THE RELATIONSHIPS BETWEEN JOINT ALIGNMENT, MUSCLE PROPERTIES, PAIN, AND GAIT BIOMECHANICS IN SENIORS WITH KNEE OSTEOARTHRITIS

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The relationships between joint alignment, muscle properties, pain, and gait biomechanics in seniors with knee osteoarthritis

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CERTIFICATE OF ORIGINALITY

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Huang Chen

ABSTRACT

The aim of this project was to investigate the relationships between joint alignment, muscle properties, pain and joint biomechanics during walking in seniors with knee osteoarthritis (OA).

Knee OA is one of the most common musculoskeletal disorders causing pain and functional limitations in the older population. It was suggested gait biomechanics in people with knee OA, including knee kinematics and kinetics, were related to the disease progression. Malalignment of the lower limb and quadriceps deficits were proposed to be contributing factors that might affect both knee kinematics and kinetics, and therefore induce excessive loading on the knee joint. Comprehensive understanding of knee joint alignment and muscle functioning for control of knee biomechanics could enhance knowledge of pathogenesis of knee OA and underpin rehabilitation for those with medial knee OA.

This project comprised both cross-sectional observational and interventional studies on seniors with symptomatic and radiographic OA. The cross-sectional study involved 47 participants with the aim to explore (1) relationships between tibial torsion and joint loading; (2) association between joint alignment, muscle properties, and knee kinematics during walking; and (3) relationships between knee joint loading and pain. The associations between exercise-induced modulations on joint biomechanics, intensity of pain, and muscle properties were studied based on an interventional study in 39 participants. The hypotheses for this project were (1) tibial torsion in addition to knee varus angle was related to early stance phase joint biomechanics; (2) passive quadriceps muscle tension and strength would be associated with early stance phase knee sagittal kinematics; (3) pain intensity would be related to joint loading; (4) Six weeks of exercise-based rehabilitation program could modulate knee joint load and pain intensity, which would be related to changes in muscle functioning and sagittal

knee kinematics during early stance phase of gait.

In Chapter 2, the associations between lower limb alignments, quadriceps muscle properties, knee joint biomechanics in early stance phase of gait cycle in participants with knee OA are reported. Joint alignment along both frontal and sagittal planes were captured and quantified in a weight-bearing position using a bi-planar low-dose x-ray system. Passive muscle tensions of the superficial heads of the quadriceps muscle were captured using an ultrasound shear-wave elastography system and the maximal quadriceps strength by a hand-held dynamometer. Joint kinetics and kinematics were captured during the early stance phase of gait cycle using a motion analysis system. Findings from the study indicated participants with moderate OA with larger external tibial torsion had larger external knee adduction moment (KAM) and showed a larger KAM index. Similarly, participants with moderate OA showed a negative association between external tibia torsion and knee flexion excursion; however, in mild knee OA, smaller knee flexion excursion was accompanied by greater passive tension of vastus lateralis. Such observations indicated that the associations between lower limb alignment, quadriceps muscle properties and knee biomechanics were OA severity specific. In mild OA, quadriceps properties, high passive tension of vastus lateralis, had stronger association with smaller knee flexion excursion; in moderate OA, it was external tibial torsion that had stronger association with more limited knee flexion and higher joint loading.

In Chapter 3, the relationships between early stance knee joint loading and pain are reported. A path analysis model was used to assess possible relationships between joint loading and knee pain intensity. The model indicated that KAM had an indirect effect on pain intensity through the mediation of external knee flexion moment (KFM). Higher KAM was associated with lower pain intensity when KFM was positively related to pain. A negative relationship was established between KAM index and pain intensity. Therefore, the intensity

of OA-related knee pain was related to loading along the frontal plane as well as the load sharing between the frontal and sagittal planes.

In Chapter 4, findings from the interventional study to assess exercise-induced modulation on knee joint biomechanics, muscle properties, intensity of knee pain, and symptoms are presented. After a six-week exercise-based rehabilitation program, an increase in KAM was found to be associated with reduction in pain intensity. An increase in KAM index was related to improvement in pain and symptom. Reduced vastus lateralis passive tension was associated with an increase in knee flexion excursion in participants with mild knee OA. These findings further supported the observations from the cross-sectional study that OA-related pain intensity and joint biomechanics were linked; passive muscle tension of quadriceps lateral head and knee flexion excursion during loading response phase was realted to an earlier stage of knee OA.

In summary, this project has revealed evidence that joint alignment, muscle properties, pain intensity, and knee gait biomechanics were linked in people with knee OA. The present study provided new evidence that (1) torsional alignment and quadriceps passive tension were linked with joint biomechanics during gait, and these links were specific to disease severity; (2) load sharing between the frontal and sagittal planes was related to pain intensity and symptoms. The knee loading re-distribution from frontal plane to sagittal plane was identified as an important biomechanical factor that had a strong link not only to improvement of pain but also to knee symptoms improvement. These findings provide insight into the pathomechanical pathway of knee OA and contribute to our understanding of muscle properties in the gait biomechanics of the knee joint. Such information might provide insights for rehabilitative strategies for knee OA.

PUBLICATIONS RISING FROM THE THESIS

Articles:

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Conference Presentations:

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Huang, C,. Fu, S.N., Li, Z., Yeung, S.S., & Chan, P.K. (2019). The relationship between passive stiffness of quadriceps femoris and knee external adduction moment in patients with symptomatic medial knee osteoarthritis. World Confederation for Physical Therapy Congress 2019. Geneva, Switzerland. 10-13th, May, 2019

Huang, C,. Fu, S.N., Li, Z., Lai, C. W. K., Yeung, S.S., & Chan, P.K. (2019). The association between patellar tendon stiffness and external knee flexion moment in patients with knee osteoarthritis. Hong Kong Physiotherapy Association Annual Conference 2019 cum 2nd Greater Bay Area Physiotherapy Forum. Hong Kong, China. 25th, May, 2019

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Huang, C., Li, Z., Yeung, S., Chan, P., & Fu, S. (2020). The relationships between passive tension of quadriceps muscle and knee flexion in female patients with knee osteoarthritis. *Osteoarthritis and Cartilage*, *28*, S170.

Huang, C., Yeung, S., Chan, P., Li, Z., & Fu, S. (2020). Transforming of peak external knee moment from the frontal to the sagittal plane during gait in patients with knee osteoarthritis after a 6-week exercise-based rehabilitation program. *Osteoarthritis and Cartilage*, *28*, S161-S162.

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LIST OF ABBREVIATIONS

Abbreviation	**Full name**
ACR	American College of Rheumatology
ASIS	Anterior superior iliac spine
BMI	Body-mass index
EULAR	European League Against Rheumatism
GBD	Global Burden of Disease
ICC	Intra-class correlation coefficient
KAM	External knee adduction moment
KFM	External knee flexion moment
KL	Kellgren and Lawrence classification of osteoarthritis
KOOS	Knee injury and Osteoarthritis Outcome Score
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
RF	Rectus femoris
ROM	Range of motion
VAS	Visual analogy scale
VL	Vastus lateralis
VMO	Vastus medialis
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Chapter 1 Introduction

1.1 Impact of knee osteoarthritis

1.1.1 Definition of osteoarthritis

The American College of Rheumatology (ACR) defines Osteoarthritis (OA) as *"A heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins"* (Altman et al., 1986). More recently, the European League Against Rheumatism (EULAR) recognized OA as a "common complex disorder" (Zhang et al., 2009). It showed the emphases were not only on structural changes but also on activity-related symptoms and function-related limitations. Among all joints, the knee joint is the one most prevalently affected by OA, followed by the hip and hand joint (Turkiewicz et al., 2014, Hunter and Bierma-Zeinstra, 2019).

1.1.2 Prevalence of knee OA and its impact on health

Prevalence of knee OA was approximately 259 million worldwide, which is much higher than that of the hip or other joints (Global Burden of Disease Collaborative Network, 2019). More importantly, the number of people with knee OA above 50 years of age increased from around 188 million to 258 million in the period from 2009 to 2019, an increase of 37.23%. In China, the prevalence of knee OA was 73 million in 2019, increasing rapidly by 43.14% in the past decade. There is a high prevalence of knee OA affecting the medial compartment, accounting for 85.42% in the western population (Felson et al., 1987) and 67.75% in the Chinese population (Zhang et al., 2001).

1.1.3 Diagnosis of knee OA

Knee OA can be diagnosed based on clinical features as clinical knee OA and radiographic characteristics as radiographic knee OA. There are two commonly referred-to guidelines provided by ACR and EULAR (Altman et al., 1986, Zhang et al., 2010) on the diagnosis of clinical knee OA. Under the ACR guideline, any subject having knee pain and satisfying three of the six listed criteria is regarded as having knee OA. The six criteria are age beyond 50, morning stiffness for less than 30 minutes, crepitus, bony tenderness, bony enlargement, and palpable warmth around the joint. The EULAR guideline is more stringent. In addition to age (beyond 45), knee pain, morning stiffness, and joint symptoms (crepitus and bony enlargement), one has to have restricted joint motion and be limited in function to be considered as having knee OA. Table 1.1 lists the criteria proposed by the two organizations.

Degenerative knee with typical radiographic OA changes is regarded as radiographic OA (Felson et al., 1997). Plain x-ray imaging should be taken of both knees in weight-bearing, semi-flexed anterior-posterior view, plus a lateral and skyline view (Zhang et al., 2009). The major radiographic features of bony change include: (1) formation of osteophytes, (2) periarticular ossicles, (3) narrowing of joint space with sclerosis of subchondral bone, (4) small pseudocysts with sclerotic wall, and (5) altered bony end shape. Formation of osteophytes is recognized as the hallmark of osteoarthritis existence, and joint space narrowing is usually used to classify the progression of osteoarthritis.

Symptomatic OA is referred to as osteoarthritis and coexists with pain and other symptoms. However, discordance is usually found among radiographic OA and symptomatic OA (Bedson and Croft, 2008): the x-ray features do not always perfectly match clinical findings in particular knee pain (Claessens et al., 1990). Diagnosis should be made with comprehensive history, complaints, risk factors, physical examination, and imaging evidence (Zhang et al., 2009).

Table 1.1 Diagnosis criteria of knee osteoarthritis

	ACR	EULAR
Risk factors		
Age	≥ 50 years ○	≥ 45 years
Symptom		
Pain	●	●
Morning stiffness <30 min	○	●
Function limitation		●
Clinical sign		
Crepitus	○	●
Bony tenderness	○	
Bony enlargement	○	●
Palpable warmth	○	
Restricted movement		●

ACR: ● necessary criteria , ○ criteria ≥3
EULAR: ● necessary criteria

*ACR: American College of Rheumatology, EULAR: European League Against Rheumatism

1.1.4 Disease radiographic severity

Knee OA is a progressive disease. Kellgren and Lawrence categorized the radiographic severity of OA into five grades (Kellgren and Lawrence, 1957) (Table 1.2). The grading is based mainly on the formation of osteophytes, narrowing of joint space and joint deformity. In the Kellgren and Lawrence (KL) grading system, grade 2 is defined as affirmed minimal severity (Kellgren and Lawrence, 1957), and is frequently adopted by researchers as the cut-off point to identify OA. The KL scoring scale has fair to excellent intra-rater reliability and fair to good inter-rater reliability (Sun et al., 1997). This grading system is still commonly used to reflect the structural degenerations of knee OA.

Table 1.2 Kellgren & Lawrence grade for osteoarthritis (Descriptions from Schiphof et al. 2008 (adapted from Kellgren, Jeffrey & Ball 1963))

Grade	Severity	Description
0	None	Absent sign of OA
1	Doubtful	Doubtful narrowing of joint space and possible osteophyte lipping
2	Minimal	Definite osteophytes and possible narrowing of joint space
3	Moderate	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
4	Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

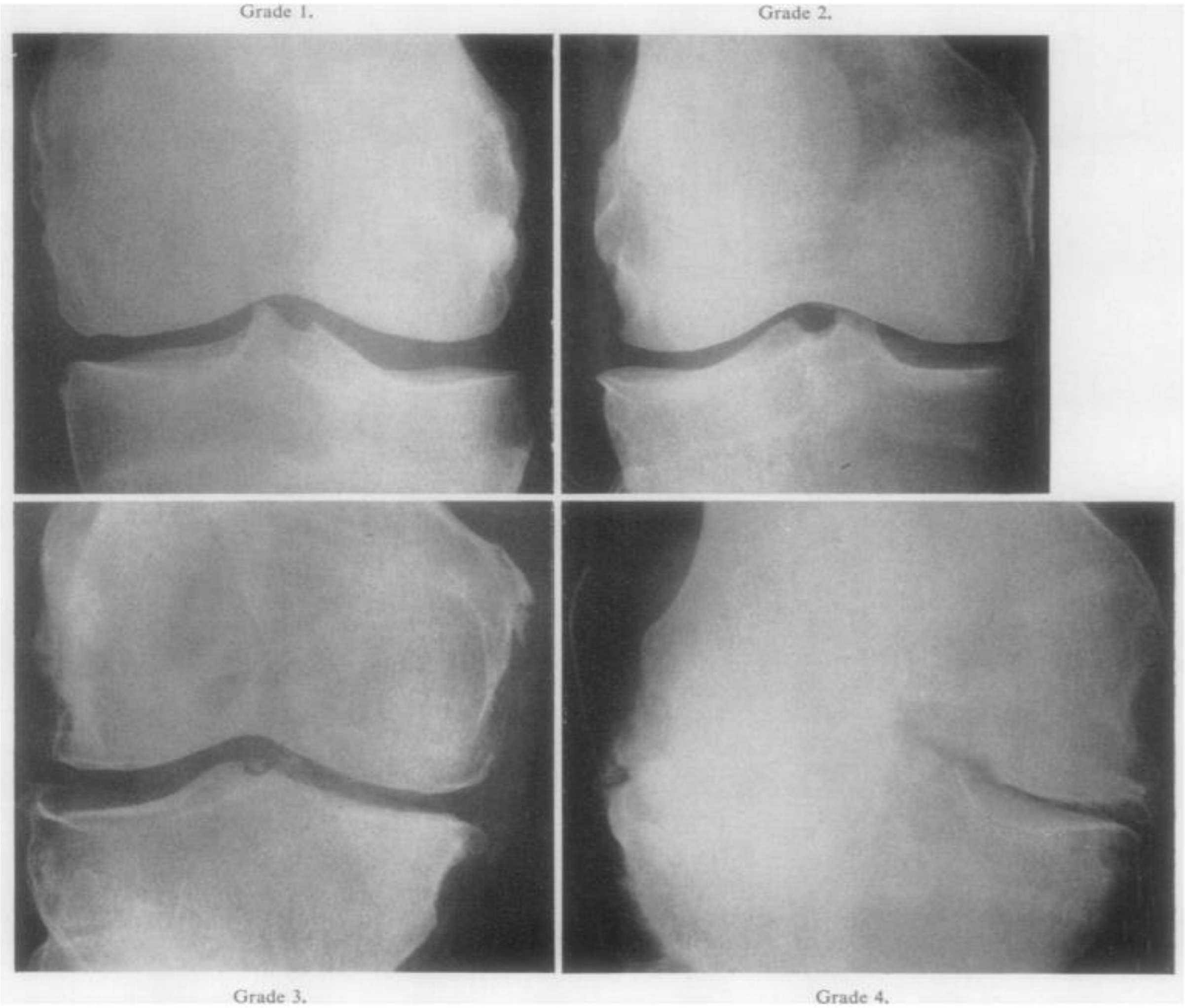

Figure 1.1 Kellgren & Lawrence OA grading system (Adapted from Kellgren & Lawrence, 1957)

1.1.5 Clinical presentation of knee OA

The EULAR diagnosis guideline emphasizes the importance of activity-related symptom and function-related limitations in addition to structural changes (Zhang et al., 2009). Pain, restriction of joint range of motion and functional limitations are recognized as key features of knee OA.

1.1.5.1 OA-related pain

Pain is the most predominant complaint in people with knee OA. OA-related pain shows a significant impact on the quality of life, affecting activity participation, sleep and mood. It is the most common reason why people with knee OA visit physicians and use non-steroidal anti-inflammatory drugs (Neogi, 2013). Pain is also the leading factor contributing to the decision of total knee replacement surgery (Hawker et al., 2008).

OA-related pain is a complicated subjective experience which is affected by interaction of biological and psychological factors (Somers et al., 2009). In addition to joint pathology, psychological and social culture, there are other factors that could influence the perception of pain intensity. OA-related pain pattern and intensity can varies from time to time that might associate with characteristics of the patient (Allen et al., 2009).

The OA-related pain can be categorized into two types, predictable sharp pain and unpredictable dull pain; the sharp pain gradually progresses to dull or aching pain from early stage OA to more advanced OA (Hawker et al., 2008). Besides the nature of pain, OA-related pain also proceeds from activity-provoked pain to more constant pain when OA is progressed to a more advanced stage (Hawker et al., 2008).

Origin and cause of OA-related pain remain largely unknown (Dieppe and Lohmander, 2005). Articular cartilage disruption is recognized as the most influenced structure in OA despite that there is a lack of nerve fiber in the articular cartilage (Hunter et al., 2003). Pain might derive from other structures such as synovium, subchondral bone, outer one-third of menisci, joint capsule, and peripheral ligament (Torres et al., 2006).

1.1.5.2 Reduction in joint range of motion

Reduction in knee joint range of motion (ROM) is common and is strongly associated with self-perceived functional disability in knee OA (Steultjens et al., 2000b). With OA progression, the limitation of knee ROM becomes worse including both knee extension and flexion (Ersoz and Ergun, 2003, Hilfiker et al., 2015).

Knee ROM is influenced by a variety of factors including pain, swelling and structural destruction in knee OA (Hilfiker et al., 2015). Marginal osteophytes formation and tibiofemoral joint space narrowing limit normal knee joint ROM, especially in more advanced knee OA (Ozdemir et al., 2006). When knee OA affects not only bone and cartilage but also surrounding soft tissues, muscle tightening might cause limitation in functional joint angle (You et al., 2009).

1.1.5.3 Functional limitation

Functional limitation is another main concern of knee OA. Common functional limitations include difficulties during walking on level surface, standing, going downstairs and/or upstairs, prolonged sitting and/or lying, postural transition, etc. (Gandek, 2015). These functional limitations are regarded as one of the criteria in the diagnosis of knee OA according to the EULAR guideline (Zhang et al., 2010) and are included in the major knee-OA-specific assessment tools including the Knee Injury and Osteoarthritis Outcome Score and the Western Ontario and McMaster Universities Osteoarthritis Index (Collins et al., 2016, Roos et al., 1998).

1.1.6 Impact of knee OA on the medical system and health

Considering large population and high prevalence, knee OA can pose a huge public health problem. An estimated 85% of OA-related health resources were spent on treating knee OA (Hunter and Bierma-Zeinstra, 2019). In the population aged beyond 55 years, knee OA accounted for about 2.67% of years lived with disability (GBD study, 2019). The percentage was even higher in China that accounted for 3.30% years lived with disability by the year 2019 according to the GBD study. In the United Kingdom, 4% of the population aged above 65 consulted at least once per year for the knee OA (Peat et al., 2001); in the United States, knee and hip OA were the main complaints accounting for 30% of physician visits (Jordan et al., 2007). In Hong Kong, knee OA broadly affected the quality of life (Woo et al., 2004) and the average waiting time of arthroplasty was as long as 66 months (Kan et al., 2019). Thus, knee OA leads to disability and causes a great demand on public health resource and primary care.

Taking together, knee OA is a highly prevalent disease in senior population. It induces large demands on the medical system and affects individual's bio-psycho-social heath.

1.2 Risk factors and pathophysiology of knee OA

1.2.1 Risk factors of knee OA

Multiple risk factors have been identified for knee OA. The common factors include age, gender, body-mass index (BMI), previous injuries, occupation, and hand OA (Silverwood et al., 2015a). Knee OA is significantly more prevalent with age (Safiri et al., 2020). In women, the prevalence of symptomatic knee OA was among 13.5-14.3% in the age of 60-69, while the number increasesd to 14.8-22.0% in the age group of 70 (Zhang et al., 2001). Female has higher prevalence than male (Safiri et al., 2020). In China, female accounted for 64.38% of total population with knee OA (Tang et al., 2016). In urban Chinese population, the prevalence of radiographic knee osteoarthritis was 42.8% in women and 21.5% in man, and about 30% of them suffered from severe osteoarthritis (Zhang et al., 2001). In rural area, the gender difference in prevalence was even higher in terms of both radiographic (14% vs. 6%) and symptomatic knee OA (13% vs. 7%) (Kang et al., 2009). Knee injury history was the strongest risk factor with odds ratio of 2.83, while overweight or obesity had odds ratio of 2.10 (Silverwood et al., 2015a). Interestingly, genetic factors had a less influenced effect on knee OA than on hand and hip OA (Jeffries, 2019). Besides, participation of sports with high impact including soccer, long-distance running, weightlifting was also identified as strong risk factor to future knee OA (Driban et al., 2017).

1.2.2 Pathophysiology of knee OA

OA has been considered as an “organ disease” of the whole joint (Loeser et al., 2012). Articular cartilage erosion is regarded as the hallmark of knee OA. Other structures, such as synovial membranes, subchondral bones, peri-articular ligaments and muscles are all involved in disease onset and progression. OA has been regarded as a joint effect of degeneration and inflammation-caused abnormal structural remodeling (Edd et al., 2018). Typical OA initiates from articular cartilage disruptions on joint surface. The chondrocytes are activated inappropriately by pro-inflammatory cytokines including interleukin 1, tumor necrosis factor, interleukin 6, etc. The chondrocytes proliferate and produce less-functioned matric proteins and matrix degrading enzymes, resulting in the matrix remodeling, abnormal hypertrophy-like maturation and cartilage calcification (Goldring and Marcu, 2009). The biomechanical properties of cartilage alter and lose their protective effects on subchondral bone. Osteoblasts and chondrocytes interact robustly in the progression of OA (Findlay and Atkins, 2014). It is believed that the pathogenesis of OA could be ascribed to bone remodeling and subchondral bone loss in the early stage and subchondral sclerosis later-on (Altman, 2011). In the end stage of OA, microstructure of subchondral bone is altered severely in the areas where overlying cartilage is badly damaged. Due to the imbalance between bone resorption and formation, subchondral bone volume increases and bone material density decreases (Li and Aspden, 1997). These changes result in bone mechanical property shift, and have a strong relationship with symptoms and progression of OA (Funck-Brentano and Cohen-Solal, 2015). Synovium inflammation is also found in early stage of osteoarthritis, featured with mononuclear cell infiltration, pro-inflammatory cytokines production and perivascular aggregation (Myers et al., 1990, Smith et al., 1997). Synovial inflammation is associated with joint cartilage lesion (Krasnokutsky et al., 2011) and symptom severity (Scanzello et al., 2011); the existence of synovial inflammation increases when OA is progressed (Scanzello et al., 2011). The sequence and causal relationship between cartilage break-down, subchondral bone damage, and synovium inflammation still need further investigation (Altman, 2011). More recently, structural changes within and/or surrounding knee joint, such as muscle, ligament and fat pad and etc. should be taken into account in terms of pathophysiology of knee OA (Favero et al., 2015).

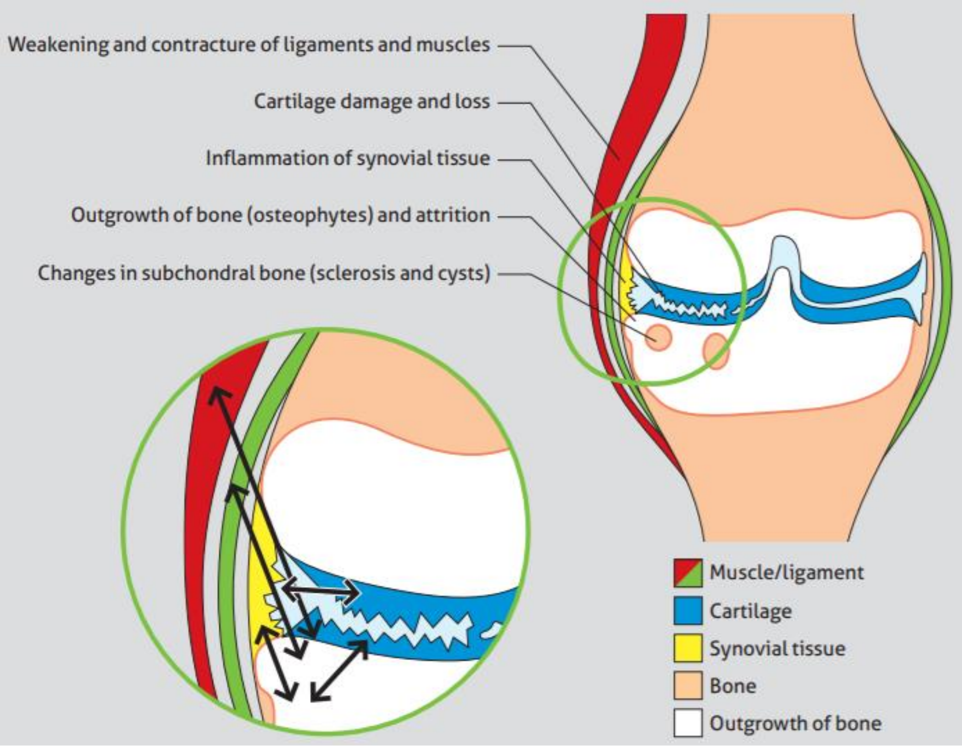

Figure 1.2 Schematic drawing of an osteoarthritic joint (From Arden et al. 2014).

1.3 Gait related pathomechanics of knee OA

Overloading during gait plays an important role in the patho-mechanical pathway of knee OA (Felson, 2013). Furthermore, it is a vital link within the interaction between biological, mechanical and structural factors in the development of knee OA (Andriacchi et al., 2015). The in-depth analysis of the kinematics and kinetics of individual joints during different phases of gait provides better identification of dysfunction in knee OA.

