Clinical and Biomechanical Effects of the Traditional Chinese Medical Treatments in Individuals with Medial Knee Osteoarthritis

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Clinical and Biomechanical Effects of the Traditional Chinese Medical Treatments in Individuals with Medial Knee Osteoarthritis

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Abbreviation Index

Osteoarthritis	OA
Activities of daily living	ADL
World Health Organization	WHO
Years lost to disability	YLD
Bone mineral density	BMD
Range of motion	ROM
National Institute for Health and Care Excellence	NICE
Gross national product	GNP
Non-steroidal anti-inflammatory drugs	NSAID
Paracetamol and cyclo-oxygenase 2	COX-2
Venous thromboembolism	VTE
Ground reaction force	GRF
Manual therapy	MT
Complementary and alternative medicine	CAM
Traditional Chinese medicine	TCM
Western Ontario and McMaster Universities Osteoarthritis Index	WOMAC
Chinese herbal	CH
Randomized controlled trial	RCT
Acupuncture treatment	AT
Chinese massage	CM
Visual analog scale	VAS
External knee adduction moment	EKAM
Control group with neutral flat insole	CN
Computerized tomography	CT
Magnetic resonance imaging	MRI
American College of Rheumatology	ACR

National Health Education Standards	NHES
Body mass index	BMI
Total knee replacement	TKA
Menopausal hormone therapy	MHT
Estrogen replacement therapy	ERT
Load-bearing axis	LBA
Hip-knee-ankle angle	HKA
Femoral mechanical	FM
Tibial mechanical	TM
Knee adduction angular impulse	KAAI
Anterior cruciate ligament	ACL
Posterior cruciate ligament	PCL
Vastus lateralis	VL
Medial hamstrings	MH
Tibialis anterior	TA
Medial gastrocnemius	MG
Semimembranosus	SM
Vastus medialis	VM
Lateral gastrocnemius	LG
Lateral hamstring	LH
Center of mass	CM
Transcutaneous electrical nerve stimulation	TENS
Lateral wedge insole	LWI
Journal of the American Medical Association	JAMA
Backward walking exercise	BWE
Centre of pressure	COP
American Academy of Orthopaedic Surgeons	AAOS
Chinese Association for Research and Advancement of Chinese Medicine	CRACM

Fufang Nanxing Zhitong Gao	FNZG
5-Lipoxygenase	5-LOX
Cartilage oligomeric matrix protein	COMP
Hyaluronic acid	HA
Malondialdehyde	MDA
Myeloperoxidase	MPO
Interleukin-1 beta	IL-1β
SiMiaoFang	SMF
Matrix metalloproteinases	MMPs
Osteoarthritis Research Society International	OARSI
Electrical acupuncture	EA
Laser acupuncture	LA
Manual acupuncture	MA
Functional magnetic resonance imaging	fMRI
Helen Hayes	HH
European league against rheumatism	EULAR
National Health Service	NHS
Swedish massage	SM
Aromatherapy massage	AM
Synovia superoxide dismutase	SOD
Nitric oxide	NO
Direct Transmission Systems	DTS
Global Coordinate System	GCS
Anterior superior iliac spine	ASIS
Posterior superior iliac spine	PSIS
Biceps femoris	BF
Semitendinosus	ST
Surface Electromyography for the Non-Invasive Assessment of Muscles	SENIAM

Maximal voluntary isometric contraction	MVIC
Degrees-of-freedom	DOF
Calibrated Anatomical System Technique	CAST
Local coordinates system	LCS
Right heel strike	RHS
Left heel strike	LHS
Right toe off	RTO
Left toe off	LTO
Interactive Operating System	IOS
Intra-class correlation coefficient	ICC
Standard error of the measurement	SEM
Minimal detectable change	MDC
Standard deviation	SD
Peak knee flexion angle at initial contact	(PKF at IC)
Peak knee flexion angle at early stance phase	PKF at ES
Knee sagittal plane ROM at stance phase	Knee_ROM_X at SP
Peak knee adduction angle at stance phase	PKADD at SP
Peak knee abduction angle at stance phase	PKABD at SP
Knee frontal plane ROM at stance phase	Knee_ROM_Y at SP
Peak knee internal rotation angle at stance phase	PKIR at SP
Peak knee External rotation angle at stance phase	PKER at SP
Knee transverse plane ROM at stance phase	Knee_ROM_Z at SP
Peak knee flexion moment	KFM
Peak knee extension moment	KEM
Peak knee internal rotation moment	KIRM
Peak knee external rotation moment	KERM
First peak of GRF	1st GRF
Second peak of GRF	2nd GRF
Body weight	BW

Height	Ht
Variance ratio	VR
Coefficient of multiple correlations	CMC
China State Food and Drug Administration	SFDA
Analysis of variance	ANOVA
Nonsteroidal anti-inflammatory drug	NASID
Food and Drug Administration	FDA

List of seminars

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Abstract

Background: Knee otesoarthritis (OA) is the most common of the arthritises, affecting an estimated over 300 million people worldwide. Traditional Chinese Medicine (TCM) therapies have been widely used in the management of knee OA in China, however, there has been a lack of studies evaluated the effects of TCM therapies on clinical and biomechanical outcomes in individuals with knee OA. This thesis was designed to identify the clinical and biomechanical effects of the Chinese herbal (CH) patch, acupuncture treatment (AT), and Chinese massage (CM) in comparison with a control group with neutral flat insole (CN), where the results could help to improve the understanding of both clinical and biomechanical effects of the different TCM therapies in the management of knee OA.

Methods: To accomplish this research, we preformed several trials; a) test-retest reliability studies on both healthy individuals and individuals with medial knee OA were conducted to determine the reliability of the outcome measures and the minimal clinically important difference for the future study; b) sixty participants with medial knee OA were recruited and randomly divided into four groups (CN, CH, AT, and CM). The six-week effect of TCM treatments on biomechanical and clinical outcomes were measured and assessed by comparing the outcomes with the baseline and six-week CN.

Results: The CH showed significant improvements in WOMAC pain and total scores when compared with baseline ($P<0.05$). Although no significant improvement was found in biomechanical variables when compared with the baseline and the six-week CN ($P>0.05$), a slight trend toward reduced muscle co-contraction was found in most of the selected paired muscles in the CH group after receiving six-week treatment. The six-week AT showed significant improvements in WOMAC pain, stiffness, function, and total scores when compared with the baseline, the six-week CN, and CH ($P<0.05$). Furthermore, the six-week AT showed significant improvements in temporal-spatial,

kinematic and kinetic variables when compared with the baseline and six-week CN ($P<0.05$). The results indicated that the improvement of clinical symptoms has resulted in the recovery in walking mobility and dynamicity even it might lead to higher joint loading in the medial compartment of the knee. Moreover, the six-week AT also showed a slight trend toward reduced muscle co-contraction when compared with the baseline and six-week CN. The six-week CM also showed significant improvements in WOMAC pain, stiffness, function, and total scores when compared with the baseline, the six-week CN, and CH ($P<0.05$). Furthermore, improvements were also found in the temporal-spatial, kinetics, and kinematics outcomes. Moreover, the six-week CM showed significant improvements in medial muscle co-contraction when compared with the baseline, the six-week CN, AT, and CH ($P<0.05$), which indicated that the CM might help to reduce the loading at the knee during gait

Conclusion: In conclusion, the results of this study confirmed the short-term clinical and biomechanical effects of CH, AT, and CM. However, a long-term study may be needed to provide more results to clarify the issues like some statistically insignificant variations.

Chapter 1 General introduction

1.1 Introduction

Osteoarthritis (OA) is one of the most common forms of muscular and skeletal disease, which affects an estimated 300 million people worldwide (Postler et al., 2018, Yucesoy et al., 2015, McAlindon et al., 2014, Kloppenburg & Berenbaum, 2020, Kolasinski et al., 2020). It is characterized by the focal areas of cartilage degeneration that leads to pain, loss of function, crepitus, local inflammation, and occasional effusion to the individuals, which can seriously affect the activities of daily living (ADL), and life quality. Based on the studies available, about 50% of the world's population aged over 65 years suffered some form of symptomatic OA (Postler et al., 2018), and 10% of men and 13% of women aged over 60 suffered knee OA (Zhang & Jordan, 2010).

The report from World Health Organization (WHO) showed that OA was the eleventh cause of years lost to disability (YLD) in the world (Vos et al., 2012). A recent study (Liu et al., 2018) showed that the number of YLD caused by knee OA was over four million in China, and the YLDs per 100,000 population was about 1000.

The incidence of OA is correlated with some risk factors such as (1) genetic factors, (2) deformities of the joint, (3) aging, (4) injury to the joint, (5) physical activity, (6) obesity, (7) bone mineral density (BMD), (8) estrogen deficiency (Stecher, 1941, Kuettner & Goldberg, 1995, Lane et al., 2000, Hart et al., 1999, Felson et al., 1997, Maetzel et al., 1997, Hadler et al., 1978, Tepper & Hochberg, 1993, van Saase et al., 1988, Felson & Zhang, 1998, Nevitt et al., 1996, Burger et al., 1996, Sowers et al., 1991). These factors play important roles in the development and progression of OA. They can not only increase susceptibility to joint degeneration but also determine the position and the severity of OA (Figure 1-1).

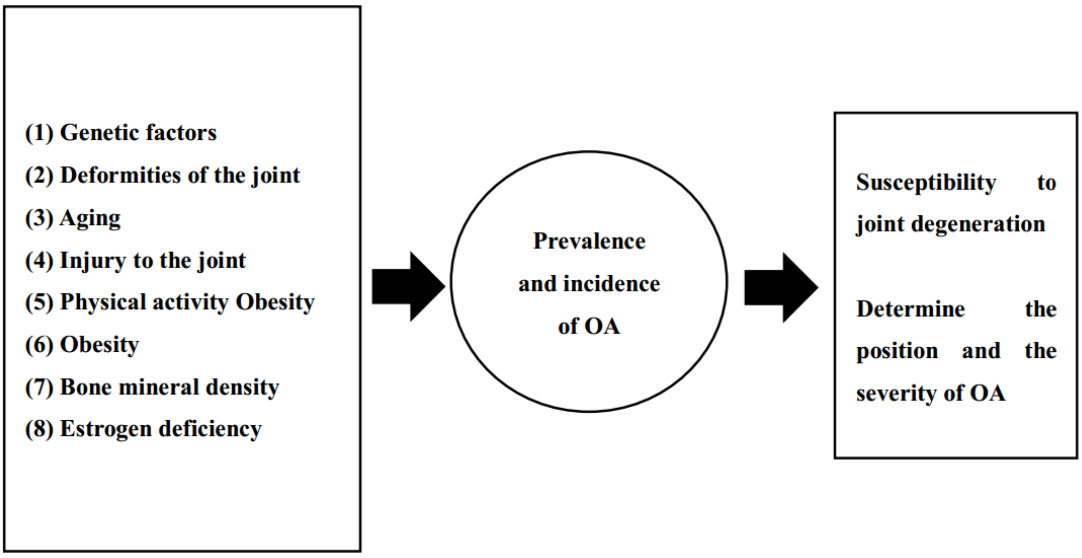


Figure 1-1 The risk factors of OA

The risk factors of OA are extremely complicated and include both biomechanical and biochemical factors (Felson et al., 2000). It is generally accepted that OA is a degenerative joint disease that is caused by the breakdown of the gross articular cartilage which serves as a cushion to protect bones and muscles from damage during the dynamic condition, the wearing away of the cartilage causes friction and damage to the bones leading to arthritic changes (Martin et al., 2001). Due to the aging of the population and the increased proportion of obesity in modern society, the prevalence of the OA increases rapidly (White et al., 2008, Altman et al., 2010), which has been almost doubled since the mid of last century (Wallace et al., 2017). Lim & Lau. (2011) predicted that in 2030, there would be at least 129 million individuals with OA in Asia, and approximately 30% of them could be severely disabled. Common symptoms of OA include chronic joint pain, stiffness, decreased joints range of motion (ROM), and swelling which could not only severely reduce the ADL for the individuals but also impose a severe economic burden to both families and the healthcare system (Salmon et al., 2019, Liu et al., 2018, Loza et al., 2009, Le Pen et al., 2005, Council 2002, Chen et al., 2012).

As one of the most common joint diseases, OA is associated with an extremely high

financial cost, which is mainly attributable to the disability and the expense of treatments (Salmon et al., 2019). Up to now, some population-based observational studies on OA prevalence have been conducted (Lethbridge-Cejku et al., 2003, Yelin et al., 2016, Loza et al., 2009, Le Pen et al., 2005, Leardini et al., 2004, Lawrence et al., 2008, March & Bachmeier, 1997). In America, the annual cost of the joint replacement due to OA was estimated at over 22 billion dollars. In Spain, the average annual cost for OA treatments per person was estimated at £1260 with 86% direct and 14% indirect cost (Loza et al., 2009). The annual cost of treating OA in France was £1297 per person, and the total cost for OA was £1.58 billion, which exceeded 1.7% of the total national health system cost. The annual cost for OA interventions per person in Italy soared to £1824, which is almost 1.5 times as much as that in Spain (Le Pen et al., 2005). According to a report from the National Institute for Health and Care Excellence (NICE) (NICE, 2014), there were over 8.7 million OA individuals in the UK, which led to 852 million pounds cost in joint replacement and 154 million pounds in pharmacological treatment (Council, 2002, Chen et al., 2012). Another study (Hiligsmann & Reginste, 2013) revealed that the mean total direct and indirect costs per OA individual-annual was about €1330 in Belgium, €2170 in Italy, €10452 in the Netherlands, €1502 in Spain, and €1511 in Germany. The NICE guideline (NICE, 2008) showed that the OA had been estimated to account for about 1% of the gross national product (GNP) in the UK, moreover, Hunter et al. (2014) reported that the burden of OA cost was about 1% to 2.5% GNP in western countries such as United States, Canada, UK, France, and Australia.

Compared with western countries, Asian nations also showed extremely high financial costs in the treatment of OA (Wang et al., 2017). A twelve-month follow-up study (Wang et al., 2017) for OA subjects showed that the direct and indirect treatment cost of knee OA in China was up to $2082 per person which was about the same as the European countries.

The prevalence of OA at the knee is higher, as it is the most important weight-bearing

joint during daily activities (Hunt, 2019, Bullock-Saxton et al., 2001). Wallace et al. (2017) reported that the prevalence of knee OA was two times higher than in the mid-20th century due to the lifetime extension and the increase of body mass. Tang et al. (2016) reported that about 8% of Chinese people aged over 60 years suffered some form of symptomatic knee OA, which was the leading cause of disability in China. Thus, the treatment of knee OA results in a heavy economic burden to individuals and the healthcare system.

The management of knee OA includes: pharmacological, non-pharmacological, and surgical treatments (Bhatia et al., 2013, NICE, 2014, Kloppenburg & Berenbaum, 2020). Although pharmacological treatments such as oral non-steroidal anti-inflammatory drugs (NSAID), paracetamol and cyclo-oxygenase 2 (COX-2) inhibitors are very effective in the relief of pain caused by knee OA (Enomoto et al., 2018, Yataba et al., 2017), it has some side effects such as ulceration and bleeding (Hippisley-Cox et al., 2005), and increasing the risk of venous thromboembolism (VTE) (Lee et al., 2016), thus, the clinicians need to consider the risk profile of specific pharmacological intervention before making a recommendation to their patients. Additionally, the reduction in pain is usually associated with increasing walking speed (Tani et al., 2018) which may lead to a higher ground reaction force (GRF) and loading at the knee during gait (Keller et al., 1996) and then accelerate knee joint cartilage deterioration (Henriksen et al., 2006, Baliunas et al., 2002), so the use of pharmacological intervention as monotherapy in the treatment of knee OA might not be a good option.

According to the UK national guidelines (NICE, 2014), the non-pharmacological treatments include healthcare education, strengthening exercise, weight loss, assistive devices, local heat and cold, shock-absorbing shoes or insoles, manual therapy (MT), and so on. In addition to the non-pharmacological interventions which are recommended by the western medical guideline (NICE, 2014, McAlindon et al., 2014) the complementary and alternative medicine (CAM) such as Traditional Chinese Medicine (TCM) interventions are increasingly used (National Center for

Complementary and Alternative Medicine, 2019) to help to relieve the symptoms caused by knee OA as there is no curative intervention available for knee OA (Nik Shafii et al., 2018).

The TCM interventions for OA are based on ancient Chinese medical practice, which include herbal remedies (e.g., herbal bath, herbal patch), acupuncture, massage (e.g., Tui Na), and exercise (e.g., Taichi) (National Center for Complementary and Integrative Health, 2019). Recently, the TCM has been advocated by some studies (Wang et al., 2012, Wang et al., 2016, Chen et al., 2015, Zhu et al., 2016). One study (Yang et al., 2013) demonstrated that about one-third of the individuals with knee OA in the United States used complementary and alternative treatments such as acupuncture. Wang et al. (2016) reported that a 12-week Taichi exercise treatment significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in individuals with knee OA, and there was no significant difference between the Taichi exercise and standard physical therapy. Moreover, the Taichi group showed significant improvements in depression and the physical component of quality of life which were maintained up to fifty-two weeks. Zhu et al. (2016) reported that individuals with knee OA achieved significant improvement in pain and extensor muscle strength after undergoing a 2-week (three times per week) massage. Wang et al. (2012) reported that using of Chinese herbal (CH) patch for a short term (seven days) could significantly improve the fear of coldness in individual with knee OA, and a meta-analysis (Chen et al., 2015) demonstrated that the CH bath therapy was a safe and effective management of knee OA.

Nonetheless, the effectiveness of TCM in knee OA is still controversial. Although the TCM has been proved to be very effective in the management of knee OA by quite some previous studies (OreiziEsfahani et al., 1996, Jubb et al., 2008, Shen et al., 2009, Chen et al., 2010, Wang et al., 2015, Wang et al., 2012, Wang et al., 2016, Chen et al., 2015, Zhu et al., 2016), several studies (Hinman et al., 2014, Scharf et al., 2006, Take & Wessel, 1994, Miller et al., 2011) indicated that there was still no enough evidence

to support such conclusions.

Based on the literature reviews, some previous TCM studies (Chen et al., 2008, Zhu et al., 2016, Shen et al., 2009) exposed some limitations. Firstly, the overall methodological quality of the randomized controlled trial (RCT) was moderate as there was no placebo-controlled group or no-treatment control group in these studies. Secondly, most of the assessments of the effectiveness of TCM treatments of knee OA were mainly based on subjective outcomes such as the WOMAC and visual analog scale (VAS) pain scores from questionnaires instead of objective variables such as kinetics, kinematics, muscle activities, and temporal-spatial parameters. Thirdly, the mechanism of TCM in the management of knee OA has not been convincingly clarified. Although some studies (Yuan et al., 2018, Xi et al., 2016, Seo et al., 2016, Bao et al., 2011) partially revealed the mechanism of TCM interventions, most of them were based on the animal models and biological parameters.

Based on the TCM theory, one of the key elements in the management of the muscular and skeletal disease is the function of the muscles (Yan et al., 2017). Previous studies (Zhao et al., 2012, Yang & He, 2012, Li et al., 2019, Zheng et al., 2006) reported that acupuncture treatment (AT), Chinese massage (CM), and CH patch could help to relieve the pain caused by knee OA via stimulating the muscles around the knee. One study (Jiang et al., 2018) revealed that the CM could not only relieve the pain but also improve the knee joint alignment. Zheng et al. (2006) reported that the CH patch could reduce knee pain and improve the Lequesne index in individual with knee OA after receiving three-week treatment. Zhao et al. (2012) reported that acupuncture could relieve the pain in individual with knee OA by relaxing the tendon of soft tissue around the pain point of the knee joint. Unfortunately, the evaluations of all these studies (Zhao et al., 2012, Yang & He, 2012, Li et al., 2019, Zheng et al., 2006) were based on subjective variables such as self-report questionnaires other than quantified objective variables such as kinematic, kinetic, and muscles function outcomes, which led to the biomechanical effects of TCM were unrevealed.

Some TCM treatments are aimed to improve the pain by stimulating the muscles around the knee (e.g., acupuncture, CM), thus, the muscles condition may play an important role in the underlying mechanism of TCM in the treatment of knee OA. It is not just TCM researchers who recognize the importance of the function of muscles around the knee, some western medicine researchers realize it as well. Previous studies (Child et al., 2004, Al-Khlaifat et al., 2016, Preece et al., 2016, Hodges et al., 2016) revealed that the individuals with knee OA demonstrated longer duration of muscles activity and co-contraction which were associated with higher external knee adduction moment (EKAM) during gait and greater progression of the disease. The reduction of the muscles co-contraction could help to reduce the pain and the loading of the knee (Al-Khlaifat et al., 2016, Preece et al., 2016), thus, the biomechanical effects of the TCM interventions in the management of knee OA may have a potential relationship with reduction of muscle co-contraction and the loading of the knee.

To date, little study has reported the biomechanical effectiveness of the TCM interventions in the management of knee OA. Zhu et al. (2016) reported the kinematic difference before and after the CM, however, they failed to compare the kinetics and muscle co-contraction variations. Lu et al. (2010) reported the effects of acupuncture on gait patterns in individuals with knee OA, however, they only investigated the immediate effect of the acupuncture intervention, and their study still did not report the muscle co-contraction changing. So far, to our knowledge, no previous study has investigated the relationship between muscle co-contraction, kinetics, and kinematics based on the TCM treatments which lead to the research gap of the current study.

To achieve the objectives above, this study was designed to investigate: (1) if the TCM treatments (CH, AT, and CM) could significantly improve the pain, stiffness, and function of the knee, and (2) the biomechanical effectiveness of TCM treatments on the knee (Figure 1-2).

1.2 Aims and objectives of thesis

1.2.1 Thesis aims

There is a lack of studies on the biomechanical effects of the TCM in the management of knee OA. This thesis aimed to identify the clinical and biomechanical effects of the CH, AT, and CM in comparison with a control group with the neutral flat insole (CN), where the results could help to improve the understanding of both clinical and biomechanical effects of the different TCM treatments in the management of knee OA.

1.2.2 Thesis objectives

(1)To determine whether three selected TCM treatments reduce the WOMAC scales (pain, stiffness, function, and total) over a period of six weeks when compared with the baseline and neutral flat insole.

(2)To determine whether three selected TCM treatments reduce the EKAM over a period of six weeks when compared with the baseline and neutral flat insole.

(3)To determine whether three selected TCM treatments reduce the muscle co-contraction over a period of six weeks when compared with the baseline and neutral flat insole.

1.3 Thesis overview

The thesis overview has been designed with a structure shown by the following flow chart (Figure 1-2).

- In chapter one, the context of the study was introduced. The aims and objectives of the study were identified.
- In chapter two, the existing literature was reviewed in terms of the management of individuals with knee OA. The reviews cover various aspects of knee OA. This

was to identify the research questions and hypotheses based on scientific research methods.

- In chapter three, the generic methods that used in the study were described. Moreover, to minimize the errors in the measurement and achieve confidence in achieving high-quality data, the test-retest reliability studies in both healthy individuals and individuals with knee OA were conducted to investigate the reliability of biomechanical outcomes.
- The clinical and biomechanical effects of TCM treatments on WOMAC pain, knee loading, muscle co-contraction, level of physical activity, kinematic, and kinetic variables in individuals with medial knee OA were investigated in chapter four.
- The general conclusion, the novelties, the limitation of the study, and the future study were addressed in chapter five.

