisfaction (Choi & Ra, 2016; Lau, Gandhi, Mahomed, & Mahomed, 2012; Matsuda, Kawahara, Okazaki, Tashiro, & Iwamoto, 2013). A recent study comparing the effect of TKR and THP on patients' satisfaction showed significantly lower satisfaction after TKR (60.44) compared to THR (69.7) (Neuprez et al., 2016). The study stated that patients' pre-operative expectation was the single best predictive factor for post-operative satisfaction results. This study raises a big question regarding why THR provide better satisfaction than TKR. Given the reduced level of satisfaction and increased cost, to name a few, conservative management should be the primary consideration when treating individuals with medial knee OA. Interestingly, in a randomised controlled trial that compared physiotherapy and surgical treatment to physiotherapy as treatments for individuals eligible for TKR, this revealed that the surgery group's KOOS score (32.5) was more improved than that of the physiotherapy group (16). However, the surgery group experienced more adverse events than the physiotherapy group (Skou et al., 2015). This emphasises a further need for conservative approaches.

2.17.2 Conservative approaches

2.17.2.1 Pharmacological modalities

In 2012, the ACR published recommendations for the use of pharmacological modalities in individuals with knee osteoarthritis (Marc C. Hochberg et al., 2012). These recommendations include using different varieties of drugs and intra-articular injections such as Acetaminophen, non-steroid anti-inflammatory drugs, and intraarticular corticosteroid injections.

Though, pharmacological treatments have disadvantages, such as not being suitable for all patients, gastrointestinal (GI) complications, and the risk of toxicity with an increase in the dosage or in individuals with special conditions (Felson et al., 2000). Furthermore, these pharmacological modalities only treat the symptoms of disease for knee OA, such as pain, and do not treat the disease itself, and they may cause OA progression if not used wisely (Dieppe, 1995). Although pain is significantly decreased in individuals with knee OA injected with intra-articular pain relief, knee loading was found to be significantly increased, which might accelerate the degeneration process (Henriksen et al., 2006; Paoloni et al., 2012; Schnitzer et al., 1993). Lane et al., (2010) evaluated the effects of Tanezumab (inhibits nerve growth factor) and showed a high reduction in pain for individuals with knee OA ranging from 45% to 62 % compared to baseline, although the rate of adverse effects was high (68%). Furthermore, since the start of the trial in 2006 until 2010, 16 participants required total joint replacement due to the progression of the OA which led the Food and Drug Administration to halt the trials for the Tanezumab (Lane et al., 2010). This study showed that such treatment might lead to progression of the OA and therefore should be used wisely. Furthermore, Henriksen et al. (2006) and Schnitzer et al. (1993) demonstrated that with pharmacological treatments aimed at reducing pain, increasing in the EKAM were seen.

2.17.2.2 Physiotherapeutic based treatments

Physiotherapy is a common conservative treatment used for individuals with medial knee OA to reduce stiffness and pain, and improve muscle strength and range of motion (Brosseau et al., 2014; Fisher et al., 1993; McAlindon et al., 2014). Different types of exercises are advocated for use in treating knee OA. These include aerobic exercises, strengthening exercises and Tai Chi exercises (Bennell & Hinman, 2011; Lee et al., 2009; Song, Roberts, Lee, Lam, & Bae, 2010; Ye, Cai,

Zhong, Cai, & Zheng, 2014), stretching exercises and postural control exercises (Pelland et al., 2004; Sazo-Rodríguez, Méndez-Rebolledo, Guzmán-Muñoz, & Rubio-Palma, 2017). Manual therapy, including stretching and range of motion exercises, has been found to increase ROM, modulate pain, improve soft tissue healing, improve function, and induce relaxation (Deyle et al., 2000). Combined or individual treatment via a self-management programme and strengthening programme have been found to be effective in individuals with early OA, and the researchers conclude that self-management programs may offer the least burdensome option for the treatment of knee OA patients (Landry et al., 2007; McKnight et al., 2010).

Exercise interventions have shown good results with respect to different outcomes, such as pain (Aoki et al., 2009; Baker et al., 2001; Carvalho, Bittar, Pinto, Ferreira, & Sitta, 2010; Chaipinyo & Karoonsupcharoen, 2009; Fransen et al., 2015; McCarthy et al., 2004; Ravaud et al., 2004; Sled, Khoja, Deluzio, Olney, & Culham, 2010) and function (Baker et al., 2001; Deyle et al., 2005; Sled et al., 2010) and should be the first course of treatment. In 2015, a randomised clinical trial compared the effect of surgical intervention (TKR) to non-surgical intervention in individual with knee OA including exercise, education, nutritional advices and insole over 12 months. The study showed 16 and 32.5 points reduction in KOOS pain score for non-surgical intervention group and surgical intervention group. Although, reduction in pain was significantly higher for surgical intervention group, the number of adverse effect was significantly higher in surgical intervention group. Furthermore, although all groups were eligible to TKR, most participants in nonsurgical intervention group did not undergo TKR (Skou et al., 2015).

Considerable functional improvement (Baker et al., 2001; Deyle et al., 2005; Sled et al., 2010), pain reduction (Aoki et al., 2009; Baker et al., 2001; Chaipinyo & Karoonsupcharoen, 2009; McCarthy et al., 2004; Ravaud et al., 2004; Sled, Khoja, Deluzio, Olney, & Culham, 2010), and improvement in range of motion and gait speed (Aoki et al., 2009), has been noted in individuals with knee OA as a result of home based exercises with well thought out appropriate guidance. However, whilst clinical outcomes are favourable, a combined reduced loading to occur at the knee joint is needed.

Muscle weakness is amongst the risk factors for knee OA and numerous studies have demonstrated improvements in muscle strength following physiotherapy treatment (Blagojevic et al., 2010;

Neelapala, 2018; Zacharias, Green, Semciw, Kingsley, & Pizzari, 2014). In an early study by Brandt et al. (1999) they found that having strong quadriceps was not associated with the progression of the knee OA after 2.5 years. Contrastingly, quadriceps strengthening exercises were found not to reduce the progression of the knee OA (Segal, Findlay, Wang, Torner, & Nevitt, 2012). Surprisingly, the higher quadriceps strength was associated with the increase the likelihood of tibiofemoral OA progression in presence of knee mal-alignment and laxity (Sharma, Dunlop, Cahue, Song, & Hayes, 2003).

Hip adductor and abductor muscles weakness have been identified in individual with knee OA which have been suggested to have a role in the knee OA progression. Hip abductor and adductor muscle strengthening was also proposed as a potential solution to reduce the EKAM (Mündermann et al., 2005) and longitudinal study found that individual with reduced hip external adduction moment showed faster OA progression (Chang et al., 2005). Bennell et al. (2010) investigated the effect of hip strengthening exercises on the EKAM, pain and physical function over 12 weeks. Although pain and physical functional improved with hip strengthening exercises compared to control group, no significant difference was identified in EKAM (Bennell et al., 2010). The effect of lower limb strengthening exercises on EKAM in individual with knee OA was investigated over 6 weeks (Al-Khlaifat, Herrington, Hammond, Tyson, & Jones, 2016) and 6 months (Foroughi et al., 2011). Both studies found no significant effect on EKAM which was supported by systematic review which concluded that exercise has no effect on EKAM (Ferreira et al., 2015). Recently, the effect of individualised strength exercise for trunk, hip and knee among individual with knee OA was investigated over 12 weeks. The study included two groups (exercise group, control group) and the results showed no significant difference between the groups in EKAM (Henriksen et al., 2017). A recent systematic review investigated the effect of the hip abductor muscles strengthening in individuals with knee OA concluded that the hip abductor muscles strengthening is not effective in reducing EKAM (Neelapala, 2018).

One of the main limitation of exercise therapy in individuals with knee OA is the lack of dosage (Bennell & Hinman, 2011). This conclusion was supported by a systematic review saying that evidence is not sufficient to provide a recommendation regarding the exercise dosage for individuals with knee OA (Fransen et al., 2015). A recent systematic review which investigated the completeness of clinical trials that form 10 clinical guidelines with knee OA stated that inadequate of the recommendation for knee OA exercise is a major issue including dose and

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application which limit the adoption of such treatment into the clinical practice (Bartholdy et al., 2018).

In terms of muscle co-contraction which has been identified as a factor related to knee OA progression and pain, lateral muscle co-contraction was significantly reduced following a six week intervention but medial muscle co-contraction did not significantly reduce (Al-Khlaifat et al., 2016). Medial muscle co-contraction is more important than lateral side since this is correlated with knee OA progression (Hodges et al., 2015). Recently, the effect of the Alexander Technique which aims to provide neuromuscular re-education was investigated in individuals with knee OA. The treatment was given for 12 weeks and showed significant reduction in pain which was maintained over 15 months. Significant reduction in medial co-contraction was seen after the treatment compared to the baseline. Although, the study showed good results, the study lacked a control group and also a lack of demographic and clinical characteristics of the study individuals. Therefore, whilst interesting, currently it is not known if this technique will reduce co-contraction in individual with medial knee OA in the longer term (Preece, Jones, Brown, Cacciatore, & Jones, 2016).

Therefore, whilst exercise treatments are at the forefront of treatments for medial knee OA, the lack of evidence in regards to biomechanical loading and also adherence problems with the treatments, other easier to use treatments which target EKAM to reduce the loading would be the focus of knee OA treatment. In addition, more gait modifiable interventions are required due their impact on OA progression, and this could be the solution if we are to find a way to mitigate the impact of knee OA on public health (Kim et al., 2004; Sled et al., 2010).

Other interventions in the hands of physiotherapists are walking devices. It has been found that using assisted walking devices such as canes increase the base of support, which means larger displacement of the centre of gravity can be tolerated before losing balance (David J Hunter, 2009). Assistive devices produce stabilising reaction forces at the hands (Murray, Gore, & Clarkson, 1971), and help reduce the weight on the lower extremities by shifting part of the body weight onto the assistive device, which means less load on the affected joints (Berman, Zarro, Bosacco, & Israelite, 1987); as well as producing horizontal ground forces that help with stopping or propulsion during walking (Bateni & Maki, 2005; Blount, 1956; Neumann, 1989; Zhang et al.,

2008). EKAM was found to decrease significantly with the use of a cane in the contralateral hand compared to no cane among individuals with medial knee OA (Kemp, Crossley, Wrigley, Metcalf, & Hinman, 2008; Simic, Bennell, Hunt, Wrigley, & Hinman, 2011). Simic et al. (2011) showed that the higher the weight is placed over the cane the lower EKAM results. However, the training to use the cane probably seems to be an issue since three participants out of 36 were not able to perform the appropriate gait needed. However, using an assisted device is not preferred by some individuals with knee OA for reasons of cosmetic appearance as previous study showed that vanity is the main reason for not using cane in individuals with OA (Shrier et al., 2006). This lack of adherence has also been demonstrated Netherlands showed that 44% of individuals with hip and knee OA own walking aid and 32% of them did not use the walking aid (Van der Esch, Heijmans, & Dekker, 2003).

Therefore, there is great need for other treatments strategies and modalities which aim to reduce the knee loading (EKAM) since this variable has been linked to knee OA progression and to help determine best possible treatments for the individuals.

2.17.2.3 *Gait strategies*

Different walking strategies might be used by individuals with knee OA to reduce the EKAM and shift the load from the medial compartment. This is achieved by altering the mechanics and gait parameters which include the following strategies:

Toe-out gait:

Walking with an increased toe out foot angle in relation to the direction of progression, has been found to reduce EKAM in individuals with knee OA (Guo, Axe, & Manal, 2007; Jenkyn, Hunt, Jones, Giffin, & Birmingham, 2008; Lynn & Costigan, 2008). The underlying mechanism is divided into two parts. First, the external rotation of the knee axis converts part of the adduction moment into flexion moment which contributes to the first peak EKAM reduction (Jenkyn et al., 2008). Second, toe out leads to lateral displacement of the center of pressure, which leads the ground reaction force (GRF) to pass more medially to the knee thereby reducing the second peak EKAM (Jenkyn et al., 2008). However, a toe out angle seems to be more effective in reducing the second peak EKAM than the first peak. An inverse correlation has been found between second

EKAM and toe out angle in individuals with knee OA (Chang et al., 2007; Hurwitz et al., 2002) and healthy individuals (Andrews, Noyes, Hewett, & Andriacchi, 1996; Teichtahl et al., 2006). During stair descending, no significant change has been observed using a toe out gait, while during ascending, the first EKAM significantly increases, and the second EKAM significantly decreases (Guo et al., 2007). Jenkyn et al. (2008) stated that in order to show a reduction in first peak EKAM with a toe out angle gait modification the movement needed to be produced by the hip and not the ankle. Recently Hunt et al. (2018) conducted a randomised clinical trial investigating the clinical and the biomechanical effect of toe out gait in individuals with medial knee OA. The study included two groups, the first one treated with progressive walking while second group with progressive walking plus increasing toe out gait. The treatment was provided for 4 months and the measurements were taken at baseline, after 4 months and one month later to investigate if the participants were able to maintain gait modification (retention). The results showed a significant increase in toe out gait after 4 months and participants were able to sustain this gait modification after one months with slight reduction in toes out gait compared after treatment. 2nd peak EKAM and KAAI reduced significantly after 4 months compared to baseline, however this significant reduction was lost after one month. Interestingly, the authors stated that both groups pain and function improved with slightly higher value (no statistical difference) for the toe out group (Hunt, Charlton, Krowchuk, Tse, & Hatfield, 2018)

Toe-in gait:

Previous research has shown that internally rotating the foot while walking can reduce the first peak EKAM (Shull, et al., 2013; Shull, Lurie, Cutkosky, & Besier, 2011; van den Noort, Schaffers, Snijders, & Harlaar, 2013). The first peak EKAM was reduced by 18% in Shull et al.'s (2013) study and 45% in van deer Noort et al.'s (2013) study. Laterally shifting the centre of pressure and medially shifting the centre of the knee at the early-stance is thought to be the reason for this reduction (Shull et al., 2013). However, in all previous studies, participants were healthy, which might not reflect many individuals with knee OA. One study showed that a six-week retraining program for individuals with knee OA reduced the first peak of EKAM by 20% and improved VAS by 2 points (Shull et al., 2013). The drawback of this strategy is that it requires permanent adaptation, which takes time and effort, and some patients might not be able to adopt it due to advanced age. Interestingly, a recent study showed that walking with toe in gait in individuals with

medial knee OA led to increased muscle co-contraction on the medial side of the knee (VM/MH) which suggests higher loading in the medial side of the knee (Charlton, Hatfield, Guenette, & Hunt, 2018).

Lateral trunk sway:

Lateral trunk sway could be used as strategy to reduce the EKAM during walking. The mechanism underlay in that lateral trunk sway shifts toward the affected weight bearing side during walking moves the centre of mass (COM) laterally closer to the centre of pressure which reduce the EKAM. The ground reaction force acts through the body's COM. This shifts the GRF closer to the knee joint and therefore reduces the adduction moment. Lateral trunk sway has been suggested as being a gait alteration mechanism used to reduce EKAM in individuals with knee OA (Hunt et al., 2008; Linley, Sled, Culham, & Deluzio, 2010; Mündermann et al., 2005). An inverse correlation has been found between the EKAM and lateral trunk sway (Hunt et al., 2008). In healthy individuals, a reduction in EKAM by 65% has been found for lateral trunk sway (Mündermann, Asay, Mündermann, & Andriacchi, 2008). Higher lateral trunk sway was noticed in severe knee OA individuals rather than in the mild group (Hunt, Wrigley, Hinman, & Bennell, 2010). As a compensatory mechanism to unload the affected side, greater lateral trunk sway requires this mechanism. Caution should be taken when introducing such mechanisms due to the risk of falling because of the greater upper body shift. Additionally, the high lumber forces might increase the risk of back pain.

Medial thrust gait:

Medial thrust gait involves deliberately pushing the knee joint in the medial direction. This re-positions the joint closer to the ground reaction force, and therefore a reduction in the moment arm and adduction moment occurs. Studies of individuals who have adapted this mechanism show marked reductions in EKAM and medial knee contact force (D'Lima, & Colwell, 2009; Fregly, Reinbolt, Rooney, Mitchell, & Chmielewski, 2007). Richards, van den Noort, van der Esch, Booij and Harlaar (2018) investigated the effect of biofeedback training for individuals with medial knee OA by combining three gait modifications (medial thrust, toes-in gait, increased step width) on EKAM. The results showed that participants were not able to reduce their EKAM with biofeedback without instruction on how to achieve the reduction. After the training, EKAM was found to

significantly reduced by 14% and participants were successful to maintain 9% reduction without the biofeedback. However, this study only showed the immediate effect and more studies need to investigate application of such method in the long term. The authors did identify a significant increase in the knee flexion moment and ankle adduction moment which may increase the load in the knee and place extra load on the ankle.

Walking barefoot:

Studies have found that walking barefoot reduces the EKAM by between 7 to 13% compared to walking with thick-soled shoes or normal shoes (Shakoor et al., 2010; Shakoor & Block, 2006). Some authors have attributed the reduction in EKAM while walking barefoot to a reduction in walking speed (Kerrigan, Karvosky, Lelas, & Riley, 2003), as previous studies have shown that walking speed reduction results in EKAM reduction as well (Mündermann et al., 2005; Robbins & Maly, 2009; Zeni & Higginson, 2009). However, when walking speed was controlled, doing so barefoot also showed a reduction in EKAM compared to wearing shoes (Kemp et al., 2008; Shakoor et al., 2010; Shakoor, Lidtke, Sengupta, Fogg, & Block, 2008; Shakoor & Block, 2006). Jones, Chapman, Parkes, Forsythe & Felson. (2015) showed significant reductions in the first peak EKAM when walking barefoot compared to shoes by 7.6% among individuals with medial knee OA. Surprisingly, the knee pain was found to increase while walking barefoot compared to participants own shoes. Even though walking barefoot could be a potential solution for EKAM reduction, it is clear that this it is not practical.

Walking with reduced speed:

A positive correlation has been identified between EKAM and walking speed in individuals with knee osteoarthritis, which means this is a possible solution for EKAM reduction and therefore reducing medial joint loading (Mündermann et al., 2004). Individuals with severe knee OA have been shown to adopt this mechanism, showing a reduction in walking speed and stride length during stair ascending (Kaufman et al., 2001) and walking on ground level (Astephen & Deluzio, 2005). Interestingly, in a study which aimed to investigate the gait and neuromuscular changes between two groups of individuals with knee OA (moderate, severe) and asymptomatic individuals showed significant difference in walking speed between all the groups. The severe knee OA group showed the lowest walking speed followed by moderate knee OA group then the asymptomatic

individuals and the authors stated that this could be reduction in speed could be due to increased pain (Astephen et al., 2008).

Altering foot and ankle position:

A strong relationship has been identified between knee OA and alteration in the centre of pressure (Lidtke, Muehleman, Kwasny, & Block, 2010; Reilly et al., 2009) with a reduction in EKAM found in individuals with knee OA who demonstrate pronated feet (Lidtke et al., 2010). Therefore, any alteration in foot position will lead to GRF modification, and dynamic and static alterations in lower limb alignment (Guichet, Javed, Russell, & Saleh, 2003).

Despite these being easy and simple gait strategies for EKAM reduction, they require permanent gait adaptation by patients, which demands a lot of time and effort. Therefore, other options which reduce loading with less effort need to be investigated. These interventions are routinely labelled orthotic or footwear-based devices and includes biomechanical footwear, bracing and insoles.

2.17.3   Footwear and orthotic based devices

The next section will review the current literature around foot-worn and orthotic devices. The aim of these devices is to alter the system of forces which are applied at the knee joint through correcting the increased moments seen in medial knee osteoarthritis. Whilst each has its place in the treatment paradigm, some are more convenient than others.

2.17.3.1 *Footwear devices*

Different types of shoes have been identified in the literature which aim to reduce the EKAM in individuals with knee OA including the following:

Mobility shoes:

Mobility shoes are designed to be flexible and light with special groves in the outsole at the major flexion point to mimic the foot motion (Shakoor et al., 2008). The mechanism is through that mobility shoe work on is that it has no heel which has been approved to increase EKAM, allowing for better GRF contract with the flexible shoe sole and improve sensation from skin contact the

ground. Shakoor et al. (2008) found that walking with mobility shoe showed significant reduction in peak EKAM by 8% and 12% compared to self-selected shoe and control shoe respectively in individuals with knee OA. Recently Jones et al. (2015) compared the effect of different types of insole and shoes on the EKAM for individuals with medial knee OA. The results were in contradict to the previous study showing no significant change in 1st and 2nd peak EKAM with the use of mobility shoe compared to control shoes although pain reduced to control shoe. This contradiction between the studies might be attributed to several factors such as type of the mobility shoes as the design look different between the study or/and different in population characteristics.

Variable stiffness shoes:

In this type of shoe, the lateral side of the outsole is stiffer than the medial side which aim to reduce the EKAM. The mechanism behind the reduction in EKAM proposed to be due to reduction in medial GRF, medial shifting in COM which is caused by dynamic adaptation to the different stiffness in of the shoe and reduction in moment arm which induced by eversion of the foot which placed the knee in valgus thrust (Teoh et al., 2013). In one year study in individuals with medial knee OA, the variable stiffness shoe showed a significant reduction in pain compared to baseline and in EKAM compared to same day (Erhart-Hledik, Elspas, Giori, & Andriacchi, 2012).

A modified version of the concept of the variable stiffness shoe – the Gel-Melbourne OA (Asics) was developed by researchers in Australia. This also have a stiffer lateral midsole than the medial. The shoe also contains lateral wedge insole with 5-degree inclination attached to the sockliner. The Gel-melbourne shoes were successful at shifting the foot pressure more laterally compared to control shoe among individuals with knee OA which will lead to a reduction in the EKAM (Van Tunen et al., 2018). In 2013, a study showed that using the Gel-melbourne shoes significantly reduced the peak EKAM and KAAI in individuals with knee OA compared to the control shoes (Bennell, Kean, Wrigley, & Hinman, 2013). Interestingly, when assessing the clinical effect they showed that the pain was not found to differ between Gel-melbourne shoe and the conventional shoe after 6 months of treatment in individuals with knee OA although both group showed significant reduction compared to baseline. The authors concluded that the shoes which aim to modify the load had no additional benefit over conventional shoe (Hinman et al., 2016). One of

the main limitation of the study is not showing the biomechanical effect (EKAM reduction) of the shoe which is considered as the key mechanism to reduce the pain.

APOS therapy:

The APOS therapy (All Phases Of Step) shoe is a customised treatment which aims to modify the COP to reduce the EKAM and generate perturbation to change to neuromuscular system and improve control (Haim, Rubin, Rozen, Goryachev, & Wolf, 2012). In a 9-month longitudinal study which looked at the effect of AOPS therapy in individuals with medial knee OA the EKAM and pain were identified to reduce significantly. The reduction in pain was supported with another study which showed 49.2% significant reduction in pain after 6 months of treatment compared to baseline in individuals with medial knee OA (Haim et al., 2013). In a recent randomised clinical trial, Reichenbach, Heldner, Lenz, Felson and Juni (2018) demonstrated a positive effect on pain in a randomised clinical trial with APOS therapy.

Although many footwears have been successful at reducing the EKAM and/or knee pain in individuals with medial knee OA, footwear has several limitations. Firstly, the prices are too high for some kind of footwear as APOS therapy where the price reach £2480 or Gel-melbourne shoe where the price is approximately £137 (ASICS, 2018; AposTherapy, 2018). Secondly, the use of such treatment will restrict the individuals with medial knee OA to use one type of shoe with no alternative which might not suit all type of clothes. This might reduce the use of such treatment therefore other type of treatment such as valgus brace and insole might be more appropriate to be used.

2.17.3.2 *Valgus knee braces*

A knee brace is a rigid orthotic device that is secured around the thigh and shank to provide knee valgusation and is customised throughout the day (Figure 2-7). It has been suggested by NICE and OARSI guidelines as a conservative treatment method for individuals with medial knee OA (NICE, 2014; McAlindon et al., 2014).

The underlying mechanism in using such a device for pain reduction is applying valgus knee force to the knee, which reduces the external adduction moment during walking, and therefore unloads the medial condyle of the affected knee (Gaasbeek, Groen, Hampsink, van Heerwaarden, &

Duysens, 2007; Komistek et al., 1999; Lewinson et al., 2014; Lindenfeld, Hewett, & Andriacchi, 1997; Pollo, Otis, Backus, Warren, & Wickiewicz, 2002; Self, Greenwald, & Pflaster, 2000). The small enhancement in knee alignment caused by the brace is believed to shorten the moment arm, and consequently reduce the external knee adduction moment. Meanwhile, the compressive load is repositioned closer to the lateral side, which improves the distribution of the compressive load over the joint surface. This can be achieved through a three point pressure system by applying abduction force via an adjustable condylar pad or strap while two opposing forces (emerging from upper and lower brace components) act proximally and distally to the joint (Ramsey & Russell, 2009; Reeves & Bowling, 2011).
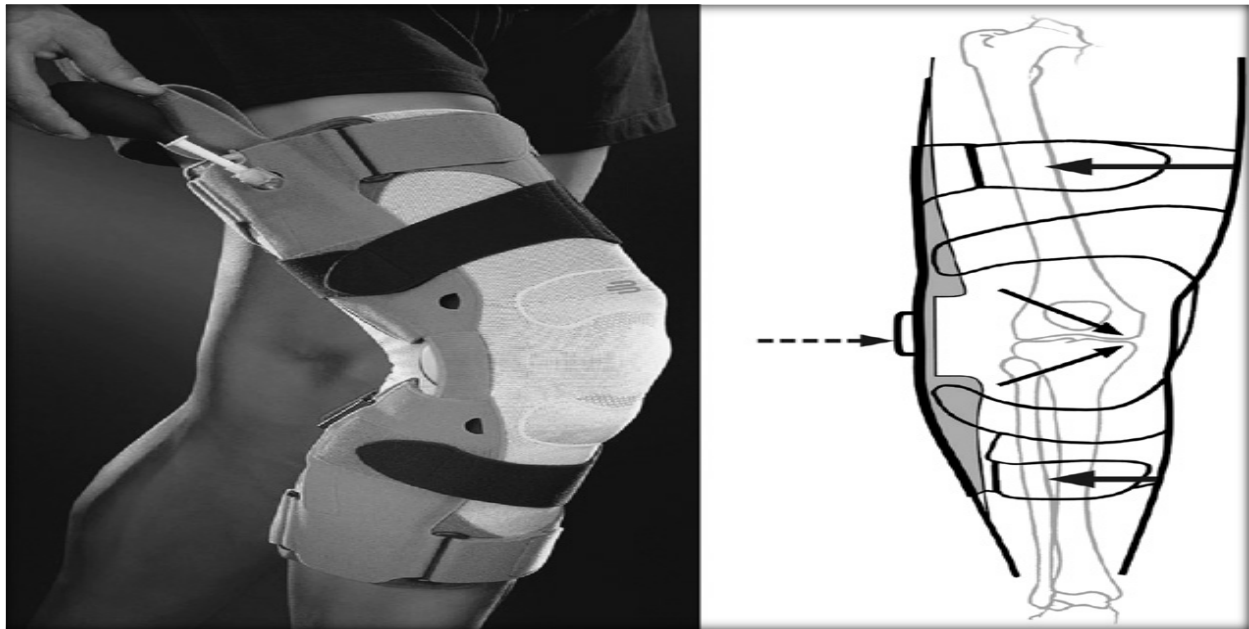
Figure 2-7 The left picture show a picture of valgus knee brace while the right picture represents the mechanism of valgus knee brace to reduce the medial knee loading (Gaasbeek et al., 2007).

The biomechanical and clinical effects of braces on medial knee OA have been investigated in many studies. Several studies investigated the clinical and biomechanical effect of valgus knee brace on individuals with knee OA and showed good results in relation to biomechanical outcomes (i.e. EKAM reduction) (Laroche et al., 2014; Toriyama et al., 2011), radiological outcome (increase condylar separation) (Komistek et al., 1999) and clinical outcome (pain reduction using questionnaires such as visual analogue scale (VAS), The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)) (Gaasbeek et al., 2007; Jones et al., 2013; Ramsey et al., 2007; Van Raaij et al., 2010).

In 2015, a systematic review and meta-analysis investigated the effect of orthosis and brace on individuals with knee OA (Duivenvoorden et al., 2015). The authors concluded that the evidence is not conclusive to support the effect of the valgus knee brace. One reason for this is might be to the low number of the studies included in the review (4 studies). Moyer et al. (2015) conducted a systematic review and meta-analysis to investigate the biomechanical effect of valgus knee brace in individuals with medial knee OA (Moyer et al., 2015). The review included 30 studies and concluded that valgus knee brace is effective at reducing EKAM and has moderate to high effect size. The same authors conducted meta-analysis to investigate the effect of valgus knee brace on pain in individuals with medal knee OA. The study concluded that valgus knee brace can produce small to moderate reduction in pain (Moyer et al., 2014). A more recent systematic review supported the previous conclusion of the effect of valgus knee brace in pain among individuals with knee OA stating that valgus knee brace is an effective treatment modality to reduce the pain secondary to medial knee OA (Gohal et al., 2018).

However, valgus knee brace compliance is low (Barnes, Cawley, & Hederman, 2002; Jones et al., 2013; Wilson et al., 2011). This can be attributed to several reasons, such as skin irritation, brace mechanical problems, poor fit, awkward shapes, difficulties taking the brace off and putting it on, difficulties wearing the brace with clothes, and brace bulkiness (Barnes et al., 2002; Fu et al., 2015; Giori, 2004; Squyer et al., 2013; Van Raaij et al., 2010). In terms of the consistency of patient brace use, authors have found that in the first year after being prescribed a brace, 76% of patients used a brace, followed by 69% in the second year and 61% in the third year. Twenty percent of patients stopped using a brace in the first 6 months, and only 6% of patients used a brace full time (Van Raaij et al., 2010). Compliance was defined as using the brace at least once a week which is low and might not be sufficient to provide pain reduction in the long term. In two studies with a longer follow up, only between 41% to 42% of participants still used their brace at 2.7 years (Barnes et al., 2002; Wilson, Rankin, & Barnes, 2011), while none still used them at 11.2 years (Wilson et al., 2011). However, when using a more restrictive definition of compliance (e.g., an hour twice a week), compliance dropped to 28% for more than 1 year, 25% for 2 years, and 21% for 3 years (Squyer et al., 2013). Most patients did not use the brace as much in the long term as in the first few years, and 26% stopped using their brace in the first year. There was a significant difference in rates of compliance when comparing insoles (71%) to braces (45%) (Van Raaij et al., 2010). Nevertheless, age was found to be correlated with compliance; 65-year-old individuals were

1.82 times more likely to stop using the brace than 49-year-olds (Giori, 2004). In 6 month study only 5 patients out of 28 were still using the brace all the time (Finger & Paulos, 2002). Squyer et al, (2013) stated that no clinical and biomechanical factors were associated with valgus knee brace compliance.

One of the main limitation which might hinder the adoption of Valgus knee brace to the clinical practice and the use by self-paid patients is the high price of valgus knee brace around £200. Therefore, the low compliance and high cost of valgus knee braces highlight the need for other treatments with better compliance and low cost such as simple knee sleeves and lateral wedge insoles.

2.17.3.3 *Knee sleeve*

A simple knee sleeve is an attractive option for individuals with knee OA (Figure 2-8). The use of orthoses such as a knee sleeve, are recommended by the ACR, the European league against rheumatology (EULAR), the Royal Australian College of General Practitioners, and as another guideline as a non-pharmacological treatment for individuals with knee OA (Beaudreuil et al., 2009; Gamble, 2000; Jordan et al., 2003; Melbourne, 2009). Knee sleeves are inexpensive and simple interventions that can be used by patients (Bryk et al., 2011). They are easy to recommend by providers and may suit those individuals with an allergy. On the other hand, knee sleeves are elastic and provide less mechanical stability than other forms of treatment such as braces and do not provide valgus or angular change in valgus position. Therefore they do not provide sufficient ligament and joint fixation (Schween et al., 2015). Some authors have mentioned that wearing a knee sleeve for several hours continuously might lead to joint swelling, which could hinder lymphatic and venous return around the knee joint (Chuang et al., 2077; Raja & Dewan, 2011). However, no studies have identified such an adverse effect from among those studies which have been conducted to investigate the impact of knee sleeve use on participants with knee OA.

Four underlying reasons have been speculated for the improvement outcomes with knee sleeve use. First, providing thermal effect; however, this mechanism has not been supported in the literature, as study which compared heat retaining sleeves did not show any superiority from this sleeve compared to a normal sleeve (Mazzuca et al., 2004). Furthermore, a study which showed the effect of a sleeve on skin and intra-muscular temperature, concluded that a sleeve has no effect

on the intra-muscular temperature before or during exercise, and that there is only a small effect on skin temperature (Miller, Knight, Feland, & Draper, 2005). Secondly, enhance proprioceptive sensation which is thought to be caused by stimulating skin receptors around the knee joint. Thirdly, reduce knee load throughout redistribution of the load between the patellofemoral joint and tibiofemoral join (Bryk et al., 2011), and a reduction in joint compression forced by reducing the joint muscle co-contraction (Schween et al., 2015). Fourthly, perceived increased stability, as indicated in two studies, which showed significant increased stability rates recorded by patients (Cudejko et al., 2017; Schween et al., 2015).
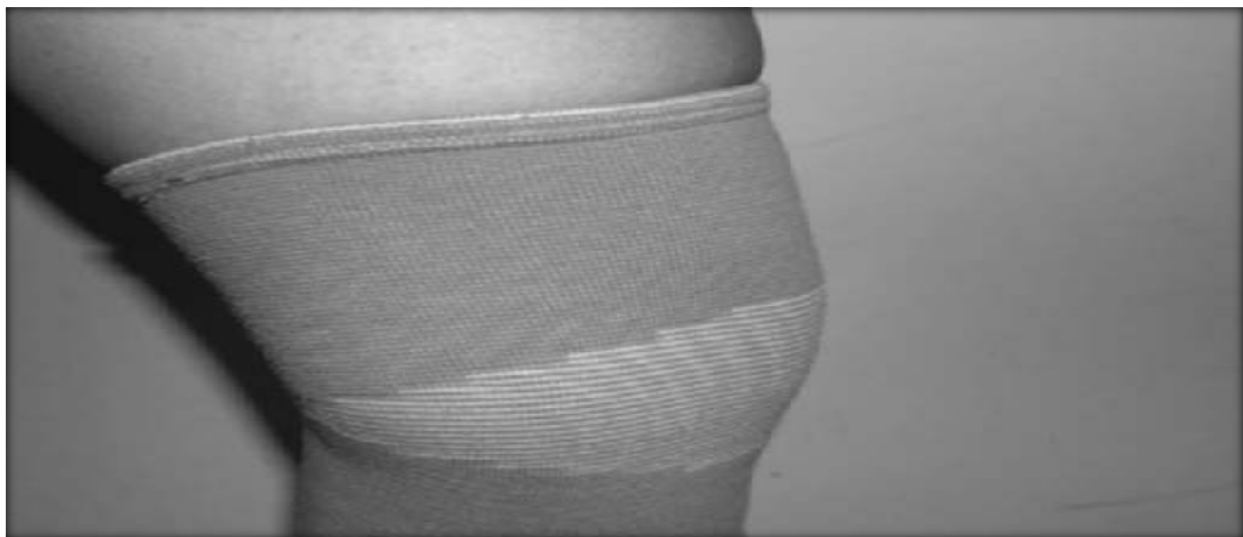
Figure 2-8 Simple knee sleeve (Chuang et al., 2007).

Proprioception has some been defined in the literature in different ways (Bayramoglu et al., 2007; Jerosch & Prymka, 1996). The most common definition is conscious and/or unconscious awareness of the position and movement of limbs or joints in space (Collins et al., 2011a; Grob, Kuster, Higgins, Lloyd, & Yata, 2002; Hurley, Scott, Rees, & Newham, 1997; Lephart, Pincivero, & Rozzi, 1998; Sharma, 1999). Knee proprioception arises from the various signals integrated from different receptors in the knee structure (Marks, Quinney, & Wessel, 1993; Pai, Rymer, Chang, & Sharma, 1997; Sharma, 1999). However, this may be influenced by other receptors such as the visual system, vestibular organs and other joint proprioception (Jerosch & Prymka, 1996; Sharma, 1999).

Three assumed functions have been described for the knee proprioception. First, guarding the knee joint from excessive and probable injuries by using reflex responses (Barrett et al., 1991;

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Bayramoglu et al., 2007; Jerosch & Prymka, 1996; Pai et al., 1997; Wada, Kawahara, Shimada, Miyazaki, & Baba, 2002). Second, accuracy of knee proprioception is proposed to be required to stabilise static knee posture (Jan, Lin, Lin, Lin, & Lin, 2009; Lin, Lin, Chai, Han, & Jan, 2007). Third, it is assumed that knee proprioception is vital in the organisation of complex motion and precise knee joint motion movements (Jan et al., 2009; Lin et al., 2007).

Previous studies have shown that knee proprioceptive accuracy seems to be impaired in knee OA individuals compared to age-matched control group for both motion sense (Barrack, Skinner, Cook, & Haddad, 1983; Hewitt, Refshauge, & Kilbreath, 2002; Koralewicz & Engh, 2000; Pai et al., 1997; Sharma et al., 1997) and position sense (Barrack et al., 1983; Garsden & Bullock-Saxton, 1999; Hassan et al., 2001; Hortobágyi et al., 2005; Hurley et al., 1997; Marks et al., 1993). Proprioceptive defects have been speculated to contribute towards or be caused by knee OA (Barrett et al., 1991; Sharma et al., 1997).

Sharma et al. (1997), theorised that different parts of the neuromuscular reflex pathway is disturbed in individuals with knee OA, which consequently results in detrimental loading of the joint. Therefore, improvement in the impaired proprioception may lead to better spatiotemporal coordination of the extremity position, resulting in more normal joint loading distribution. Proprioceptive defects have been suggested to have a role in uncoordinated muscle co-contraction, increased impact loading and joint instability in individuals with knee OA (Fitzgerald, Piva, & Irrgang, 2004; Hortobágyi et al., 2005; Mündermann et al., 2005; Radin, Yang, Riegger, Kish, & O'Connor, 1991; Schmitt & Rudolph, 2007; Sharma et al., 1998).

The studies which have investigated the effect of wearing a knee sleeve in individuals with knee OA can be divided according to the follow up period into two categories. The first category are those which investigated the immediate effect of a sleeve on individuals with knee OA (Bryk et al., 2011; Chuang et al., 2007; Collins et al., 2013; Collins et al., 2011a, 2011b, 2012; Cudejko et al., 2017; Schween et al., 2015). The second category investigated the effect of the knee sleeve on individuals with knee OA in an eight week follow up (Mazzuca et al., 2004) and after six months (Kirkley et al., 1999).

Immediate effect of knee sleeves:

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Clinical effect:

The most recent study that investigated the immediate effect of sleeves among individuals with knee OA was conducted in 2017 by Cudejko et al. The study included 55 participants and had good methodological quality. The study compared wearing no sleeve to a sleeve and wearing a tight sleeve to a non-tight sleeve. The researchers concluded that wearing a sleeve significantly reduced knee pain after level or perturbed walking and reduce the time required to perform the 10-m walking test and get up and go test. Furthermore, the results showed significant improvement in self-reported knee instability and confidence with the knee after level walking and perturbed walking. Comparing the tight to non-tight sleeve, the study showed no significant difference except a significantly better time result for the 10-m walk test. The findings supporting the results reported by Schween et al. (2015), who demonstrated a significant reduction in pain and improvement in self-reported knee stability with immediate use of the sleeve compared to no sleeve. Bryk et al. (2011) studied the immediate effect of a knee sleeve on pain and functional capacity in a randomised control trial. The study included 80 participants with knee OA. Significant improvements were seen in the VAS for pain after the stair climb power test, combined with significant reductions in the time required to perform the 8-m walking test and timed up and go test. However, the time for the stair climb power test did not show any significant change with sleeve use.

Knee sleeves have been shown to have a proprioceptive effect. Collin et al. (2011) conducted a study for investigating the effect of stochastic resonance electrical stimulation and sleeve on participation among individuals with medial knee OA. The study measured the proprioception via measuring the joint position sense in non-weight-bearing and partial weight-bearing position. The results showed a significant reduction in absolute error with sleeve use in partial weight position and not in the non-weight-bearing position. Interestingly, all the WOMAC subscales (pain, stiffness, function), total WOMAC and self-reported knee instability showed significant correlations with absolute error in partial weight-bearing and non-weight-bearing position. The main study limitation was including lower sample size than predicted sample size needed to achieve 80% power which may have increased the risk of type 2 error.

Biomechanical effect:

The effect of sleeve on kinetics and kinematics for individuals with medial knee OA was first investigated by Collins et al. (2011). These researchers showed significant increases in the knee flexion angle at initial contact, lower heel strike transient peak, loading rate calculated from initial contact to heel strike transient peak and loading rate calculated from initial contact to maximum heel strike transient with sleeve use. This study was followed up with an immediate crossover study (Collins et al., 2014) for investigating the effect of sleeve and stochastic resonance electrical stimulation as single and combined treatments. The study did not show any significant effect of the sleeve on the maximum EKAM in the first half or second half of the stance phase. The sleeve showed a significant increase in the maximum and minimum flexion angles in the first and second halves of the stance phase. The study also showed a significant reduction in the maximum external extension moment in the first half of the stance phase. However, Schween et al. (2015) showed results that contradicted those of the previous study regarding EKAM, with 10.1% and 12.9% reductions in first-peak EKAM and KAAI, respectively. The reduction in EKAM was combined with reductions in the adduction angle at initial contact and maximum adduction angle. Therefore, there is conflicting evidence on the immediate effect of knee sleeve on the biomechanics in knee OA (EKAM) , and short-term effects have not been considered.

Muscle co-contraction:

Only one study has investigated the immediate effect of sleeve on the muscle co-contraction in individuals with medial knee OA in a crossover design (Collins et al., 2011). The authors calculated the muscle co-contraction on the lateral side VL/LH of the knee joint. Fifty-two participants were included, and the data revealed significant reductions in muscle co-contraction with sleeve use in the preparatory, weight acceptance and midstance to terminal stance phases compared with no treatment

Balance:

The effect of knee sleeve on static (Chuang et al., 2007; Collins et al., 2012) and dynamic balance (Chuang et al., 2007) were measured among individuals with knee OA. Different methods were used for collecting the static balance data in both studies with the single leg stance platform test in Collins et al.'s (2012) study and standing on unstable platform with both limbs in Chuang et al.'s (2007) research. Collins et al. (2012) did not show any effect of the sleeve on static balance.

Chuang et al. (2007) divided the participants with knee OA into two groups. Group A performed the balance test without the sleeve first, then with the sleeve; group B did the opposite. The results showed a significant improvement in static balance in group A but not group B. Dynamic balance showed a significant improvement in both groups A and B in this study. The different results in static balance between the studies may be attributed to differences in the testing method, population characteristics and sleeve type.

Short-term effect of knee sleeves:

Clinical effect:

One of the earlier studies was conducted by Kirkley et al. (1999), and it included three groups of individuals with knee OA in a parallel groups study. All the groups were given a leaflet to provide some information about knee OA and maintain flexibility and use of painkillers when needed. The treatment groups included the valgus knee brace group and sleeve group. There were 119 participants included the study, and the results showed a significant reduction in the magnitude of change in pain after the 6-minute walk test and 30-second stair test in all the groups. The valgus brace group showed the highest reduction in pain, followed by the sleeve group. In the other study, performed in 2004, Mazzuca et al. compared the effect of a heat-retaining sleeve compared with a normal sleeve among individuals with tibiofemoral knee OA in a double-blinded randomised clinical trial. The study included 52 participants and showed that, in both groups, the pain score reduced significantly compared with baseline after 4 weeks, with no significant difference between the groups. After withdrawing the sleeve, both groups showed an increase in pain in the following 4 weeks

Types of the sleeve:

None of the previous studies that have investigated the effect of knee sleeves among individuals with knee OA have adopted selection criteria for the sleeve, which may have reduced the feasibility of the studies. Different off-the-shelf sleeve types have been used in previous studies including GENUTEX A2 (Cudejko et al., 2017), GENUTRAIN 7 (Schween et al., 2015), Safe-T-Sport Model # 37-350 (Collins et al., 2011a, 2011b, 2012) and Tensor-ANVISA/MS (Bryk et al., 2011). One study used custom-manufactured sleeves CB060 (Chuang et al., 2007). Other studies did not

mention the type of sleeve used in the study, thereby reducing the quality of the research (Kirkley et al., 1999; Mazzuca et al., 2004). Therefore, different types of sleeves have been used in previous studies, and it can be concluded that the sleeve type is not a key element in the pain reduction and/or functional improvement among individuals with knee OA.

Based on the previous literature, it can be concluded that the knee sleeve has an effect on knee pain in individuals with knee OA. This effect appears to be caused by one or a combination of the following factors: reducing the muscle co-contraction, improving stability, improving the confidence of the knee, reducing self-reported instability, improving balance and improving proprioception. In a recent systematic review investigating the effect of knee sleeves on knee pain and physical function (Cudejko et al., 2018a), 11 studies and the population with tibiofemoral and patellofemoral knee OA were included. The review concluded that sleeves have a moderate effect on pain and small to moderate effect of self-reported physical function in the long and short term, which supports our previous conclusion. The review highlighted the need for more studies with high quality to support the finding, since all the included RCTs were of low quality.

Several gaps can be identified in the previous literature investigating the effects of knee sleeves. The effects of sleeves on muscle co-contraction were investigated in one study, with a focus on VL/LH muscle co-contraction. However, MQ/MH co-contraction is more important, since this outcome has been correlated with the disease progression. No study has investigated the effects of sleeve on other muscle co-contractions, such as MQ/LG or LQ/LG, in healthy or individuals with knee OA. Therefore, more studies are needed that investigate the effect of knee sleeves on muscle co-contraction across different muscle pairs in healthy people and individuals with knee OA at different timepoints (immediate, short term). Furthermore, the immediate kinematic and kinetic effects of the knee sleeve were investigated in three studies, and conflicting results were found regarding EKAM. No previous study has investigated the effect of sleeves on the kinematics, kinetics and muscle co-contraction parameters in the knee among healthy people. Therefore, there is a need for more studies that investigate the effects of knee sleeves on the kinematics and kinetics of individuals with knee OA immediately, over time and in healthy populations. No previous study has compared the effect of sleeve with other types of treatment in individuals with knee OA and healthy people. Therefore, controlled trials are needed comparing the effects of sleeve with those of other treatment options in individuals with knee OA and healthy people. The effects of sleeves

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on balance was investigated in two studies, with one study only testing the dynamic balance, and more studies are needed to support the improvement in dynamic balance with knee sleeves among individuals with knee OA. Finally, no previous study has investigated the effects of knee sleeve on the pain pressure threshold, which highlights the need for more studies on this topic.

2.17.3.4 *Lateral Wedge Insoles*

A lateral wedge insole (LWI) is an orthotic device that is placed inside the shoe (Figure 2-9). It has different thicknesses, with the lateral side being thicker than the medial side. This difference in thickness leads to the lateral side being higher than the medial side, with a different angulation. The degree of angulation in lateral wedge insole studies ranges from 4 degrees to 16.8 degrees with 5 degrees being the most common. The length of the lateral wedge insole in studies also has ranged from rearfoot only to full-length insole length, however the full length lateral wedge insole has showed improved biomechanical results than rearfoot lateral wedge insole (Hinman et al., 2008). Two Japanese researchers were the first to investigate and propose the biomechanical and clinical effectiveness of lateral wedge insoles (Sasaki & Yasuda, 1987; Yasuda & Sasaki, 1987). The mechanism underlying the insole as a load-modified treatment will be discussed in the following sections.

Figure 2-9 Lateral wedge insole (Jones et al., 2014)

Mechanism:

The key biomechanical feature of using lateral wedge insoles is to modify the knee load by modifying the kinetics and kinematics of the ankle and the subtalar joint. The use of lateral wedge insoles leads to valgus of the calcaneus, which causes the femur and the tibia to have a more upright position. This laterally shifts the centre of the foot pressure leads to reduce the knee adduction moment (Kakihana et al., 2004; Levinger et al., 2010; Sasaki & Yasuda, 1987; Yasuda & Sasaki, 1987). The mechanical axes will therefore be more upright as well, which will ultimately decrease the medial loading in the medial side and the tensile force on the lateral side of the knee (Kakihana et al., 2004; Levinger et al., 2010; Sasaki & Yasuda, 1987; Yasuda & Sasaki, 1987).

Other investigators have studied the connection of lateral wedge insole use and the EKAM. The lateral wedge insole was found to align the foot into a pronation position which results in valgus moment in the ankle, which laterally shifts the centre of pressure of the ground reaction force (Crenshaw, Pollo, & Calton, 2000; Jones et al., 2014; Kerrigan et al., 2002; Maly, Culham, & Costigan, 2002). Lateral shifting in the centre of pressure reduces the knee moment arm and therefore reducing the adduction moment acting on the knee joint (Figure 2-10) (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012). A linear relationship was found between both the medial compartment loading and EKAM, and the lateral displacement of the centre of pressure (for every 1mm lateral shifting in the centre of pressure 1% and 2% reduction in medial compartment loading and EKAM respectively) (Shelburne, Torry, Steadman, & Pandy, 2008).
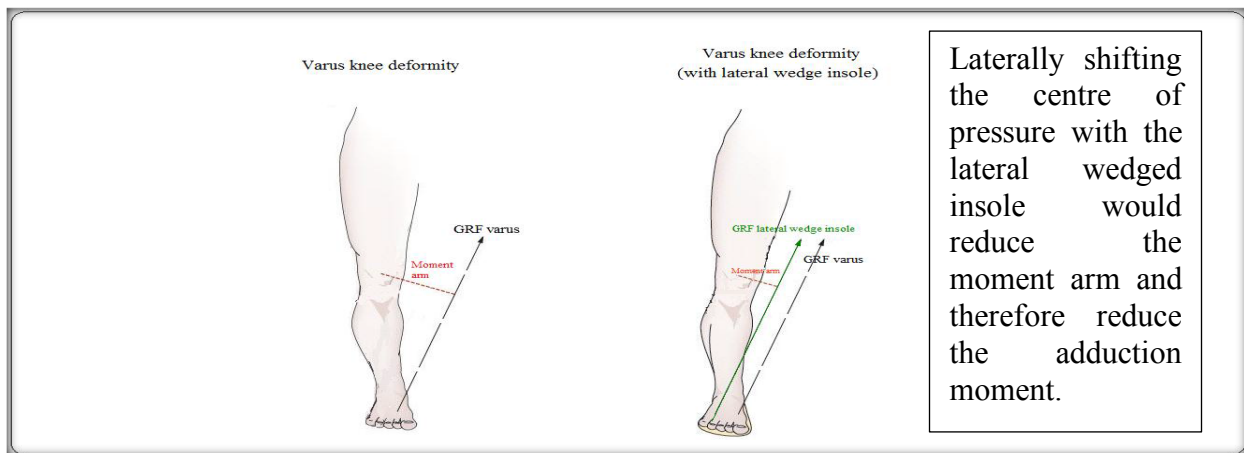
Figure 2-10 Mechanism of lateral wedge insole (Reeves & Bowling, 2011)

Since 1987, many different studies have examined the biomechanical and clinical effects of lateral wedge insoles. The first study which investigate the effect of LWI and medial wedge insole (MWE) on gait was conducted in 1997 (Ogata, Yasunaga, & Nomiyama, 1997). This study included 50 healthy and 40 medial knee OA participants. The study used uniaxial accelerometer to investigate the effect of LWI on medial and lateral thrust. The results showed that using LWI reduced the lateral thrust while using the MWI increase the thrust. Although concluded that LWI is recommended to be used by individuals with medial knee OA as the thrust is reduced and the pain is reduced, no kinetics were measured which did not allow the mechanism of insole to be investigated. Therefore, the next section will evaluate the effect of LWI on EKAM.

External knee adduction moment (EKAM):

The first study which investigate the effect of LWI in kinetics (EKAM) was conducted in 2000 using 17 healthy participants (Crenshaw et al., 2000). The study compared the effect of LWI (5 degree) to no insole in an immediate crossover study. The results showed no significant change in spatiotemporal characteristics and a significant reduction in first peak EKAM by 6.65%. The study used analytical model and showed that the medial compartment loading reduced due to EKAM reduction.

Since then several studies have investigated the effect of LWI in healthy and individuals with medial knee OA. Several studies showed significant reduction in the EKAM when using LWI (Alsancak, 2012; Chapman et al., 2015; Hinman, Bowles, & Bennell, 2009; Hinman et al., 2012; Hinman, Bowles, et al., 2008; Jones et al., 2013a, 2014; Jones, Zhang, Laxton, Findlow, & Liu, 2013c; Kakihana, Akai, Nakazawa, Naito, & Torii, 2007; Kerrigan et al., 2002).

Chapman et al. (2015) showed that using LWI (5 degree, 60 density) reduces the peak EKAM and KAAI by 5.85% and 7.95%, respectively. The study included a large number of participants (70 with medial knee OA) in an immediate randomised crossover study. The study controlled the shoe that participants wore to reduce its effect on EKAM; an Ecco Zen shoe was used for all the participants. Supporting evidence showed that using LWI (6 degree) significantly reduced the mean EKAM in individuals with medial knee OA and healthy people compared with no insole. This study was conducted on barefoot with the insole taped to the foot (Kakihana et al., 2007). In 2012, Alsanack et al. support the previous claim, showing a significant reduction in first-peak and

second-peak EKAMs with LWI (6 degree). The patients reported a reduction in pain, improvement function and reduction in analgesic use.

Hinman et al. (2008) investigated the immediate biomechanical effects of using LWI (5 degree, high density) in a randomised crossover study. The study included 40 participants with medial knee OA. The results showed significant reductions in first-peak EKAM (0.22 Nm/Bw.Ht, 4.5%), trough EKAM (0.25 Nm/Bw.Ht, 9%) and second-peak EKAM (0.15 Nm/Bw.Ht. 4.1%). This reduction was combined with a significant immediate reduction in pain during walking (24%). In 2009, Hinman et al. showed a similar immediate reduction in EKAM with LWI in individuals with medial knee OA. This reduction was maintained after 1 month, and the authors concluded that high-density LWI can maintain the reduction overtime and do not compress. In a similar population, Hinman et al. (2012) showed a significant reduction in first-peak EKAM (5.8%) and KAAI (6.3%) with the use of 5-degree high density LWI. The moment arm showed a significant reduction and the centre of foot pressure showed a significant lateral shifting with LWI use. The study included 73 participants and exhibited the mechanism behind the reduction in EKAM in the study. The study concluded that the reduction in EKAM is primarily caused by the reduction in the moment arm due to the change in the GRF position and orientation.

Other studies showed similar trends with reductions in EKAMs (first peak, trough, second peak, KAAI) ranging from 4.84% to 15.8% with LWI (5 degree) use (Jones et al., 2013, 2013c, 2014). The populations were individuals with medial knee OA in two studies (Jones et al., 2013a, 2014) and healthy individuals in one study (Jones et al., 2013c), and the design was similar among all three studies (randomised crossover investigating the immediate effect). In the long term (1 year), the effect of LWI was investigated in a randomised control trial (Barrios, Butler, Crenshaw, Royer, & Davis, 2013). Thirty-eight participants with medial knee OA were and randomly assigned to neutral insole (19 subjects) or LWI (19 subjects) with 70 density durometer. The study showed that LWI reduces EKAM and that the reduction is sustained over 12 months, while the neutral insole showed an increase in the EKAM after 12 months compared with their baseline. This provides a clear evidence that the mechanical effect of LWI is sustainable and may reduce the progression of the disease in the long term.

The biomechanical effectiveness of a lateral wedge insole on EKAM was supported by several systematic reviews. In 2012, a systematic review stated that LWI is associated with a reduction in peak EKAM among healthy people and individuals with medial knee OA (Radzimski, Mündermann, & Sole, 2012). A recent systematic review and meta-analysis included 18 studies and highlighted that using LWI resulted in small but statistically significant reduction in first-peak EKAM, second-peak EKAM and KAAI among individuals with medial knee OA (Arnold, Wong, Jones, Hill, & Thewlis, 2016). This conclusion was supported by a systematic review and meta-analysis that investigated the effect of LWI in individuals with medial knee OA. The review included 27 studies and showed that the included studies had moderate to high methodological quality. The results showed a significant small to moderate reduction in first-peak EKAM, second-peak EKAM, overall peak EKAM and KAAI in individuals with medial knee OA (Shaw et al., 2018). It can be argued that a small reduction in EKAM is important given the high increase in the risk of OA progression, which increases 6.46 times with only a 1% increase in EKAM (Miyazaki et al., 2002). Furthermore, this small reduction in EKAM may be highly important in the long run, given that individuals with knee OA are encouraged to increase their activity level in clinical guidelines (Roddy & Doherty, 2003).

Contradictory to the previous results, some studies have not identified significant reduction in EKAM with use of lateral wedge insole compared to no insole (Abdallah & Radwan, 2011; Maly et al., 2002; Moyer et al., 2013; Segal, Foster, Dhamani, Ohashi, & Yack, 2009). This might cause by several factors which have been shown to effect insole effectiveness including LWI design (angulation, length, arch support, materials) (Baker et al., 2007; Hinman et al., 2008).

Different angulation of LWI:

The difference in LWI angulation is plausible reason for the difference in EKAM reduction in previous LWI literature. Theoretically, the higher the angulation is, the higher EKAM reduction will be. However, this higher angulation may lead to ankle pain, foot discomfort and difficulty fitting the LWI into the shoe. Two previous studies examined the effects of different LWI angulations on the tibiofemoral angle and found that there was a significant reduction with using higher angulation (Rafiaee & Karimi, 2012; Toda, Tsukimura, & Kato, 2004). Interestingly, Jones et al. (2014) showed a correlation between LWI comfort and pain reduction, highlighting the

importance of this factor. Kerrigan et al. (2002) investigated the effect of using different angulations on EKAM among individuals with knee OA in an immediate crossover study. The results showed a significant reduction in first-peak EKAM (5.3%, 8.3) and second-peak EKAM (6.5, 8%) with 5-degree and 10-degree LWI compared with no insole. Although the use of 10-degree LWI showed higher reduction in EKAM, the LWI was accompanied with foot restriction and discomfort for nearly all the subjects. The authors stated that all the subjects were comfortable with the use of 5-degree LWI.

Length of LWI:

The length of the lateral wedge insole could be one of the main reasons for not identifying biomechanical and clinical effect with LWI use. The length of LWI in previous studies varied from long to rear foot LWI. The mechanism by which the rear LWI reduces EKAM requires the heel to contact the ground, as the inclination is found in the rear foot. However, the knee OA population may contact the ground with the foot flat; thus, using full-length insole will preserve the biomechanical and clinical effect of LWI. In a previous study, Hinman et al (2008) compared the effects of rear foot and full-length LWIs. The full LWI was found to reduce first and second peaks EKAM significantly compared with no insole, while the rear foot insole did not have any effect on either first or second peak EKAM. When the results for both LWIs (full length, rear length) were compared, a significant difference between the LWIs for second peak EKAM was found with better for full length (Hinman et al., 2008), highlighting the importance of choosing full length over the rear foot insole.

Arch support within the LWI:

Incorporating an arch support into the LWI could be another key factor that may increase patient compliance and produce a better clinical effect. The arch support in the LWI helps to reduce foot eversion, and therefore, it will reduce the eversion moment. Jones et al.'s (2013b) study showed that using LWI without arch support significantly increased the maximum eversion angle compared with LWI with arch support, which may place an extra load on the ankle joint. The previous claim was supported with recent study showing that reduction in pain was higher when using LWI with an arch compared with no arch or an insole with a strap (Fu et al., 2015). In a randomised clinical trial which used healthy subjects, which sought to study the effects of LWI

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with an arch versus no arch, the LWI with arch showed a better biomechanical effect. The study included four conditions, as follows: neutral insole, neutral insole with arch, LWI with arch and LWI without arch. The results showed that the mean reduction in EKAM was higher in LWI with an arch. The authors stated that the LWI with an arch allowed the participants to walk in a more natural way, so the maximum biomechanical benefit from LWI was sustained (Nakajima et al., 2009).

LWI materials:

Different LWI materials have shown significant differences in outcome, even if the same angulation was used. This shows that higher density materials may improve stability, comfort and deformability compared with low-density materials (Toda & Tsukimura, 2004a). Lower density materials may compress during walking or over time, and thus, the effect of the lateral wedge insole will be lost.

Medial compartment loading:

A small reduction in medial loading was observed with use of the lateral wedge insole compared with no insole (Kutzner et al., 2011). This study included six participants with implanted knee trays to measure the load in the medial knee compartment. In addition, Crenshaw et al. (2000) conducted a study to calculate the medial contact force based on kinematic and kinetics data using an analytical model. The study included 17 healthy participants. The results showed a significant reduction in peak medial contact force and EKAM with LWI use. The authors concluded that most of the reduction in medial contact force is caused by the reduction in EKAM by LWI (Crenshaw et al., 2000). Using a finite model, a study found that the medial contact force decreased significantly, by 16.7% and 26.5%, using 5- and 20-degree lateral wedged insoles compared with neutral insoles (Liu & Zhang, 2013).

Muscle co-contraction and muscle activity:

To the best of our knowledge (to date), no previous study has been performed that investigated the effect of LWI in muscle co-contraction. One study was identified that investigated the overall effect of LWI in LQ and MQ muscle activity (Giffin, Stanish, MacKinnon, & MacLeod, 1995). The previous study did not find any effect for LWI on this activity. However, no change in EMG

activity was expected, since no change in EKAM was observed with LWI in the same study. This can be attributed to two factors; namely using rear-foot LWI and including participants with severe knee OA who were candidates for osteotomy. Measuring the change in muscle co-contraction is important, given that increased muscle co-contraction leads to increased knee compression force (Brandon et al., 2014; Winby et al., 2013), thereby accelerating the knee OA progression (Hodges et al., 2015) and increasing the likelihood of TKR (Hubley-Kozey, Hatfield, & Stanish, 2013). Therefore, there is a need for studies considering the effects of LWI on muscle co-contraction among healthy people and individuals with medial knee OA.

Clinical effects:

Several studies have examined the effects of lateral wedge insoles on clinical outcomes in individuals with knee OA. The clinical effects (pain, analgesic intake) of LWI was first investigated in 1987 by Sasaki and Yasuda. This study included two groups of individuals with medial knee OA and monitored the participants for 1–5 years. Two parallel groups were used; one group was treated with LWI combined with indomethacin (600 mg/day), while the other group only used indomethacin (600 mg/day). The results of the study showed significant reduction in knee pain and walking ability in the LWI group compared with the other group. Since then, several studies attempted to measure the clinical effects of LWI (Arazpour et al., 2013; Ashraf et al., 2014; Baker et al., 2007; Barrios et al., 2009; Campos et al., 2015; Fang et al., 2006; Hatef, Mirfeizi, Sahebari, Jokar, & Mirheydari, 2014; Jones et al., 2013c; Rafiaee & Karimi, 2012).

In 2006, Frag et al. investigate the effect of LWI (4 degree, 60 durometers) on 28 individuals with knee OA. After 4 weeks of treatment, the group demonstrated significant improvement in the WOMAC pain (17%), stiffness and function subscales and in pain during ascending and descending stairs. Fafiee and Karimi's (2012) study supported the previous finding, showing a significant reduction in pain and quality of life after 2 months of 6-mm LWI use among individuals with medial knee OA compared with their personal baselines. A recent study compared the effectiveness of LWI with 10 mm (6 degree, 60 durometers) and a bespoke valgus knee brace in individuals with medial knee OA (Rafiaee & Karimi, 2012). The study showed significant reductions in peak EKAM and VAS pain in the LWI group after 6 weeks compared to their personal baselines, from 6.75 to 3.91 out of 10. With a similar aim to the prior study, Jones et al. (2013) compared the biomechanical and clinical effectiveness of LWI (5 degree) and off-the-shelf

valgus knee brace. The study was a crossover and included 28 participants with 2 weeks of treatment and 2 weeks' washout. The LWI demonstrated significant reductions in peak EKAM, KAAI and WOMAC pain and function compared with the baseline.

Two other studies were conducted in 2014 showed significant reduction in pain with LWI compared to the same OA group baseline. The first study was a randomised controlled trial including included 75 participants treated with medial knee OA (Hatef et al., 2014). The pain (mean reduction 29.3 from a 100-point VAS scale), function and number of NSAIDs used in the last 2 weeks of the study reduced significantly after 2 months of using LWI (5 degree). The second study had a similar design and similar population (medial knee OA) to those of the first study. The results were in agreement with the first study, showing significant reductions in pain and function after 3 months of LWI use compared with the same group baseline (Ashraf et al., 2014).

Looking at the other side of equation, in studies that compared a LWI group with a control group (neutral insole), no significant difference in the effects was identified (Baker et al., 2007; Barrios et al., 2009; Bennell et al., 2011; Campos et al., 2015; Maillefert et al., 2001; Pham et al., 2004). All these studies had matched populations (medial knee OA) and the design was parallel group (Baker et al., 2007; Barrios et al., 2009; Bennell et al., 2011; Campos et al., 2015; Maillefert et al., 2001; Pham et al., 2004) or crossover with 4 weeks of washout in between (Baker et al., 2007). The treatment periods ranged from 6 weeks to 2 years, with 6 weeks in Baker et al.'s (2007) study, 6 months in the studies by Maillefer et al. (2001) and Campos et al. (2015), 1 year in the studies by Barrios et al. (2009) and Bennell et al. (2011) and 2 years in Pham et al.'s (2004) study. The degree of inclination of LWI was fixed across all LWI group in the studies by Campos et al. (2015) 8 degree, Bennell et al. (2011) and Baker et al. (2007) 5 degree. In contrast, Barsion et al. (2009) used individualised LWI degrees of inclination based on the lateral step-down test, with average of 9.1 degrees. Two studies did not mention the degree of inclination, which is considered a limitation, although they did state that it was individualised based on pedometer evaluation (Maillefert et al., 2001; Pham et al., 2004).

The results of the previous studies showed no significant difference between the LWI and neutral insole in terms of WOMAC pain (Baker et al., 2007; Barrios et al., 2009; Bennell et al., 2011; Campos et al., 2015; Maillefert et al., 2001; Pham et al., 2004), WOMAC stiffness and function

(Barrios, Crenshaw, et al., 2009; Bennell et al., 2011; Maillefert et al., 2001; Pham et al., 2004), physical function tests (Baker et al., 2007; Barrios et al., 2009), medial cartilage volume (Bennell et al., 2011) and the joint space narrowing rate (Pham et al., 2004). When looking at rescue medication use, one study found no significant difference between the LWI and neutral insole groups, while two studies showed significant reductions in NSAIDs compared with baseline (Maillefert et al., 2001) and neutral insole use (Pham et al., 2004).

One of the major limitation of all the previous studies is that they have not included the biomechanical effect of the treatment, which is the key mechanism of LWI. Furthermore, Bennell et al. (2011) used a high-density LWI made from ethyl-vinyl acetate (similar to running shoes) that was not comfortable for participants. In 2014, Jones and other collages found a significant correlation between insole comfort and pain, which means that the comfort of the insole may affect the pain score change.

A recent systematic review showed similar results to the above review exhibiting no significant difference in pain and function between using an LWI and neutral insole among individuals with medial knee OA (Penny, Geere, & Smith, 2013). This led the authors to conclude that there is limited evidence to support the effect of LWI on pain. Parkes et al. (2013) conducted a meta-analysis for investigating the effect of LWI on pain. Twelve studies were included, of which 7 used neutral insoles as a control treatment. The results of the meta-analysis showed no association (statistically, clinically important) between LWI and pain, leading to no support for the use of LWI (Parkes et al., 2013). A recent systematic review and meta-analysis concluded that LWI has no benefit on pain when compared to neutral insole (Zhang et al., 2018).

To conclude this section based on the previous review, LWI appears to reduce the EKAM with immediate use and over the long term. LWI with a 5-degree medial inclination and arch support made of high-density material has a great effect on EKAM, providing comfort to users and exhibiting the ability to maintain the reduction over the long term. Therefore, using LWI (5-degree, arch supported) made with high-density material seems to be the most appropriate type for clinical trials. When looking at the effect of LWI on pain, the evidence supports the reduction of pain compared with the baseline. However, when considering a competitor (neutral insole), LWI failed to show a higher reduction.

The non-significant difference between LWI and neutral insole may have been caused by several factors. It may be that the treatment is not effective at targeting pain or the placebo treatment provides some effect similar to treatment. The mechanism of treatment should be known, and the placebo treatment should not provide the same mechanism or there is a significant chance that the trial will fail to detect a difference (Felson et al., 2016). In this situation, the neutral insole does not have the mechanism of shifting the centre of pressure laterally, and this emphasises that the LWI does not reduce pain. In addition, previous studies showed that some subjects do not respond to LWI (no reduction in EKAM or EKAM increase) (Butler et al., 2007; Crenshaw et al., 2000; Hinman et al., 2008a, 2008b, 2012,; Kakihana et al., 2005, 2007; Kerrigan et al., 2002). Including such subjects (non-responders) in the data analysis may mask the effect of pain reduction in those that respond to treatment. However, Jones et al. (2014) found no difference in pain reduction between responders and non-responders. Although several studies have shown good LWI compliance, pain reduction may affect long-term compliance for such treatment, since patients are interested in pain reduction. Other possible explanations for the non-significant difference between the LWI and neutral insole is that the EKAM reduction provided is not sufficient to provide pain reduction or that pain depends on EKAM and other factors as well, such as laxity, self-reported knee instability, proprioception and muscle co-contraction.

2.18 **Gaps in the literature**

One of the potential uses of LWI that has been shown to have a positive mechanical response is combining them with a device with better pain-relieving results. A combination of a LWI and a valgus knee brace has been investigated in three studies, of which two were randomised crossover trials (Al-Zahrani et al., 2013b; Moyer et al., 2013) and one was a non-randomised crossover trial (Fu et al., 2015). In all the studies, combination treatments showed a higher reduction of first or second EKAM than individual treatment did. Fu et al. (2015) investigated the effects of a 4-week treatment on pain and showed a higher reduction in the case of combined treatments; however, compliance was lower in the combined treatment group (valgus brace and LWI) than it was in the other insole groups.

Due to the low compliance with using valgus knee braces, a simple knee sleeve, which has been shown to have good compliance (Callaghan et al., 2015), could be used with LWI. Furthermore,

the simple knee sleeve, unlike the valgus knee brace, is easy to use and apply, as well as being cheaper. Through this combination of reduced muscle co-contraction, simple knee sleeve use and the EKAM via the LWI, it may be possible to achieve a consistent reduction in pain and loading. A reduction of the loading means lower knee OA progression, lower knee OA health costs and improved patient activity levels. All of these factors will minimise the potential secondary complications of knee OA. Furthermore, the use of a sleeve with LWI targeting the pain may also help in improving long-term LWI treatment compliance.

In 1999, Kirkley et al. conducted a study that compared the valgus knee brace with a simple knee sleeve. The results of this study showed a significant reduction in most clinical outcomes between the valgus and control group but not the sleeve group. Nevertheless, the simple knee group showed a significant reduction compared with the baseline in clinical outcomes (pain, function) but was not mentioned if statistically significant. As the sleeve provides little mechanical stability, another mechanism, such as co-contraction reduction, may have been responsible for this improvement. Supporting evidence showed a reduction in VL/LH muscle co-contraction with a simple knee sleeve use during walking in individuals with knee osteoarthritis (Collins et al., 2011).