Walking is a repetitive sequence of locomotion using bilateral limbs alternately to move body forwards (Andriacchi et al., 1977). Gait cycle repetitions consist of one limb supporting the body as the other swings forward to reach the next support site during walking (Kharb et al., 2011). Based on the contact of the foot, a gait cycle can be divided into two phases, stance phase and swing phase. The stance phase can be further divided into four sub-phases: 1) initial contact, 2) loading response, 3) mid-stance, 4) terminal stance and 5) pre-swing (Figure 1.3).

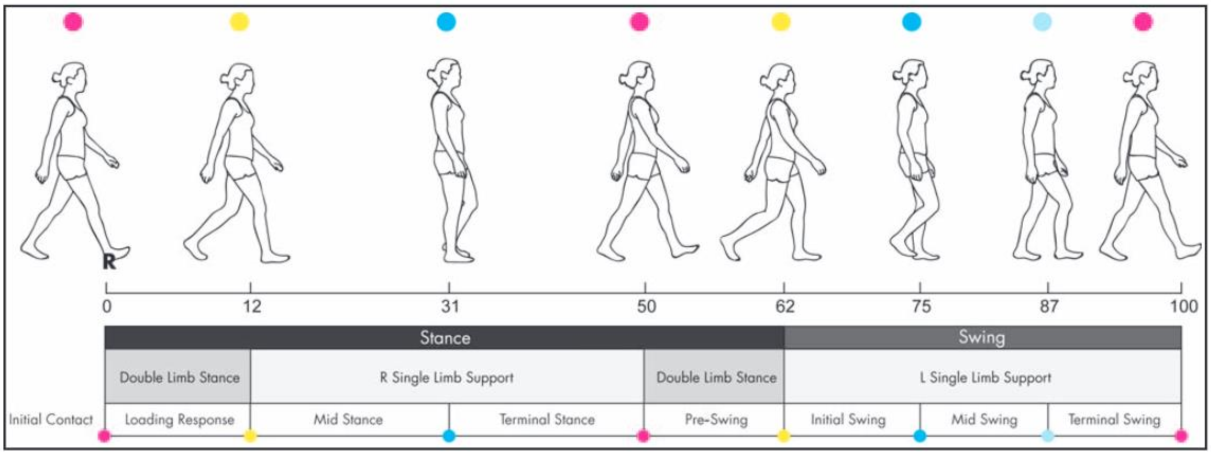

Figure 1.3 Normal gait cycle (Adapted from Adams & Cerny, 2018)

1.3.1 Alteration in gait pattern

In individuals with knee OA, alterations in gait pattern are found in both spatial and temporal parameters. People with knee OA have slower walking speed and shorter stride length. These include 14% slower in walking speed and 8.5% smaller in stride length than the healthy counterparts (Ornetti et al., 2010). With increasing severity of knee OA, walking speed decreases gradually (Zeni Jr and Higginson, 2009, Astephen et al., 2008b).

1.3.2 Gait kinetics

Initiation and progression of OA are predominantly mechanical in nature. Excessive loading could be along the frontal, sagittal and horizontal planes, in particular during the stance phase of gait cycle.

1.3.2.1 External knee adduction moment

Knee external adduction moment (KAM) is caused by a moment of ground reaction force deviating from knee joint center medially on the frontal plane (Figure 1.4). Peak of KAM in the early stance phase can describes the medial-to-lateral loading distribution of the knee joint (Maly et al., 2015), and this parameter showed good reliability in representing medial joint loading (Birmingham et al., 2007). It could explain up to 77% of total variance of change in knee joint medial contact force; the shape of KAM waveform was highly related to the shape of medial contact force of the knee joint (Zhao et al., 2007).

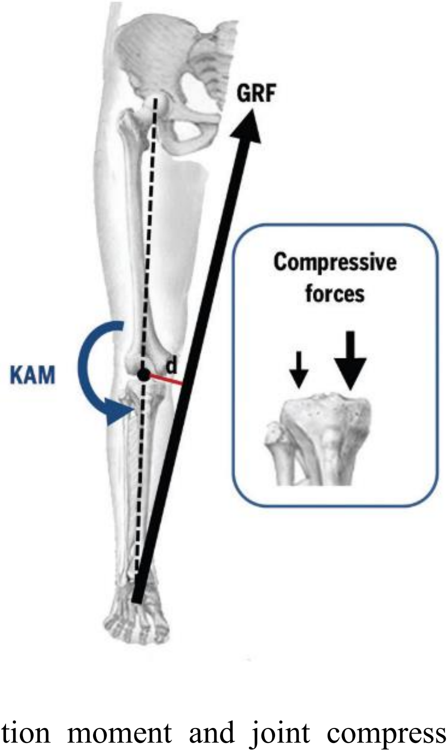

Figure 1.4 External knee adduction moment and joint compressive force in knee joint. (Adapted from Farrokhi et al., 2013)

The magnitude of KAM was correlated to the severity of articular cartilage disruption and thickness loss in the medial tibiofemoral area in individuals with medial compartment knee OA (Creaby et al., 2010), and could explain up to 44% of variance in cartilage thickness

(Maly et al., 2015). There was evidence suggesting that KAM had an impact on medial-lateral subchondral bone morphology (Vanwanseele et al., 2010a), severity of bone marrow lesion (Chang et al., 2015, Kean et al., 2012), and meniscus lesion (Vanwanseele et al., 2010a). In addition, KAM was correlated positively to radiographic severity by KL grading (Hurwitz et al., 2002, Sharma et al., 1998) and by joint space narrowing (Sharma et al., 1998). Sherma et al. (1998) reported that every 1.0 unit change of KAM was associated with a decrease of 0.63mm joint space width (Sharma et al., 1998). More importantly, the magnitude of KAM had 88% sensitivity and 83% specificity to predict KL grade progression in six years (Miyazaki et al., 2002), and one unit change of KAM increased the chance of OA progression by 1.9 folds (Henriksen et al., 2014). KAM was strongly associated with the change of femoral medial-to-lateral cartilage thickness ratio over five years (Chehab et al., 2014). Therefore, the magnitude of KAM during early stance phase is associated with structural changes, disease severity and disease progression of knee OA.

1.3.2.2 External knee flexion moment

External knee flexion moment (KFM) represents the knee joint moment on the sagittal plane during gait. Larger early stance phase KFM was reported in asymptomatic than people with knee OA (Astephen et al., 2008a, Astephen et al., 2008b) and in people with moderate than severe knee OA (Astephen et al., 2008a). Nevertheless, larger KFM was observed in people with knee OA than healthy controls (Kaufman et al., 2001, Landry et al., 2007). It is still unclear whether alteration of early stance phase KFM and knee OA are related. Similarly, conflicting results were reported between KFM and knee joint structural changes. A analysis with five-year follow-up found KFM was related to cartilage erosion at knee joint medial compartment (Chehab et al., 2014), while no association was detected in a larger cohort at 2-year follow-up (Chang et al., 2015).

1.3.2.3 External knee rotation moment

External knee rotation moment (KRM) refers to the knee moment on the transverse plane. Limited amount of literatures was reported in relation to KRM in knee OA. Though there was study showing that people with knee OA has reduced KRM compared to the healthy people (Landry et al., 2007), the contribution of KRM to the external total knee joint moment was nearly negligible (Asay et al., 2018).

1.3.2.4 Interplays between the external moments

Early stance phase peak KAM and KFM occur within the first 20% of gait cycle. A combination of both KAM and KFM provides total moments along the frontal and sagittal planes and is likely a better predictor to medial contact force of knee joint than any single one of them (Walter et al., 2010).

In this connection, the relative contribution of KAM and KFM to total knee joint moment has proposed as a crucial factor to OA disease progression. Asay et al. observed a change from a KFM-dominant loading pattern to a KAM-dominant loading pattern in nineteen subjects with knee OA in five years (Asay et al., 2018). Despite similar total joint moments, these authors observed an increase in the percentage of KAM to total knee joint moment in the five-year follow-up. A more recent study on individuals with anterior cruciate ligament reconstruction indicated that a higher percentage of KFM to total knee joint moment was associated with a less decrease of medial-to-lateral femoral cartilage thickness; higher KAM to total knee joint moment was related to greater medial-to-lateral femoral cartilage erosion in eight years (Erhart-Hledik et al., 2019).

1.3.3 Gait kinematics

Patients with knee OA exhibit altered gait patterns in relation to tibiofemoral joint motion (Bytyqi et al., 2014, Childs et al., 2004). Such alteration happens in all the three planes, namely frontal, transverse and sagittal plane (Bytyqi et al., 2014, Farrokhi et al., 2012, Gok et al., 2002). People with knee OA walked with larger knee adduction angle (Zhao et al., 2007, Farrokhi et al., 2015a), smaller tibiofemoral internal rotation (Weidow et al., 2006, Farrokhi et al., 2015a) and smaller knee flexion motion (Heiden et al., 2009, Manetta et al., 2002). The reduction in knee flexion angle and excursion were associated with OA disease severity (Astephen et al., 2008a).

1.3.3.1 Knee sagittal kinematics during gait

Altered knee sagittal kinematics in stance phase are constantly found in people with knee OA (see Figure 1.5), including knee flexion angle at initial contact (Childs et al., 2004, Heiden et al., 2009, Dixon et al., 2010, Manetta et al., 2002) and peak flexion angle during early stance phase (Astephen et al., 2008a, Zeni Jr and Higginson, 2009, Heiden et al., 2009, Farrokhi et al., 2015b, Farrokhi et al., 2012, Manetta et al., 2002). Knee flexion excursion, the range of knee flexion from initial contact to stance phase peak knee flexion (Creaby et al., 2013), is also found to be reduced in these people (Childs et al., 2004, Dixon et al., 2010, Farrokhi et al., 2015b, Farrokhi et al., 2012, Favre et al., 2014, Rudolph et al., 2007). Table 1.3 summarizes studies comparing early stance knee sagittal kinematics in healthy people to those in people with knee OA.

In the swing phase of gait cycle, OA associated knee flexion angle changes were also widely reported. There was significant reduction of peak knee flexion angle of swing phase in knee OA (Kaufman et al., 2001, Astephen et al., 2008a, Bytyqi et al., 2014); the average peak knee flexion angle was 6°-8° smaller in people with knee OA than those without.

Additionally, the overall knee flexion-extension excursion in swing phase reduced significantly (Astephen et al., 2008a, Bytyqi et al., 2014, McKean et al., 2007). It was nearly 10° lower in people with severe symptomatic knee OA than asymptomatic controls (Astephen et al., 2008a). Similar results of around 10° reduction of swing phase flexion-extension excursion were reported across studies (Bytyqi et al., 2014, McKean et al., 2007).

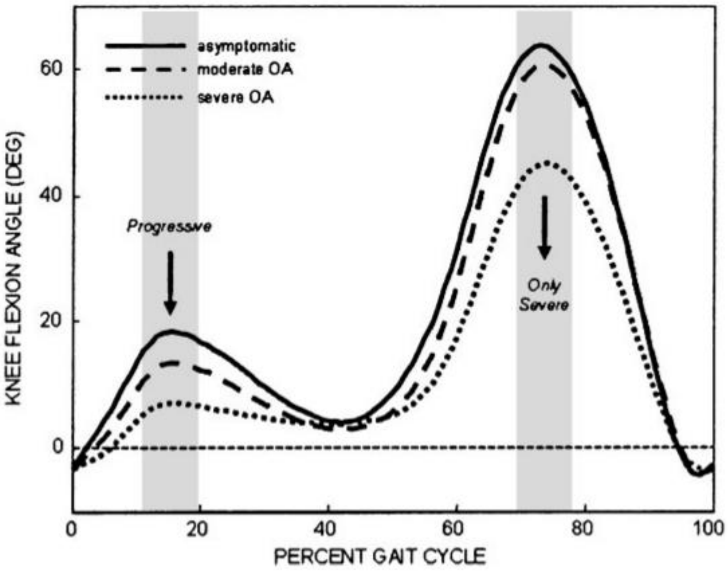

Figure 1.5 Waveform of knee flexion angle during a full gait cycle comparing people with/without knee OA (From Astephen et al. 2007)

1.3.3.2 Knee sagittal kinematics and knee OA severity

People suffering from knee OA have deviated knee sagittal kinematics in relation to the disease progression. Peak knee flexion angle in early stance phase was significantly smaller in people with moderate OA than severe OA (Astephen et al., 2008a), and the peak angle had a great reduction in both early OA and established OA from baseline to two-year follow-up (Mahmoudian et al., 2017). Knee flexion excursion was considerably smaller between people with early OA and established OA (Mahmoudian et al., 2017) and between moderate OA and severe OA (Astephen et al., 2008a). Furthermore, early stance phase knee flexion excursion became increasingly smaller with OA severity progression from mild to severe one (Nagano et al., 2012, Zeni Jr and Higginson, 2009). Current evidence indicated both peak knee flexion angle and knee flexion excursion at early stance phase of gait cycle became more restricted with the OA progression, and these reflected a stiffer gait pattern in more advanced OA stage.

Table 1.3 Knee flexion angle in people with and without knee OA

	Healthy	Knee OA	p-value
Knee flexion angle at initial contact			
Childs et al.	1.4±5.7	4.5±4.5	0.04
Dixon et al.	3.7±0.5	9.7±5.2	<0.05
Heiden et al.	1.7±4.3	7.8±5.3	<0.001
Manetta et al.	2.6±5.2	6.2±8.0	0.13
Rudolph et al.	5.56	4.68	>0.05
Peak knee flexion angle (degree)			
Manetta et al.	23.5±6.8	20.4±6.2	0.54
Astephen et al.	18.7±	8.0±6.2	<0.05
Dixon et al.	19.2±5.0	19.1±5.4	>0.05
Farve et al.	18.1	16.5	
Heiden et al.	14.3±7.1	18.6±6.3	0.005
Knee flexion excursion (degree)			
Manetta et al.	20.9±6.5	14.3±3.8	0.02
Childs et al.	19.5±5.2	15.7±5.7	0.01
Dixon et al.	15.5±3.4	9.4±4.2	>0.05
Farrokhi et al. a	17.4±4.7	9.7±3.4	<0.05
Farrokhi et al. b	11.0±4.1	7.2±3.6	0.10
Farve et al.	15.7	9.5	<0.05
Heiden et al.	12.6±5.0	10.8±4.4	0.10
Rudolph et al.	17.9	12.0	<0.05
Schmitt et al.	16.2	13.6	0.046

In brief, gait kinetics and kinematics during the stance phase might relate to OA severity and progression. Aside from external joint moments along the frontal plane, the relative contribution of KAM or KFM to the total joint moment might also associate with knee OA. It was therefore important to identify factor associated with KAM, the relative contribution of KAM to the total joint moment as well as knee sagittal kinematics during early stance phase of gait cycle.

1.4 Joint alignment and gait biomechanics

The mechanical alignment is essential to appropriate knee joint loading distribution during ambulation and weight-bearing activities (Andriacchi, 1994). Knee malalignment, either congenital or acquired one, is a strong factor leading to the onset and progression of knee OA.

1.4.1 Frontal plane malalignment

Mal-alignments along the frontal plane are widely observed in people with knee OA (Andriacchi, 1994). It is well accepted the correlation of knee malalignment with OA radiographic severity, such as varus and valgus deformities. To be specific, varus deformity is associated with increased joint space narrowing and osteophytes formation in the medial compartment, while valgus deformity is related to higher joint space narrowing and osteophytes in the lateral compartment (Tanamas et al., 2009). The risk of medial OA progression is 3.59-4.12 folds greater in patients with knee varus mal-alignment; valgus mal-alignment has a higher risk of lateral OA progression with an odd rate of 2.46-4.85 (Cerejo et al., 2002, Felson et al., 2009, Sharma et al., 2010).

Figure 1.6 Typical x-ray image of knee varus malalignment in knee OA (Adapted. From Mochizuki et al. 2019)

In the static status, load bearing axis is usually utilized to estimate medial-lateral load distribution. The load bearing axis is defined as a line linking mid-femoral head and center of ankle (Hunter et al., 2005). In varus knee, this axis passes medial to the knee joint center and generates a moment towards medial side in frontal plane, increasing load passing through medial compartment. Just the opposite, valgus angle leads to a lateral deviation of load bearing axis from the joint center, resulting in larger force across the lateral tibiofemoral compartment (Tetsworth and Paley, 1994). As much as 70% of the loading passes through the medial compartment even in neutral knee alignment (Schipplein and Andriacchi, 1991). Indeed, varus deformity predictis the peak of KAM (Hurwitz et al., 2002, Wada et al., 2001) and knee sagittal kinematics (Blakeney et al., 2019) in medial knee OA.

1.4.2 Horizontal plane malalignment

Alteration in torsional alignment along the horizontal plane was observed in people with knee OA (Nagao et al., 1998). Torsional deformity might exist in the femur, knee joint or tibia. This component is an important consideration in planning surgical management of knee OA (Steinbruck et al., 2016).

As early as 1994, Turner observed a decrease in external tibial torsion or true internal tibial torsion in knee OA compared to healthy controls (Turner, 1994). This observation was echoed in the study by Yagi & Sasaki (1986). These authors observed that external tibial torsion decreased gradually with knee OA progression. Biomechanically, decreased external tibial torsion might increase the contact force transmitting through the medial compartment of knee joint (Yazdi et al., 2016). However, Mandeville et al. (2013) found that knee OA patients with more internally rotated tibias experience higher impact throughout the entire stance phase of gait cycle.

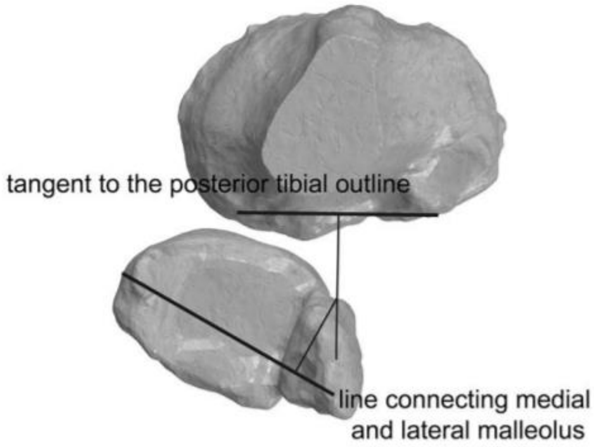

Figure 1.7 Measurement of tibial torsion (Adapted from León-Muñoz et al. 2021)

Measurement of lower limb torsion alignment by computerized tomography (CT) has been validated extensively, and is widely used as a reference standard. More recently, the EOS low-dose bi-planar x-ray system is developed and widely used in the orthopedic area. It scans lower limb with two synchronized perpendicular-placed x-ray sources in frontal and lateral positions. This technique enables measurement of lower limb torsional alignments in a weight-bearing position with superior features of low radiation exposure and high imaging quality than the conventional x-ray technique (Illés and Somoskeöy, 2012). The EOS system showed great consistency with CT system in the measurement of lower limb torsional alignments including tibial torsion (Folinais et al., 2013, Yan et al., 2019, Buck et al., 2012b). Excellent intra-rater reliability (Guenoun et al., 2012) and inter-rater reliability (Folinais et al., 2013, Guenoun et al., 2012) using EOS system had been reported. Therefore, this system is valid and reliable to examine lower limb torsional alignments.

1.4.3 Interplay between alignments in the frontal and horizontal planes

The torsional malalignment was influenced by the change in frontal alignment in healthy subjects (Stief et al., 2014), and alignments in both planes seemed to have a joint effect on medial joint loading in knee OA patients (Krackow et al., 2011). Yet, how the alignments in different planes interact and control joint loading distribution and joint motion in knee OA has not been established. The EOS system provides a better approach in capturing alignment on the frontal and horizontal plane in a weight-bearing position. This information will enhance our understanding of the alignment and how it relates to gait biomechanics during gait in knee OA.

1.5 Muscle properties and gait biomechanics

During early stance phase of gait cycle, the quadriceps muscle lengthens to control knee flexion and provides stability of the knee joint (Perry, 2010). Weakness or tightness of the quadriceps muscle might affect knee kinetics and kinematics during gait.

1.5.1 Quadriceps muscle strength and knee OA

Quadriceps weakness is one of the first symptoms in knee OA (Hurley, 1999). The quadriceps strength was nearly 20% lower in radiographic OA than the normal individuals (Slemenda et al., 1997b), and about 24-35% weaker in symptomatic knee OA than the asymptomatic counterparts (Hassan et al., 2001, Lewek et al., 2004). More essentially, quadriceps weakness is a strong risk factor to the onset of radiographic knee OA (Takagi et al., 2017, Omori et al., 2013) and joint space narrowing (Segal et al., 2010). In addition, quadriceps weakness is a significant predictor to articular cartilage loss at the medial compartment of knee joint in five years (Chin et al., 2019).

1.5.1.1 Quadriceps strength and gait kinetics

Quadriceps strength was believed to have a protective effect on knee joint by absorbing harmful impact at initial contact during gait (Jefferson et al., 1990). In stimulated model studies, quadriceps is the strongest knee stabilizer in frontal plane during normal walking (Shelburne et al., 2006, Winby et al., 2009). However, no associated between quadriceps maximal strength and KAM could be revealed in people with radiographic medial knee OA (Lim et al., 2009, Baert et al., 2013, Murray et al., 2015a, Aaboe et al., 2011). One study reported a positive association between submaximal (90% of maximal) voluntary contraction of the quadriceps and KAM in knee OA (Murray et al., 2015a). Quadriceps power (Calder et al., 2014) and endurance (Lee et al., 2015) was recorded as contributor to KAM, but the effect of both were minimal. Association between quadriceps strength and magnitude of KAM cannot be established in human studies.

Quadriceps primarily generate an internal knee extension moment to counteract KFM during loading response phase of gait cycle (Perry, 2010). There was moderate positive association between quadriceps strength and KFM during gait in healthy older people

(Samuel et al., 2011), people with anterior cruciate ligament deficiency (Lewek et al., 2002) and people with patellofemoral knee OA (Farrokhi et al., 2015b). Besides, reduction of quadriceps strength causes a significant decrease of KFM in healthy young people (Murdock and Hubley-Kozey, 2012). However, no significant association between maximal strength and KFM could be detected in tibiofemoral knee OA (Murray et al., 2015a) or end stage radiographic knee OA (Vahtrik et al., 2014). Additionally, quadriceps strengthening exercise failed to make any change of KFM (Pietrosimone et al., 2010, Bennell et al., 2014c, DeVita et al., 2018). Taking together, there is no evidence supporting that quadriceps maximal strength and KFM are related.

1.5.1.2. Quadriceps strength and knee sagittal kinematics

Quadriceps is one of the primary muscle groups controlling knee flexion/extension motion. Greater quadriceps strength was related to larger knee flexion excursion at loading response phase in radiographic knee OA (Farrokhi et al., 2015b), and a significant increase of knee flexion excursion could be achieved after a four-week quadriceps strengthening exercise program (Davis et al., 2019). The relationship between quadriceps strength and early stance peak knee flexion angle was not statistically significant in individuals with early OA (Nishino et al., 2021). However, it should be noted that the magnitude of early stance peak knee flexion angle was related to the co-contraction level between quadriceps and hamstrings (Heiden et al., 2009). In a word, stronger quadriceps strength possibly enhances early stance knee flexion excursion in knee OA.

1.5.1.3. Quadriceps strength and knee pain

The association between quadriceps strength and knee pain was explored in large scale of people with knee OA. In an cross-sectional study, O’Reilly reported that knee OA patients who had knee pain had much lower quadriceps strength and activation than people without knee pain (O'Reilly et al., 1998). It was reported in a follow-up study for 30 months that the greater baseline quadriceps strength was associated with lower intensity of knee pain (Amin et al., 2009). The protection of quadriceps strength on knee pain was especially significant for the females in the five years follow-up (Glass et al., 2013). Therefore, quadriceps strength had a protection effect on knee pain in people with knee OA in the long term. On the other hand, knee pain could have an inhibition effect on quadriceps strength. It was found that after pain reduction with local anesthetics, quadriceps strength increased by approximately 19% and activation increased by nearly 12% (Hassan et al., 2002). It indicated a vicious circle between the quadriceps weakness and deterioration of knee pain in knee OA.

1.5.2 Passive tension of the quadriceps muscle and gait biomechanics

1.5.2.1 Source of passive muscle tension

Viscoelasticity is the ability of resting skeletal muscle to resist deformation by an external force. Elasticity stands for the restoring force in response to lengthening change, while viscosity represents the force in respond to the velocity of lengthening change (Alter, 2004). During the lengthening of resting muscles, these properties combine to produce passive tension. Typical length-force relationship of passive tension is featured as an exponential curve, and the rapid increase of tension initiates from a point called slack length (Hirata et al., 2015). The vast majority of passive tension comes from two sources: collagen from extracellular matrix and titin from contractile (Lieber, 2010). The material property of these two tissues decides the magnitude of muscle passive tension. Passive tension is of tremendous importance to skeletal muscle function, which attributes to total tension production in lengthening conditions; it also influences joint range of motion as well as joint stability (Gajdosik, 2001).

1.5.2.2 Quadriceps passive tension and knee kinematics in knee OA

In knee OA, changes in both the muscular and connective tissues of the quadriceps may occur. There can be a change in muscle composition in knee OA. The ultrasound imaging system showed alteration of echogenicity of vastus lateralis (Liikavainio et al., 2008). Besides, knee OA also induces muscle fiber composition changes: greater reduction in type I than type II muscle fibers (Noehren et al., 2017), which contradicts to the normal aging effect. During normal aging process, type II fiber decreases more markedly than type I fiber (Porter et al., 1995). In addition, the amount of extracellular matrix in individuals with knee OA is 50% higher than their healthy counterparts (Noehren et al., 2017). Based on the evidence above, it could be speculated that passive tension of quadriceps is altered as a consequence of change of quadriceps material property initiated by OA. Muscle passive tension plays a role in controlling joint stiffness and joint motion (Gajdosik, 2001, Chino and Takahashi, 2015). Whether relationship exists between passive quadriceps muscle tension and knee sagittal kinematics during loading response phase of gait cycle has not been explored yet.