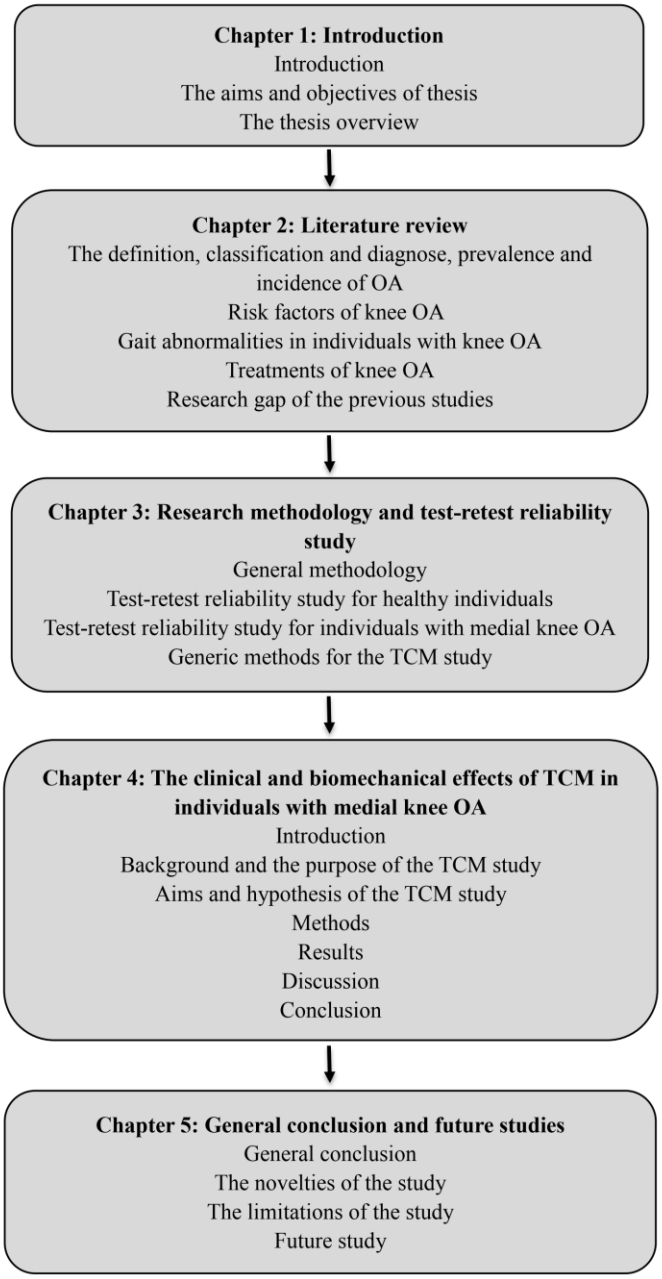


Figure 1-2 The structure of the thesis

Chapter 2 Literature review

2.1 Introduction

This chapter seeks to investigate the current literature related to TCM treatment for medial knee OA. This broad review began with the review of the incidence and prevalence globally and OA risk factors that may influence the progression of the disease. A section followed exploring the clinical assessment of OA, with a specific focus on knee and medial tibiofemoral OA. Following this, the biomechanical outcomes of knee OA and the EKAM and its correlation with OA progression were discussed.

The second part of this chapter presents an overview of the current treatment options available for individuals with medial tibiofemoral knee OA. Following this, current TCM treatments were reviewed and critiqued. The chapter concludes by formulating the hypotheses and aims of the study: to investigate the effectiveness of TCM treatments in the management of the medial tibiofemoral OA of the knee joint.

2.2 Definition of OA

OA is one of the most common degenerative joint diseases that result from the breakdown of articular cartilage and underlying bone (Arden et al., 2015). The most commonly involved joints affected by OA include the knee, hip, hand, foot, and spine (Zhang et al., 2010). Common symptoms of OA include pain, stiffness, swelling, and decreased joint ROM, which if left untreated could seriously affect the quality of life of the sufferers (Schuring et al., 2017).

Due to the aging of the population and the obesity epidemic, OA has been reported to be the fourth leading cause of disability (Woolf & Pfleger, 2003), and over 50% of the elder aged over 65 years suffered symptomatic OA worldwide (Postler et al., 2018).

Due to the high prevalence, the management of OA is associated with an extremely high financial cost (Loza et al., 2009, Liu et al., 2018). Based on a previous study (Hunter et al., 2014) the management of the OA cost in western countries was from 1% to 2.5% GNP. Recently, a twelve-month follow-up study (Wang et al., 2017) for OA subjects indicated that the cost of the management of OA in China was almost as same as in the European countries, which also put a heavy financial burden on the national health care system.

2.3 Classification and diagnosis of OA

Based on the etiology criteria of the classification of OA, it could be divided into two types: 'idiopathic' and 'secondary'. The idiopathic OA, which is also classified as primary OA, could be further divided into two types as follows: (1) the localized and (2) the generalized. The difference between localized and generalized OA is based on the position that OA occurs (Brandt et al., 1998) (Table 2-1). Localized OA usually occurs in one position or joint. OA that affects two or more than three joints or positions is classified as generalized OA.

Individuals who have potential risk factors that may cause OA could be classified into the second group (Brandt et al., 2009). Based on a previous study (Arden & Nevitt, 2006) the causes of the secondary OA include: (1) metabolic problems (such as ochronosis, acromegaly, hemochromatosis, and calcium crystal deposition), (2) anatomic problems (such as slipped capital femoral epiphysis, epiphyseal dysplasias, Blount's disease, Legge–Perthes disease, congenital dislocation of the hip, lower limbs length asymmetry, and hypermobility syndromes), (3) traumatic problems (such as joint trauma, joint fracture, underwent joint surgery, chronic injury (occupational disorders)), and (4) inflammatory problems (such as joint inflammation and septic arthritis).

Table 2-1 The location/position of OA

Joint	Location/Position
Hand	Heberden's and Bouchard's nodes, Erosive interphalangeal arthritis, Carpal-1st metacarpal
Feet	Hallux valgus, Hallux rigidus, Contracted toes, Talonavicular.
Knee	Medial compartment, Lateral compartment, Patellofemoral compartment.
Hip	Eccentric, Concentric, diffuse.
Spine	Apophyseal joints, Intervertebal joints, Spondylosis, ligamentous
Other single sites	Glenohumeral, Acromioclavicular, Tibiotalar, Sacroiliac, Temporomandibular

The radiographic diagnosis of OA relies on the images of X-rays, computerized tomography (CT), and magnetic resonance imaging (MRI), this diagnostic method is vital to clearly identify the changes of the OA affected positions and then help the clinicians to identify the stage of the OA and perform appropriate treatments. The radiographic classification scheme for OA was firstly described by Kellgren & Lawrence. (1957) which includes: (1) osteophytes formation, (2) periarticular ossicles, (3) narrowing of joint space, (4) small pseudocysts areas, (5) altered shape of the bone. Based on the severity of radiological features, Kellgren & Lawrence. (1957) divided OA into five grades: (0) Grade 0: no radiographic features of OA, (1) Grade 1: doubtful joint space narrowing and formation of osteophyte, (2) Grade 2: definite osteophyte formation with possible joint space narrowing, (3) Grade 3: multiple osteophytes with definite joint space narrowing, sclerosis and possible joint deformity, (4) Grade 4: marked osteophytes and joint space narrowing, severe sclerosis and definite joint deformity (Figure 2-1). The figure presents the typical radiological images of the different severity of OA knee which shows doubtful joint space narrowing and formation of osteophyte (Grade 1) to marked osteophytes and joint space narrowing, severe sclerosis, and definite joint deformity in Grade 4 (bone on bone).

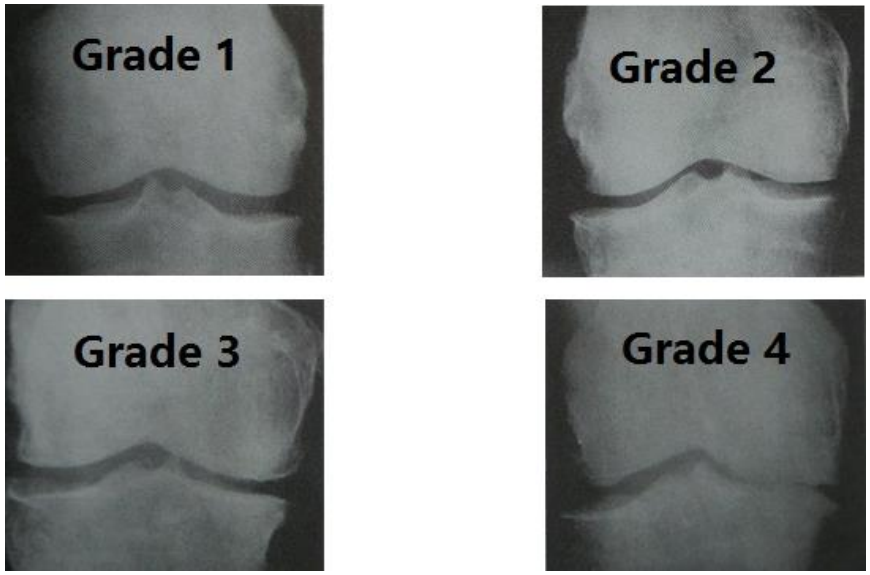


Figure 2-1 Four grades of the OA knee based on KL classification

The American College of Rheumatology (ACR) criteria for the classification and reporting of OA is one of the most commonly used diagnostic criteria for OA (Altman et al., 1986, Altman et al., 1990, Altman et al., 1991). These criteria identify the clinical OA subjects by using not only the radiographic changes but also the joint pain as the major inclusion criterion. The ACR criteria for hand, knee, and hip OA could be used not only for clinical studies but also for the RCT of new intervention studies (Arden & Nevitt, 2006) (Table 2-2).

Table 2-2 The criteria for hand, knee, and hip OA

Knee	Clinical/ Radiographic	OA is present if the items includes
	1. Knee pain for most days of prior month	1+2 or
	2.Osteophytes at joint margins	1+3+5+6 or
	3.Synovial fluid typical of OA (laboratory)	1+4+5+6
	4. Aged over 40 years	
	5.Morning stiffness ≤ 30 minutes	
	6. Crepitus on active joint motion	
Hip	1. Hip pain for most days of the prior month	1+2+3 or
	2. Erythrocyte sedimentation rate (ESR) ≤20 mm/h (laboratory)	1+2+4 or 1+3+4
	3.Radiograph femoral and/or acetabular osteophytes	
	4. Radiograph hip joint-space narrowing	
Hand	1. Hand pain, aching or stiffness for most days or prior month	1+2+3+4 or 1+2+3+5
	2. Hard tissue enlargement of two or more of ten selected hand joints	
	3. Metacarpal joint swelling in two or more joints	
	4. Hard tissue enlargement of two or more distal interphalangeal joints	
	5. Deformity of one or more of ten selected hand joints	

2.4 Prevalence and incidence of OA

The joints that are most commonly affected by OA include the hand, foot, knee, hip, and spine (Newman et al., 2003). As the most important weight-bearing joint of the human body, the hip and the knee have the greatest population impact, which leads to significant problems with immobility and disability among elder people (Liu et al.,

2018).

The estimated prevalence of OA at hand, hip, and knee have been reported by some previous studies (Van Saase et al., 1989, Lawrence et al., 1966, Felson et al., 1987, Anderson & Felson, 1988, Danielsson, 1984, Plato & Norris, 1979, Litwic et al., 2013). Nevitt et al. (2002) reported that compared with the Americans, the prevalence of hip OA in Chinese men and women was lower. However, another study (Beijing study) (Zhang et al., 2001) indicated that the Chinese women had a significantly higher prevalence of knee OA, they speculated that higher prevalence of knee OA in Chinese women might be caused by particular lifestyle such as prolonged squatting (Zhang et al., 2004). Van Saase et al. (1989) reported that over 70% of women aged over 60 years had OA of their distal interphalangeal joints, and about 15% of subjects around the age of 40 showed severe radiographic disorder of their hands or feet. Data provided by National Health Education Standards (NHES) (Lawrence et al., 1998) showed that about 30% of Americans aged over 25 years suffered hand OA. Moreover, over 30% of people who aged over 75 years in United States showed severe radiographic OA knee, which was very similar to that in Europe and China, and the prevalence of hip OA is lower than knee OA which was about 3% to 5% in elderly people.

In addition to the prevalence of radiographic changes in OA, the prevalence of joint pain and symptoms caused by OA have also been investigated, which is a help to allow accurate intervention for the individuals with OA. In the UK, the self-reported knee pain caused by OA in individuals aged over 40 was over 20% (Peat et al., 2001), and half of them showed radiographic changes of OA, and the results were very similar to another study (Jordan et al., 2004) which reported 18.1% people aged over 55 years had a clinical diagnosis of OA knees. The prevalence of symptomatic OA at the hip was less common than that in the knee (Arden & Nevitt, 2006). Zeng et al. (2015) reported that the prevalence of knee OA in Shantou, was about 13%, and the subjects who lived in buildings without elevators showed a higher prevalence than the subject who lived with elevators, which indicated that the lifestyle might have a great impact on the prevalence

of OA.

Data from the Wilson's (Wilson et al., 1990) population-based incidence survey demonstrated that the incidence of symptomatic hip OA was about 50 per 100000 person-years, and the knee OA was found to be about three times that for hip OA which reached 164 per 100000 person-years. Another study (Oliveria et al., 1995) reported the incidence rates of OA of an American north-east area were as follows: hand OA 100 per 100000 person-years, hip OA 88 per 100000 person-years, knee OA 240 per 100000 person-years. Additionally, both hand, hip, and knee OA showed an increased incidence with age, and women were diagnosed more than men, especially in people aged over 50 years.

Previous studies (Oliveria et al., 1995, Zhang et al. 2010, Felson et al., 1995) indicated that knee OA had a high incidence, especially in people aged over 65 years, and females were more vulnerable than males. Oliveria et al. (1995) claimed that the incidence of knee OA among women was about 3 times greater than in the hand and the hip. Zhang et al. (2010) reported that more than 10% of males and females aged over 60 years had symptomatic knee OA and the proportion of individuals living with knee OA is growing due to the aging of the population and the rising rates of obesity in the general population. In the Framingham study (Felson et al., 1995) the incidence of symptomatic knee OA in women aged over 70 years was about 1% per year, whereas the rate in male counterparts was about 0.7%.

The prevalence of knee OA was increasing year after year in older people (Das et al., 2008). About 10% of people aged over 60 years have degeneration in the knee cartilage and functional limitations caused by knee OA, and a quarter of the individuals with OA had serious dysfunction of the joints (Peat et al., 2001, Loeser, 2000). There could be a potential connection between the risk of the prevalence of knee OA and race. Based on a previous study (Anderson et al., 1998), the Africa American women showed a significantly higher rate of knee OA when compared with the white woman and had

almost double the number of Caucasian counterparts (Jordan et al., 2015).

According to the previous study (Muirden et al., 2005), the prevalence of knee OA was very high in developing countries, which had a close correlation with geography environment, ethnic difference, and the proportion of the people engaged in hard physical labor.

OA can affect many joints of the human body and most commonly in the weight-bearing joints such as the knee and hip. Knee OA is a chronic and widely prevalent degenerative joints disease, which commonly affects people over the age of 50 years (Jinks et al., 2004). The common symptoms of knee OA include pain, decreased joint ROM, joint deformity, muscle weakness, and joint swelling, which if left untreated could severely reduce the quality of life and result in significant health care costs (Bitton, 2009). Therefore, the following information would focus primarily on the knee joint.

2.5 Risk factors of knee OA

As mentioned above, the knee OA is one of the most common type of OA (Oliveria et al., 1995, Hunter et al., 2014), which leads to very serious social problems and put heavy finical burdens on the national health system (CAOS, 2015, Liu et al., 2018). A comprehensive understanding of the causes and risk factors of knee OA would be very helpful to the determination of tailored treatment for individuals with knee OA to delay the progression of the disease. Based on the previous studies (Sowers, 2001, Felson et al., 1997) the risk factors of knee OA could be classified into two categories which included: systemic factors and local mechanical factors.

2.5.1 Systemic factors for knee OA

Systemic factors associated with the presence of knee OA include age, race, gender, obesity, nutritional factor, genetics, BMD, and hormonal status (Hart et al., 1995). These factors could influence the development and progression of knee OA. Although

systemic factors play critical roles in the development and progression of the disease, they are not easy to resolve and avoid.

2.5.1.1 Age

Age is one of the critical risk factors for knee OA, over the past decades, some studies reported that both the incidence and the prevalence of knee OA increased directly with the age (Messier et al., 1994, Loeser et al., 2000, Felson et al., 2000). One epidemiologic study (Zeng et al., 2006) indicated that the prevalence of knee OA increased significantly in women aged over 40 years. It is probably the result of cumulative joint damage that makes joints' reparative capacity decreased and then failed to create self-healing (Zhang & Jordan, 2010).

2.5.1.2 Race

Previous studies (Golightly & Dominick, 2005, Allen et al., 2009) reported that the severity of pain symptoms which were caused by knee OA had a great relationship with racial/ethnic disparities. Compared with the Caucasians, the African American counterpart in the United States showed a significantly higher prevalence of symptomatic knee OA (Lawrence et al., 2008, Dillon et al., 2006), this might be caused by the greater risk of space loss due to the overweight and the history of knee injury (Vina et al., 2018). The Beijing knee OA study (Zhang et al., 2001) showed that compared with the women in Framingham, the Chinese women in Beijing showed a significantly higher prevalence of knee OA, and this was potentially caused by the genetic differences and heavy physical activity differences between Chinese and American. Additionally, the social lifestyle demeanor of people of different races may also have an impact on the prevalence of knee OA. Zhang et al. (2004) revealed that the reason for the higher prevalence of knee OA in Chinese women might be related to prolonged squatting posture in daily life.

2.5.1.3 Gender

Some previous studies showed that the women were more vulnerable to the knee OA, and they had not only higher incidence and prevalence of knee OA but also more severe symptoms than males at any age (Davis et al., 1988, Jordan et al., 1996, Nevitt et al., 1996, Felson et al., 2000, Srikanth et al., 2005). The results may be attributed to the sharply decreased estrogen hormone level after menopause (Felson et al., 2000). As, the estrogen hormone could protect women from some metabolic diseases such as OA (Zhang et al., 1998).

2.5.1.4 Obesity

Obesity has been identified as a risk factor for the development and progression of knee OA (Messier et al., 1994). Based on the previous studies available, knee OA was more common in individuals with significantly higher body mass index (BMI) (Messier et al., 1994, Felson et al., 1997). Obesity could lead to extremely high loading at the knee joint, which could not only increase the risk of scuffing and losing of the articular cartilage but also put an additional burden on the meniscus and ligaments which act as the protectors of the knee joint during activities.

According to the previous study (Felson et al., 2000), as soon as the bodyweight increased by one pound, the additional force that went through the knee would grow by 2 to 3 times correspondingly. This change partially explained why obesity showed a higher risk of knee OA than people of normal weight, and why most of the guidelines recommend weight loss as one of the core treatments in the management of knee OA (McAlindon et al., 2014, Singh et al., 2016, Hochberg et al., 2012, Geenen et al., 2018).

Although obesity plays an important role in the progression of knee OA, weight loss is not always effective in preventing knee OA. Niu et al. (2009) reported that obesity was not associated with the progression of knee OA for individuals with knee varus deformity. However, it led to an increased risk of progression of OA in the knee joints

with neutral or valgus alignment. Therefore, further studies are needed to explore the mechanisms.

2.5.1.5 Nutritional factors

Vitamin D level is believed to be linked to the epidemiology of knee OA (Grant et al., 2006). McAlindon et al. (1996) reported that lower levels of Vitamin D led to a higher risk of the development and progression of knee OA, which could explain why people in some developing countries, where less dietary intake of this important element has been identified, showed a higher prevalence of knee OA than the western countries counterparts, even they have lower body weight and BMI.

2.5.1.6 Genetics

Although the pathogenesis of knee OA has still not been fully investigated, several factors which influenced the progression of knee OA had a great relationship with the genetics/familial factors (Felson et al., 1998, Spector et al, 1996). Spector et al. (1996) reported that about 40-60% of the knee OA was related to genetic factors, and another study (Macgregor et al., 2008) indicated that OA at the knee was heritable. A cohort study (Zhai et al., 2004) showed that the genetic factors had not only a great relationship with the prevalence and incidence but also the severity of knee OA. Tufan et al. (2010) reported that the alignment of the tibiofemoral joint was significantly influenced by the genetics factors, moreover, Khan et al. (2015) reported that the offspring of subjects who underwent total knee replacement (TKA) not only showed a greater worsening of radiographic of the knee but also higher medial tibial cartilage volume loss.

2.5.1.7 Bone density

The relationship between BMD and knee OA has been investigated by several previous studies (Hannan et al., 1993, Nevitt et al., 1995, Hart et al., 1994, Hunter et al., 2002). Higher BMD, especially the subchondral BMD was reported as a risk factor for knee OA (Hannan et al., 1993, Nevitt et al., 1995, Hart et al., 1994, Hunter et al., 2002). Hart

et al. (2002) reported that the BMD was higher in women with knee osteophytes. Both Framingham (Hannan et al., 1993) and Chingford (Hart et al., 1994) studies showed that individuals with knee OA had an over 5% higher BMD than those without knee OA and the results were very similar to the Burgers' research (Burger et al., 1996) which reported that individuals with knee OA had a 3.53% higher femoral neck BMD. Additionally, the Rotterdam study (Burger et al., 1996) indicated that individuals with knee OA had a higher rate of bone loss. Hart et al. (2002) found that women with higher hip or spine BMD were more vulnerable to knee OA.

2.5.1.8 Hormonal level

The causes of knee OA was mainly due to the scuffing and the losing of the articular cartilage (Martin et al., 2001). Several previous studies (Eriksen et al., 1998, Richmond et al., 2000) confirmed that the estrogen hormone level played an important role in the pathophysiology of the knee OA as the articular cartilage is hormonally sensitive and has many estrogen receptors. Jung et al. (2018) reported that the postmenopausal women who accepted menopausal hormone therapy (MHT) showed a lower prevalence of knee OA. The Framingham Study (Zhang et al., 1998) indicated that the elderly white woman who underwent estrogen replacement therapy (ERT) had a moderate protective effect against the worsening of radiographic knee OA. These studies further explained the reason why women showed a higher prevalence of knee OA than men, as the estrogen level of women decreases sharply after menopause (Felson et al., 2000).

2.5.2 Local mechanical factors for knee OA

The causes of knee OA are complicated due to the interaction of multi-impact factors. The etiology of knee OA has still not been fully understood yet (Guilak, 2011). The local mechanical factors of knee OA include joint alignment, the joint moment, GRF, the history of the knee injury, muscle strength, muscle co-contraction, and occupational factors. These factors significantly influence the progression and development of the disease (Roos et al., 1995, Felson et al., 1997, Bennell et al., 2009, Muirden et al., 2005,

Hubley-Kozey et al., 2006, Hodges, et al., 2016).

2.5.2.1 Joint alignment and loading

Based on the location of the affected sides, the knee OA could be classified into three types, which include medial, lateral, and patellofemoral compartments (Brandt et al., 1998). Cooke et al. (2007) reported that the medial and lateral compartment knee OA were regarded to have a strong relationship with the varus or valgus alignment in the knee joint, with loading bearing axis excessively biased to the medial or lateral compartment of the knee, rather than through the joint centre (Figure 2-2). Normally, the femoral mechanical (FM) axis, the tibial mechanical (TM) axis should be collinear both statically and dynamically, and the component in the frontal plane of the knee angle (knee adduction angle) should be almost zero degrees (Cooke et al., 2007). With the significant increasing or decreasing of knee varus/valgus angles, the joint contact force, (i.e., knee loading), which goes through the medial or lateral compartment of the knee would increase accordingly and lead to the deterioration in the degeneration of the cartilage and then result in knee OA.