Encouraging results showing that using both a LWI with subtalar strap and knee sleeve as a treatment exhibited a greater increase in the number of individuals who could walk without pain on uneven ground than a lateral wedge insole alone did (Keyaki & Toda, 2010). However, more details about the study could not be gathered because it was published in the Japanese language.

No study has evaluated the effect of a sleeve on the MQ/MH co-contraction among healthy and individuals with medial knee OA, and this is important, since it was correlated with the progression of the disease in individuals with medial knee OA. Furthermore, the effect of a sleeve on EKAM in individuals with knee OA requires more studies, since one study showed a reduction (Schween et al., 2015) and one showed no significant change (Collins et al., 2014). Moreover, no study has investigated the effect of sleeve on kinematic, kinetics and muscle co-contraction in healthy participants in one study. Moreover, it is important to compare the effect of a sleeve among OA and healthy individuals with that of other types of treatment, such as LWI or combined treatment (LWI + sleeve). No previous study has investigated the effects of combined treatment among healthy people or individuals with knee OA. Designing such a study will help in the

recommendation for treating individuals with medial knee OA, as combining the reduction in EKAM and muscle co-contraction may lead to reduced progression of the disease and reduce pain. Balance is another important element that is expected to be improved by the treatment, as this is considered as a risk factor for falling among elderly people (Hinman et al., 2002; Wegener, Kisner, & Nichols, 1997). No previous study has investigated the effects of a sleeve, LWI and combined treatment (sleeve + LWI) on dynamic balance among individuals with medial knee OA. Therefore, there is a clear need for more studies. Finally, the effects of the sleeve, LWI and combined treatment on the pain pressure threshold has never been investigated, and this is important, since individuals with knee OA have been found to have lower pain pressure thresholds (Arendt-Nielsen et al., 2010; Imamura et al., 2008; Wessel, 1995).

To fill the gap in the literature, two studies were conducted. The first one investigated the immediate effect of LWI, sleeve, combined treatment (LWI + sleeve) and no treatment on biomechanical outcomes among healthy people in a crossover design. The second study investigated the immediate and 6-week effects of LWI, sleeve and combined treatment (LWI + sleeve) on the biomechanical and clinical outcomes in individuals with medial knee OA in a parallel group design.

2.19 Thesis aims

2.19.1 General aim of the thesis

The overall objective of the thesis is to understand the effects of combined treatments (simple knee sleeve and lateral wedge insole) and additionally to compare their effectiveness to the lateral wedge insole and simple knee sleeve, both biomechanically and clinically.

First study (healthy study) null hypotheses

Primary null hypothesis:

1- There is no significant immediate change in knee loading (first peak EKAM, trough EKAM, second peak EKAM, KAAI) when using the combined treatment (lateral wedge insole, simple knee sleeve) or individuals treatment compared to individual treatment, combined treatment or no treatment.

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2- There is no significant immediate change in muscle co-contraction when using the combined treatment (lateral wedge insole, simple knee sleeve) or individuals treatment compared to individual treatment, combined treatment or no treatment.

Secondary null hypothesis:

1- There is no significant immediate change in GRF, knee flexion moment, knee joint angles in sagittal plane (knee flexion angle at initial contact, maximum knee flexion angle at loading response, minimum knee angle at mid-stance, maximum knee flexion angle at swing) and ROM of the knee joint angle in frontal plane when using the combined treatment (lateral wedge insole, simple knee sleeve) or individuals treatment compared to individual treatment, combined treatment or no treatment.

Second study (medial knee OA study) null hypotheses:

1- There is no significant difference in EKAM when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve) (immediate, 6 weeks).

2- There is no significant difference in pain after 6 weeks when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

3- There is no significant difference in muscle co-contraction when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve) (immediate, 6 weeks).

4- There is no significant difference in dynamic balance after 6 weeks when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

5- There is no significant difference in pain pressure threshold after 6 weeks when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment.

6- There is no significant difference in functional tests (40-metre fast-paced walk test, 30-second chair-stand test, a stair-climb test) after 6 weeks when using combined treatments

(lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

Chapter 3:   Methods

3.1 Chapter overview

This chapter describes the generic methods that have been used in the thesis, which are applicable to all of the studies. Specific changes to other study protocols are considered in subsequent chapters. This chapter starts with an overview of the research environment and the criteria used to define healthy and individuals with medial knee OA. Following this, the criteria which were developed and used to select the appropriate type of the treatment to be used in this thesis are clearly stated, before a clear gait analysis description is provided. The second part of this chapter comprises two studies that were undertaken to guide the researcher for developing future studies. The first study investigates the reliability of biomechanical outcomes among healthy individuals, while the second considers the reliability of biomechanical, balance and other clinical outcomes used to investigate the treatment efficacy for individuals with knee OA.

3.2 Research Environment

The gait analysis work was completed in the two gait laboratories of the University of Salford in the United Kingdom and the gait laboratory of University of Hail in Saudi Arabia. Three gait analysis systems were used to complete the studies reported in this thesis.

3.2.1 Podiatry gait analysis lab at Salford University

A 16 camera motion analysis system (Oqus infra-red motion cameras, Qualisys AB, Gothenburg, Sweden) was used for motion capture at a sampling rate of 100 Hz. The gait lab is 15 metres long and six metres wide. Four force plates (Advanced Mechanical Technology Incorporation (AMTI) force plate, Type BP400600, Watertown, USA) installed in the floor along the walking track of the gait lab were used to collect force data at a sampling rate of 1,000 Hz (Figure 3-1).

Figure 3-1 The Podiatry gait lab at the University of Salford

3.2.2 The Brian Blatchford gait analysis lab at Salford University

A 10-camera Vicon motion analysis system (T30/40 infra-red motion cameras, Oxford Metrics, Oxford, UK) was used at a sampling rate of 100Hz. Four force platforms (Kistler force plate, Type 9286AA and Type 9281B, Winterthur, Switzerland) are mounted in a 15-metre long and six-metre wide lab. The sampling rate of the Force platforms is 1,000 Hz (Figure 3-2).
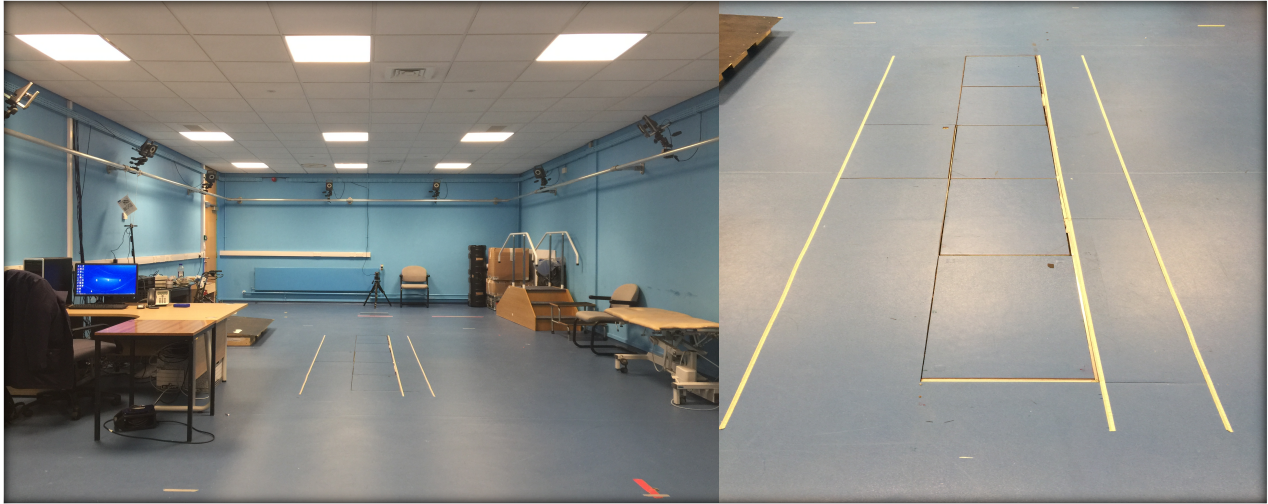
Figure 3-2 The Brian Blatchford gait lab at the University of Salford.

3.2.3 Hail University gait analysis lab at Hail University

A 10-camera Vicon motion analysis system (Vicon-Bonita infra-red motion cameras, Oxford Metrics, Oxford, UK) was used at a 100Hz sampling rate. Two force platforms (Advanced

Mechanical Technology Incorporation (AMTI) force plate, Type OR67, Watertown, USA) are mounted in a 12-metre-long and seven-metre wide lab. The sampling rate of the Force platforms used is 1,000 Hz (Figure 3-3).

Figure 3-3 The gait lab in the University of Hail.

3.3 Relation between labs

As three different labs were used to collect the data in this thesis, it was expected that each lab would provide similar kinetics and kinematics results, but it was necessary to ensure this. One subject attended the three labs (Podiatry lab, Hail lab, Brain Blatchford lab) where one investigator placed all markers. The individual performed self-selected walking trials in each of the labs to determine whether there was any difference in the primary outcome measure (EKAM) between labs. The knee sagittal angles and ROM were also compared between the three labs. As can be seen from the Table 3-1, all the labs provided similar EKAMs value. Furthermore, the knee angles and ROM in sagittal plane were similar across labs, which supports that all labs provide similar kinetics and kinematics value results during walking, regarding the type and location of the system (Table 3-1). Although three labs were used in current thesis, each participant visited one lab so they were their own control and thus any differences between the labs would not have an influence on this.

Table 3-1 EKAM and knee joint angles in sagittal plane and ROM during walking in the three labs for one participants.

Variable Mean	Podiatry gait analysis lab	The Brian Blatchford gait analysis lab	Hail University gait analysis lab
1st peak EKAM (Nm/Kg)	0.67	0.68	0.66
2nd Peak EKAM (Nm/Kg)	0.47	0.49	0.49
KAAI (Nm/kg*s)	0.21	0.20	0.22
Knee flexion angle at initial contact (degree)	2.49	6.45	4.93
Maximum knee flexion peak angle at loading response (degree)	19.81	22.87	21.11
Minimum knee flexion angle at loading mid-stance (degree)	7.86	6.09	5.32
Maximum knee flexion peak angle at swing (degree)	76.01	77.70	76.26
Knee sagittal plane ROM during walking (degree)	76.39	73.95	74.01

3.4 Recruitment

As there were two centres involved in the data collection, the recruitment of these individuals is detailed for each source:

University of Salford

The participants were recruited by advertising on posters, which were placed around the university campus, as well as invitation letters, which were sent to individuals on the Knee OA database held by Professor Richard Jones. Recruitment incorporated referrals from the Salford Royal NHS Foundation Trust at Hope Hospital, Salford; the Salford Health Matters group; and the Stockport NHS Foundation Trust. Additionally, individuals eligible through private musculoskeletal and orthopaedic clinics were recruited. Salford University ethically approved the experiments to be conducted in their labs (see Appendix A and B).

University of Hail

The participants were recruited by the researcher and physiotherapy staff at King Kalid Hospital. Hail University agreed for the experiments to be conducted in their labs (see Appendix C).

3.5 Inclusion and exclusion Criterial

3.5.1.1 *Healthy subject*

Individuals who met the following criteria were eligible to participate in this study: healthy adult aged 20–60 years old with no lower limb deformity or history of injury of the pelvis, back or lower limbs in the previous year and ability to walk without the assistance of devices or aids. Individuals with any neurological or musculoskeletal disorder known to affect their ability to walk were excluded. Any individual not able to give informed consent or with an obvious deformity of the foot or lower limb was excluded. Any subject who was unable to understand and follow the procedure was eliminated as a participant.

3.5.1.2 *Individuals with knee OA*

To be eligible to participate in the study, individuals had to have medial knee OA confirmed radiologically by a physician and using the ACR criteria by the researcher. The ACR criteria define OA as pain reported on most of the days of the previous month, accompanied by three of the following characteristics: A) age older than 50 years, B) 30 minutes of joint stiffness, C) bony enlargement, D) bony tenderness on the medial side of the knee or E) crepitus. Furthermore, participants had to be between the ages of 35 and 85 years old and able to walk without assisted devices for 100m non-stop, ensuring that they would be able to complete this study's protocol. The age range (35–85 years) was selected because this range has been identified as having highest incidence of knee OA (Losina et al., 2013); people older than 85 years were not included due to the high amount of walking they would need to complete. Individuals needed to have a diagnosis of pain during walking on a flat surface, determined via a VAS questionnaire (at least 3 out of 10) to allow room for reduction in pain with the treatment.

Individuals with knee OA were excluded if they had more pain localised to the patellofemoral or lateral joint than the medial knee side on examination. The individuals could not have had any neurological impairment or orthopaedic surgery known to affect their ability to walk at another joint. Individuals were also excluded if they had previous high tibial osteotomy, any other realignment operation or a total knee replacement on the contralateral side. Any condition contraindicating orthosis (sleeve or LWI) use. Steroid injection to the affected intra-articular knee

joint space in the previous 6 months. Current use of any orthosis or previous use in the last 6 months. Any participant who was unable to understand and follow the procedure was eliminated.

3.6 Treatments selection criteria

3.6.1 *Lateral wedge insole*

Five degree, full length, arch supported, lateral wedge insoles (70 durometer) were used in this study (see Figure 3-4). The rationale for using this LWI is that arch support LWI have been revealed to show better results than LWI without arch support (Fu et al., 2015; Jones et al., 2013c; Nakajima et al., 2009). Furthermore, the maximum eversion angle is significantly higher in LWI with no anti-pronated device, which may place an extra load on the joints (Jones et al., 2013c). Full length LWI have been found to reduce the EKAM (surrogate measurement of the loading) significantly, while the rearfoot LWI has not shown a significant reduction (Hinman et al., 2008a). Insole comfort has been identified as being correlated with pain reduction (Jones et al., 2014), which highlights the importance of this variable in choosing the most appropriate insole. A previous study has shown that all subjects were comfortable with the use of five degree lateral wedge insoles, while higher angulation was not comfortable (Kerrigan et al., 2002). Nevertheless, five degree lateral wedge insoles have shown significant reduction in EKAM (Alshawabka et al., 2014; Hinman et al., 2012; Jones et al., 2013c).

Figure 3-4 Salford lateral wedge insole.

3.6.2 Combined treatment selection criteria

Before proceeding to the next step, it was necessary to build up a criterion to help to select which treatment to combine with LWI. The following criteria were developed to select an adjunct therapy along with LWI to help reduce pain. This is consistent with our aim to provide successful treatment, which was defined as treatment that can reduce joint loading and improve pain. To select the combined therapy, the treatment had to meet the following criteria:

- Previously proven to reduce pain
- Has low side effects or no side effects
- Has good compliance
- Not expensive
- If the device can reduce loading, this will be preferred

The following Table 3-2 shows conservative treatments and application of the selection criteria based on studies from the literature review in chapter two. Based on the following table, it can be seen that a simple knee sleeve is the best choice, as it is capable of reducing pain and muscle co-contraction (loading) and has good compliance and low cost. Moreover, the sleeve is easy to use, which makes is easily and widely applicable in clinical practice.

Table 3-2 Application of the selection criteria to conservative treatment.

Treatment	Pain	EKAM	Muscle co-contraction	Compliance and ease of use	Side effects and limitations	Cost
Valgus knee brace	Improved	Decreased	Decreased	Low compliance and difficult for some patients to use	May cause irritation	Moderate to high
Pharmaceutical modalities	Improved	Increased	Not previously investigated	Compliance may be good and easy to use	May cause a lot of side effects and toxicity	High
Gait strategies	Improved	Decreased	Increased	Requires high effort from patients	May not be applicable to all patients	High due to the need for training courses
Physiotherapist modalities (exercises)	Improved	No change	Decreased	Low	No clear evidence which program is best and evidence on dose is limited	High due to physiotherapy costs
Footwear devices	Improved	Decreased	Not investigated	Depends on each device. However, compliance may be limited due to the need to use one shoe for all occasions	Not mentioned	Moderate to high
Simple knee sleeve	Improved	Contradictory study results. One study showed a decrease and one showed no change	Decreased	Good compliance and easy to use	Minimal or none	Low

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3.6.3 *Simple Knee sleeve*

Based on the previous chapter two, several mechanisms can be attributed to the pain reduction and functional improvement observed with sleeve use, as illustrated in the Figure 3-5 below. Theoretically, it is possible that one sleeve provides better pain reduction than other sleeves due to the design of the sleeve or other factors. The most important finding is that in all previous sleeve studies, in individuals with knee OA showed pain improvement, which indicates that all sleeve types reduce pain. Therefore, from a clinical practice perspective, sacrificing some of the effects (pain reduction) in favour of better compliance in the long term seems to be more important.
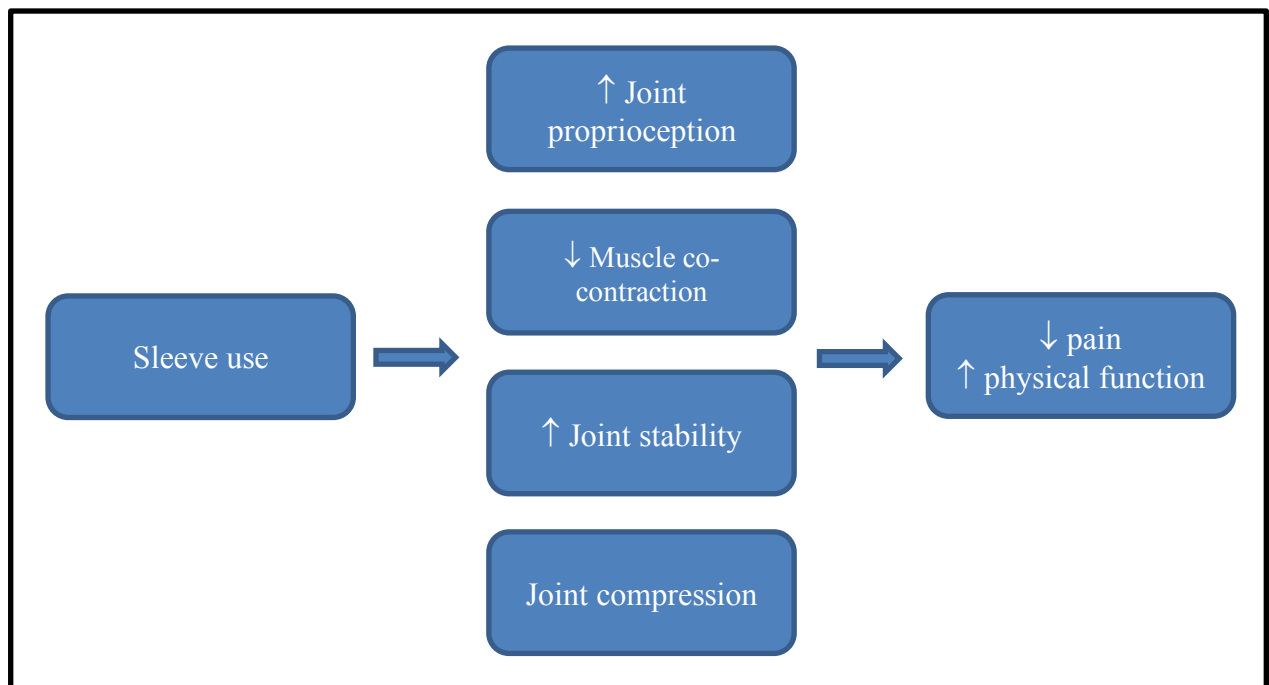
Figure 3-5 Mechanism of pain reduction with sleeve application

A previous study has investigated the effect of three different knee sleeve treatments (thermal sleeve, hinged brace, simple knee sleeve), and it showed a higher number of withdrawals for the hinged sleeve at 68.4 %, compared to 21.1% for the simple knee sleeve (Toda, 2009). Another study compared the effectiveness of lateral wedge insoles with strap use with two groups of combined treatments for the same insole (long simple sleeve, short simple sleeve). The results of the study showed a significant increase in the number of individuals who could walk without pain on uneven ground in the combined treatments groups. However, the withdrawals were higher for

the long sleeve in the combined treatment group (36.1%) than in the short sleeve combined treatment group (8.1%) (Keyaki & Toda, 2010). A sleeve that is wrapped around the joint is easier to be used than a slide-on sleeve because reduced ROM is supposed to be a characteristic for individuals with OA (Dekker, van Dijk, & Veenhof, 2009) and have limited knee ROM in flexion (Holla et al., 2011; C. R. C. Walker, Myles, Nutton, & Rowe, 2001).

Thus, the focus of the selection criteria was compliance, and the following criteria were adopted. To confirm previous studies about the preference and better compliance for short sleeves, three sleeves were chosen from the market. The characteristics of the sleeves and the possible mechanism of the effects are presented in Table 3-3.

Table 3-3 Sleeves' characteristics and possible mechanisms of the effect.

Characteristics	Sleeve A	Sleeve B	Sleeve C
Method of wear	Wrapped around the joint	Pull-through sleeve	Wrapped around the joint
Tightness	Adjustable, with two straps	Non-Adjustable	Adjustable, with three straps
Materials	Stretchable and rough	Stretchable and soft	Stretchable and soft
Anti-slip rubber	No	Yes, on the top of the sleeve	Yes, on the top and bottom
Length (cm)	29.4	33	18.5
Patellar opening	Yes	No	Yes
Patellar pad	No	Yes	Yes
Support	Two spirals for support on each side	One spring for support on each side	Two springs for support on each side
The link between the possible mechanisms of the three sleeves and their designs	-Two spirals for support, which may provide more support, increase self-confidence and reduce muscle co-contraction. -Rough material may stimulate skin receptors, improve proprioception and decrease pain signal transmission by stimulating skin receptors. -Adjustable straps, which may help increase pressure, reduce oedema and improve proprioception.	- One spring for support, which may provide support, increase self-confidence and reduce muscle co-contraction, although less so than sleeves A and B. - Soft material may simulate skin receptors, improve proprioception and decrease pain signal transmission by stimulating skin receptors, although possibly less so than sleeve A. - Constant pressure may increase pressure, reduce oedema and improve proprioception, although possibly less so than sleeve A and B.	- Two springs for support, which may provide more support, increase self-confidence and reduce muscle co-contraction. - Soft material may simulate skin receptors, improve proprioception and decrease pain signal transmission by stimulating skin receptors, although possibly less so than sleeve A. - Adjustable straps, which may help increase pressure, reduce oedema and improve proprioception.
Disadvantages	- The sleeve may migrate down the limb during activity. - Materials are rough and uncomfortable.	- No strap (constant pressure) - Difficult to wear	- Covers less area and therefore has less area to stimulate. However, this may improve compliance.

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A small randomised trial was conducted on five individuals with knee OA. Three different types of sleeves were given to each participant to test for comfort and ease of use; the participants were asked two questions (see Table 3-4). The sequence of each sleeve's use was random, and the results show that sleeve C (see Figure 3-6) was the best for both comfort and ease of use (see Table 3-5), and therefore it has been selected for use in this study.

The selected sleeve met three criteria:

- Comfortable, therefore will have better compliance.
- Easy to use, therefore will have better compliance.
- Short, which confirms the previous study showing better compliance for a short sleeve than a long sleeve.
- Has no hinge support.

Table 3-4 Questionnaire to evaluate the comfort and ease of use of three different sleeves.

Out of ten how do you rate the comfort of this sleeve during walking and sitting?	Not comfortable at all 0-1-2-3-4-5-6-7-8-9-10 max comfort
Out of ten, how do you rate the ease of sleeve use (put on and take off)?	Difficult 0-1-2-3-4-5-6-7-8-9-10 really easy to use

Table 3-5 The results of questionnaire to quantify the comfort and ease of use of three different sleeves

	Comfort			Ease of use		
Sleeve type	A	B	C	A	B	C
Average score out of ten	5.2	8.4	8.6	7.6	5.4	8.4

Figure 3-6 Different types of sleeve.

3.7 Data collection procedures

Prior to the participants' arrival, the gait lab was prepared, and all equipment was checked and calibrated. A clear verbal description of all of the equipment and the testing procedure was given to each participant. Each participant was given time to ask any questions they had before they were given the consent from. Each participant was given enough time to read and sign the consent form before starting the experiment. Each Participant then was asked to change into t-shirts and shorts, since this was important for measuring the necessary data. Demographic details such as date of birth, height, mass and shoe size were recorded.

Kinematic data were collected using motion capture cameras that emit infrared light, which is reflected from the markers to the camera in order to provide the two-dimensional position of each marker. The three-dimensional position of each marker is then calculated from the two-dimensional position and the relative position of the cameras to the laboratory's global coordinate system (Kaufman and Sutherland, 2006). The Qualisys Track Manager and Vicon Nexus programs used diverse types of external and internal camera parameters, such as the orientation of the infrared camera sensor relative to the global coordinate system and the focal length of the infrared camera lens, to modify the markers' 2D positions into a beam. This beam emitted from the infrared camera and ended (before it was reflected) at the marker location. At least two infrared cameras,

and more than one beam, are needed to identify the 3D positioning of a given marker in the global coordinate system. Three non-collinear markers or more in each segment needed to be seen by the cameras in order to identify the segment location and alignment for each marker placement adopted in this study. When adjacent segment locations and alignments were obtained in the same way, the angle between segments could be identified.

3.8 Calibration

3.8.1 Qualisys system

To calibrate the system two steps were followed. A static calibration in which the L-Frame (Figure 3-7) is used to determine the position and orientation of the cameras. The L-Frame which has 4 markers and was placed on the corner of the force plate parallel to edges (Figure 3-7). The second step was to perform the dynamic calibration in order to calibrate the volume using the T-shaped calibration wand (Figure 3-7). After placing the L-Frame on the parallel to edges of the force plate dynamic calibration start by waving the L-shaped wand in the desired volume for 60 second. Once the calibration finished the calibration residual bar will indicate if the procedure was successful or not. For the calibration to be accepted the residual volume results should be below 1mm for each camera.
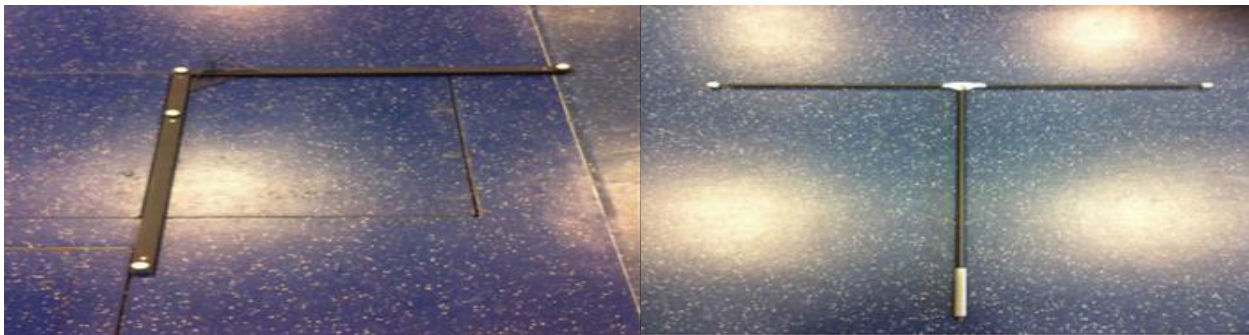
Figure 3-7 Left picture show the L-shaped frame while right picture shows the T-shaped calibration wand frame for Qualisys system.

3.8.2 Vicon system

The calibration of Vicon system is slightly different than Qualisys system although it has two steps in which each step is done separately. The first step is called cameras calibration. In this step T-shaped calibration wand with five LED markers (Figure 3-8) is waved in the desired volume until

a red light turn into green in each camera on the screen which indicate successful calibration. The image error in each camera should be equal or below 0.2 to indicate a good calibration if not the process was redone. The next step is to set the volume origin after finishing the first step. In this step the T-shaped wand is placed on the force plate parallel to two edges of the force plate (Figure 3-8). Next, the program set origin button is used to place the origin volume.
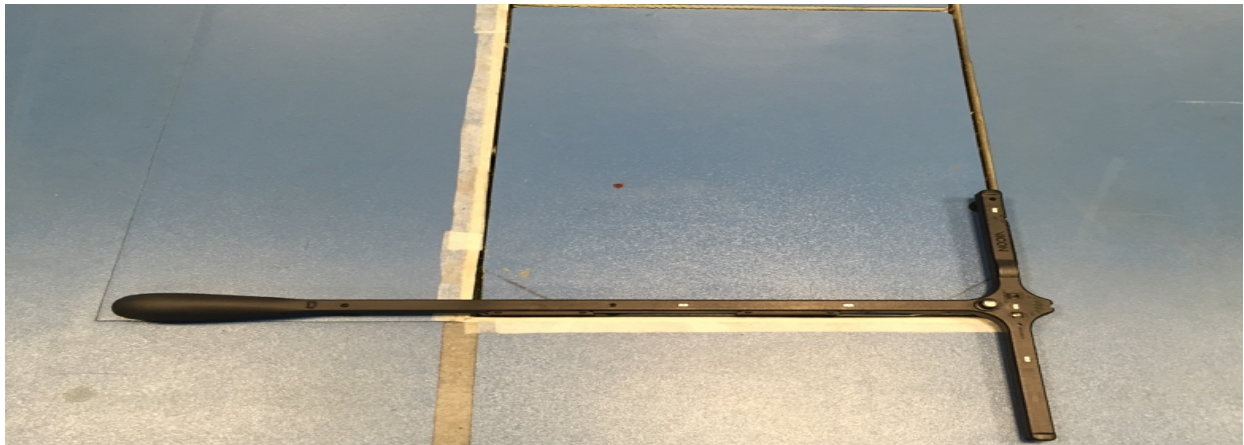
Figure 3-8 T-shaped calibration wand for Vicon system.

The laboratory global (co-ordinate) system is represented by the three axis L-Frame. The X axis is denoting for anterior to posterior axis, the Y axis denoting for medial to lateral axis while the Z axis is denoting for the vertical axis (up and down). In this thesis the X axis anterior is forward, the Y axis medially to the lift and Z axis vertical to upward.

3.9 Biomechanical assessment

Several biomechanical models have been suggested for use in gait studies. The most common in clinical studies is the Helen Hayes (HH) model, which has different variations (Kadaba, Ramakrishnan, & Wootten, 1990). The disadvantage of the HH model is that it provides only three rotational movements of the knee and hip joints and only two degrees of freedom of the ankle joint. One of the main reasons for implementing this model is that it was developed based on a less advanced measurement system (low-resolution imaging system), and so fewer markers, with larger distances between them, so the marker signals can be captured successfully (C-Motion, 2018; Della Croce, Leardini, Chiari, & Cappozzo, 2005). Moreover, the anatomical markers that were used to track the segment movements may result in errors in the distal segment due to inaccuracies

in the movement of the proximal segment. This introduced errors in the measured data (Cereatti, Camomilla, Vannozzi, & Cappozzo, 2007; Schwartz, Trost, & Wervey, 2004).

A later model, with six degrees of freedom, has since been developed, using technical markers to track each segment's movement separately, allowing for six degrees of freedom (three translational, three rotational) (Aurelio Cappozzo, Della Croce, Leardini, & Chiari, 2005; Cereatti et al., 2007). Reductions in measurement errors have been achieved using this new model (versus the old model) (Cereatti et al., 2007). Therefore, this model (Calibrated Anatomical System Technique (CAST)) is preferred for use because it overcomes some of the old model's theoretical limitations, while also producing comparable performance (Collins, Ghoussayni, Ewins, & Kent, 2009).

Marker placement

In the study, the lower limbs were assumed as seven segments, which were the pelvis, and the right and left thighs, shanks and feet. To calculate the joint kinetics and kinematics of the lower extremities in 3D, the positions and orientations of each segment that is represented by its local coordinate system must be determined with skin retro reflective markers during motion. Each foot was treated as a single segment and its motion was tracked with the four markers on the head of the first, second, and fifth metatarsal and heel (Calcaneus). The hip, knee, and ankle joints were determined by the skin mounted markers on the anatomical landmark, which were the posterior superior of the iliac spine (PSIS), the anterior superior iliac spine (ASIS), the iliac crest (IC), the greater trochanter (GT), the medial femoral condyle, the lateral femoral condyle, the lateral malleolus, and the medial malleolus (see Table 3-6).

These anatomical landmarks match the CAST method (Cappozzo, Catani, Croce, & Leardini, 1995), which has been proven to be reliable for biomechanical data collection (Benedetti, Catani, Leardini, Pignotti, & Giannini, 1998; Reinschmidt, van den Bogert, Nigg, Lundberg, & Murphy, 1997). To minimise skin artefacts, custom cluster plates made of rigid plastic material (with four markers on each) were placed on each thigh and shank, with one on the pelvis (Khan, Jones, Nokes, & Johnson, 2007). The shank and thigh clusters were securely fastened to the anterior lateral aspect of each segment at the mid-segment level using double-side tape and elastic super-wrap bandages (Fabriofoam, USA) to reduce the downward migration and rotation of these cluster pads. The

pelvis cluster pad was placed on the sacrum at the mid-point between the posterior superior iliac spines using an elastic pelvic belt with Velcro fastenings to permit the secure placement of the belt and any adjustments that were required (Figure 3-9).
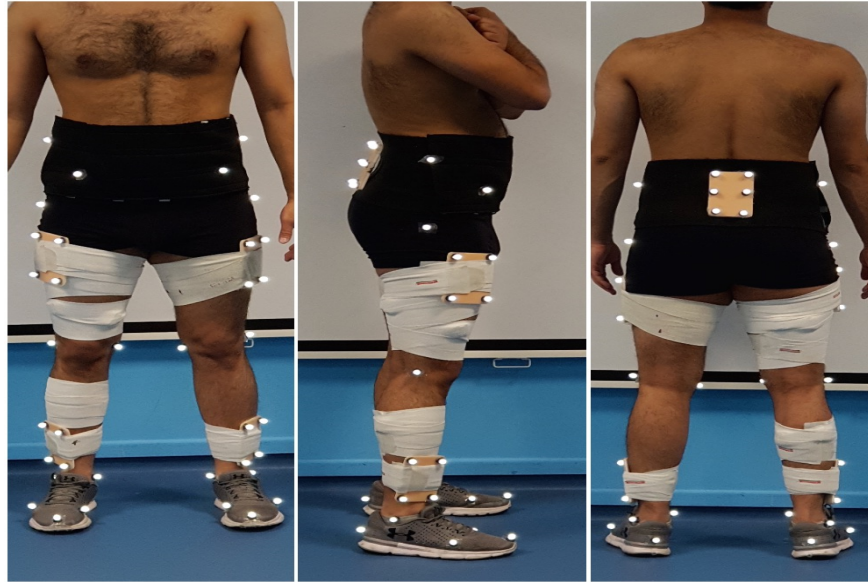
Figure 3-9 Markers placement.

Table 3-6 Anatomical landmarks.

Anterior superior iliac spines	Lateral malleolus
Posterior superior iliac spines	Medial malleolus
Iliac crests	The first metatarsal head
Greater trochanters	The fifth metatarsal head
Lateral femoral condyle	The second metatarsal head (dorsal aspect)
Medial femoral condyle	Calcaneus

3.10 Measurement of muscle activity

Muscle activity data were measured using surface electromyography (EMG). The EMG systems used in this study were a Noraxon Telemyo system (noraxon.com) and Delsys Trigno system (delsys.com). The sampling rate of the EMG systems was 1,500 Hz. In order to identify the position where the electrode was to be placed, Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) website guidelines (seniam.org) were followed.

Firstly, each participant was asked to lie down in prone position for the placement of EMG electrodes on the biceps femoris (lateral hamstring (LH)), the semitendinosus (medial hamstring (MH)), the medial gastrocnemius (MG), and the lateral gastrocnemius (LG). For the biceps femoris (LH), the electrode was placed on the middle (50%) point between the ischial tuberosity and the lateral epicondyle of the tibia. For the semitendinosus muscle (MH), the electrode was placed on the middle point between the ischial tuberosity and the medial epicondyle. For the lateral gastrocnemius, the electrode was placed one-third of the distance from the fibular heads to the heel. For the medial gastrocnemius electrode was place on the most prominent bulge of the muscle parallel to the muscle fibres. After that, each patient sat on the bed with his/her upper body leaning slightly backward and his/her knee slightly flexed, in order to place the medial quadriceps (MQ or Vastus medialis) and lateral quadriceps (LQ or Vastus lateralis) electrodes. For the medial, quadriceps the electrode was placed at 80% of the distance from the anterior superior iliac spine to the joint space in front of the medial ligament anterior border. For the lateral quadriceps the electrode was placed at two-thirds on the line from the anterior superior iliac spine to the lateral side of the patella.

Before placing the electrodes, two to three centimetres of the area was shaved. Then, to decrease the skin impedance and improve the quality of the EMG signal, the area was rubbed using hypo-allergenic gel, which was left to dry. Then, the area was wiped with an alcohol swab. The next step was preparing the electrode before placing it on the muscle belly parallel to the muscle fibres. Following the guidelines for muscle placement will reduce the risk for crosstalk.

Higher level of muscle co-contraction occurs when the muscle activation level is equal and reasonably high. There are different methods for calculating muscle co-contraction that contribute to the joint loading, including assessing the ratio of peak muscle activity (muscle 1/ muscle 2) (Hortobágyi et al., 2005) and the timing of concurrent activities (muscle 1+ muscle 2) (Unnithan, Dowling, Frost, Volpe Ayub, & Bar-Or, 1996). When the former method is used to quantify the muscle co-contraction, muscle with similar low magnitude will appear to have the same level as muscle with similar higher magnitude. However, when the latter method is used, the condition of muscle co-contraction occurs between muscles, one with low magnitude EMG and one with high, will be similar to other conditions when muscle EMG magnitude is equally low or high. Lewek et al., (2005) used a method of combining the ratio by multiplying the ratio by the sum of the EMG

magnitude. This method will be used in this study, as it is better at quantifying muscle co-contraction that reflects joint loading (Lewek et al., 2005).

3.11 Maximum voluntary isometric contraction (MVIC) collection

Prior to the gait test and after the placement of the EMG electrodes, the maximum isometric voluntary contractions for the hamstring, gastrocnemius and quadriceps muscles were collected. For the hamstring, the participant was asked to lay prone, and the pelvis was strapped with a belt. The knee joint was then flexed 55 degrees, and the participant was asked to bend his/her knee as hard as possible. For the gastrocnemius muscle, each participant was asked to stand on a single leg and asked to raise his/her feet off the floor as forcefully as he/she can. For the last group (quadriceps), each participant was asked to sit on a chair and face an adjustable metal bar. After securely strapping the pelvis and the femur, the participant's knee was adjusted to 45 degrees of flexion. The participant was then asked to extend his/her knee as hard as possible against the metal bar's resistance. Due to the lack of metal bars in Hail gait lab the quadriceps MVIC was conducted using a different method. Manipulation belt was secured in the bed and around the participant shank just above the ankle after sitting on the edge of the bed. The length of the belt was adjusted to get the right angle (45 degree of knee flexion) though electronic goniometer (Figure 3-10). Another manipulation belt was secured around the participant's thigh to prevent any chance of changing intended angle. The participant was then asked to extend his/her knee as hard as possible against the belt's resistance. Isometric voluntary contraction was conducted three times for each muscle within each subject with verbal encouragement (e.g. "push harder" or "push as much as you can") and sustained for five seconds. Before conducting the true trials, each participant was given a clear explanation as well as practical trials with 50% force to avoid fatigue and ensure a clear understanding of the task.

Figure 3-10 Electronic goniometer

3.12 **Data collection**

Prior to the testing procedure, 10 minutes of familiarisation time were given to all participants to ensure that they were comfortable with the procedure. At the beginning of each condition, each participant was asked to stand over one force plate to obtain a static position of the markers. Dynamic trials were then recorded for each participant.

3.13 **Task and events undertaken**

3.13.1 Walking task

The participants were asked to walk at their own self-selected speed. All participants were asked to perform five successful walking trials. A successful trial requires an occurrence of the contact phase on the force plate at self-selected speed with the required limb.

3.14 **Data processing**

After collecting five successful trials for each condition based on the study, the data for each participant were processed using Qualisys Track Manager Software or Vicon Nexus. In these programs, markers were labelled for each static and dynamic trial. Then, all of the trials were exported as C3D files for further computation. In the Visuals 3D program, the model of the sixth degree of freedom was built for each segment.

The six degrees of freedom for each segment, as described in the 3D space, are vertical, medial-lateral, anterior-posterior (translational movement) sagittal, frontal, and transverse (rotational movement). Each participant's mass and height, which were measured prior to starting the trials,

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were entered into the Visuals 3D program for kinetic calculations. Foot, shank, thigh and pelvic segments were determined with distal, proximal and tracking markers as described in the following Table 3-7.

Table 3-7 Visual3d segments model.

Segment	Proximal markers location	Distal markers location	Tracking markers
Pelvic	Right and left anterior superior iliac spine markers	Right and left posterior superior iliac spine markers	4 markers in pelvic cluster built
Thigh	Hip joint center	Medial and lateral condyle markers	4 markers in thigh cluster
Shank	Medial and lateral condyle markers	Medial and lateral malleolus	4 markers in shank cluster
Foot	Medial and lateral malleolus markers	1st and 5th metatarsal head markers	Heal marker, 1st metatarsal head marker, 2nd metatarsal head marker and 5th metatarsal head marker
The hip joint centre is calculated by visual3d program automatically based on posterior and anterior superior iliac spine markers throughout using the regression equation (Bell, Pedersen, & Brand, 1990).			

After that, all kinematics data were interpolated with maximum fill of ten frame and filtered with a low-pass filter. A Butterworth fourth-order bi-directional filter was used for both the kinematics and the kinetics data. The cut-off frequency for the kinetic data was 25 Hz (Schneider & Chao, 1983), and for the kinematics data was 6 Hz (Winter, 2009).

The moments at the hip, knee and ankle were resolved into a coordinate system fixed to the proximal segment. The sign conventions which were used in this thesis are presented in the following table (Table 3-8). For the center of foot pressure (COP) the positive side was considered as lateral.

Table 3-8 Sign conventions used in current thesis

	Plane	Hip	Knee	Ankle
Joint angles	Sagittal	Flexion +ve	flexion +ve	Dorsiflexion +ve
	Frontal	Adduction +ve	Adduction +ve	Inversion +ve
	Transverse	Internal rotation +ve	Internal rotation +ve	
Joint moments	Sagittal	Extension +ve	Extension +ve	Dorsiflexion +ve
	Frontal	Adduction +ve	Adduction +ve	Inversion +ve
	Transverse	Internal rotation +ve	Internal rotation +ve	

+ve = positive

To identify any changes in muscle contractions, muscle activity profiles were used. EMG data for each walking trial were synchronised with the motion and ground reaction force data. The raw EMG data for each muscle were analysed with software VISUAL 3D (V.5.02.26, C-MOTION. INC, USA). The EMG data were filtered with high pass filter 20 Hz to remove the moving artifact and the noise. Then, the waveform was fully rectified, and a fourth order bi-directional low pass filter with 6 Hz cut-off algorithm was used to produce a linear envelope (Hubley-Kozey, Deluzio, Landry, McNutt, & Stanish, 2006). Data from each muscle activity were exported to Microsoft Excel. Then, each muscle was normalised by its maximum voluntary isometric contraction (MVIC), which was applied for each trial. After that, the average muscle activity for each normalised trial was used.

Then, the gait events were created after the construction of a six degrees of freedom model. Firstly, initial contact and toes off were determined based on the force plate data when force accessed or reduced below 10 Neutron. The following gait events were created automatically base on the kinematics data of the first gait cycle using automatic pipeline throughout using pattern recognition technique. To calculate the KAAI two manual events were created base of the data of knee y moment. The first event is called start and was labeled on the curve as soon as the value of EKAM pass zero value to the positive. The second gait event was called stop and created once the value of EKAM reach zero value moving to the negative. Kinetic, EMG, GRF and centre of foot pressure (COP) data were normalised to the stance phase, while the kinematic data were normalised to the gait cycles in walking.

Muscle co-contractions between the antagonist and the agonist were calculated based on the following equation (EMGS/EMGL*(EMGS+EMGL)). EMGS is the muscle activity for least active muscle between the agonist and antagonist whereas the EMGL is the muscle activity for the high active muscle between the agonist and antagonist. Muscle co-contraction value is a unitless measurement that represents the activation between agonist and antagonist muscles.

3.15 **Determining gait events**

The kinematics and EMG data were recorded in the stance and swing phase while the kinetics, GRF and COP data were recorded in the stance phase. All the joint moments (hip, knee, ankle) presented in this thesis were the external moment. The kinematic data were normalised to 100%

of a gait cycle and Kinetic and EMG data were normalised to 100% of a stance. The mean of five trials was used to calculate the maximum, minimum or average of each interested outcome in the kinematic, kinetics, GRF data and muscle co-contraction. The joint ROM was calculated by subtracting the minimum value from the maximum value throughout the entire range (0-100%). The curve of kinematics in the hip frontal angle was divided into first peak (0-33%), trough (34%-67%) and second peak (68% to 100%). The curve in the kinematics of the knee sagittal plane was divided into four phases defined as the following: the initial contact phase (0%), the loading response phase (1%-20%), mid-stance phase (21%-50%), terminal stance phase (51% to 61%) and swing phase (62%-100%). The curves in the kinetics data in hip y moment, knee y moment and GRF were divided into first peak (0 to 33%), trough (34 to 67%) and second peak (68% to 100%). The maximum and minimum across the 101% data of the gait cycle were calculated for the following outcomes: hip x angle, hip x moment, hip y angle, knee x angle, knee x moment, knee y angle, ankle x angle, ankle x moment, ankle y angle, and ankle y moment. The average mean of muscle co-contraction was calculated in the following stance phases: early-stance (0-33%), mid-stance (34%-67%) and terminal-stance (68-100%).

Biomechanical variables were exported as spreadsheets into Microsoft Excel to conduct the analysis and construct a graphical illustration. Statistical analysis was carried out with Statistical Package for the Social Sciences (SPSS) (IBM SPSS Statistics 23). The gait cycle, which is defined as lasting from the initial contact of a foot to the subsequent initial contact of the same foot, was represented in the graphs as a sequence of 101 numbers, where 0 represented the start of the initial contact and 100 represented the start of the next cycle.

3.16 **Variables were calculated in current thesis.**

Joint angles, which were assessed in this thesis, include hip angle in the sagittal plane (the first peak, trough, the second peak) and frontal and transverse planes (maximum, minimum), knee angle in the sagittal (initial contact, loading response, mid-stance, mid-swing), frontal and transverse planes (maximum, minimum) and ankle angle in sagittal and frontal planes (maximum, minimum). Different aspects of joint moments were assessed in this study, namely, sagittal moment in the hip, knee and ankle (maximum, minimum), frontal moment in the hip and knee (the first peak, trough, the second peak), frontal moment in the ankle (maximum, minimum), transverse moment in the

hip and knee (maximum, minimum) and vertical ground reaction force (the first peak, trough, the second peak) (Figure 3-11). Muscle activity in MQ, LQ, MH, LH, MG, LG. For more details about the gait phases and calculation of joint angles, moments, GRF and muscle co-contraction please see sections 3.14 and 3.15.

Knee x angle

Knee x moment

Knee y angle

Knee y moment

Knee z angle

Knee z moment

Ankle x angle

Angle x moment

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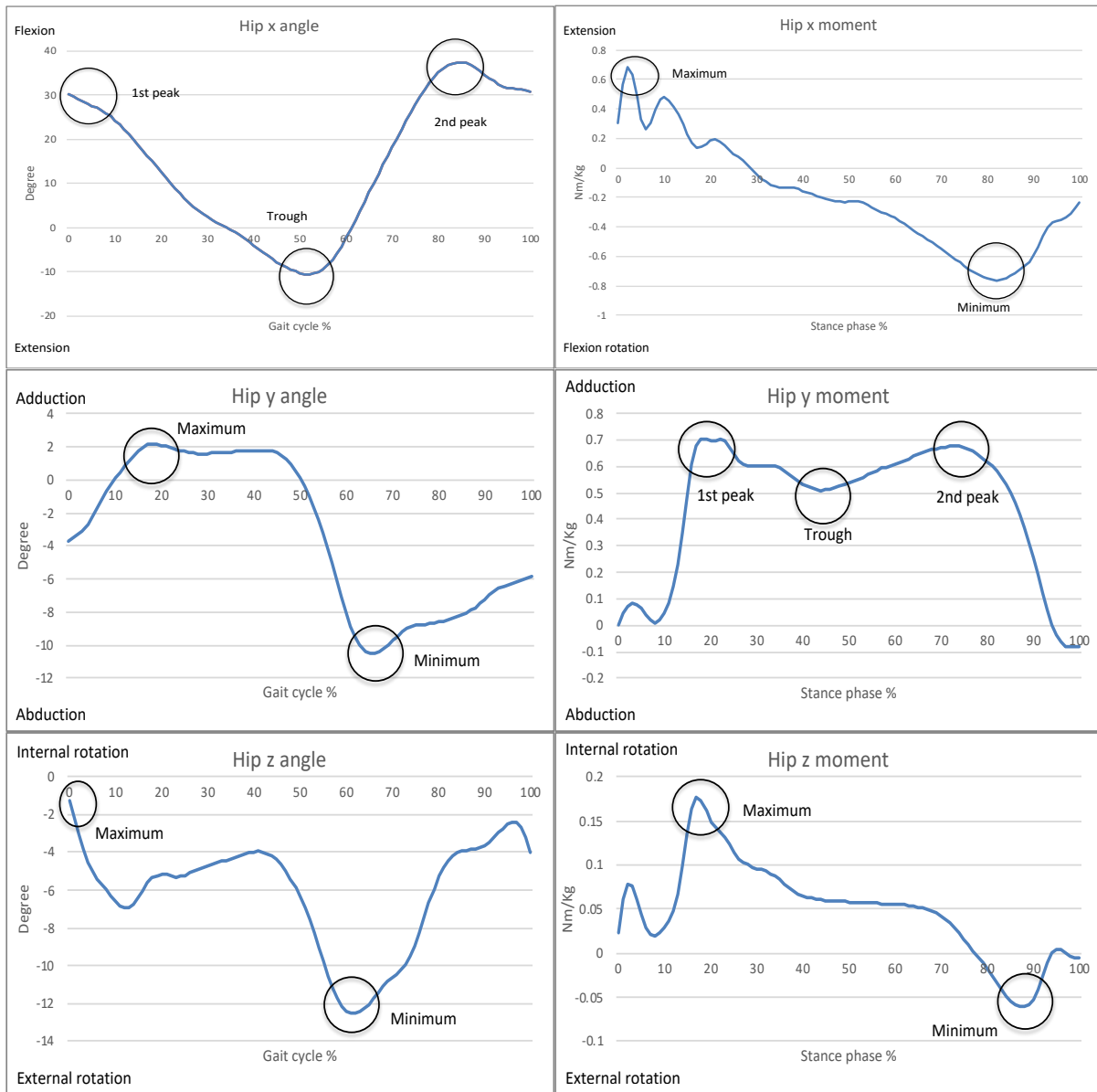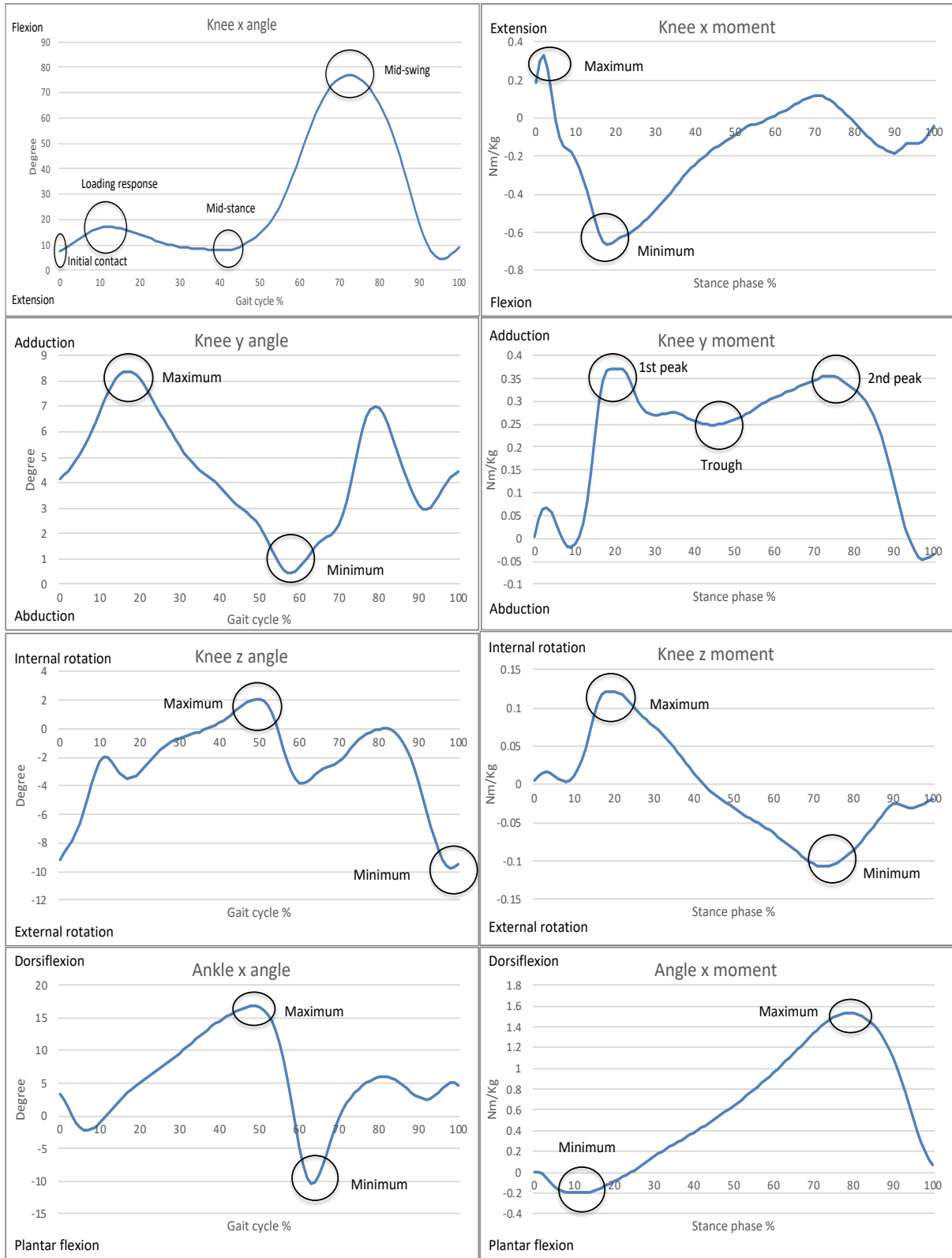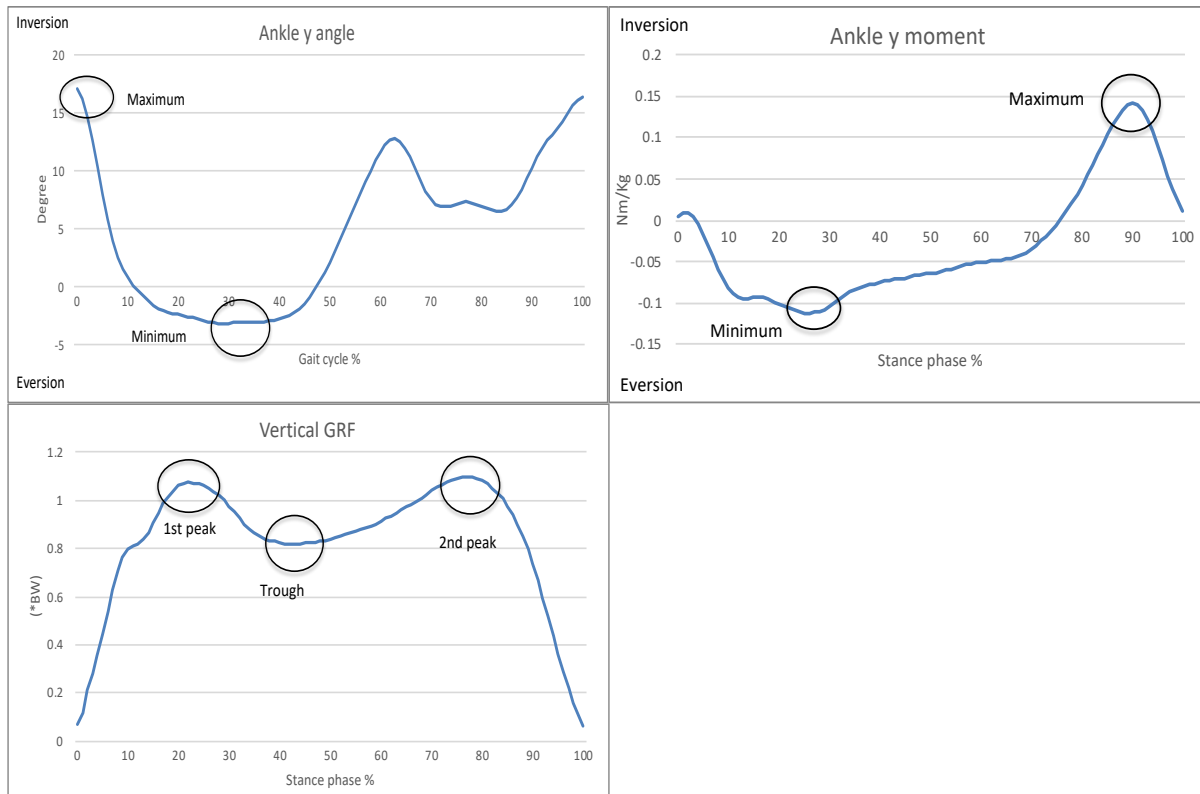
Figure 3-11 Variables of interest in kinematics, kinetics and GRF data.

3.17 **Statistical analysis**

The data were checked for a normal distribution using the frequency distribution (histogram), stem-and-leaf plot, boxplot, P-P plot (probability-probability plot), and Q-Q plot (quantile-quantile plot). Additionally, due to the unreliability of visual inspection for normality (Altman & Bland, 1995; Öztuna, Elhan, & Tüccar, 2006), Shapiro-Wilk tests were performed to compare the scores in the sample to a normally distributed set of scores with the same mean and standard deviation (Field, 2013). The Shapiro-Wilk test was chosen over the Kolmogorov-Smirnov (K-S) test due to the latter's high sensitivity to extreme values (Peat and Barton, 2005). Studies have shown that the Shapiro-Wilk test is the best option for testing normality due to its high power (Field, 2013; Ghasemi & Zahediasl, 2012; Razali & Wah, 2011; Steinskog, 2009; Thode, 2002).

Assessing the normality distribution is an important step as it helps to determine whether parametric statistical tests should be used or not, to assure correct statistical tests to be used. If the data are normally distributed, parametric tests were used, otherwise non-parametric tests were used

based on each of the different studies. Statistical significance level in this thesis was considered to be at alpha <0.05.

As multiple visits were needed by the individuals in some of the studies, it was essential to know that the researcher was reliable in placing the markers and the data collection. Therefore, the following sections will detail the reliability studies which were undertaken to demonstrate competence.

The next part of the methods section investigates the reliability of biomechanical outcomes in healthy individuals and individuals with medial knee OA. Moreover, the reliability of clinical outcomes in individuals with knee OA were investigated. Undertaking this step was necessary to understand the researcher's ability to apply the markers and conduct the same clinical test method with high consistency. The rationale for conducting the reliability procedure on healthy and OA individuals is that healthy individuals have no known deformity or injury affecting the ability to walk, while in individuals with knee OA, the symptoms or disease severity may increase the variability in walking from one week to another. Therefore, for better understanding of the measurement error and minimal detectable change in each population (healthy, knee OA), two studies were conducted, the first in healthy individuals and the second in individuals with knee OA.

3.18 Test–retest reliability for healthy individuals.

3.18.1 Introduction

Clinical gait analysis is considered an important outcome measurement for assessing different treatments' effects on kinetic and kinematic data, which can be affected by different factors during measurement. Several factors, such as marker positioning, walking speed and data processing can be controlled to reduce measurement errors (Schwartz et al., 2004). Positioning markers on bony landmarks can create variability and increase measurement errors (Cappozzo, Catani, Leardini, Benedetti, & Croce, 1996). These bony landmarks are more difficult to palpate due to the muscles and the adipose tissue covering these (Baker, 2006). The location of the markers is also important with regard to calculating and identifying joint centres, and any mistakes in marker placement can lead to errors in calculating kinematic and kinetic data (Baker, 2006; Croce, Cappozzo, Kerrigan, & Lucchetti, 1997; Stagni, Leardini, Cappozzo, Grazia Benedetti, & Cappello, 2000). A recent systematic review concluded that an error in joint angle of five degrees or less is acceptable for use in clinical situations. Several studies have shown an encouraging results in the test and re-test reliability of gait measurement in healthy participants (Andrews, Noyes, Hewett, & Andriacchi, 1996; Kadaba et al., 1989) and individuals with knee OA (Birmingham et al., 2007).

Electromyography (EMG) is commonly used as an outcome measurement to assess muscle function (Dowling, 1997). To achieve an effective EMG signal, the user should be aware of the factors that can potentially affect the data (Soderberg & Knutson, 2000). Several intrinsic and extrinsic factors which can affect the signal have been identified (De Luca, 1997). Electrode configuration is among the extrinsic factors, which include size, shape and the electrode's position in relation to the muscle fibre. The electrical signal is highly dependent on whether the electrode overlaps the muscle of interest. The electrode location determines the electrical view of the muscle; thus, consistency in the electrode placement is an important factor in EMGs taken over repeated measurement sessions.

Therefore, this study will investigate the reliability of EKAM (1st peak, trough, 2nd peak) and EMGs in healthy subjects during walking. This study was an important step before starting any study aiming to measure the effect of treatment because changes in outcome results might be due to inconsistent methods of application, rather than to the treatment itself. This study will, therefore,

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examine the intra-rater reliability within the same session and between-day measured one week apart by the same investigator. This will help to improve the researcher's understanding of the measurement error.

3.18.2 Methods

The participants' data collection was conducted in Podiatry gait analysis lab at Salford university with ethical approval number HSCR 15-131.

3.18.2.1 Inclusion criteria and Exclusion criteria

Healthy adult between the age of 20 to 60 years old were included in the study and for more details regarding the inclusion and exclusion criteria please see section 3.5.1.1.

3.18.2.2 Study design and procedure

This is a reliability study which investigated the reliability of gait and EMG variables in healthy individuals within the session and over a week. The task which was investigated was level ground walking.

In brief, a 16 Oqus camera motion capture system integrated with four AMTI force plates was used. Data was captured at 100Hz for kinematics and 1000Hz for kinetics. Following calibration (section 3.8.1) the markers were applied to the individual (section 3.9). Surface electromyography electrodes were applied on the following muscles: LH, MH, LG, MG, LQ and MQ (section 3.10). MVIC was collected for these muscles using the same method in section 3.11. The test procedure was explained to each participant and given enough time to ask and practice before signing the consent form.

The participants were asked to walk on a 10 metres' walkway at their own self-selected speed. All participants were asked to perform walking until five successful walking trials were achieved. A successful trial required an occurrence of the stance phase on one of the force plate (AMTI), walking speed was within 5% of each participant's self-selected speed. The speed was controlled with a Brower Timing Gate system (TC-Timing System, USA) set at approximately hip height.

3.18.2.3 *Variables of interest*

Variables which were assessed in this reliability study were EKAM (the first peak, trough, the second peak and muscle activity in MQ, LQ, MH, LH, MG and LG. For more details about the gait phases and calculation of the EKAM and muscle co-contraction please see sections 3.14, 3.15 and 3.16. Other kinematic and kinetics variables were calculated, and the results were presented in the Appendix D. Overall, most variables in the within-session and between-session reliability showed excellent reliability ranging from ICC=0.63 to ICC=0.99. Furthermore, most of the other kinematic and kinetics variables showed low SEM.

3.18.2.4 *Data analysis*

To calculate the within-session reliability, the means of five trials from the first session and the second session were used. Five minutes separated the first and second session in the within session reliability. Markers were not removed and this was purely to replicate the crossover study which will be conducted following this study where participant will be randomly given 4 conditions without removing the markers. The between-day reliability was calculated by the mean of 5 trials from session one and session two with 7 days in between. The data was exported to excel after being processed in Qualisys Track Manager Software and VISUAL3D (V6, C-Motion inc. USA) programs.

3.18.2.5 *Statistical analysis*

To explore the reliability of the test and re-test of a single point in the waveforms intra-class correlation coefficient (ICC) was used. Two-way mixed effects ICC mode was used in the current study to assess relative reliability. This model is the appropriate method for the current study since the principle investigator performed all the measurements, however the results of this study could not be generalised to other investigators (Koo & Li, 2016; Shrout & Fleiss, 1979). ICC is a unitless measurement, which shows to what extent the measurement of the variables is in agreement (Shrout & Fleiss, 1979). ICC values range from 0 to 1 with a higher value representing better reliability. The results of the ICC have been interpreted according to the criteria in the Table 3-9.

Table 3-9 ICC value and corresponding interpretation (Koo & Li, 2016).

ICC results	Interpretation
ICC lower than 0.50	Poor reliability
ICC between 0.50 to 0.75	Fair reliability
ICC between 0.75 to 0.90	Good reliability
ICC Higher than 0.90	Excellent reliability

ICC appears to be easily interpreted, however, when ICC is used alone it cannot provide a full picture of the reliability since it does not provide the amount of disagreement between the measurements and is not in the unit of measurement. Therefore, using standard error of measurement (SEM), which provides the amount of disagreement between the measurements, is important (Rankin & Stokes, 1998). Calculating the SEM is very useful and important for practitioners who want to determine individual improvements (Munro, Herrington, & Carolan, 2012). The SEM was computed to determine the absolute reliability, with low values representing good reliability. This was used to help the researcher estimate the real change and determine the measurement error (Baumgartner, 1989). SEM was calculated using this formula: SD pooled * √ (1-ICC) (Denegar & Ball, 1993).

The smallest detectable difference (SDD) was also calculated to represent the practical measurement error (Portney & Watkins, 2009). In other words, the amount of change in the measurement outcome is required to be determined so that the real change in the measurement achieved due to treatment effects rather than measurement error variation can be identified. Calculating SDD is essential especially for intervention studies. Without knowing the measurement error, it is difficult to confirm that these changes were caused by the treatment and not due to measurement error, such as static alignment or marker placements (Ford, Myer, & Hewett, 2007; Malfait et al., 2014; Whatman, Hing, & Hume, 2011). Small detectable differences were calculated based on the following equation: SDD = 1.96 * SEM * √2 (Kropmans, Dijkstra, Stegenga, Stewart, & de Bont, 1999).

SDD and SEM are expressed in the same unit as the measurement tool used (Newton-meter per kilogram for joint moment and degree for joint angle) (Blankevoort, van Heuvelen, & Scherder, 2013; Bruton, Conway, & Holgate, 2000).

To assess EMG reliability between-day and within-day, the coefficient of multiple correlations (CMC) was used. CMC determines the degree of consistency and agreement in the waveform between different sessions. CMC has been used in previous studies by Kadaba (1990) and Growney et al. (1997) to assess the reliability of measurement tools. CMC provides a value between 0 and 1 with no unit. The closer the result to 1, the greater the agreement between the sessions (test, re-test) will be, and values higher than 0.80 represent high reliability (Collins et al., 2009; Growney, Meglan, Johnson, Cahalan, & An, 1997). To assess if there is a significant difference in walking speed between both sessions two-tailed, paired *t*-test was used if the data was normally distributed and Wilcoxon's signed rank test was used if not (Nayak & Hazra, 2011).

3.18.3 Result

Participants demographics characteristics are presented in the Table 3-10. There was no significant difference in walking speed for both within-session (p=0.48) and between-session (p=0.78) (Table 3-11).

Table 3-10 Healthy participants' demographics characteristics.

Task Mean (SD)	Number of subjects	Age (Years)	Mass (Kg)	Height (M)	BMI (Kg/m²)
Walking (within-session)	8.00	31.5 (6.14)	69.5 (12.35)	1.71 (0.06)	23.68 (3.99)
Walking (between-session)	15.00	31.93 (5.54)	70.18 (10.44)	1.71 (0.05)	24.03 (3.07)

Table 3-11 Walking speed in healthy participants.

Speed (m/s). Mean (SD)	Test	Re-test	P-value
Walking (within-session)	1.23 (0.14)	1.19 (0.16)	0.48
Walking (between-session)	1.27 (0.15)	1.26 (0.14)	0.78

During level walking, the within-session reliability results (ICC= 0.99) were higher than for between-session (ICC=0.96 to 0.99) for all variables. The standard error of measurement for EKAM (1st peak, trough, 2nd peak) for within-session reliability and between-session reliability ranged from 0.005 to 0.2 Nm/Kg. The small detectable difference (SDD)for within-session reliability were lower than between-session EKAM (see Table 3-12).

The coefficient of multiple correlation showed good within-session reliability for the muscles activity during walking ranging from (0.84 to 0.94) (see Table 3-13). Between-session reliability in walking showed the same range as within-session (0.84 to 0.94) (see Table 3-13). Medial hamstring and lateral hamstring showed the lowest CMC in walking for both within-session and between-session reliability. The highest within-session CMC value was for lateral and medial gastrocnemius muscles during walking. Similar trend was noticed for between-session CMC during walking, as the lateral and medial gastrocnemius showed the best CMC during walking.

Table 3-12 Within-session and between-session reliability for EKAM during walking for healthy participants.

Within-session (Nm/Kg),	ICC	Mean	95% CI of ICC	SEM	SDD
Knee y moment (first Peak)	0.99	0.55	0.99-0.99	0.005	0.01
Knee y moment (Trough)	0.99	0.25	0.98-0.99	0.01	0.02
Knee y moment (second Peak)	0.99	0.43	0.96-0.99	0.01	0.03
Between-session (Nm/Kg),	ICC	Mean	95% CI of ICC	SEM	SDD
Knee y moment (first Peak)	0.98	0.47	0.94-0.99	0.02	0.06
Knee y moment (Trough)	0.96	0.18	0.87-0.99	0.01	0.04
Knee y moment (second Peak)	0.98	0.36	0.95-0.99	0.01	0.03

Table 3-13 Within-session and between-session reliability of muscles activity (EMG) in stance phase during walking for healthy.

Muscle (Within-session)	CMC mean
LG	0.94
LH	0.84
LQ	0.92
MG	0.93
MH	0.89
MQ	0.91
Muscle (Between-session)	CMC mean
LG	0.94
LH	0.85
LQ	0.93
MG	0.91
MH	0.84
MQ	0.91

3.18.4 Discussion

The aim of this study was to examine the reliability of EKAM and EMG during walking. Additionally, the calculation of the standard error of measurement and small detectable difference for EKAM variables during walking was completed.

Generally, the results of ICC for EKAM (1st peak, trough, 2nd peak) for within-session and between-session are excellent in walking (0.96 to 0.99). However, 1st peak, trough and 2nd peak of the within-session ICC results for were higher than for between-session. Previous studies have shown a similar trend during walking (Growney et al., 1997; Kadaba et al., 1989), running (Ferber, McClay Davis, Williams, & Laughton, 2002) and vertical jump (Ford et al., 2007).