1.5.2.3 Quadriceps passive tension and knee pain

Muscle passive tension could have a crucial association with knee pain. It was reported that the tightness (Smith et al., 1991) and flexibility (Piva et al., 2005) of quadriceps was associated with patellofemoral pain. Besides, quadriceps muscle passive tension could contribute to knee pain through the connection of knee lateral retinaculum; tightness of lateral retinaculum was a risk factor to patellofemoral pain. When it was well suspected that thre may be a continuum of disease in relation to patellofemoral pain and patellofemoral knee OA (Wyndow et al., 2016). The role of quadriceps passive tension in knee pain in people with knee OA was merely explored.

1.6 Joint loading and pain in knee OA

While biomechanical factor is believed as a risk factor triggering pain, the relationship between KAM and the intensity of OA-related pain is not clear. Henriksen and colleagues (2012) reported that pain intensity was correlated negatively to KAM peak in patients with mild radiographic OA (KL grade ≤ 2). The negative relationship was proposed to relate to "avoidance strategy" such that the medial compartment of knee joint could be off-load from further destroys (Henriksen et al., 2006). A later study from Hall et al. (2016) indicated the relationship between pain intensity and KAM was specific to OA radiographic severity. The authors detected no relationship in mild knee OA, positive relationship in moderate knee OA, and negative relationship in severe knee OA (Hall et al., 2016). In this context, KAM increased significantly after pain relief by anesthetic injection, glucocorticoid injection and nonsteroidal anti-inflammatory drug (Henriksen et al., 2006, Schnitzer et al., 1993, Shrader et al., 2004). Pain also shows significant influence on magnitude of KFM. KFM increased markedly after taking nonsteroidal anti-inflammatory drugs in people with knee OA (Schnitzer et al., 1993). Besides, KFM was more sensitive to pain intensity than KAM (Boyer et al., 2012). In a longitudinal study, an increase of pain intensity has a trend to be associated with a decrease of KFM at 5 years follow-up (Asay et al., 2018). Therefore, the "avoidance strategy" seems to consist of an increase of KAM and a decrease of KFM; nonetheless, there lacks a comprehensive investigation of interaction between KAM, KFM and pain intensity.

1.7 Non-pharmacological management for knee osteoarthritis

Managements for OA are divided into three categories: 1) surgical, 2) pharmacological and 3) non-pharmacological (Fernandes et al., 2013a, Kolasinski et al., 2020). The non-pharmacological management including patient education, exercise and weight control is widely accepted and recommended by international guidelines as the first line treatment for knee OA (Bannuru et al., 2019a, Fernandes et al., 2013a, Kolasinski et al., 2020).

1.7.1 Exercise intervention for knee OA

Exercise is recommended as the first line non-surgical treatment for people with knee OA by international organizations including ACR (Kolasinski et al., 2020), EULAR (Fernandes et al., 2013a) and Osteoarthritis Research Society International (OARSI) (Bannuru et al., 2019a). In a meta-analysis including over 50 studies, high quality evidence was found supporting the efficacy of exercise programs on pain reduction and function improvement (Fransen et al., 2015). Structured land-based exercise with or without dietary weight management is suggested as the standard of care for non-surgical management of knee OA by OARSI, and needs be provided to all patients with knee OA with or without comorbidity (Bannuru et al., 2019a). The structured land-based exercise is recommended to include strengthening and/or cardio and/or balance and/or neuromuscular and/or mind-body exercise (Bannuru et al., 2019a). Aside from land-based exercise program, there is also strong recommendation to include aquatic therapy for knee OA (Uthman et al., 2013).

1.7.1.1 Flexibility exercises

Stretching exercise elongates a specific muscle or a muscle group and tendon and induces mechanical and neurological alteration on muscle and tendon (Weerapong et al., 2004). This approach is widely used to enhance muscle and/or tendon flexibility as well as joint range of motion. Reduction in muscle flexibility or joint range of motion is commonly observed in people with knee OA (Steultjens et al., 2000a, van Dijk et al., 2010). An exercise program for knee OA usually includes stretching exercises for hip abductor, knee flexor, and knee extensor muscles (Thorp et al., 2010, Chang et al., 2016). The stretching exercise is always delivered as static stretching or as hold-relax-contract method (Thorp et al., 2010, Chang et al., 2016). This exercise could effectively improve knee joint range of motion and walking speed in individuals with knee OA (Aoki et al., 2009).

1.7.1.2 Strengthening exercises

Strengthening exercise induces muscle hypertrophy and improves muscle strength and endurance by loading a specific muscle or a muscle group (Atha, 1981, Grgic et al., 2020). Muscle weakness of lower limb muscles is identified as a vital risk factor to knee OA disease progression (Hurley, 1999) and functional limitation (van der Krogt et al., 2012). Major deficit of hip abductors, quadriceps and hamstrings muscles are found in knee OA (Alnahdi et al., 2012). Strengthening exercise is considered as the core element in the exercise-based management program for knee OA (Bannuru et al., 2019a). The improvement of muscle strength has been shown to reduce pain and improve function (Bartholdy et al., 2017). The beneficial effects of muscle strengthening on pain and function may relate to 1) enhancement of proprioception and motor learning, 2) facilitation of energy absorbing capacity and 3) joint stability (Beckwée et al., 2013).

The isometric and concentric resistance exercises are effective methods of increasing quadriceps strength in individuals with knee osteoarthritis (Lim et al., 2008b, Hunt et al., 2010, Huang et al., 2003). It was suggested that a minimal increase of 30% knee extensor strength would be essential to cause beneficial effect on pain and an increase of 40% knee extensor strength would introduce favorable effect on function in knee OA (Bartholdy et al., 2017).

1.7.1.3 Neuromuscular control exercise

Neuromuscular function is known as the interaction between sensory input and motor output within sensorimotor system (Ageberg et al., 2007). Muscle can be trained for unconscious response to sensory input of dynamic joint motion. Neuromuscular control exercise emphasizes 1) sensorimotor function and 2) global and local joint stabilization. Knee injury is a common cause of the onset of knee OA. Anterior cruciate ligament (ACL) related injury increases the risk of early onset of knee OA by up to 6 folds (Culvenor et al., 2015). As high as half of the people with ACL injury develop knee OA within 10-15 years (Øiestad et al., 2009). According to neuromuscular control theory, afferent sensory dysfunctions may contribute to OA progression in ACL-related post-traumatic knee OA (Roos et al., 2011). Neuromuscular exercise was initially used in people with ACL related knee OA, and it resulted in long-term improvement in knee muscle strength and functional performance for these patients (Ageberg et al., 2007). Similar sensorimotor dysfunction also possibly existed in individuals with degenerative knee OA (Roos et al., 2011). Consequently, it was incorporated into Good Life with osteoarthritis in Denmark program for older people with degenerative knee OA (Ageberg and Roos, 2015).

Neuromuscular control exercise for knee OA consists of movements involving multiple joints and muscle groups of the lower limbs in weight-bearing positions that emphasizes sensorimotor control and functional stability (Ageberg and Roos, 2015). In neuromuscular control exercise, global alignments and quality of movements are of utmost importance. The principles include 1) active movements in synergies, 2) bilateral transfer effect of motor learning, 3) close kinetics chain movement, and 4) postural control. Typical movements of neuromuscular control exercise are pelvic lift, sliding and stepping lunge, step up, squat, etc. (Ageberg et al., 2007).

The result from Good Life with osteoArthritis in Denmark demonstrated significant improvement in pain by 12.4/100 points and in quality of life by 5.4/100 points in a sample of over ten thousands participants (Skou and Roos, 2017). Other research groups have also reported reduced pain intensity, improved function, and better quality of life following the same program components (Holsgaard-Larsen et al., 2017, Bennell et al., 2014a).

1.7.1.4 Exercise and its impact on joint loading

Strengthening exercises have little impact on KAM. Strengthening of knee extensors (Bennell et al., 2014b, Lim et al., 2008a) or a combination of hip and knee muscles (Al-Khlaifat et al., 2016, Bennell et al., 2010b, Hunt et al., 2013, King et al., 2008) all failed to reduce KAM (Table 1.4). Biomechanical benefits of muscle strengthening are barely apparent on KAM.

By enhancing perception and control of joint position and motion with neuromuscular control exercise, people with knee OA were believed to have better functional stability and dynamic alignment (Farrokhi et al., 2013); thereby reduce mechanical loading in the medial compartment of knee joint. However, no significant change but even a trend of increase in KAM was found after neuromuscular control exercise (Bennell et al., 2014a). Similarly, a significant increase in KAM was observed in individuals with knee OA after an eight-week neuromuscular training program (Holsgaard-Larsen et al., 2017). These findings could not support neuromuscular training as effective approach to reduce KAM for knee OA.

Thus, exercise program including flexibility, strengthening and neuromuscular exercises can effectively reduce pain and improve functions. Reduction in KAM seems not associated with quadriceps strengthening or neuromuscular training. There is no evidence supporting exercise-induced reduction in pain and improvement in function might be associated with modulation in joint loading. Other possible mechanisms of exercise include improvement of joint range of motion, reinforcement of joint stability and an enhancement of energy absorption (Beckwée et al., 2013).

It is important to note that exercise-induced effects were assessed without controlling confounding factors, such as joint alignment and disease severity, in some studies.

Table 1.4 Effect of exercise on external knee adduction moment in people with knee OA

Author, year	Exercise	Pre KAM	Post KAM	Trend	*p-value*
Al-Khlaifat, 2016	Strengthening exercise	0.34± 0.11 Nm/kg	0.35± 0.14 Nm/kg	↑	0.57
Bennell, 2010	Strengthening exercise	3.2± 1.0 Nm/(Wt*Ht)%	3.3± 0.9 Nm/(Wt*Ht)%	↑	0.19
Bennell, 2014	Strengthening exercise	3.22± 0.88 Nm/(Wt*Ht)%	3.30± 0.79 Nm/(Wt*Ht)%	↑	>0.05
	Neuromuscular exercise	3.05± 0.91 Nm/(Wt*Ht)%	3.26± 0.95 Nm/(Wt*Ht)%	↑	>0.05
Chang, 2016	Strengthening exercise, stretching exercise	4.96± 1.14 %BW∗ LL	4.88± 0.81 %BW∗ LL	↓	0.74
Holsgaard-Larsen, 2017	Neuromuscular exercise	2.86± 0.83 Nm/(Wt*Ht)%	+0.12 Nm/(Wt*Ht)%	↑	<0.05
Hunt, 2013	Strengthening exercise	3.75± 0.91 Nm/(Wt*Ht)%	3.70± 0.91 Nm/(Wt*Ht)%	↓	-
King, 2008	Strengthening exercise	3.30± 0.72 Nm/(Wt*Ht)%	3.43± 0.49 Nm/(Wt*Ht)%	↑	>0.05
Lim, 2008	Strengthening exercise (varus aligned)	4.28± 0.63%Nm/Wt*Ht	4.40± 0.76 Nm/(Wt*Ht)%	↑	>0.05
	Strengthening exercise (neutral aligned)	3.58± 0.94%Nm/Wt*Ht	3.63± 1.11 Nm/(Wt*Ht)%	↑	>0.05
Sled, 2010	Strengthening exercise	2.97 %Nm/Wt*Ht	2.96 Nm/(Wt*Ht)%	↓	0.52
Throp, 2010	Strengthening exercise, stretching exercise	2.9± 0.8%Nm/Wt*Ht	2.6± 0.7 Nm/(Wt*Ht)%	↓	<0.05

1.7.1.5 Common exercise program

Based on present clinical guidelines of non-surgical management for knee OA, exercise-based knee OA management program are developed and practiced. The most common ones are the Better management of patient with OsteoArthritis from Sweden and the Good Life with osteoArthritis in Denmark program from Demark.

1.7.1.5.1 Better management of patient with OsteoArthritis

The Better management of patient with OsteoArthritis (BOA) is a Swedish OA management program which started in 2008 (Thorstensson et al., 2015). The BOA program builds on the theoretical model of behavioral change (Prochaska and Velicer, 1997) and self-determination theory (Deci et al., 1994). It consists of three main components: 1) education provided from physiotherapist on knowing of the disease and self-management strategies, 2) supervised neuromuscular control exercise, and 3) outcome registry. Its exercise component consists of patient education and individualized exercise either using a home-based or a physiotherapist-supervised approach (**Error! Reference source not found.**). A core component of this program is muscle strengthening exercise emphasizing neuromuscular control. The program also educates patients on the “concept of acceptable pain”. Pain intensity less than five out of ten during exercise and no intensification 24 hours after exercise is regarded as acceptable.

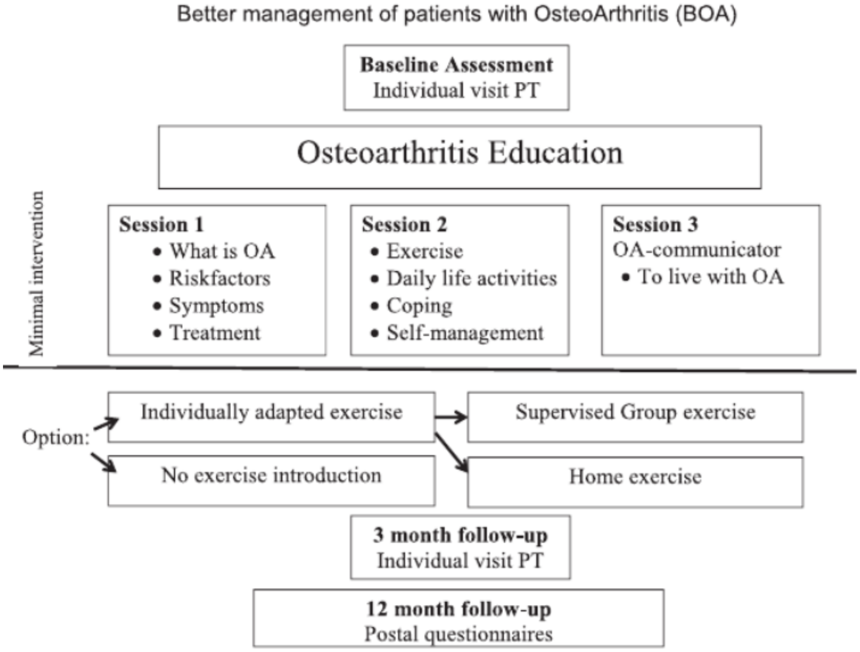

Figure 1.8 Procedure of BOA program (Adapted from Thorstensson et al., 2015)

1.7.1.5.2 Good Life with osteoArthritis in Denmark program

Good Life with osteoArthritis in Denmark (GLAD) program is built on the BOA program and initiated in 2013 from the University of Southern Denmark (Skou and Roos, 2017). It is now the most widely used OA management model in the world, which is already applied in six countries including Denmark, Canada, Australia, China, Switzerland and New Zealand. The major components of GLAD are almost identical to BOA, which also consists of education, exercises and outcome measures components. The primary difference between the GLAD and BOA program lies in how exercise program is delivered. All the patients participating in the GLAD program undergo an eight-week supervised neuromuscular control exercise program, while it is optional for patients to participate in either supervised exercise or home-based exercise in the BOA program. Only less than one third of participants in the BOA program had supervised exercise. The researchers on GLAD program believe that supervised exercise is one of the key elements leading to the success of an exercise program.

There was significant improvement in pain by 12.4/100 points and in quality of life by

5.4/100 points with an analysis of 9825 participants with knee OA in the GLAD program (Skou and Roos, 2017). The GLAD program also helped reduce risk of painkiller intake by 19.2% in people with knee OA.

Exercise programs for 6-8 weeks are proven to reduce pain and improve function in seniors with knee OA. The exercise components include muscle stretching, strengthening, balance and neuromuscular control training. Despite most of these programs demonstrated significant reduction in pain intensity and improvement in function, associations between exercise-induced modulation on joint alignment, muscle properties, pain, and joint biomechanics has not been explored comprehensively.

1.8 Rationale and objectives of this study

1.8.1 Knowledge gaps

Although joint alignment and muscle properties are suggested as being important factors related to ambulatory biomechanics in people with medial knee OA, the relationships between joint alignment and muscle properties have only been partially studied. In addition, inconsistent findings were reported between joint loadings and clinical symptoms, such as pain and dysfunction. The following important information awaits clarification.

1) Most studies on joint alignment and joint biomechanics were focused on knee varus/valgus alignment. Torsion malalignment has been a concern because of its possible associations with OA severity and progression. One of the limitations in quantifying tibial torsion is on its demand on CT. Aside from financial burden and radiation exposure; CT scans only provide alignment measurement in a non-weight bearing position in daily orthopedic practice. It is necessary to measure joint alignment in a weight-bearing position and to assess joint alignment along the

horizontal in addition to the frontal plane.

2) Most studies failed to delineate association between quadriceps muscle strength and joint loading. However, negative relationship between muscle strength and knee flexion excursion was reported in individuals with knee OA. Meanwhile, muscle performance is also related to its passive tension, particularly during eccentric contraction. The quadriceps muscle contracts eccentrically in the loading response phase of the gait cycle; relationships between passive quadriceps muscle tension and early stance knee sagittal kinematics might exist. Such information enables a better understanding of the interplay between muscle properties and joint kinematics, and provides support for exercise program design for people with knee OA.
3) Inconsistent findings regarding pain intensity and joint loading were reported. The discrepancy in these findings might relate to difference in disease severity of subjects in the reports. Furthermore, pain intensity can be affected by several factors, such as lower limb alignment, knee joint load sharing between frontal and sagittal planes, etc. Possible relationships between pain intensity and joint loading require considerations on the impact of these factors and their interactions.
4) An exercise program is recommended as the first line of management for people with knee OA. The commonly used programs in clinical practice are composed of exercises for flexibility, muscle strength, balance, and neuromuscular control. Despite the fact that most of these programs demonstrated significant reduction in pain intensity and improvement in dysfunction, associations between exercise-induced modulations on pain intensity and knee joint loading have not yet been comprehensively reported. Whether modulation on knee load sharing along the frontal and sagittal planes would provide more information than joint loading along a single plane is still an unexplored question. In addition, it remains to be investigated whether

exercise-induced modulation on quadriceps muscle properties is associated with alteration of knee gait biomechanics.

1.8.2 Aim of this project

The primary aim of this project was to investigate the role of joint alignment, quadriceps muscle properties and pain on joint biomechanics in people with mild and moderate knee OA.

1.8.3 Objectives of this study

1) To explore possible associations between lower limb torsional alignment, knee joint kinetics, and kinematics in people with medial knee OA.
2) To delineate possible relationships between quadriceps muscle properties and early stance knee kinematics during walking in people with medial knee OA.
3) To assess how KAM and pain intensity would be related in medial knee OA when taking the effects of KFM and joint alignment into consideration.
4) To investigate whether exercise-induced modulation on (a) pain intensity and joint moments and (b) muscle properties and early stance phase knee kinematics would be related.

In order to achieve the above objectives, a cross-sectional observation and an interventional study were conducted.

1.8.4 Statement of hypotheses

The hypotheses of this study were based on the literature review in this chapter.

1) There would be associations between torsional alignment and KAM. Smaller external tibial torsion and external tibiofemoral rotation would be related to larger KAM and

larger sharing of KAM to total joint moments.

2) Smaller external tibial torsion would be related to smaller early stance knee flexion excursion during gait.
3) Stronger quadriceps strength would be associated with larger peak knee flexion angle and knee flexion excursion; however, higher passive tension of quadriceps would relate to smaller peak knee flexion and flexion excursion.
4) Pain intensity would be negatively related to KAM and positively to KFM; there would be a negative relationship between pain intensity and KAM to total moments.
5) Modulation on KAM and KAM index would be related to change in pain intensity and dysfunctions after a six-week exercise-based rehabilitation program. Reduced passive muscle tension and increased strength of the quadriceps would relate to an increase in peak knee flexion angle or knee flexion excursion after the program. The above relationships might be specific to disease radiographic severity.

1.9 Outline of this thesis

In order to test the above hypotheses, a cross-sectional observation and a prospective interventional study were conducted.

Investigations in relation to the cross-sectional study are presented in Chapter 2 and Chapter 3.

In Chapter 2 we state the methodology of subject recruitment, and measurements of joint alignment, muscle passive and active properties and knee biomechanics. Relationships between lower limb alignment, especially tibial torsion and knee joint loadings during the early stance phase of the gait cycle, are described. Associations between muscle properties, lower limb alignment, and stance phase joint kinematics are reported.

In Chapter 3 we examine the relationships between early stance KAM and pain intensity with a comprehensive model using path analysis.

In Chapter 4 we describe the exercise-based rehabilitation program and present associations between exercise-induced modulations on joint kinetics, pain intensity, and functional limitation, as well as between joint kinematics and muscle properties.

In Chapter 5 we integrate findings from the cross-sectional and interventional studies, review their limitations, and make suggestions for future studies.

Chapter 6 is the overall conclusion.

Chapter 2 The relationship between lower limb alignment, quadriceps muscle and gait biomechanics in people with knee osteoarthritis

2.1 ABSTRACT

Background

Abnormal alteration of gait biomechanics was widely found in people with knee osteoarthritis (OA). Lower limb alignment and quadriceps muscle are two important factors affecting gait biomechanics. However, there lacked sufficient evidence indicating the relationship between torsional alignment and quadriceps muscle properties on knee kinetics and kinematics during walking.

Aims

Therefore, this study examined the relationships between torsional alignment and quadriceps muscle properties on knee kinetics and kinematics during gait in people with symptomatic knee OA using cross-sectional study design.

Methods

Lower limb alignments including tibial torsion, tibiofemoral rotation and varus/valgus alignments in standing were measured by EOS low-dose bi-planar x-ray system in 47 participants with mild or moderate knee OA. Passive tension of quadriceps muscle was measured by ultrasound shear-wave elastography system. The kinetic information including external knee adduction moment (KAM), flexion moment (KFM) and the KAM index which was defined as (KAM/ (KAM+KFM)*100) and kinematic information including peak knee flexion angle and knee flexion excursion in early stance phase were analyzed using a motion analysis system so as to estimate the knee loads.

Results

External tibial torsion was positively associated with KAM in participants with moderate knee OA (r=0.59, p=0.02) but not in participants with mild knee OA. On the contrary, significant association was found between knee varus/valgus alignment and KAM in the mild knee OA group (r=0.58, p<0.001) and a sign of association in the moderate knee OA group

(r=0.47, p=0.08). External tibial torsion also was related to knee flexion excursion in participants with moderate knee OA (r=-0.72, p=0.01). Passive tension of vastus lateralis was associated with early stance phase knee flexion excursion (r= -0.36, p=0.07) in mild radiographic knee OA. Vastus medialis obliquus passive tension was associated with peak knee flexion angle (r=-0.63, p=0.04) in mild knee OA.

Conclusions

We concluded tibial torsion and passive tension of the quadriceps muscles are factors associated with early stance phase knee biomechanics in participants with knee OA. The associations were specific to OA radiographic severity. Radiographic severity might need to be considered when using gait modification as a rehabilitation strategy for this condition in order to maximize treatment effect.

2.2 INTRODUCTION

Knee osteoarthritis (OA) is a common degenerative joint disorder in seniors. Among all knee OA categories, medial compartment knee OA has accounted for 67.8% in the eastern population (Zhang et al., 2001) and 85.4% in the western population (Felson et al., 1987). In people with knee OA, limitation in daily function and activities such as walking and stair climbing are their major problems (Barbour et al., 2017). Gait pattern alterations, such as knee kinematics and kinetics (Astephen et al., 2008a) are commonly observed and are associated with disease progression (Mills et al., 2013b).

People with medial knee OA were found to have significant greater external knee adduction moment (KAM), the surrogate to show lateral-to-medial joint loading distribution , which linked to the more vulnerability of developing knee OA in the medial compartment because of this higher joint load on the medial compartment of knee (Schipplein and Andriacchi, 1991). Joint malalignment, besides being a risk factor associated with knee joint load distribution during weight-bearing activities (Andriacchi, 1994), was also regarded as a predictor to articular cartilage loss (Cicuttini et al., 2004) and knee OA progression (Cerejo et al., 2002). They also walked with altered knee sagittal kinematics, including an increase of initial contact flexion angle (Childs et al., 2004), a decrease of early stance peak flexion angle (Childs et al., 2004, Manetta et al., 2002) and a decrease of flexion excursion (Astephen et al., 2008a).

Tibial torsion, defined as the rotational alignment between tibial plateau and malleoli, was altered in people with knee OA (Turner, 1994), such that they had less external tibial torsion than people without knee OA(Turner, 1994, Yagi and Sasaki, 1986, Mochizuki et al., 2017). Besides external tibial torsion being smaller, these participants also would have an increased varus malalignment as the disease progressed in the medial knee compartment (Yagi and Sasaki, 1986). A cadaveric study has reported both excessive internal tibial torsion of over 20° and more external tibial torsion would increase the medial compartment knee joint contact pressure (Kenawey et al., 2011). These findings suggested either a reduced or increased external tibial torsion would induce a change in joint contact pressure. In participants with end-stage medial knee OA and internal tibial torsion malalignment, their second peak of KAM during walking was higher than those without any torsional malalignment and the normal controls (Krackow et al., 2011). These suggested the joint contact force and mechanical load distribution of the knee might be related to tibial torsion. If this relationship did exist, then knowing how these two factors behave at the early stance phase of gait would be important because the peak KAM during stance phase of walking was a strong predictor for the long-term medial-to-lateral cartilage erosion (Chehab et al., 2014). The dynamic internal tibiofemoral rotation during the early stance phase was reduced in people with medial compartment knee OA (Bytyqi et al., 2014, Nagano et al., 2012), and the reduction became more evident when the condition had progressed (Zeng et al., 2017). Therefore, the change in the tibiofemoral rotation would affect knee flexion motion due to this disrupted “reverse screw-home” mechanism. It is therefore necessary to measure this rotation and how it relates to knee joint motions and loads during walking. Recently, low dose bi-planar x-ray scanner has become available to measure the torsional alignments, by which scanning was conducted in a weight-bearing condition (Buck et al., 2012b, Guenoun et al., 2012).