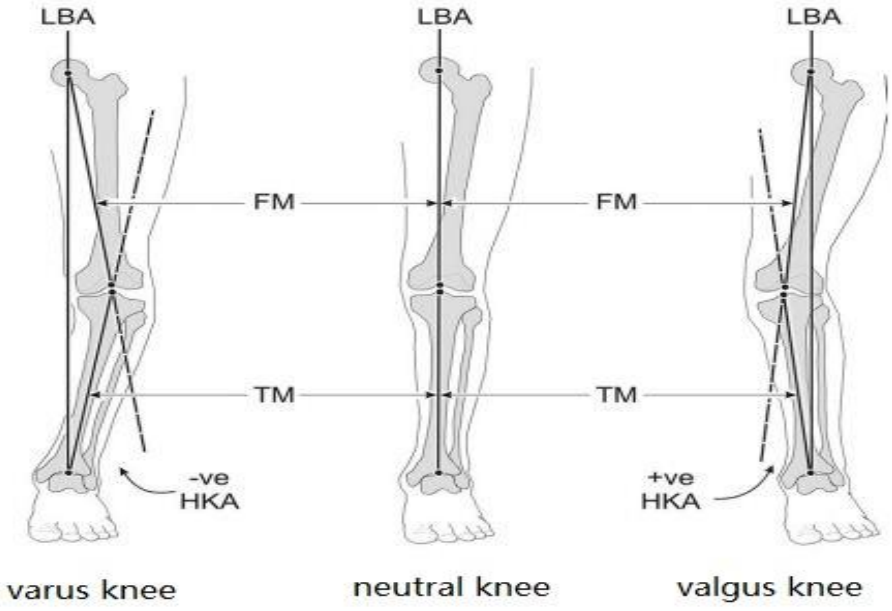


Figure 2-2 Knee alignment pattern, LBA: load-bearing axis, HKA: hip-knee-ankle angle, FM axis: femoral mechanical axis, TM axis: tibial mechanical axis

Knee OA affects both the medial or lateral compartment of the joint, with medial more commonly affected. Previous studies indicated that over 60% of the loading goes through the medial compartment of the knee during gait (Schipplein & Andriacchi, 1991), which would lead to a higher incidence of medial compartment knee OA. Ahlback. (1968) reported that the medial knee OA rate was approximately 10 times as the lateral type. Furthermore, Sharma et al. (1998) reported that the severity of knee OA had a significant relationship with the EKAM, the higher EKAM was, the more serious the medial knee pain would be.

The EKAM is the moment about the knee joint in the frontal plane (Figure 2-3), which is the product of the GRF, and the moment arm (the perpendicular distance from the centre of the knee joint to the GRF action line) of this force (Hunt et al., 2006). During walking, an increased EKAM could cause higher adduction at the knee in the frontal plane (Amin et al., 2004) which leads to extra loading in the medial compartment of the knee. The EKAM has been proved to be a surrogate of the progression of knee OA, as it directly linked the distribution of the load on the knee joint, and had a strong correlation to the severity of the disease. Miyazaki et al. (2002) reported that once EKAM increased by one percent and then the risk of progression of the knee OA would increase six times correspondingly. Furthermore, the pain index of the individuals with knee OA and knee joint alignment were associated with the magnitude of the EKAM (Sharma et al., 2001). The EKAM would lead to not only higher loading in the medial compartment of the knee joint but also the lesser knee joint space width (Sharma et al., 1998), as soon as the EKAM increased by one unit (Nm/(BW*Ht)%), the joint space width of the knee OA decreased by 0.63mm correspondingly.

During the stance phase, the EKAM has two peaks (Figure 2-3, normalized to body mass and height): the first peak which occurs in the early stance phase, and the second peak which occurs in the late stance phase with a trough in the mid-stance (Fregly et al., 2007).

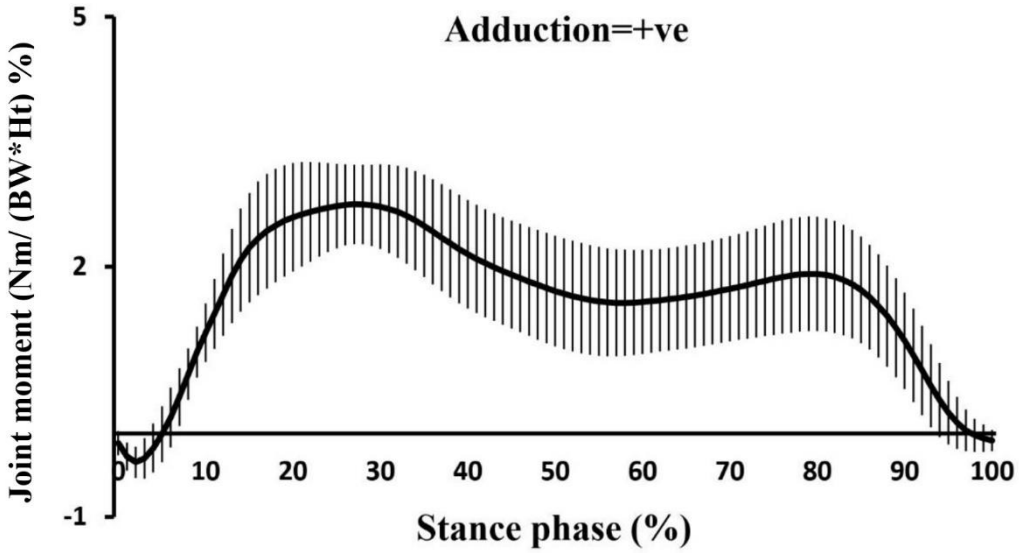


Figure 2-3 The EKAM (normalized to body mass and height) during stance phase

Although the first, second peak value and the mid-stance trough value of the EKAM could represent the variation in knee joint loading in a stance, the entire load at the knee was still not accurately measurable. Thorp et al. (2006) proposed the integration of the EKAM during stance, which was named as knee adduction angular impulse (KAAI). The KAAI is the single variable, which is incorporated with the magnitude and duration of the EKAM (Thorp et al., 2006 a). It is the area under the positive EKAM curve and horizontal axis (stance time), which represents the entire EKAM and time effect during the stance phase (Figure 2-4). It contains more information about the loading at the knee and is very useful to predict the severity of the knee OA (Thorp et al., 2007), as the peak value of the EKAM during the stance phase just represents the knee joint loading at that specific time point, while the KAAI shows the entire loading in the medial side of knee joint during stance phase, thus it is important to include the KAAI within knee OA gait evaluation. Compared with asymptomatic subjects the symptomatic subjects who had the same grade in radiographic level showed significantly higher KAAI and EKAM, and the KAAI of the individuals with late-stage knee OA is higher than the early-stage counterparts (Thorp et al., 2006 a, Thorp et al., 2007).

It is commonly believed that both EKAM and KAAI have a strong correlation with the development of knee OA, and the reduction of these two parameters during gait may delay the progression of the medial compartment knee OA (Fantini et al., 2009).

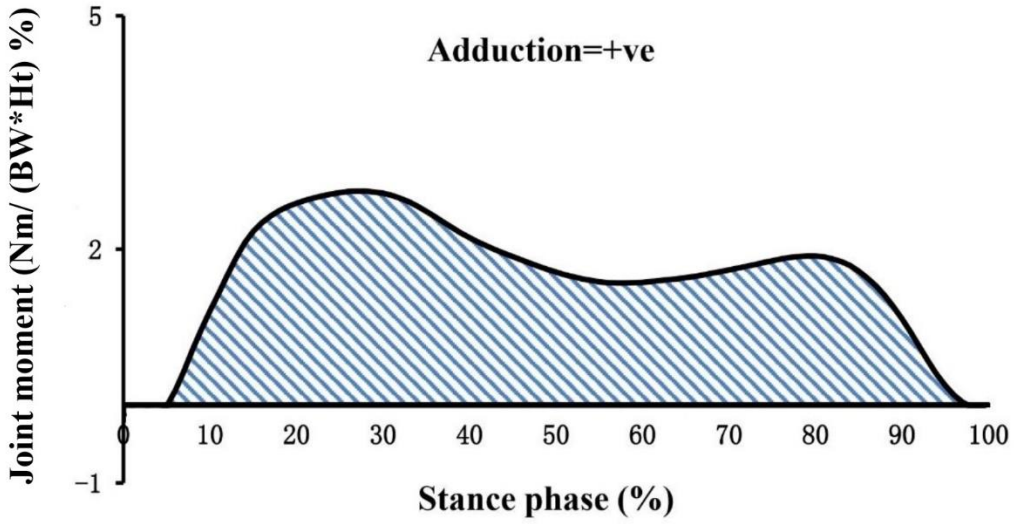


Figure 2-4 Graphic representation of a frontal plane external joint moment during stance phase, the knee adduction angular impulse (KAAI) is represented by the shaded area.

2.5.2.2 History of joint injury

The history of knee joint traumas such as meniscus injury, rupture of anterior cruciate ligament (ACL), and posterior cruciate ligament (PCL) were proved to be strong risk factors for knee OA (Roos et al., 1995). The medial and lateral collateral ligament edema were believed to be very common in the knee OA suffers (Chen et al., 2008), the injury of the ligament would lead to functional limitation and knee joint instability, which would potentially result in more excess loading on the knee during walking. Englund et al. (2009) claimed that knee meniscal damage played a vital role in the occurrence, development, and relapse of knee OA, individuals who had an injury history of menisci showed a significantly higher prevalence of knee OA than normal healthy individuals. Felson et al. (2005) reported that over 20% of the individuals with knee OA had a history of ACL rupture, this was also consistent with the findings from Amin's study (Amin et al., 2008), which indicated that individuals with knee OA who

had a complete ACL tear would have a high risk of cartilage loss.

2.5.2.3 Muscle strength

Based on the previous studies available (Slemenda et al., 1998, Oiestad et al., 2015, Hurley, 1999), there is a strong association between the knee extensor muscles strength (quadriceps) and the prevalence of the knee OA. The quadriceps femoris weakness has been proved to be one of the strongest risk factors of knee OA. The muscles, bone segments, and the ligaments around the joint work as a functional unit, and the weakness in the muscles would affect the unit function and cause a failure in maintaining the joints' balance (Spinoso et al., 2018). One study (Slemenda et al., 1998) indicated that the women with lower quadriceps strength had a higher chance of getting knee OA. Moreover, the joint deformity such as varus or valgus caused by muscle weakness would eventually lead to excess loading at the knee during walking (Bennell et al., 2009).

A series of studies (Salli et al., 2010, Jan et al., 2008, Lin et al., 2009) have shown that increased quadriceps strength could help to reduce the pain and improve the activity. Therefore, the quadriceps strengthening exercise has been widely used as the intervention of knee OA (Slemenda et al., 1997, Kus & Yeldan, 2019).

2.5.2.4 Muscle co-contraction

Muscle co-contraction is the synchronous acting between the agonist and the antagonistic muscle during a contraction (Sirin & Patla, 1987). The balance between the agonist and antagonistic muscles which act in opposition to each other is crucial in the development and the progression of knee OA (Hodges et al., 2016).

During level walking, the EKAM works to turn the knee into varus and open the lateral knee joint. To prevent the lateral knee joint from opening the agonist muscles contraction are not sufficient, and thus required antagonistic muscles contraction and the pretension of the lateral soft tissue (Schipplein & Andriacchi, 1991). Based on the

previous studies (Sharma et al., 1998, Miyazaki et al., 2002), the individuals with medial deformity showed a significantly higher EKAM during stance, thus, to keep the balance between the EKAM and the muscle groups, agonist and the antagonistic muscle showed greater muscle contraction and co-contraction during gait.

The distribution of the loading at the knee can be divided into two parts: the EKAM and the muscle force to support coordination and stability of the knee (Lewek et al., 2004), and the coordination of muscle activity around the knee has been proved to be a determinant of knee loading. Individuals with knee OA usually show knee joint laxity and instability during the dynamic condition (Lewek et al., 2004, Rudolph et al., 2007), to compensate for that, knee OA individuals usually show increased muscle co-contraction (Schmitt & Rudolph, 2008). Although increased muscle co-contraction can be considered as a self-protection system of the knee in short term (Lewek et al., 2004), it leads to higher loading during daily activity (Schipplein & Andriacchi. 1991, Lloyd & Buchanan. 2001), and then leads to the acceleration of the cartilage volume loss and then increased the likelihood of undergoing TKA at five-year follow-up (Hubley-Kozey et al., 2013). Therefore, the changing of the muscle co-contraction around the knee should be considered as one of the most important variables that targets the progression of knee OA (Booij et al., 2020).

Some experimental studies (Zeni et al., 2010, Hubley-Kozey et al., 2009, Child et al., 2004) reported that individuals with knee OA showed excessive muscular co-contraction of the flexor-extensor muscles during gait, which should work sequentially in normal individuals. In Child's study (Child et al., 2004) knee OA individuals showed not only a longer muscle activity pattern of vastus lateralis (VL), medial hamstrings (MH), tibialis anterior (TA), and medial gastrocnemius (MG), but also significantly increased muscle co-contraction (VL/MH, TA/MG) when compared with the control group. Zeni et al. (2010) reported that at the controlled walking speed, knee OA individuals (moderate to severe) showed statistically greater muscle co-contraction (VL/semimembranosus (SM)) and antagonistic muscle activity than their healthy

counterparts. Hubley-Kozey et al. (2009) compared the co-contraction (vastus medialis (VM)/MG, VM/MH, VL/lateral gastrocnemius (LG), and VL/lateral hamstring (LH)) among different severity of the individuals with knee OA, which indicated that severe knee OA individuals showed statistical co-contraction in all the muscle groups when compared with the healthy individuals, however, moderate knee OA individuals only showed significant co-contraction in VL/LH.

In individuals with knee OA, due to the simultaneous contraction of the muscles, the loading on the joint surface increased significantly, which would damage the cartilage, deteriorate the condition and increase the risk of TKA (Winby et al., 2013). Therefore, some treatments are aimed to reduce the loading at the knee by reducing the muscle co-contraction. Previous studies (Al-Khlaifat et al., 2016, Preece et al., 2016) have shown the correlation between the reduction of muscle co-contraction and the improvement of pain symptoms in individuals with knee OA. Therefore, the reduction of the muscle co-contraction around the knee can be regarded as positive clinical effects of interventions in the management of knee OA (Booij et al., 2020).

2.5.2.5 Occupational factors

Heavy manual labor jobs can cause higher loading in the knee joint and then lead to the loss of joint cartilage. Compared with the people who work in the office, the individuals who engaged in high levels of daily activity showed a threefold greater risk of developing knee OA (McAlindon et al., 1999), consequently, some undeveloped countries showed a higher prevalence rate of knee OA than European countries and the United States due to a higher proportion of heavy manual work employment in those places (Muirden et al., 2005, Felson et al., 1991). Sports activities such as football, basketball, and long-distance running may contribute to excessive knee flexion and extension motion during practice (Buckwalter et al., 1997), as these kinds of repetitive motions can lead to injury in the ACL which plays one of the most important roles in the stabilizer of the knee joint. The evidence showed that elite soccer and long-distance players were at high risk for the development of knee OA (Kujala et al., 1995, Spector

et al., 1996).

2.6 Gait abnormalities in knee OA individuals

Walking is one of the major activities in human daily life (Gok et al., 2002). The gait patterns are vulnerable to lower limb joint diseases such as knee and hip OA. Based on the previous study (Silva et al., 2002), the average steps per person per day were about 5000 to 15000, which implied that even if a small abnormal gait pattern uncorrected could lead to serious joint problems over time.

The understanding of the gait abnormalities in individuals with knee OA could not only help to design reasonable regimens but also slow down or even prevent the progression and development of the disease.

To understand the difference of gait patterns between healthy people and individuals with knee OA we should understand the changing of three types of parameters as follows: (1) temporal-spatial, (2) kinematic, and (3) kinetic data.

2.6.1 Temporal and spatial parameters

Knee OA individuals usually showed a marked reduction of temporal-spatial parameters such as: walking speed, velocity, stride length, and cadence during gait when compared with the healthy individuals (Gyory et al., 1976, Stauffer et al., 1997, Messier et al., 1992, Brinkmann et al., 1985). However, due to the laxity and instability of the affected knee, the percentage of stance phase in the affected side during the gait cycle is statistically increased (Gok et al., 2002). Individuals with knee OA are prone to decrease their walking speed, as the decreasing of walking speed is associated with the reduction of the GRF (Stansfield et al., 2001), which may help to reduce the joint stress and mitigate the pain during gait (Andriacchi et al., 1982). Additionally, the lower walking speed could help to increase the stability of the lower limb in individuals with knee OA. Mundermann et al. (2004) reported that the individuals with less severe knee

OA adapted a slower walking speed than that of control as decreasing walking speed was associated with the potential to reduce the EKAM during gait, which could help to decrease the severity of the disease.

2.6.2 Kinematic parameters

The individuals with knee OA showed significantly smaller knee flexion angle, knee joint ROM, hip flexion angle, and ankle dorsiflexion angle with the severity of knee OA increased (Astephen et al., 2008a). Several studies (Astephen et al., 2008a, Walker et al., 2001) showed that the peak knee flexion angle of normal individuals during gait was about 65 degrees, however, both Astephen (Astephen et al., 2008 a b) and Walker (Walker et al., 2001) reported that knee OA individuals only showed about 50 degrees knee flexion during level walking, as the reduction of the joint motion could help to alleviate the pain during load-bearing. Bejek et al. (2006) reported that compared with the healthy individuals, the individuals with knee OA not only showed decreased hip and knee joint ROM but also increased pelvis obliquity angle, which indicated that the knee joint degeneration might be partially compensated by the kinematics of hip and pelvis.

Moreover, Gok et al. (2002) revealed that individuals with knee OA had greater knee varus (stance phase) and knee valgus (swing phase) degrees during gait, these changes might be caused by the malalignment of the knee, which was regarded to have a strong relationship with the development and progression of knee OA (Cooke et al., 2007).

2.6.3 Kinetic parameters

The gait patterns difference between individuals with knee OA and the healthy individuals had been widely reported (Sharma et al., 1998, Brandt et al., 1998, Foroughi et al., 2009). Quite some studies focused on the kinetic parameters (e.g., EKAM) which have been proved to have a strong relationship with progression and severity of the disease (Sharma et al., 1998, Brandt et al., 1998, Foroughi et al., 2009).

Although some studies (Sharma et al., 1998, Thorp et al., 2006 a, Landry et al., 2007) investigated the biomechanical changes at the knee in individuals with knee OA, little has been reported on the difference at other joints, which lead to the knowledge shortage in understanding the gait patterns of individuals with knee OA. To fill this research gap, two studies (Astephen et al., 2008a, b) fully investigated the gait difference (hip, knee, and ankle) between knee OA and healthy subjects. The results indicated that knee OA subjects showed significantly smaller knee flexion moment, knee extension moment, knee internal rotation moment, hip abduction moment, hip flexion moment, hip internal rotation moment, and ankle dorsiflexion moment during stance phase (Astephen et al., 2008a). However, the EKAM which represents the loading of the medial compartment of the knee was statistically higher.

Based on the previous studies (Sharma et al., 1998, Thorp et al., 2006 b, Landry et al., 2007), the magnitude of the loading at the knee during gait is associated with the severity of clinical symptoms, therefore, the reduction of EKAM is the key to alleviate the pain (Baliunas et al., 2002). Quite different from the other researches (Kaufman et al., 2001, Hurwitz et al., 2002), Astephen et al. (2008 a) found that the 1st peak of the EKAM in moderate and severe knee OA individuals did not increase, however, the mid-stance EKAM was significantly higher, as the mid-stance EKAM was less speed-dependent parameter, thus, some researchers (Weidenhielm et al., 1994, Landry et al., 2007, Astephen et al., 2008a) advocated that mid-stance EKAM was more reliable in the assessment of loading at the knee during gait. Although the EKAM has been advocated as the surrogate of the loading at the knee during activity (Sharma et al., 1998, Thorp et al., 2006 a, Landry et al., 2007), it is a speed-dependent measure, thus, using the EKAM only in the assessment of loading at the knee might not be precise, some researchers (Thorp et al., 2007) used the KAAI to represent the loading at the knee, as the peak value of the EKAM just reflected the single point-in-time loading instead of the entire stance phase loading at the knee joint.

Although EKAM has been regarded as the most important measure in the evaluation of

knee loading during activity (Sharma et al., 1998, Thorp et al., 2006 a, Landry et al., 2007), it just represented 63% loading of the knee, and about 22% of loading was represented by the knee flexion moment (Manal et al., 2015). Some previous studies (Astephen et al., 2008a, Gok et al., 2002, Messier et al., 2005) reported that the individuals with knee OA showed decreased knee flexion moment, as the reduction of knee flexion could help to decrease the joint stress and then relieve the pain.

The reduction of hip adduction moment in individuals with knee OA has been reported in some studies (Mundermann et al., 2005, Chang et al., 2005, Astephen et al., 2008 a). Chang et al. (2005) reported that the higher hip abduction moment could help to decrease the progression and development of knee OA. The magnitude of hip abduction moment relied on the contraction of the hip abduction muscle, due to the weakness of these muscles, the pelvic drop excessively, and then the center of the body mass moves forward to the swing limb which leads to an increase of loading in the medial compartment of the knee and then the risk of progression of knee OA increases (Figure 2-5). Therefore, the increase of hip abduction moment might be an effective method to help against medial knee OA progression.

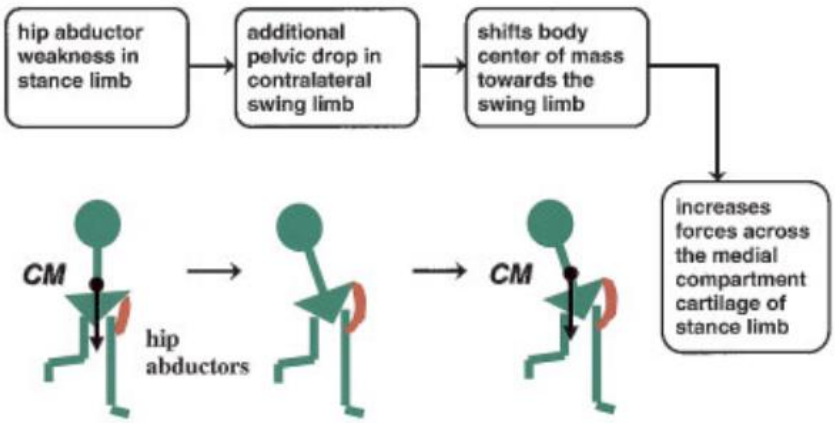


Figure 2-5 The mechanism of hip abduction weakness increases the EKAM during gait CM= center of mass

2.7 Treatments of knee OA

Based on the previous studies available, no cure medicine for knee OA exists, and the severity of symptoms depends on individual differences. The treatments of knee OA include pharmacological, surgical, and non-pharmacological interventions (Bhatia et al., 2013, NICE, 2014).

2.7.1 Pharmacological treatment

The pharmacological treatments could help with pain and stiffness caused by knee OA. Paracetamol, NSAID, COX-2 inhibitors, and opioids are commonly used as pain relief medicines to treat OA (NICE 2008). Although NSAID is very effective in reducing knee pain (Pincus et al., 2001, Towheed et al., 2006), it cannot be used for individuals who suffered the liver or renal diseases (Seifert et al., 1993, Schiodt et al., 1997, Henrich et al., 1996), and it has severe side effect such as ulceration and bleeding (Hippisley-Cox et al., 2005). Previous studies indicated that over 20% of inpatients aged over 60 died from peptic ulcers, caused by long-term use of NSAIDs (Richy et al., 2004). Pharmacological treatments could help to relieve the pain and improve the quality of life (Pincus et al., 2001, Towheed et al., 2006), however, this kind of treatment does not have effects on OA itself and repair the damage to the joints. Furthermore, the individuals' walking ability which is improved by the pharmacological treatments will lead to a higher loading on the knee joint and then cause the further deterioration of the knee joint cartilage during gait (Henriksen et al. 2006). Recently, a study (Zheng et al., 2019) showed that tramadol was associated with a significantly increased risk of mortality, thus, it might not be the best choice of intervention for knee OA.

2.7.2 Surgical treatment

Surgical interventions such as arthroscopy, articular cartilages mend, TKA, osteotomy, and arthrodesis may be required when the pharmacological, non-pharmacological treatments fail to help the individuals to relieve the pain and treat symptoms of the knee

OA, however, only the individuals who experience severe symptoms that had a substantial impact on their quality of life and are refractory to conservative treatment could consider surgical intervention (NICE, 2014), as these kinds of treatments are expensive and requiring regular revising (Griffin et al., 2007).

2.7.3 Non-pharmacological treatment

The core treatments recommended by the guideline (NICE, 2014) include activity exercise and weight loss. The non-pharmacological interventions such as thermotherapy, electrotherapy (e.g., transcutaneous electrical nerve stimulation (TENS)), aids and devices (e.g., lateral wedge insole (LWI), knee bracing, and walking stick), MT (e.g., manipulation and stretching) which were considered as an adjunct to core treatments still play an important role in the treatment of the knee OA. Based on the previous studies, the non-pharmacological interventions used in western countries and China were quite different (NICE, 2014, Zhu et al., 2009, Zhu et al., 2011, Wang et al., 2012, Zhu et al., 2016, Zhang et al., 2016).