Several factors might have contributed to the difference in reliability, such as static alignment, marker placement and difficulty of the task (Ferber et al., 2002; Ford et al., 2007; Manal, McClay, Stanhope, Richards, & Galinat, 2000). In 1989, Kadaba attributed between-session variability in 3D gait analyses to marker reapplication. In this study, only one observer applied the markers during both sessions. The high ICC between-session and within-session reflect high consistency in marker placement by the observer.

The high reliability of Knee adduction moments (1st peak, trough, and 2nd peak) during walking indicates good repeatability and the usefulness of such an outcome in clinical application and research. SEM of knee adduction moment during walking ranged from 0.005 Nm/kg to 0.02 Nm/kg and revealed that the measurement, indicating low measurement error. This finding is consistent with the previous studies that show good reliability for EKAM in healthy individuals (Andrews et al., 1996; Growney, Meglan, Johnson, Cahalan, & An, 1997; Kadaba et al., 1989a) during walking.

The reliability of within-session and between-session EMG Vestus Medials, Vestus lateralis, Medial Hamstring, Lateral Hamstring, Medial Gastrocnemius and Lateral Gastrocnemius ranged from 0.84 CMC to 0.94 CMC. The current study's EMG results indicate good reliability and therefore can be used.

Kadaba et al. (1989) showed higher than 0.8 for CMC for between- and within-session reliability for all muscles, except medial hamstring between-session (0.76). The EMG results from this study

(within-session and between-session CMC) during walking showed even higher results than Kadaba (1989). This difference might be due to electrode placement position, as the previous study placed the electrodes on muscle motor points, which increases the variables and produces less stable results than using SENIAM guidelines, as used in the current study (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000). Other studies have investigated the reliability of EMG between- and within-session (Kadaba, Wootten, Gainey, & Cochran, 1985; Winter & Yack, 1987), however a direct comparison cannot be made due to using different statistical methods.

The current study provides reference values for SEM and SDD during walking, which may be useful for evaluating intervention results. SEM is useful for determining the improvement by a clinician (Domhldt, 2005). The SEM calculation depends on the standard deviation of the outcome measurements and allows the researcher and clinician to be 68% confident that the true value lies within + or − 1 SEM. SDD is more conservative than SEM, and if outcomes improve more than SDD, confidence will increase to 95%, therefore this change is not caused by participant variability or measurement error (Atkinson & Nevill, 1998; Portney & Watkins, 2009). The SEM value for the first peak knee adduction moment during walking was 0.005 Nm/kg for within-session and 0.02 Nm/kg for between-session.

One limitation of the study is that the generalisability of results is restricted to similar laboratory settings, the model, and the researcher's ability to apply markers, although the results are consistent with the previous literature. Furthermore, this study has standardised the shoes of the participants, which does not reflect shoes used in everyday life.

3.18.5 Conclusion

Based on the results of the current study, several points can be highlighted. Firstly, the 1st peak, trough and 2nd peak adduction moment shows excellent reliability and low SEM, therefore it can be used to evaluate treatment effect within-session and between-session. Secondly, EMG can be used to investigate treatment effect within-session and between-session, as all muscles showed good CMC.

3.19 Test–retest reliability for individuals affected with knee osteoarthritis.

3.19.1 Introduction

The aim of the main study in this thesis was to investigate the effect of combined treatment (lateral wedge insole + simple sleeve) on EKAM, pain, muscle co-contraction, balance, pain pressure threshold and functional tests, and compare it to each treatment. The measurement for each treatment will be taken at baseline and after six weeks. Changes in the outcome results after using the treatment needed to be caused by the treatment and not by measurement error.

Clinical gait analysis is considered a reliable outcome measurement to assess any alteration in the lower limb caused by any pathological disorder, such as knee osteoarthritis (McGinley, Baker, Wolfe, & Morris, 2009; Zeni & Higginson, 2009). Gait analysis can be affected by several factors such as marker placement, data processing and faulty equipment errors, and can be controlled to reduce measurement errors (Schwartz et al., 2004). Several studies have shown encouraging results in the test and re-test reliability of gait measurement in healthy participants (Andrews et al., 1996; Kadaba et al., 1989) and OA patients (Birmingham et al., 2007).

EMG is commonly used as an outcome measurement to assess muscle function in individuals affected with pathology by assessing the muscle's electrical signal (Dowling, 1997). The electrodes should overlay the muscle of interest to provide a valid signal and, to achieve a reliable signal, the electrode should be positioned in the same place over time. Previous studies have shown encouraging results regarding the reliability of the EMG in healthy individuals (Kadaba et al., 1989) and individuals affected with knee OA (Hubley-Kozey, Robbins, Rutherford, & Stanish, 2013).

Balance is considered a complex neuromuscular process, which includes motor, sensory and integrated components. The inability to maintain a stable body over the supported base (leg) is defined as balance defect. Balance deficit is considered to be a risk factor in falling among elderly individuals and individuals with knee osteoarthritis (Hinman et al., 2002; Wegener, Kisner, & Nichols, 1997) and should therefore be assessed. Balance can be affected by many factors such as the ageing process, muscle weakness and/or proprioceptive impairment (Koceja, Allway, & Earles, 1999; Lin, Lin, Lin, & Jan, 2009; Slemenda et al., 1997). Several methods have been used to assess

balance, which included expensive and inexpensive methods. The Star Excursion Balance Test (SEBT) has been used to assess balance in healthy individuals with good reliability (Kinzey & Armstrong, 1998; Munro & Herrington, 2010). To the best of our knowledge there is no previous study that assesses the reliability of SEBT in individuals with medial knee osteoarthritis.

The ability to perform daily activity (physical function) is considered one of the main outcomes for individuals with knee and hip osteoarthritis (Bellamy et al., 1997). Physical activities are concerned with the ability to move around and perform daily activities. Physical disability affects independence and quality of life, which increases the risk of morbidity and mortality (Hofman, Grobbee, de Jong, & van den Ouweland, 1991; Jette & Branch, 1985). In 2013, the Osteoarthritis Research Society International (OARSI) recommended set physical function tests to be used for testing physical ability in individuals with knee osteoarthritis (Dobson et al., 2013). Thirty-second chair-stand test, 40-metre fast-paced walk test and a stair-climb test have been used in previous studies to evaluate the effects of treatment in individuals with knee osteoarthritis (Dobson et al., 2013). The reliability for such outcomes were encouraging (Gill & McBurney, 2008a; Kennedy et al., 2005; Wright et al., 2011). However, different application methods between sessions can affect the reliability of results in such tests and increase measurement error such as application procedure.

Knee pain pathophysiology is complex and local contributors probably involve raised mechanical stress on intra-articular and pre-articular tendons and ligaments, intra-osseous pressure, and synovial inflammation (Brandt et al., 2008; Dieppe & Lohmander, 2005; Kidd, 2006). Pain is considered to be subjective and relies on patients' self-reported outcomes in individuals with knee osteoarthritis. Although, self-reported outcome measurement is important, other physiological and psychological aspects might affect the result and make it difficult to be interpreted. Therefore, other objective outcome measurements are needed, such as pain pressure threshold. Previous studies have shown that individuals with osteoarthritis have a lower pain pressure threshold than the control group (Arendt-Nielsen et al., 2010; Imamura et al., 2008; Wessel, 1995). Furthermore, a high ICC was identified by a previous study for using such measurement, which indicated the importance of using it (Mutlu & Ozdincler, 2015). However, the use of such a device is based on the individual applying the pressure and thus needs to be consistent.

Therefore, this study firstly investigated the reliability of EKAM (1st peak, trough, 2nd peak, KAAI) and EMG during walking in individuals with knee osteoarthritis. Secondly, it investigated the reliability of the star excursion balance test, pain pressure threshold, 30-second chair-stand test, a stair-climb test and 40-metre fast-paced walk test. This study was an important step before starting any study. It aimed to measure the treatment effect, because changes in outcome results might be due to inconsistent methods of application, rather than to the treatment itself. This study would, therefore, examine the intra-rater reliability between days measured one week apart. This will help to improve the researcher's understanding of measurement error.

3.19.2 *Methods*

The participants' data collection was conducted in the Hail gait laboratory at Hail University and in the Brain Blatchford gait laboratory at Salford University.

3.19.2.1 *Inclusion and exclusion criteria*

To take part in this study, each participant had to be between 35 and 85 years old affected with medial knee OA. For more details regarding the definition of medial knee OA please see the inclusion and exclusion in section 3.5.1.2.

3.19.2.2 *Study design*

This is a study to examine the reliability of clinical and biomechanical outcome measurement amongst individuals affected with knee osteoarthritis over a week.

3.19.2.3 *Test procedure*

Balance assessment

Dynamic balance was assessed by using a modified star excursion balance test (SEBT). After an explanation of the procedure the participants were asked to maintain a single-leg stance on the affected leg. Depending on the direction to be tested, either facing the bar anteriorly (A) or with their side to the bar medially (B), they were asked to reach as far as possible along the bar by pushing a small block on the bar as far as possible and return the reaching leg back to the centre (see Figure 3-12). Anterior and medial directions were used in SEBT to reduce the length of the

session by not applying testing all directions and present of muscle weakness in quadriceps and gluteus muscles which targeted by these directions. The participants were asked to perform the test barefoot, keep their heel of the stance leg on the platform at all times, bend their knee of the stance leg, push the block gradually but not suddenly, and not slide it by stepping on it. If any of these instructions were not carried out by the participants, the trial was repeated. Each participant started with four training trials in each direction. To facilitate the comparison between groups the distance was normalised to the limb length, which was measured from the anterior superior iliac spine to the medial malleolus.
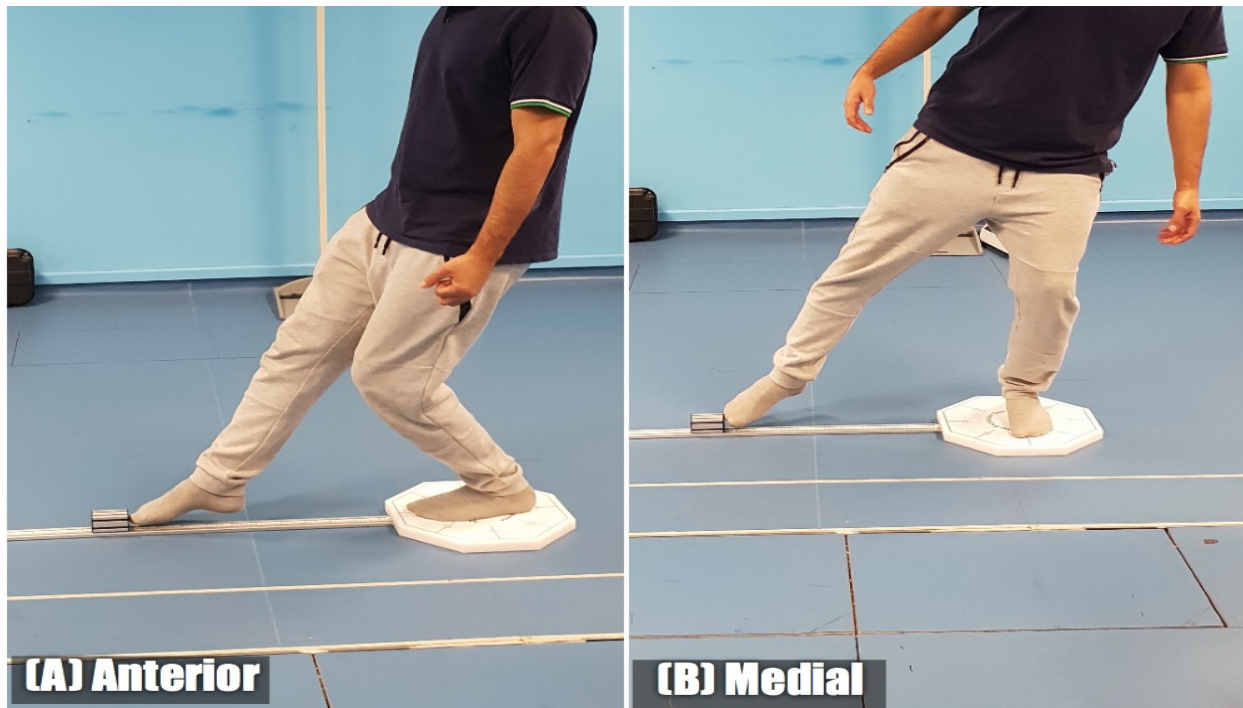
Figure 3-12 Star excursion balance test.

Pain pressure assessment:

Each participant was asked to lie on their side on the bed and the Algometer's probe was held perpendicular to the area which was tested (see Figure 3-13). Pain pressure threshold is defined as the lowest pressure intensity at which pain is felt. Each participant was instructed to say "stop" when the first sensation of pain was felt. Each patient was given two trials before starting the tests. The area that was tested was the medial side of the knee (medial condyle), as this is considered the

most painful area and medial malleolus as reference pain-free area (Wylde, Palmer, Learmonth, & Dieppe, 2011). Each test was performed three times and the average was calculated for each site.

Figure 3-13 Pressure gauge.

Physical function tests

- **Forty-metre fast-paced walk test**

Each participant was asked to walk 10 metres, four times, which was marked by a tape on the floor. Cones were placed two metres beyond the starting and the finishing lines so participants could turn safely around them. Each participant was instructed to walk and turn around the cones three times to finish the 40 metres. The instructions were as follows: "Walk as quickly as you can but as safely as you can without running." Each participant was given time to practice for two trials before starting the test. The time was measured by stopwatch and the time after passing the lines (finish, start) to turn around the cones was calculated by pausing the stopwatch. The distance (40 metres) was then divided by the time each participant took to finish the 40 metres to be expressed as speed (m/s).

- *Thirty-second chair-stand test*

This test represents the number of counts that each participant can do to stand and sit on a chair in 30 seconds as fast as possible. A 43 cm high chair without arms was placed against the wall. Each participant was asked to start from sitting to standing with his/her hips with knees fully extended and sit back with his/her bottom fully touching the chair and his/her hands crossed over the chest. This counted as one trial. If the participant could not perform any one trial, then the score was zero and an adapted test was used. In this case, using the hand against the legs or the use of an

assisted device as normally used in real life such as a walking aid was allowed. Two practice trials were done before starting the real test to ensure understanding.

- ***A stair-climb test***

In this test, the time taken by each participant to ascend nine steps and then descend the same steps was measured in seconds. Each participant was asked to ascend and descend the nine steps as quickly and safely as possible. The use of handrails and assisted devices was allowed as needed. Two practice trials were done with the researcher walking behind each participant to check for safety and ensure understanding.

Kinematic and kinetic data collection

In brief, two systems were used in this study the first one is the Brain Blatchford gait analysis lab and the second one is Hail University gait analysis lab. The Brain Blatchford gait lab is 10 T30/40 camera motion capture system with four Kistler force plates while Hail lab is 10 Bonita camera motion capture system with two AMTI force plates. Data were captured in both labs at a sampling rate of 100 Hz for kinematics and 1000 Hz for kinetics. The systems were calibrated and the laboratory were prepared before the subject's arrival (section 3.8). The informed consent form was signed after the test procedure was explained to the participant and enough time to ask and think was allowed. Each participant was asked to change into T-shirt and short to start the testing procedure. In order to enable the participant to familiarise him/herself with the equipment and test procedure, each was given enough time to practice before starting the test. The 40-metre fast-paced walk test, 30-second chair-stand test and star excursion balance test was explained to the participant and collected in order. After the electrodes were applied on the following muscles: LH, MH, LG, MG, LQ and MQ (section 3.10). MVIC was collected for these muscles using the same method described in section 3.11. The markers were applied, and five successful trials were collected. Finally, the stair-climb test was collected in the stair. A successful trial requires an occurrence of the complete stance phase on a force plate (AMTI) within each participant's self-selected speed. The same procedure and order of the tests were applied for each participant after a week. For more information about the method, please see sections 3.14, 3.15 and 3.16. All participants wore their own shoes for both session and only SEBT test were collected barefoot.

3.19.2.4 *Variables of interest*

Variables which were assessed in this reliability study were EKAM (1st peak, trough, 2nd peak, KAAI) and EMG. Muscle co-contraction in early-, mid- and late- stance phases between the following muscles LQ/LH, LQ/LG, MQ/MH and MQ/MG reliability were calculated in current study. Pain pressure threshold, balance (anterior and medial directions) and functional tests (40-metre fast-paced walk test, 30-second chair-stand test, a stair-climb test) were included as clinical outcomes in current reliability study. For more details about the gait phases and calculation EKAM, muscle co-contraction please see sections 3.14, 3.15 and 3.16. Other kinematic and kinetics variables were calculated, and the results were presented in the Appendix D. Generally, most kinematics and kinetics variables showed high reliability (ICC>0.90) and low SEM.

3.19.2.5 *Data analysis*

To calculate the between-day reliability, five trials from the first session and the second session were used. The data were exported to Microsoft Excel after being processed in Qualisys Track Manager, Vicon nexus Software and C3D programs. To explore the reliability of the test, re-testing of a single point in the waveforms and muscle co-contraction, intra-class correlation coefficient (ICC two-way mixed effects model) was used. The results of the ICC have been interpreted according to the criteria in Table 3-7. The SEM was computed to determine the absolute reliability. The small detectable difference (SDD) was also calculated to represent the practical measurement error (Portney & Watkins, 2009). To assess EMG reliability between days, the coefficient of multiple correlations (CMC) was used. To assess if there is a significant difference in walking speed between each session, a two-tailed, paired t-test was used if the data were normally distributed and Wilcoxon's signed rank test was used if not (Nayak & Hazra, 2011).

3.19.2.6 *Statistical analysis*

All statistical analysis in the current study was conducted using Microsoft Excel version 15.29.1 for Mac, and SPSS version 23 for Mac. The means of five trials from the first session and the second session after seven days were used to compute the between-day reliability.

3.19.3 Results

Nine individuals with confirmed medial knee osteoarthritis were recruited and completed this study. Six participants were collected in the Hail University gait lab and three in the Brian Blatchford gait lab. Both labs have the same gait operation system (Vicon) and EMG system (Delsys). Each participant was tested and re-tested after 7 days in the same lab and the data from both labs were combined to calculate the reliability in current study. The individuals' demographics are represented in the following Table 3-14. Walking speed did not change between the first and the second session (p-value=0.82) (Table 3-15).

Table 3-14 Participants' demographics characteristics for participants with knee OA.

Number of subjects Mean (SD)	Gender	Age (Year)	Height (M)	Mass (Kg)	BMI (Kg/m²)	Affected side
9	All male	49 (6.06)	1.72 (0.05)	89.36 (15.74)	30.28 (5.28)	Right (5) Left (4)

Table 3-15 Walking speed in participants with knee OA

Mean (SD)	Test	Re-test	P-value
Speed (m/s)	1.23 (0.24)	1.23 (0.24)	0.82

3.19.3.1 *Test re-test reliability for external knee adduction moment (1st peak, trough, 2nd peak, KAAI)*

The mean, CI, SEM, SDD and ICC for the first peak, trough and second peak knee adduction moment during walking for individuals with medial OA are represented in the following Table 3-16. Generally, between-days reliability EKAM in osteoarthritis participants are excellent ranged from ICC =0.96 to ICC=0.99.

Table 3-16 Between-day reliability for EKAM during walking for participants with knee OA.

First peak, trough and second peak (Nm/Kg), KAAI (Nm/kg*s)	ICC	mean	95% CI of ICC	SEM	SDD
Knee y moment (first Peak)	0.97	0.61	0.86-0.99	0.019	0.05
Knee y moment (Trough)	0.96	0.32	0.82-0.99	0.021	0.06
Knee y moment (second Peak)	0.96	0.41	0.83-0.99	0.02	0.05
KAAI	0.99	0.26	0.94-0.99	0.009	0.02

3.19.3.2 *Test and re-test reliability for EMG*

The reliability of the muscle activity amongst individuals with osteoarthritis showed good CMC for the following muscles: LG, LH, LQ, MG, MH, and MG, ranging from 0.83 CMC to 0.87 CMC. The mean CMC and SD for each muscle is demonstrated in the following Table 3-17. The muscle co-contraction reliability for most phases and between most muscles were good to excellent, ranging from 0.79 to 0.98 ICC. In early-stance, LQ/LQ and MQ/MH reliability were poor to "fair", ICC 0.27 and 0.67 respectively (Table 3-18).

Table 3-17 Between day reliability of muscles activity EMG in a stance during walking for participants with knee OA.

Muscle (between-day)	CMC Mean	CMC SD
LG	0.85	0.05
LH	0.87	0.05
LQ	0.84	0.06
MG	0.84	0.10
MH	0.85	0.05
MQ	0.83	0.10

Table 3-18 Between-day reliability of muscles co-contraction in a stance during walking for participants with knee OA.

Stance phase	Variables	ICC	Mean	95% CI of ICC	SEM	SDD
Early-stance	LQ/LH	0.79	0.40	0.07-0.93	0.05	0.14
	LQ/LG	0.27	0.20	-2.22-0.84	0.06	0.17
	MQ/MH	0.67	0.25	-4.48-0.93	0.03	0.09
	MQ/MG	0.88	0.14	0.46-0.97	0.01	0.03
Mid-stance	LQ/LH	0.93	0.15	0.69-0.98	0.01	0.02
	LQ/LG	0.98	0.14	0.92-0.99	0.003	0.01
	MQ/MH	0.97	0.08	0.84-0.99	0.003	0.01
	MQ/MG	0.88	0.07	0.48-0.97	0.007	0.02
Late-stance	LQ/LH	0.84	0.08	0.29-0.96	0.009	0.03
	LQ/LG	0.81	0.08	0.14-0.96	0.01	0.04
	MQ/MH	0.88	0.05	0.49-0.97	0.005	0.01
	MQ/MG	0.96	0.09	0.80-0.99	0.004	0.01

3.19.3.3 *Test and re-test reliability for the modified star excursion balance test.*

Normalised results from the modified start excursion test reliability for the affected leg are represented in the Table 3-19. The data showed excellent reliability with ICC above 0.92 for normalised modified star excursion in anterior and the medial directions.

Table 3-19 Between-day reliability of balance test for participants with knee OA.

Balance	Direction	ICC	Mean	95% CI of ICC	SEM	SDD
Normalised data to leg length (%)	Anterior	0.96	74.67	0.83-0.99	2.12	5.88
	Medial	0.93	79.78	0.69-0.98	2.97	8.24

3.19.3.4 *Test and re-test reliability for three functional activity tests.*

The ICC, mean, CI, SEM and SDD for the 30-second chair-stand test, stair-climb test and 40-metre fast-paced walk test are illustrated in Table 3-20. The ICC value for the three functional tests (30-second chair-stand test, stair-climb test and 40-metre fast-paced walk test) were excellent, at 0.92, 0.95 and 0.92 respectively.

Table 3-20 Between-day reliability of three functional tests for participants with knee OA.

Functional tests	ICC	Mean	95% CI	SEM	SDD
30-second chair-stand test (repetition)	0.92	11.67	0.81-0.99	0.86	2.38
Stair-climb test (second)	0.95	9.91	0.80-0.99	0.60	1.67
40-metre fast-paced walk test (m/s)	0.92	1.65	0.64-0.98	0.04	0.1

3.19.3.5 *Test and re-test reliability for the pain pressure threshold test.*

The results of the pain pressure threshold test demonstrated high ICC for both the medial condyle (0.92 ICC) and medial malleolus (0.96 ICC). The ICC, mean, CI, SEM and SDD for pain pressure threshold are presented in the following table Table 3-21.

Table 3-21 Between-day reliability of pain pressure threshold for participants with knee OA.

Pain pressure threshold (N/Cm^2)	ICC	Mean	95% CI	SEM	SDD
Medial condyle	0.92	7.06	0.65-0.98	0.59	1.63
Medial malleolus	0.96	8.38	0.82-0.99	0.49	1.35

3.19.4 Discussion

The aims of the current study were to examine the reliability of biomechanical and clinical outcomes, which would be used in the main study (OA study). Additionally, to calculate the standard error of measurement and small detectable difference for each outcome among individuals with knee OA. The rationale for this study was to make sure that all the changes, which would be monitored after the six weeks of treatment for individuals with knee OA, are a real change and not caused by measurement error.

In 2010, a systematic review was conducted to evaluate the psychometric properties for gait outcomes among individuals with knee and hip OA (Ornetti et al., 2010). The study stated that there is limited number of studies to make conclusion and more studies are needed to investigate the reliability. Generally, the results of ICC for between-days EKAM (1st peak, trough, 2nd peak, KAAAI) are excellent in walking (0.96 to 0.99). High between-day reliability indicates that the marker application method achieved a good accuracy and low measurement error.

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Previous studies have stated that several factors might contribute to a difference in reliability results such as marker placement and static alignment (Ferber et al., 2002; Ford et al., 2007; Manal, McClay, Stanhope, Richards, & Galinat, 2000). Kadaba et al. (1989) stated that the variability between 3D gait outcomes may be causes of the marker's reapplication. In this study, only one observer applied the markers during both sessions. The high between-day ICC reflect high consistency in marker placement by the observer.

Knee adduction moment showed excellent reliability with value 0.97, 0.96 and 0.96 to the first peak, trough and the second peak respectively. This represents good reliability for such an outcome and supports the use of this outcome in clinical practice and research. These findings are consistent with previous studies that show good reliability for EKAM in healthy individuals (Andrews et al., 1996; Growney, Meglan, Johnson, Cahalan, & An, 1997; Kadaba et al., 1989a) and individuals with knee osteoarthritis (Asay, Boyer, & Andriacchi, 2013; Birmingham, Hunt, Jones, Jenkyn, & Giffin, 2007; Robbins, Astephen Wilson, Rutherford, & Hubley-Kozey, 2013) during walking. This is the first study to calculate the ICC, SEM and SDD in one study among individual with medial knee OA.

The reliability of between-day EMG signals from Vestus Medials, Vestus lateralis, Medial Hamstring, Lateral Hamstring, Medial Gastrocnemius, and Lateral Gastrocnemius ranged from 0.83 CMC to 0.87 CMC. Kadaba et al. (1989) showed similar results for between-day reliability except medial hamstring (0.76 CMC). This might have been caused by placing the electrode in the motor unit, which increases the variability and reduces the reliability of the signals (Hermens et al., 2000). Other studies have investigated the reliability of between- and within-day EMG (Hubley-Kozey et al., 2013; Kadaba et al., 1985; Mohr, Lorenzen, Palacios-Derflingher, Emery, & Nigg, 2018; Winter & Yack, 1987), however a direct comparison could not be made due to the use of different statistical methods. Muscle co-contraction reliability was good to excellent (ICC>0.79) for all muscles except LQ/LQ and MQ/MH in early-stance, where the ICC was poor (ICC=0.27) and fair (ICC=0.67) respectively. Previous study to the OA population calculated the ICC for muscle co-contraction and showed high reliability, ranging from 0.76 to 0.89 (Hubley-Kozey et al., 2013). However, direct comparison could not be made since this study calculated the muscle co-contraction in the whole stance phase and did not divide the stance into three sub phases as in this study.

The star excursion balance test and retest reliability results showed excellent reliability for both normalised and non-normalised data in anterior and medial directions above ICC 0.92. Interestingly, the star excursion balance test in the anterior direction was more reliable than in the medial direction. This might be caused by the pain as the subject is standing on the affected side and the load is high on the medial side. This is the first study to examine the reliability of the star excursion test in individuals with medial knee osteoarthritis.

Previous healthy studies showed good reliability in the star excursion balance test in the anterior direction ICC=0.87 (Kinzey & Armstrong, 1998) and the medial direction ICC=0.86 (Munro & Herrington, 2010). The slightly lower results among the previous researches may be caused by different reasons. This study standardised a position to the static foot by line to make sure repeated foot placement and standardised the test direction order. Secondly, this study included OA subjects while previous studies included healthy participants. Healthy subjects might be able to reach longer distances than participants with OA, which increases the variability in the tests.

The usefulness and importance of functional performance tests to investigate the effect of physical training and rehabilitation is well established (Augustsson & Thomeé, 2000; Tegner, Lysholm, Lysholm, & Gillquist, 1986). Previous studies have used functional performance tests to evaluate the physical performance in individuals at high risk or with knee osteoarthritis (Sharma et al., 2003). The current study showed excellent reliability in the 30-second chair-stand test (ICC=0.92), stair-climb test (ICC=0.95) and 40-metre fast-paced walk test (ICC=0.92).

In 2005, Kennedy et al. assessed the reliability of several functional tests in individuals with hip and knee osteoarthritis (Kennedy et al., 2005). Their reliability results from the 40-metre fast-paced walk test and the stair-climb test were ICC=0.91 and ICC=0.90, respectively which agree with current study. A more recent study showed ICC=0.95 and ICC=0.81 for the 40-metre fast-paced walk test and 30-second chair-stand test, respectively (Wright et al., 2011). The difference in the 30-second chair-stand test reliability results between this study and previous study can be attributed to a difference in population (hip OA). Furthermore, high ICC was identified for the 30-second chair-stand test at three-time line, ranging from 0.95 to 0.99 in individuals with knee and hip osteoarthritis waiting for joint replacement, which agreed with this study's results in showing excellent reliability (Gill & McBurney, 2008).

Pain pressure threshold showed excellent reliability over a week for the medial condyle and medial malleolus in the affected leg. Interestingly, the medial condyle (ICC=0.92) showed lower reliability value than the medial malleolus (ICC=0.96). This might be explained by the variation in pain pressure threshold on the affected knee from one day to other.

Previous studies showed excellent reliability for the pain pressure threshold over the medial condyle ranging from 0.84 to 0.97 (Mutlu & Ozdincler, 2015; Pelfort et al., 2015) and the medial malleolus ranging from 0.93 to 0.98 (Mutlu & Ozdincler, 2015). Although the pain pressure threshold in this study and previous studies is reliable, it may be affected by several factors: age and gender were identified to affect the pain pressure threshold (Chesterton, Barlas, Foster, Baxter, & Wright, 2003; Magerl et al., 2010). In 1988, Cornwall and Doniri stated that the level of anxiety and anticipation may also affect pain pressure threshold sensitivity (Cornwall & Donderi, 1988).

The current study provides reference values for SEM and SDD for clinical and biomechanical outcomes among individuals with knee OA, which may be useful for evaluating intervention results in future studies. Furthermore, this study has used participants' own shoes, which reflect shoes used in everyday life.

As with any study, there were limitations that the generalisability of results was restricted to similar laboratory settings, the model, and the researchers' ability to apply markers, although the results are consistent with previous literature. Secondly, the time between the first and the second tests was relatively short (7 days), which might create a familiarisation effect, and this should be controlled by providing sufficient practice. Finally, the sample size could be criticised, although excellent ICC and low SEM in most of the variables were identified.

3.19.5 Conclusion

Based on the results of the current study, several points can be highlighted. Firstly, EKAM (1st peak, trough, 2nd peak, KAAI) show excellent reliability and low SEM, therefore it can be used to evaluate between-days treatment effects. Secondly, EMG can be used to investigate treatment effect between-day, as all muscles showed good CMC. ICC for LQ/LH, LQ/LG, MQ/MH and MQ/MG indicate good between-day reliability in all phases except for LQ/LG and MQ/MH in the early-stance phase. Finally, the star excursion test, the functional tests (40-metre fast-paced walk

test, 30-second chair-stand test, stair-climb test) and pain pressure threshold are reliable with low measurement error and can be used to evaluate the clinical efficacy of treatment.

3.20 **Summary of chapter**

This chapter has presented the methodology undertaken to assess the biomechanical and clinical outcomes. Furthermore, the definition and calculation methods for the desired variables were clearly stated. The participant selection criteria for defining healthy and knee OA participants were described. The healthy reliability study showed that EKAM, and most kinetics and kinematics outcomes are highly reliable outcomes within session and between sessions. The second reliability study showed a similar finding, exhibiting excellent reliability in the biomechanical and clinical outcomes among individuals with knee OA. This means that most biomechanical outcomes in healthy people and individuals with knee OA and all clinical outcomes in individuals with knee OA can be used to investigate the treatment efficacy with high accuracy. The next chapters take this into consideration and investigates the effects of LWI and simple knee sleeve in healthy people and individuals with knee OA using outcomes with good to excellent reliability.

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Chapter 4: The immediate effect of single and combined treatments on knee kinematics and kinetics on healthy during walking

4.1 Chapter overview

This chapter aims to fill the gap in the literature concerning sleeve, LWI and combined treatment and how this can be tested on healthy individuals before implementing it on individuals with medial knee OA. The introduction concludes with the aims and hypotheses of the study. The methods section relates the design of the study and recruitment plan, as well as giving brief descriptions of the laboratory and gait analysis method. Then, the statistical approach used to investigate the hypothesis is described in detail. The following section gives the detailed results based on a scientific statistical method. This chapter then ends with a discussion and conclusion, where the results are interpreted and compared with those of previous studies, while clinical applications are explained.

4.2 Background

Osteoarthritis (OA) is considered the most prevalent type of musculoskeletal disease, affecting millions of individuals and reducing their quality of life through disability (Lawrence et al., 2008). It is considered a worldwide health problem that affects approximately 8% to 15% of the population (Rat et al., 2006). In a previous study in the United Kingdom, 1 out of every 10 individuals between 35 and 75 was found to be affected by OA (Sangha, 2000). OA is one of the most common secondary causes of death due to disability. Recent reports indicate that people with knee OA are at high risk of cardiovascular disease due to disability and inactivity (Nüesch et al., 2011).

Several surgical techniques are used to treat individuals with knee OA. However, there are some individuals for whom surgery is not appropriate (e.g. too young) or who do not want surgery (Bhatia et al., 2013; Marks & Penton, 2004). Therefore, conservative management should be the primary consideration when treating individuals with medial knee OA.

Conservative management approaches have not been fully validated in the scientific literature. It is therefore important to know which techniques will have the most impact on individuals' pain and functional independence, two of the primary concerns of sufferers.

Valgus knee braces and lateral wedge insoles are common modalities used to treat individuals with medial knee OA. There is supporting evidence that using combined treatments during walking leads to a greater reduction in external knee adduction moment (EKAM) than using a single treatment. Three studies investigated the combination of a lateral wedge insole and a valgus knee brace (Al-Zahrani et al., 2013b; Fu et al., 2015; Moyer et al., 2013). In all these, this combination resulted in a greater reduction in first or second EKAM than individual treatment. However, compliance was lower in the combined treatment group (valgus brace and LWI) than in the single treatment group (LWI).

Several studies have investigated the effect of using lateral wedge insoles on individuals with knee OA. No difference was found between lateral wedge insoles and control treatments, such as neutral insoles, with regard to pain (Baker et al., 2007; Barrios et al., 2009; Bennell et al., 2011; Campos et al., 2015; Maillefert et al., 2001; Pham et al., 2004). One of the potential uses of lateral wedge insoles that has been shown to have a positive mechanical response is to combine them with a device that has better pain-relieving results.

A simple knee sleeve is another option that has been used to treat individuals with knee OA. Several studies have investigated the effect of knee sleeves on individuals with knee OA resulting in decreased pain (Bryk et al., 2011; Kirkley et al., 1999; Mazzuca et al., 2004; Schween et al., 2015), improved quality of life (Kirkley et al., 1999), improved stability (Schween et al., 2015), improved function (Bryk et al., 2011; Kirkley et al., 1999), and decreased muscle co-contraction (Collins et al., 2011). They also showed proprioceptive improvements in partial weight bearing tasks (Collins et al., 2011b) and improvement in static and dynamic balance (Chuang et al., 2007) and knee flexion angles (Collins et al., 2013, 2011).

Improving muscle co-contraction is considered an important factor, as increased medial muscle co-contraction has been correlated with medial cartilage volume loss rates in individuals with knee OA and varus alignment (Hodges et al., 2015). It is believed that increased muscle co-contraction comes at the expense of higher joint loading (Lloyd & Buchanan, 2001; Meyer et al., 2013;

Schipplein & Andriacchi, 1991) and increases OA risk (Heiden et al., 2009; Wu et al., 1990; Zeni et al., 2010).

Two studies investigated the effect of knee sleeve on EKAM during walking in individuals with knee OA. The results were contradicting with one study showing significant reduction by 10.1% (Schween et al., 2015) while other one did not show any significant change (Collins et al., 2014).

Combining lateral wedge insoles and a simple knee sleeve may be a good option to treat individuals with knee OA. With this combination of reduced muscle co-contraction, simple knee sleeve use, and the EKAM via the lateral wedge insole, it may be possible to achieve a consistent reduction in pain and loading. However, before conducting the study in individuals with knee OA one step can be taken. This step is to investigate what can the sleeve offer in kinematics, kinetics and muscle co-contraction in a healthy cohort without impairment. Recent literature review study showed that only 4 studies investigated the effect the knee sleeve on kinematics and kinetics (Mohd Sharif, Goh, Usman, & Wan Safwani, 2017). Of which three were in individuals with knee OA during walking (Collins et al., 2014, 2011; Schween et al., 2015) and in healthy during descending and landing (Giotis et al., 2011). Further research revealed one study which investigated the effect of the knee sleeve on walking and single leg hopping among healthy (Ko et al., 2017). This study only looked at segments angle (thigh, shank, foot) in relation to the floor and did not included the knee joint angles or moments. Therefore, there is a clear need for a study which look to the effect of the knee sleeve on healthy.

Interestingly, several studies investigated the effect of LWI in healthy individuals and showed a reduction in EKAM (Crenshaw et al., 2000; Jones et al., 2013c; Kakihana et al., 2005, 2004; Nakajima et al., 2009). To the best of our knowledge no previous study did investigated the effect of LWI on muscle co-contraction among healthy or individuals with knee OA. looking at muscle co-contraction is important since increase the muscle co-contraction may lead to higher joint loading (Lloyd & Buchanan, 2001; Meyer et al., 2013; Schipplein & Andriacchi, 1991) and was correlated with progression of the knee OA (Hodges et al., 2015). Furthermore, no study has investigated the effect of a combined treatment using a simple knee sleeve and a lateral wedge insole on kinematics, kinetics, and muscle activity during walking in healthy which highlight the need for more studies.

Therefore, determining whether a lateral wedge insole, a simple knee sleeve, or a combined approach reduces loads during walking is warranted. In the present study, the immediate effect of treatment conditions will be investigated first in healthy participants. After that, if the experiment yields promising results in healthy participants, participants with knee OA will be recruited.

4.3   Purpose of the study

The purpose of the study was to investigate the effect of four treatment conditions (combined treatment, simple knee sleeve, lateral wedge insole and control) and assess their impact on knee loading (first peak EKAM, trough EKAM, second peak EKAM, knee adduction angular impulse (KAAI)), ground reaction force (GRF), knee flexion moment, knee joint angles in sagittal plane (knee flexion angle at initial contact, maximum knee flexion angle at loading response, minimum knee flexion angle at mid-stance, maximum knee flexion angle at swing), frontal plane range of motion (ROM), and muscle co-contraction.

4.4   Aims and hypotheses of the study

The following are the aims and primary hypotheses of the study:

- To investigate the effect of combined treatment (lateral wedge insole and simple knee sleeve) and individual treatment on EKAM.

- Null hypothesis: There is no significant immediate change in knee loading (first peak EKAM, trough EKAM, second peak EKAM, KAAI) when using the combined treatment (lateral wedge insole, simple knee sleeve) or individual treatment compared to individual treatment, combined treatment or no treatment.

- To investigate the effect of the combined treatment (lateral wedge insole and simple knee sleeve) and individual treatment on muscle co-contraction.

- Null hypothesis: There is no significant immediate change in muscle co-contraction when using the combined treatment (lateral wedge insole, simple knee sleeve) or individual treatment compared to individual treatment, combined treatment or no treatment.

Secondary hypothesis of the study:

- To investigate the effect of combined treatment (lateral wedge insole and simple knee sleeve) and individual treatment on GRF, knee flexion moment, knee joint angles in sagittal plane (knee flexion angle at initial contact, maximum knee flexion angle at loading response, minimum knee flexion angle at mid-stance, maximum knee flexion angle at swing), and frontal plane ROM.

- Null hypothesis: There is no significant immediate change in GRF, knee flexion moment, knee joint angles in sagittal plane (knee flexion angle at initial contact, maximum knee flexion angle at loading response, minimum knee angle at mid-stance, maximum knee flexion angle at swing) and ROM of the knee joint angle in frontal plane when using the combined treatment (lateral wedge insole, simple knee sleeve) or individual treatment compared to individual treatment, combined treatment or no treatment.

4.5 Methods

The participants' data collection was conducted in Hail gait laboratory at Hail University.

4.5.1 Population

Healthy adult participants aged 20 to 60 years old were included in the study. For more details about the inclusion and exclusion criteria which define healthy please see section 3.5.1.1.

4.5.2 Study design and randomisation

This randomised crossover study investigated the immediate effect of four treatment conditions on healthy individuals during walking. The four treatment conditions were as follows: a five-degree lateral wedge insole (Figure 4-1), a simple knee sleeve (Figure 4-2), combined treatment (lateral wedge insole, simple knee sleeve) (Figure 4-1, Figure 4-2) and control (no treatment). Participants were randomly assigned to a treatment condition using randomisation blocks. For more details about the rationale for the appropriate selection criteria which has been used to select the LWI and the knee sleeve please see sections 3.6.1 and 3.6.3.

Figure 4-1 Lateral wedge insole used in the study.

Figure 4-2 Knee sleeve used in the study.

In brief, a 10-Bonita-camera Vicon analysis system with two AMTI force plates was used. Data was captured at 100 Hz for kinematics and 1000 Hz for kinetics. Following calibration (section 3.8.2, the markers were applied to the individual base of the CAST model (section 3.9). Surface electromyography electrodes were applied on the following muscles: LH, MH, LG, MG, LQ and MQ (section 3.10). MVIC was collected for these muscles (section 3.11).

The participants were asked to walk on a 12-metre walkway at their own self-selected speed. All participants were asked to perform five successful walking trials. A successful trial required the occurrence of contact on the force plate (AMTI), within 5% of each participant's self-selected speed.

The biomechanical results were computed based on data collected under the following four conditions:

- lateral wedge insole (LWI)
- simple knee sleeve (Sleeve)
- Combination of the lateral wedge insole and the simple knee sleeve (Sleeve+LWI)
- Participants own shoes (control)

4.5.3 Variables of interest

The variables of interest were walking speed, peak knee flexion moment, EKAM (first peak, trough, second peak, KAAI), GRF (first peak, trough, second peak), knee flexion angle at initial

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contact, maximum knee flexion angle at loading response, minimum knee flexion angle at mid-stance, maximum knee flexion angle at swing and knee frontal plane ROM. Muscle co-contraction in the early-stance, mid-stance and late-stance were among the variables of interest for the following pairs of muscles: LQ/LH, LQ/LG, MQ/MH and MQ/MG. For more details please see sections 3.14 and 3.15.

4.5.4   Data analysis

After processing the walking data using the Vicon nexus and Visual 3D programs, the data were exported to an Excel sheet. To select the appropriate statistical test, the data were checked for normality using a Shapiro–Wilk test. Repeated measures ANOVA was used to investigate the effect of treatments on the interested outcomes. A Friedman test was used with non-normally distributed variables. All kinematics, kinetics and walking speed data were normally distributed. The muscle co-contraction data were not normality distributed for most muscles and phases, except for mid-stance LQ/LH co-contraction in all groups.

4.6 **Results**

The number of subjects and their age, height, mass and body mass index (BMI) are presented in Table 4-1

Table 4-1 Participants' demographics characteristics.

Number of subjects Mean (SD)	Age (Years)	Mass (Kg)	Height (M)	BMI (Kg/m²)
19	21.95 (0.91)	64.88 (13.86)	1.69 (0.07)	22.56 (4.19)

A repeated measures ANOVA showed no significant difference in speed during walking (p=0.77) between all treatment conditions (Table 4-2).

Table 4-2 Walking speed.

Speed (m/s) Mean (SD)	Combined treatments	Lateral wedge insole	Simple knee sleeve	Control
Walking	1.13 (0.15)	1.14 (0.14)	1.13 (0.15)	1.14 (0.15)

4.6.1 Knee joint moments and GRF

The peak knees flexion moment showed no significant difference between treatment conditions during walking (p=0.09) (Figure 4-3, Table 4-3).

A repeated measures ANOVA showed significant changes across treatment conditions in the first peak EKAM (p<0.01). In the frontal plane, a pairwise comparison showed significant reduction in the first peak EKAM for the combined treatment compared to the control treatment (5.39%; mean difference 0.03 (0.04) Nm/kg, p=0.02). The LWI treatment showed a significant reduction in the first peak EKAM compared to the control treatment (8.46%; mean difference 0.04 (0.04) Nm/kg, p<0.01) and the sleeve treatment (6.37%; mean difference 0.03 (0.03) Nm/kg, p<0.01). No significant changes in the trough EKAM were found between treatments, based on a repeated measures ANOVA (p=0.18). The second peak EKAM showed a significant difference between treatment conditions during walking (p<0.01). A pairwise comparison showed a significant reduction in the second EKAM for the LWI treatment (4.91%; mean difference 0.02 (0.03) Nm/kg,

p=0.02;) compared to the control treatment and the sleeve treatment (6.68%; mean difference 0.02 (0.03) Nm/kg, p=0.01) (Figure 4-4, Table 4-3).

The KAAI showed significant change across treatment conditions as identified by a repeated measures ANOVA ($p<0.01$). This changes in KAAI was identified to be as a significant reduction for the combined treatment (mean difference 0.01 (0.01) Nm/kg*s, $p<0.01$) and the LWI treatment (mean difference 0.01 (0.01) Nm/kg*s, p=0.02) compared to the sleeve treatment by 4.92% and 5.64%, respectively (Figure 4-5, Table 4-3).

The first peak GRF, trough and second peak GRF did not differ significantly across treatments during walking (p=0.43, 0.08, 0.30 respectively) (Figure 4-6, Table 4-3).

Table 4-3 Knee moments, KAAI and ground reaction force during walking.

Variable Mean (SD)	Sleeve + LWI	LWI	Sleeve	Control
Peak Flexion Moment (Nm/Kg)	-0.48(0.25)	-0.46(0.22)	-0.46(0.25)	-0.47(0.26)
1st Peak EKAM (Nm/Kg)	0.46(0.14) ∂	0.44(0.14) $\partial\Omega$	0.47(0.15)	0.49(0.16)
Trough EKAM (Nm/Kg)	0.23(0.09)	0.23(0.10)	0.24(0.10)	0.24(0.10)
2nd Peak EKAM (Nm/Kg)	0.33(0.12)	0.32(0.12) $\partial\Omega$	0.34(0.13)	0.34(0.14)
KAAI (Nm/kg*s)	0.16(0.07) Ω	0.16(0.07) Ω	0.17(0.07)	0.17(.07)
GRF 1st Peak (BW)	1.08(0.07)	1.07(0.06)	1.07(0.07)	1.08(0.07)
GRF Trough (BW)	0.82(0.06)	0.82(0.06)	0.82(0.06)	0.81(0.06)
GRF 2nd Peak (BW)	1.09(0.07)	1.07(0.06)	1.07(0.07)	1.08(0.07)

∂ significant compared to control
Ω significant compared to sleeve
λ significant compared to LWI
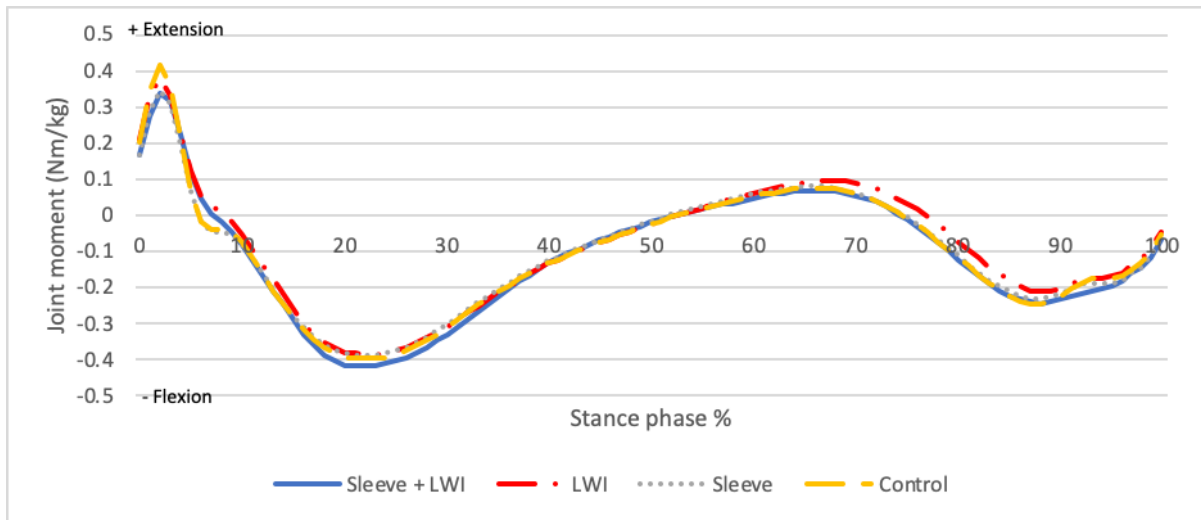
Figure 4-3 Knee joint moment in sagittal plane during walking.
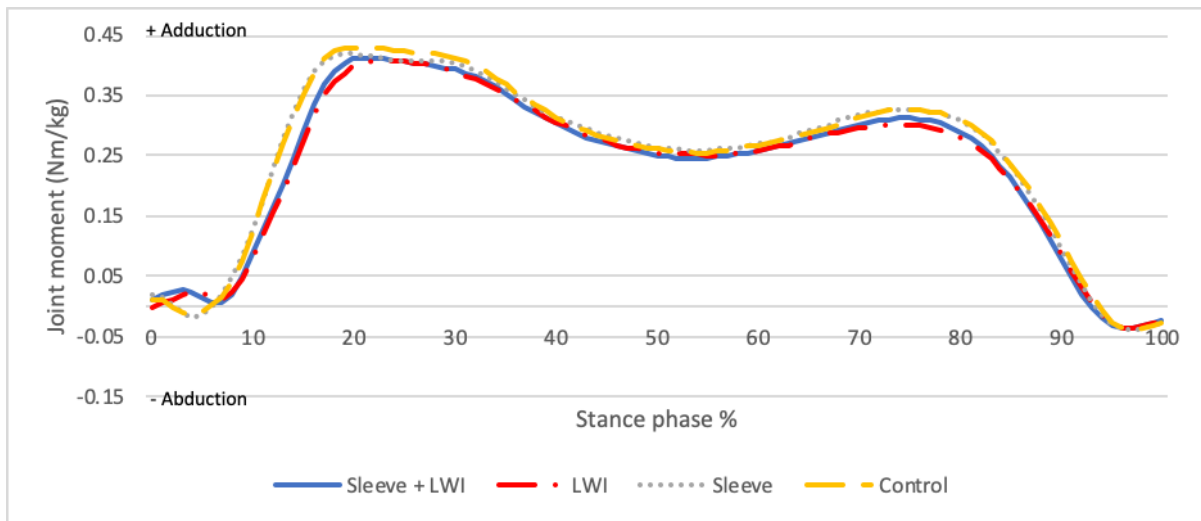
Figure 4-4 Knee joint moment in frontal plane during walking.

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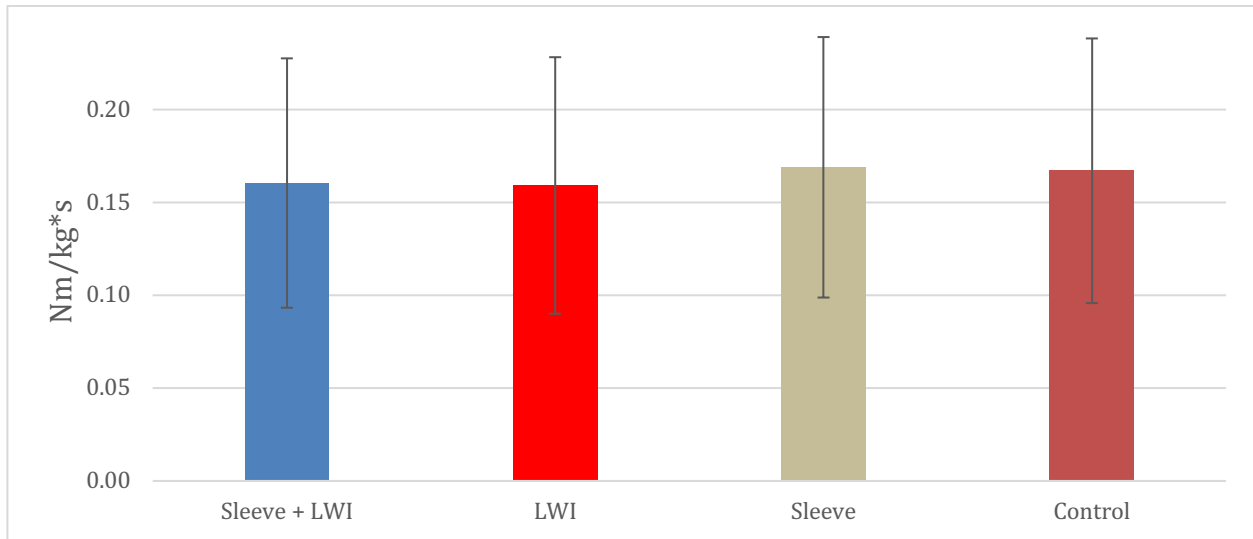
Figure 4-5 Knee adduction angular impulse (KAAI) during walking.
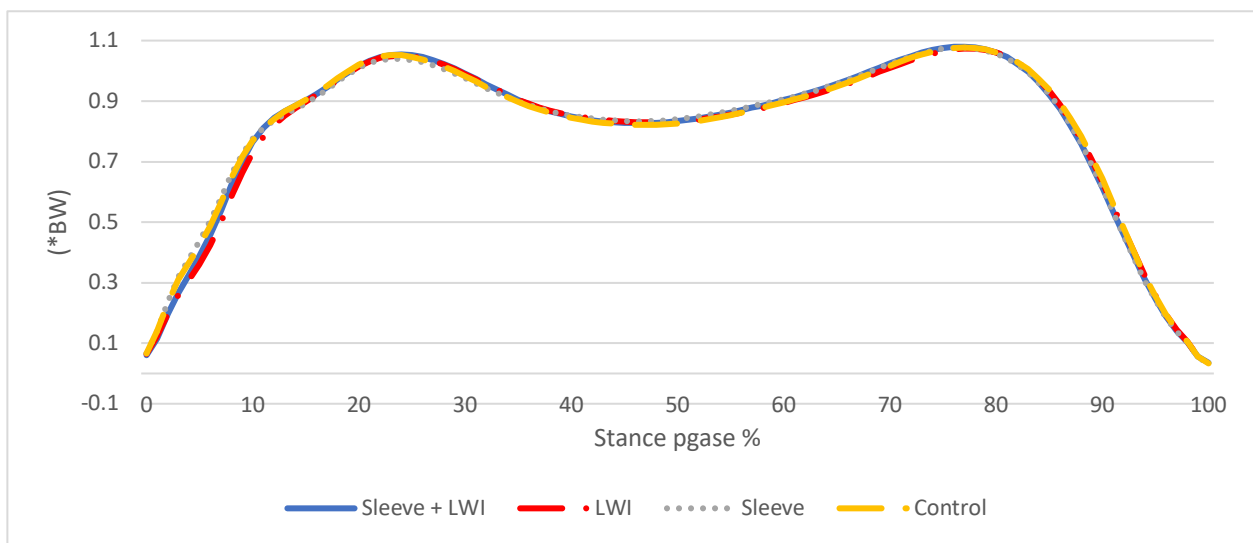
Figure 4-6 Vertical ground reaction force (GRF) during walking.

4.6.2 Knee kinematics

Regarding the sagittal plane, a repeated measures ANOVA showed no significant changes between treatments in knee flexion angle at initial contact (p=0.55), maximum knee flexion angle at loading response (p=0.60) or minimum flexion angle at mid-stance (p=0.81). However, the maximum flexion angle at late-swing showed significant changes across treatment conditions (p<0.01). A pairwise comparison showed a reduction for the combined treatment compared to the control

treatment (2.07%; mean difference 1.45 (2.07) degrees, p<0.01) and to the LWI treatment (1.71%; 1.25 (1.83) degrees, p<0.01) and for the sleeve treatment compared to the control treatment (mean difference 1.2 (1.7) degrees, p<0.01; 1.56 (2.25) degrees, p<0.01) and the LWI treatment (2.2%; mean difference 1.56 (2.25) degrees, p<0.01) (Figure 4-7, Table 4-4).

A repeated measures ANOVA showed a significant change in knee frontal ROM across treatments (p<0.01). The knee frontal plane ROM showed a significant reduction for the combined treatment compared to the control treatment (14.83%; mean difference 2.19 (2.71) degrees) and the LWI treatment (11.98%; mean difference 1.50 (1.91) degrees, p<0.01) and for the sleeve treatment compared to the control (7.61%; mean difference 1.31 (1.71) degrees, p<0.01) and LWI treatment (11.29%; mean difference 1.71 (2.21) degrees, p<0.01) (Figure 4-8, Table 4-4).

Table 4-4 Knee joint angles in sagittal plane and ROM in frontal plane during walking.

Variable	LWI + Sleeve	LWI	Sleeve	Control
Knee angle at initial contact (degree)	2.12 (3.03)	2.31(3.10)	1.95 (3.38)	2.06 (3.35)
Maximum knee flexion peak angle at loading response (degree)	8.98 (7.03)	8.74(6.82)	8.96 (7.22)	8.61 (7.13)
Minimum knee flexion angle at mid-stance (degree)	2.68 (4.47)	2.63 (4.44)	2.82 (4.72)	2.76 (4.57)
Maximum knee flexion peak angle at swing (degree)	68.16 (4.87) $\partial\lambda$	70.30 (4.80)	67.88 (4.83) $\partial\lambda$	70.33 (4.33)
ROM of the knee joint angle in frontal plane (degree)	9.81 (.3.35) $\partial\lambda$	12.49 (3.63)	10.46 (3.57) $\partial\lambda$	12.96 (4.13)

∂ significant compared to control
Ω significant compared to sleeve
λ significant compared to LWI
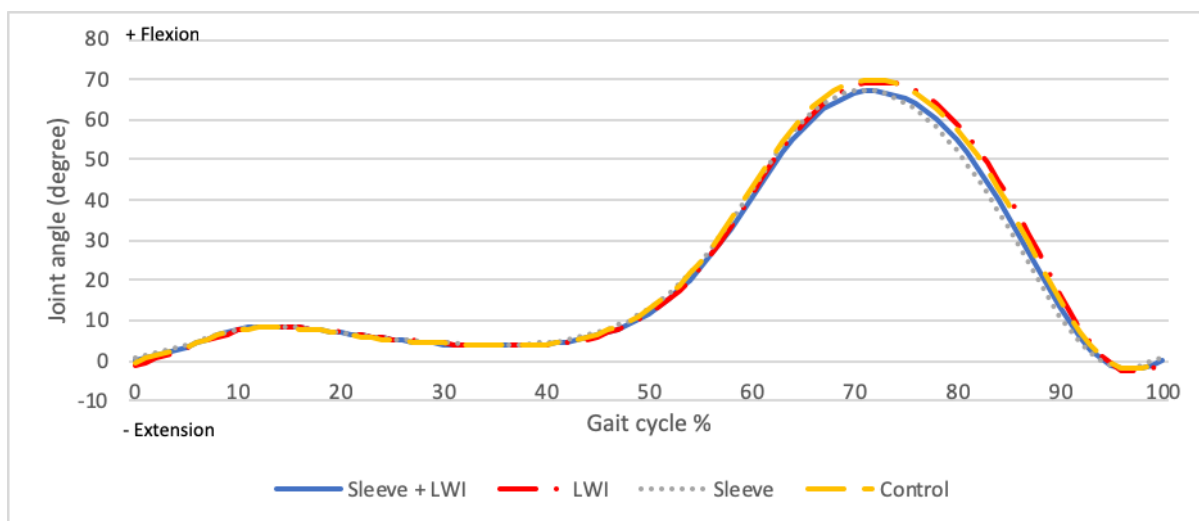
Figure 4-7 Knee joint angle in sagittal plane during walking.
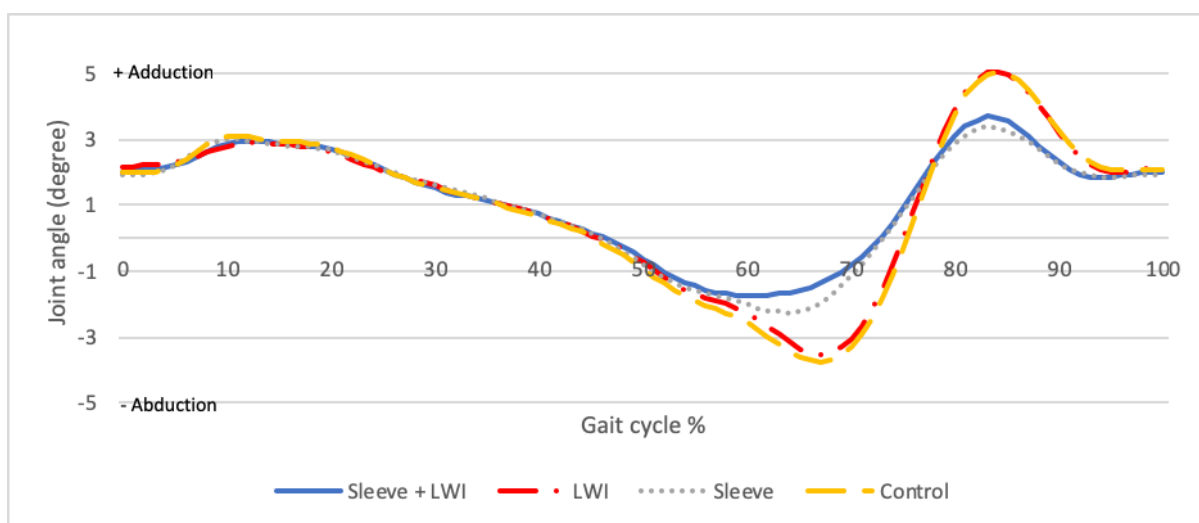
Figure 4-8 Knee joint angle in frontal plane during walking.

4.6.3   Muscle Co-Contraction

There was no significant reduction in LQ/LH co-contraction between treatments in the early and mid-stance phases ($p \geq 0.05$). However, the late-stance phase showed a significant difference between the treatments during walking ($p=0.02$). A pairwise comparison showed a reduction for the sleeve treatment compared to the LWI treatment (median difference 0.003, $p=0.03$) and nearly to be significant compared to the control treatment ($p=0.07$). The LQ/LG co-contraction showed no significant difference between all treatments in the early-, mid- and late-stance phases ($p \geq 0.05$).

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In the early, mid- and late-stances, there was no significant difference in MQ/MH co-contraction and MQ/MG co-contraction between the treatments during walking (p≥0.05) (Table 4-5, Table 4-6).

Table 4-5 Mean muscle co-contraction in walking across conditions.

Muscles	Period	condition	LWI + Sleeve	LWI	Sleeve	Control
LQ/LH	Mid-Stance	Mean	0.027	0.028	0.028	0.028
		SD	0.019	0.022	0.022	0.025

Table 4-6 Median muscle co-contraction in walking across conditions.

Muscles	Period	condition	LWI + Sleeve	LWI	Sleeve	Control
LQ/LH	Early-stance	Median	0.079	0.077	0.086	0.086
		Range	0.011-0.332	0.014-0.337	0.011-0.374	0.013-0.298
	Late-Stance	Median	0.020	0.021	0.018 λ	0.020
		Range	0.012-0.033	0.013-0.038	0.011-0.034	0.013-0.043
LQ/LG	Early-stance	Median	0.067	0.081	0.071	0.084
		Range	0.011-0.190	0.013-0.179	0.011-0.215	0.013-0.171
	Mid-Stance	Median	0.022	0.028	0.021	0.020
		Range	0.008-0.239	0.008-0.183	0.008-0.265	0.007-0.223
	Late-Stance	Median	0.015	0.017	0.016	0.016
		Range	0.007-0.046	0.009-0.041	0.007-0.076	0.007-0.040
MQ/MH	Early-stance	Median	0.032	0.037	0.047	0.035
		Range	0.007-0.242	0.005-0.192	0.004-0.148	0.006-0.209
	Mid-Stance	Median	0.012	0.011	0.013	0.011
		Range	0.004-0.060	0.003-0.049	0.004-0.047	0.004-0.046
	Late-Stance	Median	0.014	0.014	0.012	0.014
		Range	0.004-0.073	0.005-0.049	0.004-0.058	0.004-0.052
MQ/MG	Early-stance	Median	0.065	0.046	0.070	0.049
		Range	0.008-0.164	0.005-0.144	0.005-0.141	0.007-0.173
	Mid-Stance	Median	0.033	0.023	0.019	0.020
		Range	0.003-0.087	0.003-0.099	0.003-0.121	0.012-0.033
	Late-Stance	Median	0.017	0.016	0.019	0.018
		Range	0.003-0.056	0.004-0.381	0.003-0.295	0.003-0.435

∂ significant compared to control
Ω significant compared to sleeve
λ significant compared to LWI

4.7 Discussion

The purpose of this study was to examine the impact of knee sleeve on biomechanical outcomes during walking to be taken to the next stage of the study in individuals with knee OA. Furthermore, to examine the effect of LWI and combined treatment on kinematic, kinetics, GRF and muscle co-contraction in healthy.

Regarding the first aim of the study, the first peak EKAM showed a significant reduction for the combined treatment and the LWI treatment compared to the sleeve treatment and the control treatment. This reduction was seen in the first peak EKAM for the LWI (8.46%) and the combined treatment (5.39%) compared to the control treatment and for the LWI treatment (6.37%) compared to the sleeve treatment. Although the reduction in the first peak EKAM (0.03 Nm/kg) for the combined treatment compared to the sleeve treatment did not reach statistical significance, it passed the measurement error (0.01 Nm/kg) for within session, which indicates a real reduction.

The trough EKAM did not show any statistically significant changes with the LWI treatment or the combined treatment, and the reduction in trough EKAM did not pass the measurement error.

In contrast, only the LWI treatment resulted in a significant reduction in the second peak EKAM compared to the sleeve treatment (4.91%) and the control treatment (6.68%). The combined treatment resulted in a reduction in second peak EKAM compared to the control treatment and the sleeve treatment and passed the measurement error but was not statistically significant.

No significant difference was found in walking speed for any of the treatments during walking. This indicates that the significant reduction in EKAM was a result of using the lateral wedge insole rather than changes in walking speed or GRF. EKAM is determined by multiplying the GRF by the moment arm. Therefore, if the GRF did not change as a result of speed, then the moment arm must have decreased.

The decreased EKAM with LWI use in this study could be due to three main factors—an increase in the ankle eversion angle, an increase in the ankle eversion moment and shifting the centre of foot pressure laterally. Previous studies involving LWI use showed an increase in the ankle eversion angle with LWI use by changing the foot orientation relative to the floor (Butler, Barrios,

Royer, & Davis, 2009; Chapman et al., 2015). Furthermore, an increase in the eversion moment (Abdallah & Radwan, 2011; Chapman et al., 2015; Mølgaard & Kersting, 2013; Pagani, Hinrichs, & Brüggemann, 2012) and laterally shifting in centre of pressure (Chapman et al., 2015; Hinman et al., 2012; Kakihana et al., 2005; Leitch et al., 2011) have been found by previous research. Although the eversion moment increase might cause discomfort and increase the load on the ankle joint with long-term LWI use, incorporating the medial arch might reduce the risk by redistributing the force alongside the sole of the foot.

Several studies have revealed a significant reduction in EKAM with LWI use in healthy people, which is in total agreement to with the current study (Crenshaw et al., 2000; Jones et al., 2013c; Kakihana et al., 2005, 2004; Nakajima et al., 2009). Jones et al. (2013c) showed significant reductions in the first peak (8.5%) and second peak (12.5%) with 5-degree LWI among healthy individuals. Although the reduction in the second peak was higher in Jones et al. (2013c), this could be due to differences between the studies, as the current study did not control the shoes, while Jones et al. (2013c) used ECCO Zen shoes; it could also be due to a difference in demographic characteristics between studies. Direct comparison with the rest of the studies of healthy populations could not be carried out, since different methods were used in the calculation of EKAM. Kakihan et al. (2005) calculated the average EKAM when using LWI (6 degree) attached to the foot by tape compared with no LWI and showed 10.4% reduction. Crenshaw et al. (2000) showed a significant reduction after using thin a flexible shoe in peak EKAM between LWI (6 degree) and no LWI, amounting to 6.65%. In 2009, Nakaima et al. (2009) conducted a study and showed a significant reduction in peak EKAM (8.8%) with LWI (6 degree) compared with a flat insole.

Studies of LWI in individuals with knee OA showed similar reduction in first peak EKAM of 5.85% (Chapman et al., 2015), 5.6% (Kakihana et al., 2005) and 5.21% (Jones et al., 2014). Hinman et al. (2008) also obtained a similar result in the first peak (5.4%) and the second peak (5.1%) with LWI use in individuals with knee OA. Another study by Hinman et al. (2009) showed a greater reduction in the first peak (12%) and the second peak (14%). This difference in reduction could be attributed to the difference in population between the current study and the study by Hinman et al. (2009). Hinman et al. (2009) recruited subjects with versus knee alignment and pain.

Similar to the previous healthy studies, some subjects showed no difference in EKAM (increase or no change) with LWI use (Crenshaw et al., 2000; Jones et al., 2013c; Nakajima et al., 2009). Studies in individuals with knee OA showed similar trend with some subjects characterised as non-responder (Butler et al., 2007; Crenshaw et al., 2000; Hinman et al., 2008a, 2008b, 2012; Kakihana et al., 2005, 2007; Kerrigan et al., 2002). This is believed to have been caused by the ankle joint position variation in the frontal plane while walking. In 2015, Chapman et al. concluded that the ankle joint plays an important role in responders and non-responders. Furthermore, individuals with more everted ankles during walking without LWI were more likely to show a reduction in EKAM.

KAAI is known to be more sensitive than EKAM in detecting the differences between knee OA severity (Kean et al., 2012; Thorp et al., 2006). During walking, both the combined treatment and the LWI treatment resulted in a significant reduction in KAAI of 4.92% and 5.64% compared to the sleeve treatment. Although the KAAI decreased in the combined treatment and the LWI treatment compared to the control treatment, it did not reach statistical significance level.

Interestingly, the reduction in KAAI with LWI use were found in individuals with knee OA of 6.3% (Hinman et al., 2012), 5.2% (Hinman et al., 2009), 7.95% (Chapman et al., 2015), 6.38% (Jones et al., 2013) and 6.29% (Jones et al., 2014). However, direct comparison to previous studies cannot be made due to the difference in population (knee OA compared to current study (healthy).

Interestingly, the knee sleeve did not result in any significant reduction in EKAM compared to the control treatment during walking. Nor did the sleeve reduce the KAAI during walking. A comparison to other healthy studies unfortunately cannot be made due to the lack for similar study in healthy participants. Current study results were similar to previous knee OA study which showed no significant change in maximum EKAM in the first and second halves of the stance phase (Collins et al., 2014). This contradicts a previous study by Schween et al. (2015) which showed a significant reduction with sleeve use in the first peak EKAM and KAAI of 10.1% and 12.9%, respectively. This might be explained by several factors, such as using different types of sleeves and different populations (knee OA). Previous studies have shown that individuals with knee OA suffer from joint laxity (Sharma et al., 1999; Wada, Imura, Baba, & Shimada, 1996), which might explain the reduction in the previously mentioned study.