Aside from joint alignment, quadriceps muscle strength is known to associate with knee kinematics such as knee flexion excursion (Schmit and Rudolph, 2007) and peak knee flexion angle (Murray et al., 2015b) during gait in advanced knee OA. Little evidence has been reported in people with early knee OA. During the loading response phase of the gait cycle, quadriceps muscles lengthened to facilitate a smooth transfer of body center of mass to the loading limb. The elasticity of muscular and passive structures contribute to the generation of eccentric force (Hessel et al., 2017). When under a constant external force, higher muscle passive elasticity resulted in smaller joint range of motion (Sobolewski et al., 2013). A question therefore arises as whether higher quadriceps elastic properties would associate with knee kinematics during the early stance phase of gait cycle.

This study aimed to investigate the effects of tibial torsion and quadriceps muscle properties on stance phase knee sagittal kinematics in people with mild and moderate knee OA. in people with medial compartment knee OA. We hypothesized that external tibial torsion and tibiofemoral rotation were associated with the joint loads during walking. More specifically, reduced external tibial torsion and internal tibiofemoral rotation would be associated with greater external knee moments in the stance phase. By exploring such associations, we could then develop a better understanding on how torsional alignment would affect joint loading in participants with knee OA.

2.3 METHODS

2.3.1 Study design

This is a cross-sectional observational study.

2.3.2 Participants

Participants with knee OA attending the orthopaedic clinic of a local hospital were invited to join the study if they met the following criteria: 1) aged between 50 and 80 years, 2) had radiographic evidence of knee OA in the medial compartment of tibiofemoral joint with Kellgren-Lawrence (KL) grading of less than 4, 3) had a minimum pain score of 2 on an 11-point visual analog scale (VAS) in the past month while walking (Hall et al., 2017). Participants would be excluded if they had any of the followings: 1) more osteophytes in the lateral than the medial knee compartment, 2) intra-articular injection within the past 6 months,

3) rheumatoid arthritis, 4) history of surgery to either knee joint, 5) other muscular, joint or neurological conditions influencing lower limb function, 6) low back, hip, ankle or foot pain of more than 3 on VAS, 7) unable to walk without assistance and, 8) body mass index (BMI) >36 kg/m^2. The sample size calculation was conducted after a pilot study of correlating pain with quadriceps muscle passive tension. Based on that design and the findings of the pilot study revealed that for an effect size of 0.43, the sample size needed would be 38 to obtain an 80% power with α level of 0.05.

Diagnosis of knee OA was made according to ACR guideline (Altman et al., 1986), and grading of the OA severity by KL scaling system were determined by two experienced orthopedic surgeons. The severity of knee OA was categorized as mild (KL grade 1 and 2) and moderate (KL grade 3) (Henriksen et al., 2012) and these categories would be included in the analysis.

This study was approved by the Human Subjects Ethics Committee of the administrating institution. All participants gave their written informed consent before being tested.

2.3.3 Outcome measurement

2.3.3.1 Joint alignment

Joint alignment during stance was examined with a low-dose bi-planar X-ray imaging system (EOS imaging, Paris, France) (Illés and Somoskeöy, 2012) by an experienced radiographer. Subjects were asked to stand in the center of the testing gantry with their right leg shifted forward for around 4 cm to ensure clear bony structure recognition. A three-dimensional reconstruction of the lower limbs was performed with sterEOS (Version 1.6, EOS imaging, Paris, France). Anatomical reference points were identified on both the sagittal and coronal planes including femoral head, neck, greater and lesser trochanters, intercondylar notch, lateral and medial femoral condyles, tibial spine, lateral and medial tibial plateau, distal tibial articular surface and medial malleolus. Bony contours were adjusted according to the EOS guidelines by the assessor.

Knee alignment angles were computed by the sterEOS software. Tibial torsion angle was measured by drawing from the posterior tibial plateau tangent axis to the bi-malleolar axis (Figure 2.1A), whereas tibiofemoral rotation angle was measured from the posterior femoral bi-condylar axis to the posterior tibial plateau tangent axis (Figure 2.1B). A clockwise value was defined as external and a counter clockwise value was internal rotation for the right leg while the reverse applied for the left leg. Knee varus/valgus was measured as the angle between the longitudinal axes of femur and tibia. Reliability test was conducted in 6 subjects and excellent inter-day reliability was obtained for knee varus angle (ICC=0.99, p <0.001), tibial torsion (ICC=0.93, p<0.001) and tibiofemoral rotation (ICC=0.95, p<0.001). It was reported in previous literature that standard error of measurement equaled to 0.43° and minimal detectable difference equaled to 1.20° with prosthesis after total knee arthroplasty (Meijer et al., 2014).

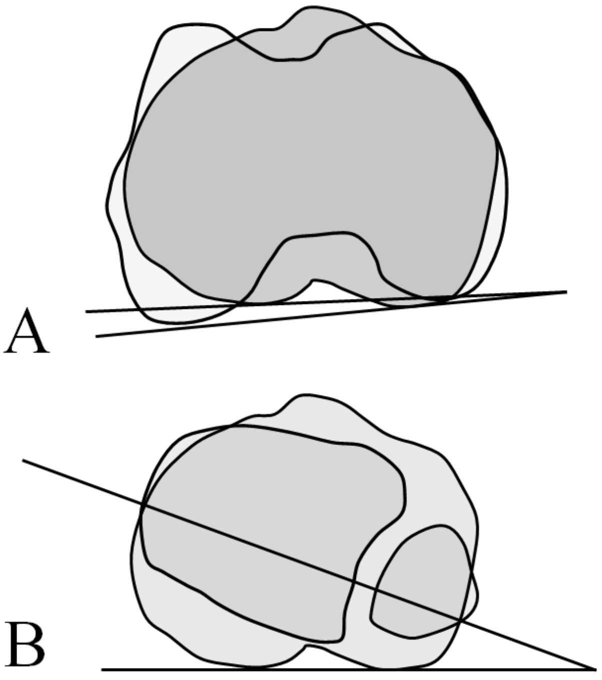

Figure 2.1 Diagram of torsional alignments measurement (A: tibiofemoral rotation, B: tibial torsion)

2.3.3.2 Knee joint loads and flexion motion during gait

Knee loads were estimated using a motion analysis system that comprised eight cameras (MX T40, Vicon, Oxford, UK) and two floor-mounted force plates (Kistler Group, Winterthur, Switzerland). The sampling rates were 1000Hz for kinematic data and 100Hz for kinetic data. The Vicon camera had a mean positioning error of 0.15mm and dynamic positioning error of below 2mm (Merriaux et al. 2017), which indicated this system had high precision and accuracy in capturing motion change. In the current study, the frame rate of the cameras was set at 100 Hz. Kistler force plate was widely used to measure the direction and also the position of force vector. The threshold of measurement was less than 10 mN (Mizoguchi & Calame 1995).

The two data sets were recorded and synchronized. Reflective skin markers were applied according to the guidelines of standard Lower limb Plug-In-Gait marker set(Hall et al., 2016). Subjects were instructed to walk unshod and without any assistive device on an 8-

meter footpath in self-selected speed. A data set was collected during static standing for lower limb model building. Practice trials were given to the subjects for them to acquaint with the testing procedures. Data collection would start after the practice trials and a minimum of five successful walking trials in each leg with clean foot strike from heel-strike to toe-off on the force plates would be recorded (Creaby et al., 2010).

External knee joint moments and knee flexion motion were calculated with Vicon Nexus software (Version 2.5, Oxford, UK) using Lower limb Plug-In-Gait model. Gait events of heel strike and toe-off were identified when the magnitude of the force plate was above and below 10N, respectively. Peak KAM and KFM in this study were respectively defined as the maximum values of knee moment in the frontal and sagittal planes during the initial 50% of stance phase. They were normalized to body weight and reported in Nm/kg. A KAM index was calculated using the formula: (KAM/ (KAM + KFM))*100, which represented the percentage of load sharing between the frontal and sagittal planes. Peak knee flexion angle was identified as the maximum knee angle between initial contact and loading response. Knee flexion excursion was defined as the knee angle range between the angle at initial contact and peak knee flexion angle (Creaby et al., 2013). All kinetic and kinematic data were estimated by the average of five trials. Moderate test-retest reliability with ICC = 0.51-0.70 for KFM (Meldrum et al., 2014) and excellent test-retest reliability ICC = 0.98 for KAM (Creaby et al., 2010) were reported when using Vicon system and Plug-in-Gait model.

2.3.3.3 Passive tension of the quadriceps

The passive tension of the three superficial heads of quadriceps was measured with an ultrasound elastography system (Aixplorer Version 4.2; Supersonic Imagine, Aix-en-Provence, France). Ultrasound shear-wave electrography was a technology to detect viscoelastic property of soft tissues. Using this imaging approach, shear modulus of individual heads of quadriceps could be quantified according to the propagation velocity of a beam of shear-wave along the longitudinal axis of the ultrasound probe. It agreed well with Young's modulus measured by material testing (Eby et al., 2013) and has been used in the study of quadriceps femoris in human (Xu et al., 2018).

A 4-15 MHz linear ultrasound transducer probe (Supersonic Imagine, Aix-en-Provence, France) was used with "Musculoskeletal" preset. Measurements were taken at vastus lateralis (VL), rectus femoris (RF) and vastus medialis obliquus (VMO). The measurement sites were marked on skin: 1) VL at distal 1/3 between anterior superior iliac spine and patella lateral boarder; 2) RF at 1/2 between ASIS and patella superior boarder; 3) VMO at distal 1/5 between anterior superior iliac spine and patella medial boarder (Xu et al., 2018). Participants lay supine on a plinth with the hip in full extension and knee in 60° flexion. Ultrasound elastography measurements were conducted after the participants had rested 10 minutes. The ambient temperature was maintained at 25°C throughout the testing. The probe was positioned perpendicularly to the muscle belly and parallel to the muscle fibers. Abundant ultrasound gel was applied and pressure from the probe was carefully controlled to avoid compressing the underlying structures. A video of 10 seconds was recorded for each muscle head and only the middle 5 frames were selected to calculate the means of shear modulus. This measurement had excellent intra-rater reliability to quantify shear modulus in 4 participants on the 3 muscle heads (ICC_{VL}= 0.84, ICC_{RF}= 0.73, ICC_{VMO}= 0.99). The standard error of measurement of the three muscle heads ranged from 0.03 to 1.80 kPa.

2.3.3.4 Knee extensors strength

Two experienced physical therapists assessed the strength of knee extension with a hand-held dynamometer (Nicholas Manual Muscle Tester, Lafayette Instrument Company, Indiana, US). Participants sat on a chair with straps fastening upper body, and the hips and knees flexed at 90°. The hand-held dynamometer was positioned anteriorly to the lower leg just above ankle joint. Three recordings were made with the therapist giving verbal encouragements to the participants to perform maximal knee extension against the dynamometer. This method has good validity and excellent reliability (Hansen et al., 2015). The mean value of three measurements was used. Knee extension torque was calculated as maximum strength multiplied by shank length and normalized to body mass (Nm/kg).

2.3.4 Statistical analysis

Statistical analysis was conducted using SPSS (Version 23.0, IBM Corp., New York, US). Distribution of each variable was assessed by Shapiro-Wilk test. Homogeneity of variance was tested by Levene's test. Demographic group differences of radiographic severity were assessed by Welch's t tests for unequal variances.

Candidate variables including age, gender, pain intensity, walking speed were pre-screened with two-tailed Spearman's correlation coefficient test at $p<0.10$ as co-variates. Partial Pearson's correlation coefficient tests were conducted to examine the association of knee alignments, quadriceps muscle properties, knee joint loads and flexion motion controlling for age, gender and pain for all participants. Interaction between OA radiographic severity and alignments was calculated with regressions. Sub-group analyses according to radiographic severity were also conducted when there was significant interaction. The missing data was one in peak knee flexion angle, knee flexion excursion and quadriceps strength respectively, and they were handled with pairwise deletion. Analysis of covariance was used to estimate group difference on joint alignment controlling for age and gender, and on knee joint loads controlling for gender, pain intensity and speed.

2.4 RESULTS

2.4.1 Demographic information

Forty-seven participants were recruited. Demographic information of the participants was shown in Table 2.1. In general, participants aged between 50 and 77 years old and 79% of them were female. Sixty-four percent of the participants had mild knee OA and 36% had moderate knee OA. Majority (91%) of them had bilateral knee OA.

Table 2.1 Demographic information of participants

	All (n=47)	Mild (n=30)	Moderate (n=17)
Age (year)	62.1 ± 6.0	60.7 ± 5.8	64.4 ±5.8 *
Gender (Female/male)	37/10	27/3	10/7 *
Height (m)	1.6 ± 8.6	1.6 ±6.6	1.6± 11.6
Weight (kg)	65.4 ± 11.5	62.8 ± 9.5	70.0 ± 13.5
BMI (kg/m^2)	26.4 ± 3.6	25.4 ± 3.4	27.8 ± 3.4 *
Pain (VAS)	5.12 ± 1.8	4.8 ±1.7	5.8 ± 1.7
Walking speed (m/s)	1.0 ± 0.2	1.1 ±0.2	0.9± 0.2*

* Difference between mild and moderate group p<0.05

2.4.2 Correlation between torsional alignments with knee kinetics

Tibial torsion demonstrated an insignificant association with KAM when analysis was done by combining both the moderate and mild OA groups (r =0.07, p=0.67; Figure 2.2A). However, when there was significant interaction of severity between tibial torsion and KAM (p=0.008), sub-group analysis revealed a significant positive association between tibial torsion and KAM in the moderate knee OA group (r =0.59, p=0.02; Figure 2.2B) but not with the mild knee OA group (r =-0.19, p=0.34; Figure 2.2C). The tibiofemoral rotation and KAM were not related with either combined or sub-group analyses. Besides, there was no relationship between joint alignments and KFM with the combined or sub-group analyses. Knee varus angle and KAM were significantly associated with one another when analyzed for all the participants (r = 0.59, p<0.001); no significant interaction was found (p=0.22). The varus angle was also associated with KAM index (r=0.34, p=0.02).

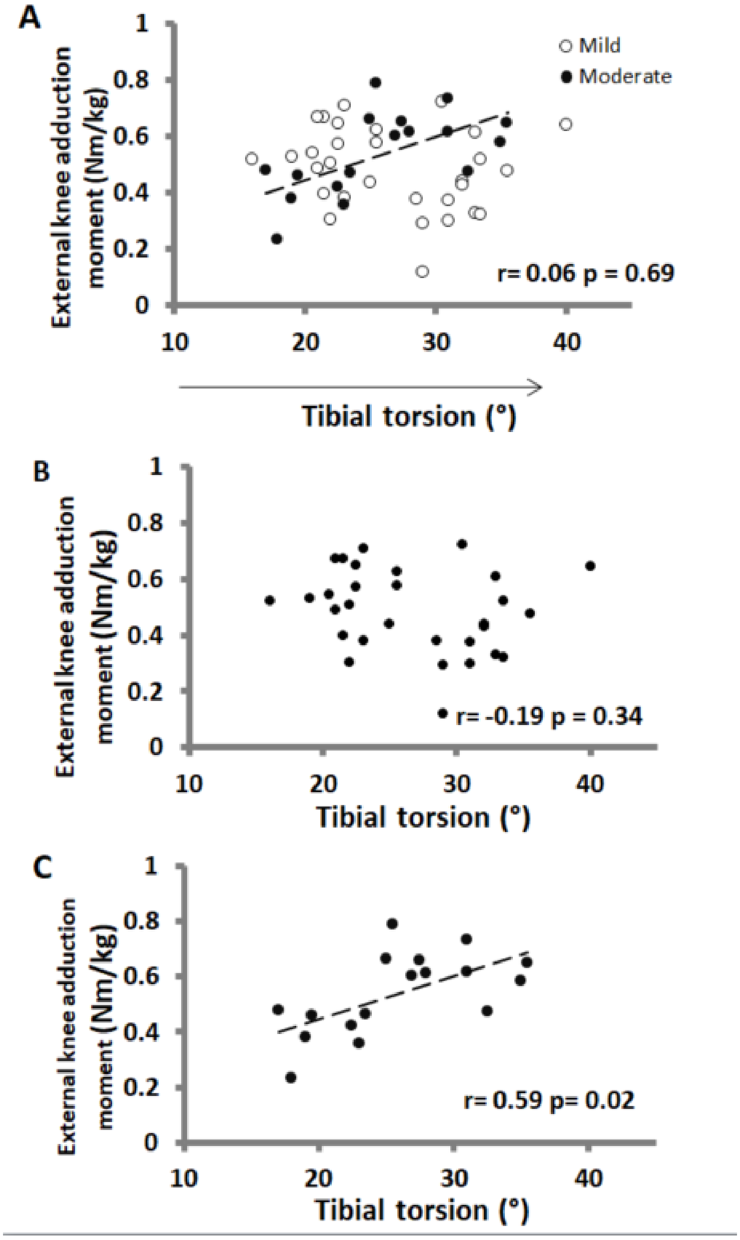

Figure 2.2 Scatter plots of external knee adduction moment and tibial torsion. (A: all participants, B: mild OA, C: moderate OA)

2.4.3 Correlation between joint alignment and knee flexion kinematics

Details of the relationships between joint alignment and knee flexion kinematics are shown in Table 2.2. Knee varus angle was negatively associated with knee flexion excursion (r=-0.39, p=0.01) in all participants.

Significant interaction was only detected between tibial torsion and OA severity for knee flexion excursion (P<0.001). It was shown in the subgroup analysis that significant association between tibia torsion and the early stance phase knee flexion excursion was established in the moderate group (r=-0.72, p=0.01; Figure 2.3B). Greater external tibial torsion was associated with less knee flexion excursion or smaller external tibial torsion was related to greater knee flexion excursion. Such observation could not be detected in those with mild radiographic changes.

Table 2.2 Association between knee sagittal kinematics and alignment

	Tibiofemoral rotation		Tibial torsion		Knee varus angle	
	Correlation coefficient	p value	Correlation coefficient	p value	Correlation coefficient	p value
Peak knee flexion angle	0.02	0.90	-0.06	0.71	-0.09	0.57
Knee flexion excursion	0.28	0.07	-0.18	0.25	-0.39	0.01

Controlling for gender, age, speed

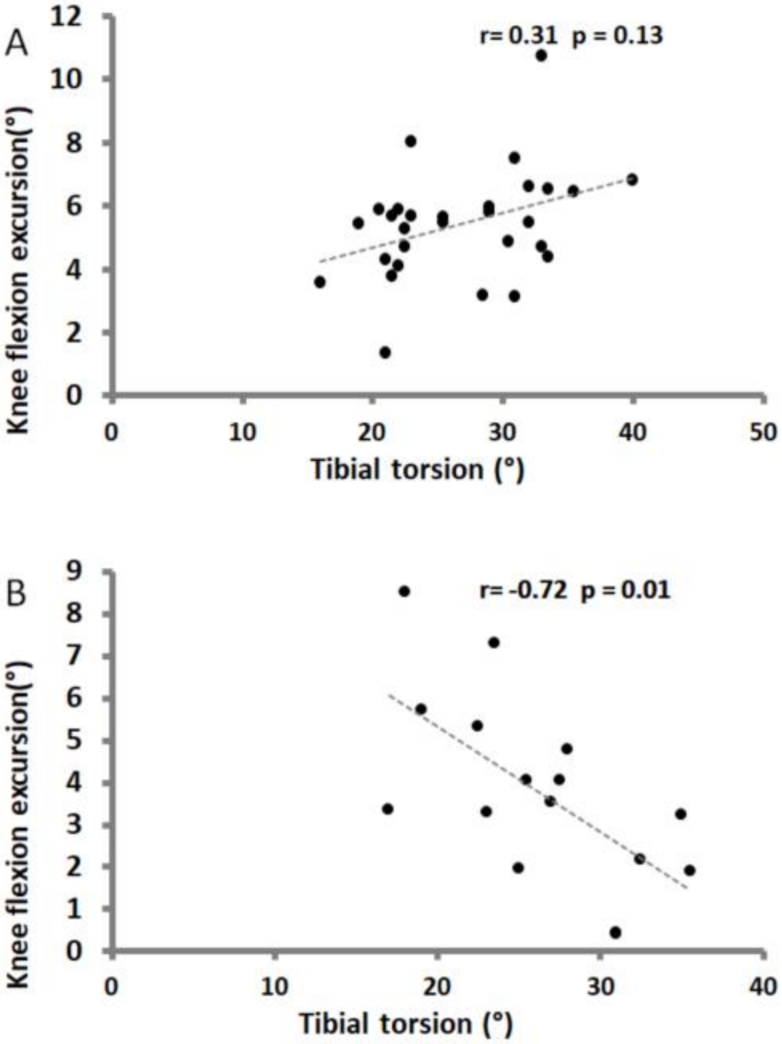

Figure 2.3 Scatter plots of relationship between tibial torsion and knee flexion excursion. (A: mild knee OA; B: moderate knee OA)

2.4.4 Correlation between muscle properties and joint kinematics

Table 2.3 shows the relationships between joint kinematics and active and passive properties of the quadriceps muscle. There was no association between muscle property and knee flexion angles in early stance phase in all subjects. There was also interaction of severity between knee flexion excursion and VL shear modulus (p=0.09), a marginal negative association was found in mild OA (r=-0.36, p=0.07) when control for gender and walking speed as shown in Figure 2.3A. Interaction effect of OA severity was found between peak knee flexion angle and VMO shear modulus (p=0.05); under the subgroup analysis, a marginal positive correlation (r=0.36, p=0.06) was found in mild OA as shown in Figure 2.4B. These findings suggested greater VL shear modulus was associated with less knee flexion excursion in participants with mild knee OA; and greater VMO shear modulus was related to larger peak knee flexion angle in participants with mild knee OA. There was no significant relationship between RF shear modulus and knee kinematics. In addition, maximum knee extension torque was not related to peak knee flexion angle or knee flexion excursion.

Table 2.3 Relationship between quadriceps muscle properties and early stance knee sagittal kinematics

	VL		RF		VMO		Extension torque	
	r	p value	r	p value	r	p value	r	p value
Peak knee flexion angle	0.06	0.73	-0.04	0.79	0.07	0.66	0.01	0.97
Knee flexion excursion	-0.27	0.10	0.04	0.80	-0.01	0.94	0.08	0.61

controlling for gender, age, speed

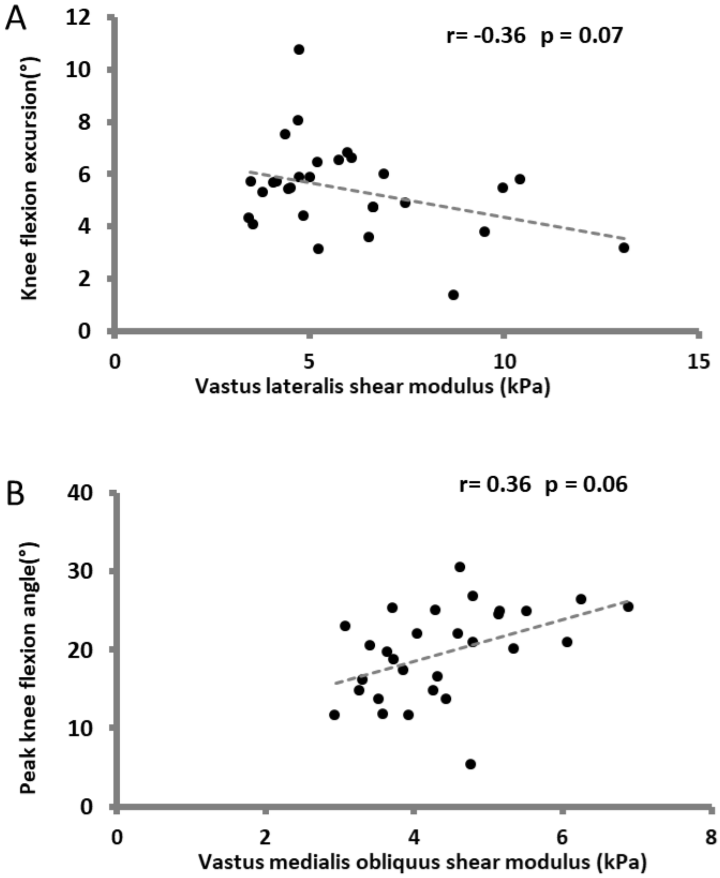

Figure 2.4 Scatter plots of relationship between muscle shear modulus and knee sagittal kinematics in early stance phase (A: VL shear modulus and knee flexion excursion; B: VMO shear modulus and peak knee flexion angle)

2.4.5 Group differences on joint alignments, knee kinetics and kinematics

There was no significant difference in tibial torsion (p=0.58), tibiofemoral rotation (p=0.15) or knee varus angle (p=0.10) between the mild and moderate knee OA groups but the moderate group had significantly higher KAM than the mild group (p=0.02). There was no significant group difference in KFM (p=0.55) or KAM index (p=0.16). Mild OA had significant larger knee flexion excursion than moderate OA (p=0.05). Details could be found in Table 2.4.

Table 2.4 Alignment and knee joint loads in mild and moderate knee OA

	All	Mild	Moderate	P value
Alignment [a]				
Tibial torsion (°)	26.5 ±5.8	26.8 ±5.8	25.9 ± 5.8	0.58
Tibiofemoral rotation (°)	1.6 ± 8.1	4.2 ± 7.9	-3.0 ± 6.2	0.15
Knee varus angle (°)	6.7 ± 5.0	4.4 ± 3.1	10.7 ± 5.1	0.10
Kinetics [b]				
External knee adduction moment (Nm/kg)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.02*
External knee flexion moment (Nm/kg)	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.2	0.55
Kinematics [b]				
Peak knee flexion angle	18.9 ± 7.2	19.7 ± 5.8	17.6 ± 9.2	0.38
Knee flexion excursion	4.7 ± 1.9	5.2 ± 1.4	3.8 ± 2.2	0.05

a. Adjusting for gender, age

b. Adjusting for gender, pain intensity and walking speed

2.5 DISCUSSION

Findings from this study provided evidence that tibial torsion was associated with both knee joint loading and knee flexion motion of early stance phase. This was the first study investigating the relationship between quadriceps passive tension and knee flexion motion in people with knee OA. Passive tension of vastus lateralis was related to knee flexion excursion and the relationship was specific to radiographic disease severity. Passive quadriceps muscle properties and knee flexion motion were related in participants with mild knee OA, while external tibial torsion was related to knee biomechanics in OA patients with moderate radiographic severity.