Based on the western guidelines (NICE, 2014, McAlindon et al., 2014, Singh et al., 2016, Hochberg et al., 2012), non-pharmacological treatments could be weight loss, physical therapy (e.g., TENS, thermotherapy), exercise, aids, devices (e.g., LWI, knee bracing), and MT (e.g., manipulation and stretching) (Figure 2-6)

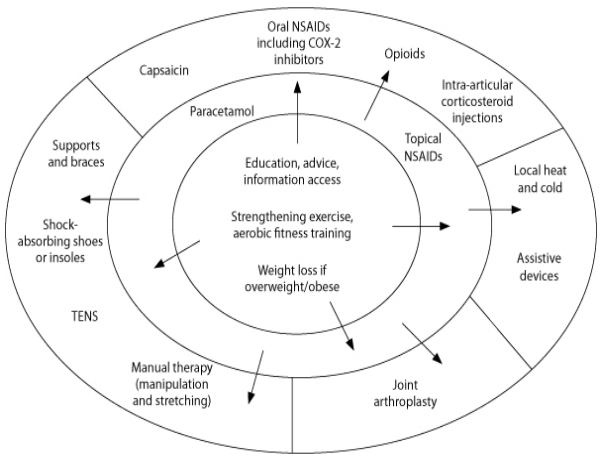


Figure 2-6 The treatments recommended by the NICE guidelines (Reproduced from NICE, 2014)

2.7.3.1 Weight loss

Overweight is generally defined as a BMI over 25 kg/m², it is one of the major risk factors in the progression and development of knee OA (Riddle et al., 2013). A meta-analysis (Jiang et al., 2012) indicated that the increase of five units in BMI was associated with over 30% increased risk of knee OA. Excess weight could lead to higher joint loading and relative muscle weakness which are regarded as systemic factors in the progression of knee OA (Wluka et al., 2013).

Weight reduction is recommended by NICE (NICE, 2014) (Figure 2-7) as core treatment of conservative intervention of knee OA individuals with excess body mass. Some previous studies (Christensene et al., 2007, Messier et al., 2013) demonstrated that weight reduction had efficacy in improving symptoms of individuals with knee OA. Christensene et al. (2007) reported that the moderate weight loss regime (reduction of 0.25% body mass per week for twenty weeks) could significantly improve the disability in individuals with knee OA. Another report (Messier et al., 2013) published in the Journal of the American Medical Association (JAMA) showed that 10% of decreasing body mass could not only significantly decrease the joint force but also lower the interleukin-6 levels.

Although the clinical improvement made by weight reduction is undoubted. If it affects the structure of the knee joint remains controversial. The latest study (Jafarzadeh et al., 2018) reported that obese individuals who underwent weight reduction surgery showed significant improvements in knee pain and joint function, however, the structural features of the knee (cartilage thickness) changed little after one year following up. The results of Gudbergsen's study (Gudbergsen et al., 2012) were very similar to Jafarzadeh's research (Jafarzadeh et al., 2018), which also showed that weight reduction resulted in clinical symptoms relieving, however, it was not associated with the slow of joint damage. On the contrary, Gersing's (Gersing et al., 2016) four-year following-up study showed that weight loss could not only help to improve the clinical symptoms (WOMAC) but also to slow the progression and development of cartilage thickness loss.

As recommended as the fundamental treatment, weight loss has been proved to be one of the effective treatments of knee OA (Riddle et al., 2013, Christensen et al., 2007), as it could help to improve the pain and the physical function scale. However, the weight loss was hard to achieve and sustain in the long term (Bliddal et al., 2014). Some studies (Kushner et al., 2015, Srivastava et al., 2018, Bastos et al., 2013) showed that even the individuals who undertook bariatric surgery failed to reach target weight loss, and the proportion was about 30%.

2.7.3.2 Exercise therapy

Among the non-pharmacological management of knee OA, the most recent guidelines recommended exercise therapy as the core treatment (National Clinical Guideline Centre (UK), 2014, McAlindon et al., 2014, Bruyere et al., 2014). Meta-analysis studies (Bartholdy et al., 2017, Lun et al., 2015) indicated that exercise could not only relieve the pain but also improve the walking ability (total walk distance and walking speed) in individuals with knee OA.

There are some types of exercise therapy for the management of knee OA, which includes: Baduanjin, Tai chi, muscles strengthening exercise, and so on (An et al., 2008, Wortley et al., 2013, Wang et al., 2016, Lee et al., 2009, Peloquin et al., 1999, Huang et al., 2003, Huang et al., 2005, Oliveira et al., 2012). An et al. (2008) reported that an eight-week Baduanjin exercise could help to reduce the pain, stiffness, and disability in individuals with knee OA, moreover, it could improve the quadriceps strength and aerobic ability as well. Several previous studies have proved the effectiveness of the Taichi exercise in the management of knee OA (Wortley et al., 2013, Wang et al., 2016, Lee et al., 2009). Wortley et al. (2013) found that the Taichi exercise could significantly improve physical activity, and both Wang et al. (2016) and Lee et al. (2009) reported that knee OA individuals who practiced eight-week Taichi exercise showed statistically significant improvements in WOMAC scales and walking ability, moreover, the positive effects produced by Taichi exercise was similar to those of standard physical

therapy (Wang et al., 2016). Although some RCT studies (Wortley et al., 2013, Wang et al., 2016, Lee et al., 2009) reported that the Taichi exercise showed significant improvements in clinical symptoms caused by knee OA, the latest meta-analysis (Hu et al., 2021) showed that the strength of evidence was low or moderate. Therefore, more high-quality RCTs are urgently needed to confirm these results.

Other studies (Peloquin et al., 1999, Huang et al., 2003, Huang et al., 2005, Aoki et al., 2009, Oliveira et al., 2012, Meisser et al., 2004, Jan et al., 2008) have also reported the beneficial effects of the strengthening exercise. Quadriceps muscle strength plays an important role in maintaining the dynamic stability of the knee joint during gait (Moxley Scarborough et al., 1999), as it could help to keep the knee joint in the right position and maintain the joint alignment. The weakness in quadriceps muscle strength would lead to poor knee joint stability and increase the risk of knee OA (Chester et al., 2008). The training exercises to increase the strength of the quadriceps muscle have been regarded as an important rehabilitation program for the prevention of knee OA. The greater the strength of the quadriceps muscle group is, the more stable knee joint will be, which would lower the risk of OA and decrease the symptoms caused by knee OA (Felson et al., 2000, Bennell et al., 2009). Aoki et al. (2009) reported that compared with the control group, knee OA individuals who underwent an eight-day home strengthing exercise showed significant improvements in knee joint ROM, pain, and walking speed. Peloquin et al. (1999) reported that strengthening exercise significantly improved pain, physical ability, muscles strength in individuals with knee OA, and the results were very similar to some other studies (Huang et al., 2003, Huang et al., 2005, Oliveira et al., 2012). Furthermore, Jan et al. (2008) reported that both high and low resistance strengthening exercises showed significant clinical effects, however, there was no statistically significant difference between the high and low resistance strengthening exercises.

Although quite some previous studies reported positive effects of strengthening exercise in the management of knee OA, this kind of intervention still has some

limitations. Firstly, in knee OA individuals with severe pain, this kind of intervention may not be suitable, and the clinicians should consider controlling the pain by using physical therapy or some other complementary and alternative treatments (e.g., acupuncture, massage) before adding greater resistance loads during exercise (Vincent & Vincent, 2012). Secondly, some exercises (e.g., weight-bearing exercise) have been shown to increase muscle strength, however, doing exercises in a standing or weight-bearing position may lead to higher loading at the knee. Therefore, this kind of exercise may aggravate symptoms such as pain, swelling, and inflammation in individuals with knee OA (Jan et al., 2009). Thus, the strengthening exercise may not be suitable for some knee OA individuals.

2.7.3.3 Gait modification training exercise

Existed studies (Sharma et al., 1998, Thorp et al., 2006 a, Landry et al., 2007) have indicated that EKAM is the key element of the development and the progression of knee OA, thus, it is undoubted that the non-surgical interventions for knee OA should aim at not only the improvements of clinical symptoms but also the reduction of loading of the knee as well. Gait modification training exercise has been reported as a conservative approach for reducing the EKAM in individuals with knee OA. To date, at least seven gait modification training programs have been proved to be effective in reducing the EKAM: (1) toe-in gait, (2) toe-out gait, (3) increasing the medial-lateral trunk sway, (4) changing the rear foot position, (5) walking barefoot, (6) decreasing walking speed and stride length, and (7) backward walking exercise (BWE).

2.7.3.3.1 Toe-in gait

Walking with decreased foot progression angle has been proved to be associated with the reduction of 1st EKAM (Shull et al., 2013a, Shull et al., 2013b). Shull et al. (2013a) reported that compared with normal walking, the 1st peak EKAM was decreased by about 13% by toe-in gait. van den Noort et al. (2013) also reported smaller EKAM during toe-in gait, surprisingly, the magnitude of EKAM reduction in their study was over 40%, which indicated that this kind of training program might be very effective in

the management of knee OA. A six-week following up trial (Shull et al., 2013b) showed that the toe-in gait training could not only improve the pain and function but also reduce the EKAM in individuals with knee OA. However, the drawback of a toe-in training program is that the usage of this kind of treatment is limited and cannot be applied to severe knee OA individual who is unable to walk (Shull et al., 2013b).

2.7.3.3.2 Toe-out gait

Previous studies (van den Noort et al., 2013, Guo et al., 2007, Andrews et al., 1996, Jenkyn et al., 2008) have shown greater foot progression angle could reduce EKAM during gait, especially in the late stance phase (2nd peak EKAM). Jenkyn et al. (2008) reported that the reduction in 1st peak EKAM (11.7%) and EKAM lever arm (6.7%) could be significantly decreased by the increased foot progression angle (i.e., toe-out gait). van den Noort et al. (2013) demonstrated that the toe-out gait decreased EKAM during late stance (56%), however, an increase in early stance EKAM (24%) and an increase in mid-stance EKAM (21%) were found, thus, further studies are needed to explore the clinical effect of toe-out gait.

2.7.3.3.3 Increasing the medial-lateral trunk sway

Walking with increased medial-lateral trunk sway has been advocated to be a strategy to reduce the EKAM during gait (Mundermann et al., 2008, Hunt et al., 2011). Mundermann et al. (2005) found that knee OA individuals naturally adopt an altered gait pattern which is driven by medial-lateral trunk sway. However, higher trunk sway during gait is associated with an increased risk of falls (Allum & Carpenter, 2005). Furthermore, knee OA individuals need to practice for a long time to master the technique of the interventions, thus, this kind of gait modification may not suitable to some individuals with knee OA.

2.7.3.3.4 Changing the rear foot position

The correlation between the centre of pressure (COP) and EKAM has been investigated by some previous studies (Lidtke et al., 2010, Reilly et al., 2009). Reduction in EKAM

is associated with the pronated foot in knee OA individuals. Changing the rear foot into pronation during stance can shift the COP laterally, which leads to the reduction of the perpendicular distance (EKAM lever arm) between the knee joint centre and the resultant GRF vector line in the stance phase (Kakihana et al., 2005, Lidtke et al., 2010), and then reduces the EKAM and the loading at the medial compartment of the knee. Although changing the rear foot position is an easy and simple gait strategy for EKAM reduction, it requires permanent gait adaptation by individuals with knee OA, which demands a lot of time and effort. Therefore, this kind of gait strategy may not be suitable for some knee OA individuals.

2.7.3.3.5 Walking barefoot

Studies (Prodromos et al., 1985, Sharma et al., 1998, Miyazaki et al., 2002) showed that aberrant force can increase the risk of incidence and progression of knee OA. Hence, several previous studies (Erhart et al., 2010a, Birmingham et al., 2001, Jones et al., 2013) focused on reducing EKAM by using selected orthotics. However, everyday footwear also influences the knee loadings in knee OA individuals, which may be a potential risk factor for the development of the disease. Shakoor et al. (2010) reported that flexibility and the height of the shoes could significantly influence the loading at the knee during gait. Thus, some studies (Shakoor et al., 2006, Kerrigan et al., 2003) investigated if walking barefoot could be used as an intervention for knee OA.

Shakoor et al. (2006) found that compared with normal shoes, walking barefoot could help to reduce the EKAM. Kerrigan et al. (2003) also reported that barefoot showed significantly smaller EKAM when compared with men's dress shoes and sneakers. Up to now, little RCT study revealed the long-term efficacy of barefoot walking, therefore, the clinical effect of this kind of treatment is needed to be further investigated.

2.7.3.3.6 Decreasing walking speed and stride length

The relationship between the temporal-spatial parameters and gait variables in knee OA individuals has been investigated by some previous studies (Mundermann et al., 2004,

Kaufman et al., 2001). Kaufman et al. (2001) reported that individuals with severe knee OA showed slower speed in level walking and up/downstairs due to the joint pain. Mundermann et al. (2004) reported that both decreased walking speed and smaller stride length could be associated with a decrease in the magnitude of EKAM during activity. However, van den Noort et al. (2013) demonstrated that slow walking was associated with an increased EKAM (40%) in mid-stance and an increased KAAI (28%) during the entire stance phase. Thus, more studies are needed to investigate the clinical effect of this gait modification training.

2.7.3.3.7 Backward walking

BWE has been reported to be an effective rehabilitative exercise for improving the equilibrium of the human body and lower extremities (Yang et al., 2005, Hackney & Earhart, 2009). Arun & Vasant. (2013) reported that BWE could be adopted as an adjunct to conventional treatment for the individual with knee OA. Zhang et al. (2015) reported that the BWE could help to reduce both 1st and 2nd EKAM during exercise. However, due to the invisible direction, there is a risk of falls during practice, therefore, knee OA individuals who undertake BWE training must be very careful during exercise.

2.7.3.4 Orthoses

Since the last few decades, biomechanical interventions (e.g., knee brace, LWI) have attracted more and more attention worldwide (Birmingham et al., 2001, Kerrigan et al., 2002, Kakihana et al., 2004, Marks et al., 2004, Jones et al., 2013). Biomechanical orthoses were recommended by the clinical guidelines of some countries (McAlindon et al., 2014, Zhang et al., 2007, NICE, 2014) for individuals with knee pain or instability.

2.7.3.4.1 Knee brace

Knee bracing has been proved to be an effective biomechanical intervention for the management of knee OA (Raja & Dewan, 2011) as it could not only shift the joint loading but also stabilized the joint alignment during gait (Birmingham et al., 2001). The knee brace works to apply EKAM through two mechanisms as follows: (1) the

hinge which offers a greater valgus alignment than the lower limb, and (2) a three-point force system made by the straps around the knee joint (Figure 2-7).

The use of Generation II OA knee bracing in the treatment of knee OA has been widely studied and reported. Previous studies (Ramsey et al., 2007, Draper et al., 2000, Matsuno et al., 1997) showed that the Generation II OA knee bracing could help to reduce the pain and improve the function of the knee OA individuals. Surprisingly, in Draper' study (Draper et al., 2000), knee OA individuals reported an immediate improvement in function after initial fitting, moreover, Ramsey et al. (2007) found that Generation II OA knee bracing could not only reduce the pain, improve the joint function, and enhance the joint stability but also decrease the muscle co-contraction around the knee, which indicated that the curative effect might be kept with the bracing off. Birmingham et al. (2001) found that the knee bracing could enhance the proprioception and postural control (balance) of the knee OA individuals, which may help to partially explain the underlying mechanisms of knee bracing in the treatment of OA in addition to the unloading the joint stress. The RCT study (Kirkley et al., 1999) showed that individuals with knee OA benefited significantly from using knee brace in addition to health education.

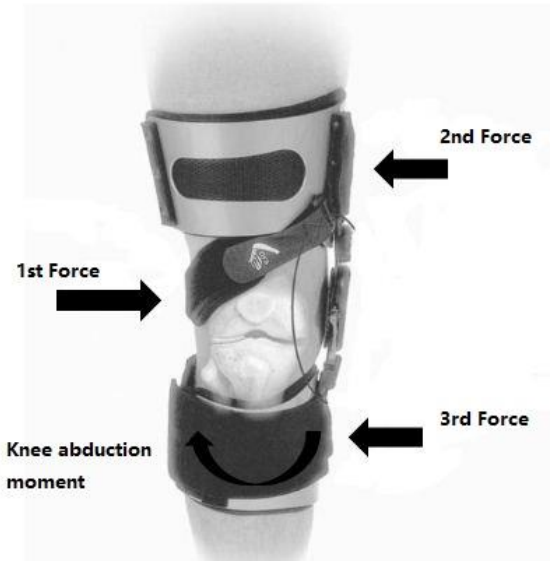


Figure 2-7 1st, 2nd, 3rd Force represents the three-point force made by the force strap tension (reproduced from Pollo et al., 2002)

Based on the results from previous studies (Ramsey et al., 2007, Draper et al., 2000, Matsuno et al., 1997, Birmingham et al., 2001), the knee brace could help to reduce the pain and improve the function during gait, however, more convincing evidence is still needed before a specific recommendation could be made.

Although knee bracing could help to improve the clinical symptoms caused by knee OA via reducing the loading and correcting the alignment of the knee (Birmingham et al., 2001), compliance with this kind of treatment is not as easy as other orthoses such as LWI as it is expensive and cumbersome (van Raaij et al., 2010).

2.7.3.4.2 Lateral wedges

The use of the LWI in the management of knee OA has been widely reported. In 1987, Sasaki & Yasuda. (1987) first reported the treatment of medial compartment knee OA by using LWI. Since then the treatment of the medial knee OA by using LWI has generated considerable interest worldwide, it has been proved to be a cheap, inoffensive, and effective intervention for the treatment of knee OA, which could not only release the pain but also improve the daily activity and quality of life of knee OA individuals (Fang et al., 2006, Jones et al., 2013).

The LWI has been proved to be effective in the management of the pain caused by knee OA (Fang et al., 2006, Jones et al., 2013, Rafiaee & Karimi, 2012, Hatef et al., 2014, Barrios et al., 2009, Felson et al., 2019), and to help to reduce the EKAM, which represented the majority of loading at the medial compartment of the knee and the development and progression of OA knee (Yilmaz et al., 2016, Alshawabka et al., 2014, Baert et al., 2014, Miyazaki et al., 2002).

Although some studies showed positive effect in the improvement of the pain caused by knee OA (Fang et al., 2006, Jones et al., 2013, Rafiaee & Karimi, 2012, Hatef et al., 2014), some individuals reported the side effect of LWI such as the ankle pain during walking, which led these individuals had to abandon the treatment.

Felson et al. (2019) demonstrated that the LWI showed a significant reduction in knee pain in comparison with neutral insoles. However, only the knee OA individuals who responded to LWI (the knee OA individuals who showed at least a 2% reduction in EKAM in LWI condition) were included in their study. Therefore, the LWI may not be suitable for knee OA individuals who do not show the biomechanical response to the treatment in the gait lab.

2.7.3.4.3 Walking shoes

In addition to knee brace and LWI, the reduction of EKAM by wearing the walking shoes have been demonstrated in some previous studies (Erhart et al., 2010 a, Erhart et al., 2010 b, Erhart-Hledik et al., 2012, Shakoor et al., 2008, Jones et al., 2015, Teoh et al., 2013, Hinman et al., 2013). Shakoor et al. (2008) reported that compared with the stability shoes, the mobility shoes which were designed to mimic essential aspects of barefoot walking showed a significant reduction in EKAM in individuals with knee OA. The longitudinal clinical and biomechanical effects of the APOS shoes were fully investigated by Haim et al. (2012). Both pain, function, 1st EKAM, 2nd EKAM, and KAAI were improved after nine-month treatment by using APOS shoe in individuals with knee OA which indicated that this kind of treatment might be very effective in the management of knee OA.

Although some previous studies reported that the walking shoes could help to reduce the EKAM and/or knee pain in individuals with knee OA, this kind of intervention still has some limitations. Firstly, it is too expensive for individuals with knee OA to afford in some low-income countries (APOS therapy. 2018). Secondly, it cannot be applied to severe knee OA individuals who are unable to walk. Thirdly, it may not improve the clinical symptoms in the short term. Therefore, other types of treatments such as TCM treatments might be more suitable in the management of knee OA.

2.7.3.5 TCM

Some previous studies reported the effectiveness of pharmacological and non-pharmacological treatments in the management of knee OA. However, the prevailing treatments show some limitations. For example, the use of NSAID and COX-2 inhibitors may lead to ulceration and bleeding (Hippisley-Cox et al., 2005), and increasing the risk of VTE (Lee et al., 2016). Surprisingly, a recent study on JAMA (Zheng et al., 2019) revealed that tramadol which is strongly recommended by the American Academy of Orthopaedic Surgeons (AAOS) guideline (American Academy of Orthopaedic Surgeons, 2013) showed a statistically increased risk of mortality over 1-year use. The clinical effects of some biomechanical interventions such as LWI are still controversial (Zhang et al., 2018, Parkes et al., 2013, Arnold et al., 2016). Felson et al. (2019) demonstrated that the effect of LWI was likely of significance in only a minority of individuals with knee OA (the knee OA individuals who showed at least a 2% reduction in EKAM in LWI condition). Moreover, some interventions such as APOS shoes were too expensive to be afforded in some low-income countries (APOS therapy. 2018). Thus, some knee OA individuals had to seek some treatments which are cheap, non-invasive, and with a few side effects.

TCM originated in ancient China, it is a part of Chinese traditional culture and has been used for thousands of years to maintain the health of Chinese people (Dong et al., 2018). TCM encompasses many different practices such as herbal, acupuncture, CM (Tuina), which have been widely used in the management of knee OA (Yang et al., 2017). Recently, a system review (Yang et al., 2017) indicated that TCM treatments could improve the pain, stiffness, and function in individuals with knee OA.

In China, the clinical experts have reached a consensus in the clinical guideline published by the Chinese Association for Research and Advancement of Chinese Medicine (CRACM) (Chen et al., 2015), which recommended that the TCM treatments be applied as an intervention to the knee OA when the pharmacological did not work or cannot be applied. Interestingly, Yang et al. (2013) reported that about one-third of

the individuals with knee OA in United States used complementary and alternative treatments such as acupuncture.

2.7.3.5.1 CH patch

As one of the common approaches of TCM, CH for external use for muscular and skeletal disease has been developed over thousands of years in China, which could be traced back to 475 B.C.-221 B.C. (Chen et al., 2015). The oldest traditional Chinese medical book reported that CH could help to improve the symptoms which were caused by the joints' problems. It is believed that the CH patch has analgesic and anti-inflammatory effects by acting on nociceptive neurons and pain pathways to relieve the pain (Zhang et al., 2008) and can improve blood circulation (Zou et al., 2013) and then improve the function of individuals with knee OA.

2.7.3.5.1.1 Effectiveness of CH patch in the management of knee OA

To date, CH patch for pain management in individuals with knee OA has been reported in large scales of clinical trials in China (He et al., 2019, Kong & Ye, 2019, Xing et al., 2018, Xia et al., 2018, Lu 2018, Jiao et al., 2018, Zhou et al., 2017, Hu & Xi, 2015, Yang et al., 2015, Liu & Jiang, 2015, Ju et al., 2013, Wang et al., 2012, Zhao & Wang, 2008). It has been proved effective in alleviating the symptom caused by knee OA (He et al., 2019, Kong & Ye, 2019, Xing et al., 2018, Xia et al., 2018, Lu 2018, Jiao et al., 2018, Zhou et al., 2017, Hu & Xi, 2015, Yang et al., 2015, Liu & Jiang, 2015, Ju et al., 2013, Zhao & Wang, 2008). He et al. (2019) reported that the CH patch showed a significant improvement in short-term (3-week) pain management. Liu & Jiang. (2015) reported that compared with the placebo patch, the CH patch showed a significant improvement in the pain symptom, and the result was consistent with Yang et al. (2015). Interestingly, Zhou et al. (2017) demonstrated that the CH patch showed significant improvements in WOMAC pain, stiffness, function, and total scores when compared with Flurbiprofen cataplasm. Moreover, Zhao & Wang. (2008) reported that the Fufang Nanxing Zhitong Gao (FNZG) showed significant improvements in WOMAC pain, stiffness, function, and total scores when compared with the placebo patch. Although

Wang et al. (2012) reported that compared with the sham herbal patch, short-term (1 week) FNZG did not show significant improvement in pain, it could significantly improve the symptom of fear of coldness which could also be regarded as a useful treatment for knee OA. Additionally, Liu et al. (2018) reported that after receiving two-week treatment, the CH patch showed significant improvements in the WOMAC scales and VAS pain scale when compared with Diclofenac diethylamine emulsion, which indicated the short-term benefit of this kind of treatment in the management of knee OA. The latest meta-analysis (Cai et al., 2020) also demonstrated that the CH patch could significantly improve the pain, stiffness, and function in individuals with knee OA.