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In terms of muscle co-contraction, sleeve use might result in a decrease, as seen in the late-stance phase LQ/LH co-contraction compared to LWI use during walking. To the best of our knowledge this is the first study to investigate the effected of LWI, sleeve and combined treatment on muscle co-contraction among healthy and therefore direct comparison cannot be made. A previous knee OA study showed a significant decrease in LQ/LH co-contraction with sleeve use during walking (Collins et al., 2011). Although the current study has shown a reduction between the same muscles in the late-stance phase, a direct comparison cannot be made due to different phase calculations, the different populations and different normalisation methods. Collins et al. (2011) divided the stance phase into two phases, used a knee OA population and normalise on maximum activity during control trials. The current study used three stance phases, recruited healthy subjects and normalised on MVIC.

A reduction in muscle co-contraction was not expected in this study, as all participants were healthy (normal muscle co-contraction was therefore expected). A previous study showed that increased muscle co-contraction correlated with medial cartilage volume loss rates in individuals with knee OA and varus alignment (Hodges et al., 2015). Therefore, if a similar reduction was seen in an OA population the reduction in co-contraction might be clinically important and decrease knee OA progression.

The current study results show a significant reduction in ROM of the knee joint angle in frontal plane with the combined treatment and the sleeve treatment compared to the control and LWI treatments during walking. Further investigation showed that this reduction was during both maximum and minimum adduction angles. No comparison could be made to healthy study because no previous study included this outcome as a variable in healthy studies. Collins et al. (2014) showed a reduction in maximum adduction angle and minimum abduction angle with sleeve use in individuals with knee OA. It could be that the sleeve provides frontal plane knee stability. The current study's population was healthy and did not complain of any knee disability or laxity. Therefore, the use of a sleeve in individuals with knee OA could be beneficial, as a previous study has shown that individuals with knee OA have frontal plane knee laxity, which correlates with greater muscle activity (Lewek et al., 2004a). Even though the reduction in the knee frontal plane ROM is appearing to be in the swing phase, this phase is important since the foot contact the

ground after that phase. Therefore, this may help to support the knee and reduce the high muscle co-contraction might be due to the laxity in individuals with medial knee OA.

Knee flexion moment showed no significant changes with the sleeve treatment or the combined treatment in current study. To the best of the authors knowledge only one study investigated the effect of sleeve on healthy and direct comparison cannot be made since this study only looked to the kinematics. Previous study in individuals with knee OA showed a significant increase in knee flexion moment with sleeve use (Collins et al., 2014), which might be caused due to an increase in the knee sagittal plane angle. Increasing the flexion moment might cause an increase in the compression force on the knee, as the contact area is smaller due to the greater flexion angle (Costigan, Deluzio, & Wyss, 2002; Taylor, Heller, Bergmann, & Duda, 2004). An increase in the knee flexion angle causes the quadriceps to work harder to pull the tibia upward and foreword (Costigan et al., 2002). The results of the current study regarding the knee flexion moment were expected, as there were no changes in the knee flexion angle at initial contact, the maximum knee flexion peak angle at loading response or the minimum flexion angle at mid-stance.

A significant reduction was noticed in the maximum flexion angle at swing for the combined treatment and the sleeve treatment compared to the control and LWI treatments. The magnitude of reductions was between 2.13 degree to 2.45 degree which were greater than SEM and SDD for within session reliability indicating real reduction. This is believed to be caused by either the sleeve elasticity reducing the range of motion or the sleeve bunching at the back of the knee and preventing the participant from reaching their normal knee flexion angle at swing. A comparison with previous studies could not be made because no study on sleeves included this variable. Although the reduction in maximum knee flexion angle at swing was significant, the amount of reduction was small, up to 2.2%, and a similar reduction might not affect the gait.

Of course, this study has several limitations. First, the investigator and participants were not blinded to the treatment conditions in the laboratory. However, being blinded to such treatments is difficult because the intervention is inserted in the shoes or is wrapped around the knee. However, kinematic and kinetic data were collected using an automatic measurement tool, which reduced assessor bias.

Secondly, the participants wore their own shoes during the session, which might affect the LWI effect. A previous study showed an interaction effect in relation to the shoes and EKAM (Mølgaard & Kersting, 2013), which may decrease LWI efficacy (Toda & Tsukimura, 2008). However, this might increase the generalisability of the data to other populations, as it reflected their daily life shoes use. Future studies could look at the effect of the same or different treatments with control shoes to eliminate the effect of other shoes on the treatment. Thirdly, this study evaluated one type of sleeve and LWI, but other types might have a different effect. Therefore, this study's results only apply to the same sleeve and LWI type, and other studies should assess different types of sleeves and LWIs. This study calculated EKAM responses to LWI and sleeve use during walking only. Therefore, future studies should calculate EKAM reduction across different activities instead of just walking to be more representative of everyday life activities.

Finally, this study investigated the impact of combined and single treatments on healthy individuals, and apart from LWI use, the impact of combined treatment use on the medial knee OA population is not known. Therefore, further studies should look at the impact of combined treatments on short- and long-term clinical and biomechanical outcomes.

4.8 Conclusion

Compared to walking with normal shoes, the LWI reduced EKAM and KAAI during walking. The sleeve was not found to change the EKAM during walking. Furthermore, use of the sleeve reduced frontal plane knee ROM during walking. Muscle co-contraction showed significant reduction with sleeve use compared to LWI condition and was border significant compared to control condition. This might indicate extra benefit from combining the sleeve with the LWI especially for individuals with knee OA as they suffer from high muscle co-contraction. GRF and walking speed were not affected between the conditions.

After considering all the weaknesses and strengths of the study, the main conclusion is that combining the sleeve with the LWI might increase the benefit of the LWI. Sleeve use will help individuals with knee OA to reduce their pain and may reduce loading throughout providing stability and reducing the muscle co-contraction. Therefore, it may be beneficial to combine the sleeve with LWI for individuals with medial knee OA, as EKAM and muscle co-contraction have been linked to knee OA progression and symptoms.

Chapter 5: Effect of a lateral wedge insole and simple knee sleeve as a single and combined treatment in biomechanical and clinical outcomes in individuals with knee osteoarthritis (The IN-SLEEVE study).

5.1 Chapter overview

This chapter will present the main study where by the comparison of single and combined treatment in individuals with medial knee OA will be assessed. This follow on from the previous healthy study in chapter four but in this chapter, it will be assessing both the immediate time point and also following an intervention period.

5.2 Introduction

Osteoarthritis (OA) is considered to be the most prevalent type of musculoskeletal disease (Lawrence et al., 2008). In a previous study in the United Kingdom, 1 out of every 10 individuals between 35 and 75 was found to be affected by OA (Sangha, 2000). Although OA occurs in many joints, the knee joint is affected most commonly (Newman et al., 2003).

There are several surgical techniques used to treat individuals with knee OA. However, for some individuals, surgery is not appropriate (e.g. the patient is too young), while others simply do not want surgery (Bhatia et al., 2013; Marks & Penton, 2004). Therefore, conservative management should be the primary consideration when treating individuals with medial knee OA. Several conservative approaches are considered options to treat individuals with knee OA. However, they have not been fully validated in the scientific literature. Therefore, other treatment approaches should also be considered. The valgus knee brace, lateral wedge insoles, and simple knee sleeves are common conservative approaches to treating individuals with knee OA. Previous research shows that combined treatment (lateral wedge insole, valgus knee brace) reduces EKAM by more than single treatment (Al-Zahrani et al., 2013b; Fu et al., 2015; Moyer et al., 2013). The main drawback of using a valgus knee brace is the low compliance rate (Barnes et al., 2002; Jones et al., 2013; Wilson et al., 2011). Therefore, in the long term, participants usually use lateral wedge

insoles and lose the valgus knee brace effect on loading and pain (Barnes et al., 2002; Jones et al., 2013; Wilson et al., 2011). This can be attributed to several factors, such as skin irritation, mechanical problems, poor fit, awkward shape, difficulties taking the brace off and putting it on, difficulties wearing the brace with clothes, and brace bulkiness (Barnes et al., 2002; Fu et al., 2015; Giori, 2004; Squyer et al., 2013; Van Raaij et al., 2010).

Lateral wedge insoles have been used extensively with knee OA patients and have been proven to reduce knee loading. However, when compared with the results of neutral wedge insoles, no significant difference in pain levels was identified (Baker et al., 2007; Barrios et al., 2009; Bennell et al., 2011; Campos et al., 2015; Maillefert et al., 2001; Pham et al., 2004). Therefore, lateral wedge insoles could be a good treatment option if combined with another treatment that targets pain. Previous studies have shown that simple knee sleeve use decreases pain (Bryk et al., 2011; Cudejko et al., 2017; Kirkley et al., 1999; Mazzuca et al., 2004; Schween et al., 2015), improves quality of life (Kirkley et al., 1999), improves stability (Cudejko et al., 2017; Schween et al., 2015), improves function (Bryk et al., 2011; Cudejko et al., 2017; Kirkley et al., 1999), improves proprioception (Collins et al., 2011b), and decreases muscle co-contraction in individuals with knee OA (Collins et al., 2011; Collins et al., 2013). Muscle co-contraction is considered an important factor since muscle activity is correlated with the progression of knee OA (Hodges et al., 2015). Therefore, combining lateral wedge insoles with simple knee sleeves may be a good option. Through this combination of reduced muscle co-contraction, simple knee sleeve use, and the EKAM via the lateral wedge insole, it may be possible to achieve consistent reductions in pain and loading. No study has investigated the effect of combined treatments on kinematics, kinetics, and muscle activity during walking. Although healthy individuals do not have knee laxity or high muscle co-contraction, our previous study, which included healthy participants, showed that using the sleeve treatment reduced muscle co-contraction, and frontal plane ROM. Therefore, combining the sleeve with LWI may result in higher reduction in pain combined by reduction in loading thought reducing EKAM and muscle co-contraction.

5.3 Purpose of the study

The purpose of the study is to compare the clinical and biomechanical outcomes of three treatment groups of individuals with knee OA (simple knee sleeve, lateral wedge insole, and a combined

treatment of simple knee sleeve and lateral wedge insole). This trial is registered in the clinical trials website with study registration number NCT03225911.

5.4 Aims and hypothesis of the study

The aim of this study was to understand the effects of combined treatments (simple knee sleeve, lateral wedge insole) and to compare its effectiveness to that of the lateral wedge insole and sleeve in individuals with medial knee osteoarthritis.

1- To investigate the effect of combined treatments (lateral wedge insole and simple knee sleeve) and individual treatment on EKAM

Null hypothesis: There is no significant difference in EKAM when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve) (immediate, 6 weeks).

2- To investigate the effect of combined treatments (lateral wedge insole and simple knee sleeve) and individual treatment on pain

Null hypothesis: There is no significant difference in pain after 6 weeks when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

3- To investigate the effect of combined treatments (lateral wedge insole and simple knee sleeve) and individual treatment on muscle co-contraction

Null hypothesis: There is no significant difference in muscle co-contraction when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve) (immediate, 6 weeks).

4- To investigate the effect of combined treatments (lateral wedge insole and simple knee sleeve) and individual treatment on balance

Null hypothesis: There is no significant difference in dynamic balance after 6 weeks when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

5- To investigate the effect of combined treatments (lateral wedge insole and simple knee sleeve) and individual treatment on pain pressure threshold

Null hypothesis: There is no significant difference in pressure pain threshold after 6 weeks when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment.

6- To investigate the effect of combined treatments (lateral wedge insole and simple knee sleeve) and individual treatment on functional tests (40-metre fast-paced walk test, 30-second chair-stand test, stair-climb test)

Null hypothesis: There is no significant difference in functional tests (40-metre fast-paced walk test, 30-second chair-stand test, a stair-climb test) after 6 weeks when using combined treatments (lateral wedge insole and simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

5.5 Methods

5.5.1 Research environment

Participants' data collection was conducted in Hail University gait lab and the Brain Blatchford gait lab. For more details about the gait labs please see section 3.2.

5.5.2 Participants

Individuals aged 35 to 85 years old who had been diagnosed with medial knee osteoarthritis were eligible. For more details about the inclusion and exclusion criteria please see section 3.5.1.2. For more details about the recruitment procedure please see section 3.4.

5.5.3 Sample size and recruitment

As this was the first study to embark on this challenging design, a convenient sample size was recruited.:

5.5.4 Study design

This was a randomised study involving parallel groups, which investigated the immediate and short-term (6 weeks) effects of three treatments on individuals with knee osteoarthritis while walking. Potential participants underwent a screening via telephone or interview to ensure they fulfilled the study criteria. Eligible participants were then assigned a treatment group using randomisation blocks via the website randomisation.com. The treatments were lateral wedge insoles (Figure 5-1), simple knee sleeves (Figure 5-2), and a combined treatment (lateral wedge insole and simple knee sleeve).

5.5.5 Treatment groups

- Lateral wedge insole group (LWI).
- Simple knee sleeve group (Sleeve).
- Combined group (Sleeve + LWI).

5.5.6 Treatments

5.5.7 Lateral wedge insole

Five-degree, full-length, arch-supported lateral wedge insoles were used in this study (Figure 5-1). For more details about the rational for selecting this type of LWI please see section 3.6.1.

5.5.7.1 Application and Duration of use of lateral wedge insole

The optimal duration of the lateral wedge insole use per day was suggested to be between 5 and 10 hours, based on an experimental study (Toda et al., 2005). Each participant was instructed to insert a pair of lateral wedge insoles into his or her shoes for 5 to 10 hours daily.

Figure 5-1 Salford lateral wedge insole.

5.5.8 Simple Knee sleeve

A short knee sleeve with no metal support (Figure 5-2) was used current study and for more details regarding the selection criteria used to select the knee sleeve please see section 3.6.3.

5.5.8.1 Knee sleeve application

The application of the simple knee sleeve was performed by the researcher. The researcher asked the participant if the sleeve was not too tight. If the participant replied yes, the test was carried out. However, if the participant replied no, the researcher loosened the sleeve until the participant felt comfortable, but not too loose.

Figure 5-2 Simple knee sleeve used in this study.

5.5.8.2 *Duration of use*

No previous study has been identified which specifies the duration of use for a simple knee sleeve. Therefore, duration of use of the sleeve will be based on valgus knee brace use, at four hours daily during activity and work, as this was identified as significantly reducing pain (Barnes, Cawley, & Hederman, 2002).

5.5.9 *Participants compliance*

Each participant was asked to keep a note of the daily use of the treatment to make sure about compliance.

5.5.10 *Procedure*

Individuals who met the criteria had the study explained to them and they received a participant information sheet and a health history questionnaire. If they agreed to participate and were eligible for the study, they were given an appointment at the gait laboratory. Upon attending the gait laboratory, they had any questions answered and signed the informed consent form. One copy was given to the participant and one was kept in the study file. The participants were informed that they were free to withdraw at any point of time from the study, without any disadvantage to them.

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1. First visit (week 0)

Individuals who were willing to participate were contacted for a first-visit appointment, and the KOOS questionnaire was given. Each participant was given a second appointment seven days after the first (Figure 5-3).

2. Second visit (week 1)

During the second visit, each participant underwent a general assessment, in which height and mass were recorded. The KOOS questionnaire and PASE were completed, and each participant was asked to change into shorts and a T-shirt. Two baselines of pain measurement were incorporated into this study to account for any possibility of pain fluctuation. The first one was given in the first appointment (week 0) and the second one was introduced in the second visit (week 1) before starting the trial. Results of 40-metre fast-paced walk test, 30-second chair-stand test and stair-climb test were obtained after two practical trials, according to the procedure mentioned previously according to the method section 3.19.2.3. The star excursion balance was measured in anterior and medial directions after four practical trials in each direction according to the method in section 3.19.2.3. Pain pressure threshold was measured in the medial condyle and the medial malleolus after two practical trials following the method in section 3.19.2.3. Following this, the gait analysis and EMG data were collected with and without the prescribed device. Each participant received the allocated treatment to be used for 6 weeks.

3. Third visit (week 6)

At the third visit, KOOS and PASE questionnaire responses were obtained. Then each step in the second visit was conducted again, following the same order and procedure. The gait analysis was conducted with the treatment only after 6 weeks.
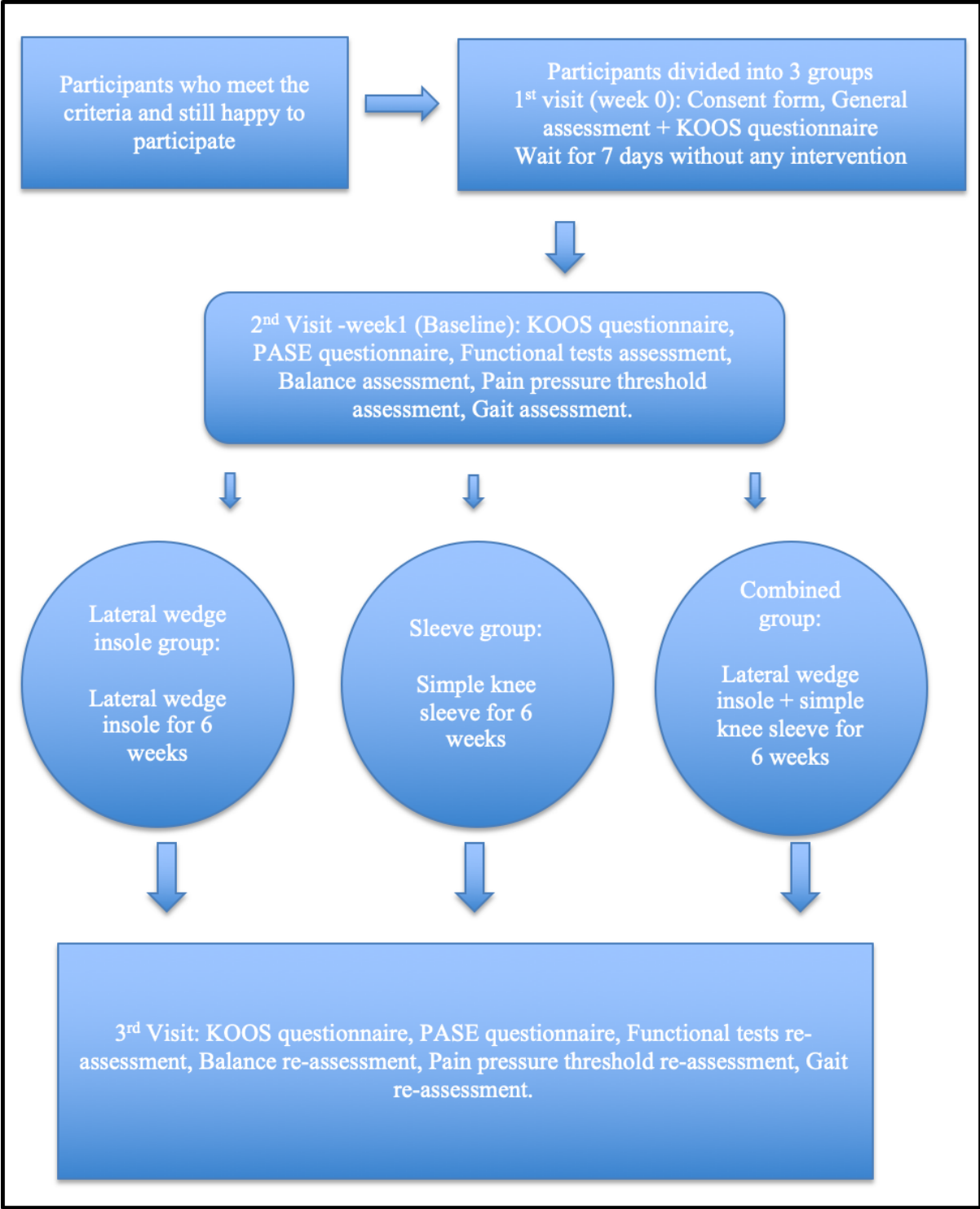
Figure 5-3 Diagram of the study protocol.

Questionnaire:

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a valid and reliable outcome measurement in knee OA individuals (Collins, Misra, Felson, Crossley, & Roos, 2011). KOOS consists of five subscales, namely pain (9 questions), symptoms (7 questions), activities of daily living (17 questions), sport and recreation (5 questions) and quality of life (4 questions). The maximum score for each KOOS subscale is 100, indicating no problem, while 0 indicates extreme problems. The KOOS score was calculated based on the Excel scoring sheet provided by http://www.koos.nu/index.html.

The Physical Activity Scale for the Elderly (PASE) is a widely used questionnaire in research for assessing individuals' physical activity level (Chmelo et al., 2013). PASE is valid, reliable and sensitive for detecting changes in individuals with knee OA (Martin et al., 1999; Washburn & Ficker, 1999). PASE combines information from light, moderate and high levels of physical activity during household, occupational and leisure activities in the past 7 days. The PASE score ranges from 0 to 400, with a higher score indicating higher physical activity. Based on the total score, the participant can be classified to have low (31–120 points), moderate (124–242 points) or high physical activity (>242 points) (Lin et al., 2013). The score was calculated based on the scoring sheet provided by http://www.neriscience.com/.

5.5.11 Assessment of biomechanical response

In brief, two gait analysis system were used. A 10 T30/40 camera motion-capture system with four Kistler force plates was used at the Salford gait lab, and a 10 Bonita camera motion-capture system with two AMTI force plates was used at the Hail gait lab. Data was captured at 100Hz for kinematics and 1000Hz for kinetics. The systems were calibrated, and the laboratories were prepared for the subject's arrival (section 3.8). Electrodes were applied to the following muscles: LH, MH, LG, MG, LQ, and MQ based on SEINAM guidelines (section 3.10). MVIC was collected for quadriceps at a 45-degree angle and for gastrocnemius from standing and hamstrings at a 55-degree angle (section 3.11). According to the CAST method, markers were attached to ASIS, PSIS, GT, IC, lateral femoral condyle, medial femoral condyle, lateral malleolus, medial malleolus, Calcaneus, fifth metatarsal head, second metatarsal head, and first metatarsal head in both limbs.

Cluster plates were applied to the pelvis, thigh, and shank to track the segment's movement in both limbs. For more details about markers and clusters please see section 3.9.

The participants were asked to walk on a 12-metre walkway at their own self-selected speed using their own shoe. All participants were asked to perform five successful walking trials. A successful trial required an occurrence of the contact phase on the force plate at self-selected speed with the effected limb. Each participant was asked to bring the same shoe which used at baseline testing to the next appointment.

5.5.12 Outcomes

5.5.12.1 Primary outcomes

These outcome measures enabled us to test hypotheses 1, 2 and 3 concerning the effect of the combined treatment (lateral wedge insole + simple knee sleeve versus single treatments alone) on clinical, biomechanical outcomes and muscle co-contraction variables.

The primary outcome measures that were assessed were:

- External knee adduction moment (EKAM)

The change in all aspects of EKAM (first peak, trough, second peak, EAAI) during level walking was investigated at baseline (week 1) without and with treatment use and 6 weeks with treatment use.

- Pain

The changes in knee pain between baseline (before providing the treatment in week1) and week 6 was investigated using the knee injury and osteoarthritis score (KOOS).

- Muscle co-contraction

The changes in muscle co-contraction between MQ/MH, LQ/LH, MQ/MG and LQ/LG were investigated at three stages (early-stance 0–33, mid-stance 34–67, and late-stance 68–100) while walking at baseline (week 1) without and with treatment use and 6 weeks with treatment use.

5.5.12.2 *Secondary outcomes*

- Dynamic balance

The modified star excursion balance test was used to investigate the effect of treatment in the anterior and medial directions balance. The balance was measured at baseline (week 1) before providing the treatment and after 6 weeks.

- Pressure pain threshold

The effect of the treatment on the pain pressure threshold was investigated using an algometer applied to medial side of the knee and the medial side of medial malleolus at baseline (before providing the treatment in week 1) and 6 weeks.

- Physical function tests

The effect of the treatment on three functional tests (40-metre fast-paced walk test, 30-second chair-stand test, and a stair-climb test) was investigated. The test was introduced at baseline (before providing the treatment in week 1) and after 6 weeks of treatment.

- Physical activity scale for elderly (PASE) and other KOOS subscales (symptoms, ADL, Sport, QOL)

The effect of the treatment on PASE and other KOOS subscales was investigated. The questionnaires were introduced at baseline (before providing the treatment in week 1) and after 6 weeks.

5.5.12.3 *Other data*

- GRF, spatio-temporal, kinematic and kinetics of the knee and ankle

The effect of the treatment on the GRF (the first peak, trough, the second peak), knee joint angles in frontal plane (maximum and minimum), spatio-temporal (speed, stance time, swing time), knee joint angles in sagittal plane (knee angle at initial contact, maximum flexion angle at loading response, minimum flexion angle at mid-stance, maximum flexion angle at swing), knee joint moments in sagittal plane (extension moment, flexion moment), ankle angles in sagittal and frontal

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planes (maximum, minimum), ankle moment in frontal and sagittal plane (maximum, minimum), centre of foot pressure (early-stance, mid-stance and late-stance) and ROM for the knee and ankle in sagittal and frontal plane were measured at baseline (with and without the treatment in week 1) and after 6 weeks (with the treatment). All the results are presented in Appendix E.

5.5.13 Data processing

After collecting five successful trials, the data was processed by Vicon Nexus Software and Visual 3D programs and exported to an Excel spreadsheet. Kinetics data was normalised to the gait cycle while kinematics, GRF and muscle activity data were normalised to the stance phase. SEBT was normalised to each individual leg length measured form anterior superior iliac spine to the medial malleolus. For more details about the gait events calculation and data processing please see sections 3-14 and 3-15. The magnitude of change was calculated by subtracting each participant's result for the specified outcome after immediate use and/or 6 weeks from baseline data. The magnitude of change was calculated in EKAM, KOOS pain, muscle co-contraction, balance, functional tests, PASE and KOOS subscales of symptoms, ADL, sport and quality of life. To calculate the pain fluctuation, the pain value in week 1 was subtracted from week 0 for each participant. The results were squared to eliminate negative value; then the square root was taken, and the average was taken as fluctuation in pain. The 6 weeks treatment effect on LQ/LG and MQ/MH was not investigated since these outcome measurements showed low ICC in chapter 3 and only immediate effect were included in the statistical analysis.

5.5.14 Statistical analysis

Statistical analysis in the current study was performed using Excel (version 15.29.1) for Mac, and SPSS (version 23) for Mac. The means of five trials for each test were used. The normality of the data was checked using the method in section 3.16. In the current study, there are two independent factors and one dependant factor. The independent factors are first, within the group with either three levels as in kinematics, kinetics data (three time points) or two levels as in the questionnaire and functional tests (two time points), and second, between the groups with three levels (three groups). The dependant factor is the outcome of interest (i.e., EKAM or pain). Therefore, two-way mixed ANOVA (ANOVA), comparing mean differences within and between groups (time), was performed on each variable. One-way ANOVA was used to determine if the groups were different

at baseline, after immediate use of the treatment, and after 6 weeks' use of the treatment. To identify the effect of the treatment within each group, either repeated-measures ANOVA (three time points) or paired sample t-test (two time points) was used, based on the time point. The magnitude of reduction after immediate use of the treatment and/or 6 weeks use in the intersected variable was compared between the groups via one-way ANOVA.

To apply two-way mixed ANOVA, the data should be approximately normally distributed and have equal covariance matrix and equal variance between the groups. If one of the previous conditions was not met, several steps were followed to solve the problem. As there is no equivalent non-parametric test for two-way mixed ANOVA either to apply transformation (RMS, Log10, Ln, Reciprocal) to the data to meet the broken condition or to break down the analysis into "between the groups" and "within the groups" without using two-way mixed ANOVA were applied. This was conducted with either via using parametric (repeated-measures ANOVA or paired sample t-test for within the groups and one-way ANOVA for between the groups) or non-parametric (the Friedman test and the Wilcoxon test for within the groups and the Kruskal-Wallis test for between the groups), based on the normality test.

Bonferroni adjustment was used on post hoc comparison in the two-way mixed ANOVA, repeated-measures ANOVA, the Friedman test, and the Kruskal-Wallis test to reduce type 1 errors. If Bonferroni adjustment failed, other adjustments (Sidak, LSD) were used. For one-way ANOVA, Turkey adjustment was used.

Most of the data had equal variance and covariance matrices and normally or mildly to moderately deviated from normality. The ANOVA model is considered as a robust against moderate deviation in normality (Ghasemi & Zahediasl, 2012) and superior to the majority of assumption violations (Lix, Keselman, & Keselman, 1996). If the data were severely deviated, had unequal covariance or unequal variance, or all of these, this is discussed in detail in the results section. The significance in this study was considered to be at alpha level 0.05.

5.6 Results

The following section represents the results of the study, which compares lateral wedge insole, sleeve, and combined (lateral wedge insole and sleeve) treatments groups. The results are organised so the primary outcomes are explained first, followed by the secondary outcomes.

5.6.1 Participant

Thirty-four participants with confirmed painful medial knee OA (31 males and 3 females) were recruited for this study. They were assigned randomly into three groups with 11 in the combined treatment group, 11 in the sleeve group, and 12 in the LWI group. Demographic details are described in Table 5-1. Interestingly, there was no significant difference between the groups in age, height, mass, or BMI.

Table 5-1 Baseline demographic characteristic of the groups.

Variables	Combined group	Sleeve group	LWI group	P-value
Age (mean years ± SD)	54.36 (10.19)	56.27 (11.97)	55.08 (10.37)	0.92
Height (mean M ± SD)	1.72 (.10)	1.73 (.09)	1.70 (.08)	0.58
Mass (mean Kg ± SD)	87.05 (14.32)	88.68 (9.78)	85.31 (20.07)	0.87
BMI (mean Kg/m² ± SD)	29.19 (2.87)	29.72 (4.49)	29.52 (6.33)	0.95
Affected side L=left R= Right	L=5 knees, R=6 knees	L=7 knees, R=4 knees	L=7 knees, R=5 knees	
Total number (male, female)	11 (10 males,1 female)	11 (10 males,1 female)	12 (11 males,1 female)	

All participants completed the trials with good compliance with the treatment. Furthermore, there was no significant difference between the groups in the daily use of the treatment across 6 weeks or the comfort of the treatment (Table 5-2).

Table 5-2 Treatments users comfort and adherence to assigned group.

Variables	Combined group	Sleeve group	LWI group	P-value
Use (hours/day (± SD))	5.27 (0.65)	5.14 (1.14)	5.96 (1.08)	0.11
Comfort (out of ten ± SD)	7.7 (1.06)	8.0 (1.01)	8.2 (1.11)	0.56

5.6.2 *Comparison between combined treatment group, LWI group and sleeve group at baseline (week 1) for the primary outcomes*

At the baseline assessment, EKAM, KAAI, and pain between the sleeve group, the LWI group, and the combined group (sleeve and LWI) showed no significant difference (Table 5-3).

Table 5-3 Mean (SD) of the speed, EKAM, KAAI and pain outcomes at baseline and P-value for the groups.

Variables	Mean (± SD)			P-value
	Combined group	Sleeve group	LWI group	
Speed (m/s)	1.22 (0.18)	1.15 (0.24)	1.15 (0.24)	0.69
EKAM (Nm/Kg)	0.59 (0.11)	0.51(0.15)	0.50 (0.12)	0.21
EKAM (%Bw.Ht)	3.50 (0.65)	3.01 (0.92)	3.03 (0.75)	0.26
KAAI ((Nm/kg).s)	0.23 (0.08)	0.20 (0.08)	0.20 (0.10)	0.69
Pain (KOOS)	52.27 (15.90)	58.84 (16.93)	51.62 (13.99)	0.49

Knee co-contraction:

There was no significant difference in the muscle co-contraction between the combined group, the sleeve group, and the LWI group at baseline in all gait phases and among all measured muscles (Table 5-4).

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Table 5-4 Mean (SD) of muscle co-contraction in early, mid and late stance phases at baseline and P-value.

Muscle co-contraction	Combined group	Sleeve group	LWI group	P-value Parametric test (one-way ANOVA)	P-value Non-parametric test (Kruska-wallis)
Early-stance					
LQ vs. LH	0.29 (0.21	0.45 (0.34)	0.40 (0.36)	0.47	0.49
LQ vs. LG	0.24 (0.18)	0.38 (0.28)	0.35 (0.19)	0.28	0.39
MQ vs. MH	0.19 (0.13)	0.38 (0.31)	0.26 (0.17)	0.18	0.23
MQ vs. MG	0.14 (0.16)	0.18 (0.10)	0.26 (0.37)	0.49	0.26
Mid-stance					
LQ vs. LH	0.13 (0.13)	0.17 (0.11)	0.20 (0.20)	0.57	0.58
LQ vs. LG	0.18 (0.15)	0.22 (0.15)	0.26 (0.22)	0.60	0.75
MQ vs. MH	0.07 (0.07)	0.10 (0.03)	0.11 (0.10)	0.47	0.14
MQ vs. MG	0.12 (0.10)	0.17 (0.14)	0.17 (0.14)	0.66	0.65
Late-stance					
LQ vs. LH	0.06 (0.06)	0.09 (0.06)	0.06 (0.03)	0.27	0.28
LQ vs. LG	0.08 (0.06)	0.15 (0.13)	0.11 (0.12)	0.39	0.48
MQ vs. MH	0.04 (0.03)	0.08 (0.04)	0.08 (0.06)	0.06	0.06
MQ vs. MG	0.08 (0.06)	0.11 (0.07)	0.13 (0.14)	0.44	0.39

5.6.3 *Fluctuation of the pain from week 0 to week 1*

The pain was measured one week before the start of the trial and at the start of the trial to account for pain fluctuation. The t-test showed no significant difference between week 0 and week 1 in pain. The fluctuation in pain is 2.15 units on the KOOS pain subscale (Table 5-5).

Table 5-5 Mean (SD) of pain from week 0 to week 1.

Mean (SD)	Week 0	Week 1	Fluctuation	T-test p-value
pain	53.35 (14.49)	54.17 (15.48)	2.29 (3.38)	0.24

5.6.4 *Knee moment in frontal plane*

First peak of EKAM:

Two way-mixed ANOVA

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When assessing the EKAM, the ANOVA showed that the group has no significant effect on EKAM (p=0.28), while the time has significant effect on EKAM (P<0.01) and there was a significant interaction between groups and time (p=0.02). The descriptive data is presented in Table 5-6.

Within each group:

Repeated measures ANOVA showed a significant reduction in EKAM across time for combined groups (P<0.01) and LWI groups (P<0.01) but not the sleeve group (p=0.85). Pairwise comparison showed significant reduction in EKAM after immediate use of combined treatment (mean difference 0.05 (0.03)) by 8.17% and 6 weeks (mean difference 0.07 (0.05)) by 12.30% compared to shod only at baseline (P<0.01, P<0.01) respectively. Furthermore, pairwise comparison identified the reduction to be with immediate LWI use (mean difference 0.05 (0.03) P<0.01) by 10.88% and 6 weeks (mean difference 0.06 (0.03) P<0.01 compared to baseline by 14.88% (Figure 5-4).

Between the groups:

One-way ANOVA was conducted to identify if there is any difference in EKAM between the groups at baseline, immediate effect and 6 week and revealed no significant difference between the groups in all timelines (p=0.21, p=0.26, p=0.28).

Trough:

Two way-mixed ANOVA

ANOVA showed that there is no significant interaction between group and time (p=0.31) and the group has no significant effect on trough (p=0.79). The time has shown significant effect on trough (P<0.01). The descriptive data is presented in Table 5-6.

Within each group

The data from the combined group (p=0.01) and the LWI group (P<0.01) showed significant changes in trough across time via using repeated measures, while the data for the sleeve group did not (p=0.16). In the combined group, the trough showed significant reduction after 6 weeks

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compared to the baseline (mean difference 0.05 (0.06) p=0.04) by 16% but not to the immediate effect (p=0.06). The LWI group showed significant reduction in trough with LWI use immediately ((mean difference 0.03 (0.03), p=0.01) by 11.04% and after 6 weeks (mean difference 0.05 (0.06) P<0.01) 27.96% compared to shod only at baseline (Figure 5-4).

Between the groups

When comparing the groups at baseline, after immediate use of the treatment and after 6 weeks with one-way ANOVA no significant difference was identified (p=0.78, 0.70, 0.84).

2nd peak of EKAM:

Two way-mixed ANOVA

The data showed no significant effect for the group on the EKAM with p-value equal to 0.49. ANOVA showed that the time had significant effect on EKAM (P<0.01) with no interaction effect (p=0.13). The descriptive data is presented in Table 5-6.

Within each group

In the combined group, the data showed significant effect for time (p=0.01) and pairwise comparison identified the reduction as reaching significant level between baseline and 6 weeks only (mean difference 0.06 (0.06), p=0.03) by 11.65% and not between baseline and immediate effect (p=0.07). The sleeve group showed no significant effect on the EKAM with p-value equal to 0.54. The data of the LWI group showed significant effect of time on EKAM (p=0.01) and the pairwise comparison showed significant reduction in EKAM with LWI immediate use (mean difference 0.03 (0.03), p=0.01) by 8.87% compared to baseline and after 6 weeks compared to baseline (mean difference 0.05 (0.06), p=0.04) by 15.70% (Figure 5-4).

Between the groups

There was no significant difference in EKAM between the groups at baseline (p=0.32), immediate (p=0.49) and 6 weeks' treatment (p=0.66).

Table 5-6 Mean (SD) of EKAM (1st peak, trough, 2nd peak) for combined, sleeve and LWI groups.

Mean (SD). Nm/kg	Week one						Week 6		
	Combined group		Sleeve group		LWI group		Combined group	Sleeve group	LWI group
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI	Shod + combined treatment	Shod + sleeve	shod + LWI
1st Peak	0.59 (0.11)	0.54 (0.12) Θ	0.51 (0.15)	0.51 (0.17)	0.50 (0.12)	0.45 (0.12) Θ	0.52 (0.09) Θ	0.50 (0.17)	0.43 (0.12) Θ
Trough	0.33 (0.13)	0.31 (0.12)	0.29 (0.14)	0.28 (0.16)	0.29 (0.16)	0.25 (0.16) Θ	0.28 (0.13) Θ	0.27 (0.16)	0.24 (0.17) Θ
2nd Peak	0.43 (0.16)	0.41 (0.15)	0.34 (0.12)	0.34 (0.14)	0.38 (0.15)	0.35 (0.15) Θ	0.37 (0.14) Θ	0.33 (0.15)	0.32 (0.15) Θ

Θ significant compared to baseline
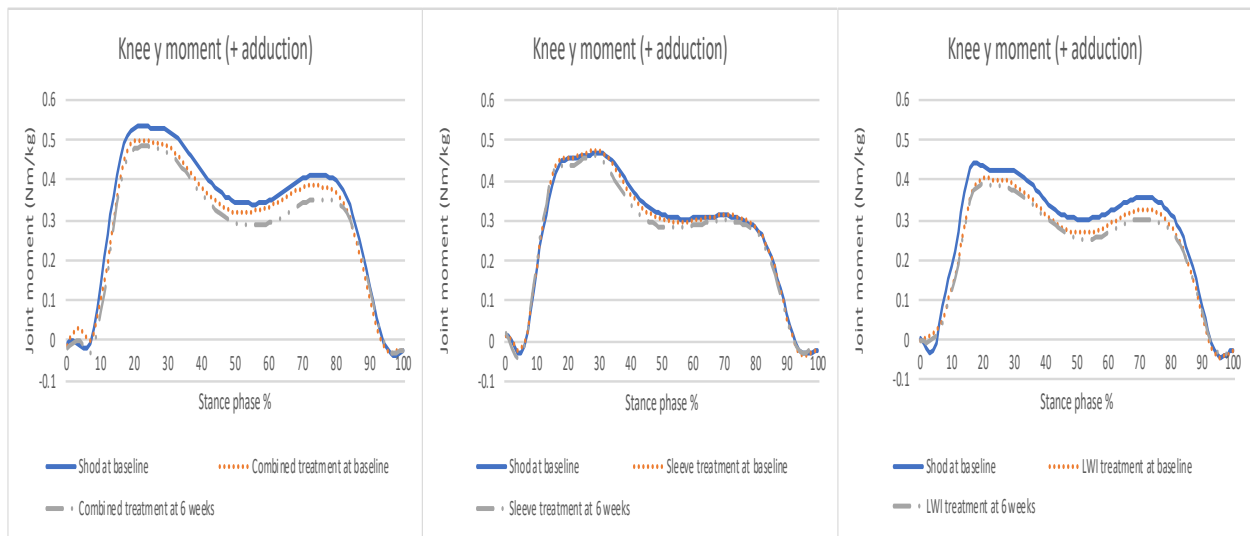
Figure 5-4 Mean (SD) of knee joint moment in frontal plane for combined (a), sleeve (b) and LWI (c) groups.

Knee adduction angular impulse (KAAI):

Two way-mixed ANOVA

To assess the knee loading across the gait cycle, knee adduction angular impulse (KAAI) was used. The data for KAAI showed no significant effect for the group (p=0.75). The ANOVA showed no significant interaction between groups and time (p=0.10), while the time was found to have significant effect on KAAI (P<0.01). The descriptive data is presented in Table 5-7.

Within each group

Repeated-measures ANOVA showed significant changes across time in KAAI for the combined group (P<0.01) and the LWI group (P<0.01), but not for the sleeve group (p=0.65). Pairwise comparison showed significant reduction in KAAI after 6 weeks of combined treatment compared to shod only at baseline (mean difference 0.03 (0.02), P<0.01) by 12.20%, but not for the immediate use compared to shod only at baseline (p=0.13). In the LWI group, the reduction was identified between immediate use compared to shod at baseline (mean difference 0.02 (0.01), P<0.01) by 9.31% and at 6 weeks compared to shod at baseline (mean difference 0.03 (0.03), p=0.01) by 15.56% (Figure 5-5).

Between the groups

One-way ANOVA showed no significant difference in EKAM between the groups at baseline (p=0.69), immediate effect (p=0.71), and after 6 weeks (p=0.77).

Table 5-7 Mean (SD) of KAAI for combined, sleeve and LWI groups.

| Mean (SD). Nm/kg*s | Week one | | | | | | Week 6 | | |
| | Combined group | | Sleeve group | | LWI group | | Combined group | Sleeve group | WLI group |
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
KAAI	0.23 (0.08)	0.22 (0.08)	0.20 (0.08)	0.20 (0.08)	0.20 (0.10)	0.19 (0.10) Θ	0.20 (0.07) Θ	0.19 (0.09)	0.18 (0.09) Θ

Θ significant compared to baseline
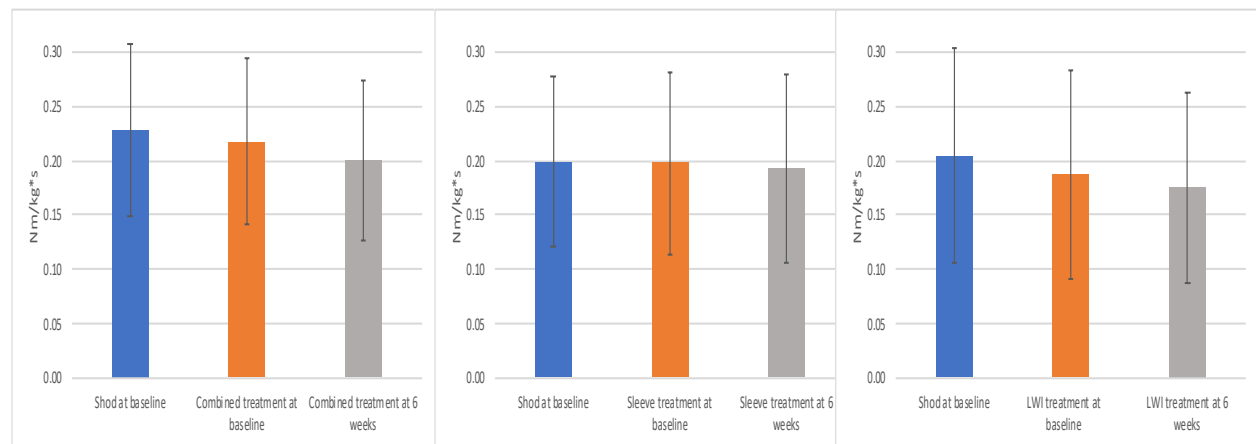
Figure 5-5 Mean (SD) of KAAI for combined (a), sleeve (b) and LWI (c) groups.

The magnitude of change in EKAM and KAAI:

One-way ANOVA was used to assess if the magnitude of change in EKAM (first peak, trough, second peak) and KAAI across two timelines (immediate and 6 weeks) was significantly different between the groups. The descriptive data is presented in Table 5-8.

First peak EKAM

A Significant change was identified in the first peak EKAM between the groups with immediate use of the treatments (P<0.01). Pairwise comparison showed significantly higher reduction in first peak EKAM for the combined group (P<0.01) and the LWI group (P<0.01) compared to sleeve group. The magnitude of change in first peak EKAM after 6 weeks was significantly different between the groups (p=0.01), and pairwise comparison showed higher reduction in first peak EKAM for the combined group (p=0.02) and the LWI group (p=0.03) compared to the sleeve group.

Trough

The magnitude of change in trough was not statistically significant between the groups after immediate use of treatment (p=0.14) or 6 weeks' use (p=0.31) (Table 5-8).

Second peak EKAM

The magnitude of change in second peak EKAM after immediate use of treatment was significant between the groups (p=0.04). Pairwise comparison showed higher reduction in the LWI group (p=0.04) than the sleeve group, but not in the combined group compared to the sleeve group (p=0.13). In contrast, the magnitude of reduction in second peak EKAM after 6 weeks' treatment was not significant between the groups (p=0.10) (Table 5-8).

KAAI

The immediate magnitude of change in KAAI was significant between the groups (p=0.03). Pairwise comparison showed higher reduction in the LWI group (p=0.03) than the sleeve group, but not in the combined group compared to the LWI group (p=0.21). In contrast, the 6 weeks'

magnitude of reduction in KAAI was not statistically significant between the groups (p=0.08) (Table 5-8).

Table 5-8 Mean (SD) of magnitude of change in EKAM (1st peak, trough, 2nd peak) and KAAI for combined, sleeve and LWI groups.

Variable Mean (SD).	Immediate magnitude of change			6 weeks' magnitude of change		
	Combined group	Sleeve group	LWI group	Combined group	Sleeve group	LWI group
1st Peak EKAM (Nm/kg)	-0.05 (0.03) Ω	-0.00 (0.03)	-0.05 (0.03) Ω	-0.07 (0.05) Ω	-0.01 (0.06)	-0.07 (0.06) Ω
Trough (Nm/kg)	-0.02 (0.03)	-0.01 (0.03)	0.03 (0.03)	0.05 (0.06)	-0.02 (0.05)	-0.05 (0.04)
2nd peak EKAM (Nm/kg)	-0.02 (0.03)	-0.00 (0.03)	-0.03 (0.03) Ω	-0.06 (0.06)	-0.01 (0.04)	-0.05 (0.06)
KAAI (Nm/kg*s)	-0.01 (0.02)	-0.00 (0.01)	-0.02 (0.01) Ω	-0.03 (0.02)	-0.01 (0.03)	0.03 (0.03)

Ω significant compared to sleeve

5.6.5 Knee pain (KOOS)

Two way-mixed ANOVA

The results showed that the group (p=0.69) had no significant effect on the knee pain, and there was no significant interaction between the group and time (p=0.08). ANOVA showed significant effect for the time (P<0.01) on the knee pain. The descriptive data is presented in Table 5-9.

Within each group

The t-test showed significant reductions in knee pain after 6 weeks of treatment in the combined group (P<0.01), the sleeve group (P<0.01), and the LWI group (p=0.01) compared to the baseline.

Between the groups

A one-way ANOVA showed no significant difference in the knee pain between the groups at baseline (p=0.49) or 6 weeks (p=0.59).

The magnitude of change in pain

When the magnitude of change in the knee pain was compared between the groups via one-way ANOVA, the result revealed no significant difference (p=0.08).

Extra-analysis

Further analysis was conducted to compare the magnitude of change between each two groups separately. The results showed that the combined group showed significantly higher magnitude of reduction in knee pain than the sleeve group (P=0.01), while the LWI group did not (P=0.31).

Table 5-9 Mean (SD) of KOOS pain score for combined, sleeve and LWI groups.

Mean (SD)	Combined group		Sleeve group		LWI group		Magnitude of change between baseline and week 6		
	Baseline	Weeks 6	Baseline	Weeks 6	Baseline	Weeks 6	Combined group	Sleeve group	LWI group
KOOS knee pain	52.27 (15.90)	68.94 (17.43) Θ	58.84 (16.93)	65.40 (15.03) Θ	51.62 (13.99)	62.50 (11.81) Θ	16.67 (11.04)	6.57 (5.01)	10.88 (12.78)

Θ significant compared to baseline

5.6.6 *Muscle co-contraction*

Early-stance

LQ/LH:

Two way-mixed ANOVA

The ANOVA showed that there was no significant interaction between the group and the time (p=0.19). There was no significant effect for the group (p=0.29) and time (p=0.36) on the early-stance LQ/LH co-contraction. The descriptive data is presented in Table 5-10.

Within each group

No change in the early-stance LQ/LH co-contraction across time was identified as an effect of the treatment in combined group (p=0.13), sleeve group (p=0.37) and LWI group (p=0.30) when conducting repeated measures ANOVA.

Between the groups

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No significant difference was identified in the early-stance LQ/LH co-contraction via one-way ANOVA between groups at baseline (p=0.47), immediate effect (p=0.42) and 6 weeks (p=0.09).

LQ/LG:

The data showed mild to moderate deviation in normality and inequality of covariance. The transformation (RMS) were successful in reducing the deviation or even produce normality (Log10, Ln) and correct for inequality of covariance (RMS, Log10, Ln). However, all tests results (transformed data, non-transformed data) agreed therefore non-transformed data were used due to the ease of interpretation.

Two way-mixed ANOVA

There was no significant effect for the group (p=0.36) and time (p=0.36) on the early-stance LQ/LG co-contraction. No interaction between the group and the time was identified (p=0.14). The descriptive data is presented in Table 5-10.

Within each group

Paired sample t-test showed no significant change in the LQ/LG after immediate use of the treatment in combined group (p=0.42), sleeve group (p=0.15) and LWI group (p=0.98).

Between the groups

One-way ANOVA showed no significant difference in the early-stance LQ/LG co-contraction between groups at baseline (p=0.28) and immediate effect (p=0.50).

MQ/MH

The data showed mild deviation in normality in the sleeve group and inequality of variance and covariance. The transformation (RMS, log10) were successful produce normality and correcting the inequality of variance and covariance. Although equality of variance and covariance were achieved via data transformation, using the transformed data was not preferred due to the disagreement between the tests. When comparing the treatment effect within the combined and the sleeve groups parametric and non-parametric tests showed significant reduction in co-contraction

with immediate use. However, when this applied to the transformed data this effect of the treatment seems to be disappear. The combined group is normally distributed and since parametric and non-parametric tests agreed the parametric tests were used due to the ease of interpretation and the transformation was not used.

Within each group

Paired sample t-test showed significant reduction in the early-stance MQ/MH co-contraction after immediate use of the combined group (p=0.04) and the sleeve group (p=0.03) compared to the baseline. However, the LWI group did not show any significant change (p=0.24). The descriptive data is presented in Table 5-10.

Between the groups

One-way ANOVA showed no significant difference in the early-stance MQ/MH co-contraction between the groups in the baseline (p=0.18) and immediate effect (p=0.13).

MQ/MG.

The data showed moderate to severe deviation in normality and inequality of covariance. The transformation (RMS, log10, Ln) were successful in reducing the deviation in normality as in (RMS) or even produce normality (Log10, Ln) and correcting the inequality of covariance (RMS, log10, Ln). The results of two way-mixed ANOVA, one-way ANOVA and repeated measures ANOVA for the transformed data were similar when all test applied on the non-transformed data or even the non-parametric test. Therefore, using parametric on the non-transformed data was preferred since all tests produced the same results and for the ease of interpretation.

Two way-mixed ANOVA

There was no significant effect for the group (p=0.54) and time (p=0.60) on the early-stance LQ/LG co-contraction. Neither there was interaction between the time and the group (p=0.39). The descriptive data is presented in Table 5-10.

Within each group

Repeated measures ANOVA showed no significant change in the early-stance LQ/LG co-contraction after using the treatment in the combined group (p=0.94), the sleeve group (p=0.33) and the LWI group (p=0.36).

Between the groups

One-way ANOVA showed no significant difference in the early-stance LQ/LG co-contraction between the groups at baseline (p=0.49) immediate effect (p=0.51) and 6 weeks (p=0.57).

Table 5-10 Mean (SD) of muscles co-contraction in early stance phase for combined, sleeve and LWI groups.

Early-stance Mean (SD)	Week one						Week 6		
	Combined group		Sleeve group		LWI group		Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment			
LQ vs. LH	0.29 (0.21)	0.27 (0.22)	0.45 (0.34)	0.44 (0.31)	0.40 (0.36)	0.40 (0.33)	0.21 (0.18)	0.37 (0.27)	0.46 (0.30)
LQ vs. LG	0.24 (0.18)	0.25 (0.21)	0.38 (0.28)	0.34 (0.21)	0.35 (0.19)	0.35 (0.19)			
MQ vs. MH	0.19 (0.13)	0.16 (0.10) Θ	0.38 (0.31)	0.32 (0.27) Θ	0.26 (0.17)	0.24 (0.18)			
MQ vs. MG	0.14 (0.16)	0.14 (0.18)	0.18 (0.10)	0.16 (0.09)	0.26 (0.37)	0.24 (0.29)	0.14 (0.10)	0.20 (0.13)	0.18 (0.13)

Θ significant compared to baseline

Mid-stance:

LQ/LH

The data showed moderate to high deviation in normality and inequality of variance. The transformation (RMS, log10, Ln, reciprocal) failed to correct the significant difference in variance. Therefore, two way-mixed ANOVA couldn't be used, and comparing between and within the groups via non-parametric test was the solution since the data showed moderate to severe deviation in normality.

Within each group

The Friedman test showed no significant changes within the combined group (p=0.18) or the sleeve group (p = 0.10). However, the LWI group showed significant changes in the mid-stance LQ/LH co-contraction (p=0.05). Pairwise comparison adjusted to Bonferroni showed significant increase in the mid-stance LQ/LH co-contraction after 6 weeks' LWI use compared to immediate use (p=0.04). The descriptive data is presented in Table 5-12.

Between the groups

The Kruskal-Wallis test showed no significant difference between the groups at baseline (p=0.58), immediate effect (p = 0.65), or 6 weeks (p=0.23) in the mid-stance LQ/LH co-contraction.

LQ/LG

The data showed mild to moderate deviation in normality in the combined group and the LWI group and inequality of covariance. The transformation (RMS, log10, Ln, reciprocal) failed to correct the significant difference in covariance. Therefore, two way-mixed ANOVA couldn't be used, and the comparing between and within the groups using either parametric or non-parametric testing was the solution. Both methods were applied and revealed different results when comparing the effect of the treatment within the sleeve group. The parametric test showed significant changes after sleeve use while the non-parametric test did not show any changes. Since the sleeve group was normally distributed and was the only group showing changes when using parametric tests, the parametric test appeared to be more appropriate.

Within each group

Repeated-measures ANOVA showed no significate difference for the time within the combined group (p=0.28) or the LWI group (p=0.24). However, the sleeve group showed significant difference for time (p=0.02). Bonferroni and Sidak adjustments failed to show any significant difference within time for the sleeve group while LSD showed significant reduction in co-contraction in the sleeve group after 6 weeks compared to baseline (p=0.03). The descriptive data is presented in Table 5-11.

Between the groups

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One-way ANOVA showed no significant difference between the groups at baseline (p=0.60), immediate use of the treatment (p=0.51), or after 6 weeks (p=0.12).

MQ/MH

The data showed moderate to severe deviation in normality and inequality of variance. All transformation failed to produce equality of variance; non-parametric tests were used because of the severity of deviation from normality. The Friedman test was used to test the effect of the treatment within each group separately, and the Kruskal-Wallis test was used to test the difference between the groups.

Within each group

The Friedman test showed no significant changes in the mid-stance MQ/MH co-contraction after using the treatment in the combined group (p=0.91), the sleeve group (p=0.31), or the LWI group (p=0.10). The descriptive data is presented in Table 5-12.

Between the groups

The Kruskal-Wallis test showed no significant difference in the mid-stance MQ/MH co-contraction between the groups at baseline (p=0.14), immediate effect (p=0.30), or 6 weeks (p=0.48) in the mid-stance MQ/MH co-contraction.

MQ/MG

The data showed mild to moderate deviation in normality and inequality of covariance. Although log10 and Ln transformations were successful in correcting the requirement for two way-mixed ANOVA (normality, covariance), non-parametric tests were used. This is because of the disagreement between the non-parametric tests and the transformed data when comparing the effect of the treatment within the groups. The transformed data showed significant change within the combined group while non-parametric test in the non-transformed data did not show any change. Therefore, comparing within and between the groups via using non-parametric tests seemed more appropriate.

Within each group

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The Friedman test showed no significant difference in the mid-stance MQ/MG co-contraction after using the treatment for the combined group (p=0.70), the sleeve group (p=0.15), or the LWI group (p=0.92). The descriptive data is presented in Table 5-12.

Between the groups

The Kruskal-Wallis test showed no significant difference in the mid-stance MQ/MG co-contraction between the groups at baseline (p=0.65), immediate effect (p=0.85), or 6 weeks (p=0.93).

Table 5-11 Mean (SD) of muscles co-contraction in mid-stance phase for combined, sleeve and LWI groups.

Mid-stance Mean (SD)	Week one						Week 6		
	Combined group		Sleeve group		LWI group		Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment			
LQ vs. LG	0.18 (0.15)	0.18 (0.15)	0.22 (0.15)	0.20 (0.14)	0.26 (0.22)	0.26 (0.22)	0.14 (0.14)	0.12 (0.07) Θ	0.30 (0.26)

Θ significant compared to baseline

Table 5-12 Median (Range) of muscles co-contraction in mid-stance phase for combined, sleeve and LWI groups.

Mid-stance Median	Combined group		Sleeve group		LWI group		Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment			
LQ vs. LH	0.07	0.07	0.18	0.11	0.13	0.09	0.05	0.08	0.21 μ
max	0.45	0.43	0.37	0.31	0.65	0.65	0.32	0.29	0.98
min	0.02	0.01	0.04	0.04	0.02	0.02	0.02	0.02	0.03
MQ vs. MH	0.05	0.04	0.09	0.08	0.08	0.07	0.04	0.07	0.06
max	0.26	0.27	0.16	0.14	0.38	0.26	0.29	0.23	0.32
min	0.01	0.01	0.05	0.04	0.02	0.01	0.01	0.02	0.02
MQ vs. MG	0.11	0.13	0.11	0.14	0.14	0.12	0.10	0.12	0.15
max	0.39	0.28	0.45	0.39	0.50	0.47	0.79	0.36	0.50
min	0.03	0.03	0.03	0.03	0.01	0.01	0.02	0.01	0.01

μ significant compared to immediate use

Late-stance:

LQ/LH

Two way-mixed ANOVA

The group (p=0.53) and time (p=0.18) had no significant effect on the late-stance LQ/LH co-contraction. ANOVA showed no significant interaction between the group and time (p=0.05). The descriptive data is presented in Table 5-13.

Within each group

Repeated-measures ANOVA showed no significant changes after using combined treatment (p=0.69), sleeve treatment (p=0.10), or LWI treatment (p=0.07) in the late-stance LQ/LH co-contraction.

Between the groups

One-way ANOVA showed no significant difference in the late-stance LQ/LH co-contraction between the groups at baseline (p=0.27), immediate effect (p=0.73), and 6 weeks (p=0.40).

LQ/LG:

The data showed moderate to severe deviation in normality and inequality of covariance. The transformation (RMS, reciprocal) were successful to reduce the deviation in normality or even show normally distributed data (log10, Ln). Furthermore, the transformations were successful to show equality of covariance (RMS, log10, Ln). However, the results of non-parametric test within the sleeve group contradict the parametric test on the transformed data. The sleeve group showed sever deviation in normality. Therefore, the using the non-parametric test seemed to be more appropriate.

Within each group

No significant changes were identified after using the combined treatment (p=0.76), sleeve treatment (p=0.06) or LWI treatment (p=0.31) in the late-stance LQ/LG co-contraction. The descriptive data is presented in Table 5-14.

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Between the groups

When comparing the groups in late-stance LQ/LG co-contraction at baseline, after immediate use of the treatment, and after 6 weeks' use of the treatment, no significant difference was identified with the Kruskal-Wallis test (p=0.48, 0.20, and 0.28, respectively).

MQ/MH:

The data showed moderate to severe deviation in normality and inequality of covariance and variance. Although log10 and Ln transformations were successful in correcting the requirement for two way-mixed ANOVA (normality, covariance, variance), non-parametric tests were used. This is because of the disagreement between the non-parametric tests and the parametric test on the transformed data when comparing the effect of the treatment within sleeve group. The non-parametric test showed significant change were the transformed data were nearly to be significant. Therefore, comparing within and between the groups via using non-parametric tests seemed more appropriate.

Within each group

Friedman test showed no significant effect in the late-stance MQ/MH co-contraction on the combined group (p=0.53) or the LWI group (p=0.37). In contrast, the sleeve group showed significant time effect in the late-stance MQ/MH co-contraction (p=0.02). Adjusted pairwise comparison showed significant reduction after 6 weeks of sleeve use compared to baseline (p=0.02). The descriptive data is presented in Table 5-14.

Between the groups

The Kruskal-Wallis test showed no significant difference in the late-stance MQ/MH co-contraction between the groups at baseline (p=0.06), immediate effect (p=0.09), and 6 weeks (p=0.47).

MQ/MG

The data showed severe deviation in normality and inequality of variance and covariance. The transformation (RMS, log10, Ln, reciprocal) failed to correct the significant difference in

covariance and variance, and because of the severe deviation in the natural data, the non-parametric tests were the most appropriate test to be chosen.

Within each group

The Friedman test showed no significant difference after treatment in the combined group (p=0.06) or the LWI group (p=0.56) in the late-stance MQ/MG co-contraction. However, the sleeve group showed significant changes in the late-stance MQ/MG co-contraction (p=0.04). Pairwise comparison adjusted to Bonferroni failed to show any significant difference while the non-adjusted test showed significant reduction after 6 weeks of sleeve use compared to baseline (p=0.03) and immediate effect (p=0.02) in the late-stance MQ/MG co-contraction. The descriptive data is presented in Table 5-14.

Between the groups

The Kruskal-Wallis test showed no significant difference between the groups at baseline (p=0.39), immediate effect (p=0.25), and 6 weeks (p=0.66) in late-stance MQ/MG co-contraction.

Table 5-13 Mean (SD) of muscles co-contraction in late-stance phase for combined, sleeve and LWI groups.

Late-stance Mean (SD)	Week one						Week 6		
	Combined group		Sleeve group		LWI group		Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment			
LQ vs. LH	0.06 (0.06)	0.05 (0.04)	0.09 (0.06)	0.07 (0.04)	0.06 (0.03)	0.06 (0.04)	0.05 (0.04)	0.07 (0.06)	0.08 (0.06)

Table 5-14 Median (Range) of muscles co-contraction in late-stance phase for combined, sleeve and LWI groups.

Mid-stance Median	Combined group		Sleeve group		LWI group		Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment			
LQ vs. LG	0.06	0.05	0.09	0.07	0.06	0.06	0.05	0.06	0.06
max	0.18	0.27	0.41	0.94	0.44	0.35	0.16	0.20	0.18
min	0.02	0.01	0.04	0.04	0.02	0.02	0.01	0.02	0.02
MQ vs. MH	0.04	0.03	0.06	0.05	0.05	0.04	0.04	0.04 Θ	0.04
max	0.09	0.09	0.14	0.10	0.16	0.13	0.09	0.19	0.09
min	0.01	0.01	0.04	0.02	0.01	0.01	0.01	0.01	0.01
MQ vs. MG	0.06	0.05	0.09	0.14	0.06	0.07	0.03	0.06 Θ μ	0.06
max	0.20	0.25	0.23	0.32	0.45	0.46	0.26	0.21	0.20
min	0.02	0.02	0.03	0.04	0.01	0.01	0.01	0.01	0.02

Θ significant compared to baseline
μ significant compared to immediate use

The magnitude of change in the muscles co-contraction

Early-stance

The immediate and 6 weeks' magnitude of change in early-stance muscle co-contraction did not reach statistical significance level between the groups ($p \geq 0.05$). The descriptive data is presented in Table 5-15.

Mid-stance

The immediate magnitude of change in mid-stance LQ/LH, LQ/LG, MQ/MH and MQ/MG co-contraction also did not show any significant difference ($p \geq 0.05$) while at 6 weeks, there was a significant difference in LQ/LH and LQ/LG between the groups ($p < 0.05$). Pairwise comparison showed significantly greater reduction in LQ/LH for the sleeve group ($p=0.03$) and the combined group ($p=0.04$) than for the LWI group. For the LQ/LG muscle co-contraction, only the sleeve group showed significantly greater reduction than the LWI group ($p=0.04$). The descriptive data is presented in Table 5-15..

Late-stance

In the late-stance, the magnitude of change showed significant difference between the group after 6 weeks use of treatment in the LQ/LH and LQ/LG (p<0.05). Pairwise comparison showed significant greater reduction in late-stance LQ/LH and LQ/LG for sleeve group compared to LWI group (p=0.049, p=0.04). The descriptive data is presented in Table 5-15.

Table 5-15 Mean (SD) of the magnitude of changes for muscles co-contraction in early, mid and late stance phases for combined, sleeve and LWI groups.

Phase	Muscles	Immediate magnitude of change			6 weeks magnitude of change		
		Combined group	Sleeve group	LWI group	Combined group	Sleeve group	LWI group
Early-stance	LQ/LH	-0.02 (0.09)	-0.02 (0.14)	-0.01 (0.07)	-0.08 (0.15)	-0.09 (0.24)	0.05 (0.17)
	LQ/LG	0.01 (0.05)	-0.05 (0.10)	-0.00 (0.05)	-0.02 (0.15)	-0.05 (0.16)	-0.02 (0.15)
	MQ/MH	-0.04 (0.05)	-0.06 (0.08)	-0.02 (0.06)	-0.02 (0.14)	-0.09 (0.21)	-0.04 (0.08)
	MQ/MG	-0.00 (0.03)	-0.02 (0.04)	-0.02 (0.08)	-0.00 (0.11)	0.02 (0.10)	-0.08 (0.28)
Mid-stance	LQ/LH	-0.02 (0.04)	-0.04 (0.06)	-0.03 (0.08)	-0.04 (0.09 λ	-0.05 (0.07) λ	0.08 (0.16)
	LQ/LG	-0.00 (0.04)	-0.02 (0.07)	-0.00 (0.06)	-0.05 (0.14)	-0.10 (0.13) λ	0.04 (0.12)
	MQ/MH	-0.00 (0.01)	-0.01 (0.02)	-0.01 (0.04)	-0.00 (0.04)	-0.02 (0.06)	-0.02 (0.03)
	MQ/MG	-0.00 (0.04)	-0.03 (0.07)	-0.01 (0.03)	0.06 (0.22)	-0.04 (0.09)	-0.00 (0.06)
Late-stance	LQ/LH	-0.01 (0.02)	-0.02 (0.03)	-0.00 (0.02)	0.06 (0.22)	-0.04 (0.09) λ	-0.00 (0.06)
	LQ/LG	-0.01 (0.04)	0.04 (0.19)	-0.00 (0.03)	-0.01 (0.04)	-0.06 (0.08) λ	0.02 (0.09)
	MQ/MH	-0.00 (0.01)	-0.01 (0.02)	-0.01 (0.01)	-0.00 (0.03)	-0.02 (0.04)	-0.01 (0.03)
	MQ/MG	-0.00 (0.03)	0.03 (0.08)	0.01 (0.03)	-0.01 (0.05)	-0.03 (0.07)	0.02 (0.13)

λ significant compared to LWI

5.6.7 *Dynamic balance test results*

Anterior direction balance (normalised to leg length)

Two way-mixed ANOVA

The group had no significant effect on the normalised anterior direction balance test (p=0.15), and there was no interaction effect (p=0.82). The time showed significant effect on the normalised anterior direction balance (p<0.01). The descriptive data is presented in Table 5-16.

Within each group

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The t-test showed significant improvement in the normalised anterior direction balance test for the combined group (p=0.02) and the LWI group (p=0.02), but not for the sleeve group (p=0.11).

Between the groups

There was no significant difference between the groups at baseline (p=0.37) or after 6 weeks of treatment (p=0.06) in the normalised anterior direction balance test.

Magnitude of change between the groups

The magnitude of change in the normalised anterior direction balance test after 6 weeks of treatment was not significant between the groups (p=0.82)

Medial direction balance (normalised to leg length)

Two way-mixed ANOVA

ANOVA showed no significant interaction between the group and time (p=0.77) and no group effect (p=0.61) on the normalised medial direction balance. However, the time showed significant effect (p<0.01). The descriptive data is presented in Table 5-16.

Within each group

After 6 weeks of treatment, the combined group showed significant improvement in the normalised medial direction balance test compared to baseline (p=0.02), but the sleeve group (p=0.11) and the LWI group (p=0.10) did not.

Between the groups

The data showed that there was no significant difference in the normalised medial direction balance test between the groups at baseline (p=0.56) or after 6 weeks (p=0.75).

Magnitude of change between the groups

The magnitude of change in the normalised medial direction balance test after 6 weeks of treatment was not significantly different between the groups (p=0.77).

Table 5-16 Mean (SD) of dynamic balance tests for combined, sleeve and LWI groups.

Mean (SD)	Combined group		Sleeve group		LWI group		Magnitude of change between baseline and week 6		
	Baseline	Weeks 6	Baseline	Weeks 6	Baseline	Weeks 6	Combined group	Sleeve group	LWI group
Anterior (% to leg length)	71.50 (13.82)	79.21 (6.43) Θ	64.28 (9.82)	70.68 (5.63)	70.03 (12.22)	75.36 (10.05) Θ	7.71 (8.83)	6.40 (11.26)	5.32 (6.55)
Medial (% to leg length)	73.14 (11.52)	79.84 (9.20) Θ	69.87 (8.32)	76.59 (9.18)	74.88 (11.96)	79.14 (11.91)	6.70 (7.90)	6.72 (12.06)	4.26 (8.20)

Θ significant compared to baseline

5.6.8 Pain pressure threshold results

Two way-mixed ANOVA

The interaction effect between the group and intervention time was not significant for the pain pressure threshold in the medial condyle pressure threshold or the medial malleolus pressure threshold ($p \geq 0.05$). Neither the group nor the time had any significant effect on the medial condyle pressure threshold or the medial malleolus pressure threshold ($p \geq 0.05$). The descriptive data is presented in Table 5-17.

Within each group

After 6 weeks of treatment, no significant changes were identified in the medial condyle pain pressure threshold or the medial malleolus pain pressure threshold in the combined group, the sleeve group, or the LWI group ($p \geq 0.05$).