We adopted the tibial torsion and tibiofemroal rotation as measures of torsional alignments and the values obtained in this study were similar to those reported in the literature that tibial torsion was between 25° and 27° (Buck et al., 2012b, Duparc et al., 2014, Bombaci et al., 2011) whereas tibiofemoral rotation was between 2^{o} and 4° (Matsui et al., 2005, Duparc et al., 2014) which were reportedly measured by computed tomography in people with medial knee OA. The fact that we had used a relatively new approach of EOS and the measurements were taken in a weight-bearing condition and generated similar values as those reports using computed tomography is suggestive that our method can be applied in future for weight-bearing activities to simulate more functional testing.

The finding of present study indicated that tibia torsion was related to both knee joint loadings and flexion excursion in moderate knee OA. Greater external tibial torsion was associated with larger KAM and KAMI in participants with moderate knee OA. This result indicated that participants with more external tibial torsion were likely to have larger medial compartment joint load in participants with moderate knee OA. It was consistent with a previous cadaveric study by Kenawey et al. (Kenawey et al., 2011) which measured joint contact pressure directly. They found the joint contact pressure of knee medial compartment had a linear trend of increase within the range from 10° internal tibial torsion to 60° external tibial torsion (Kenawey et al., 2011). In this study, the external tibial torsion ranged from 16° to 40° that fell into the range mentioned by Kenawey et al.; increase in external tibial torsion would associate with joint contact pressure of knee medial compartment within this range. Furthermore, increase in external tibial torsion was associated with higher KAM, and lower KAM was likely to be found in those with more internal tibial torsion. Although medial joint contact pressure began to increase after 10° of internal tibial torsion, the contact pressure at 20° of internal tibial torsion was still similar to that at neutral position (Kenawey et al., 2011). This indicated a small internal tibial torsion of less than 20^{o} might be biomechanically beneficial to people with moderate knee OA. However, since none of our participants had excessive internal tibial torsion, it cannot be ruled out that higher internal tibial torsion might increase the medial compartment load (Lindgren and Seireg, 1989). Also, tibial torsion was strongly associated with foot progression angle in the adult population (Hudson, 2016). Toe-out gait pattern was observed in participants with greater external tibial torsion (Hudson, 2016), and increased early stance KAM was observed in those walked with toe-out gait whereas the KAM would reduce in those with toe-in gait in participants suffering from medial compartment knee OA (Simic et al., 2013, Khan et al., 2017, Shull et al., 2013). Therefore, these might explain the present findings that more external tibial torsion was associated with greater KAM. Besides, the association between tibial torsion and KAM was only revealed in the moderate group but not in the mild knee OA group. In participants with moderate knee OA, tibial torsion could have a stronger effect on the knee rotational compensatory mechanism (Moussa, 1994, Cooke et al., 1990), which would help to shift the force transmission from the frontal to the sagittal plane that might reduce KAM. In addition, we found that external tibial torsion angle was also negatively associated with knee flexion excursion during early stance phase of gait in the moderate knee OA. Tibial torsion angle was compensatory for the lower limb torsional alignments to neutralize foot progression angle (Cooke et al., 1990), and the amount of tibial torsion angle was consistently associated with foot progression angle (Hudson, 2016). Alteration of foot progression angle might reduce the peak knee flexion angle (Cui et al., 2019), thus the overall knee flexion excursion. Further study is suggested to investigate the relationship between tibial torsion and foot progression angle.

Originally, we thought tibiofemoral rotation would be related to knee biomechanics during early stance phase of gait cycle in people with knee OA. However, our findings could not establish any relationship between tibiofemoral rotation and external knee moments or knee flexion angles. The dynamic internal tibiofemoral rotation toward the end of knee extension was described as the “screw-home mechanism”, which has a functional importance to lock the knee and stabilize the joint (Hallen and Lindahl, 1966). This mechanism was altered in people with knee OA (Bytyqi et al., 2014) and even disappeared in those with advanced stage of knee OA (Hamai et al., 2009). Absence of the "screw-home mechanism" could affect the joint stability; thus it disturbed knee flexion-extension motion and increased the joint load. However, our results did not reveal tibiofemoral rotational alignment during static standing had any relationship with either external knee moments or knee flexion motion. It implied that the role of tibiofemoral rotation on joint loading and flexion motion under static standing and dynamic walking conditions was different, and this needs to be further explored.

It has been well reported KAM was directly related to varus deformity in people with knee OA (Foroughi et al., 2009). Biomechanically, larger varus deformity was related to longer level arm from the joint center on the frontal plane thus leading to greater KAM. Correction of knee varus deformity was still regarded as the optimal management strategy to reduce KAM in people who had total knee replacement due to knee OA (Ro et al., 2019). Besides, it was also revealed in present study that larger knee varus angle were accompanied with smaller knee flexion excursion. Therefore, knee varus deformity should still be one of the main target in order to enhance gait performance in people with medial knee OA.

This study also detected the association between passive tension of the quadriceps muscle heads and knee kinematics during gait. Passive tension of VL and early stance knee flexion excursion was negatively related in people with mild radiographic knee OA. Such findings partially support our hypothesis that people with greater VL shear modulus walked with less knee flexion excursion during the early stance phase of gait. Quadriceps muscles contract eccentrically and the elasticity of each individual muscle head could contribute to eccentric force generation that control knee motion during the loading phase of gait (Hessel et al., 2017). The VL, being the largest muscle of the quadriceps group that accounts for over 30% of total volume (Ema et al., 2017), might contribute the most to control knee motion during the loading response phase. The RF, being a two-joint muscle, would contribute to control both hip extension and knee flexion movements. During the loading phase, the inter-joint movements between the hip and knee joints might reduce the effects of RF tension on knee motion. The major role of VMO was a medial patellofemoral joint stabilizer during end range of knee extension with its fibers inserting at 65° medial to femoral axis (Flandry and Hommel, 2011). We assumed that greater VMO passive tension would enhance patellofemoral joint stability and might enable greater knee flexion during early stance phase, the result was consistent with our assumption. It was possible that greater shear modulus of VMO might provide patellofemoral joint stability during gait in people with knee OA. Thus, difference of morphology and alignment of the three superficial heads of the quadriceps might lead to their unique effects on the overall knee sagittal kinematics during gait.

No association was found between knee extension torque and early stance flexion angles. It disagreed with findings from Farrokhi et al. that extension strength and peak knee flexion angle were related in more advanced knee OA (Farrokhi et al., 2015b). We postulated that due to increase in joint instability in individuals with more advanced degeneration, greater muscle strength would be needed to enhance dynamic joint stability for joint excursion. Also, during the early stance phase, people with knee OA only developed less than 60% of the maximal quadriceps force (Hubley-Kozey et al., 2006). This could partially explain the non-significant relationship between maximal voluntary quadriceps strength and knee flexion excursion in our participants.

The relationship between passive muscle properties and knee joint kinematics was more likely detected in participants with mild knee OA, which was consistent with our assumption that association between muscle properties and knee flexion kinematics would be more evidenced in people with less structural changes. The radiographic severity specific relationships between quadriceps muscle properties and knee early stance biomechanics implied that quadriceps muscle properties could have a more influential role in the earlier stage of knee OA. In view of the relationship between knee joint kinematics, joint force and disease progression, it is important to maintain adequate knee flexion excursion and knee flexion angle during the early phase of gait. Findings from the present study might suggest the importance of passive properties of the superficial heads of the quadriceps, especially the VL passive tension to be intervened when the disease is in its early stage. Muscle strengthening including the quadriceps muscle is one of the recommendations for patients with knee OA. Improvement on quadriceps muscle strength (Raposo et al.) and clinical symptoms (Goh et al., 2019) have been reported. Taking together, both passive and active components of the quadriceps muscle should be assessed and be maintained with exercises for optimization of knee joint kinematics in people with knee OA, in particularly in the early stage of disease with less structural changes.

There were a few limitations in this study. First, joint loading on the transverse plane was not reported. The reason we did not report the transverse joint loading was because of its minimal contribution at the stance phase (Asay et al., 2018) and its relatively low accuracy when captured using the motion analysis system (Duffell et al., 2014). Second, muscle passive tension of quadriceps was measured in a static status of non-weight-bearing position. Ultrasound shear-wave electrography was a technology to detect viscoelastic property of soft tissues. Using this imaging approach, shear modulus of individual heads of quadriceps could be quantified according to the propagation velocity of a beam of shear-wave along the longitudinal axis of the ultrasound probe. It agreed well with Young’s modulus measured by material testing (Eby et al., 2013) and has been used in the study of quadriceps femoris in human (Xu et al., 2018). Yet, shear modulus quantified by this technology could only reflect passive tension of superficial heads of quadriceps in a static status. Measuring real-time passive viscoelastic property of skeletal muscle in vivo has not been reported due to technological limitation. Third, the measurements of the quadriceps mechanical properties and muscle strength were examined in lying and sitting positions, respectively. The knee joint was at an open chain condition. During the early stance phase of gait, the knee joint was functioned in a close kinetic chain manner where co-contraction of other muscles, such as the hamstrings and gastrocnemius muscles. Further study might include measurements of the muscle mechanical properties and muscle strength under closed chain condition. Four, we did not include participants with advanced knee OA, who usually have severe joint malalignment. The excessive torsional malalignment would likely have a significant effect on knee biomechanics during gait. However, there is a technical difficulty to examine people with advanced knee OA because of the massive osteophytes in their knee joints would obscure the bony contours in the bi-planar x-ray images rendering it difficult to identify the torsional angles.

2.6 CONCLUSIONS

In conclusion, the finding of present study showed OA severity specific association in relation to lower limb alignments, quadriceps muscle properties and knee biomechanics during gait in people with knee OA. In mild OA, shear modulus of vastii was a factor associated with knee flexion performance; in moderate knee OA, tibial torsion was associated with both knee joint loadings and knee flexion excursion. Tibial torsion angle should therefore be considered when designing biomechanical modification for people with moderate knee OA. Besides, it also hinted that strategies for enhancing knee biomechanical performance in early stance phase may need to be designed according to radiographic severity of knee OA.

Chapter 3 Exploring the relationship between pain intensity and knee moments in participants with knee osteoarthritis: a cross-sectional study

Huang, C., Chan, P. K., Chiu, K. Y., Yan, C. H., Yeung, S. S., & Fu, S. N. (2021). Exploring the relationship between pain intensity and knee moments in participants with medial knee osteoarthritis: a cross-sectional study. *BMC Musculoskeletal Disorders*, 22(1), 1-9.

3.1 ABSTRACTS

Background

High biomechanical loading is believed to be a risk factor to pain in people with knee osteoarthritis (OA), but controversial findings were reported on the relationship between external knee adduction moment (KAM) and pain previously. A more comprehensive analysis considering other factor such as external knee flexion moment (KFM) could help better reveal this relationship.

Aims

This study explored the relationship between external knee adduction moment and pain intensity in subjects with knee osteoarthritis (OA) using an integrated path analysis model.

Methods

This study is a cross-sectional study based on laboratory setting. Forty-seven subjects with clinical and radiographic medial knee OA were analyzed for their external knee adduction moment (KAM) and knee flexion moment (KFM) during walking using a motion analysis system. Pain intensity was measured by visual analogue scale (VAS) and the pain subscale of the Knee Injury and Osteoarthritis Outcome Score. Varus/valgus alignment was captured and quantified using a bi-planar X-ray system. Using a path analysis model, the relationships between pain intensity, KAM, KFM, OA radiographic severity, knee varus angle and walking speed were examined.

Results

The proposed path model met the goodness-of-fit criteria. Based on this model, KAM had a negative effect on VAS pain indirectly through the mediation of KFM. The model indicated KAM and KFM were negatively related to one another; and KFM was positively related to

VAS. The KAM index, defined as (KAM/ (KAM+KFM))*100, was negatively related to VAS.

Conclusions

Path analysis enabled the construction of a more integrated pathokinetic framework for people with knee OA. The KAM index which reflected the load sharing on the frontal and sagittal planes also revealed its relationship with pain. Re-distribution of mechanical loading from frontal to sagittal plane might be a strategy for pain avoidance associated with mechanical irritation.

3.2 INTRODUCTION

Knee osteoarthritis (OA) is a common problem in the senior population worldwide (James et al., 2018) and activity-related pain is the most predominant disabling symptom of this condition (Felson, 2005). More importantly, there is an upward trend in the prevalence of knee pain associated with OA (Nguyen et al., 2011). In people over 55 years of age, about 10% had mild-to-moderate knee pain, and between 2% to 4.8% would suffer from severe pain and disability caused by OA (Peat et al., 2001, Liu et al., 2018). The pain and disability would lessen their willingness to participate in physical and social activities (Stubbs et al., 2015), and strongly affect their health-related quality of life (Alkan et al., 2014).

Most pain in knee OA is activity triggered especially in weight-bearing situations (Neogi, 2013, Hawker et al., 2008). Extrinsic and intrinsic factors that increase joint mechanical loading lead to greater intensity of knee pain (Felson, 2013). Physically demanding occupations, habitual and intense physical activities had strong relationship with knee pain and joint degeneration (Silverwood et al., 2015b); people who were over-weight had over two fold higher risk of knee OA and obesity was related to 24.6% of new onset of knee pain (Silverwood et al., 2015b). Excessive knee loading during gait, in particular, the external knee adduction moment (KAM), has been proposed as an essential intrinsic factor for OA related pain. Amin et al. found that seniors with higher peak KAM were more likely to develop chronic knee pain within 3-4 years (Amin et al., 2004). Nevertheless, studies in search of relationship between KAM and pain intensity reported inconsistent findings (Astephen et al., 2017, Hall et al., 2016, Henriksen et al., 2012, Thorp et al., 2007). In participants with mild radiographic knee OA, peak KAM was significantly higher in the symptomatic than the asymptomatic groups (Thorp et al., 2007, Astephen et al., 2017). However, a negative relationship between peak KAM and pain intensity was reported by Henriksen et al. (Henriksen et al., 2012). It was also found that greater KAM impulse was related to higher pain intensity in participants with moderate radiographic knee OA (Henriksen et al., 2012, Hall et al., 2016), but this was associated with lower pain intensity in participants with severe radiographic knee OA (Hall et al., 2016). It is essential to consider the degree of OA severity when exploring the relationship between KAM and pain intensity in view of the fact that such a relationship was very likely to be specific to radiographic severity,

Peak external knee flexion moment (KFM) reflected joint loading, and the load would trigger pain in participants with knee OA. In people with symptomatic mild knee OA, the KFM at early stance phase was lower than their asymptomatic counterparts (Astephen et al., 2017), but people with higher KFM were more likely to develop pain after exercises (Boyer and Hafer, 2019). In view that KAM and KFM occur nearly simultaneously with the first peak of medial joint contact force at about the initial 23% of the total gait cycle (Manal et al., 2015), Simic et al. reported that increase in KFM was associated with a reduction in KAM with gait modification (Simic et al., 2013). They also found that KAM would drop but KFM would rise with toe-in gait; whereas the opposite was observed with toe-out gait during the first half of stance phase in people with knee OA (Simic et al., 2013). These findings suggested an inverse relationship existed between KAM and KFM (Uhlrich et al., 2018). In order to better understand the relationship between KAM and pain, an analysis on the simultaneous change between KAM and KFM when taking into considerations of factors such as joint alignment (Hurwitz et al., 2002) and walking speed (Robbins and Maly, 2009) might better explain the direct relationship between KAM and pain.

Load sharing among the three anatomical planes has emerged as one of the mechanical outcome considerations in participants with knee OA. Asay et al. reported a transition of KFM-dominated total joint loading to a KAM-dominated loading in the long term, and the percentage of KAM over the total joint moment appeared to be associated with radiographic OA progression at follow-ups over a period of 5 years (Asay et al., 2018). The percentage of KAM in total joint moment was associated with the change in medial-to-lateral knee articular cartilage thickness ratio in an 8-year follow-up. Hence, the proportion of KAM was possibly one key biomechanical factor linking to joint structure destruction in the initiation and progression of knee OA. Besides, the KFM and KAM contributed to 73% of variance of the total joint force (Richards et al., 2018). The external knee moment on the horizontal plane accounted for less than 1% of total external joint moment (Asay et al., 2018) which was relatively low during the stance phase, thus its influence had been less emphasized. Therefore we aimed to explore whether the KAM index, which was the percentage of KAM over the sum of KAM and KFM, was associated with pain intensity in participants with medial knee OA. A cross-sectional relationship between KAM index and OA-related pain would help to establish their causal relationship.

The main goal of this study was to investigate the relationships between KAM and pain intensity in people with mild-to-moderate medial knee OA by path analysis taking the effects of KFM, disease severity, joint alignment and walking speed into considerations. We also explored whether load sharing represented by KAM index would have a relationship with pain intensity. It was hypothesized that 1) pain intensity could be determined by early stance KAM directly and indirectly through KFM; 2) there would be a positive association between KAM index and pain intensity in participants with mild-to-moderate medial knee OA.

3.3 METHODS

3.3.1 Study design

This was a cross-sectional observational study

3.3.2 Participants

Participants were recruited from the department of orthopedics and traumatology of a regional hospital. Inclusion and exclusion criterion were detailed under Chapter 2, section 2.3.2.

3.3.3 Outcome measurement

3.3.3.1 Pain intensity

Pain intensity was measured by both VAS and the pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS). The maximal level of pain intensity during walking in the past week was measured by an 11-point VAS with “0” represented no pain and 10 represented the worst pain. It quantified pain intensity in particular during walking in particular. Pain subscale from KOOS was also used to assess the pain intensity more comprehensively in different functional conditions instead of just walking as measured with the VAS. For each subscale, a 0-100 score scale was used with “0” represented the most severe knee problem, while “100” indicated no problem; thus higher scores indicated less pain. Convincing evidence from meta-analysis suggested KOOS had adequate content validity, internal consistency and construct validity (Collins et al., 2016), and excellent test-retest reliability of translated version has also been reported (Collins et al., 2016). Participants were required to complete the subscale without any assistance from the assessor.

3.3.3.2 Knee joint kinetics

Knee joint loading during the gait cycle was captured using a motion analysis system. Details of the capturing procedures and computation of joint loading (KAM, KFM and KAM index) were detailed in Chapter 2, section 2.3.3.2.

3.3.4 Statistical analysis

Statistical analysis was conducted with R software (Version 4.02). For participants with bilateral symptoms, analyses were conducted on the more painful leg. All the variables were normally distributed as assessed by Shapiro-Wilk test. Correlations between VAS pain, KOOS pain, KAM, KFM, radiographic severity, knee varus angle and walking speed were assessed by two-tailed Pearson correlation coefficient. The relationship between pain intensity and KAM were estimated by path analysis with maximum likelihood estimation. There was one missing data in the KOOS pain subscale and it was handled by pairwise deletion in the analysis.

Path analysis was an extension of multiple regression analysis using correlational data to discover the strength of effect of a hypothesized system (Klem, 1995). It had the advantage to estimate both direct and indirect effects between variables. Pain intensity, KAM and KFM were the endogenous variables whereas walking speed, OA radiographic severity and knee varus angle were the exogenous variables. The results of correlation between exogenous variables were not shown in the model. The goodness-of-fit criteria was assessed by Chi-square, Comparative Fit Index, Tucker-Lewis Index, Root Mean Square Error of Approximation and Standardized Root Mean Square Residual (Kline, 2015). The model proposed in this study was a conceptual model of the relationships between knee joint loadings and pain intensity sourced from the literature.

Correlations between VAS pain, KOOS pain and KAM index were assessed by partial Pearson correlation coefficient test controlling for radiographic severity, knee varus angle and walking speed.

3.4 RESULTS

3.4.1 Demographic information

A total of 100 participants with knee OA were initially screened and 47 who satisfied the study criteria were recruited. Main reasons for exclusion were low back pain, recent knee injury or surgery and lateral knee OA. The Information of the included participants was shown in Table 3.1. Their mean age was 62.1 ± 6.0 years old and 78% of the participants were females. Thirty participants (64%) were categorized as mild knee OA. All except four participants had bilateral knee OA.

Table 3.1 Descriptive information of participants

Characteristics	(n=47)
Demographic information	
Age (years)	62.06 ± 6.01
BMI (kg/m^2)	26.25 ± 3.56
Gender (female/male)	37/10
Mild/Moderate	30/17
Bilateral/Unilateral	43/4
Knee varus angle (°)	6.02 ± 5.27
Walking speed (m/s)	1.00 ± 0.17
Knee joint kinetics	
External knee adduction moment (Nm/kg)	0.50 ± 0.15
External knee flexion moment (Nm/kg)	0.47 ± 0.26
KAM index (%)	54.12 ± 17.41
Pain	
VAS	5.15 ± 1.76
KOOS	63.08 ± 14.02

3.4.2 Relationships between self-perceived pain and joint loading

As shown in by the KOOS (r=-0.39, p=0.01).

Table 3.2, VAS self-perceived pain intensity was positively related to KFM (r=0.43, p=0.003) and it had a negative association with KAM (r= -0.29, p=0.05). The KAM had a negative relationship with KFM (ρ=-0.40, p=0.01) and positive association with knee varus angle (r=0.55, p<0.001). There was less likely any relationship between KOOS pain intensity and KAM (r=-0.13, p=0.40) or KFM (r=-0.01, p=0.63). Nevertheless, greater pain intensity measured by VAS was associated with greater pain intensity measured by the KOOS (r=-0.39, p=0.01).

Table 3.2 Correlation coefficient of variables in path analysis

	VAS Pain	KOOS pain	KAM	KFM	Severity	Walking speed	Knee varus angle
VAS pain§		-0.39**	-0.29*	0.43**	0.27	-0.02	0.04
KOOS pain§			-0.13	-0.07	0.01	0.01	-0.05
KAM				-0.40**	0.18	0.01	0.55**
KFM					0.01	0.149	-0.06
Severity						-0.33*	0.62
Walking speed							-0.31*

* p<0.05, ** p<0.01, ***p<0.001

§ High VAS pain score indicates high pain intensity; low KOOS pain score indicates high pain intensity.

3.4.3 Path analysis

The model including VAS pain intensity was examined to be of good fit according to Chi-square test (χ^2= 4.89, df=4, p= 0.30), Comparative Fit Index (CFI= 0.98) and Tucker Lewis Index (TLI= 0.93), which met the cut-off criterion (Bentler and Bonett, 1980). The value for Standardized Root Mean Square Residual was 0.06 and that for Root Mean Square Error of Approximation was 0.07, and both were smaller than the threshold of 0.08. The effects of path model were shown in Table 3.3.

Table 3.3 Decomposition of effects from path analysis

Effect	Estimate	Standard error	Standard estimate	95%CI	P value
Model 1					
On VAS pain (R^2=0.265)					
KAM	-2.50	1.61	-0.21	-5.66, 0.67	0.12
KFM	2.26	0.89	0.35	0.51, 4.01	0.01
Severity	1.09	0.45	0.31	0.20, 1.98	0.02
On KAM (R^2=0.365)					
Varus angle	0.02	0.00	0.74	0.01, 0.03	<0.01
Walking speed	0.13	0.11	0.16	-0.07, 0.34	0.21
Severity	-0.07	0.05	-0.23	-0.16, 0.02	0.12
On KFM (R^2=0.192)					
Walking Speed	0.29	0.20	0.19	-0.10, 0.68	0.15
KAM	-0.71	0.24	-0.40	-1.17, -0.25	<0.01
Model 2					
On KOOS pain (R^2=0.036)					
KAM	-18.06	15.04	-0.19	-47.53, 11.41	0.23
KFM	-7.76	8.34	-0.15	-24.11, 8.59	0.35
Severity	1.04	4.25	0.04	-7.29, 9.38	0.81
On KAM (R^2=0.358)					
Varus angle	0.02	0.00	0.74	0.01, 0.03	0.02
Walking speed	0.13	0.11	0.16	-0.08, 0.34	0.21
Severity	-0.07	0.05	-0.23	-0.16, 0.02	0.15
On KFM (R^2=0.183)					
Walking Speed	0.28	0.20	0.19	-0.11, 0.67	0.16

KAM	-0.69	0.24	-0.39	-1.16, -0.23	<0.01

KAM was found to have an indirect effect on VAS pain intensity through mediation of KFM (see

Table 3.4). No direct effect was found between KAM and VAS pain intensity. However, there existed a moderate negative relationship between KAM and KFM; the magnitude of KFM had a direct effect on VAS pain intensity. The effect of radiographic severity, knee varus angle and walking speed had been demonstrated in the path model (Table 3.3 and Figure 3.1).

Table 3.4 Effects of external knee adduction moments on intensity of pain measured by VAS and KOOS.