Some previous studies reported the positive effect of the CH patch in the management of knee OA, however, the effectiveness of this kind of treatment is still controversial. A meta-analysis (Cai et al., 2020) indicated that previous CH patch studies had some methodological deficiencies which might lead to the risk of bias. For example, there was no no-treatment control group in the included trials, and only one study (Yang et al., 2017) admitted single blinding of assessors. Although some studies (He et al., 2019, Kong & Ye, 2019, Xing et al., 2018) showed the positive effect of CH patch, the levels of the evidence were lower, and the evaluations of all these studies were based only on subjective variables such as pain scales (e.g., WOMAC, VAS) rather than quantitative biomechanical outcomes. Moreover, change in pain in questionnaires may not accurately reflect the biomechanical condition of the OA knees (e.g., loading at the knee during gait), which plays a critical role in the development and progression of knee OA (Jones et al., 2014). According to some previous studies (Henriksen et al., 2006, Hurwitz et al., 2000), the improvements in clinical symptoms might lead to greater walking speed and higher loading (e.g., EKAM, knee flexion moment) during gait. Additionally, the distribution of the loading at the medial compartment of the knee also depends on the activity of the muscles around the knee. Increased co-contraction of the selected paired muscles around the knee would also lead to the higher loading on the knee joint, which is not reflected by the EKAM (Walter et al., 2010). Some previous

studies (Al-Khlaifat et al., 2016, Preece et al., 2016) demonstrated that the relief of the pain was associated with the reduction of muscle co-contraction even though the EKAM was not reduced. Therefore, the changing of the muscle co-contraction around the knee should also be considered as one of the most important variables that target the progression of knee OA (Booij et al., 2020). So far, to our knowledge, no previous study investigated both the clinical and biomechanical effects of the CH patch in individuals with knee OA, which led to the relationship between the change of pain and biomechanical variables (e.g., EKAM, muscle co-contraction) after receiving CH patch is still unclear.

2.7.3.5.1.2 Mechanism of CH patch in the management of knee OA

So far, the mechanism of the CH patch in the management of knee OA is still not very clear. Some researchers (Chen et al., 2015, Mao 2016) believed the theory behind that is the key ingredients in the herbal could help to reduce sodium channel currents, inhibit 5-Lipoxygenase (5-LOX) and COX-2, inhibits TNF-α expression, NF-KAPPA B activation, which play important roles in the development and progression of knee OA. Chen (Chen et al., 2015) reported that the herbal reduced the knee OA rats' serum levels of cartilage oligomeric matrix protein (COMP), hyaluronic acid (HA), malondialdehyde (MDA), myeloperoxidase (MPO), Interleukin-1 beta (IL-1β) and then shows a chondroprotective and therapeutic effect. Mao. (2016) showed that the herbal demonstrated cartilage protection via controlling MMPs and improving anti-oxidant levels. Xu et al. (2013) found CH (SiMiaoFang (SMF)) could suppress the expression of matrix metalloproteinases (MMPs) -3 and -13 and aggrecanases-4 and -5 and then inhibit cartilage matrix degradation.

However, some TCM doctors have different opinions (Wang et al., 2012, Chen et al., 2015) on the mechanism based on the TCM theories, the mechanism of CH patch is defined as relieving joint pain by improving the muscle function around the joint. Thus, based on the TCM theories, the underlying mechanism of the CH patch in the management of knee OA is the ingredients (e.g., Gastrodia, Notopterygium) could help

to relieve muscle spasms, stiffness, and improve blood circulation. Several previous studies (Al-Khlaifat et al., 2016, Preece et al., 2016, Collins et al., 2011) reported that the reduction of the activity of the muscle (co-contraction) could help to decrease the loading at the knee and then relieve pain, which is very similar to the description in TCM theories.

Due to the strong stickiness, the CH patches have a slight fixation effect and can act as the tape around the knee during the dynamic condition (Wang et al., 2012). Interestingly, one study (Hinman et al., 2003) showed that the tape around the knee could significantly improve the pain and disability in individuals with knee OA, the theory behind that might be the tape around the knee can act as a sleeve and give the support to the knee and increase the knee stability during the dynamic condition. Collins et al. (2011) reported that the sleeve could significantly decrease the VL/LH muscle co-contraction during walking, moreover, Schween et al. (2015) reported that the sleeve could significantly reduce the knee adduction angle, EKAM, and KAAI, which indicated that the biomechanical effect of the CH patches in the management of knee OA might have a relationship with that.

However, no previous study was performed to investigate the biomechanical effect of the CH patch in individuals with knee OA such as on muscle co-contraction and EKAM. It can be the reason that the biomechanical effect of the CH patch is still unclarified.

2.7.3.5.2 Acupuncture

Acupuncture is one of the oldest practices of TCM, which is believed to have originated in ancient China (Lu et al., 2018, Zhang et al., 2018). It is another popular form of TCM treatment for pain relief and functional restoration for individuals with knee OA (Lu et al., 2018, Zhuang et al., 2018, Wang et al., 2017). Based on historical records, the first document which mentioned the effect and mechanism of acupuncture treatment is “Yellow Emperor's Classic of Internal medicines” (Lu et al., 2018). Different from the instruments which are used for acupuncture treatment in modern medicine, sharped

stones and bones were used in ancient China (White et al., 2004). The therapeutic principles of acupuncture are based on the concepts of meridians (Wang et al., 2017), however, the precise acupuncture point locations were developed in modern China.

In the 1950s, the Chinese government established the first acupuncture research institute in Beijing, after that, more and more western-style hospitals in China accepted it as a complementary and alternative treatment (White & Ernst, 2004) for some diseases which cannot be cured such as knee OA. During the same period, some researchers (Han & Terenius, 1982) found that acupuncture could help to release neurotransmitters such as opioid peptides, which partially explain the analgesic mechanism of this kind of treatment.

Nowadays, as a therapeutic intervention, acupuncture has been widely used not only in China but also in western countries (NIH Consensus Conference, 1998, Hickstein et al., 2018). One study (Nahin et al., 2016) estimated that about three million American adults who suffered chronic musculoskeletal pain were treated with acupuncture each year. In Germany, due to the high utilization of acupuncture in the management of knee OA and the OA individuals' preference for alternative complementary medicine, the premiums for knee OA individuals treated with acupuncture were paid by the statutory health insurance (Hickstein et al., 2018). Yang et al. (2012) revealed that over one-third of the individuals with knee OA in the United States used alternative complementary medicine such as acupuncture. In Australia, acupuncture has been widely acknowledged as an effective treatment to alleviate the symptoms caused by OA knees (Cohen et al., 2005). Portugal researchers (Teixeira et al., 2018) also reported effective results in the treatment of knee OA by using acupuncture, which could reduce the pain, improve the function, and lead to a better quality of life of individuals.

2.7.3.5.2.1 Effectiveness of acupuncture in the management of knee OA

As one of the most common chronic musculoskeletal diseases worldwide, knee OA causes a serious social problem and puts heavy financial burdens on the national

healthcare system (Salmon et al., 2019, Liu et al., 2018). As there is no cure for knee OA, the latest interventions mainly focus on improving clinical symptoms such as pain, stiffness, and function (Hafez et al., 2013, Bannuru et al., 2019). In individuals who suffer knee OA, where pharmacological treatment may be ineffective or damaging to the individuals (e.g., gastrointestinal disorders), or they may not be willing to accept surgical intervention, other pain management interventions should be considered (Vas et al., 2004). Yang et al. (2013) identified that approximately one-third of the individuals with knee OA in the United States used alternative complementary medicine (e.g., acupuncture) believing that these therapies can help to relieve the pain they were suffering and improve their ADL. In China, the latest diagnosis and management of knee osteoarthritis: Chinese medicine expert consensus (Chen et al., 2015) recommended acupuncture as one of the most important interventions in the management of knee OA.

Clinical trials (Teixeira et al., 2018, Hickstein et al., 2018, Zhang et al., 2016, Vas et al., 2004) demonstrated that acupuncture showed significant clinical benefits in individuals with knee OA when compared with the waiting list or usual care. Recently, a meta-analysis (Zheng et al., 2020) indicated that acupuncture was effective in alleviating pain and improving knee function. Moreover, the Osteoarthritis Research Society International (OARSI) guideline (McAlindon et al., 2014) also reported that compared with the usual care, acupuncture showed clinically relevant benefits.

However, the effectiveness of acupuncture in the management of knee OA is affected by many factors such as the types of acupuncture, selecting of the acupoints, Deqi sensation during treatment, and the depth of needle's insertion (Tu et al., 2021, Wang et al., 2020, Lin et al., 2018, Zhang et al., 2016, Helianthi et al., 2016, Ashraf et al., 2014, Hinman et al., 2014, Chen et al., 2013, Jubb et al., 2008, Scharf et al., 2006, Vas et al., 2004, Tukmachi et al., 2004, Berman et al., 1999).

In some previous studies, four reported the clinical effect of electrical acupuncture (EA),

two reported the effect of laser acupuncture (LA), and eleven reported the effect of manual acupuncture (MA), which led to the clinical effect of acupuncture is still controversial.

Both Vas et al. (2004) and Jubb et al. (2008) reported that acupuncture produced a significant effect in pain symptoms when compared with sham acupuncture, in which the Deqi sensation was reported (a needle sensation to check if the needle was performed correctly). To the patients, the Deqi sensation manifests as soreness, numbness, and distention when they were undergoing treatment. To the acupuncturists, the Deqi sensation manifests as needle grasping, which is regarded as one of the most important variables in the studies of the mechanism and efficacy of acupuncture (Yang et al., 2013). The functional magnetic resonance imaging (fMRI) studies (Hui et al., 2005, 2009) showed that the Deqi sensation resulted in clinical benefits, thus some previous acupuncture studies (Ashraf et al., 2014, Helianthi et al., 2016), which failed to report Deqi sensation might not reflect the true effectiveness of the acupuncture.

The selection of acupoints may also have a great influence on the effectiveness of acupuncture. Three studies (Berman et al., 2004, Vas et al., 2004, Jubb et al., 2008) that reported selecting over 8 acupoints showed that acupuncture produced a significant effect in clinical symptoms when compared with sham acupuncture. Conversely, the studies (Hinman et al., 2014, Takeda et al., 1994) which reported selecting 5 to 7 acupoints showed that acupuncture did not perform any better than sham acupuncture. Although Lin's study (Lin et al., 2018), which selected 8 to 10 acupoints in individuals with knee OA showed that the effectiveness of acupuncture was not more effective than sham acupuncture, the acupoints in this study for each subject were not consistent, thus, the results might be influenced.

The depth of needle insertion was also quite different between studies (Takeda et al., 1994, Ashraf et al., 2014, Chen et al., 2013, Berman et al., 2004, Jubb et al., 2008). Both Takeda et al. (1994) and Ashraf et al. (2014) reported that needles were inserted

deeper until subjects experienced Deqi sensation or full depth of needles (25mm) if no Deqi sensation was experienced. Chen et al. (2013) reported that the depth of the needle insertion was from 2 to 30mm, depending on the location of the selected acupoints and the body size of the individuals. The depth of the needle insertion in studies by Berman et al. (2004), and Jubb et al. (2008) were from 10 to 15mm. Interestingly, two studies (Berman et al., 2004, Jubb et al., 2008) which reported 10 to 15mm depth of the needle insertion showed that the acupuncture achieved significant improvements in clinical symptoms when compared with the control group, and other studies (Takeda et al., 1994, Ashraf et al., 2014, Chen et al., 2013) which reported the depth of needle insertion about 25mm demonstrated that the acupuncture did not perform any better than the control group. Therefore, the difference between the depths of the needle insertion indicated that the effectiveness of acupuncture might be influenced by this factor.

Clinical evidence of acupuncture in the management of knee OA is common (Teixeira et al., 2018, Hickstein et al., 2018, Zhang et al., 2016, Vas et al., 2004), however, the relief of the clinical symptoms may not guarantee the slowing of the progression of the disease. Previous studies (Henriksen et al., 2006, Hurwitz et al., 2000) demonstrated that the decreases in pain among individuals with medial knee OA were related to the increased loading of the joints during gait, and then led to the acceleration of the cartilage volume loss. However, most of these studies only compared the subjective variables such as pain scale (e.g., WOMAC, KOSS, and VAS) other than quantified objective variables related to functional movements, such as kinetic outcomes (e.g., EKAM). This may lead to bias in the results, as the scores of the questionnaire could be influenced by different factors such as mental factors. Moreover, as mentioned in previous studies (Liu et al., 2017, Jeong et al., 2019), the reduction of the pain might lead to the improvement of the function such as walking speed and daily walking steps, which ultimately, may increase the loading at the knee during daily activities. Therefore, it is critical to include the biomechanical conditions when evaluating the effects of the treatment in individuals with knee OA.

To date, only three studies investigated the biomechanical effect (Wang et al., 2017, Lu et al., 2010, Liu et al., 2017) of acupuncture in individuals with knee OA. Wang et al. (2017) reported that three-week EA could significantly improve the speed, ankle plantarflexion moment, and second peak of EKAM during descending and ascending stairs. However, they failed to report the kinematic variables, which also play important role in the progression of the disease. Lu et al. (2010) reported that compared with sham acupuncture, acupuncture could significantly improve the pain after receiving 30-minute treatment, and the relief of pain was associated with the alteration of the gait pattern. The knee OA individuals in the acupuncture group showed significant improvements in walking speed, cadence, knee flexion angles at toe-off, peak knee flexion angle at swing phase, and ankle plantarflexion angle at toe-off when compared with the baseline. Additionally, hip flexion moment, knee extension moment, ankle dorsiflexion moment, and hip abduction moment at the beginning of the single stance phase were also significantly higher when compared with the baseline. Additionally, the biomechanical model used in Lu's study (Lu et al., 2010) was based on the Helen Hayes (HH) model, which might lead to inaccurate kinetic and kinematic data, especially on the frontal plane. According to previous studies (Amin et al., 2004, Miyazaki et al., 2002), the EKAM on the frontal plane was the most important evaluation variable of loading at the knee joint during the stance phase, thus the results in their study might not be reliable. Liu et al. (2017) also demonstrated that acupuncture could significantly increase the walking speed, step length, hip flexion, knee flexion, ankle plantarflexion angle at toe-off, and knee flexion angle at swing phase when compared with baseline. Moreover, the ankle plantar moment, hip abduction moment, and knee extension moment were also significantly increased. The results were agreed with the previous study (Lu et al., 2010). However, both Lu et al. (2010) and Liu et al. (2017) only investigated the immediate clinical and biomechanical effects of acupuncture, therefore, it is not known if the immediate effects were similar to short-term (e.g., six weeks) as no previous study has reported the six-week effect of acupuncture on kinematic and kinetic measures.

Admittedly, some OA guidelines such as OARSI (McAlindon et al., 2014), the European League Against Rheumatism (EULAR) (Fernandes et al., 2013), the NICE (NICE, 2014), the ACR (Kolasinski et al., 2020), and the AAOS (Jevsevar et al., 2013) have not recommended using acupuncture for knee OA yet that means further studies are still needed. Therefore, the study that included the temporal-spatial, kinematic, kinetic, and muscle co-contraction variables might help to identify a potential underlying biomechanical mechanism of acupuncture in the management of knee OA, which has not been assessed by previous studies.

2.7.3.5.2.2 Mechanism of acupuncture in the management of knee OA

Previous studies (Itoh et al., 2008, Helianthi et al., 2016, Park and Cho 2017, Zhang et al., 2016) reported that the efficacy of acupuncture for reducing the pain and improving the physical function in individuals with knee OA, however, little study investigated the underlying mechanism of this kind of intervention.

Yuan et al. (2018) reported that acupuncture could inhibit the expression of the IL-1beta by activating the CB2 receptor, which leads to a reduction of pain in the knee OA mouse. Some researchers (Xi et al., 2016) reported that the mechanism of acupuncture in the treatment of knee OA is associated with the blocking expression of collagen type/DDR2/MMP13. Seo et al. (2016) reported that the analgesic mechanisms of acupuncture are caused by the 5-HT1, 5-HT3, and muscarinic cholinergic receptor antagonists. Bao et al. (2011) found that acupuncture could help to inhibit MMP-1 and MMP-3 and increase the expression of TIMP1 and then protect cartilage from OA. Although these studies (Yuan et al., 2018, Xi et al., 2016, Seo et al., 2016, Bao et al., 2011) partially explained the mechanism of acupuncture treatment, most of these studies were based on the animal models and biological parameters.

Based on the National Health Service (NHS) introduction, the mechanism of acupuncture in the treatment of knee OA could be divided into two parts: western medicine and the TCM theories. Western medicine believes that acupuncture works to

stimulate sensory nerves under the skin and the muscles which may help to improve the muscles' function and then relieve the pain. TCM theory which is used in the treatment of musculoskeletal disorders such as knee OA is very similar to western medicine as TCM doctors also believe that muscle activity plays an important role in the progression and development of musculoskeletal disease (Wang et al., 2012).

To date, the relationship between the pain and biomechanical changes in gait of individuals with knee OA the knee after receiving acupuncture is poorly understood, and the potential biomechanical mechanism of the acupuncture has not been further investigated. Moreover, the rationale behind acupuncture is still a subject of controversy. Some researchers (Qaseem et al., 2017, Linde et al., 2016, McAlindon et al., 2014) believe that the theories behind acupuncture in the management of knee OA are that it has an analgesic effect. Additionally, some researchers (Sandberg et al., 2003) reported that acupuncture could increase the blood flow in the lower limb muscles such as the tibial anterior, and the increased peak blood flow was associated with the increase of muscle strength in elder people (Kim et al., 2017). Based on the previous studies (Hall et al., 2018, Al-Khlaifat et al., 2016) the increase of the strength of the muscles around the knee could help to improve the pain and physical function in individuals with knee OA, therefore, the potential underlying biomechanical mechanism of acupuncture in the management of knee OA may have a relationship with it.

2.7.3.5.3 Massage

Massage is the manipulation involving pressing, stretching, and rubbing of the soft tissues and muscles in the focused area with certain forces. There are several different types of massage in the world (e.g., CM (Wang et al., 2015), Thai massage (Chiranthanut et al., 2014), and Swedish massage (SM) (Juberg et al., 2015). Although the operation of different massage might slightly differ from each other, all the massages include pressing and stretching, with which the therapist could relieve the stiffness and pain by stimulating the soft tissue and muscles manually and improve local

blood circulation and muscle function (Wang et al., 2015， Chiranthanut et al., 2014， Juberg et al., 2015).

2.7.3.5.3.1 Effectiveness of the massage in the management of knee OA

Some previous RCT studies (Islam et al., 2021, Alkhawajah & Alshami, 2019, Pehlivan & Karadakovan, 2019, Efe Arslan et al., 2018, Perlman et al., 2018, Mutlu et al., 2018, Nasiri et al., 2016, Cruz-Montecinos et al., 2015, Field et al., 2015, Dwyer et al., 2015, Atkins et al., 2013, Perlman et al., 2012, Yip et al., 2008, Pollard et al., 2008, Perlman et al., 2006, Deyle et al., 2000) reported the positive clinical effects of massage in the management of knee OA. However, the types of the massage, the sessions of treatments, and the control group between studies were quite different. Interestingly, most of the massage groups (e.g., aromatherapy massage (AM), SM, MT, Self-massage) produced significant improvements in clinical symptoms when compared with the baseline and control group, except the studies by Chiranthanut et al. (2014) and Islam et al. (2021) showed there was no significant difference between the intervention group and the control group. The session of the massage was also quite different between studies which were from 1 to 20 with two studies (Alkhawajah & Alshami. 2019, Cruz-Montecinos et al., 2015) only reported the short-term effect of the massage. Moreover, the control groups in some previous studies were also quite different, with only four studies using sham massage or light touch and three studies using the waiting list as control. Perlman et al. (2018) reported that the eight-week short-term massage could relieve the pain symptom caused by knee OA, however, fifty-two-week long-term massage therapy did not show additional benefit beyond usual care. Nasiri & Mahmodi. (2018) claimed that compared with the control group (no massage), the massage group showed an immediate effect, however, there was no significant difference between groups after the treatment. Tanaka et al. (2018) reported that short-term massage therapy could help to enhance the pressure-pain threshold and then lead to the improvement in the pain during rest and walking, however, it did not affect the spasm of the muscle in the OA knees. A system review (Bervoets et al., 2015) concluded that massage could help to reduce the pain and improve the function in individuals with

knee OA, however, compared with other treatments, no significant benefits were evident. Juberg et al. (2015) reported that knee OA individuals who accepted eight-week massage therapy showed significant improvements in WOMAC, VAS pain, and knee joint ROM, however, there was no improvement in the time of walking 50 feet. Chiranthanut et al. (2014) reported that compared with the oral Ibuprofen, the massage could provide comparable clinical efficacy after receiving a three-week intervention without any side effects which were caused by the NSAIDs, thus, this kind of treatment should be considered as the complementary and alternative treatments for knee OA. Atkins et al. (2013) claimed that individuals with knee OA who received thirteen sessions of self-massage showed significant improvements in WOMAC pain, stiffness, function subscales, and total WOMAC scores in comparison with their counterparts in the wait-list control group.

Massage, which is also called Tui Na in TCM, also plays an important role in the management of knee OA in China (Zhu et al., 2015, Zhou et al., 2012, Deng et al., 2012, Li et al., 2019, et al., Wang 2005, Zhu et al., 2009, Zhu 2011). The TCM doctors believe that massage could make the muscle relax and open up the channels of the meridian system that could help to relieve the symptoms caused by the disease (Wang et al., 2015). Some previous studies (Wang et al., 2015, Zhu et al., 2009, Zhu, 2011, Zhou et al., 2012) reported that CM could relieve the pain symptoms and improve the quality of life in individuals with knee OA. Zhou et al. (2012) reported that compared with the oral administration of meloxicam, the knee OA individuals who were treated with the CM achieved a better therapeutic effect. Deng et al. (2012) reported that the CM could improve the scores of pains, joint mobility, and malformation in individuals with knee OA. Li et al. (2019) claimed that the WOMAC and the muscle tension of knee flexors and extensors were significantly improved by the CM in individuals with knee OA. Jin et al. (2017) demonstrated that the massage could significantly relieve pain, improve muscle strength, and walking speed in individuals with knee OA, and the results were consistent with Zhu's study (Zhu et al., 2015) which also demonstrated that the CM could improve not only the pain symptoms but also the muscle strength. Therefore, the

latest diagnosis and management of knee OA: Chinese medicine expert consensus (Chen et al., 2015) recommend massage as one of the most important interventions in the management of knee OA. However, the latest western guideline (e.g., ACR, NICE, OARSI) demonstrated that the massage is conditionally recommended against in individuals with knee OA and should be considered as an adjunct to core intervention (Kolasinski et al., 2020, Bannuru et al., 2019, NICE, 2014, Zhang et al., 2007).