Between the groups

Comparing the groups at baseline and after 6 weeks of treatment revealed no significant difference between the groups in the medial condyle pain pressure threshold or the medial malleolus pain pressure threshold ($p \geq 0.05$).

Magnitude of change between the groups

The magnitude of change in the pain pressure threshold in the medial condyle and medial malleolus between the groups did not reach significant levels ($p \geq 0.05$).

Table 5-17 Mean (SD) of pain pressure threshold tests for combined, sleeve and LWI groups.

Mean (SD)	Combined group		Sleeve group		LWI group		Magnitude of change between baseline and week 6		
	Baseline	Weeks 6	Baseline	Weeks 6	Baseline	Weeks 6	Combined group	Sleeve group	LWI group
Medial condyle (N/Cm²)	7.23 (1.87)	6.78 (.74)	6.04 (1.38)	6.27 (1.33)	6.19 (1.79)	6.34 (1.78)	-0.45 (1.59)	0.23 (1.26)	0.15 (1.19)
Medial malleolus (N/Cm²)	7.77 (0.85)	7.99 (1.75)	6.71 (1.42)	7.07 (1.50)	8.16 (1.87)	7.00 (1.64)	0.22 (1.49)	0.37 (1.17)	-1.16 (2.34)

5.6.9 Functional tests results

Thirty-second chair-stand test

Two way-mixed ANOVA

ANOVA showed no significant effect for the groups (p=0.62), and there was no interaction between group and time (p=0.80). The time showed significant effect on the stair 30-second chair-stand test (p<0.01). The descriptive data is presented in Table 5-18.

Within each group

The t-test showed significant improvement in the 30-second chair-stand test for the combined group (p=0.048) and the LWI group (p=0.02) after 6 weeks of treatment, but not for the sleeve group (p=0.14).

Between the groups

One-way ANOVA showed no significant difference in the number of repetitions for the 30-second chair-stand test between the groups at baseline (p=0.66) or 6 weeks (p=0.61).

Magnitude of change between the groups

When comparing the magnitude of change between the groups, no significant difference was identified (p=0.80).

40-metre fast-paced walk test

Two way-mixed ANOVA

The data showed that the group had no significant effect on 40-metre fast-paced walk test speed (p=0.77), and there was no interaction between groups and time (p=0.72). The time showed significant effect on the 40-metre fast-paced walk test speed (p=0.03). The descriptive data is presented in Table 5-18.

Within each group

After 6 weeks of treatment use no significant change was observed with in the combined group (P=0.10), sleeve group (p=0.21) and LWI (p=0.49) compared to baseline.

Between the groups

The difference in the 40-metre fast-paced walk test speed between the groups did not reach a statistically significant level at baseline (p=0.80) or after 6 weeks of treatment (p=0.73).

Magnitude of change between the groups

The magnitude of change (improvement) in 40-metre fast-paced walk test speed after 6 weeks' treatment was not significant between the groups (p=0.72).

A stair-climb test

The data showed normal distribution; however, the variance was unequal. The transformation (RMS, log10, Ln, reciprocal) failed to correct the significant difference in variance. Therefore, two-way mix ANOVA couldn't be used, and comparing between and within the groups using parametric testing was the solution since the data was normally distributed. The descriptive data is presented in Table 5-18.

Within each group

The time spent to ascend and descend nine steps significantly decreased after 6 weeks of combined treatment use (p<0.01), but not after sleeve use (p=0.15) or LWI use (p=0.51) when tested via t-test.

Between the groups

One-way ANOVA showed no significant difference between the groups at baseline (p=0.94) or 6 weeks (p=0.31) in the time spent to ascend and descend nine steps.

Magnitude of change between the groups

When comparing the magnitude of change in time after for stair-climb test treatment between the groups, no significant difference was identified (p=0.49).

Table 5-18 Mean (SD) of functional tests results for combined, sleeve and LWI groups.

Mean (SD)	Combined group		Sleeve group		LWI group		Magnitude of change between baseline and week 6		
	Baseline	Week 6	Baseline	Week 6	Baseline	Week 6	Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
30-seond chair-stand test (count)	11.64 (2.85)	12.68 (4.06) Θ	11.26 (2.90)	11.96 (3.16)	12.38 (3.18)	13.42 (3.23) Θ	1.05 (1.54)	0.69 (1.44)	1.04 (1.37)
40-metre fast-paced walk (m/s)	1.67 (0.35)	1.76 (0.30)	1.60 (0.29)	1.66 (0.29)	1.68 (0.29)	1.72 (0.26)	0.09 (0.17)	0.07 (0.16)	0.04 (0.18)
Stair-climb test (second)	10.95 (1.71)	9.02 (1.44) Θ	11.23 (2.72)	10.63 (2.75)	10.86 (3.12)	10.04 (2.85)	-1.93 (1.91)	-0.60 (1.29)	-0.82 (4.12)

Θ significant compared to baseline

5.7 Discussion

Nonsurgical orthotic management of knee osteoarthritis, such as lateral wedge insoles (LWI) and knee sleeve are recommended by National Institute for Health and Care Excellence (NICE) and Osteoarthritis Research Society International (OARSI) guidelines (ACR, 2012; Buttgereit, Burmester, & Bijlsma, 2015; McAlindon et al., 2014; NICE, 2014) .

The reduction in the knee loading with lateral wedge insole use has been proven in the majority of clinical trials, with pain and functional improvement compared to baseline. However, when the lateral wedge insole was compared to the control treatment (neutral insole), which does not reduce the knee loading, the pain reduction does not appear. Therefore, the conflict between the clinical and biomechanical trials makes the adoption of the treatment to the clinical practice quite challenging since clinicians are driven by pain reduction more than loading reduction. Previous studies have found that combining the LWI with the valgus knee brace provides more reduction in pain and knee loading. However, the compliance with valgus knee brace is low because of its size and the difficulty of applying it, which shows the failure of adopting this in clinical practise. Therefore, there is a need for better treatment to help reduce knee pain and loading and provide functional improvement. The simple knee sleeve has been identified as a good treatment targeting pain and muscle co-contraction (loading). The simple knee sleeve could be a good treatment for reducing pain and loading and providing further functional improvement if combined with the lateral wedge insole. Therefore, this study investigated the effect of combined treatment (lateral wedge insole and simple knee sleeve) and compared it to each treatment individually after immediate use and after 6 weeks.

At baseline, there was no significant difference between the groups in demographic characteristics, EKAM, muscle co-contraction, or pain.

Thirty-four participants were enrolled in this study: thirty-one males and three females. The mean age was 55.24 (10.55) years (age range 40–77 years), the mean height was 1.72 (0.09) metres (height range 1.54–1.9 m), the mean mass was 86.96 (15.05) kg (mass range 45.6–123.9 kg), and the mean BMI was 29.48 (4.69) kg/m² (BMI range 19.23–40 kg/m²). The mean of EKAM, KAAI, and knee pain at baseline were 0.53 (0.13) Nm/kg, 3.18 (0.81) %Bw.ht, 0.21 (0.08) (Nm/kg).s, and 54.17 (15.48), respectively.

The EKAM value (0.53 Nm/kg) for the current OA study population is in agreement with previous studies by Arazpour et al. (2013), Fu et al. (2015), Maly et al. (2002), Jones et al. (2013), and Toriyama et al. (2011), where EKAMs were 0.56 Nm/kg, Nm/kg to 0.57 Nm/kg, 48 Nm/kg, 0.55 to 0.56 Nm/kg, and 0.54 Nm/kg, respectively. Collins et al. (2014), Hinman et al. (2008) and Schween et al. (2015) studies showed higher EKAM at baseline than the current study (3.72%Bw.ht, 3.60 %Bw.ht, 0.85 Nm/kg respectively). This might be explained by the higher walking speed at baseline than in the current study (1.32m/s) or different in demographic characteristics. Furthermore, a lower EKAM (0.46 Nm/kg) was identified in a previous study than in the current study, which might be explained by lower walking speed (0.98 m/s) (Laroche et al., 2014). As anticipated, the knee adduction angular impulse (KAAI) in this study was similar to that in previous studies by Jones et al. (2013) where KAAI were 0.24 (Nm/kg).s respectively.

Henriksen et al. (2010) showed that KOOS pain in mild knee OA (K/L$\leq$2) was 57.9 while in more severe OA (K/L>2) it was 53. (Henriksen, Graven-Nielsen, Aaboe, Andriacchi, & Bliddal, 2010) The current population in this study recorded a baseline of 54 for KOOS pain which aligns with the previous study.

Interestingly, the proportion of females to males was greater in most previously motioned knee OA studies (Arazpour et al., 2013; Collins et al., 2014; Fu et al., 2015; Henriksen et al., 2010; Toriyama et al., 2011). This is in contrast to current study, which included more males than females; this may reduce the generalisability of the results, especially for female knee OA populations. Although the studies of Jones et al. (2013), Maly et al. (2002) and Schween et al. (2015) had higher ratios of males to females, the proportions of females to males were higher than in current study. The age in previous OA studies ranged from 50 to 68.43 years, with most of the study participants around 59 years old, while the body mass index ranged from 23 Kg/m² to 32.42 Kg/m², with most studies in the middle range (28 Kg/m²). The current study age (55.24 years old) and body mass index (29.48 Kg/m²) agreed with previous studies. Therefore, the baseline data for age and body mass index, EKAM, KAAI, knee injury and osteoarthritis outcome score for pain agreed with previous literature. This indicates that the current knee OA population is a typical medial OA population and allows us to broaden the knowledge in this context.

5.7.1 Summary of the result on EKAM, muscle co-contraction, pain, balance, physical function tests, PASE and other KOOS subscales

The following is a brief summary of the results at both the immediate phase of the trial and also the short-term effects of the treatments.

5.7.1.1 *Immediate effect of treatment use*

After immediate use of the assigned treatment, there was significant reduction in first peak EKAM for the combined group and the LWI group compared to baseline. In the trough and second peak EKAM, only the LWI group showed significant reduction compared to baseline; the combined group was bordering significance level. When comparing between the groups, there was no significant difference identified in the first peak, trough, or second peak EKAM. KAAI showed significant reduction in the LWI group, compared to baseline with no significant difference between the groups. The immediate magnitude of change between the groups was significantly higher in first peak EKAM for the combined and LWI groups compared to the sleeve group and in second peak EKAM, and KAAI for the LWI group compared to sleeve group.

In muscle co-contraction, only MQ/MH early-stance muscle co-contraction reduced significantly after immediate use of the combined treatment and the sleeve compared to the baseline but not the LWI, with no significant difference between the groups. No significant difference in the magnitude of change in muscle co-contraction was identified between the groups.

5.7.1.2 *After 6 week of treatment use*

After using the assigned treatment for 6 weeks, there was a significant reduction in the first peak EKAM, trough, second peak EKAM, and KAAI for the LWI and combined groups compared to baseline, with no significant difference between the groups. The combined and LWI groups showed significantly higher magnitude of change in first peak EKAM than the sleeve group, but not in trough, second peak EKAM, or KAAI.

Significant reductions in pain were identified in the LWI group, the sleeve group, and the combined group compared to baseline, with no significant difference between the groups. The magnitude of change in pain was not significant when comparing all groups one test. However,

when comparing each two groups separately, only the combined group showed significantly higher magnitude of change than the sleeve group.

From a functional improvement perspective, after 6 weeks of treatment, only the combined group showed a significant reduction in the time needed to ascend and descend nine steps, with no difference between the groups. The combined and LWI groups showed significant increases in the maximum number of repetitions achieved by the participants standing from and sitting in a chair in 30 seconds, with no significant difference between the groups. No statistically significant change in the 40-metre fast-paced walk test was observed compared to baseline or between the groups, with only the combined group showing nearly significant reduction compared to baseline. The magnitude of change in the stair-climb test, the 30-second char-stand test, and the 40-metre fast-paced walk test did not show statistical difference between the groups.

Significant improvements were seen in the anterior direction balance test for the combined group and LWI group compared to baseline. No significant difference was identified between the groups; neither did the magnitude of change show any significant results. In the medial direction balance test, only the combined group showed significant improvements compared to baseline, with no significant difference between the groups. The magnitude of change in the medial direction balance test was not significant between the groups.

In mid-stance muscle co-contraction, only the sleeve group showed a significant reduction in LQ/LG after 6 weeks compared to baseline. In contrast, the LWI group showed significant increases in mid-stance LQ/LH muscle co-contraction after 6 weeks compared to immediate use. In the late-stance, the sleeve group showed significant reduction in muscle co-contraction after 6 weeks of treatment use compared to baseline between the following muscles: MQ/MH, and MQ/MG, compared to immediate use of the treatment between the following muscles: MQ/MG. The magnitude of change showed significant higher reduction in mid-stance LQ/LH muscle co-contraction in the sleeve group and the combined group compared to the LWI group. Furthermore, the sleeve group showed a significantly higher magnitude of change in LQ/LG muscle co-contraction after 6 weeks of treatment than the LWI group. In the late-stance phase, only sleeve group showed significant higher magnitude of change in muscle co-contraction compared to LWI group between the following pairs LQ/LH and LQ/LG.

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The results achieved in the current study will now be discussed in terms of where they fit within the current literature, concentrating on the specific hypotheses stated earlier in the chapter.

5.7.2 Effect of the treatment on EKAM

Null hypothesis: There is no significant difference in EKAM when using combined treatments (lateral wedge insole, simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve) (immediate, 6 weeks).

This hypothesis was partially rejected, as there was no significant difference between the groups in any part of EKAMs (first peak, trough, second peak, KAAI) between the groups after immediate use of the treatment or after 6 weeks. However, the magnitude of change in first peak EKAM was significantly higher for the combined and LWI groups than the sleeve group. In second peak EKAM and KAAI, the magnitude of change was statistically significant higher for the LWI group compared to sleeve group.

The non-significant difference observed between the groups after immediate and 6 weeks use of treatments in EKAM value may be partially explained by three factors. First, the combined group had slightly higher EKAM at baseline than the other groups, but the difference was not statistically significant and could be explained by a non-significant slightly higher walking speed (1.22 m/s) than the other groups (1.15 m/s) or biomechanical factors such as increased varus angle. Secondly, ANOVA test rely on the basic concept that if there is no within-group variability (different between subject in the same groups and the same time), then any between-group variability counts (different between groups or time). Therefore, with a high variability within the group, the statistical power is reduced. Thirdly, the low sample size in each of the group might contribute to the non-significant difference. When looking at EKAM using different methods, the magnitude of change and not the real value of EKAM after immediate and 6 weeks using one-way ANOVA, the test showed significant differences between the groups.

The combined and LWI groups showed a significant reduction in EKAM compared to baseline, and the mechanism that underlies this is by laterally shifting the centre of foot pressure. This shifts the GRF more laterally and therefore reduces the moment arm. When considering the centre of foot pressure, the combined group and the LW group showed lateral shifting in early-, mid- and

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late-stance phases during walking (Appendix E). The maximum effect of the lateral wedge insole occurs in the early-stance phase where the first peak is. This can be explained by the design of the LWI as the inclination at the heel is 5 degrees, gradually decreasing to 0 at the metatarsal head. The LWI group and combined group showed reduction in all aspects of EKAM (first peak, trough, second peak, KAAI) compared to baseline. This reduction in EKAM translates into potential reductions in knee loading and therefore may reduce the disease progression (Miyazaki et al., 2002).

The reduction in EKAMs in the combined group and the LWI group ranged from 8.17% to 14.88% compared to baseline for first peak EKAM and 9.31% to 15.56% compared to baseline for KAAI. The reduction in this study is generally in agreement with previous studies investigating the effect of the lateral wedge insole (Butler et al., 2009; Chapman et al., 2015; Fu et al., 2015; Hinman et al., 2012; Hinman et al., 2008a; Jones et al., 2013a, 2013b; Kerrigan et al., 2002). Percentages of reduction in first peak EKAM similar to those in the current study were seen in previous studies: 12% (Hinman et al., 2008a), 13.7% (Fu et al., 2015), 10% (Butler et al., 2009), and 12% (Jones et al., 2013b). Furthermore, Jones et al. (2013b) conducted two-week crossover trials and showed a 16.1% reduction in KAAI, which is in agreement with the current study.

Interestingly, in a randomised crossover study by Chapman et al. (2015), the reduction in first peak EKAM with lateral wedge insole use was found to be 5.85% in the whole group. The study highlighted that some participants showed an increase in EKAM with the lateral wedge insole; when this population was excluded, the reduction increased to 11.39%.

Other studies have shown lower EKAM reductions than the current study for first peak EKAM (5.8%) and KAAI (6.3%) (Hinman et al., 2012b); peak EKAM (6%) (Kerrigan et al., 2002); and 4.84% first peak EKAM and 6.38% KAAI on the affected side (Jones et al., 2013a). This difference in EKAM reduction in previous studies to current study can be attributed to several factors such as presence or absence of the arch support, including some participants who did not respond to the treatment, difference in insole materials, different in footwear used.

The current study used lateral wedge insoles with medial arch supports while Hinman et al. (2012b) did not use arch supports. A previous study showed that a lateral wedge insole with an arch has a better effect biomechanically among healthy on EKAM than a lateral wedge insole with no arch

(Nakajima et al., 2009). Jones et al. (2015) showed that LWI with arch produced comparable results in EKAM and KAAI to LWI with no arch. However, LWI with arch showed higher comfort score that LWI with no arch and significantly reduced in pain with LWI compared with no arch LWI.

Several studies have identified inconsistencies in EKAM reduction among individuals. This suggests that some individuals exhibit more benefit from using LWI than others (Hinman et al., 2008; Kakihana et al., 2007; Kutzner et al., 2011). Recent studies identified that individuals with higher peak ankle eversion angle at EKAM are more likely to be among responders (EKAM reduced with LWI use). This might be due to a limited range of motion in non-responders, which limits ankle pronation and therefore limits the ability of the LWI to alter the knee loading (Chapman et al., 2015). Hinman et al, (2012) showed that some participants experience an increase in EKAM with LWI which was not observed in current study.

Participants in the current study used their own shoes while Jones et al. (2013b) standardised the shoes. The type of footwear used was found to affect EKAM, muscle power, and activity. Interaction between LWI and shoe was found, which means that LWI effect is dependent on footwear (Mølgaard & Kersting, 2013) and may decrease LWI efficacy (Toda & Tsukimura, 2008). The current study used LWI with a durometer score of 70 while previous studies used lateral wedge insoles with lower density, such as Hinman et al. (2012), with a durometer score of 57.5, and Kerrigan et al. (2002), with a durometer score of 55. Different LWI materials showed significant differences in outcome, even though the same angulation was used. This shows that higher-density materials might improve stability, comfort, and deformability more than low-density materials (Toda & Tsukimura, 2004a).

The current study results show that using the sleeve did not show any significant change in any part of EKAM (1st peak, trough, 2nd peak, KAAI). Previous study by Collins et al. (2014) showed no significant change in the first peak EKAM and the second peak EKAM with immediate sleeve use among individuals with knee OA which agree with current study results. However, contrasting results which showed significant reduction in first peak EKAM (10.1%) with immediate use of the simple knee sleeve in the OA population. Several reason can be attributed to this such as difference in the type of the sleeve, difference in demographic characteristics (lower BMI, lower age).

Another potential reason is that Schween et al. (2015) participants had higher maximum adduction angle in the first 50% of the stance phase (14.1 degree) compared to current study (approximately 3 degree) which provide more room for the sleeve to reduce the high varus.

Maintaining the reduction in EKAM over time is important if you aim to reduce the knee OA progression. Hinman, et al. (2009) conducted a study to investigate if the EKAM reduction caused by lateral wedge insoles persists after one month and concluded that the reduction in EKAM did not appear to decline over time. The current study shows that the LWI group and the combined group showed an immediate reduction of 8.17% and 10.88%, respectively, and a 6-week reduction of 12.30% and 14.18%, respectively, which is consistent with previous study conclusions.

Putting the reduction in EKAM in clinical view, previous studies showed that EKAM and KAAI are associated with cartilage thickness loss in the knee over 12 months (Bennell et al., 2011) and 24 months (Chang et al., 2015). Furthermore, the reduction in joint space width after 6 years among individuals with knee OA was correlated with peak EKAM (Foroughi et al., 2009). Interestingly, a 1% increase in EKAM was shown to increase the risk of progression by 6.46 times (Miyazaki et al., 2002). Therefore, the reduction in the current study with LWI use either in the LWI group or the combined group may reduce or delay the progression of the knee OA but this would need to be confirmed in a longer term study assessing structural aspects of the knee joint which was outside the remit of this thesis.

5.7.3 *Effect of the treatment on pain*

Null hypothesis: There is no significant difference in pain after 6 weeks when using combined treatments (lateral wedge insole, simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

One of the primary aims of prescribing an intervention in an individual with knee osteoarthritis is to reduce the pain and if the pain reduced it is hoped to be a combined with physical function improvement. Therefore, it is important to understand the change in pain in each group. When comparing each group to its baseline all the groups showed a significant reduction in pain, which was higher than pain fluctuation 2.15 units of pain in KOOS. However, when all the groups were compared after 6 weeks no significant difference was detected, neither was there any significant

difference in the magnitude of the pain change between the groups. Therefore, the null hypothesis was accepted in regards to there being no significant difference in pain between the groups.

Previous studies showed significant improvement in pain with lateral wedge insole use compared to baseline which is in agreement in general with current study results (Ashraf et al., 2014; Barrios et al., 2009; Campos et al., 2015; Fu et al., 2015; Hatef et al., 2014; Hinman et al., 2008b; Jones et al., 2013b; Rubin & Menz, 2005).

In contrast, two studies showed no significant reduction in pain with lateral wedge insole use compared to baseline (Baker et al., 2007; Bennell et al., 2011). Several reason for not identifying a reduction in can be highlighted. First; the biomechanical effectiveness (EKAM reduction) which is considered as the mechanism of pain reduction was not mentioned. Therefore, it is not known if the LWI used provided EKAM reduction. Secondly, use of LWI with low density, 57.5 durometer in Bennell et al. (2011) study and 48 durometer in Baker et al. (2007), compared to current study 70 durometer. Thirdly, Baker et al. (2002) did not mentioned the comfort of the LWI while Bennell et al. (2011) showed back and foot pain with LWI use. Intermittingly. Jones et al. (2014) showed strong correlation between LWI comfort and pain rating. Therefore, pain response may be affected with LWI comfort. Finally, Bennell et al. (2011) measured the pain at baseline and after 12 months and it is not known if there is any change in between.

Sleeve use showed significant improvement in pain compared to baseline which was similar to previous studies (Bryk et al., 2011; Mazzuca et al., 2004; Schween et al., 2015). Schween et al. (2015) investigated the immediate effect of the knee sleeve and showed small significant reduction in pain. One of the limitations of the study is not measuring the pain before providing the treatment and instead the authors provided the participants with 10 visual analogue scale (VAS) after wearing the sleeve. The authors used a visual analog scale where number 5 indicated no change in pain compared to before the treatment. The authors showed a significant reduction in pain (5.5) after the sleeve use. This reduction in pain is roughly 10%, which is similar to that in the current study (11.6%). The participants' ability to remember the pain before the treatment may have been affected by memory issues, and therefore, measuring the pain before providing the treatment was a better option.

Bryk et al. (2011) invesigated the immediate effect of knee sleeve on the knee pain during Stair Climb Power Test. The results showed significant reduction in both (dominant and non-dominant leg) by 1 point on a 10-point VAS. Futhermore, the effect of heat-retairning sleeve and simple sleeve was investigated on a double blind randomised control trial. The treatments was provided for 4 weeks and both group had significant improvement in pain by 16% for heat-retairning sleeve and and 9% for simple sleeve with no significant difference between the groups (Mazzuca et al., 2004).

Only one study was identified which investigated the effect of combining an elastic knee sleeve and a lateral wdge insole with subtalar strap (Keyaki & Toda, 2010). This LWI is incorporate an elastic strap to fix the subtalar joint. The aim of the study was to investigate if adding the simple knee sleeve provided futher pain reduction when walking on uneven ground over 4 weeks. The sample was divided into 3 groups; control group (LWI with stap), treatment group1 (LWI with stap + long sleeve) and treatment group 2 (LWI with stap + short sleeve). All the group showed significant reduction in pain compared to baseline with no futher details between the groups. However, the number of participants who were able to walk on unevn ground without knee pain increased significantly in both treatment groups but not in control group.

However, looking further into the results, it could be seen that there was a further reduction in pain seen for the combined group. When looking to the percentage of reduction compared to baseline, the sleeve group showed 11.16%, LWI group showed 21.1% while the combined group showed 31.88%. The reduction in combined group seems to be as accumulative reduction from LWI group and sleeve group which agree with the study above. Further analysis was undertaken out to compare each of the two groups separately with a t-test, whist this is understood it could create a type 1 error, this seemed sensible to determine if there really was a difference. The results revealed statistically significant magnitude of change reductions in pain for only the combined group compared to sleeve group. This does provide some support that combining a lateral wedge insole and simple knee sleeve could provide further pain reduction than single treatment alone. Interestingly, NICE guidelines recommendation highlighted the need for more trials investigating the effect of the combined treatment and stated that individuals with OA may receive several treatments at the same time in their OA journey. Therefore, it is important to understand if

combined treatment provide better effect. Furthermore, NICE recommended LWI to be used in adjunct to other treatment and using sleeve could be an option (NICE, 2014).

Other potential causes which might affect the pain results is using the subjective knee pain score (self-reported questionnaires) which have been identified to be affected by human memory, which might be weak in older population, and lead to providing inaccurate answers. However, this is believed to have minimal effect or no effect on the results as all the groups has similar age. Furthermore, the reduction in pain may be affected by placebo effect which can be defined as an improvement in an individual's symptoms (i.e. knee pain) caused by using placebo due to individual's expectation. Placebo effect is not believed to affect the study results as all subjects were randomly allocated to the treatment and had no knowledge about other treatment conditions. However, all of the treatments are designed for knee osteoarthritis and thus a reduction in clinical symptoms was expected. Further randomised clinical trials that evaluate combined treatments with neutral insoles may be a future direction.

5.7.4   *Effect of the treatment on muscle co-contraction*

Null hypothesis: There is no significant difference in muscle co-contraction when using combined treatments (lateral wedge insole, simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve) (immediate, 6 weeks).

Muscle co-contraction has been identified to be higher in individuals with knee osteoarthritis (Childs et al., 2004; Hubley-Kozey et al., 2009; Zeni et al., 2010), which could come at the expense of higher joint loading (Lu et al., 1997; Trepczynski et al., 2014). Additionally, increased levels of muscle co-contraction have been associated with greater changes in degeneration (Hodges et al., 2015). Therefore, targeting muscle co-contraction is seen as a sensible option with the treatments.

This study showed significant reductions in muscle co-contraction with sleeve use in early-, mid- and late-stance phases compared to baseline, while the combined group showed a reduction in co-contraction only in the early-stance phase compared to baseline. The LWI group showed a slight increase in mid-stance muscle co-contraction after 6 weeks compared to immediate LWI use but not baseline. When comparing the groups after immediate and 6 weeks' use of the treatment, no significant differences were identified. However, the magnitude of change after 6 weeks was

significantly higher in the mid-stance LQ/LH co-contraction for the sleeve and combined groups than for the LWI group and in mid-stance LQ/LG co-contraction for the sleeve group compared to the LWI group. In the late-stance, the sleeve group showed significantly higher magnitude of change than the LWI group in both LQ/LH and LQ/LG. Therefore, the null hypothesis was partially rejected as the magnitude of change in co-contraction reached significant levels.

When looking at the muscle co-contraction data, the LQ/LH co-contraction while walking was higher than MQ/MH co-contraction for all groups in early- and mid-stance phases. This is in agreement with previous research, which showed higher VL/LH co-contraction than VM/MH co-contraction in the early-stance phase (Andriacchi, 1994; Hubley-Kozey et al., 2009; Ramsey et al., 2007) and mid-stance phase (Schmitt & Rudolph, 2007) while walking. The internal moment plays an important role in providing an abduction moment to resist the varus position in the knee, which occurs due to EKAM attempt to adduct the shank. Therefore, if the agonist muscle cannot resist the EKAM, the co-contraction between agonist and antagonist muscles is important to stabilise the joint (Schipplein & Andriacchi, 1991). Collins et al. (2011) conducted a study to investigate the effect of the knee sleeve and electrical stimulation on muscle co-contraction and impulsive loading. The study results showed significant reduction in the LQ/LH co-contraction in the first half and second half of the stance phase. In the current study, the data shows a reduction in LQ/LH muscle co-contraction with sleeve use (immediate, week 6) in early-, mid-, and late-stance phases compared to baseline, but it did not reach significance. This might propose a decrease in the internal moment (muscles) to resist the external moment (EKAM), due to the support that is provided to the knee joint with sleeve use, making the muscles more relaxed.

There are several plausible explanations for the reduction in muscle co-contraction with sleeve use. Firstly, providing stabilisation of the knee OA reduces the space between the medial condyles, therefore reducing the soft tissue stabilisation (ligaments). This leads to an increase in the demand on the active stabilisation (muscles) to provide support to the joint. Lewek et al. (2004a) showed a correlation between the knee joint laxity and VM/MG co-contraction. Secondly, providing self-reported stability, since previous research showed that individuals with self-reported instability affecting their ADL had higher medial muscle co-contraction than individuals (Lewek et al., 2005).

It has been proposed that reducing the muscle co-contraction may lead to a reduction in the knee OA progression (Pagani et al., 2012). Our results show significant reduction in muscle co-contraction while walking with sleeve use, which may indicates a reduction in the total knee compartment loading (Trepczynski et al., 2014). Therefore, combining the sleeve with the lateral wedge insole may provide further reduction in knee loading and reduce the knee OA progression. The combination of reduced muscle co-contraction and reduced EKAM as in the combined group could be a proposed mechanism to reduce the medial knee compartment loading (Trepczynski et al., 2014). However, this speculation needed to be confirmed in medium-long term studies where structural, clinical and biomechanical outcomes are collated.

5.7.5 *Effect of the treatment on dynamic balance*

Null hypothesis: There is no significant difference in dynamic balance after 6 weeks when using combined treatments (lateral wedge insole, simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

Dynamic balance in the current study was measured in the anterior and medial directions. Previous studies have shown that individuals with knee OA have balance defects (Hinman et al., 2002; Wegener, Kisner, & Nichols, 1997), with balance impairments identified to increase the risk of falling and disability in the elderly (Dionyssiotis, 2012).

Although all groups showed an increase in dynamic balance in both directions, only the combined and LWI groups showed statistically significant increases. Dynamic balance was improved significantly for the combined group in anterior and medial directions compared to baseline by 13.73% and 10.45%. The LWI group showed significant improvement in anterior direction dynamic balance by 8.83% Interestingly, the amount of the improvement in balance for all the groups exceeded the measurement error (chapter 3), which indicates real improvement.

When the groups were compared after 6 weeks, no significant differences were identified; neither did the magnitude of change in balance show any significant difference between the groups. Therefore, the null hypothesis was accepted in terms of there being no significant difference in balance between the groups. The specific cause of balance impairment is not yet clear; however, there are several components that have been found to affect balance. Previous research highlighted

that the aging process, knee pain, muscle weakness, and/or proprioceptive impairment have an effect on balance (Hassan et al., 2001; Koceja et al., 1999; Lin et al., 2009; Slemenda et al., 1997). Therefore, the improvement in dynamic balance could be explained by the significant pain or muscle co-contraction reduction. The reduction in pain may have allowed the participants to load their knees and/or bend their knees more during the test. This explanation is in agreement with a previous study, which found that higher pain in an OA individual with muscle weakness is associated with balance impairment (Hassan et al., 2001).

Another potential reason to enhance balance is the reduction in muscle co-contraction. Hertel et al. (2000) stated that SEBT requires neuromuscular control and muscle co-contraction on the standing leg. Previous studies show an increase in muscle co-contraction in individuals affected with knee OA, the current study shows significant reduction in muscle co-contraction with sleeve use. The relation between the dynamic balance and muscle co-contraction has not been investigated. However, the reduction in co-contraction might lead to selective muscle activation, which leads to better dynamic balance.

Limited research has investigated the effect of conservative treatment on SEBT among individuals with knee OA. Only one study was identified that has investigated the effect of exercise for individuals with knee OA on dynamic balance (Al-Khlaifat et al., 2016). The results showed significant improvement in anterior and medial directions balance tests after the exercise program. The current study results are in agreement with the previous study, which highlights that combined treatments might have a similar effect on dynamic balance. The clinical implication of increasing the dynamic balance could transfer to a reduction of the risk of falling and therefore enhance safety.

5.7.6   *Effect of the treatment on pain pressure threshold*

Null hypothesis: There is no significant difference in pain pressure threshold after 6 weeks when using combined treatments (lateral wedge insole, simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

Individuals with knee OA have been found to have low pressure pain thresholds compared to healthy individuals (Arendt-Nielsen et al., 2010; Imamura et al., 2008). Furthermore, symptomatic knee osteoarthritis was identified to correlate with pain pressure threshold while radiological knee

OA was not (Goode, Shi, Gracely, Renner, & Jordan, 2014). This highlights the importance of investigating the effect of the treatment on the pain pressure threshold. In 2015, Mutul and Ozdincler conducted research to investigate the reliability of pain pressure threshold and the effect of physiotherapy treatment on pain pressure threshold among individuals with knee OA. Their results showed a change in pain pressure threshold over the medial condyle with large effect size. Two major limitations in this study: first, not mentioning what type of physiotherapy was used as a treatment and second, not mentioning if the change in pain pressure threshold reached significant levels. The current study did not show any change in pain pressure threshold after 6 week of treatment, which contradicts the previous study. This can be attributed to several factors. The current study population had a pain pressure threshold of 6.46 N/Cm² before the treatment, which is higher than previous study's pre-treatment value of 5.47 N/Cm². Secondly, the type of treatment might be a key factor. The previous study used physiotherapy as a treatment, which might have included hydrotherapy or electrical therapy, which might have had a direct effect on the sensation. Thirdly, the time might play an important factor. Current study treatment period is 6 weeks and perhaps more time is needed to show a reduction in pain pressure threshold.

The current study showed that the pain pressure threshold in the medial condyle and the medial malleolus did not change significantly after the treatment within each group or between the groups after the treatment. Neither has the magnitude of changes reached significant levels between the groups. Therefore, the null hypothesis was accepted in terms of there being no significant difference in the pain pressure threshold between the groups.

Not finding a change in the pain pressure threshold after the treatment might indicate a good result. Since there is no change in the sensitivity of the patient to the pain (threshold) while the pain severity is reduced, this might indicate a real change in pain caused by load reduction rather than the sensitivity of pain change. Interestingly, the pain pressure threshold in the medial condyle is lower than in the medial malleolus in all the groups, which is consistent with the previous study (Mutlu & Ozdincler, 2015). This might indicate local sensitisation as previous research mentioned that hypersensitivity on the affected side might indicate local sensitisation while to the distal part might indicate central and peripheral sensitisation (Arendt-Nielsen & Yarnitsky, 2009). This local sensitisation might be a protective mechanism to reduce the damage on the joint. Mechanical stress, intra-osseous pressure, and synovial inflammation have been proposed to be local contributors to pain (Brandt et al., 2008; Dieppe & Lohmander, 2005; Kidd, 2006). Another

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possible explanation could be that the medial condyle has more pain receptors than the medial malleolus.

5.7.7   *Effect of the treatment on functional tests*

Null hypothesis: There is no significant difference in functional tests (40-metre fast-paced walk test, 30-second chair-stand test, a stair-climb test) after 6 weeks when using combined treatments (lateral wedge insole, simple knee sleeve) compared to individual treatment (lateral wedge insole or simple knee sleeve).

Functional tests have been identified as important outcomes among individuals with knee osteoarthritis to measure the subjects' ability to move around and perform daily activities (Bennell, Dobson, & Hinman, 2011; Dobson et al., 2013). The 40-metre fast-paced walk test, the 30-second chair-stand test, and the stair-climb test are activities that have been found to be affected in individuals with knee osteoarthrosis and have a good response as a measure of treatment efficacy (Bennell et al., 2011). One of the main aim of providing intervention is reduce pain and improve function. The data showed that combined treatment showed significant improvement in the stair-climb test and the 30-second chair-stand test compared to baseline, while the LWI group showed significant improvement only in the stair-climb test. The sleeve group did not show any significant change compared to baseline. When comparing the groups after the treatment, no significant difference was identified, nor did the magnitude of change reach a significant level. Therefore, the null hypothesis was accepted.

The improvement in functional tests with treatment could be a result of the pain reduction. As the pain reduced, the participants were more willing to load their joints to perform faster. For the 40-metre fast-paced walk test, no group showed significant improvement, and this could be because walking is easier than performing other tasks and needs more improvement in pain or is not as affected as other tasks. Perhaps more time was needed to show significant improvement since the improvement in the combined treatment nearly passed the measurement error.

Limited researches have investigated the effect of LWI or sleeve on the functional tests, which highlights the importance and strength of the current study (Baker et al., 2007; Barrios et al., 2009; Kirkley et al., 1999). Kirkley et al. (1999) investigated the effect of the valgus brace and the sleeve

on individuals with knee osteoarthritis against a control group. Treatment time was 6 months, and the results revealed no significant difference between the groups in a 30-second stair-climb test and a 6-minute walking test. The study did not mention if the results within the groups reached significant levels or not. Barrios et al. (2009) and Baker et al. (2007) compared the effect of the lateral wedge insole and the neutral wedge insole on clinical outcomes and functional tests. Baker et al. (2007) conducted a randomised crossover study for 6 weeks with 4 weeks washout. No significant difference was identified between the treatment groups in a 50-foot walking time test or a 5-minute chair-stand time test, and the authors did not mention if the LWI group showed significant difference compared to baselines. Barrios et al. (2009) conducted a randomised parallel group study for a year. The results showed significant improvement in a 6-minute walking-distance test and a stair negotiation test for both groups compared to baseline with no significant difference between the groups. One of the major limitations of both studies was not including the biomechanical effect of the treatment, which is considered the mechanism by which the LWI targets the loading.

It is hoped that, with functional improvement observed in two functional tests with combined treatment, patients are better able to perform in these activities of daily living. Intermittently, although there was no significant difference between the groups, the combined group showed significant improvement in two functional tests where the other groups did not. This shows a trend toward better improvement with combined treatment.

5.7.8   *PASE scale and other KOOS subscales (Appendix E)*

Symptoms, ADL, sports and recreation activity, and quality of life subscales of KOOS showed significant improvement in all the groups (combined group, LWI group, sleeve group) compared to their baselines. However, when comparing between the groups, no significant difference was identified after 6 weeks, nor did the magnitude of change show any significant difference. This improvement in KOOS subscales is thought to be caused by the pain reduction, which is caused by EKAM and/or muscle co-contraction reduction. Therefore, pain reduction is reflected in symptoms, ADL, sports activity, and quality of life.

Most previous studies of lateral wedge insoles used the WOMAC questionnaire, which consists of three subscales: pain, function, and symptoms. WOMAC subscales are included in KOOS, where

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WOMAC function equals ADL in KOOS, WOMAC pain is included in KOOS pain, and WOMAC stiffness is included in KOOS symptoms (Engelhart et al., 2012). KOOS was used by one study, and the aim of the study was to compare the effect of concurrent use of ankle support with lateral wedge insole (Segal et al., 2009). Therefore, the authors reported differences between the groups rather than within the groups. Other studies showed significant reduction in WOMAC function and/or WOMAC stiffness subscales with the use of lateral wedge insoles (Ashraf et al., 2014; Barrios et al., 2009; Fang et al., 2006). An improvement in WOMAC function and stiffness subscales with lateral wedge insole use was reported in two studies (Maillefert et al., 2001; Pham et al., 2004). However, this improvement was not mentioned if reached statistical significant level or not, and this might be because the main aim of both studies was to compare neutral insoles and lateral wedge insoles. Jones et al. (2013b) compared the effect of the valgus brace and the lateral wedge insole. The results showed significant improvement in pain and function with the lateral wedge insole and valgus brace compared to baseline, with no significant difference between the treatments. The stiffness subscale did not show any significant reduction, which could be attributed to the short treatment period (2 weeks) compared to the current study (6 weeks).

To the best of our knowledge, only one study that investigated the effect of the sleeve on WOMAC pain, function, and stiffness subscales could be identified (Kirkley et al., 1999). The study showed significant improvement in the function subscale compared to the control group, but not the stiffness subscale. Our results in ADL subscale are consistent with their function results. However, our function subscales, which include WOMAC stiffness, show significant improvement with sleeve use compared to baseline, which is in contrast to the previous study. This might be because KOOS symptoms subscale has the stiffness questions from KOOS and other questions which might be more sensitive to detect the changes. Other possible explanations are using a different sleeve and a different treatment period.

Interestingly, all the groups showed an improvement in PASE but not a significant one compared to baseline except the combined group. This is thought to be caused by the pain reduction. The higher increase in PASE for the combined group than the other groups and the significance compared to baseline might be explained by using two treatments: the lateral wedge insole, which reduces the EKAM and therefore reduces the pain, and the sleeve, which provides a sense of stability and reduces the muscle co-contraction and therefore reduces the pain. This improvement

in physical activity level would be seen as a positive effect of the combined treatment. From a public health perspective, this means that the participant is more active, which improves his or her well-being and general level of social interaction. This change might be more pronounced in future studies if more participants were included and the treatment duration was longer.

Interestingly, this increase in physical activity may cause hinder the reduction in pain via increasing the cumulative loading on the knee and therefore reduce the effect of combined treatment on pain. This also could be a contributing factor in not finding a significant difference between in pain after 6 weeks between the groups.

Bennell et al. (2011) investigated the effect of the lateral wedge insole and showed non-significant reduction in PASE after 12 months of treatment, which contradicts the current study, which shows a slight increase. One of the main disadvantages of the previous study was not including the biomechanical effect of the LWI (EKAM), which is considered the main mechanism to reduce the loading. Therefore, it is not known if the lateral wedge insole used reduced the EKAM. This is the first study that investigated the effect of combined treatment (lateral wedge insole and simple knee sleeve) on physical activity level. Therefore, comparison could not be made to the previous studies.

The clinical importance of increasing activity level lies in the high risk of other diseases, such as diabetes, obesity, and cardiovascular disease, with inactivity (Warburton et al., 2006). Therefore, reducing inactivity via combined treatment may lead to reduced risk of weight gain and cardiovascular disease and improved muscle power (Bravata et al., 2007; Warburton et al., 2006). Furthermore, increasing activity time is important for cartilage structure as a previous study found association between physical activity level and cartilage volume loss, where low-activity participants showed higher cartilage volume loss (Lin et al., 2013; Stehling et al., 2011). Interestingly, absence of the knee normal loading in cases of spinal cord injuries was found to cause cartilage atrophy (Vanwanseele, Eckstein, Knecht, Stüssi, & Spaepen, 2002).

5.7.9 *Secondary kinematic and kinetic outcomes (Appendix E)*

Treatments for knee osteoarthritis, if effective, may also result in changes in angles and moments (kinematics and kinetics) during walking. Thus, it is important in understanding the mechanism of

effect of the interventions to explore for differences in these variables. On the whole, there were only a minimal set of differences between-visits.

In spatiotemporal characteristics, the swing time showed significant reduction in the LWI group after immediate use of treatment and 6-week use compared to baseline, while stance time increased with immediate use of the combined treatment compared to baseline. A previous knee OA study showed significant reduction in stance time in the affected limb compared to the contralateral side (Mootanah et al., 2013). Therefore, this might indicate that the participants might be more willing to load their joints, which could be due to pain reduction caused by the reduction in loading.

Kinematics

The knee angle at initial contact in the sagittal plane showed a significant time effect with immediate and 6-week reduction compared to baseline. However, this reduction is not thought to be that important since the mean difference is small with both the immediate effect (0.38 degrees) and the 6-week effect (1.02 degrees) and did not exceed the measurement error (1.04 degrees).

Ankle frontal plane ROM showed time effect with significant increase with immediate and 6-week use of the treatment compared to baseline. Use of the lateral wedge insole could explain this finding by placing the foot in a more everted position. Maximum eversion angle showed significant time effect with significant increase with immediate use of treatment by mean difference of 1 degree. This amount of change is believed to be too small and barely exceeded the measurement error (0.90 degrees). When looking at each group individually, the LWI group showed significant increase in ankle ROM frontal plane with immediate and 6-week use of treatment compared to baseline, which can be explained by the use of the lateral wedge insole. However, one can ask why the combined group did not show the same although they also used the lateral wedge insole. LWI group ankle frontal plane ROM (12.51 degrees) was slightly lower than that of the combined group (13.75 degrees) and the sleeve group (13.34 degrees) at baseline, which provided more room for improvement. The ankle frontal plane ROM after 6 weeks of treatment was similar among the lateral wedge insole group (14.98 degrees), the combined group (14.42 degrees), and the sleeve group (14.16 degrees).

Finally, the centre of foot pressure showed significant lateral shifting in all phases with immediate use of the LWI and combined treatment compared to baseline and with the combined treatment after 6 weeks compared to baseline. This is the mechanism that is provided by the LWI to reduce the EKAM. Previous studies showed similar shifting in the centre of foot pressure, which is consistent with the current study (Hinman et al., 2012b; Jones et al., 2013c).

Kinetics

External knee extension moment in the combined group was higher at baseline than in the LWI group. This is believed not to have affected our experiment since this moment is not one of our main outcomes and is generated by initial contact. Furthermore, the combined group showed significant reduction in extension moment with immediate use of treatment compared to baseline and week 6. This could be explained by the reduction in speed in this group, which was nearly significant (p=0.055). Interestingly, this happened even though participants were given enough time to practice before starting the real trials, and it could be due to having two treatments, and the individuals felt that different to their normal walking (not comfortable). Most important, this was not observed after 6 weeks.

The second peak of GRF (push-off|) showed a significant increase in the combined and sleeve groups with immediate and 6-week use of the treatment and in the LWI group with immediate use of the treatment. A previous study showed similar results in terms of significant increase in loading and push-off GRF with brace use (Richards, Sanchez-Ballester, Jones, Darke, & Livingstone, 2005). These results possibly reflect an improvement in participants' ability to push off using the affected leg. These increases in push-up force could be due to the biomechanical changes (reduction in loading), the physiological changes (reduction in muscle co-contraction), and the clinical changes (pain reduction).

For the same reason (reduction in speed with immediate use of the combined treatment), the combined group showed a significant reduction in ankle dorsiflexion moment with immediate use of treatment but not after 6 weeks. In addition, ankle plantar flexion moment showed significant change in the combined group, which could not be identified with any adjustment. Therefore, this change is too small to be identified, and the reduction in speed could be the cause.

Lateral wedge insole group showed significant increase in the ankle eversion moment after 6 weeks compared to the baseline and shifting the centre of pressure more laterally is believed to be responsible for this increase. The combined group did not show this change although they used the LWI, which can be explained by the slightly lower ankle eversion moment in the LWI group than in the combined group at baseline, which provided more room for increase in the LWI group.

5.7.10 Limitations of the study

As with any study, this one had limitations. First, the assessor and the participants were not blind to the type of treatment used in the gait lab. However, to reduce the bias, the participants were told that all types of treatment are effective with knee osteoarthritis. Gait data was collected with an automatic measurement instrument, so the bias was low in terms of the investigator. The questionnaires for the study were collected without comment to the participants and were analysed at the end of the study without knowledge of the biomechanical data.

This study used parallel design in which the participants were randomly allocated to one type of treatment. The participants then followed the treatment, and their responses to the allocated treatment were monitored. At the end of the study, the groups were compared to investigate the effect of the treatments. This study design is commonly used in clinical trials to compare two or three types of treatment without any fear of learning effect or carryover effect, which may be experienced in crossover design. Therefore, to conduct a crossover study, longer periods between treatments are needed. These are called washout periods, and they reduce the carryover effect. The randomisation is considered the most important aspect to reduce the risk of bias and ensure the results are accurate with parallel group design. The parallel design was chosen over crossover design because parallel design does not require an equal number of participants in each group, has no learning or carryover effects, and requires shorter periods of time than crossover design. The researcher has limited time since this study is a part of his thesis.

This study has a low sample size, and this could be a cause of accepting the null hypothesis as with pain. However, the researcher included all possible participants who met the inclusion and exclusion criteria in the limited study time. Observed power was calculated with SPPS for pain. The observed power was 0.49 for the interaction effect, which indicates low power. Power calculation was conducted via G-power to investigate how many participants were needed in each

group to find statistically significant differences interaction effect with an 80% power and an alpha level equal to 0.05 (Prajapati, Dunne, & Armstrong, 2010). The results revealed that 59 participants were needed to achieve 80% power, which was rounded to 60, with 20 participants in each group. More males than females were included in this study although both genders were invited equally.

The duration of the treatment in the current study was 6 weeks, and it is likely that better results might be obtained in a longer period of time. The researcher measured the immediate biomechanical effect of the treatment and the effect after 6 weeks, which allowed a comparison to be made. However, clinical outcomes were only measured at baseline and after 6 weeks, and future studies are needed to collect data in between for better understanding of the results. Other outcome measurements were not included in the study, such as structural progression of the OA, because of limited time and resources. More than 6 weeks are needed to measure structural changes unless expensive MRI is used. Interestingly, when evaluating the role of a patellofemoral brace it was shown that this reduced patellofemoral bone marrow lesion size and pain after 6 weeks compared to control group with no treatment (Callaghan et al., 2015). However, to conduct such trial requires the use of MRI which is costly.

Lastly, not including a control group with no treatment is a limitation to current study since all groups showed significant improvement in pain. Including such group will allow to more confidence that changes are caused by treatment and these changes are not observed in the control group. However, since the aim from combining the LWI and sleeve was to provide further reduction in pain compared to LWI and the limited time we though that including control group is not important.

5.8 Conclusion

The aims of this study were to determine whether combining the lateral wedge insole with the knee sleeve provides greater improvement in pain than individual treatment (knee sleeve or lateral wedge insole) and whether these improvements are concurrent with knee loading reduction and muscle co-contraction reduction among individuals with medial knee OA. The literature review identified that while many studies have shown the biomechanical effects of the lateral wedge insole and the pain effect compared to baseline, the clinical effect (pain) was not significantly different than that of the control group (neutral insole). Combing the lateral wedge insole with the valgus brace showed better results than individual treatment. However, previous studies have showed a

low compliance with the valgus brace. Therefore, the simple knee sleeve could be an attractive solution if combined with the lateral wedge insole. No previous studies have investigated the effect of combining the knee sleeve and the lateral wedge insole on biomechanics, pain, muscle co-contraction, and clinical outcomes in one study. It was hypothesised that combining the lateral wedge insole with the simple knee sleeve would have an effect on knee loading, pain, muscle co-contraction, and clinical outcomes.

The results of this study found that combining the lateral wedge insole with the simple knee sleeve is not superior in pain reduction to single treatment (simple knee sleeve or lateral wedge insole). However, there is a trend toward better improvement in pain and clinical outcomes as the combined treatment reduced EKAM by insole and muscle co-contraction by knee sleeve.

The low statistical power might have caused accepting the overall null hypothesis in this study and thus future studies should include more subjects to test this hypothesis. Furthermore, structural changes need to be assessed in future studies to identify if the combined treatment (lateral wedge insole and knee sleeve) can reduce knee OA progression.

It is also unknown if other types of sleeve might provide better clinical outcomes than the sleeve used in the current study. Therefore, future studies might investigate this. However, combining exercise with the simple knee sleeve and LWI might be an attractive and superior treatment to exercise alone as previous studies showed a reduction in co-contraction and pain with exercise but were not effective on knee loading (EKAM). In conclusion, the results of this study do give rise to a future combined study looking at simple and effective combined treatments for medial knee osteoarthritis.

Chapter 6: General conclusion and future studies

6.1 Summary

The aim of this thesis was to determine the effectiveness of combined treatment (LWI and simple knee sleeve) on biomechanical and clinical outcomes and compare it to each treatment individually. In this thesis, the primary outcome measures of EKAM, pain and muscle co-contraction were assessed alongside other clinical outcomes (i.e. balance, functional tests).

The main driver for the current thesis is based on my own clinical and personal experience. As I am working as a lecturer and physiotherapist in Saudi Arabia, the standard and the core physiotherapy treatment for knee OA is exercises according to the Ministry of Health' guideline in Saudi Arabia. My mother was diagnosed with knee OA 10 years ago and is suffering from it. This has motivated me to read more about the topic in order to deliver optimal treatment for such sufferers. In addition to physiotherapy treatment, analgesic medication is provided to patients to reduce pain, which may lead to increased loading and place the patient at higher risk of progression. Interestingly, previous research has shown that pathological loading is a key factor in the progression of knee OA. Therefore, targeting loading and pain may help reduce knee OA progression and improve physical activity levels. If it were possible to slow the progression, the cost of OA would be reduced, and if we were able to improve physical activity levels, the risk of complication and death due to inactivity would be reduced.

Previous studies have shown that using biomechanical treatment such as LWI in individuals with knee OA reduces pain and joint loading (EKAM) significantly compared to baseline. However, pain reduction was not superior with LWI compared to the control treatment (neutral insole), which do not target EKAM. This may affect patient compliance and the treatment decisions of health practitioners, as they are driven by pain more than by mechanics. Reduction in pain and loading may be possible if LWI are combined with another treatment. This idea is in the line with NICE guidelines, which advocates the use of combined treatment, stating that patients naturally use combined treatments in their journey, and there is a need for more trials to investigate the effect of combined treatment (NICE, 2014). Previous studies have supported this idea, showing better effects for combined treatment (LWI + valgus brace) than for single treatment (Al-Zahrani et al.,

2013b; Moyer et al., 2013). However, compliance with the valgus brace is low (Barnes, Cawley, & Hederman, 2002; Jones et al., 2013; Wilson et al., 2011), and there is no clinical benefit with no use. A more straightforward and easier option is a simple knee sleeve, which has been shown to reduce knee pain (Cudejko et al., 2018b) and muscle co-contraction (Collins et al., 2011).. Therefore, this thesis aimed to investigate the combined effect of LWI and a simple knee sleeve and compare this to the effect of each treatment individually among healthy individuals (biomechanical outcomes) and individuals with medial knee OA (biomechanical and clinical outcomes).

To test the effect of any treatment on the outcome, the outcomes that are chosen should be reliable and sensitive to detect the change. Therefore, in chapter three, test re-test reliability studies were undertaken. The first study was to investigate reliability on healthy individuals, while the second one was on individuals with knee OA. The results revealed that most of the clinical and biomechanical outcomes have excellent reliability with low SEM. This made it possible to take the outcomes with good reliability forward to the next step to test the hypotheses. Furthermore, this allowed the researcher to make sure that changes observed later had already passed the measurement error. In addition to the reliability study in chapter three, it was necessary to choose the right LWI and sleeve based on selection criteria. The literature on LWI enabled the researcher to select the right LWI. However, there is limited research on knee sleeves, which motivated the design of clinical selection criteria based on a clinical overview to improve compliance. Three sleeves were selected and the sleeve that provided the best comfort and ease of use was chosen as the treatment in the current thesis.

Before applying this treatment to individuals with knee OA, it was necessary to investigate the effect on healthy subjects (chapter four). This was as a concept prove study and to make sure not to place individuals with knee OA at any risk. Furthermore, there is limited knowledge about the effect of sleeves on EKAM, which highlights the importance of this study. Nineteen healthy participants were recruited to investigate the immediate effects of the four treatment conditions (knee sleeve, LWI, simple knee sleeve and LWI, control) in a randomised crossover study. The results of this study showed that LWI reduce EKAM, while knee sleeves were able to reduce the frontal plane knee ROM. Both effects were observed in the combined group, which might provide support and help reduce joint loading in individuals with knee OA.

In chapter five, following on from the previous study of healthy subjects, the effect of combining a simple knee sleeve with LWI was investigated in individuals with medial compartment OA. Thirty-four participants affected by medial knee OA were recruited and randomised into 3 groups, with 11 in the combined group, 11 in the sleeve group, and 12 in the LWI group. Each participant was assessed at baseline without the treatment, immediately after use of the treatment at baseline and after 6 weeks. The results showed no significant difference between the groups at baseline, which allowed a valid comparison to be conducted. The LWI group showed a significantly higher magnitude of change in EKAM than the sleeve group. The sleeve group showed a significantly higher magnitude of change in muscle co-contraction than the LWI group. The combined group showed both of the effects that were observed in the LWI and sleeve groups (EKAM and muscle co-contraction reduction). In the combined treatment group, the pain was reduced more than in the other groups (LWI, sleeve), which is thought to be due to combining the effect of both treatments, although the difference was not statistically significant. Most other outcomes (functional tests) followed the pain outcome by showing a better trend for the combined treatment group.

This is the first study of its kind in Saudi Arabia. It highlights the need for the Ministry of Health to adopt biomechanical treatments such as LWI and knee sleeves to treat knee OA. This recommendation is further supported considering the low cost of both treatments and the low likelihood of adverse events. However, the main challenge in promoting such treatment is to improve the awareness of physiotherapists and clinical practitioners about biomechanical treatments. This can be achieved by conducting workshops and courses to improve physiotherapists' and clinical practitioners' understanding of biomechanical treatments and their mechanisms in treating individuals with knee OA.

This study data will allow a multicentre trial with a larger sample and including a structural change outcome (i.e. MRI) to be conducted by the Ministry of Health in Saudi Arabia. Perhaps the next step is conducting a study that investigates the effect of combined treatment (LWI and simple knee sleeve) with physiotherapy treatment and compares it to physiotherapy treatment alone. This may help in further reducing knee OA pain by targeting it from different prospective, improving muscle strength, reducing pathological loading and improving physical activity levels. All of these factors may in turn have a high benefit for patients by reducing the progression of the disease and the effects of physical inactivity, which will lead to reducing expenditures on OA.

6.2 Thesis novelty and strength

No previous study has investigated the effect of combining LWI and a simple knee sleeve on biomechanical and clinical outcomes among individuals with knee OA. Thus, this is the first study to investigate the effect of combined treatment on the kinematics, kinetics and muscle co-contraction in individuals with medial knee OA. Interestingly, this is the first study to investigate the effect of LWI in muscle co-contraction amongst individuals with knee OA. Moreover, this is the first study to compare the effects of LWI, a knee sleeve and combined treatment (LWI, simple knee sleeve) in individuals with knee OA. Conducting this trial is important for clinical practice because direct comparisons help practitioners identify the best treatment.

This is the first study to investigate the effect of combined treatment (LWI and simple knee sleeve) and single treatment (LWI or simple knee sleeve) on dynamic balance (excursion balance test), functional tests and pain pressure threshold in individuals with medial knee OA and to compare combined treatment to each treatment individually.

This is the first study to assess the effect of combined treatment (LWI and simple knee sleeve) in healthy individuals. Therefore, this is the first study to investigate four treatment conditions in kinematic, kinetics and muscle co-contraction while walking in a randomised crossover study. This involves EKAM, KAAI, KFM, muscle co-contraction, and knee sagittal and frontal angles. This is also the first study to investigate the effect of LWI and sleeves in muscle co-contraction among healthy individuals.

This is the first study that has examined the reliability of dynamic balance via the modified star excursion test among individuals with medial knee OA. Furthermore, the reliability of muscle co-contraction divided into three phases has not been previously investigated in individuals with medial knee OA. This will help researchers in future studies determine the reliability of these measurement and the measurement error.

The outcome measures in the current thesis were selected based on the hypotheses. For example, EKAM was selected to reflect internal loading, as previous studies have shown that EKAM is correlated with loading and is a valid and reliable measurement for joint loading (Kutzner et al., 2013; Schipplein & Andriacchi, 1991). Furthermore, muscle co-contraction has recently been

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found to correlate with loading (Brandon et al., 2014; Sritharan et al., 2017; Winby et al., 2013) and may cause higher loading even if EKAM remains the same (Lu et al., 1997; Trepczynski et al., 2014). Moreover, Walter et al. (2010) highlighted that a reduction in EKAM may not guarantee a reduction in loading due to the increase in the knee flexion moment. This highlights the importance of combining several outcomes in the same study as EKAM, muscle co-contraction and the knee flexion moment, as it is important that a reduction in one outcome that reflects internal loading is not offset by an increase in another one. This underscores the strength of the current thesis for gaining a full picture and a better view of what is going on with treatment. This thesis will therefore add much knowledge to the current literature concerning healthy individuals and individuals with knee OA, which can help to inform practice for clinicians and experimenters.

6.3 Future studies

In chapters four and five, the effect of LWI was investigated in healthy individuals and in individuals with knee OA while walking. However, to gain a better picture of the effect of LWI, one should look across activities rather than at only one activity to represent loading in everyday activities such as ascending and descending and going from sitting to standing. Stair negotiation is a frequent and common activity that is physiologically and biomechanically more challenging than level walking (Andriacchi, Andersson, Fermier, Stern, & Galante, 1980; Nadeau, McFadyen, & Malouin, 2003). In 2008, a study characterised knee loading across different activities (walking, ascending, descending, golf swings, sit to stand and stand to sit) and showed that ascending and descending stairs yields the highest knee compression force compared to other activities (Mündermann et al., 2008b). This higher loading in the stair negotiation activity might explain the result of a more recent study that showed that knee pain is more likely to first appear in the stair negotiation activity among individuals with knee OA or at high risk of knee OA (Hensor, Dube, Kingsbury, Tennant, & Conaghan, 2015). Trepczynski et al. (2014) stated that stair negotiation showed the highest medial compression force across activities, and it might offer increased sensitivity for the differential treatment effect.

The study population in the current thesis were mostly male; only three females were included. This was due to regulations for male practitioners treating females in Saudi Arabia. A previous meta-analysis study showed that females have a higher prevalence, incidence and severity of knee

OA than males do (Srikanth et al., 2005b). Furthermore, recent studies have shown that females with knee OA are more prone to central sensitisation than males are (Bartley et al., 2016; Dell'Isola & Steultjens, 2018). The cause of gender differences in OA is not fully understood and could be attributed to hormonal, anatomical and genetic differences (Hame & Alexander, 2013). Interestingly, previous studies have shown contradicting results regarding EKAM, with one study showing no gender differences in EKAM among individuals with knee OA (McKean et al., 2007), while another study did show gender differences (Sims et al., 2009). However, the most important finding is that LWI is expected to reduce the EKAM with no difference between gender, which was shown in Chapman et al.'s (2015) study. While it was out of my control, including mostly males does affect the external validity of the study. The generalisability of the current thesis is therefore reduced, and the current results are more applicable to males. Future studies should include an equal or slightly higher number of females to males; Arthritis Research (2012) has shown that a slightly higher number of females are affected with knee OA compared to males in the UK. This will help improve the generalisability and applicability of the results to the general population.

In the main study (OA study), the combined treatment (LWI and knee sleeve) and the individual treatments were conducted over 6 weeks, and it is not known if a longer period would provide better results. Therefore, future studies should investigate the effects of longer intervention periods to investigate whether pain and muscle co-contraction decrease further over time.

In the study of healthy individuals and the knee OA study, the effect of a specific knee sleeve was based on a clinical selection criterion focusing on compliance. However, based on previous literature on knee sleeves, several mechanisms can be highlighted that may help in pain reduction (improve joint proprioception, reduce muscle co-contraction, improve joint stability and self-confidence, joint compression) (Figure 3-5). Therefore, to gain more pain reduction and functional improvement these mechanisms should be the focus of the selection criteria in future studies. Moreover, it is not known if other types of sleeve provide different results. Therefore, future studies should compare the effects of different types of sleeves on biomechanical and clinical outcomes.

Interestingly, as stated earlier, several mechanisms could be attributed to pain reduction and improvement of physical function with sleeve use in knee OA individuals. Therefore, it is important for future studies to investigate the sleeve design and what can be changed to provide more pain reduction and more functional improvement. For example, proprioception could be improved by adding textured textile to the sleeve, and the effect could be measured by measuring joint position sense and movement sense. Other aspects of sleeve design that might help improve joint stability, muscle co-contraction and joint compression should be investigated, including materials and tightness of the sleeve. A study with a randomised crossover design should investigate this. This study design is superior to other designs because it controls between subject factors that might influence the results. The study should include outcomes such as muscle activity, joint ROM and a subjective questionnaire to measure stability and compression. One of the most important aspects of such a design is controlling for the carry-over effect by providing a sufficient wash-out period.

One of the most important factors for physiotherapists is patient compliance with treatment because if patients are not using a treatment, there is no point in providing it. Sleeve design may play a key role in patient compliance and should be a focus of future studies. Based on the current study and previous experience, several factors can be pointed out, such as sleeve materials, ease of use, sleeve weight and sleeve thickness. The ideal sleeve design may be one that wraps around the joint, as this easier for knee OA patients than slip-on sleeves with soft materials and rubber edges to prevent the sleeve from moving down during activity. In addition, the sleeve should be light and thin so it is easy to wear under clothes like jeans, and it should not be too long, as a previous study showed that a long sleeve has less compliance that a short one (Keyaki & Toda, 2010).

Balance is controlled by the integration of sensory and motor neuromuscular components, and proprioception is among these factors and was measured in the current thesis. One of the main limitations of the current study is that the direct effect of treatment on proprioception via joint position sense and motion sense was not measured. It might be that the contribution of knee proprioception has a small effect on balance and therefore improvement in proprioception cannot be seen in dynamic balance unless a high change occurs. In addition, it might be that change in proprioception measured directly (motion sense, joint position sense) has better clinical value and

correlates with pain more than dynamic balance. Future studies should investigate the direct effect of treatment on proprioception.

In experimental studies, the success of the treatment may depend on the treatment itself or on the selected population. Several studies have suggested that OA is a group of disorders with a similar end-point result (Dell'Isola, Allan, Smith, Marreiros, & Steultjens, 2016; Dell'Isola & Steultjens, 2018; Paul A. Dieppe & Lohmander, 2005). These groups of disorders are called *phenotypes* and can be defined as the "observable properties of an organism" (Rieger, Michaeli, & Green, 1991). A recent systematic review identified and summarised previous knee OA study phenotypes (Dell'Isola et al., 2016). The study concluded that there are 6 phenotypes: chronic pain, inflammatory, metabolic, bone and cartilage mechanism, minimal joint disease and mechanical overload. Therefore, in order to optimise the treatment efficacy, it is necessary to tailor the treatment to each phenotype, which is consistent with the recommendation in the NICE guidelines (Driban, Sitler, Barbe, & Balasubramanian, 2010; Felson, 2010; Hinman & Crossley, 2007). The applicability of these phenotypes in the field was tested in a recent study, and the results showed that 84% of the patients were successfully allocated to one or more than one phenotype (complex OA) (Dell'Isola & Steultjens, 2018). Interestingly, in the chronic phenotype group, more females were allocated than males compared to other groups, and the widespread pain in this group indicates sensitivity and central sensitisation problems. Therefore, the success of the treatment may rely on the phenotype, and future studies should address these criteria in their participant selection to see if better improvement can be achieved.

Current knee OA studies included the PASE questionnaire as a measurement for physical activity. Although physical activity was not neglected and was measured, more objective outcomes (i.e. accelerometers) might give better results. The questionnaire results might have been affected by patient recall, which could have affected the overall findings. This is less likely to be the case in the current study, as only the combined treatment group showed significant improvement in physical activity levels. However, using an activity monitor would help calculate cumulative loading, which is thought to increase the risk of knee OA (Coggon et al., 2000; Vignon et al., 2006). This significant increase in physical activity in combined group could be a cause of not finding significant differences in pain between the groups. The basic mechanism behind this is that as pain decreases, participants become more active and load their joints more, which increases

their pain level. Therefore, one can assume if participants' activity level is sustained, more reduction in pain would be seen.

The current study used a parallel group design; however, this study design could be improved by using a crossover design, which would provide further control for between-subject variability. However, such a design needs to be carefully planned, and a suitable washout period is needed to prevent any carryover effect. It is recommended that future studies implement such a design to gain stronger evidence.

Finally, the effect of combined treatment on structural changes has not been measured in the current study. The aim behind targeting joint loading (EKAM, muscle co-contraction) is to reduce the progression of the disease, and future studies should include structural changes such as bone marrow lesions as outcomes in a long-term study. If the combined treatment in the current study indeed reduces loading, a change in a bone marrow lesion would be seen.

In summary, regarding the combined treatment, this study is only the beginning in this area. Future studies are needed to further investigate the effect of combined treatment longitudinally with a larger sample. The next study could be a randomised clinical trial to investigate the effect of combined treatment on individuals' treatment and control treatment (no treatment). While this study most importantly assesses clinical findings, the mechanism of treatment should also be assessed biomechanically, structurally (MRI changes, e.g., bone marrow lesions) and determine changes in physical behaviour patterns (activity monitor).

References:

Abdallah, A. A., & Radwan, A. Y. (2011). Biomechanical changes accompanying unilateral and bilateral use of laterally wedged insoles with medial arch supports in patients with medial knee osteoarthritis. *Clinical Biomechanics*, *26*(7), 783–789.

Ahlbäck, S. (1968). Osteoarthrosis of the knee. A radiographic investigation. *Acta Radiologica: Diagnosis*, Suppl 277:7-72.

Ahlberg, A., Linder, B., & Binhemd, T. A. (1990). Osteoarthritis of the hip and knee in Saudi Arabia. *International Orthopaedics*, *14*(2), 29–30.

Al-Arfaj, A. S., & Al-Boukai, A. A. (2002). Prevalence of radiographic knee osteoarthritis in Saudi Arabia. *Clinical Rheumatology*, *21*(2), 142–145.

Al-Arfaj, A. S., Alballa, S. R., Al-Saleh, S. S., Al-Dalaan, A. M., Bahabry, S. a., Mousa, M. a., & Al-Sekeit, M. a. (2003). Knee osteoarthritis in Al-Qaseem, Saudi Arabia. *Saudi Medical Journal*, *24*(3), 291–293.

Al-khlaifat, L. (2012). *Toward improvement efficay of exercise programmes in the Knee osteoarthritis*. (Unpublished PhD thesis), University of Salford, Salford.

Al-Khlaifat, L., Herrington, L. C., Hammond, A., Tyson, S. F., & Jones, R. K. (2016). The effectiveness of an exercise programme on knee loading, muscle co-contraction, and pain in patients with medial knee osteoarthritis: A pilot study. *Knee*, *23*(1), 63–69.

Al-Zahrani, K. S., & Bakheit, A. M. O. (2002). A study of the gait characteristics of patients with chronic osteoarthritis of the knee. *Disability and Rehabilitation*, *24*(5), 275–80.

Al-Zahrani, Y. (2014). *Effectiveness of a valgus knee brace on biomechanical and clinical outcomes during walking and stair climbing in individuals with knee osteoarthritis.* (PhD thesis), University of Salford, Salford. Retrived from http://usir.salford.ac.uk/32833/1/Yousef_Al-zahrani_Thesis_%28Sep-2014%29.pdf

Al-Zahrani, Y., Herrington, L., Liu, A. M., Hutchins, S. W., & Jones, R. K. (2013). Comparison of isolated and combined orthotic devices on knee loading whilst ascending stairs in patients with medial knee osteoarthritis. *Osteoarthritis and Cartilage*, *21*(APRIL), S105.

Alentorn-Geli, E., Samuelsson, K., Musahl, V., Green, C. L., Bhandari, M., & Karlsson, J. (2017). The Association of Recreational and Competitive Running With Hip and Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Journal of Orthopaedic & Sports Physical Therapy*, *47*(6), 373–390.