	Estimate	Standard error	Standard estimate	95%CI	P value
VAS					
Direct	-2.50	1.61	-0.21	-5.66, 0.67	0.12
Indirect	-1.61	0.83	-0.14	-3.23, 0.02	0.05
Total	-4.10	0.16	-0.35	-7.21, -1.00	0.01
KOOS					
Direct	-18.06	15.04	-0.19	-47.53, 11.41	0.23
Indirect	5.38	6.07	0.08	-6.52, 17.27	0.38
Total	-12.69	14.09	-0.13	-40.30, 14.93	0.37

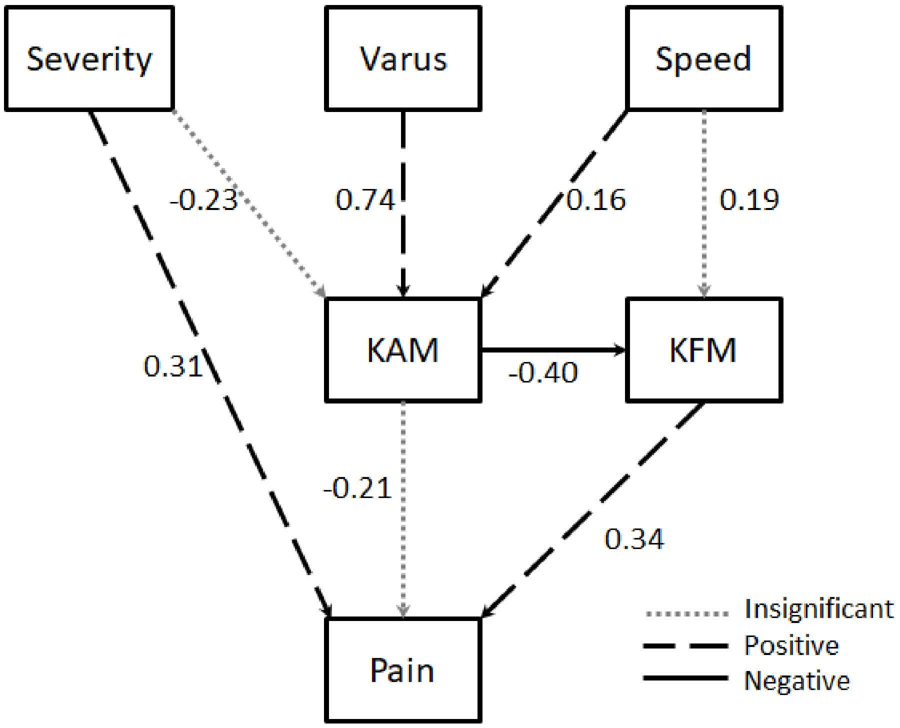

Figure 3.1 Diagram of path analysis. Solid and dotted lines indicate significant and not significant relationships, respectively. (Pain: intensity of pain using visual analogue scale. KAM: external knee adduction moment. KFM: external knee flexion moment. Varus: knee varus angle)

3.4.4 Relationships between self-perceived pain and KAM index

Figure 3.2 showed the scatter plot between KAM index and pain intensity. There existed a negative association between the two variables (r= -0.45, p= 0.002) after controlling for radiographic severity, knee varus angle and walking speed. Hence, higher intensity of pain was associated with lower KAM index in subjects with knee OA.

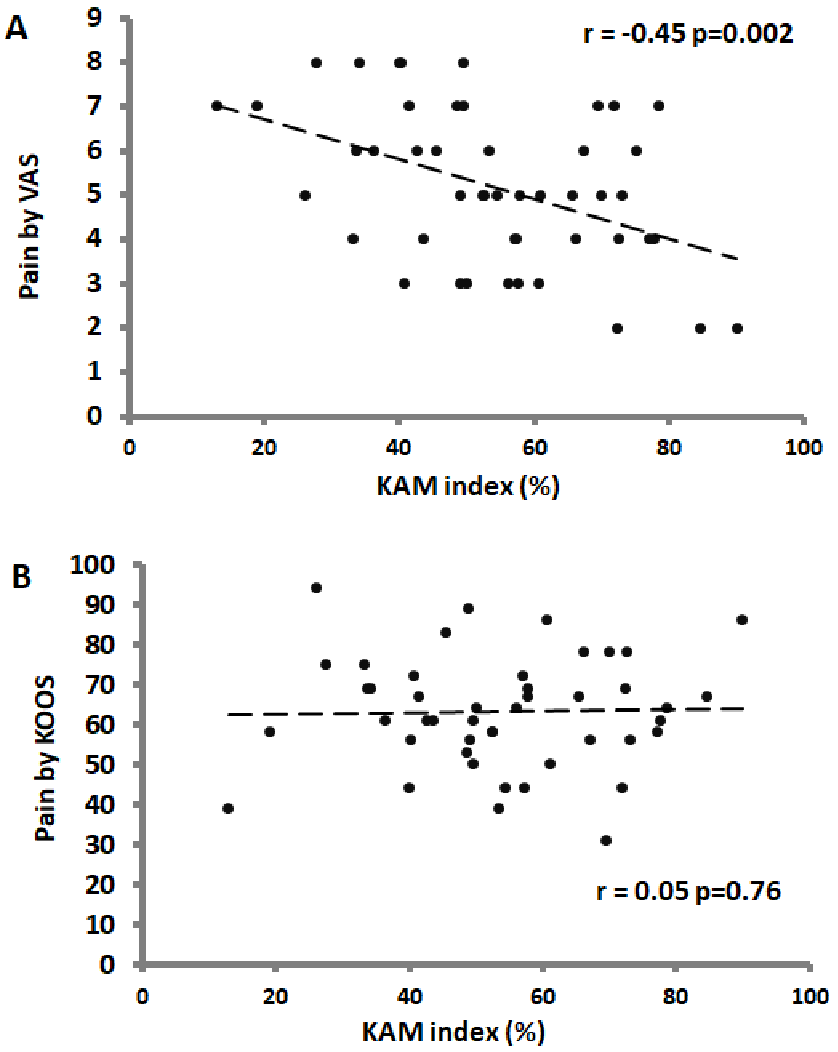

Figure 3.2 Scatter plots between pain intensity and KAM index**.** Controlling for disease severity, knee varus angle and walking speed. (VAS: visual analogue scale; KOOS: Knee Injury and Osteoarthritis Outcome Score)

3.5 DISCUSSION

This study aimed to explore the relationships between pain intensity and knee joint loading in people with mild-to-moderate medial knee OA. Using path analysis, a more integrated conceptual framework was constructed. The findings suggested KAM had a negative effect on pain with KFM as its mediator. By using the KAM index, we also revealed a negative relationship with pain intensity in our participants.

Based on these findings, it is suggested that magnitude of KAM had a negative effect on pain intensity. The effect of KAM on pain was through the mediation of KFM. Negative relationship between VAS pain and KAM were reported in previous studies in people with mild radiographic severity of OA (Henriksen et al., 2012, O'Connell et al., 2016). The authors proposed such relationship could be an avoidance mechanism in response to pain provoking stimuli. Indeed, experimental pain induced in infrapatellar fat pad would significantly reduce the KAM and KFM during gait in healthy participants (Henriksen et al., 2010). The authors further proposed the modulation on KAM and KFM was related to alteration in trunk motion, foot progression angle or muscle-coordination. However, OA-related pain is usually chronic and trigged by loading activity (Hawker et al., 2008) and findings from healthy participants with experimentally induced pain might not be translated to participants with knee OA. Besides, during gait modification, reduction in KAM was associated with increase in KFM in participants with knee OA (Henriksen et al., 2010) which agreed with the present finding that moderate negative association was detected between KAM and KFM. In participants with knee OA, mechanical modification was proposed as the mechanism for the interchange between KAM and KFM.

We used the KAM index as an estimation of the percentage of KAM to the sum of KAM and KFM and found a negative relationship between this index and VAS pain intensity when adjusting for radiographic severity, knee varus angle and walking speed. This concurred with the results from path analysis that participants with lower share of mechanical loading on the frontal plane had less pain in walking. Since this was a cross-sectional observational study, a causal relationship could not be established. There could be other de-loading mechanisms adopted by the participants in response to painful stimuli via re-distribution of load between the frontal and sagittal planes, or higher load sharing on the frontal plane could have happened to minimize the walking pain. However, greater percentage of KAM to total external knee moment was linked with radiographic joint structural degeneration as measured by KL grading in 5 years (Asay et al., 2018). Considering this point with the present findings, a higher KAM index would therefore be detrimental to the knee joint in the long run; its apparent association with lower pain was more likely to be associated with some other potential pain avoidance strategies, for instance, knee kinematics asymmetry between two limbs in mild-to-moderate knee OA (Mills et al., 2013a). However, this study cannot answer this question and further study is warranted to examine the mechanisms of how KAM index would modulate the pain intensity.

The KFM was found to be a mediator for the relationship between KAM and pain intensity in mild-to-moderate knee OA. In view KAM and KFM were antagonistic to one another, the present finding of a positive relationship between pain intensity and KFM echoed with the report of O’Connell et al. (O'Connell et al., 2016) that higher KFM was demonstrated in participants with moderate-to-severe pain than those with less pain (O'Connell et al., 2016). Previous study had reported KFM was more sensitive to change in pain intensity than KAM over time in people with medial compartment OA (Asay et al., 2013). The KFM was balanced with contraction of the quadriceps muscle which produced an internal knee extension moment (Creaby, 2015). The internal knee extension moment resulted from quadriceps contraction would induce a compressive force across the tibiofemoral joint (Walter et al., 2010) that might trigger pain.

Interestingly, the KOOS pain intensity and KAM were not likely interrelated either directly or indirectly. Likewise, pain intensity measured with the pain subscale of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was also not associated with the magnitude of KAM in radiographic medial compartment knee OA (Maly et al., 2008, Astephen Wilson et al., 2011). A possible explanation might be because VAS was a unidimensional pain measurement tool focused on pain intensity localized at the knee joint whereas both KOOS and WOMAC were multidimensional measuring tools with more emphasis on disease progression and joint function. In fact, the KOOS pain subscale was an extension of WOMAC pain subscale , and they both measured pain intensity with Likert-type scales during several daily activities, including but not limited to level walking (Bellamy et al., 1988). Apart from that, questions in KOOS and WOMAC pain subscales were not focused on a specific knee; thereby the pain on both knees for those with bilateral knee OA would influence the outcome. Though it is clarified that area of interest of is the knee in KOOS, low back pain and other musculoskeletal pain could also have an impact on the pain intensity scores when doing these physical activities (Suri et al., 2010). Considering these holistic factors, KOOS and WOMAC pain subscales might have weaker relationship with magnitude of joint loading variables than knee pain in walking.

There were some limitations in this study that should be addressed. First, the sample size was considered small especially that of KL grade 3, which had restricted the model building. If the sample size was larger, a more comprehensive model could have been built. Second, the fact that severe knee OA participants were not included in the study has restricted the findings to be only applicable to patients with radiographic knee OA with KL grade less than 4. Finally, due to the cross-sectional nature of the study, measurements at a time point could not justify if any causal relationship did exist between pain intensity, KAM and other variables. Future interventional study will shed lights on how changes on KAM, KFM and pain intensity are interrelated.

3.6 CONCLUSIONS

To conclude, in people with radiographic mild-to-moderate knee OA, KAM had a negative effect on self-perceived intensity of walking-related pain with KFM as its mediator. In these people, greater KAM index was associated with less walking pain. The distribution of knee joint loading from frontal to sagittal planes could be a pain avoidance strategy which has an application value for management of pain in people mild-to-moderate knee OA.

Chapter 4 Relationships between modulation on pain gait biomechanics and muscle properties after a six-week comprehensive management program in people with knee osteoarthritis

4.1 ABSTRACT

Background

Exercise is used as primary treatment for knee osteoarthritis (OA) and has been proved to reduce pain and enhance function. The associations between clinical improvements, muscle properties and joint biomechanics are unclear.

Aims

This study aimed to explore associations between intervention-induced modulation on pain and joint loading as well as modulation on quadriceps muscle properties and joint kinematics during gait in individuals with knee OA.

Methods

Thirty-nine participants with symptomatic medial knee OA were assessed for external knee adduction moment (KAM), flexion moment (KFM), peak knee flexion angle and flexion excursion during early stance phase of the gait cycle using a motion analysis system. Pain intensity and impairments were measured by visual analogue scale (VAS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS). Passive muscle tension and strength of the quadriceps muscle were measured using ultrasound shear-wave elastography and hand-held dynamometer, respectively. The assessments were conducted before and after a 6-week exercise-based rehabilitation program.

Results

We found that reduction in pain intensity was associated with an increase in KAM (r= -0.32, p= 0.07). The increase in KAM index was related to improvement of pain (r= -0.35, p= 0.05) and symptom (r= -0.43, p= 0.01). Change of knee flexion excursion was associated with symptom (r=0.34, p= 0.06). Also, reduced vastus lateralis passive tension was associated with an increase in knee flexion excursion (r= -0.67, p= 0.01) in mild OA.

Conclusions

Exercise program induced OA-severity-specific treatment effects by modulating knee joint loading and joint motion. Passive muscle tension of vastus lateralis might be a factor which controlled knee sagittal movement.

4.2 INTRODUCTION

Knee osteoarthritis (OA) is prevalent in the aged population (Safiri et al., 2020) and was one of leading causes of disability world-wide (Collaborators, 2017). Pain (Dieppe and Lohmander, 2005), muscle weakness (Bennell et al., 2008), and joint range of motion limitation (Steultjens et al., 2000a) are the common complaints by individuals with knee OA. Functionally, these impairments alter gait patterns (Henriksen et al., 2010, Radin et al., 1991) thus affecting walking ability (Mills et al., 2013c). Exercise therapy is an evidenced-based effective intervention for pain relief and functional restoration for individuals with knee OA (Fernandes et al., 2013b, Bannuru et al., 2019b).

One goal of exercise therapy is to minimize joint loading through the enhancement of joint stabilization, movement or gait re-training (Farrokhi et al., 2013). This is because excessive joint loading has been identified as the mechanical factor associated with OA-induced pain and functional limitation (Amin et al., 2004); thus, it advances the disease progression (Miyazaki et al., 2002). Despite positive reports on exercise on reducing pain and functional limitation in individuals with knee OA (Goh et al., 2019), their effects on joint loading has not been well established. For example, neuromuscular training exercises have significant effects on pain relief and functional regain (Goh et al., 2019), but Bennell et al. could not detect significant modulation on joint loading after an eight-week neuromuscular rehabilitation training program in participants, the majority of whom had moderate-to-severe radiographic knee OA (Bennell et al., 2014a). Holsgaard-Larsen et al., however, reported a significant increase in KAM on participants with knee OA after an 8-week neuromuscular exercise program (Holsgaard-Larsen et al., 2017). The contribution of KAM to total joint moment has been associated with disease progression (Asay et al., 2018), which suggested the importance of load sharing in frontal plane could be a target in the knee OA management. It was therefore questioned whether exercise-induced modulation of pain might be related to the percentage of KAM to the total external adduction and flexion moment viz. the KAM index.

Reduced joint range of motion, such as a decrease in peak knee flexion angle at early stance (Childs et al., 2004, Manetta et al., 2002) and flexion excursion (Astephen et al., 2008a) is commonly detected in participants with knee OA. Reduced knee flexion excursion during stance might alter the tibiofemoral contact characteristics and induce adverse loading on joint cartilage. A recent study on the range-of-motion-based rehabilitation program was found to be effective for improving joint range, pain and dysfunction in participants with mild to severe knee OA (Benner et al., 2019). However, it remains unclear whether exercise-induced modulation on joint flexion excursion and pain during walking would be interrelated in people with knee OA.

The present study aimed to explore associations between exercise-induced change in joint kinetics, kinematics, pain and dysfunctions on participants with knee OA. The roles of active and passive properties of the quadriceps muscle on joint kinetics and kinematics during gait was also studied. It was hypothesized that (1) a decrease in medial-to-lateral joint loading and an increase in knee flexion excursion would be associated with a decrease in pain and functional limitation; (2) reduced passive muscle tension and increased strength of the quadriceps would relate to an increase in peak knee flexion angle or knee flexion excursion in participants with knee OA after a six-week exercise-based rehabilitation program. The associations might be OA severity specific.

4.3 METHODS

4.3.1 Participant

Participants were recruited from the Department of Orthopaedic and Traumatology, Queen Mary Hospital, Hong Kong. The diagnosis and grading of OA was made by orthopedic surgeons. The inclusion criteria were: 1) age between 50 and 80 years; 2) having minimal knee pain of 2 on an 11-point VAS during level walking and with most painful site located in the medial compartment; 3) plain x-ray evidence of more degenerative change in the medial than lateral tibiofemoral compartment, 4) Kellgren & Lawrence grade 2 and 3. Exclusion criteria were: 1) history of lower back or lower limb injury within the past 12 months; 2) have lower back or lower limb joint pain of 3 or above in the VAS; 3) rheumatoid arthritis, 4) history of knee joint replacement or other knee surgery; 5) any other muscular, joint or neurological condition influencing lower limb function; 6) unable to walk independently without external assistance; and 7) body mass index (BMI) >36 (Hall et al., 2016). The data collection continued in the study period and 47 eligible subjects were included in this study.

This study was approved by the Human Participants Ethics Committee of the administrating institution. The study was registered on ClinicalTrials.gov (ID: NCT03628508). All the participants gave their informed written consent before the commencement of the study.

4.3.2 Exercise program

The exercise program was title as “Comprehensive Osteoarthritis ManagEment programme” (COME). It started with individual assessment session with physiotherapists after referring by orthopedic surgeons at Queen Mary Hospital. The contents of COME program follow present international and regional non-surgical guidelines and include multidisciplinary efforts (Kan et al., 2019):

- 1 session of 3-hour patient education by nurse
- 12 sessions of 1.5-hour supervised exercises by physiotherapist
- 5-8 sessions of disease coping strategy and fatigue management by occupational therapist

Each group in the exercise class usually included 8-10 patients supervised by one physiotherapist. The supervised exercise sessions included five types of exercises: function, stretching, strengthening, neuromuscular control and cardiopulmonary exercise. Each patient received an individual-tailored exercise contents. The progression of exercise was based on the performance and capacity of patient.

- Function exercise: coping skills of basic functional activities including kneeling, squatting, up-and-down stairs, and sit-to-stand transition of different height.
- Stretching exercise: static self-stretching on knee flexor, knee extensor, ankle plantar flexor, hold for 10 seconds * 3 repetitions.
- Strengthening exercise: progressive resistance strengthening with sandbag on hip abductor, hip flexor, knee extensor and knee flexor, hold for 5 seconds *10 repetitions * 3 sets.
- Neuromuscular control exercise: including lunge, step-up, pelvic lift, slide with cloth under foot, etc. on posture control and dynamic motion control, 10 repetitions * 3 sets.
- Cardiopulmonary exercise: aerobic exercise at 60% maximal heart rate consisting of fast walking and aerobic dance with and without equipment.

Figure 4.1 Function exercise used in COME program

4.3.3 Outcome measurements

4.3.3.1 Pain, other symptoms and function limitation

Pain intensity and dysfunctions were measured using visual analogue scale and the Knee injury and Osteoarthritis Outcome Score. Detailed description of these two scales could be found in Chapter 4, section 4.3.3.1. In brief, participants were asked to quantify their pain intensity in past seven days on the VAS; and responded to KOOS questions relating to pain, function and activity of daily life.

4.3.3.2 Joint kinetics and kinematics during gait

Gait biomechanics including knee kinetics and kinematic during early stance phase were captured using the Vicon motion analysis system. Details had been described under Chapter 2 (kinetics), section 2.3.3.2 and Chapter 3 (kinematics), section 3.3.2.1. In brief, each participant was requested to walk along an eight-meter path at self-selected speed. Joint loading including KAM, KFM, KAM index and knee kinematics including knee flexion exclusion, peak knee flexion during the early stance phase were computed.

4.3.3.3 Knee extensors strength and passive tension of the quadriceps muscle

Muscle properties including strength of the quadriceps and passive tension of the superficial heads of the quadriceps muscles were captured using the same approached as described in Chapter 3, section 3.3.2.3 (strength) and 3.3.2.4 (passive tension).

4.3.4 Statistical analysis

All statistical analysis was conducted on SPSS (Version 23.0, IBM Corp., New York, US). Normality of all variables was assessed by Shapiro-Wilk test. Potential confounders were pre-screened with Spearman's rho correlation coefficient test with alpha level at 0.10. Differences on the outcome measures between baseline and follow-up were assessed with repeated measured analysis of variance taking gender, disease severity and varus/valgus alignments as co-variates. Interaction of OA severity was evaluated with linear regression for the change of outcomes from baseline to follow-up with alpha level of 0.10. Correlations between changes in pain, functional limitation, knee kinetic and kinematic variables were assessed by two-tailed partial Pearson correlation coefficient test controlling for radiographic disease severity, gender and varus/valgus alignment. Sub-group analyses were also conducted according to OA radiographic severity when there was significant interaction. Using the same approach, correction between changes in knee kinetic and kinematic variables, active and passive elements of the quadriceps muscles were assessed. Missing data were handled with pairwise deletion.

4.4 RESULTS

4.4.1 Demographic information

Thirty-nine participants that satisfied our inclusion and exclusion criteria were included in the study (Table 4.1). Participants on average were aged 63.1 ± 5.5 years old; and 79.2% of them were females. Twenty-two of them had mild knee OA (KL grade 2) and 17 had moderate knee OA (KL grade 3). Majority of the participants had bilateral knee OA.

Table 4.1 Demographic information of participants

Characteristics	**All** **(n=39)**	**KL grade 2** **(n=22)**	**KL grade 3** **(n=17)**
Age (years)	63.1 ± 5.5	61.2 ± 5.2	65.6 ± 4.9
BMI (kg/m^2)	26.7 ± 3.5	25.7 ± 3.6	28.0 ±3.1
Gender (female/male)	29/10	18/4	11/6
Knee varus angle (°)	6.6 ± 5.4	4.2 ± 3.1	9.6 ±6.2
Bilateral/unilateral OA	36/3	20/2	16/1
Walking speed (m/s)	1.0 ± 0.2	1.0 ±0.2	0.9 ±0.2

4.4.2 Interventional effects on pain, functional limitation, knee kinetics and kinematics during gait

Table 4.2 present the intervention effects after the 6-week rehabilitation program. The VAS pain intensity was significantly reduced by 26.6% ($p< 0.001$). Scores of KOOS pain, symptom and daily life activity were significantly increased by 17.29% ($p< 0.001$), 25.25% ($p= 0.001$) and 12.02% ($p= 0.001$), respectively. There was a significant increase in KFM by 49.69% ($p= 0.001$) and a reduction of KAM index by 8.99% ($p= 0.011$). A tendency of reduction in KAM was detected (by less than 10%; p=0.091). A significant increase in knee flexion excursion by 44.10% (p= 0.001) was detected. The normalized knee torque was significantly increased from 1.94 ± 0.62 Nm/kg to 2.27 ±0.64 Nm/kg (p< 0.001). There was not any significant change on passive tension on any of the quadriceps muscle heads.

Table 4.2 Pain, symptom, muscle properties, knee kinetics and kinematics comparison at baseline and after exercise program

	Baseline	Follow-up	Change	95% CI	P value
Pain and other symptoms					
VAS pain	5.15 ± 1.80	3.78 ± 1.97	-1.38 ± 2.15	-0.21, -0.66	<0.001*
KOOS pain	61.37 ± 15.23	69.69 ± 14.56	8.32 ± 11.91	4.41, 12.23	<0.001*
KOOS symptom	58.84 ± 19.18	66.39 ± 15.63	7.55 ± 12.74	3.42, 11.68	0.001*
KOOS Activity of daily life	74.71 ± 13.55	81.90 ± 13.36	7.18 ± 10.91	3.55, 10.82	<0.001*
Knee kinetics					
KAM (Nm/kg)	0.49 ± 0.15	0.45 ± 0.14	-0.04 ±0.13	-0.08, 0.01	0.091
KFM (Nm/kg)	0.48 ± 0.28	0.61 ± 0.31	0.13 ± 0.24	0.05, 0.21	0.001*
KAM index (%)	52.91 ± 18.10	45.66 ± 18.54	-7.21 ± 16.53	-12.64, -1.78	0.011*
Knee kinematics					
Peak knee flexion angle (°)	19.65 ± 6.20	20.94 ± 5.72	1.08 ± 5.63	-0.77, 2.93	0.243
Knee flexion excursion (°)	4.78 ± 2.10	5.80 ± 2.11	1.04 ± 1.73	0.47, 1.62	0.001*
Muscle property					
Knee extension torque (Nm/kg)	1.94 ± 0.62	2.27 ±0.64	0.33 ±0.38	0.19, 0.47	<0.001*
VL passive tension (kPa)	5.93 ± 2.13	6.21 ± 2.33	0.28 ± 2.20	-0.47, 1.04	0.452
RF passive tension (kPa)	10.67 ± 4.20	11.20 ± 3.30	0.53 ± 3.33	-0.62, 1.67	0.357
VMO passive tension (kPa)	4.40 ± 1.01	4.29 ± 0.75	0.11 ±1.05	-0.47, 0.25	0.541

VAS: visual analogy scales, KOOS: Knee Injury and Osteoarthritis Outcome Score, KAM: external knee adduction moment, KFM: external knee flexion moment, VL: vastus lateralis, RF: rectus femoris, VMO: vastus medialis obliquus

4.4.3 Relationship between modulation on pain, symptom, muscle properties, knee kinetics and kinematics

Significant interactions of OA radiographic severity were found between KAM and KOOS ADL (p=0.08), between KFM and VAS pain (p=0.01), between KFM and KOOS symptom (p=0.05). Table 4.3 presents the relationship between modulations on pain, symptom with gait biomechanics in all participants with insignificant interaction. There was marginal association between change of KAM and KOOS pain (r= -0.32, p= 0.07). Change of KAM index was negatively associated with KOOS pain (r= -0.35, p= 0.05) and KOOS symptom (r= -0.43, p= 0.01). It indicated the increase of KAM index was accompanied by improvement of pain and symptom. There also was marginal association between knee flexion excursion and KOOS symptom (r= 0.34, p= 0.06). However no association was found between quadriceps muscle properties and pain or symptom.

The subgroup analysis showed that there was no association between KAM and KOOS ADL in either mild OA or moderate OA. In mild group, change of KFM was positively associated with KOOS symptom (r= 0.53, p= 0.03). In moderate OA, change of KFM was associated with change of VAS pain (r= 0.74, p= 0.01).