Although the clinical effect of the massage has been proved by some studies, most of the previous studies only compared the subjective variables such as pain scale, less study investigated the biomechanical effect of the massage, which indicates that the difference in kinetic variables at pre-and post-treatment is still unclear. Symptoms management is typically the priority of treatments for knee OA (Hunter & Felson. 2006). Previous studies (Jin et al., 2017, Zhu et al., 2015, Atkins and Eichler. 2013) have reported positive clinical effects of massage in the management of knee OA, however, the relief of the clinical symptoms may not guarantee the slowing of the progression of the disease. Some previous studies (Henriksen et al., 2006, Hurwitz et al., 2000) demonstrated that the reduction of pain was related to higher loading of the knee (e.g., EKAM) during gait and then led to the acceleration of the cartilage volume loss. To date, the relationship between the pain and biomechanical changes during gait in individuals with knee OA after receiving CM is poorly understood and the potential biomechanical mechanism of the CM has not been further investigated.

To date, only three studies have reported the biomechanical effectiveness of massage in individuals with knee OA (Cruz-Montecinos et al., 2017, Zhu et al., 2016, Zhu et al., 2015). Cruz-Montecinos et al. (2017) showed that massage could increase the lateral muscle co-contraction in knee OA individuals' gait during stair ambulation. However, they just investigated the effects of one session of massage on muscle co-contraction. Zhu et al. (2015) reported that two-week CM significantly reduced pain symptoms, and the relief of pain was associated with increased muscle strength. Another study (Zhu et al., 2016) indicated that two-week CM could also significantly reduce pain, stiffness,

and function in individuals with knee OA. Additionally, the improvement of clinical symptoms was associated with the increase of walking speed and step width. However, no significant improvement in the kinematics of the hip, knee, or ankle was found. Unfortunately, none of these studies investigated the kinetic variables in the frontal and transverse planes, and muscle activity. To date, the relationship between the change of pain and biomechanical variables (e.g., EKAM and muscle co-contraction) after receiving a short-term massage has not been investigated. Based on previous studies, muscle co-contraction has a strong relationship with loading at the knee (Hodges et al., 2016), which plays an important role in the development and progression of the knee OA, thus, the CM may have some biomechanical effects on the OA knees. So far, to our knowledge, no previous study has investigated the effects of CM on both kinematics, kinetics, and muscle co-contraction variables in individuals with knee OA.

2.7.3.5.3.2 Mechanism of massage in the management of knee OA

Several previous studies have proved that massage therapy is very effective in the treatment of knee OA, however, no consensus on the mechanism of massage has been achieved. Huang et al. (2008) reported that the massage therapy could help to increase the activity of the synovia superoxide dismutase (SOD) and decrease the MDA and nitric oxide (NO) contents in the knee joint of rabbit, which might help to delay the progression of knee OA. Meanwhile, Huang et al. (2007) revealed that massage therapy could suppress the expression of the synovia IL-1beta and TNF-α, which partially indicated the possible mechanisms of the massage therapy in the treatment of the OA knees. However, these studies (Huang et al., 2008, Huang et al., 2007) were based on tests on animals.

The functioning mechanisms of all types of massage are quite similar (NHS, 2019, Jiang et al., 2018). It is commonly believed that massage could help to relieve the stiffness of the muscles and improve blood circulation. Jiang et al. (2018) reported that the CM could help to correct the knee joint alignment by reducing the muscle spasm and stiffness. Cruz-Montecinos et al. (2015) reported that the reduction of the pain in

individuals with knee OA was associated with the increased lateral muscle co-contraction, as this could help to generate an internal abduction moment and reduce the loading (EKAM) at the medial compartment of the knee. However, they only reported biomechanics effects of one session of MT, therefore, the results might not be reliable. Zhu et al. (2015) reported that two-week CM treatment could significantly reduce the pain, and the relief of pain was associated with increased quadriceps muscle strength. Based on the previous studies available (Slemenda et al., 1998, Oiestad et al., 2015, Hurley, 1999), quadriceps muscle weakness is an important risk factor in the development of knee OA, Therefore, the biomechanical mechanism of massage in the management of knee OA might be correlated with this.

There are significant limitations with the previous studies on massage used in individuals with knee OA. Firstly, quite some studies didn't have a no-treatment control group at all. Secondly, less study compared the kinetic and muscle performance outcomes such as EKAM and muscle co-contraction. Therefore, further researches are needed to further investigate the effect of the CM on individuals with knee OA.

2.8 Research gap

Although quite some studies have concluded that the TCM interventions were very effective in the management of knee OA (OreiziEsfahani et al., 1996, Jubb et al., 2008, Shen et al., 2009, Chen et al., 2010, Wang et al., 2015), other studies have indicated there was still no enough evidence to support such conclusions (Take & Wessel, 1994, Miller et al., 2011, Hinman et al., 2014). There are still some questions about TCM treatments in the management of knee OA, which can be summarised as follows:

(1) Little studies have investigated the biomechanical effect of TCM interventions. There is still a lack of a consensus on whether TCM treatments could help to decrease the loading at the knee joint (e.g., EKAM, muscle co-contraction), which is believed to have a strong correlation with the development and progression of the knee OA.

(2) The majority of the assessments to the effectiveness of TCM treatments of knee OA have been summative and qualitative based on the subjective variables such as the WOMAC and VAS, other than quantified objective variables such as kinetic, kinematic, muscle activities, and temporal-spatial parameters. Consequently, the biomechanical effects of the TCM treatments have not been revealed.

To develop an understanding of the short-term (six weeks) clinical and biomechanical effects of the TCM treatments in individuals with medial knee OA, an RCT was conducted on three interventional groups (i.e., CH, AT, and CM) and one control group (CN). A total of sixty medial knee OA participants were recruited from the Shuguang Hospital (Shanghai, China). The participants were asked to sign the informed consent and then contribute baseline data before they were randomly allocated to intervention groups and the control group. The medial knee OA participants were assessed for clinical symptoms and biomechanical function before and after six-week CN, CH, AT, and CM. Further clinical and biomechanical function comparisons were then made between the TCM groups and the control group.

Chapter 3 Research methodology and test-retest reliability study

3.1 Introduction

The effect of treatments for knee OA could be assessed with either qualitative measures such as pain scales (e.g., WOMAC, VAS) (Hinman et al., 2014) or quantitative measures such as the biomechanical results (e.g., EKAM) based on the gait analysis test (Al-Khlaifat et al., 2016). The pain score is normally acquired by asking the patients to answer the designed questions, which reflect the clinical effect (Hinman et al., 2014). Since it is simple and easy to acquire the data it has been frequently used. However, the pain score doesn't reveal the true knee biomechanical conditions, which play a critical role in the development and progression of knee OA. Therefore biomechanical assessments need to be performed. In current study, both methods were used in the assessment of the TCM treatments effect. The motion capture system, force platforms, and muscle activities measuring system and the methods for system calibration, markers and sensors placement, data processing, biomechanical modelling, kinematics, and kinetics computation and results presentation were introduced in this chapter.

Although using biomechanical outcomes such as joint angles, joint moments, and GRF could accurately quantify the assessment to functions and treatment effect, the accuracy of the outcomes depends on the laboratory settings and the proficiency and consistency of the investigator in markers and sensors placement, system operation, data procession, and computation. To minimize the errors in the measurement and achieve confidence in achieving high-quality data, test-retest reliability studies were conducted after learning and practicing the entire experiment process. The results of the test-retest reliability study were presented in this chapter after the introduction of the methods.

This chapter aimed to: (1) introduce the methodology used in the study, (2) assure that the investigator was familiarized with and mastered the operation of experimental

instruments, (3) enhance the investigator's awareness of the data quality and minimizing the operational and system setting error.

3.2 Research environment

3.2.1 Gait analysis system

The data collection for this study was performed in the gait laboratory of Shuguang Hospital, Shanghai, China. A sixteen-camera (VICON MX T40 series, UK) three-dimensional motion analysis system (NEXUS 1.8.5) with a sampling rate of 100 Hz, and with four integrated force plates (BP400600, AMTI, USA) with a sampling rate of 1000 Hz were used to collect kinematic and kinetic data during gait (Figure 3-1).

Figure 3-1 VICON motion analysis system in the gait laboratory of Shuguang Hospital affiliated to the Shanghai University of TCM

3.2.2 sEMG system

A sixteen-channel wireless sEMG system (TeleMyo 2400T Direct Transmission Systems (DTS), Noraxon USA Inc., USA) with a sampling rate of 1500 Hz was

synchronized with the VICON system to collect surface sEMG signals.

3.3 System setup and calibration

3.3.1 Position and installation of the infrared cameras

The positions of infrared cameras were adjusted and fixed on the wall of the laboratory to guarantee that the VICON gait motion system captured all retro-reflective markers. Such an installation could prevent the position of each camera from being moved during the test, and every marker could be captured by at least two infrared cameras during the test so that a three-dimensional model could be reconstructed (Kirtley, 1985).

3.3.2 Calibration and setting up of the laboratory coordinative system

The VICON system must be calibrated and pass the calibration test before performing any static and dynamic trials. Firstly, the investigator must remove all the reflective markers or stuff and map the irremovable reflections in the capture volume, and then perform a wand calibration by waving a five markers active Wand & L frame for a designed time length. After that, the investigator placed the five markers active Wand & L frame (Figure 3-2) flat on the floor, normally at the corner of a chosen force plate so that the two axes of the calibration and setting up of the laboratory coordinative system that is regarded as the Global Coordinate System (GCS) in the modelling and computation would align with the two sides of the force plate. The positions of any markers during any trials would be recorded relative to the GCS.

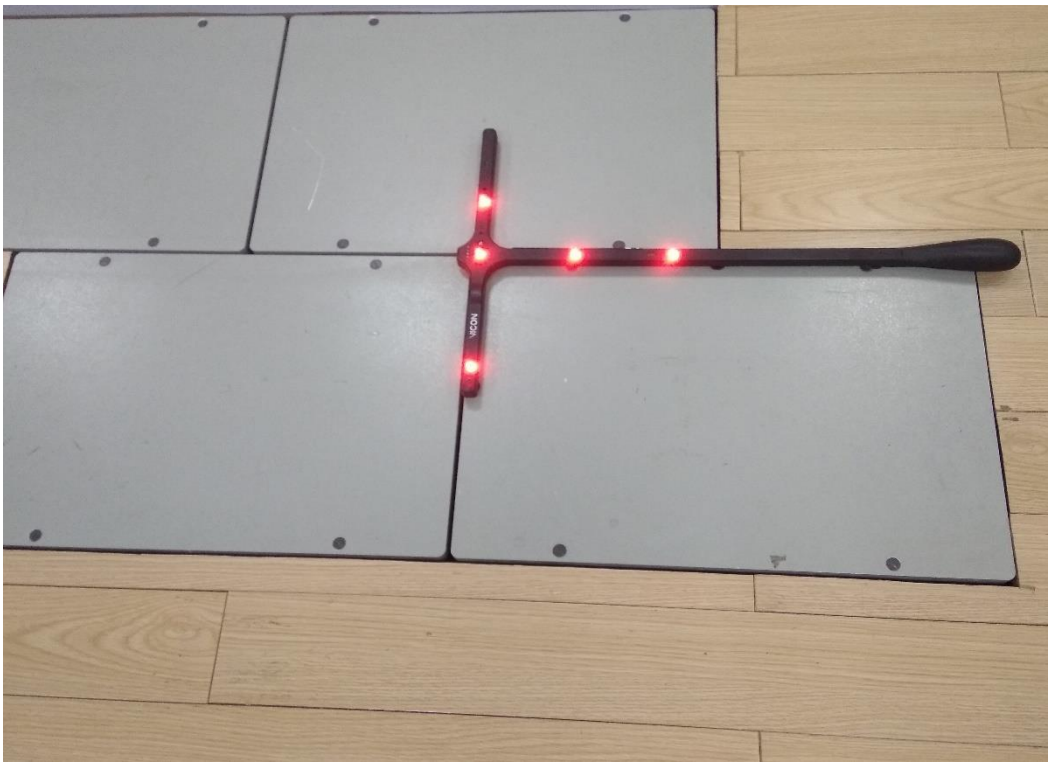


Figure 3-2 VICON calibration wand & L frame with five active markers.

3.3.3 Position and orientation of the force plates

The force plate is normally factory calibrated with high accuracy and delivered with a calibration matrix. However, errors in the installation of the force plates and setting up in the motion capture space relative to the GCS could affect the quality of the biomechanical data. Any small mistakes in the parameter settings or calibration parameters could lead to a significant error in the kinetic outcomes. Therefore, the setting quality must be assessed before performing any gait test because the accuracy and repeatability of the biomechanical data are critical to clinical studies.

For the GCS, the origin was the corner of the force plate 1 and Y is along the walkway. Walking along the Y direction, the subject's medial and lateral direction (the direction from left to right) was the positive direction of the X-axis, the Z was the axis determined by X and Y. The positive Z-axis was the upward vertical direction when the X-Y plane represented the level plane (floor).

3.4 Placement of the markers and sEMG sensors

3.4.1 Marker placement

Forty-four retro-reflective markers (diameter: 14mm) were used in the study. Twenty-four markers were attached with self-adhesive tape on the bony prominences of each participant's lower limbs at the anterior superior iliac spine (ASIS), posterior superior iliac spine (PSIS), Iliac crest, greater trochanter, medial epicondyles, lateral epicondyles, lateral malleolus, medial malleolus, 1st, 2nd, and 5th metatarsal head and calcaneal tubercle (Table 3-1). Twenty markers were used to form five 4-marker clusters (Table 3-2). The movement of each femur and shank was tracked with a curved shaped marker cluster with four non-collinear markers. Another flat-shaped marker cluster (4-marker) was used to track the movement of the pelvis (Figure 3-3). These marker clusters were secured with elastic bandages (Super Wrap, Fabrifoam, USA) on the lateral aspect of the leg, thigh and at the back of the pelvis (Figure 3-4) (Cappozzo et al., 1995). Each foot was assumed to be one rigid segment body and tracked with the four markers described above (Table 3-2).

Figure 3-3 Marker cluster plates (with four nonlinear reflective markers)

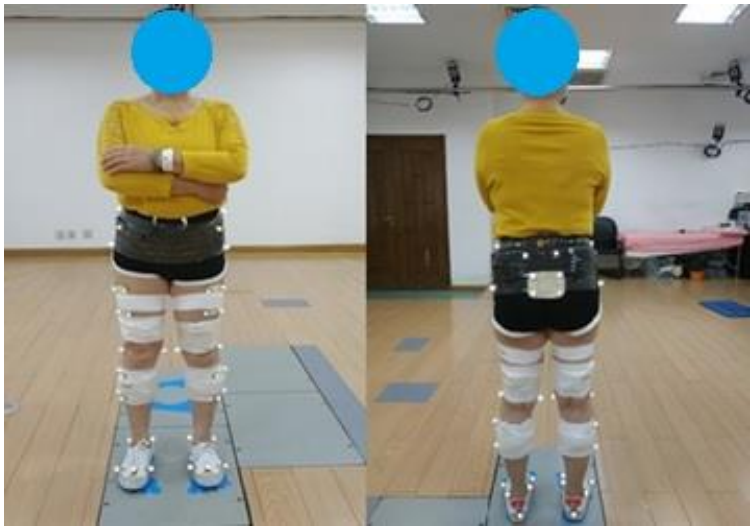


Figure 3-4 The anterior and posterior view of the subject with markers and sEMG sensors (fixed and covered by elastic tapes)

The markers attached on the bony landmarks were defined as anatomical markers, which were used to define the coordinative system of each segment and the joints' centre (Cappozzo, 1995). The pelvis was defined by the left/right ASIS and PSIS and the height of the subject, the centre of the hip was defined by left/right ASIS, PSIS. The centre of the knee was defined by bilateral medial and lateral epicondyles, and the centre of the ankle was defined by medial and lateral malleolus (Cappozzo, 1995) (Figure 3-5).

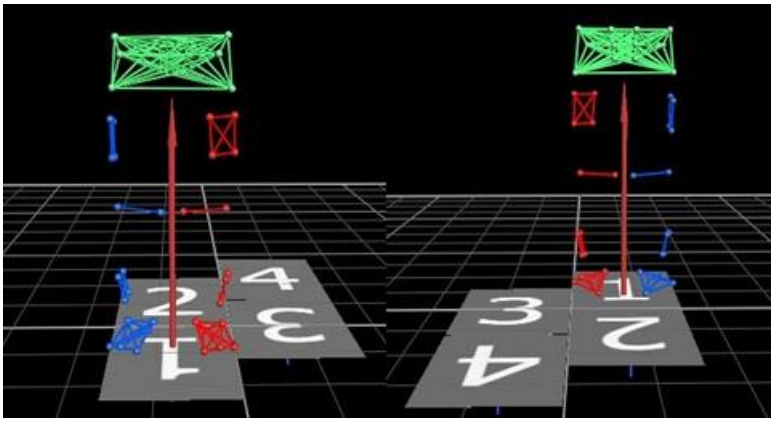


Figure 3-5 The digitized markers shown in anterior and posterior views in VICON Nexus 1.8.5 software

All of the markers remained attached to the subject during dynamic trials even though

only the tracking markers would be kept for the calculation of kinematic and kinetic results, and pen marks were made to remember the position reflective markers would be attached to ensure that the reflective markers could be put back in the same position once they dropped during the walking test. This protocol was designed to ensure the dropped markers' replacement during the test to be consistent so that the errors were minimal.

Table 3-1 The anatomical landmarkers

Markers	
ASIS	PSIS
Iliac crests	Greater trochanters
Lateral femoral condyle	Medial femoral condyle
Lateral malleolus	Medial malleolus
The 1st metatarsal head	The 2nd metatarsal head
The 5th metatarsal head	Calcaneus

Table 3-2 The technical markers

Segement	Markers
Pelvis	Pelvis cluster pad (4 tracking markers)
L/R thigh	Thigh cluster pad (4 tracking markers)
L/R shank	Shank cluster pad (4 tracking markers)
L/R foot	The 1st metatarsal head, the 2nd metatarsal head, the 5th metatarsal head, and the Calcaneus

3.4.2 sEMG sensors placement and skin preparation

The Noraxon Dual sEMG electrodes (Noraxon, USA, Inc) were attached to the bilateral VL, VM, biceps femoris (BF), semitendinosus (ST), MG, LG, TA (Figure 3-6) for the muscle performance measurement. All the DTS surface electrodes were attached based on the recommendations published by the Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) guideline (Hermans et al., 1999) (Table 3-3). Before the sEMG electrodes were attached, the attachment areas should be shaved and then cleaned with an alcohol swab and rubbed with hypo-allergenic gel to decrease skin impedance and improve sEMG signal recording.

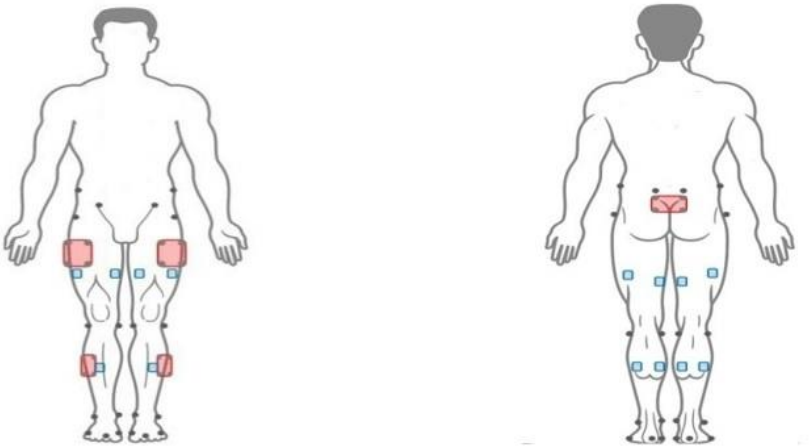
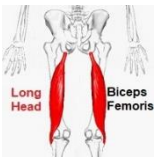
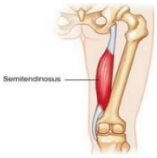
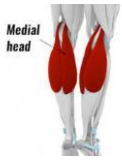


Figure 3-6 The anterior and posterior view of the electrodes placement (blue) and the kinematic markers (grey dots and red boxes)

Table 3-3 The location of the sEMG sensors

Muscles	sEMG sensors location
Vastus lateralis (VL) 	Two-thirds on the line from the ASIS to the lateral side of the ipsilateral patella.
Vastus medialis (VM) 	Four-fifth on the line between the ASIS and the joint space in front of the anterior border of the medial ligament.
Biceps femoris (BF) 	The midpoint on the line between the ischial tuberosity and the lateral epicondyle of the tibia.
Semitendinosus (ST) 	The midpoint on the line between the ischial tuberosity and the medial epycondyle of the tibia.
Medial gastrocnemius (MG) 	The most prominent bulge of the muscle.
Lateral gastrocnemius (LG) 	One-third on the line between the fibula head and the heel.
Tibialis anterior (TA) 	One-third on the line between the tip of the fibula and the tip of the medial malleolus.

3.5 Maximal voluntary isometric contraction

All the participants were asked to complete the **maximal voluntary isometric contraction (MVIC)** test before gait analysis. The MVIC data were used for normalizing the sEMG data during the walking trials. Considering the participants in this study with varying degrees of knee OA severity and levels of mobility, the positions for MVIC collection should be easy for them to complete the test without any difficulties. For the VL and VM, participants were asked to sit on a padded side-table, and back against the wall with hips flexed approximately 90 degrees, and knee flexed approximately 45 degrees. For the ST and BF, the participants were asked to lie face down on the bed with the knee flexed approximately 20 degrees. For the LG, MG, and TA the participants were asked supine with hip and knee flexed at approximately 90 degrees, ankles in a neutral position. Manual resistance offered by the investigator was applied to oppose the flexion/extension of the knee and plantarflexion/dorsiflexion of the ankle. None of the participants were able to overcome the manual resistance during the MVIC trials. During the MVIC test investigator provided visual feedback of the sEMG signal magnitude and verbal encouragement to help the participants to push maximally during each trial (Zeni et al., 2010).

3.6 Biomechanical modelling and computations

3.6.1 Calibrated Anatomical System Technique

The calculation of the kinematic data is based on the marker location (marker set). The most common model in clinical studies is based on some variation of the HH model (Kadaba et al., 1990). However, the joint angle calculation based on the HH model is only constrained with three rotational degrees-of-freedom (DOF), due to the low resolution of infrared cameras so had to have fewer markers, as far as possible (Della et al., 2005). Moreover, the HH model introduces unnecessary errors to joint angle calculation as the segment definition relies on the markers shared with the proximal segment (e.g. the definition of the shank relies on the markers on the knee shared with

the thigh) (Cereatti et al., 2007).

To avoid the errors in the calculation of kinematics in the gait model, the Calibrated Anatomical System Technique (CAST) technique has been developed to track the movement of each segment independently, allowing 6DOF (translational and rotational) at each joint during level walking trials in the current study.

3.6.2 Segment modelling

The Global (laboratory) coordinates system was used to define the position of the markers in three-dimensional space. A virtual laboratory system based on both the GCS and an indicator marker was established to solve the problem that the sign of certain biomechanical data would change with the walking direction (Figure 3-7).

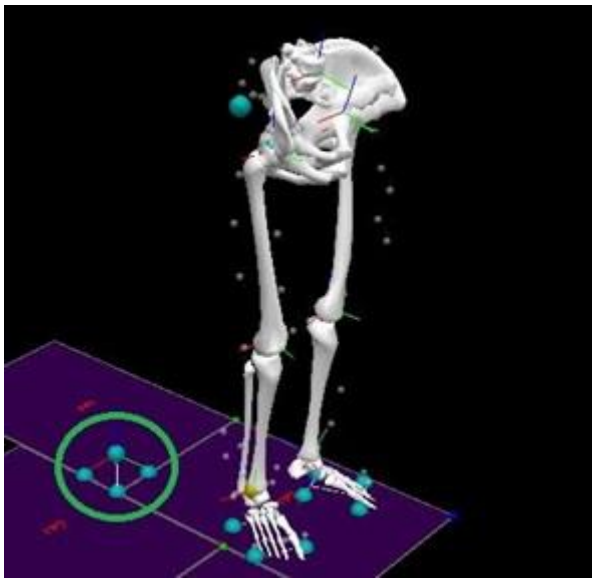


Figure 3-7 Virtual laboratory system based on both the global coordinates system and an indicator marker (the green circle represented the virtual laboratory)

For this study, a lower limb model consisting of the pelvis, left/right (L/R) thigh, L/R shank, and L/R foot should be built in the software of Visual 3D based on the markers on the anatomical landmarks. The CODA pelvic model (Bell et al., 1990) was used for this study. The proximal joint of the thigh was defined by the ipsilateral great trochanter

and the center of the hip joint, the distal joint and radius were defined by the ipsilateral medial/lateral epicondyles, the tracking markers used for calculating the trajectories of the thigh were the four non-collinear markers on the cluster which was attached to the anterior lateral of the thigh. The proximal joint of the shank was defined by ipsilateral medial/lateral epicondyles, the distal joint and radius were defined by the ipsilateral medial/lateral malleolus markers, and the tracking makers used for calculating the trajectories of the shank were the four non-collinear markers on the cluster which was attached on the anterior lateral of the leg. The foot proximal joint and the distal joint were defined by medial/lateral malleolus and 1st metatarsal/ 5th metatarsal head markers, the tracking landmarks were the markers on the tuberosity calcaneus (heel), 1st metatarsal, 2nd metatarsal, and 5th metatarsal. To remove the inclination offset of the ankle angle to make a clinically meaningful ankle angle the calculation of the kinematics of the ankle were between virtual foot and shank, whereby the virtual foot was established by using the four virtual markers projected to the floor so that a zero-ankle angle in neutral position could be achieved. The four markers used to project to the floor were medial/lateral malleolus and 1st metatarsal/ 5th metatarsal head markers.