Alliston, T., Hernandez, C. J., Findlay, D. M., Felson, D. T., & Kennedy, O. D. (2018). Bone marrow lesions in osteoarthritis: What lies beneath. *Journal of Orthopaedic Research. 36*(7), 1818-1825.

Alnahdi, A. H., Zeni, J. a., & Snyder-Mackler, L. (2012). Muscle Impairments in Patients With Knee Osteoarthritis. *Sports Health*, *4*(4), 284–292.

Alsancak, S. (2012). Long term effects of laterally wedged insoles on knee frontal plane biomechanics in patients with medial knee osteoarthritis. *Fizyoterapi Rehabilitasyon*, *23*(3), 111–118.

Alshawabka, A. Z., Liu, A., Tyson, S. F., & Jones, R. K. (2014). The use of a lateral wedge insole to reduce knee loading when ascending and descending stairs in medial knee osteoarthritis patients. *Clinical Biomechanics*, *29*(6), 650–656.

Altman, D., & Bland, J. (1995). Statistics notes: the normal distribution. *BMJ: British Medical Journal*, *310*(6975), 298.

Altman, R. D., Abadie, E., Avouac, B., Bouvenot, G., Branco, J., Bruyere, O., … Reginster, J.-Y. (2005). Total joint replacement of hip or knee as an outcome measure for structure modifying trials in osteoarthritis. *Osteoarthritis and Cartilage*, *13*(1), 13–19.

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., … Wolfe, F. (1986). Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. *Arthritis and Rheumatism*, *29*(8), 1039–1049.

Amin, S., Luepongsak, N., McGibbon, C. A., LaValley, M. P., Krebs, D. E., & Felson, D. T. (2004). Knee adduction moment and development of chronic knee pain in elders. *Arthritis Care & Research*, *51*(3), 371–376.

Anderson, J. J., & Felson, D. T. (1988). Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. *American Journal of Epidemiology*, *128*(1), 179–189.

Andrews, M., Noyes, F. R., Hewett, T. E., & Andriacchi, T. P. (1996). Lower limb alignment and foot angle are related to stance phase knee adduction in normal subjects: A critical analysis of the reliability of gait analysis data. *Journal of Orthopaedic Research*, *14*(2), 289–295.

Andriacchi, T. P. (1994). Dynamics of knee malalignment. *The Orthopedic Clinics of North America*, *25*(3), 395–403.

Andriacchi, T. P., & Mündermann, A. (2006). The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. *Current Opinion in Rheumatology*, *18*(5), 514–518.

Andriacchi, T. P., Andersson, G. B., Fermier, R. W., Stern, D., & Galante, J. O. (1980). A study of lower-limb mechanics during stair-climbing. *The Journal of Bone and Joint Surgery.*, *62*(5), 749–757.

Andriacchi, T. P., Andersson, G. B., Ortengren, R., & Mikosz, R. P. (1984). A study of factors influencing muscle activity about the knee joint. *Journal of Orthopaedic Research*, *1*(3), 266–275.

Andriacchi, T. P., Ogle, J. A., & Galante, J. O. (1977). Walking speed as a basis for normal and abnormal gait measurements. *Journal of Biomechanics*, *10*(4), 261–268.

Aoki, O., Tsumura, N., Kimura, A., Okuyama, S., Takikawa, S., & Hirata, S. (2009). Home Stretching Exercise is Effective for Improving Knee Range of Motion and Gait in Patients with Knee Osteoarthritis. *Journal of Physical Therapy Science*, *21*(2), 113–119.

AposTherapy. Treatment plans and pricing guide. Retrieved 8/10/2018 from https://www.apostherapy.co.uk/pricing-guide/

Arazpour, M., Bani, M. A., Maleki, M., Ghomshe, F. T., Kashani, R. V., & Hutchins, S. W. (2013). Comparison of the efficacy of laterally wedged insoles and bespoke unloader knee orthoses in treating medial compartment knee osteoarthritis. *Prosthetics and Orthotics International*, *37*(1),

50–57.

Arden, N., & Nevitt, M. C. (2006). Osteoarthritis: epidemiology. *Best Practice and Research. Clinical Rheumatology*, *20*(1), 3–25.

Arendt-Nielsen, L., & Yarnitsky, D. (2009). Experimental and Clinical Applications of Quantitative Sensory Testing Applied to Skin, Muscles and Viscera. *The Journal of Pain*, *10*(6), 556–572.

Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581.

Arnold, J. B., Wong, D. X., Jones, R. K., Hill, C. L., & Thewlis, D. (2016). Lateral Wedge Insoles for Reducing Biomechanical Risk Factors for Medial Knee Osteoarthritis Progression: A Systematic Review and Meta-Analysis. *Arthritis Care & Research*, *68*(7), 936–951.

Arthritis research. Osteoarthritis in general practice, (2012). Retrieved from https://www.arthritisresearchuk.org/~/media/Files/Policy%20files/Policy%20pages%20files/Osteoarthritis%20in%20general%20practice%20%20July%202013%20%20Arthritis%20Research%20UK%20PDF%20421%20MB.ashx

Asay, J. L., Boyer, K. A., & Andriacchi, T. P. (2013). Repeatability of gait analysis for measuring knee osteoarthritis pain in patients with severe chronic pain. *Journal of Orthopaedic Research*, *31*(7), 1007–1012.

Ashraf, A., Zarei, F., Hadianfard, M. J., Kazemi, B., Mohammadi, S., Naseri, M., … Sayadi, M. (2014). Comparison the effect of lateral wedge insole and acupuncture in medial compartment knee osteoarthritis: A randomized controlled trial. *Knee*, *21*(2), 439–444.

ASICS Corporation. GEL-MELBOURNE OA. Retrieved 8/10/2018 from https://www.asics.com/au/en-au/gel-melbourne-oa-%28d%29/p/0010125149.0192

Astephen, J. L., & Deluzio, K. J. (2005). Changes in frontal plane dynamics and the loading response phase of the gait cycle are characteristic of severe knee osteoarthritis application of a multidimensional analysis technique. *Clinical Biomechanics*, *20*(2), 209–217.

Astephen, J. L., Deluzio, K. J., Caldwell, G. E., & Dunbar, M. J. (2008). Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. *Journal of Orthopaedic Research*, *26*(3), 332–341.

Astephen, J. L., Deluzio, K. J., Caldwell, G. E., Dunbar, M. J., & Hubley-Kozey, C. L. (2008). Gait and neuromuscular pattern changes are associated with differences in knee osteoarthritis severity levels. *Journal of Biomechanics*, *41*(4), 868–876.

Atkinson, G., & Nevill, A. M. (1998). Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. *Sports Medicine*, *26*(4), 217–238.

Augustsson, J., & Thomeé, R. (2000). Ability of closed and open kinetic chain tests of muscular strength to assess functional performance. *Scandinavian Journal of Medicine & Science in Sports*, *10*(3), 164–168.

Aujla, R. S., & Esler, C. N. (2017). Total Knee Arthroplasty for Osteoarthritis in Patients Less Than Fifty-Five Years of Age: A Systematic Review. *The Journal of Arthroplasty*, *32*(8), 2598–

2603.

Baker, K. R (2006). Gait analysis methods in rehabilitation. *Journal of Neuroengineering and Rehabilitation*, *3*(1), 3–4.

Baker, K. R., Nelson, M. E., Felson, D. T., Layne, J. E., Sarno, R., & Roubenoff, R. (2001). The efficacy of home based progressive strength training in older adults with knee osteoarthritis: a randomized controlled trial. *The Journal of Rheumatology*, *28*(7), 1655–1665.

Baker, K. R., Xu, L., Zhang, Y., Nevitt, M., Niu, J., Aliabadi, P., … Felson, D. (2004). Quadriceps weakness and its relationship to tibiofemoral and patellofemoral knee osteoarthritis in Chinese: the Beijing osteoarthritis study. *Arthritis and Rheumatism*, *50*(6), 1815–1821.

Baker, K., Goggins, J., Xie, H., Szumowski, K., LaValley, M., Hunter, D. J., & Felson, D. T. (2007). A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. *Arthritis and Rheumatism*, *56*(4), 1198–1203.

Baliunas, A. J., Hurwitz, D. E., Ryals, a. B., Karrar, A., Case, J. P., Block, J. a., & Andriacchi, T. P. (2002). Increased knee joint loads during walking are present in subjects with knee osteoarthritis. *Osteoarthritis and Cartilage*, *10*(7), 573–579.

Barnes, C., Cawley, P., & Hederman, B. (2002). Effect of CounterForce brace on symptomatic relief in a group of patients with symptomatic unicompartmental osteoarthritis: a prospective 2-year investigation.. *American Journal of Orthopedics*, *31*(7), 396–401.

Barrack, R. L., Skinner, H. B., Cook, S. D., & Haddad, R. J. (1983). Effect of articular disease and total knee arthroplasty on knee joint-position sense. *Journal of Neurophysiology*, *50*(3), 684–687.

Barrett, D. S., Cobb, A. G., & Bentley, G. (1991). Joint proprioception in normal, osteoarthritic and replaced knees. *The Journal of Bone and Joint Surgery*, *73*(1), 53–56.

Barrios, J. A., Crenshaw, J. R., Royer, T. D., & Davis, I. S. (2009). Walking shoes and laterally wedged orthoses in the clinical management of medial tibiofemoral osteoarthritis: A one-year prospective controlled trial. *Knee*, *16*(2), 136–142.

Barrios, J. A., Higginson, J. S., Royer, T. D., & Davis, I. S. (2009). Static and dynamic correlates of the knee adduction moment in healthy knees ranging from normal to varus-aligned. *Clinical Biomechanics*, *24*(10), 850–854.

Bartel, D. L. (1992). Unicompartmental arthritis: biomechanics and treatment alternatives. *Instructional Course Lectures*, *41*, 73–76.

Bartholdy Y Z, C., Nielsen, S. M., Warming, S., Hunter, D. J., Christensen Y K, R., & Henriksen, M. (2018). Poor replicability of recommended exercise interventions for knee osteoarthritis: a descriptive analysis of evidence informing current guidelines and recommendations. *Osteoarthritis and Cartilage, S1063-4584*(18) 31470-31475.

Bartley, E. J., King, C. D., Sibille, K. T., Cruz-Almeida, Y., Riley, J. L., Glover, T. L., … Fillingim, R. B. (2016). Enhanced Pain Sensitivity among Individuals with Symptomatic Knee Osteoarthritis: Potential Sex Differences in Central Sensitization. *Arthritis Care and Research, 68*(4), 472–480.

Bateni, H., & Maki, B. E. (2005). Assistive devices for balance and mobility: benefits, demands, and adverse consequences. *Archives of Physical Medicine and Rehabilitation*, *86*(1), 134–145.

Baumgartner, T. A. (1989). *Norm-referenced measurement: reliability. Measurement Concepts in Physical Education and Exercise Science*. Champain, Illinois: Human Kinetics.

Bayramoglu, M., Toprak, R., & Sozay, S. (2007). Effects of osteoarthritis and fatigue on proprioception of the knee joint. *Archives of Physical Medicine and Rehabilitation*, *88*(3), 346–350.

Beaudreuil, J., Bendaya, S., Faucher, M., Coudeyre, E., Ribinik, P., Revel, M., & Rannou, F. (2009). Clinical practice guidelines for rest orthosis, knee sleeves, and unloading knee braces in knee osteoarthritis. *Joint Bone Spine*, *76*(6), 629–636.

Bell, A. L., Pedersen, D. R., & Brand, R. A. (1990). A comparison of the accuracy of several hip center location prediction methods. *Journal of Biomechanics*, *23*(6), 617–21.

Bellamy, N., Kirwan, J., Boers, M., Brooks, P., Strand, V., Tugwell, P., … Lequesne, M. (1997). Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *The Journal of Rheumatology*, *24*(4), 799–802.

Benedetti, M., Catani, F., Leardini, A., Pignotti, E., & Giannini, S. (1998). Data management in gait analysis for clinical applications. *Clinical Biomechanics*, *13*(3), 204–215.

Bennell, K. L., & Hinman, R. S. (2011). A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. *Journal of Science and Medicine in Sport*, *14*(1), 4–9.

Bennell, K. L., Bowles, K.-A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A., … Hinman, R. S. (2011). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ: British Medical Journal*, *342*, d2912.

Bennell, K. L., Bowles, K.-A., Wang, Y., Cicuttini, F., Davies-Tuck, M., & Hinman, R. S. (2011). Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. *Annals of the Rheumatic Diseases*, *70*(10), 1770–1774.

Bennell, K. L., Dobson, F., & Hinman, R. (2011). Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. *Arthritis Care and Research*, *63*(S11), S350–S370.

Bennell, K. L., Hunt, M. A., Wrigley, T. V., Hunter, D. J., McManus, F. J., Hodges, P. W., … Hinman, R. S. (2010). Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomised controlled trial. *Osteoarthritis and Cartilage*, *18*(5), 621–628.

Bennell, K. L., Kean, C. O., Wrigley, T. V., & Hinman, R. S. (2013). Effects of a modified shoe on knee load in people with and those without knee osteoarthritis. *Arthritis & Rheumatism*, *65*(3), 701–709.

Berman, A. T., Zarro, V. J., Bosacco, S. J., & Israelite, C. (1987). Quantitative gait analysis after unilateral or bilateral total knee replacement. *The Journal of Bone and Joint Surgery*, *69*(9), 1340–1345.

Besier, F., Lloyd, G., & Ackland, R. (2003a). Muscle activation strategies at the knee during running and cutting maneuvers. *Medicine and Science in Sports and Exercise*, *35*(1), 119–127.

Besier, F., Sturnieks, D. L., Alderson, J. A., & Lloyd, D. G. (2003b). Repeatability of gait data using a functional hip joint centre and a mean helical knee axis. *Journal of Biomechanics*, *36*(8), 1159–1168.

Bhatia, D., Bejarano, T., & Novo, M. (2013). Current interventions in the management of knee osteoarthritis. *Journal of Pharmacy and Bioallied Sciences*, *5*(1), 30–38.

Birmingham, T. B., Hunt, M. A., Jones, I. C., Jenkyn, T. R., & Giffin, J. R. (2007). Test-retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. *Arthritis Care and Research*, *57*(6), 1012–1017.

Birmingham, T. B., Moyer, R., Leitch, K., Chesworth, B., Bryant, D., Willits, K., … Giffin, J. R. (2017). Changes in biomechanical risk factors for knee osteoarthritis and their association with 5-year clinically important improvement after limb realignment surgery. *Osteoarthritis and Cartilage, 25*(12), 1999–2006.

Blagojevic, M., Jinks, C., Jeffery, A., & Jordan, K. P. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *18*(1), 24–33.

Blankevoort, C. G., van Heuvelen, M. J. G., & Scherder, E. J. A. (2013). Reliability of six physical performance tests in older people with dementia. *Physical Therapy*, *93*(1), 69–78.

Bliddal, H., Leeds, A. R., & Christensen, R. (2014). Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity*, *15*(7), 578–86.

Blount, W. P. (1956). Don't throw away the cane. *The Journal of Bone and Joint Surgery*, *38*(3), 695–708.

Blumenfeld, O., Williams, F. M. K., Hart, D. J., Spector, T. D., Arden, N., & Livshits, G. (2013). Association between cartilage and bone biomarkers and incidence of radiographic knee osteoarthritis (RKOA) in UK females: a prospective study. *Osteoarthritis and Cartilage*, *21*(7), 923–929.

Bradley, L. A. (2004). Recent Approaches to Understanding Osteoarthritis Pain. In Journal of Rheumatology, 70(31), 54–60.

Brandon, S. C. E., Miller, R. H., Thelen, D. G., & Deluzio, K. J. (2014). Selective lateral muscle activation in moderate medial knee osteoarthritis subjects does not unload medial knee condyle. *Journal of Biomechanics*, *47*(6), 1409–1415.

Brandt, K. D. (1989). Pain, synovitis, and articular cartilage changes in osteoarthritis. *Seminars in Arthritis and Rheumatism*, *18*(4 Suppl 2), 77–80.

Brandt, K. D., Dieppe, P., & Radin, E. L. (2008). Etiopathogenesis of osteoarthritis. *Rheumatic Diseases Clinics of North America*, *34*(3), 531–559.

Brandt, K. D., Heilman, D. K., Slemenda, C., Katz, B. P., Mazzuca, S. A., Braunstein, E. M., & Byrd, D. (1999). Quadriceps strength in women with radiographically progressive osteoarthritis of the knee and those with stable radiographic changes. *The Journal of Rheumatology*, *26*(11), 2431–2437.

Bravata, D. M., Smith-Spangler, C., Sundaram, V., Gienger, A. L., Lin, N., Lewis, R., … Sirard, J. R. (2007). Using Pedometers to Increase Physical Activity and Improve Health. *The Journal of the American Medical Association, 298*(19), 2296.

Briem, K., & Snyder-Mackler, L. (2009). Proximal gait adaptations in medial knee OA. *Journal of Orthopaedic Research*, *27*(1), 78–83.

Briem, K., Ramsey, D. K., Newcomb, W., Rudolph, K. S., & Snyder-Mackler, L. (2007). Effects of the amount of valgus correction for medial compartment knee osteoarthritis on clinical outcome, knee kinetics and muscle co-contraction after opening wedge high tibial osteotomy. *Journal of Orthopaedic Research*, *25*(3), 311–318.

Brignardello-Petersen, R., Guyatt, G. H., Buchbinder, R., Poolman, R. W., Schandelmaier, S., Chang, Y., … Vandvik, P. O. (2017). Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review. *BMJ Open*, *7*(5), e016114.

Brinkmann, J. R., & Perry, J. (1985). Rate and range of knee motion during ambulation in healthy and arthritic subjects. *Physical Therapy*, *65*(7), 1055–1060.

Brosseau, L., Rahman, P., Toupin-April, K., Poitras, S., King, J., De Angelis, G., … McEwan, J. (2014). A systematic critical appraisal for non-pharmacological management of osteoarthritis using the appraisal of guidelines research and evaluation II instrument. *PloS One*, *9*(1), e82986.

Brouwer, G. M., van Tol, A. W., Bergink, A. P., Belo, J. N., Bernsen, R. M. D., Reijman, M., … Bierma-Zeinstra, S. M. A. (2007). Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. *Arthritis and Rheumatism*, *56*(4), 1204–1211.

Brouwer, R. W., Huizinga, M. R., Duivenvoorden, T., van Raaij, T. M., Verhagen, A. P., Bierma-Zeinstra, S. M., & Verhaar, J. A. (2014). Osteotomy for treating knee osteoarthritis. *Cochrane Database of Systematic Reviews*, (12), CD004019.

Brouwer, R. W., van Raaij, T. M., Bierma-Zeinstra, S. M., Verhagen, A. P., Jakma, T. T. S. C., & Verhaar, J. A. (2007). Osteotomy for treating knee osteoarthritis. In R. W. Brouwer. *Cochrane Database of Systematic Reviews,* 18(3), CD004019.

Bruton, A., Conway, J. H., & Holgate, S. T. (2000). Reliability: What is it, and how is it measured? *Physiotherapy*, *86*(2), 94–99.

Bryk, F. F., de Jesus, J. F., Fukuda, T. Y., Moreira, E. G., Marcondes, F. B., & dos Santos, M. G. (2011). Immediate effect of the elastic knee sleeve use on individuals with osteoarthritis. *Revista Brasileira de Reumatologia*, *51*(5), 434–446.

Buchanan, T. S., Kim, A. W., & Lloyd, D. G. (1996). Selective muscle activation following rapid varus/valgus perturbations at the knee. *Medicine and Science in Sports and Exercise*, *28*(7), 870–876.

Butler, R. J., Barrios, J. A, Royer, T., & Davis, I. S. (2009). Effect of laterally wedged foot orthoses on rearfoot and hip mechanics in patients with medial knee osteoarthritis. *Prosthetics and Orthotics International*, *33*(2), 107–116.

Butler, R. J., Marchesi, S., Royer, T., & Davis, I. S. (2007). The effect of a subject-specific amount of lateral wedge on knee mechanics in patients with medial knee osteoarthritis. *Journal of Orthopaedic Research*, *25*(9), 1121–1127.

Buttgereit, F., Burmester, G.-R., & Bijlsma, J. W. J. (2015). Non-surgical management of knee osteoarthritis: where are we now and where do we need to go? *RMD Open*, *1*(1), e000027–e000027.

C-Motion. (2018). Retrieved form http://www.c-motion.com/v3dwiki/index.php/Tutorial:_Building_a_Conventional_Gait_Model

Callaghan, M. J., Parkes, M. J., Hutchinson, C. E., Gait, A. D., Forsythe, L. M., Marjanovic, E. J., … Felson, D. T. (2015). A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. *Annals of the Rheumatic Diseases*, *74*(6), 1164–70.

Campbell, A. J., Borrie, M. J., & Spears, G. F. (1989). Risk factors for falls in a community-based prospective study of people 70 years and older. *Journal of Gerontology*, *44*(4), M112–M117.

Campi, S., Tibrewal, S., Cuthbert, R., & Tibrewal, S. B. (2018). Unicompartmental knee replacement – Current perspectives. *Journal of Clinical Orthopaedics and Trauma*, *9*(1), 17–23.

Campos, G. C. De, Rezende, M. U., Pasqualin, T., Frucchi, R., & Bolliger Neto, R. (2015). Lateral wedge insole for knee osteoarthritis: randomized clinical trial. *Sao Paulo Medical Journal*, *133*(1), 13–19.

Cappozzo, A., Catani, F., Croce, U. Della, & Leardini, A. (1995). Position and orientation in space of bones during movement: anatomical frame definition and determination. *Clinical Biomechanics*, *10*(4), 171–178.

Cappozzo, A., Catani, F., Leardini, A., Benedetti, M. G., & Croce, U. Della. (1996). Position and orientation in space of bones during movement: experimental artefacts. *Clinical Biomechanics*, *11*(2), 90–100.

Cappozzo, A., Della Croce, U., Leardini, A., & Chiari, L. (2005). Human movement analysis using stereophotogrammetry. Part 1: theoretical background. *Gait and Bosture*, *21*(2), 186–196.

Carvalho, N. A. de A., Bittar, S. T., Pinto, F. R. de S., Ferreira, M., & Sitta, R. R. (2010). Manual for guided home exercises for osteoarthritis of the knee. *Clinics*, *65*(8), 775–780.

Cereatti, A., Camomilla, V., Vannozzi, G., & Cappozzo, A. (2007). Propagation of the hip joint centre location error to the estimate of femur vs pelvis orientation using a constrained or an unconstrained approach. *Journal of Biomechanics*, *40*(6), 1228–1234.

Chaipinyo, K., & Karoonsupcharoen, O. (2009). No difference between home-based strength training and home-based balance training on pain in patients with knee osteoarthritis: a randomised trial. *The Australian Journal of Physiotherapy*, *55*(1), 25–30.

Chang, a. H., Moisio, K. C., Chmiel, J. S., Eckstein, F., Guermazi, A., Prasad, P. V., … Sharma, L. (2015). External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. *Osteoarthritis and Cartilage*, *23*(7), 1–8.

Chang, A., Hurwitz, D., Dunlop, D., Song, J., Cahue, S., Hayes, K., & Sharma, L. (2007). The relationship between toe-out angle during gait and progression of medial tibiofemoral osteoarthritis. *Annals of the Rheumatic Diseases*, *66*(10), 1271–1275.

Chapman, G. J., Parkes, M. J., Forsythe, L., Felson, D. T., & Jones, R. K. (2015). Ankle motion influences the external knee adduction moment and may predict who will respond to lateral wedge insoles?: An ancillary analysis from the SILK trial. *Osteoarthritis and Cartilage*, *23*(8), 13160–

1322.

Charlton, J. M., Hatfield, G. L., Guenette, J. A., & Hunt, M. A. (2018). Toe-in and toe-out walking require different lower limb neuromuscular patterns in people with knee osteoarthritis. *Journal of Biomechanics*, *76*, 112–118.

Chehab, E. F., Favre, J., Erhart-Hledik, J. C., & Andriacchi, T. P. (2014). Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. *Osteoarthritis and Cartilage*, *22*(11), 1833–1839.

Chen, a., Gupte, C., Akhtar, K., Smith, P., & Cobb, J. (2012). The Global Economic Cost of Osteoarthritis: How the UK Compares. *Arthritis*, *2012*, 1–6.

Cheng, Y., Macera, C. A., Davis, D. R., Ainsworth, B. E., Troped, P. J., & Blair, S. N. (2000). Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor?. *Journal of Clinical Epidemiology*, *53*(3), 315–322.

Chesterton, L. S., Barlas, P., Foster, N. E., Baxter, G. D., & Wright, C. C. (2003). Gender differences in pressure pain threshold in healthy humans. *Pain*, *101*(3), 259–266.

Childs, J. D., Sparto, P. J., Fitzgerald, G. K., Bizzini, M., & Irrgang, J. J. (2004). Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis. *Clinical Biomechanics*, *19*(1), 44–49.

Chmelo, E., Nicklas, B., Davis, C., Miller, G. D., Legault, C., & Messier, S. (2013). Physical activity and physical function in older adults with knee osteoarthritis. *Journal of Physical Activity and Health*, *10*(6), 777–783.

Choi, Y.-J., & Ra, H. J. (2016). Patient Satisfaction after Total Knee Arthroplasty. *Knee Surgery & Related Research*, *28*(1), 1–15.

Christensen, R., Bartels, E. M., Astrup, A., & Bliddal, H. (2006). Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Annals of the Rheumatic Diseases*, *66*(4), 433–439.

Chuang, S.-H., Huang, M.-H., Chen, T.-W., Weng, M.-C., Liu, C.-W., & Chen, C.-H. (2077). Effect of knee sleeve on static and dynamic balance in patients with knee osteoarthritis. *International Journal of Medical Sciences*, *23*(8), 405–411.

Clark, A. G., Jordan, J. M., Vilim, V., Renner, J. B., Dragomir, A. D., Luta, G., & Kraus, V. B. (1999). Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project. *Arthritis and Rheumatism*, *42*(11), 2356–2364.

Coggon, D., Croft, P., Kellingray, S., Barrett, D., McLaren, M., & Cooper, C. (2000). Occupational physical activities and osteoarthritis of the knee. *Arthritis and Rheumatism*, *43*(7), 1443–1439.

Collins, A. T., Blackburn, J. T., Olcott, C. W., Jordan, J. M., Yu, B., & Weinhold, P. S. (2012). The assessment of postural control with stochastic resonance electrical stimulation and a neoprene knee sleeve in the osteoarthritic knee. *Archives of Physical Medicine and Rehabilitation*, *93*(7), 1123–1128.

Collins, A. T., Blackburn, J. T., Olcott, C. W., Miles, J., Jordan, J., Dirschl, D. R., & Weinhold, P. S. (2011b). Stochastic resonance electrical stimulation to improve proprioception in knee osteoarthritis. *Knee*, *18*(5), 317–322.

Collins, A. T., Blackburn, J. T., Olcott, C., Yu, B., & Weinhold, P. (2011a). The impact of stochastic resonance electrical stimulation and knee sleeve on impulsive loading and muscle co-contraction during gait in knee osteoarthritis. *Clinical Biomechanics*, *26*(8), 853–858.

Collins, A. T., Blackburn, T., Olcott, C., Jordan, J. M., Yu, B., & Weinhold, P. (2013). A kinetic and kinematic anlaysis of the effect of stochastic resonance electrical stimulation and knee sleeve during giat in osteoarthritis of the knee. *Journal of Applied Biomechanics*, *30*(1), 104–112.

Collins, A. T., Blackburn, T., Olcott, C., Jordan, J. M., Yu, B., & Weinhold, P. (2014). A Kinetic and Kinematic Analysis of the Effect of Stochastic Resonance Electrical Stimulation and Knee Sleeve during Gait in Osteoarthritis of the Knee. *Journal of Applied Biomechanics*, *30*(1), 104–112.

Collins, A. T., Richardson, R. T., & Higginson, J. S. (2014). Interlimb symmetry of dynamic knee joint stiffness and co-contraction is maintained in early stage knee osteoarthritis. *Journal of Electromyography and Kinesiology*, *24*(4), 497–501.

Collins, N. J., Misra, D., Felson, D. T., Crossley, K. M., & Roos, E. M. (2011). Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS). *Arthritis Care and Research*, *63*(11), S208–S228.

Collins, T. D., Ghoussayni, S. N., Ewins, D. J., & Kent, J. A. (2009). A six degrees-of-freedom marker set for gait analysis: repeatability and comparison with a modified Helen Hayes set. *Gait and Posture*, *30*(2), 173–180.

Colloca, L., & Benedetti, F. (2006). How prior experience shapes placebo analgesia. *Pain, 124*(1–2), 126–133.

Cooper, C., McAlindon, T., Coggon, D., Egger, P., & Dieppe, P. (1994). Occupational activity and osteoarthritis of the knee. *Annals of the Rheumatic Diseases*, *53*(2), 90–93.

Cornwall, A., & Donderi, D. C. (1988). The effect of experimentally induced anxiety on the experience of pressure pain. *Pain*, *35*(1), 105–113.

Costigan, P. A., Deluzio, K. J., & Wyss, U. P. (2002). Knee and hip kinetics during normal stair climbing. *Gait and Posture*, *16*(1), 31–37.

Creamer, P., Lethbridge-Cejku, M., & Hochberg, M. C. (1998). Where does it hurt? Pain localization in osteoarthritis of the knee. *Osteoarthritis and Cartilage, 6*(5), 318–323.

Crenshaw, S. J., Pollo, F. E., & Calton, E. F. (2000). Effects of lateral-wedged insoles on kinetics at the knee. *Clinical Orthopaedics and Related Research*, *375*, 185–192.

Croce, U. Della, Cappozzo, A., Kerrigan, C., & Lucchetti, L. (1997). Bone position and orientation errors: Pelvis and lower limb anatomical landmark identification reliability. *Gait and Posture*, *5*(2), 156–157.

Cruz-Almeida, Y., Sibille, K. T., Goodin, B. R., Petrov, M. E., Bartley, E. J., Riley, J. L., … Fillingim, R. B. (2014). Racial and Ethnic Differences in Older Adults With Knee Osteoarthritis. *Arthritis and Rheumatology*, *66*(7), 1800–1810.

Cudejko, T., van der Esch, M., van der Leeden, M., Roorda, L. D., Pallari, J., Bennell, K. L., …

Dekker, J. (2018). Effect of Soft Braces on Pain and Physical Function in Patients With Knee Osteoarthritis: Systematic Review With Meta-Analyses. *Archives of Physical Medicine and Rehabilitation*, *99*(1), 153–163.

Cudejko, T., van der Esch, M., van der Leeden, M., van den Noort, J. C., Roorda, L. D., Lems, W., … Dekker, J. (2017). The immediate effect of a soft knee brace on pain, activity limitations, self-reported knee instability, and self-reported knee confidence in patients with knee osteoarthritis. *Arthritis Research and Therapy*, *19*(1), 260.

da Silva, R. R., Santos, A. A. M., de Sampaio Carvalho Júnior, J., & Matos, M. A. (2014). Quality of life after total knee arthroplasty: systematic review. *Revista Brasileira de Ortopedia (English Edition)*, *49*(5), 520–527.

Dahaghin, S., Bierma-Zeinstra, S. M. A., Ginai, A. Z., Pols, H. A. P., Hazes, J. M. W., & Koes, B. W. (2005). Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Annals of the Rheumatic Diseases*, *64*(5), 682–687.

Dandy, D. J., & Edwards, D. J. (2009). *Essential Orthopaedics and Trauma*. India: Elsevier Health Sciences.

De Luca, C. (1997). The use of surface electromyography in biomechanics. *Journal of Applied Biomechanics*, *13*(2), 135–163.

Dearborn, J. T., Eakin, C. L., & Skinner, H. B. (1996). Medial compartment arthrosis of the knee. *American Journal of Orthopedics*, *25*(1), 18–26.

Dekker, J., van Dijk, G. M., & Veenhof, C. (2009). Risk factors for functional decline in osteoarthritis of the hip or knee. *Current Opinion in Rheumatology*, *21*(5), 520–554.

Dell'Isola, A., & Steultjens, M. (2018). Classification of patients with knee osteoarthritis in clinical phenotypes: Data from the osteoarthritis initiative. *PLoS ONE, 13*(1).

Dell'Isola, A., Allan, R., Smith, S. L., Marreiros, S. S. P., & Steultjens, M. (2016). Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *Musculoskeletal Disorders, 17*(1), 1–12.

Della Croce, U., Leardini, A., Chiari, L., & Cappozzo, A. (2005). Human movement analysis using stereophotogrammetry. Part 4: assessment of anatomical landmark misplacement and its effects on joint kinematics. *Gait and Posture*, *21*(2), 226–237.

Denegar, C. R., & Ball, D. W. (1993). Assessing Reliability and Precision of Measurement: An Introduction to Intraclass Correlation and Standard Error of Measurement. *Journal of Sport Rehabilitation*, *2*(1), 35–42.

Deyle, G. D., Allison, S. C., Matekel, R. L., Ryder, M. G., Stang, J. M., Gohdes, D. D., … Garber, M. B. (2005). Physical therapy treatment effectiveness for osteoarthritis of the knee: a randomized comparison of supervised clinical exercise and manual therapy procedures versus a home exercise program. *Physical Therapy*, *85*(12), 1301–1317.

Deyle, G. D., Henderson, N. E., Matekel, R. L., Ryder, M. G., Garber, M. B., & Allison, S. C. (2000). Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. *Annals of Internal Medicine*, *132*(3), 173–181.

Dieppe, P. (1995). Management of hip osteoarthritis. *British Medical Journal*, *311*(7009), 853–

857.

Dieppe, P. A. (2005). Relationship between symptoms and structural change in osteoarthritis: What are the important targets for therapy?. *The Journal of Rheumatology, 32*(6), 1147-1149.

Dieppe, P. A., & Lohmander, L. S. (2005). Pathogenesis and management of pain in osteoarthritis. *Lancet*, *365*(9463), 965–973.

Dieppe, P., Cushnaghan, J., Tucker, M., Browning, S., & Shepstone, L. (2000). The Bristol "OA500 study": progression and impact of the disease after 8 years. *Osteoarthritis and Cartilage*, *8*(2), 63–68.

Dieppe, P., Cushnaghan, J., Young, P., & Kirwan, J. (1993). Prediction of the progression of joint space narrowing in osteoarthritis of the knee by bone scintigraphy. *Annals of the Rheumatic Diseases*, *52*(8), 557–563.

Dionyssiotis, Y. (2012). Analyzing the problem of falls among older people. *International Journal of General Medicine*, *5*, 805–13.

Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., … Bennell, K. L. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis and Cartilage*, *21*(8), 1042–1052.

Dowling, J. J. (1997). The use of electromyography for the noninvasive prediction of muscle forces. Current issues. *Sports Medicine*, *24*(2), 82–96.

Driban, J. B., Sitler, M. R., Barbe, M. F., & Balasubramanian, E. (2010). Is osteoarthritis a heterogeneous disease that can be stratified into subsets?. *Clinical Rheumatology, 29(*2):123-31.

Dubois, M. Y., Gallagher, R. M., & Lippe, P. M. (2009). Pain medicine position paper. *Pain Medicine*, 10(6), 972–1000.

Duivenvoorden, T., Brouwer, R. W., van Raaij, T. M., Verhagen, A. P., Verhaar, J. A., & Bierma-Zeinstra, S. M. (2015). Braces and orthoses for treating osteoarthritis of the knee. *Cochrane Database of Systematic Reviews*.

Duivenvoorden, T., van Raaij, T. M., Horemans, H. L. D., Brouwer, R. W., Bos, P. K., Bierma-Zeinstra, S. M. a., … Reijman, M. (2014). Do Laterally Wedged Insoles or Valgus Braces Unload the Medial Compartment of the Knee in Patients With Osteoarthritis?. *Clinical Orthopaedics and Related Research*, *473*(1), 265–274.

Earl, J. E., & Hertel, J. (2001). Lower-Extremity Muscle Activation during the Star Excursion Balance Tests. *Journal of Sport Rehabilitation*, *10*(2), 93–104.

El-Azab, H. M., Morgenstern, M., Ahrens, P., Schuster, T., Imhoff, A. B., & Lorenz, S. G. F. (2011). Limb alignment after open-wedge high tibial osteotomy and its effect on the clinical outcome. *Orthopedics*, *34*(10), e622–e628.

Engelhart, L., Nelson, L., Lewis, S., Mordin, M., Demuro-Mercon, C., Uddin, S., … Farr, J. (2012). Validation of the Knee Injury and Osteoarthritis Outcome Score Subscales for Patients With Articular Cartilage Lesions of the Knee. *The American Journal of Sports Medicine*, *40*(10), 2264–2272.

Enohumah, K. O., & Imarengiaye, C. O. (2008). Pain in osteoarthritis: A review of literature. *Southern African Journal of Anaesthesia and Analgesia. 14*(3), 29-33.

Erhart-Hledik, J. C., Elspas, B., Giori, N. J., & Andriacchi, T. P. (2012). Effect of variable-stiffness walking shoes on knee adduction moment, pain, and function in subjects with medial compartment knee osteoarthritis after 1 year. *Journal of Orthopaedic Research*, *30*(4), 514–521.

Ettinger, W. H., Davis, M. A., Neuhaus, J. M., & Mallon, K. P. (1994). Long-term physical functioning in persons with knee osteoarthritis from NHANES. I: Effects of comorbid medical conditions. *Journal of Clinical Epidemiology*, *47*(7), 809–815.

Fang, M. A, Taylor, C. E., Nouvong, A., Masih, S., Kao, K. C., & Perell, K. L. (2006). Effects of footwear on medial compartment knee osteoarthritis. *Journal of Rehabilitation Research and Development*, *43*(4), 427–434.

Fantini Pagani, C. H., Willwacher, S., Kleis, B., & Brüggemann, G. P. (2013). Influence of a valgus knee brace on muscle activation and co-contraction in patients with medial knee osteoarthritis. *Journal of Electromyography and Kinesiology*, *23*(2), 490–500.

Faucher, M., Poiraudeau, S., Lefevre-Colau, M. M., Rannou, F., Fermanian, J., & Revel, M. (2002). Algo-functional assessment of knee osteoarthritis: comparison of the test–retest reliability and construct validity of the Womac and Lequesne indexes. *Osteoarthritis and Cartilage*, *10*(8), 602–610.

Felson, D. T. (1990). The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. *Seminars in Arthritis and Rheumatism*, *20*(3 Suppl 1), 42–50.

Felson, D. T. (2005). The sources of pain in knee osteoarthritis. *Current Opinion in Rheumatology, 17*(5), 624–628.

Felson, D. T. (2010). Identifying different osteoarthritis phenotypes through epidemiology. *Osteoarthritis and Cartilage, 18*(5), 601–604.

Felson, D. T. (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis and Cartilage*, *21*(1), 10–15.

Felson, D. T., & Zhang, Y. (1998). An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis and Rheumatism*, *41*(8), 1343–1355.

Felson, D. T., Couropmitree, N. N., Chaisson, C. E., Hannan, M. T., Zhang, Y., McAlindon, T. E., … Myers, R. H. (1998). Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: the Framingham Study. *Arthritis and Rheumatism*, *41*(6), 1064–1071.

Felson, D. T., Gross, K. D., Nevitt, M. C., Yang, M., Lane, N. E., Torner, J. C., … Hurley, M. V. (2009). The effects of impaired joint position sense on the development and progression of pain and structural damage in knee osteoarthritis. *Arthritis Care and Research, 61*(8), 1070–1076.

Felson, D. T., Hannan, M. T., Naimark, A., Berkeley, J., Gordon, G., Wilson, P. W., & Anderson, J. (1991). Occupational physical demands, knee bending, and knee osteoarthritis: results from the Framingham Study. *The Journal of Rheumatology*, *18*(10), 1587–1592.

Felson, D. T., Lawrence, R. C., Dieppe, P. A., Hirsch, R., Helmick, C. G., Jordan, J. M., … Fries, J. F. (2000a). Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Annals of Internal Medicine*, *133*(8), 635–646.

Felson, D. T., Lawrence, R. C., Hochberg, M. C., McAlindon, T., Dieppe, P. A., Minor, M. A., … Goldberg, V. (2000b). Osteoarthritis: new insights. Part 2: treatment approaches. *Annals of*

Internal Medicine, *133*(9), 726–737.

Felson, D. T., McLaughlin, S., Goggins, J., LaValley, M. P., Gale, M. E., Totterman, S., … Gale, D. (2003). Bone Marrow Edema and Its Relation to Progression of Knee Osteoarthritis. *Annals of Internal Medicine, 139*(5), 330-336.

Felson, D. T., Niu, J., Gross, K. D., Englund, M., Sharma, L., Cooke, T. D. V., … Nevitt, M. C. (2013). Valgus malalignment is a risk factor for lateral knee osteoarthritis incidence and progression: Findings from the multicenter osteoarthritis study and the osteoarthritis initiative. *Arthritis and Rheumatism*, *65*(2), 355–362.

Felson, D. T., Redmond, A. C., Chapman, G. J., Smith, T. O., Hamilton, D. F., Jones, R. K., … Conaghan, P. G. (2016). Recommendations for the conduct of efficacy trials of treatment devices for osteoarthritis: a report from a working group of the Arthritis Research UK Osteoarthritis and Crystal Diseases Clinical Studies Group. *Rheumatology*, *55*(2), 320–326.

Felson, D. T., Zhang, Y., Anthony, J. M., Naimark, A., & Anderson, J. J. (1992). Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Annals of Internal Medicine*, *116*(7), 535–539.

Ferber, R., McClay Davis, I., Williams, D. S., & Laughton, C. (2002). A comparison of within- and between-day reliability of discrete 3D lower extremity variables in runners. *Journal of Orthopaedic Research*, *20*(6), 1139–1145.

Ferreira, G. E., Robinson, C. C., Wiebusch, M., Viero, C. C. de M., da Rosa, L. H. T., & Silva, M. F. (2015). The effect of exercise therapy on knee adduction moment in individuals with knee osteoarthritis: A systematic review. *Clinical Biomechanics*, *30*(6), 521–527.

Field, A. (2013). *Discovering statistics using IBM SPSS statistics*. London; Sage.

Finger, S., & Paulos, L. E. (2002). Clinical and biomechanical evaluation of the unloading brace. *The Journal of Knee Surgery, 15(3)*, 155–158.

Fisher, N. M., & Pendergast, D. R. (1997). Reduced muscle function in patients with osteoarthritis. *Scandinavian Journal of Rhabilitation Medicine*, *29*(4), 213–221.

Fisher, N. M., Gresham, G. E., Abrams, M., Hicks, J., Horrigan, D., & Pendergast, D. R. (1993). Quantitative effects of physical therapy on muscular and functional performance in subjects with osteoarthritis of the knees. *Archives of Physical Medicine and Rehabilitation*, *74*(8), 840–847.

Fitzgerald, G. K., Piva, S. R., & Irrgang, J. J. (2004). Reports of joint instability in knee osteoarthritis: Its prevalence and relationship to physical function. *Arthritis Care and Research*, *51*(6), 941–946.

Ford, K. R., Myer, G. D., & Hewett, T. E. (2007). Reliability of landing 3D motion analysis: Implications for longitudinal analyses. *Medicine and Science in Sports and Exercise*, *39*(11), 2021–2028.

Foroughi, N., Smith, R. M., Lange, A. K., Baker, M. K., Fiatarone Singh, M. A., & Vanwanseele, B. (2011). Lower limb muscle strengthening does not change frontal plane moments in women with knee osteoarthritis: A randomized controlled trial. *Clinical Biomechanics*, *26*(2), 167–174.

Foroughi, N., Smith, R., & Vanwanseele, B. (2009). The association of external knee adduction moment with biomechanical variables in osteoarthritis: A systematic review. *Knee, 16*(5), 303–

309.

Fransen, M., McConnell, S., & Bell, M. (2002). Therapeutic exercise for people with osteoarthritis of the hip or knee. A systematic review. *The Journal of Rheumatology*, *29*(8), 1737–1745.

Fransen, M., McConnell, S., Harmer, A. R., Van der Esch, M., Simic, M., & Bennell, K. L. (2015). Exercise for osteoarthritis of the knee: a Cochrane systematic review. *British Journal of Sports Medicine*, *49*(24), 1554–7.

Fregly, B. J., D'Lima, D. D., & Colwell, C. W. (2009). Effective gait patterns for offloading the medial compartment of the knee. *Journal of Orthopaedic Research*, *27*(8), 1016–1021.

Fregly, B. J., Reinbolt, J. A., Rooney, K. L., Mitchell, K. H., & Chmielewski, T. L. (2007). Design of patient-specific gait modifications for knee osteoarthritis rehabilitation. *IEEE Transactions on Bio-Medical Engineering*, *54*(9), 1687–1695.

Frei, B. (1994). Reactive oxygen species and antioxidant vitamins: mechanisms of action. *The American Journal of Medicine*, *97*(3A), 5S–13S.

Fu, H. C., Lie, C. W., Ng, T., Chen, K., Tse, C., & Wong, W. (2015). Prospective study on the effects of orthotic treatment for medial knee osteoarthritis in Chinese patients: clinical outcome and gait analysis. *Hong Kong Medical Journal*, *21*(2), 98–106.

Gaasbeek, R. D. A, Groen, B. E. B., Hampsink, B., van Heerwaarden, R. J., & Duysens, J. (2007). Valgus bracing in patients with medial compartment osteoarthritis of the knee: a gait analysis study of a new brace. *Gait and Posture*, *26*(1), 3–10.

Gamble, R. (2000). Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis and Rheumatism*, *43*(9), 1905–1915.

Gamsa, A. (1990). Is emotional disturbance a precipitator or a consequence of chronic pain?. *Pain, 42*(2), 183–195.

Ganz, R., Leunig, M., Leunig-Ganz, K., & Harris, W. H. (2008). The etiology of osteoarthritis of the hip: an integrated mechanical concept. *Clinical Orthopaedics and Related Research*, *466*(2), 264–272.

Garsden, L. R., & Bullock-Saxton, J. E. (1999). Joint reposition sense in subjects with unilateral osteoarthritis of the knee. *Clinical Rehabilitation*, *13*(2), 148–155.

Ghasemi, A., & Zahediasl, S. (2012). Normality tests for statistical analysis: a guide for non-statisticians. *International Journal of Endocrinology and Metabolism*, *10*(2), 486–489.

Giffin, J. R., Stanish, W. D. W., MacKinnon, S. N., & MacLeod, D. A. (1995). Application of a lateral heel wedge as a nonsurgical treatment for varum gonarthrosis. *Journal of Prosthetics and Orthotics*, *7*(1), 23–28

Gill, S., & McBurney, H. (2008). Reliability of performance-based measures in people awaiting joint replacement surgery of the hip or knee. *Physiotherapy Research International*, *13*(3), 141–152.

Giori, N. J. (2004). Load-shifting brace treatment for osteoarthritis of the knee: a minimum 2 1/2-year follow-up study. *Journal of Rehabilitation Research and Development*, *41*(2), 187–194.

Giotis, D., Tsiaras, V., Ristanis, S., Zampeli, F., Mitsionis, G., Stergiou, N., & Georgoulis, A. D. (2011). Knee braces can decrease tibial rotation during pivoting that occurs in high demanding

activities. *Knee Surgery, Sports Traumatology, Arthroscopy*, *19*(8), 1347–1354.

Gohal, C., Shanmugaraj, A., Tate, P., Horner, N. S., Bedi, A., Adili, A., & Khan, M. (2018). Effectiveness of Valgus Offloading Knee Braces in the Treatment of Medial Compartment Knee Osteoarthritis: A Systematic Review. *Sports Health: A Multidisciplinary Approach*, *10*(6), 500–514

Goode, A. P., Shi, X. A., Gracely, R. H., Renner, J. B., & Jordan, J. M. (2014). Associations between Pressure-Pain Threshold, Symptoms, and Radiographic Knee and Hip Osteoarthritis: The Johnston County Osteoarthritis Project. *Arthritis Care and Research*, *66*(10), 1513–1519.

Graven-Nielsen, T., & Arendt-Nielsen, L. (2002). Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. *Current Rheumatology Reports*, *4*(4), 313–321.

Gribble, P. A., Hertel, J., & Plisky, P. (2012). Using the star excursion balance test to assess dynamic postural-control deficits and outcomes in lower extremity injury: A literature and systematic review. *Journal of Athletic Training*, *47*(3), 339–357.

Gribble, P. A., Kelly, S. E., Refshauge, K. M., & Hiller, C. E. (2013). Interrater reliability of the star excursion balance test. *Journal of Athletic Training*, *48*(5), 621–626.

Griffin, T., Rowden, N., Morgan, D., Atkinson, R., Woodruff, P., & Maddern, G. (2007). Unicompartmental knee arthroplasty for the treatment of unicompartmental osteoarthritis: a systematic study. *ANZ Journal of Surgery*, *77*(4), 214–221.

Grob, K. R., Kuster, M. S., Higgins, S. A., Lloyd, D. G., & Yata, H. (2002). Lack of correlation between different measurements of proprioception in the knee. *The Journal of Bone and Joint Surgery*, *84*(4), 614–618.

Growney, E., Meglan, D., Johnson, M., Cahalan, T., & An, K.-N. (1997). Repeated measures of adult normal walking using a video tracking system. *Gait and Posture*, *6*(2), 147–162.

Guccione, A. A., Felson, D. T., & Anderson, J. J. (1990). Defining arthritis and measuring functional status in elders: methodological issues in the study of disease and physical disability. *American Journal of Public Health*, *80*(8), 945–949.

Guccione, A. A., Felson, D. T., Anderson, J. J., Anthony, J. M., Zhang, Y., Wilson, P. W., … Kannel, W. B. (1994). The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *American Journal of Public Health*, *84*(3), 351–358.

Guichet, J.-M., Javed, A., Russell, J., & Saleh, M. (2003). Effect of the foot on the mechanical alignment of the lower limbs. *Clinical Orthopaedics and Related Research*, *415*, 193–201.

Guo, M., Axe, M. J., & Manal, K. (2007). The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. *Gait and Posture*, *26*(3), 436–441.

Gupta, S., Hawker, G. A., Laporte, A., Croxford, R., & Coyte, P. C. (2005). The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. *Rheumatology*, *44*(12), 1531–1537.

Hafez, A. R., Alenazi, A. M., Kachanathu, S. J., Alroumi, A. M., & Mohamed, E. S. (2014). Knee Osteoarthritis: A Review of Literature. *Physical Medicine and Rehabilitation International, 1*(5),

8.

Haim, A., Rubin, G., Rozen, N., Goryachev, Y., & Wolf, A. (2012). Reduction in knee adduction moment via non-invasive biomechanical training: A longitudinal gait analysis study. *Journal of Biomechanics*, *45*(1), 41–45.

Haim, A., Segal, G., Elbaz, A., Mor, A., Agar, G., Bar-Ziv, Y., … Atoun, E. (2013). The outcome of a novel biomechanical therapy for patients suffering from anterior knee pain. *The Knee*, *20*(6), 595–599.

Hame, S. L., & Alexander, R. A. (2013). Knee osteoarthritis in women. *Current Reviews in Musculoskeletal Medicine, 6*(2), 182–187.

Hannan, M. T., Anderson, J. J., Zhang, Y., Levy, D., & Felson, D. T. (1993). Bone mineral density and knee osteoarthritis in elderly men and women. The Framingham Study. *Arthritis and Rheumatism*, *36*(12), 1671–1680.

Hannan, M. T., Felson, D. T., & Pincus, T. (2000). Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *The Journal of Rheumatology*, *27*(6), 1513–1517.

Haq, S. A., Davatchi, F., Dahaghin, S., Islam, N., Ghose, A., Darmawan, J., … Rasker, J. J. (2010). Development of a questionnaire for identification of the risk factors for osteoarthritis of the knees in developing countries. A pilot study in Iran and Bangladesh. An ILAR-COPCORD phase III study. *International Journal of Rheumatic Diseases*, *13*(3), 203–214.

Hardcastle, S. A., Dieppe, P., Gregson, C. L., Davey Smith, G., & Tobias, J. H. (2015). Osteoarthritis and bone mineral density: are strong bones bad for joints? *BoneKEy Reports*, *4*(JANUARY), 624.

Harrington, I. J. (1976). A bioengineering analysis of force actions at the knee in normal and pathological gait. *Biomedical Engineering*, *11*(5), 167–172.

Hasan, M., & Shuckett, R. (2010). Clinical features and pathogenetic mechanisms of osteo - arthritis of the hip and knee. *British Columbia Medical Journal, 52*(8), 393–398.

Hassan, B. S., Doherty, S. A., Mockett, S., & Doherty, M. (2002). Effect of pain reduction on postural sway, proprioception, and quadriceps strength in subjects with knee osteoarthritis. *Annals of the Rheumatic Diseases, 61*(5), 422–428.

Hassan, B. S., Mockett, S., & Doherty, M. (2001). Static postural sway, proprioception, and maximal voluntary quadriceps contraction in patients with knee osteoarthritis and normal control subjects. *Annals of The Rheumatic Diseases*, *60*(6), 612–618.

Hatef, M. R., Mirfeizi, Z., Sahebari, M., Jokar, M. H., & Mirheydari, M. (2014). Superiority of laterally elevated wedged insoles to neutrally wedged insoles in medial knee osteoarthritis symptom relief. *International Journal of Rheumatic Diseases*, *17*(1), 84–88.

Hawker, G. A., Croxford, R., Bierman, A. S., Harvey, P. J., Ravi, B., Stanaitis, I., & Lipscombe, L. L. (2014). All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. *PloS One*, *9*(3), e91286.

Health Quality Ontario, H. Q. (2005). Total knee replacement: an evidence-based analysis. *Ontario Health Technology Assessment Series*, *5*(9), 1–51.

Heidari, B. (2011a). Knee osteoarthritis diagnosis, treatment and associated factors of progression: part II. *Caspian Journal of Internal Medicien*, *2*(3), 249–255.

Heidari, B. (2011b). Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. *Caspian Journal of Internal Medicine*, *2*(2), 205–212.

Heiden, T. L., Lloyd, D. G., & Ackland, T. R. (2009). Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait. *Clinical Biomechanics*, *24*(10), 833–841.

Henriksen, M., Graven-Nielsen, T., Aaboe, J., Andriacchi, T. P., & Bliddal, H. (2010). Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. *Arthritis Care and Research*, *62*(4), 501–509.

Henriksen, M., Klokker, L., Bartholdy, C., Schjoedt-Jorgensen, T., Bandak, E., & Bliddal, H. (2017). No effects of functional exercise therapy on walking biomechanics in patients with knee osteoarthritis: exploratory outcome analyses from a randomised trial. *BMJ Open Sport & Exercise Medicine*, *2*(1).

Henriksen, M., Simonsen, E. B., Alkjaer, T., Lund, H., Graven-Nielsen, T., Danneskiold-Samsøe, B., & Bliddal, H. (2006). Increased joint loads during walking--a consequence of pain relief in knee osteoarthritis. *The Knee*, *13*(6), 445–50.

Hensor, E. M. A., Dube, B., Kingsbury, S. R., Tennant, A., & Conaghan, P. G. (2015). Toward a clinical definition of early osteoarthritis: onset of patient-reported knee pain begins on stairs. Data from the osteoarthritis initiative. *Arthritis Care and Research*, *67*(1), 40–47.

Hermens, H. J., Freriks, B., Disselhorst-Klug, C., & Rau, G. (2000). Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology*, *10*(5), 361–374.

Herrington, L., Hatcher, J., Hatcher, A., & McNicholas, M. (2009). A comparison of star excursion balance test reach distances between ACL deficient patients and asymptomatic controls. *Knee*, *16*(2), 149–152.

Hertel, J., Braham, R. A., Hale, S. A., & Olmsted-Kramer, L. C. (2006). Simplifying the Star Excursion Balance Test: Analyses of Subjects With and Without Chronic Ankle Instability. *Journal of Orthopaedic and Sports Physical Therapy*, *36*(3), 131–137.

Hertel, J., Miller, S. J., & Denegar, C. R. (2000). Intratester and intertester reliability during the Star Excursion Balance Tests. *Journal of Sport Rehabilitation*, *9*(2), 104–116.

Hewitt, B. A., Refshauge, K. M., & Kilbreath, S. L. (2002). Kinesthesia at the knee: the effect of osteoarthritis and bandage application. *Arthritis and Rheumatism*, *47*(5), 479–483.

Hill, C. L., Gale, D. G., Chaisson, C. E., Skinner, K., Kazis, L., Gale, M. E., & Felson, D. T. (2001). Knee effusions, popliteal cysts, and synovial thickening: Association with knee pain in osteoarthritis. *The Journal of Rheumatology*, 28(6), 1330–1337.

Hill, C. L., Hunter, D. J., Niu, J., Clancy, M., Guermazi, A., Genant, H., … Felson, D. T. (2007). Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Annals of the Rheumatic Diseases, 66*(12), 1599–1603.

Hill, K. D., Bernhardt, J., McGann, A. M., Maltese, D., & Berkovits, D. (1996). A New Test of Dynamic Standing Balance for Stroke Patients: Reliability, Validity and Comparison with Healthy

Elderly. *Physiotherapy Canada*, *48*(4), 257–262.

Hinman, R. S., & Bennell, K. L. (2009). Advances in insoles and shoes for knee osteoarthritis. *Current Opinion in Rheumatology*, *21*(2), 164–170.

Hinman, R. S., & Crossley, K. M. (2007). Patellofemoral joint osteoarthritis: An important subgroup of knee osteoarthritis. *Rheumatology, 46*(7), 1057–1062.

Hinman, R. S., Bennell, K. L., Metcalf, B. R., & Crossley, K. M. (2002). Balance impairments in individuals with symptomatic knee osteoarthritis: a comparison with matched controls using clinical tests. *Rheumatology*, *41*(12), 1388–1394.

Hinman, R. S., Bowles, K. A., & Bennell, K. L. (2009). Laterally wedged insoles in knee osteoarthritis: do biomechanical effects decline after one month of wear? *BMC Musculoskeletal Disorders*, *10*(1), 146.

Hinman, R. S., Bowles, K. A., Metcalf, B. B., Wrigley, T. V., & Bennell, K. L. (2012). Lateral wedge insoles for medial knee osteoarthritis: Effects on lower limb frontal plane biomechanics. *Clinical Biomechanics, 27*(1), 27–33.

Hinman, R. S., Bowles, K. A., Payne, C., & Bennell, K. L. (2008a). Effect of length on laterally-wedged insoles in knee osteoarthritis. *Arthritis and Rheumatism*, *59*(1), 144–147.

Hinman, R. S., Hunt, M. a., Creaby, M. W., Wrigley, T. V., McManus, F. J., & Bennell, K. L. (2010). Hip muscle weakness in individuals with medial knee osteoarthritis. *Arthritis Care and Research*, *62*(8), 1190–1193.

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008b). Lateral wedges in knee osteoarthritis: What are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome?. *Arthritis Care and Research*, *59*(3), 408–415.

Hinman, R. S., Wrigley, T. V., Metcalf, B. R., Campbell, P. K., Paterson, K. L., Hunter, D. J., … Bennell, K. L. (2016). Unloading Shoes for Self-management of Knee Osteoarthritis. *Annals of Internal Medicine*, *165*(6), 381.

Hochberg, M. C. (1996). Prognosis of osteoarthritis. *Annals of the Rheumatic Diseases, 55*(9), 685–8.

Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., McGowan, J., … Tugwell, P. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care and Research*, *64*(4), 465–474.

Hodges, P. W., van den Hoorn, W., Wrigley, T. V., Hinman, R. S., Bowles, K.-A., Cicuttini, F., … Bennell, K. (2015). Increased duration of co-contraction of medial knee muscles is associated with greater progression of knee osteoarthritis. *Manual Therapy*, *21*, 151–158.

Hofman, A., Grobbee, D. E., de Jong, P. T., & van den Ouweland, F. A. (1991). Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *European Journal of Epidemiology*, *7*(4), 403–22.

Holla, J. F. M., Steultjens, M., Van Der Leeden, M., Roorda, L. D., Bierma-Zeinstra, S. M. A., Den Broeder, A. A., & Dekker, J. (2011). Determinants of range of joint motion in patients with

early symptomatic osteoarthritis of the hip and/or knee: an exploratory study in the CHECK cohort. *Osteoarthritis and Cartilage, 19 (4)*, 411–419.

Hootman, J. M., Fitzgerald, S. J., Macera, C. A., & Blair, S. N. (2004). Lower Extremity Muscle Strength and Risk of Self- Reported Hip or Knee Osteoarthritis Lower Extremity Muscle Strength and Risk of Self-Reported Hip or Knee Osteoarthritis. *Journal of Physical Activity and Health Journal of Physical Activity and Health Journal of Physical Activity and Health*, 1(1), 321–330.

Hortobágyi, T., Westerkamp, L., Beam, S., Moody, J., Garry, J., Holbert, D., & DeVita, P. (2005). Altered hamstring-quadriceps muscle balance in patients with knee osteoarthritis. *Clinical Biomechanics*, *20*(1), 97–104.

Huang, S.-C. C., Wei, I.-P. P., Chien, H.-L. L., Wang, T.-M. M., Liu, Y.-H. H., Chen, H.-L. L., … Lin, J.-G. G. (2008). Effects of severity of degeneration on gait patterns in patients with medial knee osteoarthritis. *Medical Engineering and Physics*, *30*(8), 997–1003.

Hubley-Kozey, C. L, Deluzio, K., & Dunbar, M. (2008). Muscle co-activation patterns during walking in those with severe knee osteoarthritis. *Clinical Biomechanics*, *23*(1), 71–80.

Hubley-Kozey, C. L., Hill, N. A., Rutherford, D. J., Dunbar, M. J., & Stanish, W. D. (2009). Co-activation differences in lower limb muscles between asymptomatic controls and those with varying degrees of knee osteoarthritis during walking. *Clinical Biomechanics*, *24*(5), 407–414.

Hubley-Kozey, C. L., Robbins, S. M., Rutherford, D. J., & Stanish, W. D. (2013). Reliability of surface electromyographic recordings during walking in individuals with knee osteoarthritis. *Journal of Electromyography and Kinesiology*, *23*(2), 334–341.

Hunt, M. A., Birmingham, T. B., Bryant, D., Jones, I., Giffin, J. R., Jenkyn, T. R., & Vandervoort, A. A. (2008). Lateral trunk lean explains variation in dynamic knee joint load in patients with medial compartment knee osteoarthritis. *Osteoarthritis and Cartilage*, *16*(5), 591–599.

Hunt, M. A., Charlton, J. M., Krowchuk, N. M., Tse, C. T., & Hatfield, G. L. (2018). A randomized controlled trial investigating clinical and biomechanical changes following toe-out gait modification for knee osteoarthritis. *Osteoarthritis and Cartilage*, *26*, S16–S17.

Hunt, M. A., Wrigley, T. V., Hinman, R. S., & Bennell, K. L. (2010). Individuals with severe knee osteoarthritis (OA) exhibit altered proximal walking mechanics compared with individuals with less severe OA and those without knee pain. *Arthritis Care and Research*, *62*(10), 1426–1432.

Hunter, D. J. (2009). Imaging insights on the epidemiology and pathophysiology of osteoarthritis. *Rheumatic Diseases Clinics of North America*, *35*(3), 447–63.

Hunter, D. J., Guermazi, A., Roemer, F., Zhang, Y., & Neogi, T. (2013). Structural correlates of pain in joints with osteoarthritis. *Osteoarthritis and Cartilage, 21*(9), 1170–1178.

Hunter, D. J., Niu, J., Felson, D. T., Harvey, W. F., Gross, K. D., McCree, P., … Zhang, Y. (2007). Knee alignment does not predict incident osteoarthritis: the Framingham osteoarthritis study. *Arthritis and Rheumatism*, *56*(4), 1212–1218.

Hurley, M. V, Scott, D. L., Rees, J., & Newham, D. J. (1997). Sensorimotor changes and functional performance in patients with knee osteoarthritis. *Annals of The Rheumatic Diseases*, *56*(11), 641–8.

Hurwitz, D. E., Ryals, a. B., Case, J. P., Block, J. A., & Andriacchi, T. P. (2002). The knee

adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. *Journal of Orthopaedic Research, 20*(1), 101–107.

Hurwitz, D. E., Sumner, D. R., Andriacchi, T. P., & Sugar, D. A. (1998). Dynamic knee loads during gait predict proximal tibial bone distribution. *Journal of Biomechanics*, *31*(5), 423–30.

Iannone, F., & Lapadula, G. (2003). The pathophysiology of osteoarthritis. *Aging Clinical and Experimental Research*, *15*(5), 364–372.

Imamura, M., Imamura, S. T., Kaziyama, H. H. S., Targino, R. A., Hsing, W. T., de Souza, L. P. M., … Camanho, G. L. (2008). Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. *Arthritis and Rheumatism*, *59*(10), 1424–1431.

Institute of Medicine (2011). *Relieving Pain in America: A Blueprint for Transforming Prevention, Cure, Education and Researech.* Washington, DC: The National Academies Press.

Jadelis, K., Miller, M. E., Ettinger, W. H., & Messier, S. P. (2001). Strength, balance, and the modifying effects of obesity and knee pain: Results from the observational arthritis study in seniors (OASIS). *Journal of the American Geriatrics Society*, *49*(7), 884–891.

Jan, M. H., Lin, C. H., Lin, Y. F., Lin, J. J., & Lin, D. H. (2009). Effects of Weight-Bearing Versus Nonweight-Bearing Exercise on Function, Walking Speed, and Position Sense in Participants With Knee Osteoarthritis: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*, *90*(6), 897–904.

Jenkyn, T. R., Hunt, M. a., Jones, I. C., Giffin, J. R., & Birmingham, T. B. (2008). Toe-out gait in patients with knee osteoarthritis partially transforms external knee adduction moment into flexion moment during early stance phase of gait: A tri-planar kinetic mechanism. *Journal of Biomechanics*, *41*(2), 276–283.

Jerosch, J., & Prymka, M. (1996). Proprioception and joint stability. *Knee Surgery, Sports Traumatology, Arthroscopy*, *4*(3), 171–179.

Jette, A. M., & Branch, L. G. (1985). Impairment and disability in the aged. *Journal of Chronic Diseases*, *38*(1), 59–65.

Jiang, L., Rong, J., Zhang, Q., Hu, F., Zhang, S., Li, X., … Tao, T. (2012a). Prevalence and associated factors of knee osteoarthritis in a community-based population in Heilongjiang, Northeast China. *Rheumatology International*, *32*(5), 1189–2295.

Jiang, L., Tian, W., Wang, Y., Rong, J., Bao, C., Liu, Y., … Wang, C. (2012b). Body mass index and susceptibility to knee osteoarthritis: A systematic review and meta-analysis. *Joint Bone Spine*, *79*(3), 291–297.

Johnson, F., Leitl, S., & Waugh, W. (1980). The distribution of load across the knee. A comparison of static and dynamic measurements. *The Journal of Bone and Joint Surgery*, *62*(3), 346–349.

Jones, R. K., Chapman, G. J., Findlow, A. H., Forsythe, L., Parkes, M. J., Sultan, J., & Felson, D. T. (2013a). A new approach to prevention of knee osteoarthritis: Reducing medial load in the contralateral knee. *The Journal of Rheumatology*, *40*(3), 309–315.

Jones, R. K., Chapman, G. J., Forsythe, L., Parkes, M. J., & Felson, D. T. (2014). The relationship

between reductions in knee loading and immediate pain response whilst wearing lateral wedged insoles in knee osteoarthritis. *Journal of Orthopaedic Research*, *32*(9), 1147–1154.

Jones, R. K., Chapman, G. J., Parkes, M. J., Forsythe, L., & Felson, D. T. (2015). The effect of different types of insoles or shoe modifications on medial loading of the knee in persons with medial knee osteoarthritis: a randomised trial. *Journal of Orthopaedic Research*, *33*(11), 1646–1654.

Jones, R. K., Nester, C. J., Richards, J. D., Kim, W. Y., Johnson, D. S., Jari, S., … Tyson, S. F. (2013b). A comparison of the biomechanical effects of valgus knee braces and lateral wedged insoles in patients with knee osteoarthritis. *Gait and Posture*, *37*(3), 368–372.

Jones, R. K., Zhang, M., Laxton, P., Findlow, A. H., & Liu, A. (2013c). The biomechanical effects of a new design of lateral wedge insole on the knee and ankle during walking. *Human Movement Science*, *32*(4), 596–604.

Jordan, J. M., Linder, G. F., Renner, J. B., & Fryer, J. G. (1995). The impact of arthritis in rural populations. *Arthritis Care and Research*, *8*(4), 242–250.

Jordan, K. M., Arden, N. K., Doherty, M., Bannwarth, B., Bijlsma, J. W. J., Dieppe, P., … Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT. (2003). EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of The Rheumatic Diseases*, *62*(12), 1145–1155.

Kadaba, M. P., Ramakrishnan, H. K., & Wootten, M. E. (1990). Measurement of lower extremity kinematics during level walking. *Journal of Orthopaedic Research*, *8*(3), 383–392.

Kadaba, M. P., Ramakrishnan, H. K., Wootten, M. E., Gainey, J., Gorton, G., & Cochran, G. V. B. (1989). Repeatability of kinematic, kinetic, and electromyographic data in normal adult gait. *Journal of Orthopaedic Research*, *7*(6), 849–860.

Kadaba, M. P., Wootten, M. E., Gainey, J., & Cochran, G. V. B. (1985). Repeatability of phasic muscle activity: Performance of surface and intramuscular wire electrodes in gait analysis. *Journal of Orthopaedic Research*, *3*(3), 350–359.

Kakihana, W., Akai, M., Nakazawa, K., Naito, K., & Torii, S. (2007). Inconsistent knee varus moment reduction caused by a lateral wedge in knee osteoarthritis. *American Journal of Physical Medicine and Rehabilitation*, *86*(6), 446–454.

Kakihana, W., Akai, M., Nakazawa, K., Takashima, T., Naito, K., & Torii, S. (2005). Effects of laterally wedged insoles on knee and subtalar joint moments. *Archives of Physical Medicine and Rehabilitation*, *86*(7), 1465–1471.

Kakihana, W., Akai, M., Yamasaki, N., Takashima, T., & Nakazawa, K. (2004). Changes of joint moments in the gait of normal subjects wearing laterally wedged insoles. *American Journal of Physical Medicine and Rehabilitation*, *83*(4), 273–278.

Kaklamanis, P., Leeb, B., Lequesne, M., Lohmander, S., Mazieres, B., Martin-Mola, E., … Jordan, K. (2005). EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Annals of The Rheumatic Diseases*, *64*(5), 669–681.

Kaufman, K. and Sutherland, D. (2006). *Kinematics of normal human walking.* Philadelphia: Lippincoti Williams and Wilkins.

Kaufman, K. R., Hughes, C., Morrey, B. F., Morrey, M., & An, K. N. (2001). Gait characteristics of patients with knee osteoarthritis. *Journal of Biomechanics*, *34*(7), 907–915.

Kean, C. O., Birmingham, T. B., Garland, S. J., Bryant, D. M., & Giffin, J. R. (2011). Preoperative strength training for patients undergoing high tibial osteotomy: a prospective cohort study with historical controls. *The Journal of Orthopaedic and Sports Physical Therapy*, *41*(2), 52–59.