Table 4.3 Correlation coefficient between modulations on pain, other symptoms and knee kinetics and kinematics during early stance of gait

	VAS pain	KOOS pain	KOOS symptom	KOOS ADL
Knee kinetics				
External knee adduction moment	-0.22	-0.32	-0.30	-0.18
External knee flexion moment	0.15	0.27	0.36*	0.11
KAM index	-0.18	-0.37	-0.43*	-0.22
Knee kinematics				

Peak knee flexion angle	-0.13	0.23	0.18	0.39*
Knee flexion excursion	-0.07	0.17	0.34	0.25
Quadriceps muscle properties				
Knee extension torque	-0.01	0.13	0	0.11
VL shear modulus	0.26	0.07	0.08	0.09
RF shear modulus	-0.09	0.28	0.13	0.15
VMO shear modulus	0.03	0.15	0.27	0.16

Controlling for gender and knee varus angle and speed for knee kinetics and kinematics
Controlling for gender and knee varus for muscle properties
* p-value < 0.05; **p-value< 0.01

4.4.4 Relationship between modulation on muscle properties and knee flexion motion

Interactions of radiographic severity were found between peak knee flexion angle and knee extension torque (p=0.02), between knee flexion excursion and VL shear modulus (p=0.11). Table 4.4 reveals that when the analyses were conducted in all participants, there was no significant association between quadriceps muscle properties and knee flexion motion in early stance phase. In sub-group analyses, associations were detected between modulation on knee flexion excursion and VL passive tension (r= -0.67, p= 0.01) in participants with mild knee OA but not in those with moderate knee OA (r= 0.04, p= 0.89). Hence, larger improvement on knee flexion excursion was related to a greater reduction in muscle tension of the VL. However, no association could be found in relation to quadriceps strength and knee flexion motion.

Table 4.4 Correlation coefficient between modulation on muscle properties and knee kinematics during gait

	Peak knee flexion angle	Knee flexion excursion
Knee extension torque	-0.01	-0.10
VL shear modulus	0.02	-0.23
RF shear modulus	-0.25	-0.08
VMO shear modulus	0.14	0.01

Controlling for gender, knee varus angle.
* p-value < 0.05; **p-value< 0.01

4.5 DISCUSSION

In individuals with medial knee OA, the therapeutic effects of a six-week exercise-based rehabilitation program on pain and symptoms were related to modulation on knee joint loading and joint angle during gait. More specifically, the amount of increase in KAM index and knee flexion excursion in early stance phase was related to the extent of improvement on pain and symptom. Besides, this is the first study reporting quadriceps passive tension, especially VL, was associated with knee flexion excursion in people with mild knee OA.

Loading on the frontal plane is proposed as one of the key mechanical stimuli aggravating pain in knee OA. Despite the magnitude of KAM being a significant predictor of the likelihood of chronic knee pain (Amin et al., 2004), a negative relationship between KAM and pain intensity had been reported (Hall et al., 2016, Henriksen et al., 2012), which was thought to be a pain avoidance mechanism. The KFM constituted to loading on the sagittal plane has been reported to be associated with the intensity of pain (Boyer et al., 2012). One would expect to see an increase in KAM and decrease in KFM when pain intensity was reduced after the exercise program. However, Ferreira et al. concluded that the beneficial effects of exercise on pain and function was not associated with change of KAM in their meta-analysis (Ferreira et al., 2015). In this study, we used knee alignment as co-variates to minimize the effects of joint structure and alignment on the outcomes. Findings from our study suggested that modulation on pain and joint kinetics was related. The increase of KAM but not KFM was associated with improvement of pain even though it did not reach statistical significant level. This association indicated a pain avoidance mechanism: an increase in KAM would be expected with a reduction in pain. However our finding showed this association when pain intensity was measured by KOOS pain subscale but not by VAS. The KOOS pain subscale included nine questions acquiring self-perceived intensity of pain during resting, active movements and weight-bearing activities. These composite scores would provide more comprehensive information on joint pain, though VAS targeted specifically on the intensity of pain during walking. The reason why no association could be detected between VAS pain and KAM remained unclear.

Besides, findings of this study provided evidence that modulation on KAM index was associated with modulation not only on pain intensity but also on symptom. Greater increase in KAM index was associated with greater improvements in pain and symptoms. These findings suggested an overall avoidance mechanism when reduction in pain and symptom might be associated with the magnitude of loading distribution on the frontal plane. KAM index could be a more sensitive biomechanical parameter in relation to the clinical changes.

Our findings had also revealed intervention-induced modulation on passive muscle tension of the quadriceps was associated with change in knee sagittal kinematics of early stance phase. In participants with mild OA, reduction in VL passive tension was associated with an increase in knee flexion excursion. The vastii muscles control knee flexion during early stance phase of gait cycle (Perry, 2010).VL was the largest muscle head of quadriceps and was major knee extensor with fibers merging into the patellar tendon and contributing to knee extensor mechanism in sagittal plane (Flandry and Hommel, 2011), while VMO was a patellofemoral joint stabilizer primarily (Andrikoula et al., 2006). These findings indicated the importance of muscle passive tension on knee flexion excursion. Besides, we also found increase on knee flexion excursion was related to improvement on symptoms of OA. Therefore, targeting on relieving VL passive tension would be beneficial for improving knee sagittal kinematic in mild knee OA.

The present findings revealed disease severity specific relationships between modulation on passive muscle tension and knee flexion motion in early stance phase. However, we could not delineate any relationship between improvement of quadriceps strength and joint biomechanics during the early stance phase of gait cycle. The muscle strength measured in the present study was the maximal voluntary contraction in an open kinetic chain condition. Two reasons could lead to the insignificant association between change of quadriceps strength and knee flexion motion during gait. First, it did not require maximal quadriceps strength in early stance phase, so that the increase of its strength could have minimal effect on change of knee flexion-extension motion range.

Participants in our study trained using a routine exercise program which was provided in a public rehabilitation center. The program comprised strengthening, balance, neuromuscular control and aerobic exercises. Despite stretching of the hip abductors, quadriceps and hamstrings being performed in the beginning of each session, stretching exercise was not a major component of this exercise program. Therefore, no significant change in passive muscle tension was detected after the 6-week training. If pliability of VL could enhance joint kinematics, then further study incorporating muscle tension release in the exercise program would be warranted to testify its therapeutic effects. Based on the present findings, a disease severity specific exercise program should be designed and implemented for alleviating pain and dysfunction in participants with knee OA.

There are some limitations to this study. Firstly, this was a single arm interventional study which did not have a comparative group trained with a different exercise program. In view the primary goal of this study was to explore the gait biomechanics leading to pain modulation and the physical factors leading to modulation on joint kinetics and kinematics after an exercise rehabilitation program, such a design was deemed reasonable. Having the positive findings in this study, the next step would be to compare this program with another program that has different exercise components. Secondly, the sample size of this study was quite small especially when doing the subgroup analysis thus the power was compromised. Information generated might induce some insight for future studies. Furthermore, the intervention program in this study followed an existing clinical program. Although that program was commonly used in the clinic and proven to be effective, it was not discriminative in the level of disease and pattern of symptoms. Our findings of the different outcomes between the mild and the moderate OA participants suggested future design of the exercise program should be differentiated according to the specific stage of the disease.

4.6 CONCLUSIONS

In conclusion, modulation on gait biomechanics was associated with improvement in pain and symptoms. Modulation on quadriceps passive tension and early stance phase knee flexion excursion were related in mild knee OA. Exercise program targeting to modulate the passive muscle tension of the quadriceps could be proposed, in particular in earlier stage of knee OA.

Chapter 5 Integration of key findings

Chapter 5

5.1 Introduction

Mechanical overloading is detrimental to the knee joint (Felson, 2013, Moyer et al., 2014) and is a trigger for pain (Wluka et al., 2006). The aim of this project was to investigate the relationships between joint alignment, muscle properties, pain, and joint biomechanics during walking in seniors with knee osteoarthritis. A cross-sectional observational study was conducted on 47 senior adults with knee OA and an interventional study was performed amongst thirty subjects to evaluate treatment outcomes after a six-week exercise-based rehabilitation program. In this chapter, main findings on the relationships between joint alignment, muscle properties and intensity of pain on knee kinetics and kinematics during gait, and exercise-induced modulation on knee kinetics and kinematics are presented. Clinical applications arising from these findings will be discussed.

5.2 Joint alignment, muscle properties, and joint biomechanics

Malalignment, particularly knee varus/valgus deformity and its impact on joint biomechanics during gait have been extensively studied in adults with knee OA (Tanamas et al., 2009, Felson et al., 2009). The impact of tibia torsion on knee joint loading and movement during gait has not been explored. Aside from joint alignment, muscle strength was found to be related to stance phase knee flexion excursion (Schmit and Rudolph, 2007). Knowing that passive muscle tension would affect joint motion (Sobolewski et al., 2013) and muscle function (Hessel et al., 2017), it was our intent in this study to assess passive muscle tension and strength of the quadriceps muscle on gait kinematics controlling for joint alignments.

5.2.1 Using state-of-the-art EOS system on quantifying joint alignment in a weight-bearing position

In order to quantify tibial torsion in a weight-bearing position, we used a relatively new technology, the EOS imaging system, to measure lower limb torsional alignment, including tibial torsion and tibiofemoral rotation, with low-dose radiation. The EOS system is valid (Buck et al., 2012b) and had excellent intra-rater reliability on fifteen participants (with $ICC_{Tibia\text{-}torsion} = 0.93$, $ICC_{Tibiofemoral\text{-}rotation} = 0.95$); and the tibial torsion and tibiofemoral rotation angles captured by the EOS system in this study were of similar values as those measured by computed tomography (Bombaci et al., 2011, Buck et al., 2012a, Duparc et al., 2014). The EOS imaging system enabled measurement of lower limb alignment in a more functional position.

5.2.2 Relationships between torsional alignment, knee joint kinetics, and kinematics during gait

Findings from our project indicated significant relationships between tibial torsion and gait biomechanics in participants with radiographic moderate knee OA. More specifically, in pariticpants with radiographic moderate knee OA, larger external tibial torsion was associated with greater KAM and smaller knee flexion excursion (details in Chapter 2) during the early stance phase of the gait cycle. Such associations could not be detected in participants with mild radiographic changes. These findings highlight (1) the importance of joint alignment along the horizontal plane on gait biomechanics and (2) the existence of disease severity specific association. When joint contact pressure of the knee medial compartment had a linear trend of increase within the range from 10° internal tibial torsion to 60° external tibial torsion (Kenawey et al., 2011), modulation on the external tibial torsion might be a strategy in reducing joint contact pressure as well as joint loading and improving joint kinematics during gait in people with moderate OA disease severity.

Cooke et al. (1990) proposed that tibial torsion was a link within the compensatory mechanism for lower limb torsional alignment to neutralize foot progression angle. Toe-out gait, referring to larger outward foot progression, was observed in people with greater external tibial torsion (Hudson, 2016). Toe-in gait leads to a decrease of early stance KAM when people with medial knee OA use toe-in gait as gait modification (Simic et al., 2013, Khan et al., 2017, Shull et al., 2013). Whether the effects would be more profound in people with moderate knee OA awaits further study.

Our study could not delineate relationships between tibiofemoral rotation and early stance knee kinetics and kinematics during gait. During the final 30° of knee extension, the femur rotates medially on the tibia, a movement known as “screw home mechanism” (Hallen and Lindahl, 1966). This rotation stretches the knee cruciate ligaments and provides stability to the knee joint (Meyer and Haut, 2008). This mechanism was altered in people with knee OA (Bytyqi et al., 2014) and disappeared in the advanced stage of knee OA (Hamai et al., 2009). The disrupted screw home mechanism might not only affect joint stability but also knee motion at the end of extension. The coupling path of knee flexion and internal tibiofemoral rotation is determined by bone geometry, and this coupling path varied between knees (Wilson et al., 2000). The bony geometry was altered in varying degrees because of knee degenerative changes among different patients; as a result, the influence of tibiofemoral rotation on knee kinematics and joint loading might be weakened.

5.2.3 Quadriceps muscle properties and joint kinematics

In Chapter 2, we reported significant relationships between passive muscle tension and early stance knee flexion angle in participants with radiographic mild OA. No significant association between quadriceps muscle strength and knee flexion angles was detected. More specifically, in participants with mild knee OA, vastus lateralis shear modulus (an index of muscle passive tension) was negatively related to knee flexion excursion during early stance phase of the gait cycle. The negative association might imply that (1) greater VL passive tension might restrain early stance knee flexion excursion, or (2) greater passive tension was adopted to control knee flexion excursion as a strategy during the stance phase. Such relationship could not be detected in participants with moderate knee OA. Coupling with the above findings on joint alignments and joint kinematics, quadriceps muscle properties seem to induce their impact when knee OA is at an earlier stage with less affected joint structure and alignment. Such information highlights the importance of quadriceps muscle properties on early detection and early management of knee OA.

During the loading response phase of the gait cycle, quadriceps lengthen to decelerate knee flexion and to facilitate smooth transferring of body center of mass to the loading limb (Theologis, 2009). Viscoelasticity of both muscular and passive structure contribute to the eccentric force generation (Hessel et al., 2017). Findings from this project supported such notion. Nevertheless, the relationship could only be established (1) between the vastus lateralis and knee flexion excursion, and (2) in participants with mild radiographic changes. Vastus lateralis, being the largest muscle head of the quadriceps group, accounting for over 30% of total volume (Ema et al., 2017), contributes the most to restrain or control knee motion during the loading response phase. In the interventional study of this PhD project, It was found that the reduction of VL passive tension had a tendency of being associated with an increase of knee flexion excursion in mild knee OA. Since reduced knee flexion excursion was associated with high knee joint loading rate (de Oliveira Silva et al., 2015), modulation on the passive tension of the vastus lateralis might increase early stance knee flexion excursion and could be one of the strategies for prevention of disease progression.

Rectus femoris, being a two-joint muscle across both hip and knee, would contribute to control both hip extension and knee flexion movements. During the pre-swing phase of gait, the muscle head contracts eccentrically to decelerate hip extension and knee flexion motions. Passive tension of the muscle head would increase and restrict knee flexion during the pre-swing and initial swing phase (Fox et al., 2009). Further study is suggested to assess a possible relationship between passive tension of RF and the pre-swing knee flexion angle.

Weakness in the quadriceps muscle of 20-35% was detected in people with symptomatic knee OA when compared with healthy controls (Hassan et al., 2001, Lewek et al., 2004, Slemenda et al., 1997a). During the loading response phase of the gait cycle, active contraction of the quadriceps muscle decelerates knee flexion, modulates loading impact, and maintains stability (Perry, 2010). Deficit in quadriceps muscle strength might lead to fear of knee collapse and result in quadriceps avoidance gait, which is characterized as reduction or complete elimination of knee flexion in the loading response phase. Indeed, weaker quadriceps muscle strength was found to be related to smaller early stance phase knee flexion excursion in individuals with moderate and severe knee OA (Farrokhi et al., 2015b). Unfortunately, relationship between quadriceps muscle strength and early stance phase knee flexion angles in knee OA could not be established from present study.

5.2.4 Knee joint loading and pain in knee OA

Pain and functional limitations are the common concerns for people with knee OA (Felson, 2005). Mechanical overloading is one of the factors associated with OA-related pain (Wluka et al., 2006). In view of the multi-factorial causes of mechanical overloading, we adopt a path analysis model to delineate a possible relationship between stance phase joint loading and intensity of pain.

In Chapter 3, we reported a negative relationship between magnitude of KAM and intensity of pain through the mediation of KFM. The relationship between KAM and pain was established via the negative relationship between joint loadings along the frontal and sagittal planes. A significant negative relationship was delineated between KAM index and intensity of pain.

Abnormal knee joint loading accelerates destruction of joint tissues and triggers pain. Structural changes, including those affecting the bone marrow (Beckwée et al., 2015, Bennell et al., 2010a, Vanwanseele et al., 2010b) and meniscus (Vanwanseele et al., 2010b, Davies-Tuck et al., 2008), and effusion-synovitis (Atkinson et al., 2021) were observed in people with knee OA and are closely associated with the incidence and aggravation of knee pain (Driban et al., 2013, Felson et al., 2001, Zhang et al., 2011). KAM is the surrogate of abnormal knee joint loading distribution. Greater KAM indicates a greater portion of loading at the medial to lateral part of the knee joint. Our results were consistent with previous reports that greater KAM was associated with lower intensity of self-reported pain， which was considered as a pain avoidance mechanism (Henriksen et al., 2012, O'Connell et al., 2016, Hurwitz et al., 2002, Hurwitz et al., 2000).

Furthermore, we found that the relationship between KAM and pain intensity existed through the mediation of KFM. The magnitude of KAM and KFM were negatively related. Greater magnitude of KAM was associated with lower magnitude of KFM; lower magnitude of KAM was associated with greater magnitude of KFM. KAM and KFM occurred nearly simultaneously at about 23% of total gait cycle (Manal et al., 2015). During toe-in or toe-out gait, changes in the magnitude of KAM were coupled with opposite changes in the magnitude of KFM (Simic et al., 2013). Coupling of KAM and KFM during the early stance phase of gait could be a load-sharing strategy between the frontal and sagittal planes such that the impact at the medial-to-lateral cartilage could be reduced, and thereby, there would be less stress at the painful structures. Re-distribution of loading from the sagittal to the frontal planes was observed in people with knee OA within five-year follow-up; the transition co-existed with medial-to-lateral cartilage disruption (Asay et al., 2018). These authors proposed that KAM index represented the relative contribution of KAM and KFM to total knee joint moment and was a crucial predictor of knee articular cartilage disruption (Asay et al., 2018, Erhart-Hledik et al., 2019).

More importantly, our study delineated a negative relationship between KAM index and both pain intensity and symptom. This negative relationship indicated that relatively greater contribution of KAM to total knee moment was associated with lower intensity of pain and symptom or vice versa. These relationships were stronger than KAM or KFM were alone. It implied that KAM index could be used as a better biomechanical marker in relation to clinical changes.

5.2.5 Knowledge generated from the cross-sectional study

The key findings of the cross-sectional study are listed below.

1) The relationships between joint alignment, quadriceps muscle properties and knee biomechanics in early stance phase were specific to OA radiographic severity.
2) Tibial torsion and knee joint biomechanics were related in participants with moderate knee OA: external tibial torsion was associated with early stance phase KAM and knee flexion excursion.
3) Passive muscle tension of vastus lateralis was related to early stance knee flexion excursion in participants with mild knee OA.
4) KAM was negatively associated with pain intensity through mediation of KFM.
5) KAM and KFM were negatively related.
6) KAM index was negatively related to pain intensity.

Based on these discoveries, an interventional study was conducted to further establish the relationship between quadriceps muscle properties, gait biomechanics and pain.

5.2.6 Exercise-induced modulation on joint loading and joint pain

Exercise-based intervention is recommended for managing OA-related pain (Fernandes et al., 2013a). In Chapter 4, exercise-induced modulation on joint biomechanics, and intensity of pain were explored. The exercise program was targeted at minimizing joint loading through the enhancement of joint stabilization, and movement and gait re-training (Farrokhi et al., 2013). This pre-post interventional study enabled a better understanding of the relationship between modulation on joint loading and intensity of pain.

Our findings demonstrated that exercise-induced modulation in pain intensity was related negatively to modulation on KAM. These findings suggested that there was a greater increase in KAM in participants with greater reduction in pain intensity. Therefore, exercise-induced modulation on pain intensity and joint loading was related. These findings echoed with the observation from the cross-sectional study: both KAM were related to pain intensity in knee OA. Indeed, modulation on KAM and KFM was negatively related. Greater reduction in KAM was associated with a greater increase in KFM. Exercise-induced modulation on pain might relate to loading re-distribution between the frontal and sagittal plane.

Besides, findings of this study provided evidence that modulation on KAM index was also associated with modulation on pain intensity. In addition, modulation on KAM index had a negative correlation with changes in symptom. Hence, greater reduction in KAM index was associated with greater improvements in pain and symptoms. These findings suggested that reduction in pain and dysfunctions might be associated with re-distribution of joint loading from the frontal to the sagittal plane. KAM index could be a more sensitive biomechanical parameter in relation to the clinical change.

In the cross-sectional study, we observed a negative relationship between vastus lateralis passive tension and early stance knee flexion excursion in participants with mild knee OA. The interventional study also revealed a similar relationship between changes of vastus lateralis passive tension and knee flexion excursion in mild OA; besides, it should also be noted that no significant change of knee flexion excursion resulted from the current exercise rehabilitation program. Exercises from the COME program included static stretching and range of motion exercise; however, the main foci of the program were on muscle strength and neuromuscular control. The findings from present study provided clues for further investigation on the effect of VL passive tension on knee flexion motion in early stance phase.

5.3 Limitations and suggestions for future studies

In this project, we recruited participants with mild to moderate knee OA from the Department of Traumatology and Orthopaedics of Queen Mary Hospital. It was our intention to exclude people with advanced knee OA because of its predicted inferior results from exercise intervention. The destruction of joint structure (Hunter et al., 2005), joint malalignment (Cerejo et al., 2002), pain intensity (Murphy et al., 2011), and functional limitation (Jordan et al., 1997) would be associated with knee OA severity. Thus, our results could only be generalized to people with mild to moderate knee OA.

Second, the sample size in both two studies was relatively small. The subgroup analyses might not yield sufficient statistical power, especially in the moderate OA group. Based on the findings of current study, the trend of association between alignment, quadriceps muscle properties and knee biomechanics in different OA severity groups was showed and provided information for further study.

Third, knee joint loading was assessed along the frontal and sagittal planes. Though the external knee rotation moment is also a component of total knee joint moment, it provided minimal contribution to the total joint moment at the stance phase of the gait cycle (Asay et al., 2018). In addition, using the current Plug-in-gait lower limb model to estimate the external knee rotation moment would be relatively low in accuracy (Duffell et al., 2014). Therefore, only KAM and KFM were included in this project.

Fourth, quadriceps passive tension was measured in a static status with an ultrasound shear-wave elastography system. To our knowledge, measuring real-time passive viscoelastic properties of skeletal muscle *in vivo* had not been reported in clinical study due to technological limitations. The ultrasound shear-wave elastography estimated the shear modulus of skeletal muscle by assuming linearity and pure elasticity of material property of skeletal muscle. This estimation neglected non-linearity, viscoelasticity, and anisotropy of skeletal muscle (Hug et al., 2015). Though several assumptions were made, shear modulus quantified by the ultrasound shear-wave elastography system could reflect elasticity of skeletal muscle (Hug et al., 2015) and be utilized in clinical settings. Only the superficial muscle heads of quadriceps were measured in this project. Vastus intermedius is located beneath rectus femoris, and muscle belly of vastus intermedius muscle can be too deep for the ultrasound shear-wave elastography system to estimate reliable shear modulus; therefore, its passive tension was not included in the current study.

We used an interventional study to further explore the relationship between knee joint biomechanics and pain intensity, as well as to explore the relationship between modulation on muscle properties and joint biomechanics. Despite the fact that associations between modulation on joint loading and pain intensity were established, the association between passive muscle tension and knee kinematics needed further study to substantiate. Nowadays, the commonly-used exercise programs focus on muscle strength, dynamic motion control, and altering gait pattern (Skou and Roos, 2017). Future studies that are specifically designed for changing joint biomechanics and quadriceps passive tension are warranted.

5.4 Significance of the project and its clinical application

Knee osteoarthritis is a highly prevalent musculoskeletal disorder in the older population globally. The consequences of knee OA, including pain, mobility disability, reduction of quality of life, decrease of social participation, and surgery, have great impact on both individual and society. It burdens public health resources heavily and accounts for lifelong medical costs for individuals.

The significance of this project stands in the potential benefit of providing comprehensive investigation on the potential factors related to joint loading and joint motions using a cross-sectional study and a prospective interventional study. The new information would underpin new management strategies for people with knee OA.

1) Excessive external tibia torsion could be a detrimental factor to knee biomechanics in moderate knee OA. Special attention should be given to patients with excessive external tibial torsion in biomechanical management.
2) Passive property of quadriceps, particularly vastus lateralis, involves the control of sagittal knee kinematics in mild knee OA. Early detection of high vastus lateralis passive tension and early intervention are essential in order to maintain correct gait biomechanics. Muscle flexibility programs targeting the vastus lateralis might enhance improvement of knee kinematics.
3) Knee joint loading distribution between frontal and sagittal plane can be introduced as a biomechanical marker that is more sensitive to pain and symptom.
4) Rehabilitation programs need to be specific to OA disease severity so as to provide clinical and biomechanical benefits to patients.

Chapter 6 Conclusions

Joint biomechanics is one of the crucial factors in the pathogenesis of knee OA and is associated with the onset of OA-related pain. This project aimed to comprehensively investigate the impact of joint alignment, muscle properties, and pain intensity on joint loading and motion during walking in seniors with knee osteoarthritis.

This project included a cross-sectional and a prospective interventional study on seniors with clinical and radiographic knee OA. Our findings from the cross-sectional study indicated that malalignment along the horizontal plane was associated with gait biomechanics in people with moderate knee OA. More specifically, external tibial torsion was negatively related to early stance phase external knee adduction moment and knee flexion excursion during gait in participants with moderate knee OA. Such findings highlight the importance of alignment along the horizontal plane in addition to varus/valgus alignment along the frontal plane. Further study might explore factors leading to excessive external tibial torsion.

Our second main finding was regarding the association between quadriceps passive tension and knee kinematics in people with mild knee OA. In these participants, passive tension of vastus lateralis was negatively associated with early stance phase knee flexion excursion. Nevertheless, no relationship between quadriceps strength and gait kinematics was established. These findings highlight the role of passive muscle properties on knee sagittal kinematics during the earlier stage of OA disease. Our interventional study provided further evidence that it was highly possible that exercise-induced modulation on passive tension of vastus lateralis was related to changes in early stance phase knee flexion excursion in mild knee OA. Future preventive and management programs for knee OA might include strategies to vastus lateralis passive tension.

In this study we also observed coupling of joint loading along the frontal and sagittal planes during the early stance phase of gait. First, we observed a significant relationship between external knee adduction and knee flexion moments from the cross-sectional observational study; and from the interventional study, intervention-induced modulation on KAM and KFM were also negatively related. Such findings highlight the importance of assessing the magnitudes of loading along the frontal and sagittal planes as well as the relative loading between the two planes (KAM index). Indeed, from the cross-sectional study, KAM was found to be negatively associated with pain intensity through the mediation of KFM, and KAM index was found to be negatively related to pain intensity. After six weeks of exercise intervention, modulation on KAM was also associated with changes in pain, while modulation on KAM index was related to pain and symptom changes. Thus, joint sharing along the frontal and sagittal planes might provide more information on OA-related pain and symptom than joint loading along either the frontal or sagittal plane.