The segment (local) coordinate system was defined by the markers on bony prominences of the subjects' lower limbs. (Table 3-4, Figure 3-8)

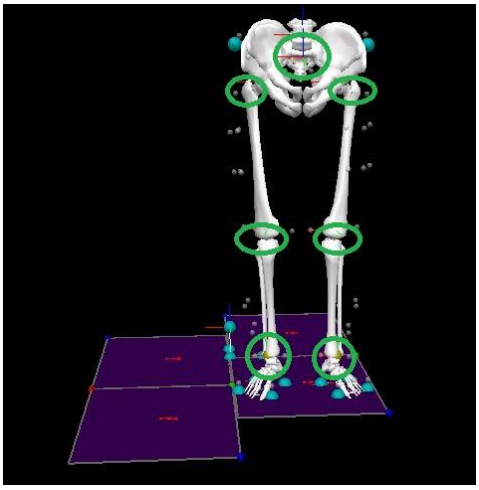


Figure 3-8 Local coordinates system (LCS) (The green circle indicates the LCS, pelvis, left/right hips, knees, and ankles)

Table 3-4 The definition the joint segment (local) coordinates system in Visual 3D

Segment	Joint Origin	X axis	Y axis	Z axis
Pelvis	The origin is defined as the midpoint between the ASIS markers	The x-axis is defined from the origin toward the right ASIS (Direction from origin to right ASIS is defined as positive)	The y-axis is then the cross product of the z-axis and x-axis (Anterior direction is defined as positive)	The z-axis is perpendicular to the (x-y) plane. The (x-y) plane of the segment coordinate system is defined as the plane passing through the right and left ASIS markers, and the mid-point of the right and left PSIS markers. (Direction from distal to proximal, proximal as positive)
Thigh	The origin is created automatically when the CODA pelvis segment is created	The x-axis is defined from the origin toward to the greater trochanters (Direction from origin to right is defined as positive)	y-axis is orthogonal to the (x-z) plane (Anterior direction is defined as positive)	The z-axis is defined by the vector from midpoint between medial femoral condyle and lateral femoral condyle toward the origin (Direction from distal to proximal, proximal as positive)
Shank	The origin is defined as the midpoint between medial femoral condyle and lateral femoral condyle	The x-axis is defined from the origin toward to the lateral femoral condyle (Direction from origin to lateral femoral condyle is defined as positive)	y-axis is orthogonal to the (x-z) plane (Anterior direction is defined as positive)	The z-axis is defined by the vector from midpoint between medial malleolus and lateral malleolus toward the origin (Direction from distal to proximal, proximal as positive)
Foot	The origin is defined as the midpoint between medial malleolus and lateral malleolus	The x-axis is defined from the origin toward to the lateral malleolus (Direction from origin to lateral femoral condyle is defined as positive)	y-axis is orthogonal to the (x-z) plane (Anterior direction is defined as positive)	The z-axis is defined by the vector from midpoint between the first metatarsal head and the fifth metatarsal head toward the origin (Direction from distal to proximal, proximal as positive)

The positions and trajectories of markers exported in the c3d format were used to model each segment and calculate the 6DOF for all segments in the dynamic condition. The 6DOF movement of a segment in three-dimensional space included three translation degrees of freedom (X, Y, Z) and three angular movements (α, β, γ) about the reference frame. These have been widely used to calculate the biomechanical outcomes for individuals with musculoskeletal or neurological disease (Kepple et al., 1988).

3.6.3 Biomechanical parameters calculation

3.6.2.1 Gait events

The gait events such as right heel strike (RHS), right foot makes initial contact with a force plate (RON), right foot finish the contact with the force plate (ROFF) and right foot toe left the floor (RTO) were automatically created in Visual 3D by running the "Automatic_Gait_Events". Gait events were very important for the presentation of gait biomechanical data and gait analysis. Checking the events and making sure the wrong events to be deleted are very important for enhancing the data quality.

3.6.2.2 Joint kinematics calculation

The angular movements of the pelvis, hip, knee, and ankle joint in the sagittal, frontal, and transverse planes are calculated in Visual 3D based on Euler theory, the joint angle was defined as the distal segment rotate about the proximal segment. The Cardan rotation sequence used in the current study was the default Cardan sequence used in Visual3D. The Cardan sequence was the ordered sequence of rotations (x, y, z) that assumed that the Z-axis was in the up/down/axial direction and the Y-axis was anterior/posterior, or the direction of travel (Kadaba et al., 1990) (X= flexion/extension, Y=abduction/adduction, Z=longitudinal rotation). The signs of each component of the joint angle follow the right-hand rule (Watson 1998). The convention and relationship between the sign of the angle component and the clinical descriptions were listed in Table 3-5.

Table 3-5 Convention of joint angle calculation

Parameter	Range begin/end	Segment	Segment reference	Positive/negative
Hip flexion/extension	RHS to RTO	Thigh	Pelvis	Flexion=positive
	LHS to LTO			Extension=negative
Hip ab/adduction	RHS to RTO	Thigh	Pelvis	Abduction=positive
	LHS to LTO			Adduction=negative
Hip internal/external rotation	RHS to RTO	Thigh	Pelvis	Internal=positive
	LHS to LTO			External=negative
Knee flexion/extension	RHS to RTO	Shank	Thigh	Flexion=positive
	LHS to LTO			Extension=negative
Knee varus/valgus	RHS to RTO	Shank	Thigh	Varus=positive
	LHS to LTO			Valgus=negative
Knee external/internal rotation	RHS to RTO	Shank	Thigh	External=positive
	LHS to LTO			Internal=negative
Ankle dorsi/plantarflexion	RHS to RTO	Virtual foot	Shank	Dorsiflexion=positive
	LHS to LTO			Plantarflexion=negative
Ankle inve/eversion	RHS to RTO	Virtual foot	Shank	Inversion=positive
	LHS to LTO			Eversion=negative
Foot progression	RHS to RTO	Foot	Virtual	Internal=positive
	LHS to LTO		Laboratory	External=negative

Abbreviation: Right heel strike=RHS, left heel strike=LHS, right toe off=RTO, left toe off=LTO

3.6.2.3 Joint kinetics calculation

Based on the kinematic results and the GRF data, the moments of the hip, knee, and ankle joint in the sagittal, frontal, and transverse planes could be calculated in Visual 3D. The resolution coordinate system was set as that of the distal segment and the moment discussed in this study were all external moments. Although joint moments in the stance phase (RHS-RTO, LHS-LTO) always exist, they could be calculated only when the stance phase happens on a force plate. Therefore, the valid stance phase for the calculation of joint moments is defined as RON to ROFF, LON to LOFF. The convention and definition of the joint moment calculation, signs, and clinical descriptions were listed in Table 3-4. Based on the EKAM results, the KAAI was calculated in VISUAL3D, which is the integration of EKAM in a stance (Table 3-6).

Table 3-6 Convention of joint moment calculation

Parameter	Rang begin/end	Segment	Resolution coordinate system	Normalization (Default)	Positive/negative
Hip flexion/extension	RON to ROFF LON to LOFF	Hip	Pelvis	Body weight and height	Extension=positive Flexion=negative
Hip ab/adduction	RON to ROFF LON to LOFF	Hip	Pelvis	Body weight and height	Addition=positive Abduction=negative
Knee flexion/extension	RON to ROFF LON to LOFF	Knee	Thigh	Body weight and height	Extension=positive Flexion=negative
Knee ad/abduction	RON to ROFF LON to LOFF	Knee	Thigh	Body weight and height	Adduction=positive Abduction=negative+
Ankle dorsi/plantarflexion	RON to ROFF LON to LOFF	Ankle	Shank	Body weight and height	Plantarflexion=positive Dorsiflexion=negative
Ankle in/eversion	RON to ROFF LON to LOFF	Ankle	Shank	Body weight and height	inversion=positive Eversion=negative

3.6.2.4 GRF

GRF of each foot in the stance phase was calculated in Visual 3D (Table 3-7).

Table 3-7 Convention for GRF

Parameter	Rang begin/end	segment	Resolution coordinate system	Normalization (Default)	Positive/negative
Ant/post RGF	RON to ROFF LON to LOFF	Foot	Virtual Laboratory	Body weight	Anterior=positive Posterior=negative
Medial/lateral GRF	RON to ROFF LON to LOFF	Foot	Virtual Laboratory	Body weight	Medial=positive Lateral=negative
Vertical GRF	RON to ROFF LON to LOFF	Foot	Virtual Laboratory	Body weight	Vertical upward=positive

3.6.2.5 sEMG data (muscle co-contraction)

To date, some different methods for calculating muscle co-contraction have been reported: ① the ratio of peak muscle activity (agonist and antagonist) (Hortobágyi et al., 2005), ② the magnitude of concurrent activities (agonist + antagonist) (Preece et al., 2021), ③1-antagonist mean EMG/agonist mean EMG (If agonist means EMG＞ antagonist means EMG), or 1 - agonist mean EMG / antagonist mean EMG (If agonist means EMG＜antagonist means EMG) (Heiden et al., 2009), ④ Muscles co-contraction was defined as the average of simultaneous activation of a pair of agonist and antagonistic muscles. Muscle co-contraction=EMG lower/EMG higher × (EMG lower +EMG higher)*100%, the EMG lower was the level of activity in the less active muscle, and EMG higher was the level of activity in more active muscle. (Rudolph et al., 2001).

When the first method is used to calculate the muscle co-contraction, the magnitude of the co-contraction depends on the ratio of agonist and antagonist, which means even two muscles with similar low magnitude will still show greater muscle co-contraction. When the second method is used, the ratio of paired muscles would be neglected. For the third method, if the magnitude of the agonist and antagonist are very close, the muscle co-contraction can be taken arbitrarily close to 0. For these reasons, Rudolph et al. (2001) reported a method of combining the ratio by multiplying the ratio by the sum of the EMG magnitude. This equation will be used in this study, as it overcomes the drawbacks of the other equation (Rudolph et al., 2001).

The equation used to calculate the co-contraction of the muscle for this study was based on Rudolph's study (Rudolph et al., 2001). EMG lower/EMG higher × (EMG lower +EMG higher)*100%, the EMG lower was the level of activity in the less active muscle, and EMG higher was the level of activity in more active muscle between the two antagonists

The changes in muscle co-contraction between VM/ST, VL/BF, VM/MG, and VL/LG TA/MG will be investigated at three stages (early-stance 0–33, mid-stance 34–67, and late-stance 68–100) while walking.

3.7 Daily number of steps

The level of physical activity (daily number of steps) was collected using Wechat app (Version 6.7.4, Tencent, China) on the smartphone. The participants were instructed to carry the smartphone for seven consecutive days and not to remove the phone for the entirety of the seven days, except for bathing, showering, or doing exercise (e.g., running, swimming). The WeChat app automatically records the daily walking steps.

3.8 Data processing

3.8.1 Data digitizing and gap interpolation

The trajectories of the markers (kinematics) and the GRF (kinetics) data were recorded during walking. All the tracking markers should be reconstructed and digitized (i.e., delete the wrong ones and label the true maker with a name). All the un-needed trajectories were deleted, all the gaps in all trajectories were filled using cubic spline interpolation and the limitation on the size of the gap set at less than 10 frames as filling larger gaps might produce erroneous data. The start and end of the static trial and dynamic trials were cropped and ensure the trial did not include too much unnecessary data before they were saved or exported to the C3D file.

3.8.2 Kinematics and kinetics raw data filtering

A cut-off frequency of 6Hz low pass filter was used for kinematics signals (Winter. 2009) and 25Hz for the raw GRF signals (Schneider & Chao, 1983).

3.8.3 sEMG raw data filtering and rectifying

sEMG data of each walking trial was synchronized with gait data. The C3D files were exported to Visual 3D included the sEMG signal. The signals were filtered with a 20Hz

high pass FFT filter and a 500Hz low pass FFT filter to remove noise and movement artifact, and then rectified the signal (to make signal positive) before applying for the low pass Butterworth filter (6Hz) to smooth a linear envelope (Hubley-Kozey et al., 2006), after that the sEMG signals could be presented as time normalized to the stance phase of both left and right limbs using gait event data calculated from the force platforms (Preece et al., 2016).

3.9 Test-retest reliability for healthy individuals: between sessions

3.9.1 Introduction

Although using biomechanical outcomes such as joint angles, joint moments and GRF could accurately quantify the assessment to functions and treatment effect in individuals with knee OA (Hinman, et al., 2012, Perrece et al., 2016, Al-Khlaifat et al., 2016), the accuracy of the outcomes depend on the laboratory settings and the proficiency and consistency of the investigator in markers and sensors placement, system operation, data procession, and computation. To minimize the errors in the measurement and achieve the confidence in achieving high-quality data, the test-retest reliability study was performed after learning and practicing the entire experiment process.

3.9.2 Recruitment

Twelve healthy individuals who met the eligibility criteria of the study were recruited from the postgraduate students and staff in the Shuguang Hospital by posters and emails. This study was approved by the University of Salford Research, Enterprise and Engagement Ethical Approval Panel (Reference number: HSR1617-173) and China ethics committee of registering clinical trials (Reference number ChiECRCT 20170055).

3.9.2.1 Inclusion and exclusion criteria

The eligibility criteria for inclusion in the test-retest reliability study for healthy individuals were as follows: (1) the individuals aged over 18 years with no history of injuries and deformities in the lower extremities; (2) the individuals with no musculoskeletal or neurological diseases that may affect gait pattern; (3) the individuals with at least one smartphone with Apple Interactive Operating System (IOS) systems or Google Android system; (4) the individuals who were willing to participate in the study and sign the consent form.

The exclusion criteria for participants were as follows: (1) the individuals who did not

meet the eligibility criteria for inclusion; (2) the individuals who were unable to understand and follow the procedure.

3.9.3 Sample size

Based on Price's study (Price et al., 2017), nine subjects were enough for a test-rest reliability study for the gait analysis of healthy individuals. In this study, a convenience sample of twelve subjects was recruited.

3.9.4 Procedure

1. The first visit

The participants who met the eligibility criteria of the study would be given the information on the purpose of the study orally and a participant information sheet. If the participants were willing to participate, the researchers further explained the details of the study which included the description of the equipment and the testing procedure. After that, the participants were given time to ask any questions they had before making the final decision and returning the consent form (Reference number ChiECRCT 20170055 (approved by the China ethics committee of registering clinical trials), HSR1617-173 (approved by the University of Salford)). Each participant was given at least 24 hours to read and sign the consent form before joining the study.

Participants were informed that their participation in the test-retest reliability study was completely voluntary, and they were free to withdraw from the study at any point of time without any explanation needed to be given. In the event of their withdrawal, the collected data would not be deleted unless they wished for this to happen. The participants were instructed to install the Wechat app on their smartphone and they would be instructed to use the WeChat App to record their daily number of steps.

Then the participants were invited to come to the Shuguang Hospital gait lab after 7 days, during which they kept their routine daily life and recorded daily activity with mobile and daily diaries. The appointment was made immediately after the participant

agreed to take a part in the study and the investigator confirmed. A reminder was sent via telephone, Wechat message, or e-mail. (For more details about daily physical activity (daily number of steps) please see **3.7 Daily number of steps**)

2. The second visit (day1)

On arrival at the gait lab, the participants were welcomed and explained about the experiment protocol. After that, the participants were asked to return the signed consent form and show the latest seven days' daily number of steps to the investigator and the mean value of the seven days' daily number of steps and then they were asked to wear shorts and a T-shirt and then the body mass and height for each participant was recorded before the formal gait test, to avoid the reading error and minimize the errors which might cause by using different instruments (i.e., different types body scale) the body mass was measured by the AMTI force platform. After that, the investigator put the electrodes on the selected muscles and asked the participants to finish the MVIC test. The MVIC data for each muscle was used for normalizing the sEMG data during the walking trials. (For more details about the sEMG sensors placement and the MVIC test please see **3.4.2 sEMG sensors placement and skin preparation** and **3.5 Maximal voluntary isometric contraction**)

After finishing the MVIC test, the retro-reflective markers were attached to the participants' skin over bony landmarks on both lower limbs, with all electrodes in place, the participants were asked to stand on top of one force platform to perform a static standing trial, after a test trial to confirm that all the markers were able to be obtained by the VICON system. The participants were asked to walk for a short time to allow adaptation to the test environment and to determine the best starting point from which they would start walking to hit on the force platforms accurately, this helped to ensure the successful walking trials could be completed in a short time. (For more details about the placement of markers please see **3.4.1 Markers placement**)

The participants were asked to walk at self-selected speed until at least ten good trials

were completed. The data from the first session were used as the baseline, and a repetitive test was held one week after, when the same gait test was repeated to ensure there was no significant difference in gait and sEMG parameters, which might be caused by the errors in the placement of anatomic markers, tracking markers and wireless surface sEMG electrodes. During the test, the walking speed was monitored by a stopwatch app on the investigator's smartphone (Xiaomi Max, China), and the trial with a walking speed higher or lower than 5% of the average speed was excluded from the final analysis.

To minimize the errors which might be caused by wearing different shoes, participants in this study were asked to wear the same type of standard shoes (Huili, Shanghai Huili Footwear Co. Ltd, China, http://www.warriorshoes.com) which were offered by the investigators during the gait test (Figure 3-9).

The appointment for the second gait test was made immediately after the participants finished the first gait test. The participants were also asked to keep their routine daily life and recorded daily activity with mobile and daily diaries. A reminder was sent via telephone, Wechat message, or e-mail.

Figure 3-9 Standard shoes used in the current study (Huili)

3. The third visit (day 8)

At the third visit, the same steps in the second visit (day 1) were conducted again, following the same order and procedure.

3.9.5 Monitoring of walking speed and walking trials quality

3.9.5.1 Monitoring of walking speed

Both the kinematic and kinetic data could be influenced by the walking speed. The walking speed should be monitored and controlled for the study on healthy participants. Otherwise different walking speeds could cause the changes in biomechanical outcomes that affected the observation to the effect of other factors or the data repeatability. However, for clinical gait analysis on participants, the investigator could only ask the participants to walk with their self-selected speed, as any improvements in walking speed could be the effect of the treatment as well, the biomechanical outcomes should be analyzed and interpreted based on the overall observation of all the measurements.

3.9.5.2 Monitoring of walking trials quality

Bad walking trials could also lead to inaccurate outcomes, so each trial should be carefully observed and checked during data collection to ensure only good trials to be used in the analysis and the bad trials to be excluded. A successful trial should satisfy the following requirements:

a. The participants walk nice and steadily with balance at any moment, for studies on healthy participants, the walking speed should be within a specific acceptable range.
b. The participants do not change their speed or step length to land their foot on the force plates.
c. All the tracking markers should be collected together with GRF and sEMG signals;
d. Only one foot has a clean contact with the surface of a force plate during a stance phase.

3.9.6 Variables of interest

The individuals with knee OA show various kinematic knee alterations during the stance phase during gait (Kawaji et al., 2019), and several previous studies (Schmitt & Rudolph, 2007, Dixon et al., 2010, Farrokhi et al., 2012) reported the kinematic of the knee during stance phase. Therefore, kinematic and kinetic data in this test-retest reliability study for healthy individuals was focused on the stance phase of the gait.

Temporal-spatial data, which were assessed in this test-retest reliability study, included walking speed, step length, cadence, double support time, stance phase percentage, and daily numbers of steps.

kinematic data, which were assessed in this test-retest reliability study, included knee angle in the sagittal (knee flexion angle at initial contact, peak knee flexion angle during early stance phase, knee sagittal plane ROM during stance phase), knee angle in the frontal plane (peak knee adduction angle during stance phase, peak knee abduction angle during stance phase, and knee frontal plane ROM during stance phase), and knee angle in the transverse plane (peak knee internal rotation angle during stance phase, peak knee external rotation angle during stance phase, and knee transverse plane ROM during stance phase).

Kinetic data, which were assessed in this test-retest reliability study, included knee moment in the sagittal plane (knee flexion moment, knee extension moment), knee moment in the frontal plane (1st peak of EKAM, 2nd peak of EKAM, and KAAI), knee moment in the transverse plane (knee internal rotation moment, knee external rotation moment), and vertical GRF (the first peak, and the second peak).

Muscle co-contraction data, which were assessed in the test-retest reliability study, included VL/BF, VL/LG, VM/ST, VM/MG, TA/MG muscle co-contraction at three stages (early stance 0–33% of stance phase, mid-stance 34–67% of stance phase, and

late stance 68–100% of stance phase). (For more details about the calculation of joint angles, moments, GRF, muscle co-contraction, and daily number of steps please see sections **3.6 Biomechanical modelling and computations** and **3.7 Daily number of steps**)

3.9.7 Data processing

After collecting ten successful trials, the data was processed by VICON Nexus Software (Version 1.8.5) and Visual 3D software (V 6.01.16) and then exported to Microsoft Excel. Kinetic, kinematic, GRF, and muscle activity data were normalized to the stance phase. (For more detail about biomechanical modelling and computations, data digitizing, and gap interpolation, kinematics, kinetics, and sEMG raw data filtering, please see section 3.6 **Biomechanical modelling and computations** and 3.8 **Data processing**)

The individuals with knee OA show various kinematic knee alterations during gait (Kawaji et al., 2019), and previous studies (Schmitt & Rudolph, 2007, Dixon et al., 2010, Farrokhi et al., 2012) reported the kinematic of the knee during stance phase. Therefore, the test-retest reliability study for healthy individuals should be focused on the kinematics knee alterations during the stance phase.

3.9.8 Statistical analyses

For the test-retest reliability study on healthy participants, the **intra-class correlation coefficient (ICC), standard error of the measurement (SEM)**, and the **minimal detectable change (MDC)** were calculated for the following variables: (1) temporal-spatial data: steps length, cadence, double support time, stance phase percentage, and daily numbers of step; (2) kinematic data: the peak joint angles of knee and knee joint ROM in the sagittal, frontal, and transverse planes during stance phase; (3) kinetic data: the peak joint moments of the knee at sagittal and frontal plane during stance phase andthe peak vertical GRF during stance phase; (4) muscle co-contraction data: the VL/BF, VL/LG, VM/ST, VM/MG, TA/MG muscle co-contraction in early, mid-, and

late stance. (For more details about the statistical analyses please see 3.9.6 **statistical analyses**)

The ICC values calculated based on the comparison of peak values within subjects varied for the two sessions. SEM and MDC were calculated using Equation as follows (Price et al., 2017):

$$\mathrm{SEM} = \mathrm{SD} \cdot \sqrt{(1 - \mathrm{ICC})}$$

$$\mathrm{MDC} = \mathrm{SEM} \cdot 1.96 \cdot \sqrt{2}$$

For kinematics data, the standard deviation (SD) is the SD of the data collected during the stance phase. For kinetics data, the SD is the SD of the data collected during the stance phase.