Kean, C. O., Hinman, R. S., Bowles, K. A., Cicuttini, F., Davies-Tuck, M., & Bennell, K. L. (2012). Comparison of peak knee adduction moment and knee adduction moment impulse in distinguishing between severities of knee osteoarthritis. *Clinical Biomechanics*, *27*(5), 520–523.

Keating, E. M., Faris, P. M., Ritter, M. A., & Kane, J. (1993). Use of lateral heel and sole wedges in the treatment of medial osteoarthritis of the knee. *Orthopaedic Review*, *22*(9), 921–924.

Kemp, G., Crossley, K. M., Wrigley, T. V, Metcalf, B. R., & Hinman, R. S. (2008). Reducing joint loading in medial knee osteoarthritis: shoes and canes. *Arthritis and Rheumatism*, *59*(5), 609–614.

Kennedy, D. M., Stratford, P. W., Wessel, J., Gollish, J. D., & Penney, D. (2005). Assessing stability and change of four performance measures: a longitudinal study evaluating outcome following total hip and knee arthroplasty. *BMC Musculoskeletal Disorders*, *6*(1), 3.

Kerrigan, D. C., Karvosky, M. E., Lelas, J. L., & Riley, P. O. (2003). Men's shoes and knee joint torques relevant to the development and progression of knee osteoarthritis. *The Journal of Rheumatology*, *30*(3), 529–533.

Kerrigan, D. C., Lelas, J. L., Goggins, J., Merriman, G. J., Kaplan, R. J., & Felson, D. T. (2002). Effectiveness of a lateral-wedge insole on knee varus torque in patients with knee osteoarthritis. *Archives of Physical Medicine and Rehabilitation*, *83*(7), 889–893.

Keyaki, K., & Toda, Y. (2010). The Efficacy and Compliance of an Elastic Knee Sleeve Combined With the Subtalar Strapped Insole for Patients With Osteoarthritis of the Knee. *Osteoarthritis and Cartilage*, *18*(18), S229.

Khan, M., Evaniew, N., Bedi, A., Ayeni, O. R., & Bhandari, M. (2014). Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis. *Canadian Medical Association Journal*, *186*(14), 1057–1064.

Khan, T., Alvand, A., Prieto-Alhambra, D., Culliford, D. J., Judge, A., Jackson, W. F., … Price, A. J. (2018). ACL and meniscal injuries increase the risk of primary total knee replacement for osteoarthritis: a matched case-control study using the Clinical Practice Research Datalink (CPRD). *British Journal of Sports Medicine*, 2017-097762.

Khan, W. S., Jones, R. K., Nokes, L., & Johnson, D. S. (2007). The relationship of the angle of immobilisation of the knee to the force applied to the extensor mechanism when partially weight-bearing. A gait-analysis study in normal volunteers. *The Journal of Bone and Joint Surgery*, *89*(7), 911–914.

Kharb, A., Saini, V., Jain, Y., & Dhiman, S. (2011). A review of gait cycle and its parameters. *International Journal of Computational Engineering and Managemen*, *13*(July), 78–83.

Kidd, B. L. (2006). Osteoarthritis and joint pain. *Pain*, *123*(1–2), 6–9.

Kim, W. Y., Richards, J., Jones, R. K., & Hegab, A. (2004). A new biomechanical model for the functional assessment of knee osteoarthritis. *The Knee*, *11*(3), 225–231.

Kinds, M. B., Welsing, P. M. J., Vignon, E. P., Bijlsma, J. W. J., Viergever, M. A., Marijnissen, A. C. A., & Lafeber, F. P. J. G. (2011). A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. *Osteoarthritis and Cartilage*, *19*(7), 768–778.

Kinzey, S. J., & Armstrong, C. W. (1998). The reliability of the star-excursion test in assessing dynamic balance. *The Journal of Orthopaedic and Sports Physical Therapy*, *27*(5), 356–60.

Kirkley, a, Webster-Bogaert, S., Litchfield, R., Amendola, A., MacDonald, S., McCalden, R., & Fowler, P. (1999). The effect of bracing on varus gonarthrosis. *The Journal of Bone and Joint Surgery.*, *81*(4), 539–548.

Ko, C.-Y., Chang, Y., Jeong, B., Kang, S., Ryu, J., & Kim, G. (2017). Effects of knee sleeves on coordination of lower-limb segments in healthy adults during level walking and one-leg hopping. *PeerJ*, *5*, e3340.

Koceja, D. M., Allway, D., & Earles, D. R. (1999). Age differences in postural sway during volitional head movement. *Archives of Physical Medicine and Rehabilitation*, *80*(12), 1537–1541.

Kohatsu, N. D., & Schurman, D. J. (1990). Risk factors for the development of osteoarthrosis of the knee. *Clinical Orthopaedics and Related Research*, (261), 242–246.

Komistek, R. D., Dennis, D. A., Northcut, E. J., Wood, A., Parker, A. W., & Traina, S. M. (1999). An in vivo analysis of the effectiveness of the osteoarthritic knee brace during heel-strike of gait. *Journal of Arthroplasty*, *14*(6), 738–742.

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine*, *15*(2), 155–63.

Koralewicz, L. M., & Engh, G. A. (2000). Comparison of proprioception in arthritic and age-matched normal knees. *The Journal of Bone and Joint Surgery*, *82–A*(11), 1582–1588.

Kosek, E., & Ordeberg, G. (2000). Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. *European Journal of Pain*, *4*(3), 229–238.

Kropmans, T. J., Dijkstra, P. U., Stegenga, B., Stewart, R., & de Bont, L. G. (1999). Smallest detectable difference in outcome variables related to painful restriction of the temporomandibular joint. *Journal of Dental Research*, *78*(3), 784–789.

Kutzner, I., Damm, P., Heinlein, B., Dymke, J., Graichen, F., & Bergmann, G. (2011). The effect of laterally wedged shoes on the loading of the medial knee compartment-in vivo measurements with instrumented knee implants. *Journal of Orthopaedic Research*, *29*(12), 1910–1915.

Kutzner, I., Trepczynski, A., Heller, M. O., & Bergmann, G. (2013). Knee adduction moment and medial contact force--facts about their correlation during gait. *PloS One*, *8*(12), e81036.

Landry, S. C., McKean, K. A., Hubley-Kozey, C. L., Stanish, W. D., & Deluzio, K. J. (2007). Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. *Journal of Biomechanics*, *40*(8), 1754–1761.

Lane, N. E., Schnitzer, T. J., Birbara, C. A., Mokhtarani, M., Shelton, D. L., Smith, M. D., &

Brown, M. T. (2010). Tanezumab for the Treatment of Pain from Osteoarthritis of the Knee. *New England Journal of Medicine*, *363*(16), 1521–1531.

Laroche, D., Morisset, C., Fortunet, C., Gremeaux, V., Maillefert, J. F., & Ornetti, P. (2014). Biomechanical effectiveness of a distraction-rotation knee brace in medial knee osteoarthritis: Preliminary results. *Knee*, *21*(3), 710–716.

Lau, R. L., Gandhi, R., Mahomed, S., & Mahomed, N. (2012). Patient Satisfaction after Total Knee and Hip Arthroplasty. *Clinics in Geriatric Medicine*, *28*(3), 349–365.

Lawrence, R. C., Felson, D. T., Helmick, C. G., Arnold, L. M., Choi, H., Deyo, R. A., … Wolfe, F. (2008). Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis and Rheumatism*, *58*(1), 26–35.

Ledingham, J., Regan, M., Jones, A., & Doherty, M. (1993). Radiographic patterns and associations of osteoarthritis of the knee in patients referred to hospital. *Annals of The Rheumatic Diseases*, *52*(7), 520–526.

Lee, A. S., Ellman, M. B., Yan, D., Kroin, J. S., Cole, B. J., van Wijnen, A. J., & Im, H.-J. (2013). A current review of molecular mechanisms regarding osteoarthritis and pain. *Gene, 527*(2), 440–447.

Lee, H.-J., Park, H.-J., Chae, Y., Kim, S.-Y., Kim, S.-N., Kim, S.-T., … Lee, H. (2009). Tai Chi Qigong for the quality of life of patients with knee osteoarthritis: a pilot, randomized, waiting list controlled trial. *Clinical Rehabilitation*, *23*(6), 504–511.

Leitch, K. M., Birmingham, T. B., Jones, I. C., Giffin, J. R., & Jenkyn, T. R. (2011). In-shoe plantar pressure measurements for patients with knee osteoarthritis: Reliability and effects of lateral heel wedges. *Gait and Posture*, *34*(3), 391–396.

Lephart, S. M., Pincivero, D. M., & Rozzi, S. L. (1998). Proprioception of the ankle and knee. *Sports Medicine*, *25*(3), 149–155.

Lespasio, M. J., Piuzzi, N. S., Husni, M. E., Muschler, G. F., Guarino, A., & Mont, M. A. (2017). Knee Osteoarthritis: A Primer. *The Permanente Journal*, *21*.

Levine, D., Richards, J., & Whittle, M. (2012). *Whittle's gait analysis*. Churchill Livingstone/Elsevier.

Levinger, P., Menz, H. B., Fotoohabadi, M. R., Feller, J. a, Bartlett, J. R., & Bergman, N. R. (2010). Foot posture in people with medial compartment knee osteoarthritis. *Journal of Foot and Ankle Research*, *3*(1), 29.

Lewek, M. D., Ramsey, D. K., Snyder-Mackler, L., & Rudolph, K. S. (2005). Knee stabilization in patients with medial compartment knee osteoarthritis. *Arthritis and Rheumatism*, *52*(9), 2845–2853.

Lewek, M. D., Rudolph, K. S., & Snyder-Mackler, L. (2004a). Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. *Osteoarthritis and Cartilage*, *12*(9), 745–751.

Lewek, M. D., Rudolph, K. S., & Snyder-Mackler, L. (2004b). Quadriceps femoris muscle weakness and activation failure in patients with symptomatic knee osteoarthritis. *Journal of Orthopaedic Research*, *22*(1), 110–115.

Lewek, M. D., Scholz, J., Rudolph, K. S., & Snyder-Mackler, L. (2006). Stride-to-stride variability of knee motion in patients with knee osteoarthritis. *Gait and Posture*, *23*(4), 505–511.

Lewinson, R. T., Collins, K. H., Vallerand, I. a, Wiley, J., Woodhouse, L. J., Reimer, R. a, … Stefanyshyn, D. J. (2014). Reduced knee joint loading with lateral and medial wedge insoles for management of knee osteoarthritis: a protocol for a randomized controlled trial. *BMC Musculoskeletal Disorders*, *15*(1), 405.

Lidtke, R. H., Muehleman, C., Kwasny, M., & Block, J. A. Foot center of pressure and medial knee osteoarthritis. *Journal of the American Podiatric Medical Association*, *100*(3), 178–184.

Liikavainio, T., Bragge, T., Hakkarainen, M., Karjalainen, P. A., & Arokoski, J. P. (2010). Gait and muscle activation changes in men with knee osteoarthritis. *Knee*, *17*(1), 69–76.

Lim, B. W., Hinman, R. S., Wrigley, T. V., Sharma, L., & Bennell, K. L. (2008). Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. *Arthritis Care and Research*, *59*(7), 943–951.

Lin, D. H., Lin, Y. F., Chai, H. M., Han, Y. C., & Jan, M. H. (2007). Comparison of proprioceptive functions between computerized proprioception facilitation exercise and closed kinetic chain exercise in patients with knee osteoarthritis. *Clinical Rheumatology*, *26*(4), 520–528.

Lin, D.-H., Lin, C.-H. J., Lin, Y.-F., & Jan, M.-H. (2009). Efficacy of 2 Non-Weight-Bearing Interventions, Proprioception Training Versus Strength Training, for Patients With Knee Osteoarthritis: A Randomized Clinical Trial. *Journal of Orthopaedic and Sports Physical Therapy*, *39*(6), 450–457.

Lin, W., Alizai, H., Joseph, G. B., Srikhum, W., Nevitt, M. C., Lynch, J. A., … Link, T. M. (2013). Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. *Osteoarthritis and Cartilage*, *21*(10), 1558–1566.

Lindenfeld, T. N., Hewett, T. E., & Andriacchi, T. P. (1997). Joint loading with valgus bracing in patients with varus gonarthrosis. *Clinical Orthopaedics and Related Research*, (344), 290–297.

Linley, H. S., Sled, E. A., Culham, E. G., & Deluzio, K. J. (2010). A biomechanical analysis of trunk and pelvis motion during gait in subjects with knee osteoarthritis compared to control subjects. *Clinical Biomechanics*, *25*(10), 1003–3010.

Liu, X., & Zhang, M. (2013). Redistribution of knee stress using laterally wedged insole intervention: Finite element analysis of knee-ankle-foot complex. *Clinical Biomechanics*, *28*(1), 61–67.

Lix, L. M., Keselman, J. C., & Keselman, H. J. (1996). Consequences of Assumption Violations Revisited: A Quantitative Review of Alternatives to the One-Way Analysis of Variance "F" Test. *Review of Educational Research*, *66*(4), 579.

Lloyd, D. G., & Buchanan, T. S. (2001). Strategies of muscular support of varus and valgus isometric loads at the human knee. *Journal of Biomechanics*, *34*(10), 1257–1267.

Lohmander, L. S., Lark, M. W., Dahlberg, L., Walakovits, L. A., & Roos, H. (1992). Cartilage matrix metabolism in osteoarthritis: markers in synovial fluid, serum, and urine. *Clinical Biochemistry*, *25*(3), 167–74.

Lohmander, L. S., Ostenberg, A., Englund, M., & Roos, H. (2004). High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis and Rheumatism*, *50*(10), 3145–3152.

Lonner, J. H. (2009). Indications for unicompartmental knee arthroplasty and rationale for robotic arm-assisted technology. *American Journal of Orthopedics*, *38*(2 Suppl), 3–6.

Losina, E., Weinstein, A. M., Reichmann, W. M., Burbine, S. A., Solomon, D. H., Daigle, M. E., … Katz, J. N. (2013). Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care and Research*, *65*(5), 703–711.

Lu, T.-W. W., Taylor, S. J. G., O'Connor, J. J., & Walker, P. S. (1997). Influence of muscle activity on the forces in the femur: An in vivo study. *Journal of Biomechanics*, *30*(11–12), 1101–1106.

Lundblad, H., Kreicbergs, A., & Jansson, K.-å. (2008). Prediction of persistent pain after total knee replacement for osteoarthritis. *The Journal of Bone and Joint Surgery. British Volume*, *90–B*(2), 166–171.

Lynn, S. K., & Costigan, P. A. (2008). Effect of foot rotation on knee kinetics and hamstring activation in older adults with and without signs of knee osteoarthritis. *Clinical Biomechanics*, *23*(6), 779–786.

Macfarlane, G. J. (2010). *Life-course influences on chronic pain in adults. In Chronic Pain Epidemiology: From Aetiology to Public Health.* Oxford, England: Oxford University Press.

Magerl, W., Krumova, E. K., Baron, R., Tölle, T., Treede, R.-D., & Maier, C. (2010). Reference data for quantitative sensory testing (QST): Refined stratification for age and a novel method for statistical comparison of group data. *PAIN®*, *151*(3), 598–605.

Maillefert, J. F., Hudry, C., Baron, G., Kieffert, P., Bourgeois, P., Lechevalier, D., … Dougados, M. (2001). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: A prospective randomized controlled study. *Osteoarthritis and Cartilage*, *9*(8), 738–745.

Malfait, B., Sankey, S., Azidin, R. M. F. R., Deschamps, K., Vanrenterghem, J., Robinson, M. A., … Verschueren, S. (2014). How reliable are lower-limb kinematics and kinetics during a drop vertical jump?. *Medicine and Science in Sports and Exercise*, *46*(4), 678–685.

Maly, M. R., Costigan, P. A., & Olney, S. J. (2006). Determinants of Self-Report Outcome Measures in People With Knee Osteoarthritis. *Archives of Physical Medicine and Rehabilitation, 87*(1), 96–104.

Maly, M. R., Culham, E. G., & Costigan, P. a. (2002). Static and dynamic biomechanics of foot orthoses in people with medial compartment knee osteoarthritis. *Clinical Biomechanics*, *17*(8), 603–610.

Manal, K., McClay, I., Stanhope, S., Richards, J., & Galinat, B. (2000). Comparison of surface mounted markers and attachment methods in estimating tibial rotations during walking: An in vivo study. *Gait and Posture*, *11*(1), 38–45.

March, L. M., & Bachmeier, C. J. M. (1997). Economics of osteoarthritis: A global perspective. *Bailliere's. Clinical Rheumatology*, *11*(4), 817–834.

Marks, R., & Penton, L. (2004). Are foot orthotics efficacious for treating painful medial compartment knee osteoarthritis? A review of the literature. *International Journal of Clinical*

Practice, *58*(1), 49–57.

Marks, R., Quinney, H. A., & Wessel, J. (1993). Proprioceptive sensibility in women with normal and osteoarthritic knee joints. *Clinical Rheumatology*, *12*(2), 170–175.

Marriott, K. A., Birmingham, T., Moyer, R., Kanko, L., Pinto, R., Primeau, C., & Giffin, R. (2017). Association between high external knee adduction moment and increased pain during walking: within-limb comparisons in patients with medial compartment knee osteoarthritis. *Osteoarthritis and Cartilage*, *25*, S112.

Martin, K. A., Rejeski, W. J., Miller, M. E., James, M. K., Ettinger, W. H., & Messier, S. P. (1999). Validation of the PASE in older adults with knee pain and physical disability. *Medicine and Science in Sports and Exercise*, *31*(5), 627–33.

Mathers, C., & Penm, R. (1999). *Health System Costs of Injury, Poisoning and Musculoskeletal Disorders in Australia, 1993-94*. Australian Institute of Health and Welfare.

Matsuda, S., Kawahara, S., Okazaki, K., Tashiro, Y., & Iwamoto, Y. (2013). Postoperative Alignment and ROM Affect Patient Satisfaction After TKA. *Clinical Orthopaedics and Related Research®*, *471*(1), 127–133.

Mazzuca, S. a., Page, M. C., Meldrum, R. D., Brandt, K. D., & Petty-Saphon, S. (2004). Pilot study of the effects of a heat-retaining knee sleeve on joint pain, stiffness, and function in patients with knee osteoarthritis. *Arthritis Care and Research*, *51*(5), 716–721.

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., … Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage*, *22*(3), 363–388.

McAlindon, T. E., Jacques, P., Zhang, Y., Hannan, M. T., Aliabadi, P., Weissman, B., … Felson, D. T. (1996). Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis?. *Arthritis and Rheumatism*, *39*(4), 648–656.

McCarthy, C. J., Mills, P. M., Pullen, R., Richardson, G., Hawkins, N., Roberts, C. R., … Oldham, J. A. (2004). Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis. *Health Technology Assessment*, *8*(46), iii–iv.

McGinley, J. L., Baker, R., Wolfe, R., & Morris, M. E. (2009). The reliability of three-dimensional kinematic gait measurements: A systematic review. *Gait and Posture*, *29*(3), 360–369.

McKean, K. A., Landry, S. C., Hubley-Kozey, C. L., Dunbar, M. J., Stanish, W. D., & Deluzio, K. J. (2007). Gender differences exist in osteoarthritic gait. *Clinical Biomechanics, 22(*4), 400–409.

McKnight, P. E., Kasle, S., Going, S., Villanueva, I., Cornett, M., Farr, J., … Zautra, A. (2010). A comparison of strength training, self-management, and the combination for early osteoarthritis of the knee. *Arthritis Care and Research*, *62*(1), 45–53.

Melbourne, S. (2009). *Guideline for the non-surgical management of hip and knee osteoarthritis*. The Royal Australian College of General Practitioners.

Meng, X. L., Zhang, Z. Q., Sun, S. Y., Wu, J. K., & Wong, W. C. (2012). Biomechanical model-based displacement estimation in micro-sensor motion capture. *Measurement Science and*

Technology, *23*(5), 055101.

Messier, S. P. (2008). Obesity and osteoarthritis: disease genesis and nonpharmacologic weight management. *Rheumatic Diseases Clinics of North America*, *34*(3), 713–729.

Messier, S. P., DeVita, P., Cowan, R. E., Seay, J., Young, H. C., & Marsh, A. P. (2005). Do older adults with knee osteoarthritis place greater loads on the knee during gait? A preliminary study. *Archives of Physical Medicine and Rehabilitation*, *86*(4), 703–709.

Messier, S. P., Loeser, R. F., Hoover, J. L., Semble, E. L., & Wise, C. M. (1992). Osteoarthritis of the knee: effects on gait, strength, and flexibility. *Archives of Physical Medicine and Rehabilitation*, *73*(1), 29–36.

Messier, S. P., Loeser, R. F., Miller, G. D., Morgan, T. M., Rejeski, W. J., Sevick, M. A., … Williamson, J. D. (2004). Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis and Rheumatism*, *50*(5), 1501–1510.

Meyer, A. J., D'Lima, D. D., Besier, T. F., Lloyd, D. G., Colwell, C. W., & Fregly, B. J. (2013). Are external knee load and EMG measures accurate indicators of internal knee contact forces during gait?. *Journal of Orthopaedic Research*, *31*(6), 921–929.

Miller, A. A., Knight, K. L., Feland, J. B., & Draper, D. O. (2005). Neoprene thigh sleeves and muscle cooling after exercise. *Journal of Athletic Training*, *40*(4), 264–270.

Mills, K., Hunt, M. A., & Ferber, R. (2013). No evidence of a consistent alteration in the external knee adduction moment during gait in individuals with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis and Cartilage* (Vol. 21).

Misra, D., Booth, S. L., Tolstykh, I., Felson, D. T., Nevitt, M. C., Lewis, C. E., … Neogi, T. (2013). Vitamin K Deficiency Is Associated with Incident Knee Osteoarthritis. *The American Journal of Medicine*, *126*(3), 243–248.

Mistry, D. A., Chandratreya, A., & Lee, P. Y. F. (2018). An Update on Unloading Knee Braces in the Treatment of Unicompartmental Knee Osteoarthritis from the Last 10 Years: A Literature Review. The *Surgery Journal*, *4*(3), e110–e118.

Miyazaki, T., Wada, M., Kawahara, H., Sato, M., Baba, H., & Shimada, S. (2002). Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Annals of The Rheumatic Diseases*, *61*(7), 617–622.

Mohd Sharif, N. A., Goh, S.-L., Usman, J., & Wan Safwani, W. K. Z. (2017). Biomechanical and functional efficacy of knee sleeves: A literature review. *Physical Therapy in Sport*, *28*, 44–52.

Mohr, M., Lorenzen, K., Palacios-Derflingher, L., Emery, C., & Nigg, B. M. (2018). Reliability of the knee muscle co-contraction index during gait in young adults with and without knee injury history. *Journal of Electromyography and Kinesiology*, *38*, 17–27.

Mølgaard, C. M., & Kersting, U. G. (2013). The effect of shoe design and lateral wedges on knee load and neuromuscular control in healthy subjects during walking. *Footwear Science*, *6*(1), 51–58.

Mootanah, R., Hillstrom, H. J., Gross, K. D., Niu, J., Nevitt, M. C., Lewis, C. E., … Felson, D. (2013). Stance and single support time asymmetry identify unilateral knee OA and the involved

limb: the multicenter osteoarthritis study. *Osteoarthritis and Cartilage*, *21*, S246–S247.

Morrison, J. B. (1970). The mechanics of the knee joint in relation to normal walking. *Journal of Biomechanics*, *3*(1), 51–61.

Moyer, R. F., Birmingham, T. B., Bryant, D. M., Giffin, J. R., Marriot, K. a, & Leitch, K. M. (2014). Valgus bracing for knee osteoarthritis: A meta-analysis of randomized trials. *Arthritis Care and Research*, *67*(4), 493–501.

Moyer, R. F., Birmingham, T. B., Bryant, D. M., Giffin, J. R., Marriott, K. a., & Leitch, K. M. (2015). Biomechanical effects of valgus knee bracing: a systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(2), 178–188.

Moyer, R. F., Birmingham, T. B., Dombroski, C. E., Walsh, R. F., Leitch, K. M., Jenkyn, T. R., & Giffin, J. R. (2013). Combined effects of a valgus knee brace and lateral wedge foot orthotic on the external knee adduction moment in patients with varus gonarthrosis. *Archives of Physical Medicine and Rehabilitation*, *94*(1), 103–112.

Muir, S. W., Berg, K., Chesworth, B., Klar, N., & Speechley, M. (2010). Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis. *Journal of Clinical Epidemiology*, *63*(4), 389–406.

Mündermann, A., Asay, J. L., Mündermann, L., & Andriacchi, T. P. (2008a). Implications of increased medio-lateral trunk sway for ambulatory mechanics. *Journal of Biomechanics*, *41*(1), 165–170.

Mündermann, A., Dyrby, C. O., & Andriacchi, T. P. (2005). Secondary gait changes in patients with medial compartment knee osteoarthritis: Increased load at the ankle, knee, and hip during walking. *Arthritis and Rheumatism*, *52*(9), 2835–2844.

Mündermann, A., Dyrby, C. O., D'Lima, D. D., Colwell, C. W., & Andriacchi, T. P. (2008b). In vivo knee loading characteristics during activities of daily living as measured by an instrumented total knee replacement. *Journal of Orthopaedic Research*, *26*(9), 1167–1172

Mündermann, A., Dyrby, C. O., Hurwitz, D. E., Sharma, L., & Andriacchi, T. P. (2004). Potential Strategies to Reduce Medial Compartment Loading in Patients With Knee Osteoarthritis of Varying Severity: Reduced Walking Speed. *Arthritis and Rheumatism*, *50*(4), 1172–1178.

Munro, A. G., & Herrington, L. C. (2010). Between-session reliability of the star excursion balance test. *Physical Therapy in Sport*, *11*(4), 128–132.

Munro, A., Herrington, L., & Carolan, M. (2012). Reliability of 2-dimensional video assessment of frontal-plane dynamic knee valgus during common athletic screening tasks. *Journal of Sport Rehabilitation*, *21*(1), 7–11.

Murray, M. P., Gore, D. R., & Clarkson, B. H. (1971). Walking patterns of patients with unilateral hip pain due to osteo-arthritis and avascular necrosis. *The Journal of Bone and Joint Surgery*, *53*(2), 259–274.

Mutlu, E. K., & Ozdincler, A. R. (2015). Reliability and responsiveness of algometry for measuring pressure pain threshold in patients with knee osteoarthritis. *Journal of Physical Therapy Science*, *27*(6), 1961–5.

Nadeau, S., McFadyen, B. J., & Malouin, F. (2003). Frontal and sagittal plane analyses of the stair

climbing task in healthy adults aged over 40 years: what are the challenges compared to level walking?. *Clinical Biomechanics, 18*(10), 950–959.

Nakajima, K., Kakihana, W., Nakagawa, T., Mitomi, H., Hikita, A., Suzuki, R., … Fukui, N. (2009). Addition of an arch support improves the biomechanical effect of a laterally wedged insole. *Gait and Posture, 29*(2), 208–213.

National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions--United States, 2003. (2007). *Morbidity and Mortality Weekly Report, 56*(1), 4–7.

National Institute for Health and Care Excellence (NICE). Osteoarthritis, 2006. Retrieved from https://www.nice.org.uk/guidance/cg177/documents/osteoarthritis-update-final-scope2.

National Institute for Health and Clinical Excellence (NICE). NICE guidelines: Osteoarthritis - Care and Management; 2014 Available at:https://www.nice.org.uk/guidance/cg177/chapter/1-Recommendations#non-pharmacological-management-2. Accessed May 24, 2017

Nayak, B. K., & Hazra, A. (2011). How to choose the right statistical test?. *Indian Journal of Ophthalmology, 59*(2), 85–6.

Neelapala, M. B. P. S. (2018). Hip Muscle Strengthening for Knee Osteoarthritis: A Systematic Review of Literature. *Journal of Geriatric Physical Therapy*. doi: 10.1519/JPT.0000000000000214

Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and Cartilage, 21*(9), 1145–1153.

Neogi, T., Felson, D., Niu, J., Nevitt, M., Lewis, C. E., Aliabadi, P., … Zhang, Y. (2009). Association between radiographic features of knee osteoarthritis and pain: Results from two cohort studies. *British Medical Journal 339*(7719), 498–501.

Neumann, D. A. (1989). Biomechanical analysis of selected principles of hip joint protection. *Arthritis Care and Research, 2*(4), 146–155.

Neuprez, A., Delcour, J.-P., Fatemi, F., Gillet, P., Crielaard, J.-M., Bruyère, O., & Reginster, J.-Y. (2016). Patients' Expectations Impact Their Satisfaction following Total Hip or Knee Arthroplasty. *Plos One, 15*(12), 11.

Nevitt, M. C., Lane, N. E., Scott, J. C., Hochberg, M. C., Pressman, A. R., Genant, H. K., & Cummings, S. R. (1995). Radiographic osteoarthritis of the hip and bone mineral density. The Study of Osteoporotic Fractures Research Group. *Arthritis and Rheumatism, 38*(7), 907–916.

Newell, R. S., Hubley-Kozey, C. L., Stanish, W. D., & Deluzio, K. J. (2008). Detecting differences between asymptomatic and osteoarthritic gait is influenced by changing the knee adduction moment model. *Gait and Posture, 27*(3), 485–492.

Newman, A. B., Haggerty, C. L., Goodpaster, B., Harris, T., Kritchevsky, S., Nevitt, M., … Visser, M. (2003). Strength and muscle quality in a well-functioning cohort of older adults: the Health, Aging and Body Composition Study. *Journal of the American Geriatrics Society, 51*(3), 323–330.

Nigg, B. M., MacIntosh, B. R., & Mester, J. (2000). *Biomechanics and biology of movement*. Champaign, Illinois: Human Kinetics.

Niu, Jingbo, Felson, David T., Neogi, Tuhina, Zhang, Y. (2012). Radiographic Osteoarthritis

Severity Is Associated With An Increased Risk Of Developing Knee Pain: Findings From The Osteoarthritis Initiative. *Arthritis Rheum. 64*, S111.

Nüesch, E., Dieppe, P., Reichenbach, S., Williams, S., Iff, S., & Jüni, P. (2011). All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ: British Medical Journal*, *342*, d1165.

O'Reilly, S. C., Jones, A., Muir, K. R., & Doherty, M. (1998). Quadriceps weakness in knee osteoarthritis: the effect on pain and disability. *Annals of the Rheumatic Diseases*, *57*(10), 588–594.

Ogata, K., Yasunaga, M., & Nomiyama, H. (1997). The effect of wedged insoles on the thrust of osteoarthritic knees. *International Orthopaedics*, *21*(5), 308–312.

Øiestad, B. E., Juhl, C. B., Eitzen, I., & Thorlund, J. B. (2015). Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(2), 171–177.

Oliveria, S. A., Felson, D. T., Reed, J. I., Cirillo, P. A., & Walker, A. M. (1995). Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis and Rheumatism*, *38*(8), 1134–1141.

Olmsted, L. C., Carcia, C. R., Hertel, J., & Shultz, S. J. (2002). Efficacy of the Star Excursion Balance Tests in Detecting Reach Deficits in Subjects With Chronic Ankle Instability. *Journal of Athletic Training*, *37*(4), 501–506.

Ornetti, P., Maillefert, J.-F., Laroche, D., Morisset, C., Dougados, M., & Gossec, L. (2010). Gait analysis as a quantifiable outcome measure in hip or knee osteoarthritis: a systematic review. *Joint, Bone, Spine*, *77*(5), 421–425.

Osteoarthritis: National Clinical Guideline for Care and Management in Adults - PubMed - NCBI. (2008). Royal College of Physicians.

Öztuna, D., Elhan, A., & Tüccar, E. (2006). Investigation of four different normality tests in terms of type 1 error rate and power under different distributions. *Turkish Journal of Medical Sciences, 36*(3), 171–176.

Pagani, C. H. F., Hinrichs, M., & Brüggemann, G. P. (2012). Kinetic and kinematic changes with the use of valgus knee brace and lateral wedge insoles in patients with medial knee osteoarthritis. *Journal of Orthopaedic Research*, *30*(7), 1125–1132.

Pai, Y. I. C., Rymer, W. Z., Chang, R. W., & Sharma, L. (1997). Effect of age and osteoarthritis on knee proprioception. *Arthritis and Rheumatism*, *40*(12), 2260–2265.

Palmieri-Smith, R. M., Thomas, A. C., Karvonen-Gutierrez, C., & Sowers, M. F. (2010). Isometric Quadriceps Strength in Women with Mild, Moderate, and Severe Knee Osteoarthritis. *American Journal of Physical Medicine and Rehabilitation*, *89*(7), 541–548.

Paoloni, M., Di Sante, L., Dimaggio, M., Bernetti, A., Mangone, M., Di Renzo, S., & Santilli, V. (2012). Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. *Clinical Biomechanics*, *27*(7), 661–665.

Parkes, M. J., Maricar, N., Lunt, M., LaValley, M. P., Jones, R. K., Segal, N. a, … Felson, D. T. (2013). Lateral wedge insoles as a conservative treatment for pain in patients with medial knee

osteoarthritis: a meta-analysis. *The Journal of the American Medical Association*, *310*(7), 722–30.

Patla, A., Frank, J., & Winter, D. (1990). Assessment of balance control in the elderly: major issues. *Physiotherapy Canada*, *42*(2), 89–97.

Pavlaković, G., & Petzke, F. (2010). The Role of Quantitative Sensory Testing in the Evaluation of Musculoskeletal Pain Conditions. *Current Rheumatology Reports*, *12*(6), 455–461.

Pelfort, X., Torres-Claramunt, R., Sánchez-Soler, J. F., Hinarejos, P., Leal-Blanquet, J., Valverde, D., & Monllau, J. C. (2015). Pressure algometry is a useful tool to quantify pain in the medial part of the knee: An intra- and inter-reliability study in healthy subjects. *Orthopaedics & Traumatology: Surgery and Research*, *101*(5), 559–563.

Pelland, L., Brosseau, L., Wells, G., MacLeay, L., Lambert, J., Lamothe, C., … Tugwell, P. (2004). Efficacy of strengthening exercises for osteoarthritis (Part I): A meta-analysis. *Physical Therapy Reviews*, *9*(2), 77–108.

Penny, P., Geere, J., & Smith, T. O. (2013). A systematic review investigating the efficacy of laterally wedged insoles for medial knee osteoarthritis. *Rheumatology International*, *33*(10), 2529–2538.

Peregoy, J., & Wilder, F. V. (2011). The effects of vitamin C supplementation on incident and progressive knee osteoarthritis: a longitudinal study. *Public Health Nutrition*, *14*(04), 709–715.

Perry, J., Burnfield, J. M., & Cabico, L. M. (2010). *Gait analysis : normal and pathological function*. Slack.

Peter, W. F. H., Jansen, M. J., Hurkmans, E. J., Bloo, H., Dekker-Bakker, L. M. M. C. J., Dilling, R. G., … Vliet Vlieland, T. P. M. (2011). Physiotherapy in hip and knee osteoarthritis: Development of a practice guideline concerning initial assessment, treatment and evaluation. *Acta Reumatologica Portuguesa, 36*(3), 268–281.

Pham, T., Maillefert, J. F., Hudry, C., Kieffert, P., Bourgeois, P., Lechevalier, D., & Dougados, M. (2004). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis. A two-year prospective randomized controlled study. *Osteoarthritis and Cartilage*, *12*(1), 46–55.

Pollo, F. E., Otis, J. C., Backus, S. I., Warren, R. F., & Wickiewicz, T. L. (2002). Reduction of medial compartment loads with valgus bracing of the osteoarthritic knee. *The American Journal of Sports Medicine*, *30*(3), 414–421.

Portney, L., & Watkins, M. (2009). *Foundations of Clinical Research: Applications to Practice*. *New Jersey: Pearson Education,Inc.*

Prajapati, B., Dunne, M., & Armstrong, R. (2010). Sample size estimation and statistical power analyses. *Optometry today*, *16*(07), 10-18.

Preece, S. J., Jones, R. K., Brown, C. A., Cacciatore, T. W., & Jones, A. K. P. (2016). Reductions in co-contraction following neuromuscular re-education in people with knee osteoarthritis. *BMC Musculoskeletal Disorders*, *17*(1), 372.

Prodromos, C. C., Andriacchi, T. P., & Galante, J. O. (1985). A relationship between gait and clinical changes following high tibial osteotomy. *The Journal of Bone and Joint Surgery*, *67*(8), 1188–1194.

Radin, E. L., Yang, K. H., Riegger, C., Kish, V. L., & O'Connor, J. J. (1991). Relationship between

lower limb dynamics and knee joint pain. *Journal of Orthopaedic Research*, *9*(3), 398–405.

Radzimski, A. O., Mündermann, A., & Sole, G. (2012). Effect of footwear on the external knee adduction moment - A systematic review. *Knee*, *19*(3), 163–175.

Rafiaee, M., & Karimi, M. T. (2012). The effects of various kinds of lateral wedge insoles on performance of individuals with knee joint osteoarthritis. *International Journal of Preventive Medicine*, *3*(10), 693–698.

Raja, K., & Dewan, N. (2011). Efficacy of knee braces and foot orthoses in conservative management of knee osteoarthritis: a systematic review. *American Journal of Physical Medicine and Rehabilitation*, *90*(3), 247–262.

Ramsey, D. K., & Russell, M. E. (2009). Unloader Braces for Medial Compartment Knee Osteoarthritis: Implications on Mediating Progression. *Sports Health*, *1*(5), 416–426.

Ramsey, D. K., Briem, K., Axe, M. J., & Snyder-Mackler, L. (2007a). A mechanical theory for the effectiveness of bracing for medial compartment osteoarthritis of the knee. *The Journal of Bone and Joint Surgery*, *89*(11), 2398–2407.

Ramsey, D. K., Snyder-Mackler, L., Lewek, M., Newcomb, W., & Rudolph, K. S. (2007b). Effect of anatomic realignment on muscle function during gait in patients with medial compartment knee osteoarthritis. *Arthritis Care and Research*, *57*(3), 389–397.

Rankin, G., & Stokes, M. (1998). Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. *Clinical Rehabilitation*, *12*(3), 187–199.

Rat, A.-C., Pouchot, J., Coste, J., Baumann, C., Spitz, E., Retel-Rude, N., … Guillemin, F. (2006). Development and testing of a specific quality-of-life questionnaire for knee and hip osteoarthritis: OAKHQOL (OsteoArthritis of Knee Hip Quality Of Life). *Joint, Bone, Spine*, *73*(6), 697–704.

Rau, G., Disselhorst-Klug, C., & Schmidt, R. (2000). Movement biomechanics goes upwards: from the leg to the arm. *Journal of Biomechanics*, *33*(10), 1207–1216.

Ravaud, P., Giraudeau, B., Logeart, I., Larguier, J. S., Rolland, D., Treves, R., … Dougados, M. (2004). Management of osteoarthritis (OA) with an unsupervised home based exercise programme and/or patient administered assessment tools. A cluster randomised controlled trial with a 2x2 factorial design. *Annals of The Rheumatic Diseases*, *63*(6), 703–708.

Razali, N., & Wah, Y. (2011). Power comparisons of shapiro-wilk, kolmogorov-smirnov, lilliefors and anderson-darling tests. *Journal of Statistical Modeling and Analytics, 2*(1), 21–33.

Reeves, N. D., & Bowling, F. L. (2011). Conservative biomechanical strategies for knee osteoarthritis. *Nature Reviews Rheumatology*, *7*(2), 113–122.

Reichenbach, S., Heldner, S., Lenz, A., Felson, D., & Jüni, P. (2018). Biomechanical therapy for osteoarthritis of the knee: a randomised controlled trial (BIOTOK). *Annals of the Rheumatic Diseases*, *77*(Suppl 2), 82–83

Reilly, K., Barker, K., Shamley, D., Newman, M., Oskrochi, G. R., & Sandall, S. (2009). The role of foot and ankle assessment of patients with lower limb osteoarthritis. *Physiotherapy*, *95*(3), 164–169.

Reinschmidt, C., van den Bogert, A. J., Nigg, B. M., Lundberg, A., & Murphy, N. (1997). Effect of skin movement on the analysis of skeletal knee joint motion during running. *Journal of*

Biomechanics, *30*(7), 729–732.

Rejeski, W. J., Ettinger, W. H., Schumaker, S., James, P., Burns, R., & Elam, J. T. (1995). Assessing performance-related disability in patients with knee osteoarthritis. *Osteoarthritis and Cartilage*, *3*(3), 157–167.

Richards, J. D., Sanchez-Ballester, J., Jones, R. K., Darke, N., & Livingstone, B. N. (2005). A comparison of knee braces during walking for the treatment of osteoarthritis of the medial compartment of the knee. *The Journal of Bone and Joint Surgery*, *87*(7), 937–939.

Richards, R. E., van den Noort, J. C., van der Esch, M., Booij, M. J., & Harlaar, J. (2018). Effect of real-time biofeedback on peak knee adduction moment in patients with medial knee osteoarthritis: Is direct feedback effective?. *Clinical Biomechanics*, *57*, 150–158.

Rieger, R., Michaelis, A., & Green, M. M. (1991), *A Glossary of Genetics and Cytogenetics: Classical and Molecular*. Fourth ed. Springer-Verlag, Berlin, Heidelberg, New York.

Roach, H. I., & Tilley, S. (2007). The Pathogenesis of Osteoarthritis. *In Bone and Osteoarthritis*. *4*, 1–18.

Robbins, S. M. K., & Maly, M. R. (2009). The effect of gait speed on the knee adduction moment depends on waveform summary measures. *Gait and Posture*, *30*(4), 543–546.

Robbins, S. M., Astephen Wilson, J. L., Rutherford, D. J., & Hubley-Kozey, C. L. (2013). Reliability of principal components and discrete parameters of knee angle and moment gait waveforms in individuals with moderate knee osteoarthritis. *Gait and Posture*, *38*(3), 421–427.

Robinson, R. H., & Gribble, P. A. (2008). Support for a Reduction in the Number of Trials Needed for the Star Excursion Balance Test. *Archives of Physical Medicine and Rehabilitation*, *89*(2), 364–370.

Roddy, E., & Doherty, M. (2003). Guidelines for management of osteoarthritis published by the American College of Rheumatology and the European League Against Rheumatism: why are they so different?. *Rheumatic Diseases Clinics of North America*, *29*(4), 717–31.

Roemer, F. W., Frobell, R., Hunter, D. J., Crema, M. D., Fischer, W., Bohndorf, K., & Guermazi, A. (2009). MRI-detected subchondral bone marrow signal alterations of the knee joint: terminology, imaging appearance, relevance and radiological differential diagnosis. *Osteoarthritis and Cartilage*. *17*(9), 1115-1131.

Rogers, M. W., & Mille, M.-L. (2003). Lateral stability and falls in older people. *Exercise and Sport Sciences Reviews*, *31*(4), 182–187.

Rönn, K., Reischl, N., Gautier, E., & Jacobi, M. (2011). Current Surgical Treatment of Knee Osteoarthritis. *Arthritis*, *2011*, 1–9.

Roos, E. M. (2005). Joint injury causes knee osteoarthritis in young adults. *Current Opinion in Rheumatology*, *17*(2), 195–200.

Roos, E., Ostenberg, A., Roos, H., Ekdahl, C., & Lohmander, L. S. (2001). Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. *Osteoarthritis and Cartilage*, *9*(4), 316–324.

Rose, J., Gamble, J., & Adams, J. (2006). *Human walking*. Philadelphia, Lippincott Williams and Wilkins

Rubin, R., & Menz, H. B. (2005). Use of laterally wedged custom foot orthoses to reduce pain associated with medial knee osteoarthritis: a preliminary investigation. *Journal of the American Podiatric Medical Association*, *95*(4), 347–352.

Rudolph, K. S., Schmitt, L. C., & Lewek, M. D. (2007). Age-related changes in strength, joint laxity, and walking patterns: are they related to knee osteoarthritis?. *Physical Therapy*, *87*(11), 1422–1432.

Sangha, O. (2000). Epidemiology of rheumatic diseases. *Rheumatology*, *39*(suppl 2), 3–12.

Sarzi-Puttini, P., Cimmino, M. A., Scarpa, R., Caporali, R., Parazzini, F., Zaninelli, A., … Canesi, B. (2005). Osteoarthritis: an overview of the disease and its treatment strategies. *Seminars in Arthritis and Rheumatism*, *35*(1 Suppl 1), 1–10.

Sasaki, T., & Yasuda, K. (1987). Clinical evaluation of the treatment of osteoarthritic knees using a newly designed wedged insole. *Clinical Orthopaedics and Related Research*, *221*, 181–187.

Sazo-Rodríguez, S., Méndez-Rebolledo, G., Guzmán-Muñoz, E., & Rubio-Palma, P. (2017). The effects of progressive neuromuscular training on postural balance and functionality in elderly patients with knee osteoarthritis: a pilot study. *Journal of Physical Therapy Science*, *29*(7), 1229–1235.

Schipplein, O. D., & Andriacchi, T. P. (1991). Interaction between active and passive knee stabilizers during level walking. *Journal of Orthopaedic Research*, *9*(1), 113–119.

Schmitt, L. C., & Rudolph, K. S. (2007). Influences on knee movement strategies during walking in persons with medial knee osteoarthritis. *Arthritis Care and Research*, *57*(6), 1018–1026.

Schneider, E., & Chao, E. Y. (1983). Fourier analysis of ground reaction forces in normals and patients with knee joint disease. *Journal of Biomechanics*, *16*(8), 591–601.

Schnitzer, T. J., Popovich, J. M., Andersson, G. B., & Andriacchi, T. P. (1993). Effect of piroxicam on gait in patients with osteoarthritis of the knee. *Arthritis and Rheumatism*, *36*(9), 1207–1213.

Schuster, P., Geßlein, M., Schlumberger, M., Mayer, P., Mayr, R., Oremek, D., … Rg Richter, J. (2018). Ten-Year Results of Medial Open-Wedge High Tibial Osteotomy and Chondral Resurfacing in Severe Medial Osteoarthritis and Varus Malalignment. *The American Journal of Sports Medicine*, *46*(6), 1362–1370.

Schwartz, M. H., Trost, J. P., & Wervey, R. A. (2004). Measurement and management of errors in quantitative gait data. *Gait and Posture*, *20*(2), 196–203.

Schween, R., Gehring, D., & Gollhofer, A. (2015). Immediate Effects of an Elastic Knee Sleeve on Frontal Plane Gait Biomechanics in Knee Osteoarthritis. *Plos One*, *10*(1), e0115782.

Segal, N. A., Findlay, C., Wang, K., Torner, J. C., & Nevitt, M. C. (2012). The longitudinal relationship between thigh muscle mass and the development of knee osteoarthritis. *Osteoarthritis and Cartilage*, *20*(12), 1534–1540.

Segal, N. a., Foster, N. a., Dhamani, S., Ohashi, K., & Yack, H. J. (2009). Effects of Concurrent Use of an Ankle Support with a Laterally Wedged Insole for Medial Knee Osteoarthritis. *Physical Medicne and Rehabilitation*, *1*(3), 214–222.

Segal, N. A., Torner, J. C., Felson, D., Niu, J., Sharma, L., Lewis, C. E., & Nevitt, M. (2009). Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a

longitudinal cohort. *Arthritis and Rheumatism*, *61*(9), 1210–1217.

Self, B. P., Greenwald, R. M., & Pflaster, D. S. (2000). A biomechanical analysis of a medial unloading brace for osteoarthritis in the knee. *Arthritis Care and Research*, *13*(4), 191–197.

Shakoor, N., & Block, J. A. (2006). Walking barefoot decreases loading on the lower extremity joints in knee osteoarthritis. *Arthritis and Rheumatism*, *54*(9), 2923–2927.

Shakoor, N., Lidtke, R. H., Sengupta, M., Fogg, L. F., & Block, J. A. (2008). Effects of specialized footwear on joint loads in osteoarthritis of the knee. *Arthritis and Rheumatism*, *59*(9), 1214–1220.

Shakoor, N., Sengupta, M., Foucher, K. C., Wimmer, M. A., Fogg, L. F., & Block, J. A. (2010). Effects of common footwear on joint loading in osteoarthritis of the knee. *Arthritis Care and Research*, *62*(7), 917–923.

Shan, L., Shan, B., Suzuki, A., Nouh, F., & Saxena, A. (2015). Intermediate and Long-Term Quality of Life After Total Knee Replacement. *The Journal of Bone and Joint Surgery*, *97*(2), 156–168.

Shane Anderson, A., & Loeser, R. F. (2010). Why is osteoarthritis an age-related disease? *Best Practice & Research. Clinical Rheumatology*, *24*(1), 15–26.

Sharma, L. (1999). Proprioceptive impairment in knee osteoarthritis. *Rheumatic Disease Clinics of North America*, *25*(2), 299–314.

Sharma, L., Cahue, S., Song, J., Hayes, K., Pai, Y.-C., & Dunlop, D. (2003). Physical functioning over three years in knee osteoarthritis: Role of psychosocial, local mechanical, and neuromuscular factors. *Arthritis and Rheumatism*, *48*(12), 3359–3370.

Sharma, L., Dunlop, D. D., Cahue, S., Song, J., & Hayes, K. W. (2003). Quadriceps Strength and Osteoarthritis Progression in Malaligned and Lax Knees. *Annals of Internal Medicine*, *138*(8), 613–619.

Sharma, L., Hayes, K. W., Felson, D. T., Buchanan, T. S., Kirwan-Mellis, G., Lou, C., … Dunlop, D. D. (1999a). Does laxity alter the relationship between strength and physical function in knee osteoarthritis?. *Arthritis and Rheumatism*, *42*(1), 25–32.

Sharma, L., Hurwitz, D. E., Thonar, E. J. M. A., Sum, J. A., Lenz, M. E., Dunlop, D. D., … Andriacchi, T. P. (1998). Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. *Arthritis and Rheumatism*, *41*(7), 1233–1240.

Sharma, L., Lou, C., Felson, D. T., Dunlop, D. D., Kirwan-Mellis, G., Hayes, K. W., … Buchanan, T. S. (1999b). Laxity in healthy and osteoarthritic knees. *Arthritis and Rheumatism*, *42*(5), 861–870.

Sharma, L., Pai, Y. I. C., Holtkamp, K., & Rymer, W. Z. (1997). Is knee joint proprioception worse in the arthritic knee versus the unaffected knee in unilateral knee osteoarthritis?. *Arthritis and Rheumatism*, *40*(8), 1518–1525.

Sharma, L., Song, J., Felson, D. T., Cahue, S., Shamiyeh, E., & Dunlop, D. D. (2001). The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *The Journal of the American Medical Association, 286*(2), 188–195.

Sharma, S. K., Yadav, S. L., & Singh, U. (2014). Comparative Study of Co-Activation of Quadriceps and Hamstrings Muscles Around Knee Joint Before and After Muscle Strengthening

Exercises in Primary Osteoarthritis Knee Patients. *The American Academy of Physical Medicine and Rehabilitation*, *6*(9), S187.

Shaw, K. E., Charlton, J. M., Perry, C. K. L., de Vries, C. M., Redekopp, M. J., White, J. A., & Hunt, M. A. (2018). The effects of shoe-worn insoles on gait biomechanics in people with knee osteoarthritis: a systematic review and meta-analysis. *British Journal of Sports Medicine*, *52*(4), 238–253.

Shelburne, K. B., Torry, M. R., Steadman, J. R., & Pandy, M. G. (2008). Effects of foot orthoses and valgus bracing on the knee adduction moment and medial joint load during gait. *Clinical Biomechanics*, *23*(6), 814–821.

Shimada, S., Kobayashi, S., Wada, M., Uchida, K., Sasaki, S., Kawahara, H., … Baba, H. (2006). Effects of disease severity on response to lateral wedged shoe insole for medial compartment knee osteoarthritis. *Archives of Physical Medicine and Rehabilitation*, *87*(11), 1436–1441.

Shrier, I., Feldman, D. E., Gaudet, M.-C., Rossignol, M., Zukor, D., Tanzer, M., … Dumais, R. (2006). Conservative non-pharmacological treatment options are not frequently used in the management of hip osteoarthritis. *Journal of Science and Medicine in Sport*, *9*, 81–86.

Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin*, *86*(2), 420–428.

Shull, P. B., Lurie, K. L., Cutkosky, M. R., & Besier, T. F. (2011). Training multi-parameter gaits to reduce the knee adduction moment with data-driven models and haptic feedback. *Journal of Biomechanics*, *44*(8), 1605–1609.

Shull, P. B., Shultz, R., Silder, A., Dragoo, J. L., Besier, T. F., Cutkosky, M. R., & Delp, S. L. (2013a). Toe-in gait reduces the first peak knee adduction moment in patients with medial compartment knee osteoarthritis. *Journal of Biomechanics*, *46*(1), 122–128.

Shull, P. B., Silder, A., Shultz, R., Dragoo, J. L., Besier, T. F., Delp, S. L., & Cutkosky, M. R. (2013b). Six-week gait retraining program reduces knee adduction moment, reduces pain, and improves function for individuals with medial compartment knee osteoarthritis. *Journal of Orthopaedic Research*, *31*(7), 1020–1025.

Silverwood, V., Blagojevic-Bucknall, M., Jinks, C., Jordan, J. L., Protheroe, J., & Jordan, K. P. (2015). Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(4), 507–515.

Simic, M., Bennell, K. L., Hunt, M. a., Wrigley, T. V., & Hinman, R. S. (2011). Contralateral cane use and knee joint load in people with medial knee osteoarthritis: The effect of varying body weight support. *Osteoarthritis and Cartilage*, *19*(11), 1330–1337.

Sims, E. L., Carland, J. M., Keefe, F. J., Kraus, V. B., Guilak, F., & Schmitt, D. (2009). Sex differences in biomechanics associated with knee osteoarthritis. *Journal of Women and Aging*, *21*(3), 159–170.

Sirin, A. V, & Patla, A. E. (1987). Myoelectric changes in the triceps surae muscles under sustained contractions. Evidence for synergism. *European Journal of Applied Physiology and Occupational Physiology*, *56*(2), 238–244.

Skou, S. T., Roos, E. M., Laursen, M. B., Rathleff, M. S., Arendt-Nielsen, L., Simonsen, O., & Rasmussen, S. (2015a). A Randomized, Controlled Trial of Total Knee Replacement. *The New*

England Journal of Medicine, *373*(17), 1597–1606.

Skou, S. T., Simonsen, O., & Rasmussen, S. (2015b). Examination of Muscle Strength and Pressure Pain Thresholds in Knee Osteoarthritis. *Journal of Geriatric Physical Therapy*, *38*(3), 141–147.

Sled, E. A., Khoja, L., Deluzio, K. J., Olney, S. J., & Culham, E. G. (2010). Effect of a home program of hip abductor exercises on knee joint loading, strength, function, and pain in people with knee osteoarthritis: a clinical trial. *Physical Therapy*, *90*(6), 895–904.

Slemenda, C., Brandt, K. D., Heilman, D. K., Mazzuca, S., Braunstein, E. M., Katz, B. P., & Wolinsky, F. D. (1997). Quadriceps weakness and osteoarthritis of the knee. *Annals of Internal Medicine*, *127*(2), 97–104.

Slemenda, C., Heilman, D. K., Brandt, K. D., Katz, B. P., Mazzuca, S. A., Braunstein, E. M., & Byrd, D. (1998). Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women?. *Arthritis and Rheumatism*, *41*(11), 1951–1959.

Soderberg, G. L., & Knutson, L. M. (2000). A guide for use and interpretation of kinesiologic electromyographic data. *Physical Therapy*, *80*(5), 485–498.

Song, R., Roberts, B. L., Lee, E.-O., Lam, P., & Bae, S.-C. (2010). A randomized study of the effects of t'ai chi on muscle strength, bone mineral density, and fear of falling in women with osteoarthritis. *Journal of Alternative and Complementary Medicine*, *16*(3), 227–233.

Spector, D., & MacGregor, J. (2004). Risk factors for osteoarthritis: Genetics. *Osteoarthritis and Cartilage*, *12*, 39–44.

Spector, T. D., Cicuttini, F., Baker, J., Loughlin, J., & Hart, D. (1996). Genetic influences on osteoarthritis in women: a twin study. *BMJ: British Medical Journal*, *312*(7036), 940–943.

Squyer, E., Stamper, D. L., Hamilton, D. T., Sabin, J. a., & Leopold, S. S. (2013). Unloader knee braces for osteoarthritis: Do patients actually wear them?. *Clinical Orthopaedics and Related Research*, *471*(6), 1982–1991.

Srikanth, V. K., Fryer, J. L., Zhai, G., Winzenberg, T. M., Hosmer, D., & Jones, G. (2005). A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis and Cartilage*, *13*(9), 769–781.

Sritharan, P., Lin, Y. C., Richardson, S. E., Crossley, K. M., Birmingham, T. B., & Pandy, M. G. (2017). Musculoskeletal loading in the symptomatic and asymptomatic knees of middle-aged osteoarthritis patients. *Journal of Orthopaedic Research, 35*(2), 321–330.

Stagni, R., Leardini, A., Cappozzo, A., Grazia Benedetti, M., & Cappello, A. (2000). Effects of hip joint centre mislocation on gait analysis results. *Journal of Biomechanics*, *33*(11), 1479–1487.

Stehling, C., Luke, A., Stahl, R., Baum, T., Joseph, G., Pan, J., & Link, T. M. (2011). Meniscal T1rho and T2 measured with 3.0T MRI increases directly after running a marathon. *Skeletal Radiology*, *40*(6), 725–735.

Steinskog, D. (2009). A cautionary note on the use of the Kolmogorov-Smirnov test for normality. *Monthly Weather Review*, *135*(3), 1151–1157.

Stevens, K. N., Lang, I. A., Guralnik, J. M., & Melzer, D. (2008). Epidemiology of balance and dizziness in a national population: findings from the English Longitudinal Study of Ageing. *Age*

and Ageing, *37*(3), 300–305.

Stratford, P. W., & Kennedy, D. M. (2006). Performance measures were necessary to obtain a complete picture of osteoarthritic patients. *Journal of Clinical Epidemiology*, *59*(2), 160–167.

Stratford, P. W., Kennedy, D. M., & Woodhouse, L. J. (2006). Performance measures provide assessments of pain and function in people with advanced osteoarthritis of the hip or knee. *Physical Therapy*, *86*(11), 1489–1496.

Stratford, P. W., Kennedy, D., Pagura, S. M. C., & Gollish, J. D. (2003). The relationship between self-report and performance-related measures: questioning the content validity of timed tests. *Arthritis and Rheumatism*, *49*(4), 535–540.

Tanamas, S., Hanna, F. S., Cicuttini, F. M., Wluka, A. E., Berry, P., & Urquhart, D. M. (2009). Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. *Arthritis and Rheumatism*, *61*(4), 459–467.

Taylor, W. R., Heller, M. O., Bergmann, G., & Duda, G. N. (2004). Tibio-femoral loading during human gait and stair climbing. *Journal of Orthopaedic Research*, *22*(3), 625–632.

Tegner, Y., Lysholm, J., Lysholm, M., & Gillquist, J. (1986). A performance test to monitor rehabilitation and evaluate anterior cruciate ligament injuries. *The American Journal of Sports Medicine*, *14*(2), 156–159.

Teichtahl, A. J., Morris, M. E., Wluka, A. E., Baker, R., Wolfe, R., Davis, S. R., & Cicuttini, F. M. (2006). Foot rotation--a potential target to modify the knee adduction moment. *Journal of Science and Medicine in Sport*, *9*(1–2), 67–71.

Teichtahl, A. J., Wang, Y., Heritier, S., Wluka, A. E., Strauss, B. J., Proietto, J., … Cicuttini, F. M. (2016). The interaction between physical activity and amount of baseline knee cartilage. *Rheumatology*, *55*(7), 1277–1284.

Teoh, J. C., Low, J. H., Lim, Y. B., Shim, V. P.-W., Park, J., Park, S.-B., … Lee, T. (2013). Investigation of the biomechanical effect of variable stiffness shoe on external knee adduction moment in various dynamic exercises. *Journal of Foot and Ankle Research*, *6*, 39.

Terwee, C. B., Mokkink, L. B., Steultjens, M. P. M., & Dekker, J. (2006). Performance-based methods for measuring the physical function of patients with osteoarthritis of the hip or knee: a systematic review of measurement properties. *Rheumatology*, *45*(7), 890–902.

The osteoarthritis research society international (OARSI). Osteoarthritis: A Serious Disease, 2016. Retrieved from https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf

Thode, H. C. (2002). *Testing for normality*. Boca Raton, Taylor and France Group

Thorp, L. E., Sumner, D. R., Block, J. A., Moisio, K. C., Shott, S., & Wimmer, M. A. (2006a). Knee joint loading differs in individuals with mild compared with moderate medial knee osteoarthritis. *Arthritis and Rheumatism*, *54*(12), 3842–3849.

Thorp, L. E., Sumner, D. R., Wimmer, M. a., & Block, J. a. (2007). Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. *Arthritis Care and Research*, *57*(7), 1254–1260.

Thorp, L. E., Wimmer, M. A., Block, J. A., Moisio, K. C., Shott, S., Goker, B., & Sumner, D. R. (2006b). Bone mineral density in the proximal tibia varies as a function of static alignment and knee adduction angular momentum in individuals with medial knee osteoarthritis. *Bone*, *39*(5), 1116–1122.

Thorstensson, C. A., Henriksson, M., von Porat, A., Sjödahl, C., & Roos, E. M. (2007). The effect of eight weeks of exercise on knee adduction moment in early knee osteoarthritis--a pilot study. *Osteoarthritis and Cartilage*, *15*(10), 1163–1170.

Thumboo, J., Chew, L. H., & Soh, C. H. (2001). Validation of the Western Ontario and Mcmaster University osteoarthritis index in Asians with osteoarthritis in Singapore. *Osteoarthritis and Cartilage*, *9*(5), 440–446.

Timmins, K. A., Leech, R. D., Batt, M. E., & Edwards, K. L. (2017). Running and Knee Osteoarthritis: A Systematic Review and Meta-analysis. *The American Journal of Sports Medicine*, *45*(6), 1447–1457.

Toda, Y. (2009). An Orthotic Device for Patients with Osteoarthritis of the Knee—The Efficacy of a Soft Orthotic Device for the Knee with Subtalar Strapped Insole—. *Japanese Journal of Joint Diseases*, *28*(1), 93–99.

Toda, Y. (2011). An Orthotic Device for Patients with Osteoarthritis of the Knee—The Efficacy of a Soft Orthotic Device for the Knee with Subtalar Strapped Insole&mdash. *Japanese Journal of Joint Diseases*, *28*(1), 93–99.

Toda, Y., & Tsukimura, N. (2004). A comparative study on the effect of the insole materials with subtalar strapping in patients with medial compartment osteoarthritis of the knee. *Modern Rheumatology*, *14*(6), 459–465.

Toda, Y., & Tsukimura, N. (2008). Influence of concomitant heeled footwear when wearing a lateral wedged insole for medial compartment osteoarthritis of the knee. *Osteoarthritis and Cartilage*, *16*(2), 244–253.

Toda, Y., Tsukimura, N., & Kato, A. (2004). The effects of different elevations of laterally wedged insoles with subtalar strapping on medial compartment osteoarthritis of the knee. *Archives of Physical Medicine and Rehabilitation*, *85*(4), 673–677.

Toda, Y., Tsukimura, N., & Segal, N. (2005). An optimal duration of daily wear for an insole with subtalar strapping in patients with varus deformity osteoarthritis of the knee. *Osteoarthritis and Cartilage*, *13*(4), 353–360.

Toriyama, M., Deie, M., Shimada, N., Otani, T., Shidahara, H., Maejima, H., … Ochi, M. (2011). Effects of unloading bracing on knee and hip joints for patients with medial compartment knee osteoarthritis. *Clinical Biomechanics*, *26*(5), 497–503.

Torres, L., Dunlop, D. D., Peterfy, C., Guermazi, A., Prasad, P., Hayes, K. W., … Sharma, L. (2006). The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis and Cartilage, 14*(10), 1033–1040.

Trepczynski, A., Kutzner, I., Bergmann, G., Taylor, W. R., & Heller, M. O. (2014). Modulation of the relationship between external knee adduction moments and medial joint contact forces across subjects and activities. *Arthritis and Rheumatology*, *66*(5), 1218–1227.

Trouvin, A. P., & Perrot, S. (2018). Pain in osteoarthritis. Implications for optimal management.

Joint Bone Spine. 85(4), 429-434.

Tsushima, H., Morris, M. E., & McGinley, J. (2003). Test-retest reliability and inter-tester reliability of kinematic data from a three-dimensional gait analysis system. *Journal of the Japanese Physical Therapy Association*, *6*(1), 9–17.

Unnithan, V. B., Dowling, J. J., Frost, G., Volpe Ayub, B., & Bar-Or, O. (1996). Cocontraction and phasic activity during GAIT in children with cerebral palsy. *Electromyography and Clinical Neurophysiology*, *36*(8), 487–494.

van den Noort, J. C., Schaffers, I., Snijders, J., & Harlaar, J. (2013). The effectiveness of voluntary modifications of gait pattern to reduce the knee adduction moment. *Human Movement Science*, *32*(3), 412–424.

Van der Esch, M., Heijmans, M., & Dekker, J. (2003). Factors contributing to possession and use of walking aids among persons with rheumatoid arthritis and osteoarthritis. *Arthritis and Rheumatism*, *49*(6), 838–842.

Van Raaij, T. M., Reijman, M., Brouwer, R. W., Bierma-Zeinstra, S. M. a, & Verhaar, J. a N. (2010). Medial knee osteoarthritis treated by insoles or braces a randomized trial. *Clinical Orthopaedics and Related Research*, *468*(7), 1926–1932.

van Saase, J. L., van Romunde, L. K., Cats, A., Vandenbroucke, J. P., & Valkenburg, H. A. (1989). Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Annals of The Rheumatic Diseases*, *48*(4), 271–280.

Van Tunen, J. A. C., Paterson, K. L., Wrigley, T. V, Metcalf, B. R., Thorlund, J. B., & Hinman, R. S. (2018). Effect of knee unloading shoes on regional plantar forces in people with symptomatic knee osteoarthritis-an exploratory study. *Journal of Foot and Ankle Research*, *11*, 34.

Vanwanseele, B., Eckstein, F., Knecht, H., Stüssi, E., & Spaepen, A. (2002). Knee cartilage of spinal cord-injured patients displays progressive thinning in the absence of normal joint loading and movement. *Arthritis and Rheumatism*, *46*(8), 2073–2078.

Verweij, L. M., van Schoor, N. M., Deeg, D. J. H., Dekker, J., & Visser, M. (2009). Physical activity and incident clinical knee osteoarthritis in older adults. *Arthritis and Rheumatism*, *61*(2), 152–157.

Vignon, E., Valat, J.-P., Rossignol, M., Avouac, B., Rozenberg, S., Thoumie, P., … Hilliquin, P. (2006). Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). *Joint, Bone, Spine*, *73*(4), 442–455.

Villemure, C., Slotnick, B. M., & Bushnell, M. C. (2003). Effects of odors on pain perception: Deciphering the roles of emotion and attention. *Pain, 106*(1–2), 101–108.

Von Porat, A. (2004). High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Annals of the Rheumatic Diseases*, *63*(3), 269–273.

Wada, M., Imura, S., Baba, H., & Shimada, S. (1996). Knee laxity in patients with osteoarthritis and rheumatoid arthritis. *British Journal of Rheumatology*, *35*(6), 560–563.

Wada, M., Kawahara, H., Shimada, S., Miyazaki, T., & Baba, H. (2002). Joint proprioception

before and after total knee arthroplasty. *Clinical Orthopaedics and Related Research*, (403), 161–167.

Wada, M., Maezawa, Y., Baba, H., Shimada, S., Sasaki, S., & Nose, Y. (2001). Relationships among bone mineral densities, static alignment and dynamic load in patients with medial compartment knee osteoarthritis. *Rheumatology*, *40*(5), 499–505.

Wager, T. D. (2005). Expectations and anxiety as mediators of placebo effects in pain. Pain, 115(3), 225–226.

Walker, C. R. C., Myles, C., Nutton, R., & Rowe, P. (2001). Movement of the knee in osteoarthritis: the use of electrogoniometry to assess function. *The Bone and Joint Journal*, *83B*(2), 195–198.

Walker, L. S., Garber, J., Van Slyke, D. A., & Greene, J. W. (1995). Long-term health outcomes in patients with recurrent abdominal pain. *Journal of Pediatric Psychology, 20*(2), 233–245.

Wallace, I. J., Worthington, S., Felson, D. T., Jurmain, R. D., Wren, K. T., Maijanen, H., … Lieberman, D. E. (2017). Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proceedings of the National Academy of Sciences*, *114*(35), 9332–9336.

Walter, J. P., D'Lima, D. D., Colwell, C. W., & Fregly, B. J. (2010). Decreased knee adduction moment does not guarantee decreased medial contact force during gait. *Journal of Orthopaedic Research*, *28*(10), 1348–1354.

Wang, J. W., Kuo, K. N., Andriacchi, T. P., & Galante, J. O. (1990). The influence of walking mechanics and time on the results of proximal tibial osteotomy. *The Journal of Bone and Joint Surgery*, *72*(6), 905–909.

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. D. (2006). Health benefits of physical activity: the evidence. *Canadian Medical Association Journal*, *174*(6), 801–809.

Washburn, R. A., & Ficker, J. L. (1999). Physical Activity Scale for the Elderly (PASE): the relationship with activity measured by a portable accelerometer. *The Journal of Sports Medicine and Physical Fitness*, *39*(4), 336–340.

Wegener, L., Kisner, C., & Nichols, D. (1997). Static and dynamic balance responses in persons with bilateral knee osteoarthritis. *The Journal of Orthopaedic and Sports Physical Therapy*, *25*(1), 13–8.

Weidenhielm, L., Olsson, E., Broström, L. A., Börjesson-Hederström, M., & Mattsson, E. (1993). Improvement in gait one year after surgery for knee osteoarthrosis: a comparison between high tibial osteotomy and prosthetic replacement in a prospective randomized study. *Scandinavian Journal of Rehabilitation Medicine*, *25*(1), 25–31.

Wessel, J. (1995). The reliability and validity of pain threshold measurements in osteoarthritis of the knee. *Scandinavian Journal of Rheumatology*, *24*(4), 238–242.

Wessel, J. (1996). Isometric strength measurements of knee extensors in women with osteoarthritis of the knee. *The Journal of Rheumatology*, *23*(2), 328–331.

Westacott, C. I., Webb, G. R., Warnock, M. G., Sims, J. V, & Elson, C. J. (1997). Alteration of cartilage metabolism by cells from osteoarthritic bone. *Arthritis and Rheumatism*, *40*(7), 1282–1291.

Whatman, C., Hing, W., & Hume, P. (2011). Kinematics during lower extremity functional screening tests-Are they reliable and related to jogging?. *Physical Therapy in Sport*, *12*(1), 22–29.

Wilson, B., Rankin, H., & Barnes, C. L. (2011). Long-term results of an unloader brace in patients with unicompartmental knee osteoarthritis. *Orthopedics*, *34*(8), e334–e337.

Wilson, J. L., Deluzio, K. J., Dunbar, M. J., Caldwell, G. E., & Hubley-Kozey, C. L. (2011). The association between knee joint biomechanics and neuromuscular control and moderate knee osteoarthritis radiographic and pain severity. *Osteoarthritis and Cartilage, 19*(2), 186–193.