We concluded from the above findings that joint alignment along the horizontal plane, passive quadriceps muscle tension, and pain were associated with gait biomechanics in people with knee OA. The relationships were specific to OA radiographic severity. Future rehabilitation programs might attend to passive quadriceps tension, particularly during the early stage of disease, as well as strategies to manage external tibial torsion during the moderate stage of OA disease. The effectiveness of such programs would be assessed on their impact on load sharing between the frontal and sagittal planes as well as its clinical signs and symptoms.

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APPENDICES

Appendix I Ethical approval

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學

To Fu Siu Ngor (Department of Rehabilitation Sciences)

From TSANG Wing Hong Hector, Chair, Departmental Research Committee

Email rshtsang@ Date 14-Apr-2017

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 02-May-2016 to 30-Apr-2019:

Project Title: The effect of altered muscle stiffness and tibia torsion on joint loading in people with knee osteoarthritis

Department: Department of Rehabilitation Sciences

Principal Investigator: Fu Siu Ngor

Project Start Date: 02-May-2016

Reference Number: HSEARS20170406003

You will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Human Subjects Ethics Sub-committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

TSANG Wing Hong Hector Chair

Departmental Research Committee

Appendix II Information consent (English version)

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project title: **The effect of altered muscle stiffness and tibia torsion on joint loading in people with knee osteoarthritis**

Investigator(s): Name, highest academic degree, and position of all investigators including student(s) of this project must be provided.

FU Siu Ngor, PhD. Associate Professor. Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

Lai Chris, Wai-Keung, PhD, Assistant Professor. Department of Health technology and Informatics, The Hong Kong Polytechnic University

Huang Chen, PhD student. Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

<u>Project information:</u>

The overall aim of this project is to determine the role of passive muscle mechanical properties and tibial torsion on knee loading during walking.

You will have 3 assessments.

(1) You will be positioned in supine lying. Your knee will be passively move from 0° to maximal flexion for 6 times. During each movement, an ultrasound transducer will be used to estimate the stiffness of the 3 superficial heads of the thigh muscle.

(2) You will be required to walk along a 8-meter walkway for 10 times. Before the walk, 16 reflective balls will be positioned on your lower legs. Your walking pattern will be captured by 8 cameras.

(3) You will be in standing position while perpendicular biplanar radiographs will be conducted.

The evaluation will be conducted at the Duchess of Kent Children Hospital. The total time will be about 1.5 hours

The evaluation will not cause any pain, tiredness nor radiation on your body. The findings from this project enable better understandings on increased joint loading in subjects with knee osteoarthritis. New strategies can be proposed for reducing joint loading on these individuals.

Consent:

I, ___________________________, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the chief investigator, Dr __Amy Fu__ at telephone 27666726_ for any questions about this study. If I have complaints related to the investigator(s), I can contact Ms Vangie Chung, Secretary of the Departmental Research Committee, at 2766 4329. I know I will be given a signed copy of this consent form.

Signature (subject): Date:

Signature (witness): Date:

Appendix III Information consent (Chinese version)

香港理工大學康復治療科學系科研同意書

科研題目：

肌肉彈性與脛骨扭轉的改變對膝關節炎患者關節載荷的影響

科研人員：

符少娥博士，副教授，香港理工大學康復治療科學系

賴偉強博士，助理教授，香港理工大學醫療科技及資訊學系

黄琛女士，博士研究生，香港理工大學康復治療科學系

科研內容：

這項研究的主要目的在於探究肌肉被動機械性質與脛骨扭轉在膝關節炎患者步行時對關節載荷的影響。

您將接受三項評估：

1. 您將保持仰臥姿勢，我們將讓你的膝關節從完全伸直被動活動至最大屈曲角度，共計六次。在每次的被動中，超聲波探頭將被放置于您股四頭肌的三個淺層頭上來測量肌肉彈性。

2. 您將在一條八米長的走道上完成十次步行測試。在開始步行前，十六顆反光小球將被黏貼在您的腿上。所有的步行數據將被 8 台攝像機記錄下來。

3. 您將保持站立的姿勢來完成一項雙平面影像學檢查。

所有的評估將在根德公爵夫人兒童醫院進行，大約需時 1.5 小時。

對項目參與人仕和社會的益處：

這項研究能幫助我們更好的理解關節載荷對膝關節炎患者的影響。由此，我們能夠更加有效的擬定治療方案來減小關節載荷對此類患者病情的加劇。

潛在危險性：

該研究包含的三項評估將不會對您的身體引起任何疼痛、疲勞及輻射損傷。

同意書：

本人____________已瞭解此次研究的具體情況。本人願意參加此次研究, 本人有權在任何時候、無任何原因放棄參與此次研究, 而此舉不會導致我受到任何懲罰或不公平對待。本人明白參加此研究

課題的潛在危險性以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片不會出現在任何出版物上。

本人可以用電話 27666726 來聯繫此次研究課題負責人， 符少娥 博士。若本人對此研究人員有任何投訴，可以聯繫鍾小姐（部門科研委員會秘書），電話：2766 4329。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）：______________ 日期：

簽名（證人）： ______________ 日期：

Appendix IV Clinical trial registration

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: March 1, 2021

ClinicalTrials.gov ID: NCT03628508

Study Identification

Unique Protocol ID: HSEARS20170406003
Brief Title: Muscle Property, Alignment and Joint Loading in People With Knee Osteoarthritis
Official Title: External Tibia Torsion and Passive Muscle Stiffness of Quadriceps as Two Important Contributors of Joint Loading During Walking in People With Knee Osteoarthritis
Secondary IDs:

Study Status

Record Verification: August 2018
Overall Status: Completed
Study Start: March 1, 2017 [Actual]
Primary Completion: December 31, 2019 [Actual]
Study Completion: December 31, 2019 [Actual]

Sponsor/Collaborators

Sponsor: The Hong Kong Polytechnic University
Responsible Party: Sponsor
Collaborators: Queen Mary Hospital, Hong Kong

Oversight

U.S. FDA-regulated Drug: No
U.S. FDA-regulated Device: No

- Page 1 of 9 -

U.S. FDA IND/IDE: No
Human Subjects Review: Board Status: Approved
Approval Number: HSEARS20170406003
Board Name: Human Subject Ethics Sub-committee
Board Affiliation: The Hong Kong Polytechnic University
Phone: 3400 3635
Email: rohsesc@[redacted]
Address:

Research Office, The Hong Kong Polytechnic University
Data Monitoring: No
FDA Regulated Intervention: Yes
Section 801 Clinical Trial: Yes

Study Description

Brief Summary: Knee osteoarthritis (KOA) is a common chronic painful musculoskeletal condition among older adults. It poses great challenge to the health care system due to its inability to be cured. Understanding factors associated with disease progression in KOA should assist the development of novel prevention/rehabilitation strategies. This study investigate factors including muscle properties, lower limb alignment and joint loading in patients with knee osteoarthritis before and after a six-week exercise program.
Detailed Description:

Conditions

Conditions: Osteoarthritis, Knee
Keywords: muscle tension
alignment
knee osteoarthritis
loading

Study Design

Study Type: Interventional
Primary Purpose: Treatment
Study Phase: N/A
Interventional Study Model: Single Group Assignment

- Page 2 of 9 -

Number of Arms: 1
Masking: None (Open Label)
Allocation: N/A
Enrollment: 40 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Exercise Six-week exercise including stretching, strengthening, endurance and gait modification	Exercise Comprehensive exercise program including strengthening, stretching, gait modification etc.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 50 Years
Maximum Age: 80 Years
Sex: All
Gender Based: No
Accepts Healthy Volunteers: Yes
Criteria: Inclusion Criteria:

1. Age between 50-80
2. having radiographic tibiofemoral joint OA in the medial compartment defined as Kellgren and Lawrence grade = 2 to 3
3. having medial knee pain on most days of the month
4. having a minimum average pain score of 2 on an 11-point numerical rating scale in the past week while walking

Exclusion Criteria:

1. having lateral tibiofemoral compartment osteophytes greater than the medial side.
2. having undergone intra-articular corticosteroid injection or knee surgery to either knee within the past 3 months
3. having a systemic arthritic condition (e.g., rheumatoid arthritis)
4. having a knee joint replacement or high tibial osteotomy in the past
5. having any other muscular, joint or neurological condition influencing lower limb function
6. unable to walk unaided
7. having low back, hip, ankle or foot pain > 3 on numerical rating scale

8. having a body mass index (BMI) >36 kg/ m2

Contacts/Locations

Central Contact Person: Chen Huang, MS
Telephone: 27666713
Email: cece.huang@[redacted]

Central Contact Backup:

Study Officials: Siu Ngor Fu, PhD
Study Principal Investigator
The Hong Kong Polytechnic University

Locations: **Hong Kong**
Queen Mary Hospital
Hong Kong, Hong Kong
Contact: Division of Joint Replacement Surgery

IPDSharing

Plan to Share IPD: No

References

Citations:
Links:
Available IPD/Information:

Documents

Study Protocol and Statistical Analysis Plan
Document Date: July 27, 2020
Uploaded: 02/24/2021 22:53

Informed Consent Form
Document Date: July 27, 2020
Uploaded: 02/24/2021 22:53

Study Results

Participant Flow

Reporting Groups

	Description
Exercise	Six-week exercise including stretching, strengthening, endurance and gait modification Exercise: Comprehensive exercise program including strengthening, stretching, gait modification etc.

Overall Study

	Exercise
Started	40
Completed	39
Not Completed	1
Lost to Follow-up	1

Baseline Characteristics

Reporting Groups

	Description
Exercise	Six-week exercise including stretching, strengthening, endurance and gait modification Exercise: Comprehensive exercise program including strengthening, stretching, gait modification etc.

Baseline Measures

		Exercise
Overall Number of Participants		40
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	40 participants
		63 (6)

		Exercise
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	40 participants
	Female	29 72.5%
	Male	11 27.5%
Race and Ethnicity Not Collected [1] Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	0 participants
		---
		[1] Measure Analysis Population Description: Race and Ethnicity were not collected from any participant.
Region of Enrollment Measure Type: Number Unit of measure: participants	Number Analyzed	40 participants
Hong Kong		40

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change of External Knee Adduction Moment as Assessed by Visual Motion Analysis System
Measure Description	External knee moment in the frontal plane during early stance phase of walking
Time Frame	At baseline and one week after intervention

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Exercise	Six-week exercise including stretching, strengthening, endurance and gait modification Exercise: Comprehensive exercise program including strengthening, stretching, gait modification etc.

Measured Values

	Exercise
Overall Number of Participants Analyzed	40
Change of External Knee Adduction Moment as Assessed by Visual Motion Analysis System Mean (Standard Deviation) Unit of measure: Nm/kg	0.50 (0.13)

2. Secondary Outcome Measure:

Measure Title	Change of Pain Severity Score as Assessed by Knee Injury and Osteoarthritis Outcome Score
Measure Description	Pain intensity measured by the pain subscale of Knee injury and Osteoarthritis Outcome Score (KOOS). The minimum value is 0 and maximum value is 100. The higher scores mean a better outcome.
Time Frame	At baseline and one week after intervention
Anticipated Reporting Date	December 2020

Outcome Measure Data Not Reported

3. Secondary Outcome Measure:

Measure Title	Tibial Torsion as Assessed by X-ray Imaging
Measure Description	The angle between tibial and femur in the transverse plane
Time Frame	At baseline

Outcome Measure Data Not Reported

4. Secondary Outcome Measure:

Measure Title	Change of Young's Modulus of Quadriceps as Assessed by Ultrasound Elastography
Measure Description	Young's modulus by ultrasound elastography
Time Frame	At baseline and one week after intervention

Outcome Measure Data Not Reported

Reported Adverse Events

Time Frame	6 weeks since start of exercise program 1 year after finishing the exercise program
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Exercise	Six-week exercise including stretching, strengthening, endurance and gait modification Exercise: Comprehensive exercise program including strengthening, stretching, gait modification etc.

All-Cause Mortality

	Exercise
	Affected/At Risk (%)
Total All-Cause Mortality	0/40 (0%)

Serious Adverse Events

	Exercise
	Affected/At Risk (%)
Total	0/40 (0%)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Exercise
	Affected/At Risk (%)
Total	0/40 (0%)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:
All Principal Investigators ARE employed by the organization sponsoring the study.

Results Point of Contact:
Name/Official Title: Dr Amy Fu
Organization: The Hong Kong Polytechnic University
Phone: 8522766 6726
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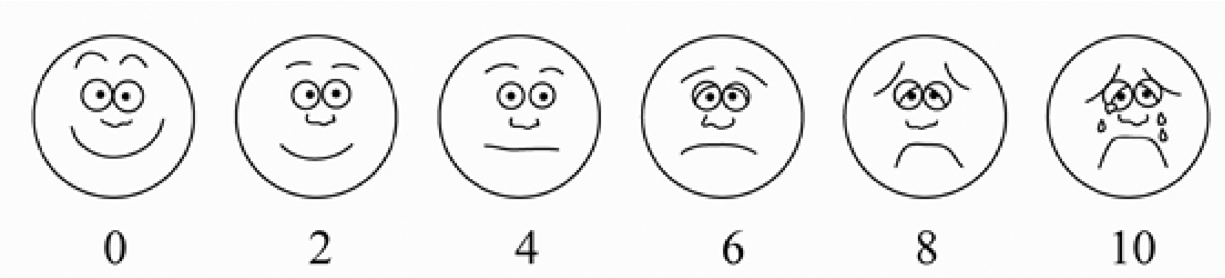
Appendix V Pain assessment form

疼痛評估

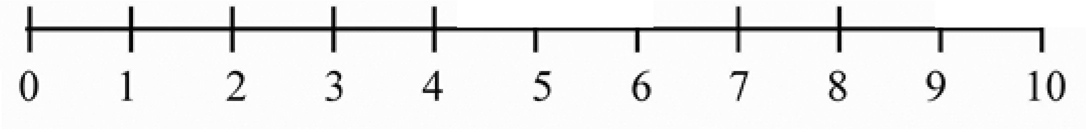
請根據目前您膝關節在過去一個月内的疼痛程度在標尺上做下記號：

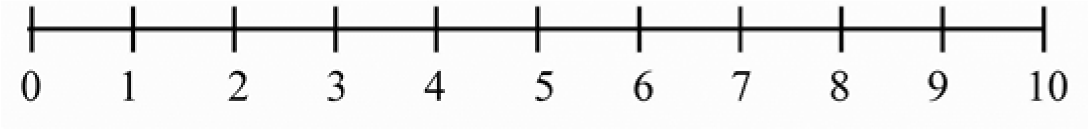


走路：

完全不痛　中等痛　不能忍受的痛痛

左腿



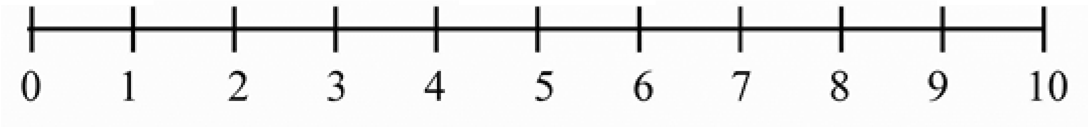


右腿

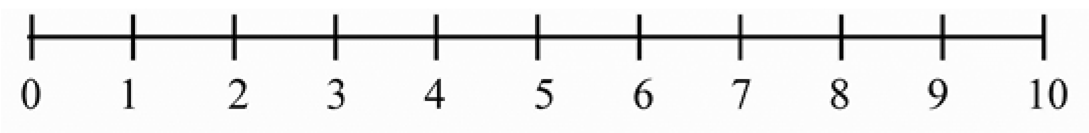
上落樓梯：

完全不痛　中等痛　不能忍受的痛痛

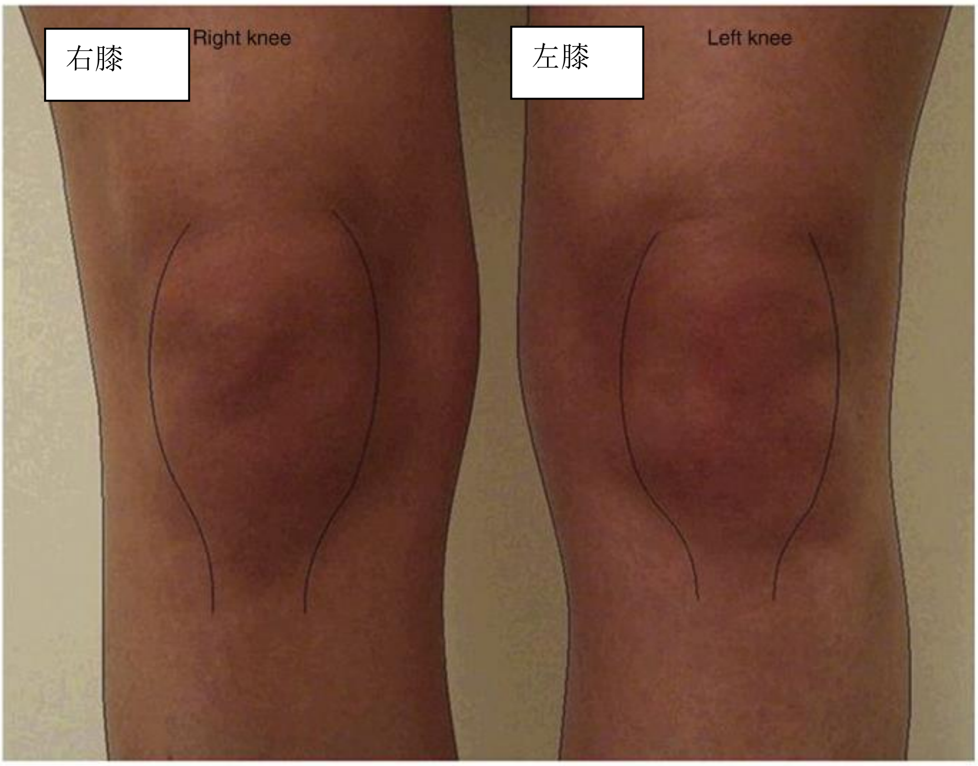
左腿



右腿



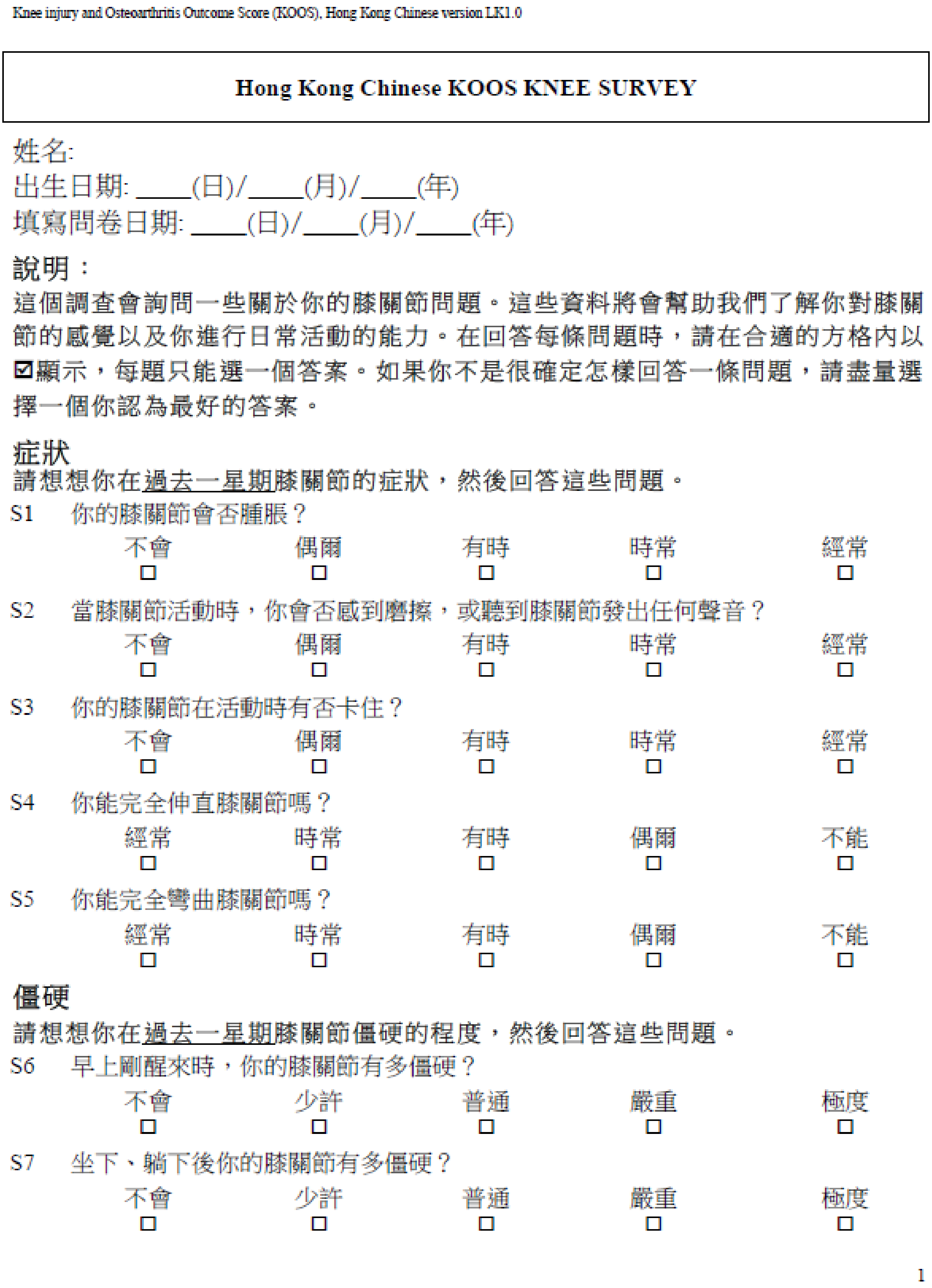
請在下面圖在用“x”標示出您膝痛的位置：



如果你覺得左膝後面有疼痛，請在橫線上畫勾

如果你覺得右膝後面有疼痛，請在橫線上畫勾

Appendix VI Knee injury and Osteoarthritis Outcome Score (Hong Kong Chinese version)



Knee injury and Osteoarthritis Outcome Score (KOOS), Hong Kong Chinese version LK1.0

Hong Kong Chinese KOOS KNEE SURVEY

姓名:
出生日期: ____(日)/____(月)/____(年)
填寫問卷日期: ____(日)/____(月)/____(年)

說明：

這個調查會詢問一些關於你的膝關節問題。這些資料將會幫助我們了解你對膝關節的感覺以及你進行日常活動的能力。在回答每條問題時，請在合適的方格內以☑顯示，每題只能選一個答案。如果你不是很確定怎樣回答一條問題，請盡量選擇一個你認為最好的答案。

症狀

請想想你在過去一星期膝關節的症狀，然後回答這些問題。

S1　你的膝關節會否腫脹？

不會 □　偶爾 □　有時 □　時常 □　經常 □

S2　當膝關節活動時，你會否感到磨擦，或聽到膝關節發出任何聲音？

不會 □　偶爾 □　有時 □　時常 □　經常 □

S3　你的膝關節在活動時有否卡住？

不會 □　偶爾 □　有時 □　時常 □　經常 □

S4　你能完全伸直膝關節嗎？

經常 □　時常 □　有時 □　偶爾 □　不能 □

S5　你能完全彎曲膝關節嗎？

經常 □　時常 □　有時 □　偶爾 □　不能 □

僵硬

請想想你在過去一星期膝關節僵硬的程度，然後回答這些問題。

S6　早上剛醒來時，你的膝關節有多僵硬？

不會 □　少許 □　普通 □　嚴重 □　極度 □

S7　坐下、躺下後你的膝關節有多僵硬？

不會 □　少許 □　普通 □　嚴重 □　極度 □

疼痛

P1 你多常感到膝痛？

從不	每月一次	每週一次	每日一次	經常
□	□	□	□	□

過去一星期，你在進行以下活動時會感到什麼程度的痛楚？

P2 以膝關節為中心扭動或轉動身體

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

P3 完全伸直膝關節

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

P4 完全彎曲膝關節

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

P5 在平地步行

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

P6 上或下樓梯

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

P7 晚上就寢

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

P8 坐下或躺下

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

P9 挺直站立

沒有痛楚	輕微疼痛	頗為疼痛	非常疼痛	極度疼痛
□	□	□	□	□

日常生活

過去一星期，你在進行以下活動時膝關節使你感到有多困難？

A1 下樓梯

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

過去一星期，你在進行以下活動時膝關節使你感到有多困難？

A2　上樓梯

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A3　從坐姿站起

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A4　站立

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A5　彎腰至地／在地上檢起物品

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A6　在平地步行

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A7　上車／下車

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A8　逛街購物

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A9　穿襪子／絲襪

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A10　起床

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A11　脫掉襪子／絲襪

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A12　躺在床上 （轉身，維持膝關節姿勢）

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

過去一星期，你在進行以下活動時膝關節使你感到有多困難？

A13 進出浴缸

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A14 坐下

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A15 坐上／離開坐廁

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A16 做粗重的家務 （剷雪、擦地等）

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

A17 做輕巧的家務 （煮食、除塵等）

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

運動與休閒

過去一星期，你在進行以下活動時膝關節有否使你感到困難？

SP1 蹲坐

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

SP2 跑步

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

SP3 跳躍

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

SP4 轉動／扭動受傷的膝關節

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

SP5 跪下

沒有困難	少許困難	頗大困難	非常困難	極大困難
□	□	□	□	□

膝關節對生活質量的影響

Q1　你多常注意到你的膝關節問題？

從不	每月一次	每星期一次	每日一次	經常
□	□	□	□	□

Q2　你有否改變生活模式來避免一些有機會傷及膝關節的活動？

沒有改變	少許改變	頗大改變	很大改變	完全改變
□	□	□	□	□

Q3　你是否對你的膝關節缺乏信心？

完全沒有	少許	普通	嚴重	極度
□	□	□	□	□

Q4　總括來說，你的膝關節對你的生活造成多大影響？

完全沒有	少許	頗大	非常大	極大
□	□	□	□	□

～非常感謝您完成了這份調查中所有的問題～