Winby, C. R., Gerus, P., Kirk, T. B., & Lloyd, D. G. (2013). Correlation between EMG-based co-activation measures and medial and lateral compartment loads of the knee during gait. *Clinical Biomechanics*, *28*(9–10), 1014–1019.

Winter, D. A. (1983). Knee flexion during stance as a determinant of inefficient walking. *Physical Therapy*, *63*(3), 331–333.

Winter, D. A. (1984). Kinematic and kinetic patterns in human gait: Variability and compensating effects. *Human Movement Science*, *3*(1–2), 51–76.

Winter, D. A. (1991). *The Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological*. Waterloo, Canada: UW press.

Winter, D. A. (2009). *Biomechanics and motor control of human gait*. Walterloo: John Wiley & Sons.

Winter, D. A., & Yack, H. J. (1987). EMG profiles during normal human walking: stride-to-stride and inter-subject variability. *Electroencephalography and Clinical Neurophysiology*, *67*(5), 402–411.

Winter, D. A., Patla, A. E., & Frank, J. S. (1990). Assessment of balance control in humans. *Medical Progress through Technology*, *16*(1–2), 31–51.

Wise, B. L., Niu, J., Yang, M., Lane, N. E., Harvey, W., Felson, D. T., … Multicenter Osteoarthritis (MOST) Group. (2012). Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African Americans. *Arthritis Care and Research*, *64*(6), 847–52.

World Health Organization (WHO). Physical activity, 2018. Retrieved from http://www.who.int/news-room/fact-sheets/detail/physical-activity.

Wright, A. A., Cook, C. E., Baxter, G. D., Dockerty, J. D., & Abbott, J. H. (2011a). A Comparison of 3 Methodological Approaches to Defining Major Clinically Important Improvement of 4 Performance Measures in Patients With Hip Osteoarthritis. *Journal of Orthopaedic and Sports Physical Therapy*, *41*(5), 319–327.

Wright, A. A., Hegedus, E. J., Baxter, G. D., & Abbott, J. H. (2011b). Measurement of function in hip osteoarthritis: developing a standardized approach for physical performance measures. *Physiotherapy Theory and Practice*, *27*(4), 253–262.

Wu, D. D., Burr, D. B., Boyd, R. D., & Radin, E. L. (1990). Bone and cartilage changes following experimental varus or valgus tibial angulation. *Journal of Orthopaedic Research*, *8*(4), 572–585.

Wylde, V., Palmer, S., Learmonth, I. D., & Dieppe, P. (2011). Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. *Osteoarthritis and Cartilage*,

19(6), 655–658.

Yasuda, K., & Sasaki, T. (1987). The mechanics of treatment of the osteoarthritic knee with a wedged insole. *Clinical Orthopaedics and Related Research*, (215), 162–172.

Ye, J., Cai, S., Zhong, W., Cai, S., & Zheng, Q. (2014). Effects of tai chi for patients with knee osteoarthritis: a systematic review. *Journal of Physical Therapy Science*, *26*(7), 1133–7.

Zacharias, A., Green, R. A., Semciw, A. I., Kingsley, M. I. C., & Pizzari, T. (2014). Efficacy of rehabilitation programs for improving muscle strength in people with hip or knee osteoarthritis: a systematic review with meta-analysis. *Osteoarthritis and Cartilage*, *22*(11), 1752–1773.

Zeni, J. A., & Higginson, J. S. (2009). Differences in gait parameters between healthy subjects and persons with moderate and severe knee osteoarthritis: a result of altered walking speed?. *Clinical Biomechanics*, *24*(4), 372–378.

Zeni, J. a., Rudolph, K., & Higginson, J. S. (2010). Alterations in quadriceps and hamstrings coordination in persons with medial compartment knee osteoarthritis. *Journal of Electromyography and Kinesiology*, *20*(1), 148–154.

Zhang, B., Yu, X., Liang, L., Zhu, L., Dong, X., Xiong, Y., … Sun, Y. (2018). Is the Wedged Insole an Effective Treatment Option When Compared with a Flat (Placebo) Insole: A Systematic Review and Meta-Analysis. *Evidence-Based Complementary and Alternative Medicine*, *2018*, 1–13

Zhang, L. Q., Xu, D., Wang, G., & Hendrix, R. W. (2001). Muscle strength in knee varus and valgus. *Medicine and Science in Sports and Exercise*, *33*(7), 1194–1199.

Zhang, W., Moskowitz, R. W. W., Nuki, G., Abramson, S., Altman, R. D. D., Arden, N., … Tugwell, P. (2008). OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and Cartilage*, *16*(2), 137–162.

Zhang, W., Nuki, G., Moskowitz, R. W., Abramson, S., Altman, R. D., Arden, N. K., … Tugwell, P. (2010). OARSI recommendations for the management of hip and knee osteoarthritis. Part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis and Cartilage*, *18*(4), 476–499.

Zhang, Y., & Jordan, J. M. (2010). Epidemiology of osteoarthritis. *Clinics in Geriatric Medicine*, *26*(3), 355–369.

Zhang, Y., Hannan, M. T., Chaisson, C. E., McAlindon, T. E., Evans, S. R., Aliabadi, P., … Felson, D. T. (2000). Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. *The Journal of Rheumatology*, *27*(4), 1032–1037.

Zhang, Y., Xu, L., Nevitt, M. C., Aliabadi, P., Yu, W., Qin, M., … Felson, D. T. (2001). Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing Osteoarthritis Study. *Arthritis and Rheumatism*, *44*(9), 2065–2071.

Zhao, D., Banks, S. A., Mitchell, K. H., D'Lima, D. D., Colwell, C. W., & Fregly, B. J. (2007). Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. *Journal of Orthopaedic Research*, *25*(6), 789–797.

Zubieta, J. K., Smith, Y. R., Bueller, J. A., Xu, Y., Kilbourn, M. R., Jewett, D. M., … Stohler, C. S. (2001). Regional Mu opioid receptor regulation of sensory and affective dimensions of pain. *Science, 293*(5528), 311–315.

Appendices

Appendix A: **Ethical approval**

**Research, Innovation and Academic
Engagement Ethical Approval Panel**

Research Centres Support Team
G0.3 Joule House
University of Salford
M5 4WT

T +44(0)161 295 2280

www.salford.ac.uk/

2 December 2015

Dear Omar,

**RE: ETHICS APPLICATION HSCR 15-131 – Reliability of biomechanical outcome measures when
wearing an insole and knee sleeve in healthy individuals and individuals with knee osteoarthritis**

Based on the information you provided, I am pleased to inform you that application HSCR15-131 has
been approved.

If there are any changes to the project and/ or its methodology, please inform the Panel as soon as
possible by contacting Health-ResearchEthics@salford.ac.uk

Yours sincerely,

Sue McAndrew
Chair of the Research Ethics Panel

Appendix B: **Ethical approval**

Research, Innovation and Academic Engagement Ethical Approval Panel

Research Centres Support Team
G0.3 Joule House
University of Salford
M5 4WT

T +44(0)161 295 2280

www.salford.ac.uk/

7 October 2016

Dear Omar Althomali,

RE: ETHICS APPLICATION HSCR 16-91 – **Effect of a lateral wedge insole and simple knee sleeve as a single and combined treatment on biomechanical and clinical outcomes in individuals with knee osteoarthritis (The IN-SLEEVE study)**

Based on the information you provided, I am pleased to inform you that application HSCR16-91 has been approved.

If there are any changes to the project and/ or its methodology, please inform the Panel as soon as possible by contacting Health-ResearchEthics@salford.ac.uk.

Yours sincerely,

Sue McAndrew
Chair of the Research Ethics Panel

Appendix C:**Ethical approval**

Kingdom of Saudi Arabia
Ministry of Education
University of Hail
Research Ethics Committee

جامعة حائل
University of Hail

موافقة اللجنة الدائمة لأخلاقيات البحث العلمي على إجراء بحث
Ethical Approval of Scientific Research Ethics Committee

Dear Researcher/s:

This is to inform you that the Ethics Committee at the University of Hail has reviewed and approved your Ethics Application for the following study:

No. of Research Project	H-2016-020	رقم المشروع البحثي
Title of Research Project and its Duration	Effect of a lateral wedge insole and simple knee sleeve as a single and combined treatment on biomechanical and clinical outcomes in individuals with knee osteoarthritis (The IN-SLEEVE study)	عنوان المشروع البحثي ومدته
Principal Investigator	Omar Waslallah Althomali	اسم الباحث الرئيسي
College/Centre	Applied Medical Sciences	الكلية/المركز
Mobile/e-mail	tt7uu@hotmail.com	جوال/بريد الكتروني
Type of Research	Research project	نوع البحث

Name of principal researcher and signature

اسم الباحث الرئيسي وتوقيعه:

Approval of Scientific Research Ethics Committee.
Approval Number: H-2016-020
Date: _____
This approval is valid until
_____

Chairman of the committee signature:
_____

موافقة اللجنة الدائمة لأخلاقيات البحث العلمي
الرقم : H-2016-020
التاريخ: ١٧/١/٢٠١٦م
هذه الموافقة سارية حتى:
_____

توقيع رئيس اللجنة:

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Appendix D: **Reliability studies results for kinematics, kinetics and GRF data.**

Healthy reliability study:

Within-session reliability for joints angles in gait cycle during walking for healthy participants.

Walking - Joint Angle in degree (Within-session)	ICC	Mean	95% CI of ICC	SEM	SDD
Hip x angle (1st peak)	0.99	30.88	0.98-0.99	0.49	1.35
Hip x angle (Trough)	0.99	-6.35	0.97-0.99	0.43	1.20
Hip x angle (2nd peak)	0.99	35.76	0.99-0.99	0.30	0.83
Hip y angle (Maximum)	0.98	5.86	0.87-0.99	0.45	1.23
Hip y angle (Minimum)	0.99	-7.67	0.98-0.99	0.23	0.64
Hip z angle (Maximum)	0.97	3.54	0.82-0.99	1.06	2.93
Hip z angle (Minimum)	0.98	-8.37	0.91-0.99	0.83	2.30
Knee x angle (Initial contact)	0.96	2.09	0.82-0.99	0.69	1.91
Knee x angle (Loading response)	0.96	17.99	0.80-99	1.00	2.76
Knee x angle (Mid-stance)	0.97	5.57	0.87-0.99	0.63	1.74
Knee x angle (Swing)	0.96	71.58	0.78-0.99	0.75	2.08
Knee y angle (Maximum)	0.98	7.78	0.89-0.99	0.69	1.93
Knee y angle (Minimum)	0.92	-3.70	0.61-0.99	1.11	3.06
Knee z angle (Maximum)	0.99	1.76	0.98-0.99	0.22	0.61
Knee z angle (Minimum)	0.98	-17.22	0.91-0.99	0.68	1.87
Ankle x angle (Minimum)	0.99	19.45	0.97-0.99	0.26	0.71
Ankle x angle (Maximum)	0.85	-9.50	0.26-0.97	0.76	2.12
Ankle y angle (Maximum)	0.99	8.52	0.96-0.99	0.39	1.09
Ankle y angle (Minimum)	0.94	-5.27	0.70-.99	0.41	1.15

X=sagittal plane (flexion-extension), Y=frontal plane (adduction-abduction), Z=transverse plane (internal rotation-external rotation)

Within-session reliability for joints moments and ground reaction force in stance during walking for healthy participants.

Walking - Joint Moment (Nm/Kg) and GRF (*BW) (Within-session)	ICC	Mean	95% CI of ICC	SEM	SDD
Hip x moment (Maximum)	0.99	1.12	0.97-0.99	0.03	0.07
Hip x moment (Minimum)	0.97	-0.61	0.86-0.99	0.03	0.07
Hip y moment (1st Peak)	0.99	0.88	0.92-0.99	0.01	0.04
Hip y moment (Trough)	0.99	0.55	0.95-0.99	0.01	0.03
Hip y moment (2nd Peak)	0.99	0.89	0.96-0.99	0.01	0.03
Hip z moment (Maximum)	0.99	0.26	0.98-0.99	0.01	0.02
Hip z moment (Minimum)	0.99	-0.12	0.94-0.99	0.01	0.02
Knee x moment (Maximum)	0.98	0.54	0.87-0.99	0.02	0.04
Knee x moment (Minimum)	0.97	-0.66	0.87-0.99	0.03	0.08
Knee z moment (Maximum)	0.99	0.06	0.93-0.99	0.005	0.01
Knee z moment (Minimum)	0.99	-0.16	0.99-0.99	0.004	0.01
Ankle x moment (Maximum)	0.98	1.53	0.90-0.99	0.03	0.07
Ankle x moment (Minimum)	0.97	-0.21	0.86-0.99	0.01	0.03
Angle y moment (Maximum)	0.98	0.11	0.92-0.99	0.01	0.03
Ankle y moment (Minimum)	0.95	-0.16	0.74-0.99	0.02	0.06
GRF (1st Peak)	0.99	1.10	0.96-0.99	0.01	0.02
GRF (Trough)	0.99	0.72	0.96-0.99	0.01	0.02
GRF (2nd Peak)	0.99	1.08	0.97-0.99	0.01	0.02

X=sagittal plane (flexion-extension), Y=frontal plane (adduction-abduction), Z=transverse plane (internal rotation-external rotation)

Between-session reliability for joints angles in gait cycle during walking for healthy participants.

Walking – Joint Angle in degree (Between-session)	ICC	Mean	95% CI of ICC	SEM	SDD
Hip x angle (1st peak)	0.92	33.74	0.76-0.97	2.20	6.10
Hip x angle (Trough)	0.86	-4.81	0.59-0.95	2.25	6.25
Hip x angle (2nd peak)	0.88	39.64	0.65-0.96	2.63	7.29
Hip y angle (Maximum)	0.83	6.40	0.49-0.94	0.98	2.71
Hip y angle (Minimum)	0.73	-7.41	0.20-0.91	1.21	3.35
Hip z angle (Maximum)	0.91	6.07	0.73-0.97	1.81	5.03
Hip z angle (Minimum)	0.92	-7.35	0.75-0.97	1.84	5.09
Knee x angle (Initial contact)	0.79	1.55	0.38-0.93	2.22	6.16
Knee x angle (Loading response)	0.91	17.55	0.73-0.97	2.10	5.81
Knee x angle (Mid-stance)	0.85	4.98	0.60-0.95	1.61	4.46
Knee x angle (Swing)	0.82	72.40	0.46-0.94	2.38	6.61
Knee y angle (Maximum)	0.94	8.41	0.82-0.98	1.31	3.63
Knee y angle (Minimum)	0.81	-4.68	0.45-0.94	1.24	3.45
Knee z angle (Maximum)	0.67	2.39	0.01-0.89	1.97	5.47
Knee z angle (Minimum)	0.79	-18.15	0.37-0.93	2.20	6.10
Ankle x angle (Minimum)	0.90	20.47	0.70-0.97	0.67	1.85
Ankle x angle (Maximum)	0.86	-11.46	0.60-0.96	1.30	3.59
Ankle y angle (Maximum)	0.96	7.11	0.88-0.99	0.65	1.80
Ankle y angle (Minimum)	0.82	-5.32	0.46-0.94	0.76	2.10

X=sagittal plane (flexion-extension), Y=frontal plane (adduction-abduction), Z=transverse plane (internal rotation-external rotation)

Between-session reliability for joints moments and ground reaction force in stance during walking for healthy participants.

Walking - Joint Moment (Nm/Kg) and GRF (*BW) (Between-session)	ICC	Mean	95% CI of ICC	SEM	SDD
Hip x moment (Maximum)	0.98	1.13	0.92-0.99	0.05	0.14
Hip x moment (Minimum)	0.94	-0.65	0.81-0.98	0.04	0.11
Hip y moment (1st Peak)	0.96	0.85	0.87-0.99	0.03	0.09
Hip y moment (Trough)	0.94	0.48	0.81-0.98	0.03	0.08
Hip y moment (2nd Peak)	0.94	0.85	0.82-0.98	0.04	0.10
Hip z moment (Maximum)	0.94	0.30	0.83-0.98	0.03	0.07
Hip z moment (Minimum)	0.86	-0.11	0.57-0.95	0.03	0.08
Knee x moment (Maximum)	0.94	0.55	0.83-0.98	0.03	0.08
Knee x moment (Minimum)	0.88	-0.64	0.64-0.96	0.08	0.23
Knee z moment (Maximum)	0.78	0.06	0.35-0.93	0.02	0.05
Knee z moment (Minimum)	0.93	-0.17	0.80-0.98	0.02	0.05
Ankle x moment (Maximum)	0.97	1.51	0.90-0.99	0.03	0.08
Ankle x moment (Minimum)	0.86	-0.22	0.59-0.95	0.02	0.06
Angle y moment (Maximum)	0.75	0.08	0.24-0.91	0.03	0.09
Ankle y moment (Minimum)	0.63	-0.17	-0.11-0.88	0.05	0.15
GRF (1st Peak)	0.99	1.11	0.96-0.99	0.02	0.04
GRF (Trough)	0.96	0.70	0.88-0.99	0.02	0.05
GRF (2nd Peak)	0.98	1.08	0.94-0.99	0.01	0.04

X=sagittal plane (flexion-extension), Y=frontal plane (adduction-abduction), Z=transverse plane (internal rotation-external rotation)

Knee OA reliability study:

Between-day reliability for joints ROM in a gait cycle during walking for participants with knee OA.

ROM in degree	ICC	Mean	95% CI of ICC	SEM	SDD
Hip x ROM	0.97	40.80	0.97-0.99	1.15	3.18
Hip y ROM	0.96	12.82	0.93-0.99	0.94	2.61
Hip z ROM	0.90	11.66	0.57-0.97	0.79	2.20
Knee x ROM	0.99	70.53	0.97-0.99	0.84	2.31
Knee y ROM	0.87	10.81	0.43-0.97	1.29	3.57
Knee z ROM	0.92	18.90	0.64-0.98	1.10	3.04
Ankle x ROM	0.93	31.85	0.70-0.98	1.16	3.21
Ankle y ROM	0.96	13.50	0.83-0.99	0.62	1.71

X=sagittal plane (flexion-extension), Y=frontal plane (adduction-abduction), Z=transverse plane (internal rotation-external rotation)

Between-day reliability for joints angles during walking in a gait cycle during walking for participants with knee OA.

Joint angle in degree	ICC	mean	95% CI of ICC	SEM	SDD
Hip x angle (1st peak)	0.96	33.77	0.82-0.99	1.24	3.45
Hip x angle (Trough)	0.98	-0.14	0.89-0.99	1.10	3.06
Hip x angle (2nd peak)	0.91	40.64	0.619-0.98	1.96	5.44
Hip y angle (Maximum)	0.79	5.60	-0.57-0.96	1.23	3.42
Hip y angle (Minimum)	0.76	-7.12	-0.64-0.95	2.05	5.68
Hip z angle (Maximum)	0.77	2.35	-0.02-0.95	2.41	6.69
Hip z angle (Minimum)	0.83	-9.31	0.23-0.96	2.12	5.88
Knee x angle (Initial contact)	0.91	-0.08	61-98	1.57	4.36
Knee x angle (Loading response)	0.97	14.00	85-99	1.24	3.45
Knee x angle (Mid-stance)	0.97	6.60	87-99	1.06	2.94
Knee x angle (Swing)	0.97	67.95	85-99	1.44	3.99
Knee y angle (Maximum)	0.84	6.49	0.27-0.96	1.42	3.95
Knee y angle (Minimum)	0.43	-4.03	-1.84-0.49	2.08	5.78
Knee z angle (Maximum)	0.90	-1.33	0.55-0.98	1.34	3.70
Knee z angle (Minimum)	0.90	-20.24	0.54-0.98	1.39	3.86
Ankle x angle (Minimum)	0.96	-11.53	0.84-0.99	1.03	2.85
Ankle x angle (Maximum)	0.96	20.33	0.82-0.99	0.73	2.02
Ankle y angle (Maximum)	0.93	7.34	0.70-0.98	0.90	2.49
Ankle y angle (Minimum)	0.58	-6.16	-0.85-0.91	0.84	2.34

X=sagittal plane (flexion-extension), Y=frontal plane (adduction-abduction), Z=transverse plane (internal rotation-external rotation)

Between-day reliability for joints moments and ground reaction force in a stance during walking for participants with knee OA.

Joint Moment (Nm/Kg), KAAI (Nm/kg*s) and GRF (*BW)	ICC	mean	95% CI of ICC	SEM	SDD
Hip x moment (Maximum)	0.95	1.00	0.76-0.99	0.062	0.17
Hip x moment (Minimum)	0.92	-0.81	0.64-0.98	0.072	0.20
Hip y moment (1st Peak)	0.70	0.97	-0.37-0.93	0.089	0.25
Hip y moment (Trough)	0.92	0.63	0.64-0.98	0.036	0.10
Hip y moment (2nd Peak)	0.82	0.84	0.18-0.96	0.050	0.14
Hip z moment (Maximum)	0.94	0.36	0.71-0.99	0.025	0.07
Hip z moment (Minimum)	0.93	-0.07	0.68-0.98	0.011	0.03
Knee x moment (Maximum)	0.99	0.49	0.93-0.99	0.017	0.05
Knee x moment (Minimum)	0.98	-0.53	0.91-0.99	0.041	0.11
Knee z moment (Maximum)	0.99	0.08	0.95-0.99	0.005	0.01
Knee z moment (Minimum)	0.90	-0.13	0.53-0.98	0.020	0.05
Ankle x moment (Maximum)	0.94	1.45	0.74-0.99	0.038	0.11
Ankle x moment (Minimum)	0.94	-0.21	0.73-0.99	0.025	0.07
Angle y moment (Maximum)	0.83	0.16	0.26-0.96	0.030	0.08
Ankle y moment (Minimum)	0.90	-0.10	0.55-0.98	0.016	0.04
GRF (1st Peak)	0.96	1.15	0.80-0.99	0.023	0.06
GRF (Trough)	0.98	0.78	0.93-0.99	0.020	0.05
GRF (2nd Peak)	0.99	1.08	0.95-0.99	0.007	0.02

X=sagittal plane (flexion-extension), Y=frontal plane (adduction-abduction), Z=transverse plane (internal rotation-external rotation)

Appendix E: **Main study kinematics, kinetics, GRF, COP and PASE data and other KOOS subscales data.**

- Knee moment in sagittal plane
- External knee extension moment:

The data showed mild deviation in normality and inequality of variance. The transformations (RMS, log10, Ln) were successful in producing equality of variance. The results of two way-mixed ANOVA, between groups test (one-way ANOVA), and within group test (repeated-measures ANOVA) for the transformed data and the non-transformed data were similar. Furthermore, the non-parametric tests between and within groups were similar to the parametric tests (transformed and non-transformed). Therefore, for easier interpretation of the results, the parametric test was used on the non-transformed data. The descriptive data is presented in Table E-1.

Within each group

Repeated-measures ANOVA showed a significant effect for the time within the combined group (p<0.01) but not for the sleeve (p=0.57) or LWI (p=0.17) group. Immediate effect in the combined group showed significant lower extension moment compared to baseline (p<0.01) and after 6 weeks (p=0.02) (Figure E-1).

Between the groups

One-way ANOVA showed significant difference between the groups in the knee extension moment at baseline (p=0.01) but not after immediate use of the treatment (p=0.07) or after 6 weeks' use (p=0.06). Pairwise comparison showed that the combined group had significantly higher extension moment compared to the LWI group only (p=0.04).

- Knee flexion moment

Two way-mixed ANOVA

ANOVA showed no significant effect for groups in the knee flexion moment (p=0.24). Neither the time (p=0.45) nor the interaction between group and time showed any significance (p=0.40). The descriptive data is presented in Table E-1.

Within each group

Repeated-measures ANOVA showed no significant effect for the time within the combined group (p=0.75), the sleeve group (p=0.94), or the LWI group (p=0.19) (Figure E-1).

Between the groups

One-way ANOVA showed no significant difference between the groups in the baseline (p=0.27), immediate effect (p=0.25), or 6 weeks (p=0.20).

Table E-1 Mean (SD) of knee joint moments in frontal plane for combined, sleeve and LWI groups.

Mean (SD). Nm/kg	Week one						Week 6		
	Combined group		Sleeve group		LWI group		Combined group	Sleeve group	LWI group
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	Shod + LWI treatment
Maximum extension moment	0.41 (0.15) λ	0.34 (0.11) Θ τ	0.43 (0.20)	0.41 (0.15)	0.27 (0.09)	0.28 (0.10)	0.39 (0.13)	0.41 (0.13)	0.30 (0.10)
Maximum flexion moment	-0.61 (0.34)	-0.62 (0.35)	-0.41 (0.27)	-0.42 (0.28)	-0.56 (0.26)	-0.59 (0.25)	-0.63 (0.36)	-0.41 (0.25)	-0.51 (0.22)

λ significant compared to LWI
Θ significant compared to baseline
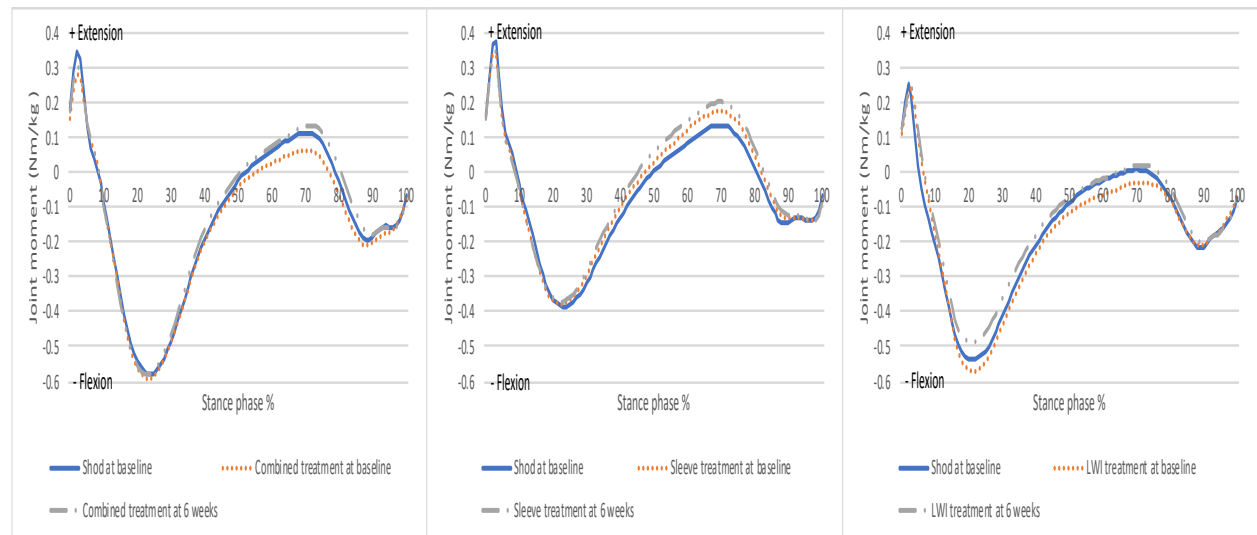τ significant compared to 6 weeks

Figure E-1 Mean (SD) of knee joint moment in frontal plane for combined (a), sleeve (b) and LWI (c) groups.

- Vertical GRF

The EKAM is contributed to from the magnitude of the GRF Therefore, it is important to monitor the GRF and assess if any change occurred between the groups and across time within each group.

- First peak of GRF

Two way-mixed ANOVA

The groups (p=0.33) and time (p=0.58) had no significant effect on first peak GRF. There was no significant interaction between group and time on the first peak GRF (p=0.38). The descriptive data is presented in Table E-2.

Within each group

No significant difference was identified within the combined group (p=0.60), the sleeve group (p=0.55), or the LWI group (p = 0.19) via repeated measures ANOVA (Figure E-2).

Between the groups

One-way ANOVA showed no significant difference between the groups in the first peak GRF at baseline (p=0.29), immediate (p=0.38), or 6 weeks (p=0.33).

- GRF trough

Two way-mixed ANOVA

The data showed that the group had no significant effect on trough GRF (p=0.38). Neither the time (p=0.56) nor the interaction between the time and group (p=0.46) showed any significant change. The descriptive data is presented in Table E-2.

Within each group

Repeated-measures ANOVA was conducted and showed no significant change within the combined group (p=0.44), the sleeve group (p=0.53), or the LWI group (p=0.57) (Figure E-2).

Between the groups

No significant difference was identified between the groups in the trough at baseline (p=0.25), immediate (p=0.52), or 6 weeks (p=0.43) using one-way ANOVA.

- Second peak of GRF

Two way-mixed ANOVA

The groups had no significant effect on the second peak of GRF (p=0.40), and there was no significant interaction between group and time (p=0.23). The time showed significant effect on second peak EKAM (p<0.01). The descriptive data is presented in Table E-2.

Within each group

Repeated-measures ANOVA showed significant difference within the combined group, the sleeve group, and the LWI group, with p-value equal to p<0.01, p<0.01, and p=0.02, respectively. Pairwise comparison showed significant increase in second peak GRF for the combined group between baseline and immediate effect (p<0.01) and baseline and 6 weeks (p<0.01). Similar results were revealed by pairwise comparison for the sleeve group, showing significant increase in second peak GRF between baseline and immediate effect (p=0.03) and baseline and 6 weeks (p=0.03). In the LWI group, only the immediate use showed significant increase in second peak GRF compared to baseline (p=0.048) as identified by pairwise comparison (Figure E-2).

Between the groups

One-way ANOVA showed no significant difference in the second peak EKAM between the groups at baseline (p=0.45), immediate (p=0.38), and 6 weeks (p=0.33).

Table E-2 Mean (SD) of GRF (1st peak, trough, 2nd peak) for combined, sleeve and LWI groups.

| Mean (SD). *BW | Week one | | | | | | Week 6 | | |
	Combined group		Sleeve group		LWI group		Combined group	Sleeve group	LWI group
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatm ent
1st peak	1.17 (0.08)	1.16 (0.08)	1.10 (0.12)	1.10 (0.13)	1.12 0.12	1.11 (0.11)	1.17 (0.10)	1.11 (0.14)	1.10 (0.11)
Trough	0.75 (0.07)	0.77 0.08	0.81 (0.09)	0.81 (0.11)	0.80 (0.08)	0.80 (0.08)	0.76 (0.09)	0.80 (0.12)	0.81 (0.07)
2nd peak	1.05 (0.05)	1.16 (0.08) Θ	1.02 (0.08)	1.10 (0.13) Θ	1.05 (0.07)	1.11 (0.11) Θ	1.17 (0.10) Θ	1.11 (0.14) Θ	1.10 (0.11)

Θ significant compared to baseline
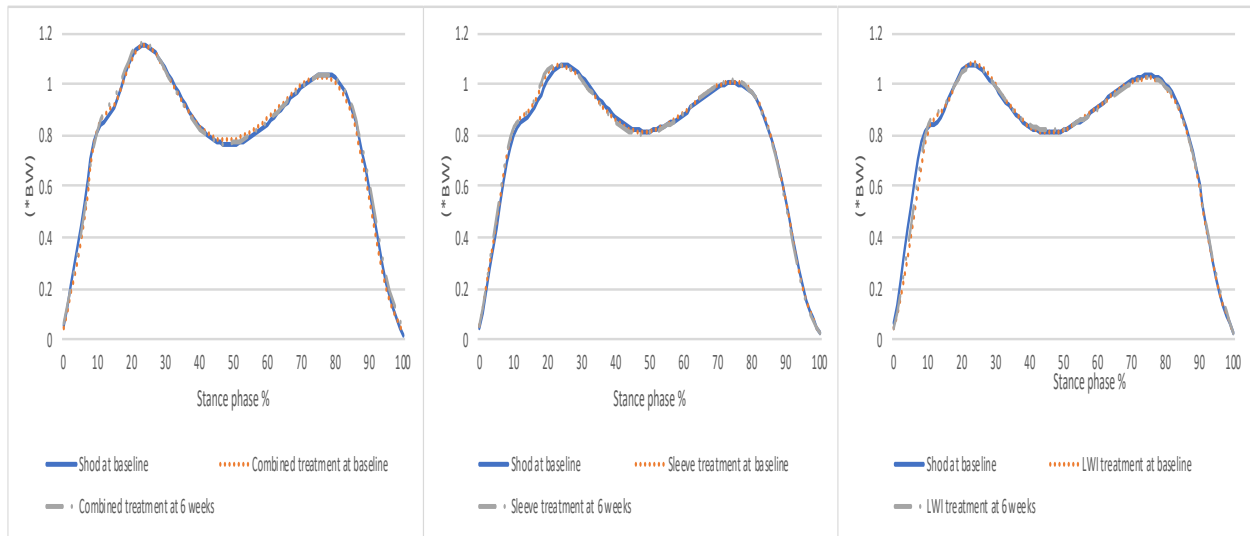
Figure E-2 Mean (SD) of GRF for combined (a), sleeve (b) and LWI (c) groups.

- Kinematics results:
- Temporal and special data:
- Speed:

Two way-mixed ANOVA

There was no significant effect for the duration of intervention (time) and the groups (combined group, sleeve group, LWI group) on the walking speed (p=0.51 and p=0.86, respectively). Neither was there any interaction between group and time (p=0.06). The descriptive data is presented in Table E-3.

Within each group

The treatment had no significant effect on the speed within the groups (combined group, p=0.06; sleeve group, p=0.53; LWI group, p=0.70).

Between the groups

The difference in speed between the groups did not reach significant levels at baseline (p=0.69), immediate effect (p=0.97), or after 6 weeks (p=0.75) when conducting one-way ANOVA.

- Stance time

Two way-mixed ANOVA

For the stance time, the group had no significant effect (p=0.98); neither was there a significant interaction between group and time (p=0.47) while the time showed significant effect (p=0.013). The descriptive data is presented in Table E-3.

Within each group

Repeated-measures ANOVA showed a significant difference in the time within the combined group (p=0.04). However, no significant change was observed for the sleeve group (p=0.51) or the LWI group (p=0.21). Bonferroni and Sidak adjustments failed to show any significant difference within the combined group. Further investigation showed significant increase in stance time only between baseline and immediate effect (p=0.02) using LSD adjustment.

Between the groups

When comparing the groups at baseline (p=0.92), immediate effect (p=0.89), and after 6 weeks (p=0.96), one-way ANOVA showed no significant difference in the swing time.

- Swing time

Two way-mixed ANOVA

There was no significant effect on swing time for the groups (p=0.48), and the time showed no significant effect on swing time (p=0.49). However, there was an interaction between group and time (p=0.02) on the swing time. The descriptive data is presented in Table E-3.

Within each group

Repeated-measures ANOVA showed no significant difference to the time with the combined group (p=0.26) or the sleeve group (p=0.61). The LWI group showed significant effect to the swing time (p=0.02). However, Bonferroni and Sidak adjustments failed to show any significant difference within the LWI group times. Further investigation showed significant reduction in swing time between baseline and immediate effect (p=0.03) and baseline and 6 weeks (p=0.04) using LSD adjustment.

Between the groups

One-way ANOVA showed no significant difference between the groups across the three timelines (baseline, p=0.29; immediate effect, p=0.48; 6 weeks, p=0.43).

Table E-3 Mean (SD) of temporal and spatial data for combined, sleeve and LWI groups.

| Mean (SD). | Week one | | | | | | Week 6 | | |
| | Combined group | | Sleeve group | | LWI group | | Combined group | Sleeve group | LWI group |
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	Shod + LWI treatment
Speed (m/s)	1.22 (0.18)	1.16 (0.15)	1.15 (0.24)	1.17 (0.23)	1.15 (0.24)	1.15 (0.24)	1.22 (0.17)	1.15 (0.26)	1.17 (0.21)
Stance time (second)	0.69 (0.07)	0.73 (0.06) Θ	0.70 (0.07)	0.71 (0.06)	0.71 (0.11)	0.73 (0.12)	0.71 (0.08)	0.72 (0.07)	0.72 (0.10)
Swing time (second)	0.43 (0.04)	0.43 (0.03)	0.42 (0.03)	0.42 (0.02)	0.45 (0.04)	0.43 (0.03) Θ	0.44 (0.04)	0.42 (0.03)	0.43 (0.03) Θ

Θ significant compared to baseline

- Knee angle in sagittal plane:

Two way-mixed ANOVA

The group had no significant effect and ANOVA showed no interaction between group and time on the knee angle at initial contact, the maximum knee flexion angle at loading response, the minimum knee flexion angle at mid-stance, the maximum knee flexion angle at swing, or the knee sagittal plane ROM ($p \geq 0.05$). The time showed no significant effect on the knee maximum flexion angle at loading response, the minimum knee flexion angle at mid-stance, the maximum knee flexion angle at swing, or the knee sagittal plane ROM ($p \geq 0.05$). In contrast the time showed significant effect on the knee angle at initial contact ($p < 0.05$). (Table E-4).

Within each group

Repeated measures ANOVA showed no significant difference in the time for the combined group, the sleeve group, or the LWI group in the knee angle at initial contact, the maximum knee flexion angle at loading response, the minimum knee flexion angle at mid-stance, the maximum knee flexion angle at swing, or the knee sagittal plane ROM ($p \geq 0.05$) (Figure E-3)

Between the groups

The initial contact angle, the maximum knee angle at loading response, the knee extension angle at mid-stance, maximum knee flexion angle at mid swing, and the knee ROM showed no significant difference between the groups at baseline, immediate effect, or 6 weeks ($p \geq 0.05$)

Table E-4 Mean (SD) of knee joint angles in sagittal plane for combined, sleeve and LW groups.

| Mean (SD). degree | Week one | | | | | | Week 6 | | |
| | Combined group | | Sleeve group | | LWI group | | Combined group | Sleeve group | LWI group |
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	Shod + LWI treatment
IC	2.75 (4.04)	2.30 (3.93)	-1.29 (4.85)	-1.80 (4.87)	-0.12 (3.38)	-0.29 (3.50)	1.49 (4.29)	-1.88 (5.92)	-1.33 (3.27)
Maximum flexion angle at lading response	16.18 (7.11)	16.57 (7.27)	12.62 (7.4)	12.34 (7.45)	17.28 (6.57)	17.44 (6.93)	15.58 (7.53)	12.35 (7.29)	16.24 (6.07)
Minimum mid-stance flexion angle	5.31 (6.00)	6.22 (5.74)	5.12 (5.1)	4.50 (4.86)	9.95 (8.82)	10.22 (8.84)	4.57 (6.09)	5.57 (5.57)	9.32 (8.00)
Maximum flexion angle at swing	67.73 (4.59)	68.52 (4.54)	64.42 (5.6)	63.58 (5.79)	66.40 (6.27)	67.61 (5.89)	67.49 (4.82)	62.67 (4.96)	66.82 (5.45)
ROM	68.15 (4.76)	68.56 (3.83)	66.49 (6.43)	65.72 (6.16)	63.54 (7.85)	64.89 (7.51)	67.96 (4.42)	64.89 (4.96)	64.67 (6.13)
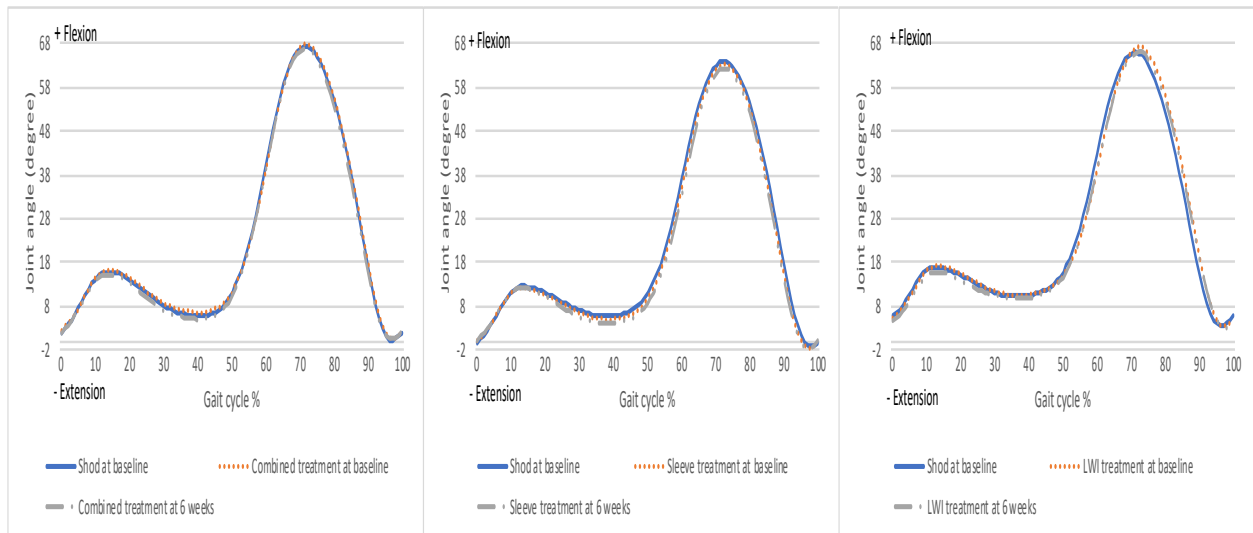
Figure E-3 Mean (SD) of knee joint angle in sagittal plane for combined (a), sleeve (b) and LWI (c) groups.

- Knee angle in frontal plane:
- Maximum adduction angle

Two way-mixed ANOVA

The group and time showed no significant effect on the maximum adduction angle, maximum abduction angle, or the knee frontal plane ROM ($p \geq 0.05$). Neither was there any interaction between the group and the time on the maximum adduction angle, maximum abduction angle, or knee frontal plane ROM using ANOVA ($p \geq 0.05$). The descriptive data is presented in Table E-5.

Within each group

Repeated-measures ANOVA showed no significant change in the maximum adduction angle, maximum abduction angle, or the knee frontal plane ROM after using the treatment within the combined group, sleeve group, or LWI group ($p \geq 0.05$) (Figure E-4).

Between the groups

The difference in the maximum adduction angle, maximum abduction angle, and knee frontal plane ROM between the groups was not statistically significant at baseline, immediate use, or after 6 weeks ($p \geq 0.05$).

Table E-5 Mean (SD) of knee joint angles in frontal plane for combined, sleeve and LWI groups.

| Mean (SD). degree	Week one						Week 6		
	Combined group		Sleeve group		LWI group		Combined group	Sleeve group	LWI group
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	Shod + LWI treatment
Maximum adduction	7.44 (4.60)	6.23 (4.56)	6.31 (6.31)	5.42 (5.70)	5.68 (4.18)	5.33 (3.81)	7.53 (5.28)	6.48 (6.25)	5.70 (4.86)
Maximum abduction	-4.91 (3.98)	-4.05 (3.67)	-4.70 (4.72)	-4.64 (4.87)	-5.91 (4.20)	-6.37 (4.22)	-3.04 (3.51)	-4.95 (5.26)	-7.33 (5.02)
ROM	12.35 (3.08)	10.28 (3.58)	11.01 (3.56)	10.06 (2.60)	11.59 (3.73)	11.70 (3.82)	10.58 (3.25)	11.42 (4.11)	13.03 (4.48)
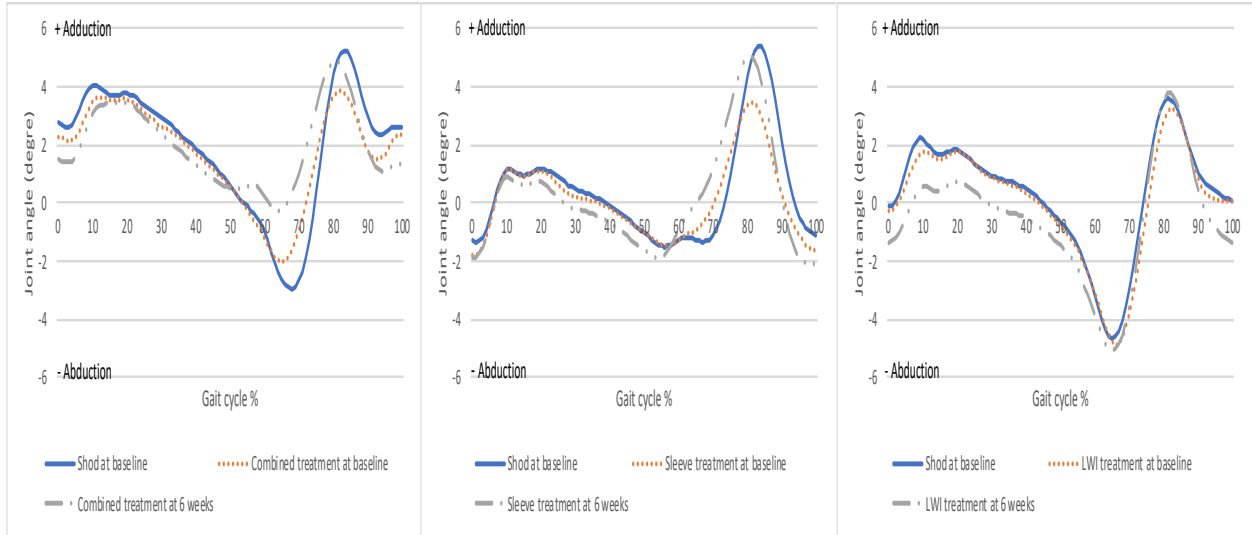
Figure E-4 Mean (SD) of knee joint angle in sagittal plane for combined (a), sleeve (b) and LWI (c) groups.

- Ankle angle in sagittal plane

Two way-mixed ANOVA

The group and time had no significant effect and ANOVA showed no interaction between group and time in the ankle maximum dorsiflexion angle, maximum planter flexion angle, or ankle sagittal plane ROM (p≥0.05). The descriptive data is presented in Table E-6.

Within each group

Repeated-measures ANOVA showed no significant change within the combined group, the sleeve group, and the LWI group in the ankle maximum dorsiflexion angle, maximum planter flexion angle, or ankle sagittal plane ROM (p≥0.05) (Figure E-5).

Between the groups

The ankle maximum dorsiflexion angle, maximum planter flexion angle, and ankle sagittal plane ROM did not differ between the groups at baseline, immediate effect, or 6 weeks (p≥0.05).

Table E-6 Mean (SD) of ankle joint angles in sagittal plane for combined, sleeve and LWI groups.

| Mean (SD). degree	Week one						Week 6		
	Combined group		Sleeve group		LWI group				
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
Maximum dorsiflexion	19.87 (2.62)	20.21 (2.52)	18.79 (2.08)	18.17 (2.50)	19.83 (3.29)	20.23 (3.72)	20.11 (2.31)	19.95 (3.31)	20.17 (3.73)
Maximum plantar flexion	-8.40 (4.09)	-8.00 (3.61)	-8.75 (4.16)	-9.22 (4.73)	-8.37 (4.66)	-7.58 (4.45)	-8.60 (4.22)	-7.82 (3.90)	-8.13 (4.94)
ROM	28.27 (4.82)	28.20 4.73)	27.54 (3.32)	27.38 (3.31)	28.57 (2.35)	28.16 (3.27)	28.72 (5.08)	27.77 (3.29)	28.79 (3.36)
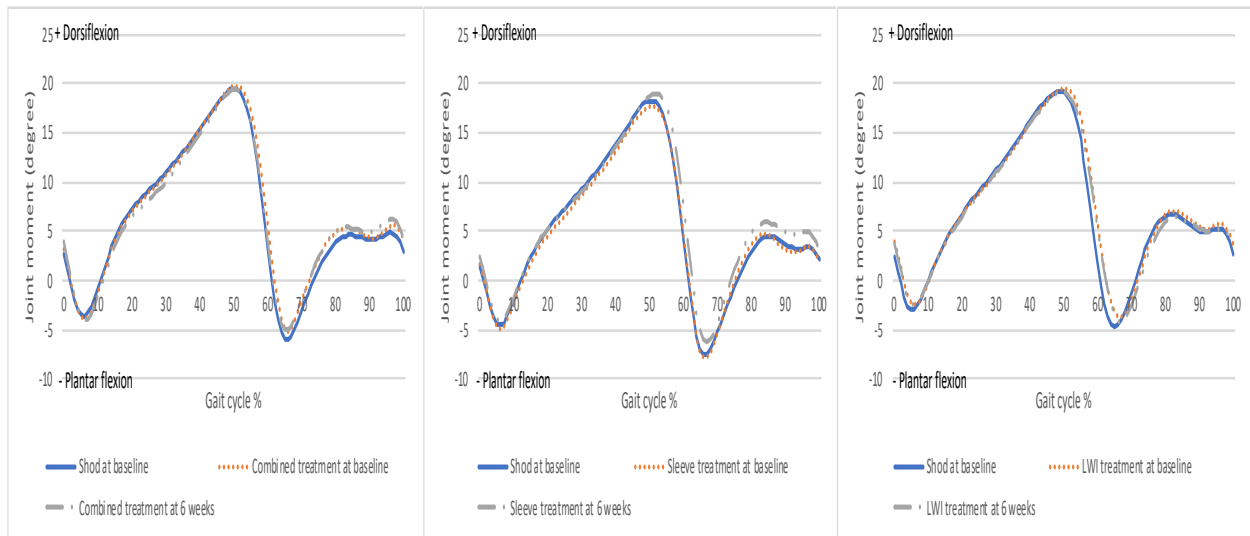
Figure E-5 Mean (SD) of ankle joint angle in sagittal plane for combined (a), sleeve (b) and LWI (c) groups.

- Ankle angle in frontal plane.

Two way-mixed ANOVA

The interaction between the group and time was not significant in the maximum inversion angle, maximum eversion angle, or ankle frontal plane ROM ($p \geq 0.05$). The data showed that the group had no significant effect on the maximum inversion angle, maximum eversion angle, or ROM ($p \geq 0.05$). The time showed significant effect on the maximum inversion angle and ROM ($p < 0.05$) but not on the maximum eversion angle ($p \geq 0.05$). The descriptive data is presented in Table E-7.

Within each group

After using the treatment for 6 weeks, there was no statistically significant effect on the maximum inversion angle or the maximum eversion angle in all groups (p≥0.05). The ankle frontal plane ROM showed significant change within the LWI group (p<0.05), but not for the combined group or the sleeve group (p≥0.05). Pairwise comparison showed significant increase in ankle frontal plane ROM between baseline and immediate effect (p<0.01) and between baseline and 6 weeks (p<0.01) (Figure E-6).

Between the groups

The difference between the groups in the maximum inversion angle, maximum eversion angle, and ROM at baseline, after immediate use of the treatment, and after 6 weeks' use of the treatment did not reach a statistically significant level (p<0.05).

Table E-7 Mean (SD) of ankle joint angles in frontal plane for combined, sleeve and LWI groups.

| Mean (SD). degree	Week one						Week 6		
	Combined group		Sleeve group		LWI group		Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment			
Maximum inversion	9.00 (3.67)	9.60 (4.11)	7.96 (2.74)	9.48 (4.70)	8.60 (3.35)	9.49 (3.23)	9.75 (3.67)	9.05 (3.41)	10.26 ()3.58
Maximum eversion	-4.74 (2.04)	-5.09 (2.22)	-5.37 (2.34)	-5.34 (3.05)	-3.85 (2.52)	-4.56 (2.81)	-4.67 (2.23)	-5.10 (1.97)	-4.84 (2.98)
ROM	13.75 (3.32)	14.69 (3.28)	13.34 (2.26)	14.82 (3.09)	12.51 (2.87)	13.94 (3.36) Θ	14.42 (4.55)	14.16 (3.10)	14.98 (3.96) Θ

Θ significant compared to baseline
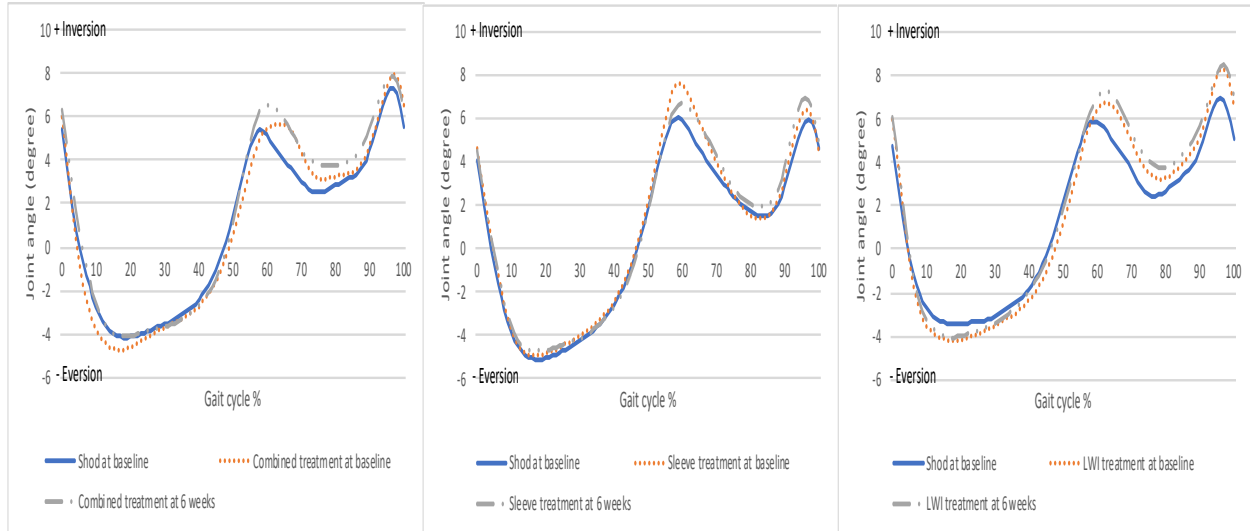
Figure E-6 Mean (SD) of ankle joint angle in frontal plane for combined (a), sleeve (b) and LWI (c) groups.

- Foot centre of pressure

Two way-mixed ANOVA

ANOVA showed that the group had no significant effect, and there was no significant interaction between group and time on the early-, mid- and late-stance COP ($p \geq 0.05$). The time showed significant effect on early-stance COP, mid-stance COP, and late-stance COP ($p < 0.05$). The descriptive data is presented in Table E-8.

Within each group

Repeated measures ANOVA showed significant time effect for the combined and LWI groups in the early-stance COP ($p<0.05$), mid-stance COP ($p<0.05$), and late-stance COP ($p<0.05$), but not for the sleeve group ($p\geq0.05$). Pairwise comparison showed significant lateral shifting in COP in the combined and LWI groups after immediate treatment compared to baseline in early-stance COP ($p=0.01$, $p<0.01$), mid-stance COP ($p<0.01$, $p=0.041$), and late-stance COP ($p<0.01$, $p=0.04$). After 6 weeks of treatment, only the combined group showed significant lateral shifting compared to baseline in early-stance ($p=0.02$), mid-stance ($p<0.01$), and late-stance ($p<0.01$) COP (Figure E-9).

Between the groups

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No statistical difference was identified in early-stance, mid-stance, or late-stance COP between the groups at baseline, immediate effect, and 6 weeks ($p \geq 0.05$).

Table E-8 Mean (SD) of centre of foot pressure in early, mid and late stance phases for combined, sleeve and LWI groups

| Mean (SD). Cm | Week one | | | | | | Week 6 | | |
| | Combined group | | Sleeve group | | group | | | | |
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
Early-stance	1.08 (0.36)	1.35 (0.45) Θ	1.34 (0.70)	1.34 (0.65)	1.17 (0.53)	1.52 (0.60)Θ	1.38 (0.32) Θ	1.38 (0.49)	1.39 (0.46)
Mid-stance	0.46 (0.43)	1.02 (0.45) Θ	0.74 (0.55)	0.83 (0.60)	0.55 (0.40)	0.98 (0.45)Θ	1.02 (0.28) Θ	0.97 (0.45)	0.88 (0.52)
Late-stance	-0.64 (0.61)	-0.11 (0.69) Θ	-0.46 (0.65)	-0.27 (0.74)	-0.43 (0.56)	-0.08 (0.62)Θ	-0.05 (0.55) Θ	-0.23 (0.58)	-0.14 (0.66)
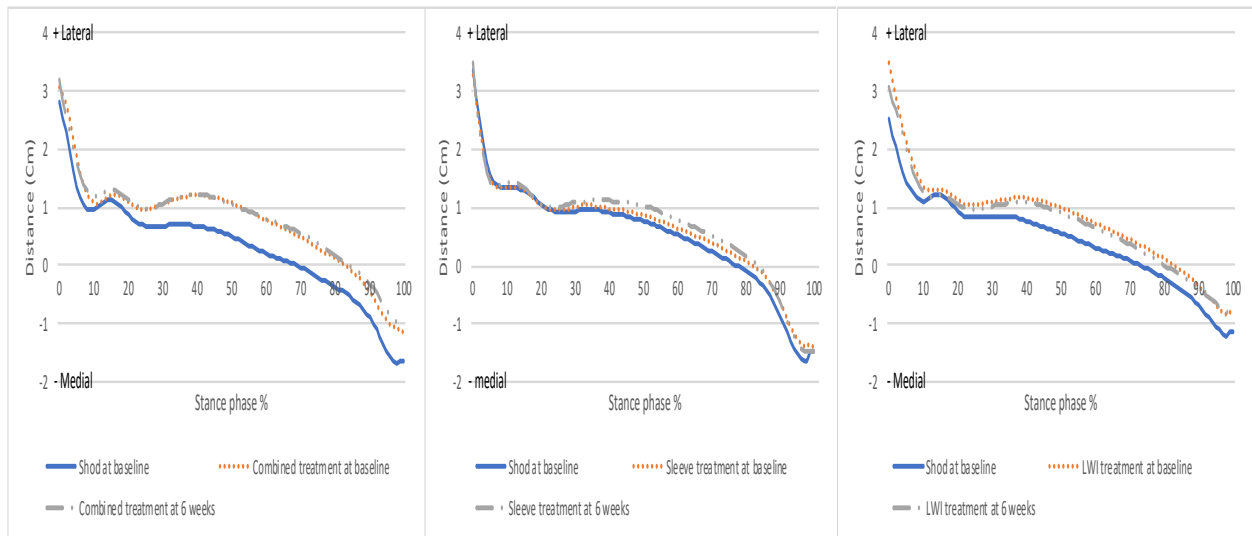
Figure E-7 Mean (SD) of centre of foot pressure for combined (a), sleeve (b) and LWI (c) groups.

- Kinetics data of the ankle:
- Ankle moment in sagittal plane.
- Ankle dorsiflexion moment

Two way-mixed ANOVA

The data showed no significant effect on the ankle dorsiflexion moment for the groups (p=0.84). ANOVA showed significant time effect (p=0.04) but no interaction between time and group (p=0.07). The descriptive data is presented in Table E-9.

Within each group

Repeated-measures ANOVA showed significant time effect for the combined group (p<0.01) but not for the sleeve group (p=0.63) or the LWI group (p=0.30). Pairwise comparison showed significant reduction in ankle dorsiflexion moment with immediate use of the combined treatment (p<0.01) but not after 6 weeks (p=0.06) (Figure E-8).

Between the groups

One-way ANOVA showed no significant difference between the groups in the ankle dorsiflexion moment at baseline (p=0.60), immediate effect (p=0.90), or after 6 weeks (p=0.89).

- Plantar flexion moment

Two way-mixed ANOVA

There was no significant interaction between group and time (p=0.23); neither the group (p=0.84) nor the time (p=0.23) had a significant effect on the ankle plantar flexion moment. The descriptive data is presented in Table E-9.

Within each group

Repeated-measures ANOVA showed significant time effect for the combined group (p=0.049), but not for the sleeve group (p=0.56) or the LWI group (p=0.53). Pairwise comparison adjusted to Bonferroni, Sidak, and LSD failed to identify any significant change within the combined group (Figure E-8).

Between the groups

One-way ANOVA showed no significant difference between the groups in ankle plantar flexion moment at baseline (p=0.87), immediate effect (p=0.80), or after 6 weeks (p=0.65).

Table E-9 Mean (SD) of sagittal plane knee moments for combined, sleeve and LWI groups.

| Mean (SD). Nm/kg | Week one | | | | | | Week 6 | | |
| | Combined group | | Sleeve group | | LWI group | | Combined group | Sleeve group | LWI group |
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	Shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
Maximum plantarflexion moment	-0.20 (0.07)	-0.21 (0.06) Θ	-0.19 (0.13)	-0.20 (0.12)	-0.21 (0.10)	-0.23 (0.11)	-0.24 (0.07)	-0.20 (0.13)	-0.21 (0.10)
Maximum dorsiflexion moment	1.38 (0.16)	1.32 (0.17)	1.30 (0.17)	1.32 (0.17)	1.32 (0.20)	1.29 (0.22)	1.34 (0.14)	1.31 (0.19)	1.31 (0.20)
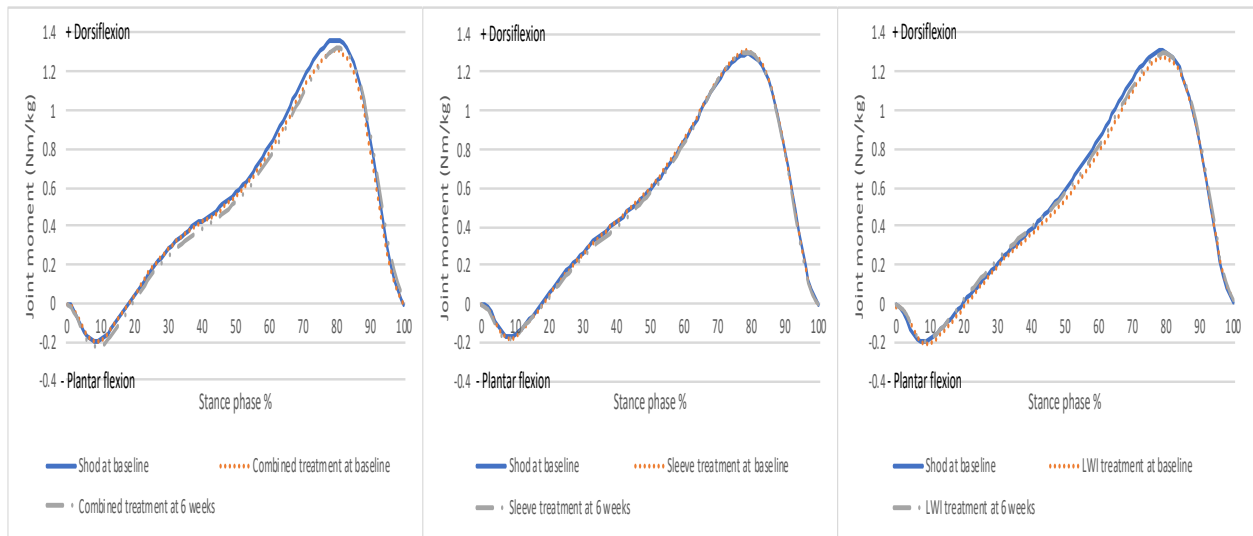
Figure E-8 Mean (SD) of sagittal plane ankle moment for combined (a), sleeve (b) and LWI (c) groups.

- Ankle moment in frontal plane:
- Ankle inversion moment

The data showed mild to moderate deviation in normality in the sleeve group and inequality of variance. The transformation (RMS, log10, Ln, reciprocal) failed to correct the significant difference in variance and the deviation in normality. Therefore, two way-mixed ANOVA could not be used, and two choices were available to compare time within each group and among the groups via non-parametric (Friedman test, Kruskal-Wallis test) or parametric (repeated-measures

ANOVA, one-way ANOVA) testing. When comparing the treatment effect within each group via the non-parametric test, the LWI group showed significant reduction in inversion moment after immediate use of the treatment compared to baseline. However, this is not believed to be accurate since the LWI and combined groups were normally distributed, and the results of the parametric test revealed no significant changes. Therefore, the parametric test was preferred since the changes were only in the normally distributed group when using the non-parametric test.

Within each group

Repeated-measures ANOVA showed no significant changes in the inversion moment within the combined group (p=0.07), the sleeve group (p=0.06), or the LWI group (p=0.18). The descriptive data is presented in Table E-10.

Between the groups

One-way ANOVA showed significant difference between the groups in inversion moment at baseline (p=0.048), but not for immediate effect (p=0.49) or after 6 weeks (p=0.11). All adjustments failed to identify any changes between the groups (Figure E-9)

Ankle eversion moment

The data showed mild to moderate deviation in normality in the sleeve group and the combined group and inequality of covariance. The transformation (RMS, log10, Ln, reciprocal) failed to correct the significant difference in normality and covariance. Therefore, two way-mixed ANOVA could not be used, and two choices were available to compare time within each group and between the groups via non-parametric (Friedman test, Kruskal-Wallis test) or parametric (repeated-measures ANOVA, one-way ANOVA) testing. When comparing the groups at baseline, immediate effect of treatment, and after 6 weeks of treatment, both parametric and non-parametric tests revealed similar results. However, when the effect of the treatment within each group was investigated, parametric testing showed a significant increase in eversion moment after 6 weeks use of LWI compared to baseline, while non-parametric testing showed a significant increase in eversion moment after immediate use of LWI compared to baseline. Choosing parametric tests was thought to be more appreciate since the LWI group data was normally distributed and the change was only observed in this group.

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Within each group

Repeated-measures ANOVA showed no change after using the treatment in the combined group (p=0.35) or the sleeve group (p=0.07). However, the LWI group showed significant change in eversion moment (p=0.03). Pairwise comparison showed significant increase in eversion moment only after 6 weeks compared to baseline (p=0.03). The descriptive data is presented in Table E-10.

Between the groups

One-way ANOVA showed no significant difference in the eversion moment between the groups in baseline (p=0.76), immediate effect (p=0.88), or after 6 weeks (p=0.78) (Figure E-9).

Table E-10 Mean (SD) of ankle joint moments in frontal plane for combined, sleeve and LWI groups.

| Mean (SD). Nm/kg | Week one | | | | | | Week 6 | | |
| | Combined group | | Sleeve group | | LWI group | | Combined group | Sleeve group | LWI group |
	Shod	Shod + combined treatment	Shod	Shod + sleeve treatment	shod	shod + LWI treatment	Shod + combined treatment	Shod + sleeve treatment	shod + LWI treatment
Maximum inversion moment	0.18 (0.16)	0.14 (0.13)	0.08 (0.06)	0.09 (0.07)	0.16 (0.10)	0.12 (0.10)	0.14 (0.13)	0.05 (0.07)	0.12 (0.09)
Maximum eversion moment	-0.12 (0.06)	-0.14 (0.08)	-0.13 (0.09)	-0.13 (0.09)	-0.11 (0.04)	-0.14 (0.07)	-0.13 (0.06)	-0.15 (0.08)	-0.15 (0.05) Θ

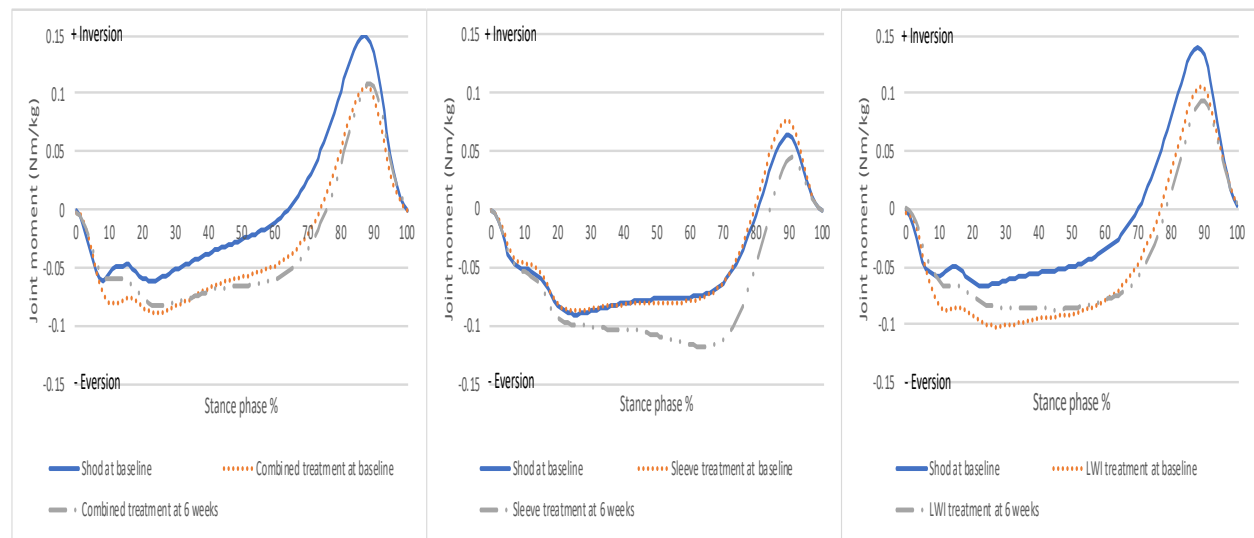Θ significant compared to baseline

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Figure E-9 Mean (SD) of ankle joint moment in frontal plane for combined (a), sleeve (b) and LWI (c) groups.

- KOOS Symptoms, ADL, sport, QOL subscales and PASE scale:

Two way-mixed ANOVA

ANOVA showed no significant interaction, and the group had no effect on KOOS symptoms, ADL, sport, QOL subscales, or PASE scale ($p \geq 0.05$). The time showed significant effect on the KOOS symptoms, ADL, sport, and QOL subscales ($p < 0.05$), but not for PASE ($p \geq 0.05$). descriptive data is presented in Table E-11.

Within each group

Significant improvement was identified after 6 weeks of LWI, sleeve, and combined treatment use compared to the baseline in KOOS symptoms, ADL, sport, and QOL subscales ($p < 0.05$). Interestingly, only the combined group showed significant increase in PASE compared to baseline ($p < 0.05$).

Between the groups

One-way ANOVA showed no significant difference between the groups at baseline and after 6 weeks of treatment in KOOS symptoms, ADL, sport, QOL subscales, or PASE scale ($p \geq 0.05$).

Magnitude of change between the groups

When the magnitude of change in KOOS symptoms, ADL, sport, QOL subscales, and PASE scale were compared between the groups, no significant difference was identified ($p \geq 0.05$).

Table E-11 Mean (SD) of symptoms, ADL, sport and QOL KOOS subscales and PASE for combined, sleeve and LWI groups.

Mean (SD)	Combined group		Sleeve group		LWI group		Magnitude of change between baseline and week 6		
	Baseline	Weeks 6	Baseline	Weeks 6	Baseline	Weeks 6	Combined group	Sleeve group	LWI group
Symptoms	62.01 (20.16)	72.73 (16.23) Θ	67.86 (18.14)	73.70 (21.56) Θ	55.06 (16.71)	64.29 (21.70) Θ	10.71 (9.72)	5.84 (6.24)	9.23 (10.38)
ADL	56.95 (18.49)	71.79 (17.07) Θ	61.23 (21.89)	70.45 (20.13) Θ	65.69 (17.88)	73.04 (16.45) Θ	14.84 (11.44)	9.22 (9.37)	7.35 (8.78)
Sport	27.27 (12.52)	44.55 (16.65) Θ	28.64 (13.06)	37.27 (13.11) Θ	28.75 (17.73)	36.25 (26.55) Θ	17.27 (14.21)	8.64 (7.10)	10.00 (15.52)
QOL	34.09 (14.62)	45.45 (18.35) Θ	44.32 (21.19)	51.70 (19.18) Θ	35.42 (17.74)	42.19 (22.79) Θ	11.36 (10.76)	7.39 (4.69)	6.77 (10.13)
PASE	92.86 (49.06)	113.04 (47.67) Θ	86.69 (63.74)	94.13 (55.49)	98.80 (62.01)	104.69 (77.81)	20.17 (29.85)	7.44 (25.51)	5.88 (45.00)

Θ significant compared to baseline