ICC is a unitless value, which indicates the consistency of the data (Shrout & Fleiss, 1979). The values of ICC range from 0 to 1 with a higher value representing better reliability. The values of the ICC and corresponding interpretation was showed in Table 3-8.

Table 3-8 ICC value and statistical interpretation

ICC values	Statistical interpretation
ICC≤0.5	Poor reliability
0.5 < ICC≤0.75	Fair reliability
0.75 < ICC≤0.90	Good reliability
ICC > 0.90	Excellent reliability

3.9.9 Results

3.9.9.1 Test participants

Twelve healthy individuals participated in this study, seven women and five men (mean age 25.75±1.22 years, mean height 1.66±0.08 m, and mean body mass 59.58±7.76kg) (Table 3-9). All the participants attended two sessions separated by seven days.

Table 3-9 Healthy participants' demographics characteristics

Variables	Healthy subjects (n=12, male=5, female=7)
Age (years)	25.75±1.22
Height (m)	1.66±0.08
Body Mass (kg)	59.58±7.76

3.9.9.2 Test-retest reliability of temporal spatial, kinematics, kinetics, and muscle co-contraction variables

There was no significant difference in walking speed between the two sessions (Table 3-10). During level walking, the between-session reliability study for healthy participants showed fair to excellent consistency (ICC from 0.71 to 0.98) for temporal-spatial, kinematic, kinetic, and muscle co-contraction variables, with most data in the excellent range (27 out of 38 variables) (Table 3-11, 3-12, 3-13, 3-14). The lowest test-retest reliability was VL/BF muscle co-contraction in mid-stance with an ICC of 0.71. The primary outcomes which were used in the TCM study were the EKAM and muscle co-contraction showed good reliability during walking.

Table 3-10 The between session test-retest reliability measure of walking speed (Mean±SD) for healthy participants

Variables	Test	Retest	P value
Walking speed (m/s)	1.35±0.13	1.36±0.15	0.30

Table 3-11 The between sessions test–retest reliability measures of temporal-spatial variables (Mean±SD) for healthy participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
Step length (m)	0.68±0.06	0.68±0.07	0.98 (0.93-0.99)	0.01	0.03
Cadence (steps/min)	119.50±5.40	120.83±5.51	0.95 (0.83-0.99)	1.22	3.38
Double support time (s)	0.10±0.01	0.10±0.01	0.93 (0.74-0.98)	0.00	0.01
Stance phase percentage (%)	60.16±0.84	60.17±1.00	0.95 (0.82-0.99)	0.21	0.57

Daily numbers of steps (steps/day)	5490.67 ±972.34	5625.17 ±1222.22	0.98 (0.94-0.99)	74.76	670.80

Table 3-12 The between sessions test–retest reliability measures of kinematic variables (Mean±SD) in stance during gait for healthy participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
PKF at IC (°) Flexion (+), Extension (-)	4.45±4.46	5.02±4.52	0.93 (0.84-0.97)	1.19	3.29
PKF at ES (°) Flexion (+), Extension (-)	16.68±5.56	17.07±5.37	0.95 (0.89-0.98)	1.22	3.39
Knee_ROM_X at Stance (°)	48.18±3.15	48.61±3.25	0.94 (0.86-0.98)	0.78	2.17
PKADD at stance (°) Abduction (+), Adduction (-)	-2.54±3.11	-2.28±2.90	0.87 (0.69-0.95)	1.08	3.00
PKABD at stance (°) Abduction (+), Adduction (-)	4.61±3.49	3.93±3.26	0.90 (0.78-0.96)	1.07	2.96
Knee_ROM_Y at stance (°)	7.15±2.62	6.21±2.41	0.73 (0.37-0.88)	1.31	3.62
PKIR at stance (°) Internal rotation (+), External rotation (-)	2.24±4.88	1.70±4.20	0.96 (0.91-0.98)	0.91	2.52
PKER at stance (°) Internal rotation (+), External rotation (-)	-13.17±3.67	-13.01±3.85	0.89 (0.72-0.95)	1.25	3.46
Knee_ROM_Z at stance (°)	15.41±5.65	14.71±5.14	0.98 (0.94-0.99)	0.76	2.11

Abbreviation: peak knee flexion angle at initial contact= PKF at IC, peak knee flexion angle at early stance phase=PKF at ES, knee sagittal plane ROM at stance phase= Knee_ROM_X at SP, peak knee adduction angle at stance phase= PKADD at SP, peak knee abduction angle at stance phase= PKABD at SP, knee frontal plane ROM at stance phase= Knee_ROM_Y at SP, peak knee internal rotation angle at stance phase= PKIR at SP, peak knee External rotation angle at stance phase= PKER at SP, knee transverse plane ROM at stance phase= Knee_ROM_Z at SP.

Table 3-13 The between sessions test–retest reliability measures of kinetic variables (Mean±SD) in stance during gait for healthy participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
KFM (Nm/(BW*Ht) %) Flexion (+), Extension (-)	3.18±0.93	3.41±0.95	0.91(0.78-0.97)	0.28	0.78
KEM (Nm/(BW*Ht) %) Flexion (+), Extension (-)	-2.13±0.44	-2.07±0.34	0.83 (0.57-0.93)	0.16	0.45
EKAM1 (Nm/(BW*Ht) %) Adduction (+), Abduction (-)	2.91±0.62	2.96±0.59	0.95 (0.88-0.98)	0.14	0.37
EKAM2 (Nm/(BW*Ht) %) Adduction (+), Abduction (-)	1.72±0.70	1.72±0.69	0.98 (0.95-1.00)	0.10	0.27
KAAI (Nm · s/(BW *Ht)%)	1.03±0.24	1.04±0.21	0.97 (0.90-0.99)	0.04	0.11
KIRM (Nm/(BW*Ht) %) Internal rotation (+), External rotation (-)	0.95±0.41	0.97±0.38	0.96 (0.90-0.98)	0.08	0.22
KERM (Nm/(BW*Ht) %) Internal rotation (+), External rotation (-)	-0.82±0.22	-0.81±0.21	0.95 (0.90-0.98)	0.05	0.13
1st GRF (BW)	1.15±0.11	1.16±0.11	0.98 (0.99-1.00)	0.02	0.04
2nd GRF (BW)	1.20±0.10	1.20±0.10	0.98 (0.95-0.99)	0.01	0.04

Abbreviation: peak knee flexion moment= KFM, peak knee extension moment= KEM, knee adduction angular impulse=KAAI, peak knee internal rotation moment=KIRM, peak knee external rotation moment=KERM, first peak of ground reaction force=1st GRF, second peak of ground reaction force=2nd GRF, BW=body weight, Ht=height.

Table 3-14 The between sessions test–retest reliability measures of muscle co-contraction variables (Mean±SD) (expressed as % MVIC)in stance during gait for healthy participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
VL/BF Early stance	23.79±5.64	23.34±7.74	0.88 (0.72-0.95)	2.32	6.42
VL/BF Mid stance	7.45±3.70	8.40±4.06	0.71 (0.34-0.88)	2.09	5.79
VL/BF Late stance	3.83±1.76	3.36±1.60	0.84 (0.64-0.93)	0.67	1.86
VL/LG Early stance	11.82±6.12	11.17±5.65	0.98 (0.94-0.99)	0.83	2.31
VL/LG Mid stance	6.91±6.43	7.17±7.14	0.98 (0.96-0.99)	0.96	2.66
VL/LG Late stance	4.91±3.05	5.26±4.12	0.87 (0.68-0.95)	1.29	3.58
VM/ST Early stance	21.83±5.20	20.70±6.03	0.84 (0.64-0.93)	2.25	6.23
VM/ST Mid stance	8.36±7.23	9.49±7.49	0.97 (0.94-0.99)	1.27	3.53
VM/ST Late stance	3.84±2.76	3.77±2.77	0.95 (0.89-0.98)	0.62	1.71
VM/MG Early stance	9.75±8.30	10.02±7.15	0.93 (0.84-0.97)	2.04	5.67
VM/MG Mid stance	6.82±5.71	7.18±6.56	0.84 (0.64-0.93)	2.45	6.80
VM/MG Late stance	6.28±6.18	5.86±6.05	0.97 (0.93-0.99)	1.06	2.94
TA/MG Early stance	9.05±7.19	8.44±4.40	0.85 (0.66-0.94)	2.24	6.22
TA/MG Mid stance	7.60±4.35	6.99±2.85	0.84 (0.63-0.93)	1.44	3.99
TA/MG Late stance	6.24±5.01	5.69±4.77	0.96 (0.91-0.98)	0.98	2.71

3.9.10 Discussion

The walking speed between the two sessions showed no difference, which was consistent with the previous studies (Kadaba et al., 1989, Fernades et al., 2016). This high repeatability was caused by the monitoring of walking speed during gait by a stopwatch app on the smartphone (Xiaomi Max, China) (walking speed higher or lower than 5% of the average speed was excluded from the final analysis).

Both sagittal/frontal knee joint angles showed ICCs greater than 0.70 (0.73-0.95), these results were in accord with Fernades et al. (2016), with the joint angles in the sagittal

plane seem to be more repeatable. In line with the previous study (McGinley et al., 2009), the reliability of the frontal plane was generally lower than the sagittal plane, this might be caused by the kinematic cross-talk between sagittal and frontal plane during walking (Kadaba et al., 1990). Although several previous studies (Kadaba et al., 1985, Kadaba et al., 1989) reported the test-retest reliability of gait analysis, it is hard to compare the results of different studies directly due to the difference of methodology, biomechanical model, and the participants. However, the SEM of the kinematics parameters showed a measurement error from 0.76° to 1.31°, which was very similar to the previous report (McGinley et al., 2009).

The reliability of knee joint moments peak values during the stance phase showed ICCs greater than 0.80 (0.83 to 0.98), and these results agreed with the previous study (Wilken et al., 2012). Additionally, the SEM of joint moments showed an SEM from 0.04 to 0.28 Nm/ (BW*Ht) %, which was similar to Wilken et al. (2012). The reliability of vertical GRF was also excellent (ICC: 0.98), and this might be a result of monitoring of walking speed and the quality of the trial (only the good trials were included for analysis and the bad trials were excluded).

In this study muscle activity showed fair to excellent repeatability between sessions for VL/BF, VL/LG, VM/ST, VM/MG, and TA/MG muscles co-contraction in the early, mid-, and late stance phase, which was similar to the previous studies (Kadaba et al., 1985, 1989). Kadaba et al. (1985, 1989) investigated the test-retest repeatability of muscle activity of healthy subjects and showed high test-retest reliability for the muscle activity. However, they used the variance ratio (VR) and coefficient of multiple correlations (CMC) rather than the ICC. Thus, the result of this study cannot be compared with these studies directly, however, the placement of the sEMG electrodes in this study was conducted in strict accordance with SENIAM guidelines (Hermans et al., 1999), which indicated that the results of this study might be reliable.

Based on the classical textbook (Fleiss, 1999), ICC over 0.50 indicated fair to good

repeatability. In this study, all the parameters showed fair to excellent repeatability (ICC: 0.71-0.97), which indicated that the variations in biomechanical outcomes that were identified in the TCM study truthfully reflected the effect of different treatment interventions rather than the error of the markers and electrodes placement. With the confidence that the errors in the measurement were low and the investigator's reliability was good, this allowed the study to move to the primary research questions.

Although the reliability of the temporal-spatial, kinematic, kinetic, GRF, and muscle co-contraction variables were consistent with several previous studies (Kadaba et al., 1989, Feber et al., 2002, Ford., et al., 2007). Same as previous studies, there were still some limitations in the current study. Firstly, the generalisability of results was restricted to similar gait analysis system settings, markers location, and the investigators' ability to markers placement. Secondly, the time between sessions was relatively short (one week), which might influence the results due to the familiarisation effect.

3.9.11 Conclusion

In conclusion, the temporal-spatial, kinematic, kinetic, GRF, and muscle co-contraction variables were quite repeatable in this group of healthy participants during walking at their natural speed. Therefore, it could be used to evaluate between-days intervention effects.

3.10 Test-retest reliability for individuals with medial knee OA: between sessions

3.10.1 Introduction

Although the test-retest reliability study for healthy individuals showed fair to excellent reliability in temporal-spatial, kinematic, kinetic, and muscle co-contraction variables, the gait patterns between healthy individuals and individuals with medial knee OA were quite different (Preece et al., 2016, Astephen et al., 2008). Thus, to understand the error of measurement and learn how to reduce the error by applying the correct methods and professional operational skills, a test-retest reliability study on individuals with medial knee OA was performed.

3.10.2 Recruitment

Ten medial knee OA individuals who met the eligibility criteria of the study were recruited from the Shuguang Hospital. This study was approved by the University of Salford Research, Enterprise and Engagement Ethical Approval Panel (Reference number: HSR1617-173) and China ethics committee of registering clinical trials (Reference number ChiECRCT 20170055).

3.10.2.1 Inclusion and exclusion criteria

Individuals aged 40 to 70 years old who had been diagnosed with medial knee OA were eligible. Diagnosis of knee OA was completed by a designated doctor with regards to the ACR criteria for the classification and reporting of OA of the knee joint (Hochberg et al., 1995).

The eligibility criteria for inclusion in the study were as follows: (1) the individuals aged 40 to 70 years old who had been diagnosed with medial knee OA by a clinician; (2) the individuals could walk independently at least 200 meters without any help; (3) the individuals did not have any other musculoskeletal or neurological diseases which may affect gait pattern; (4) the individuals with at least one smartphone with Apple IOS

systems or Google Android system; (5) the individuals who were willing to participate in the study and sign the consent form.

Exclusion criteria for participants were as follows: (1) the individuals who did not meet the eligibility criteria for inclusion; (2) the individuals who were unable to understand and follow the procedure.

3.10.3 Sample size

Based on Price's study (Price et al., 2017), nine subjects were enough for the gait analysis reliability study. In this study, a convenience sample of ten subjects with medial knee OA was recruited.

3.10.4 Procedure

1. The first visit

The participants who met the eligibility criteria of the study would be given the information on the purpose of the study orally and a participant information sheet. If the participants were willing to participate, the researchers further explained the details of the study which included the description of the equipment and the testing procedure. After that, the participants were given time to ask any questions they had before making the final decision and returning the consent form (Reference number ChiECRCT 20170055 (approved by the China ethics committee of registering clinical trials), HSR1617-173 (approved by the University of Salford)). Each participant was given at least 24 hours to read and sign the consent form before joining the study.

Participants were informed that their participation in the test-retest reliability study was completely voluntary, and they were free to withdraw from the study at any point of time without any explanation needed to be given. In the event of their withdrawal, the collected data would not be deleted unless they wished for this to happen. The participants were instructed to install the Wechat app on their smartphone and they would be instructed to use the WeChat App to record their daily number of steps.

Then the participants were invited to come to the Shuguang Hospital gait lab after 7 days, during which they kept their routine daily life and recorded daily activity with mobile and daily diaries. The appointment was made immediately after the participant agreed to take a part in the study and the investigator confirmed. A reminder was sent via telephone, Wechat message, or e-mail. (For more details about daily physical activity (daily number of steps) please see **3.7 Daily number of steps**)

2. The second visit (day1)

On arrival at the gait lab, the participants were welcomed and explained about the experiment protocol. After that, the participants were asked to return the signed consent form and show the latest seven days' daily number of steps to the investigator and the mean value of the seven days' daily number of steps and then they were asked to wear shorts and a T-shirt and then the body mass and height for each participant was recorded before the formal gait test, to avoid the reading error and minimize the errors which might cause by using different instruments (i.e., different types body scale) the body mass was measured by the AMTI force platform. After that, the investigator put the electrodes on the selected muscles and asked the participants to finish the MVIC test. The MVIC data for each muscle was used for normalizing the sEMG data during the walking trials. (For more details about the sEMG sensors placement and the MVIC test please see **3.4.2 sEMG sensors placement and skin preparation** and **3.5 Maximal voluntary isometric contraction**)

After finishing the MVIC test, the retro-reflective markers were attached to the participants' skin over bony landmarks on both lower limbs, with all electrodes in place, the participants were asked to stand on top of one force platform to perform a static standing trial, after a test trial to confirm that all the markers were able to be obtained by the VICON system. The participants were asked to walk for a short time to allow adaptation to the test environment and to determine the best starting point from which they would start walking to hit on the force platforms accurately, this helped to ensure

the successful walking trials could be completed in a short time. (For more details about the placement of markers please see **3.4.1 Markers placement**)

The participants were asked to walk at self-selected speed until at least ten good trials were completed. The data from the first session were used as the baseline, and a repetitive test was held one week after, when the same gait test was repeated to ensure there was no significant difference in gait and sEMG parameters, which might be caused by the errors in the placement of anatomic markers, tracking markers and wireless surface sEMG electrodes. During the test, the walking speed was monitored by a stopwatch app on the investigator's smartphone (Xiaomi Max, China), and the trial with a walking speed higher or lower than 5% of the average speed was excluded from the final analysis.

To minimize the errors which might be caused by wearing different shoes, participants in this study were asked to wear the same type of standard shoes (Huili, Shanghai Huili Footwear Co. Ltd, China, http://www.warriorshoes.com) which were offered by the investigators during the gait test (Figure 3-9).

The appointment for the second gait test was made immediately after the participants finished the first gait test. The participants were also asked to keep their routine daily life and recorded daily activity with mobile and daily diaries. A reminder was sent via telephone, Wechat message, or e-mail.

3. The third visit (day 8)

At the third visit, the same steps in the second visit (day 1) were conducted again, following the same order and procedure.

3.10.5 Monitoring of walking speed and walking trials quality

3.10.5.1 Monitoring of walking speed

Both the kinematic and kinetic data could be influenced by the walking speed. The walking speed should be monitored and controlled for studies on individuals with knee OA. Otherwise different walking speeds could cause the changes in biomechanical outcomes that affected the observation to the effect of other factors or the data repeatability. However, for clinical gait analysis on participants, the investigator could only ask the participants to walk with their self-selected speed, as any improvements in walking speed could be the effect of the treatment as well, the biomechanical outcomes should be analyzed and interpreted based on the overall observation of all the measurements.

3.10.5.2 Monitoring of walking trials quality

Bad walking trials could also lead to inaccurate outcomes, so each trial should be carefully observed and checked during data collection to ensure only good trials to be used in the analysis and the bad trials to be excluded. (For more details about the requirements for successful trial please see 3.9.5 **the monitoring of walking trials quality**)

3.10.6 Variables of interest

The individuals with knee OA show various kinematic knee alterations during the stance phase during gait (Kawaji et al., 2019), and several previous studies (Schmitt & Rudolph, 2007, Dixon et al., 2010, Farrokhi et al., 2012) reported the kinematic of the knee during stance phase. Therefore, kinematic and kinetic data in this test-retest reliability study for healthy individuals was focused on the stance phase of the gait.

Temporal-spatial data, which were assessed in this test-retest reliability study, included walking speed, step length, cadence, double support time, stance phase percentage, and daily numbers of steps.

kinematic data, which were assessed in this test-retest reliability study, included knee angle in the sagittal (knee flexion angle at initial contact, peak knee flexion angle during early stance phase, knee sagittal plane ROM during stance phase), knee angle in the frontal plane (peak knee adduction angle during stance phase, peak knee abduction angle during stance phase, and knee frontal plane ROM during stance phase), and knee angle in the transverse plane (peak knee internal rotation angle during stance phase, peak knee external rotation angle during stance phase, and knee transverse plane ROM during stance phase).

Kinetic data, which were assessed in this test-retest reliability study, included knee moment in the sagittal plane (knee flexion moment, knee extension moment), knee moment in the frontal plane (1st peak of EKAM, 2nd peak of EKAM, and KAAI), knee moment in the transverse plane (knee internal rotation moment, knee external rotation moment), and vertical GRF (the first peak, and the second peak).

Muscle co-contraction data, which were assessed in the test-retest reliability study, included VL/BF, VL/LG, VM/ST, VM/MG, TA/MG muscle co-contraction at three stages (early stance 0–33% of stance phase, mid-stance 34–67% of stance phase, and late stance 68–100% of stance phase). (For more details about the calculation of joint angles, moments, GRF, muscle co-contraction, and daily number of steps please see sections **3.6 Biomechanical modelling and computations** and **3.7 Daily number of steps**)

3.10.7 Data processing

After collecting ten successful trials, the data was processed by VICON Nexus Software (Version 1.8.5) and Visual 3D software (v 6.01.16) and then exported to Microsoft Excel. Kinetic data were normalized to the gait cycle while kinematic, GRF, and muscle activity data were normalized to the stance phase. (For more detail about biomechanical modelling and computations, data digitizing, and gap interpolation, kinematics, kinetics, and sEMG raw data filtering, please see section 3.6 **Biomechanical modelling and**

computations and 3.8 **Data processing**)

3.10.8 Statistical analyses

For the test-retest reliability study on medial knee OA participants, the ICC, SEM, and the MDC were calculated for the following variables: (1) temporal-spatial data: steps length, cadence, double support time, stance phase percentage, and daily numbers of walking step; (2) kinematic data: the peak joint angles of knee and knee joint ROM in the sagittal, frontal, and transverse planes during stance phase; (3) kinetic data: the peak joint moments of the knee at sagittal and frontal plane during stance phase andthe peak vertical GRF during stance phase; (4) muscle co-contraction data: the VL/BF, VL/LG, VM/ST, VM/MG, TA/MG muscle co-contraction in early, mid-, and late stance. (For more details about the statistical analyses please see 3.9.6 **statistical analyses**)

3.10.9 Results

3.10.9.1 Test participants

Ten individuals with medial knee OA who met the eligibility criteria of the study were recruited for this study, nine women and one man (mean age 65.50±3.87 years, mean height 1.60±0.06 m, and mean body mass 64.84±6.66kg) (Table 3-15). All the participants attended two sessions separated by seven days.

Table 3-15 Knee OA participants' demographics characteristics

Variables	Healthy subjects (n=10, male=1, female=9)
Age (years)	65.50±3.87
Height (m)	1.60±0.06
Body Mass (kg)	64.84±6.66

3.10.9.2 Test-retest reliability of temporal spatial, kinematics, kinetics, and muscle co-contraction variables

There was no significant difference in walking speed between the two sessions (Table 3-16). During level walking, the between-session reliability study for medial knee OA participants showed fair to excellent consistency (ICC from 0.68 to 0.98) for temporal-spatial, kinematic, kinetic, and muscle co-contraction variables, with many data in the excellent range (12 out of 38 variables) (Table 3-17, 3-18, 3-19, 3-20). The lowest test-retest reliability was VL/LG muscle co-contraction in mid-stance and TA/MG in early stance with an ICC of 0.68. The primary outcomes which were used in this study were the EKAM and muscle co-contraction and these showed good reliability during walking (ICC from 0.68 to 0.98).

Table 3-16 The between session test-retest reliability measure of walking speed (Mean±SD) for medial knee OA participants

Variables	Test	Retest	P value
Walking speed (m/s)	1.01±0.07	1.02±0.07	0.53

Table 3-17 The between sessions test–retest reliability measures of temporal-spatial variables (Mean±SD) for medial knee OA participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
Step length (m)	0.56±0.04	0.57±0.05	0.88 (0.59-0.97)	0.02	0.04
Cadence (steps/min)	107.50±5.97	106.60±5.80	0.95 (0.83-0.99)	1.26	3.50
Double support time (s)	0.12±0.01	0.12±0.01	0.92 (0.71-0.98)	0.00	0.01
Stance phase percentage (%)	60.76±0.93	61.06±1.24	0.69 (0.45-0.91)	0.82	0.60
Daily numbers of steps (steps/day)	3955.90 ±470.33	3930.80 ±493.86	0.98 (0.96-0.99)	68.18	188.98

Table 3-18 The between sessions test–retest reliability measures of kinematic variables (Mean±SD) in stance during gait for medial knee OA participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
PKF at IC (°) Flexion (+), Extension (-)	9.58±5.52	8.78±4.91	0.89 (0.73-0.96)	1.73	4.79
PKF at ES (°) Flexion (+), Extension (-)	16.17±6.01	16.24±5.10	0.88 (0.71-0.95)	1.92	5.33
Knee_ROM_X at Stance (°)	35.83±4.08	36.76±4.11	0.81 (0.56-0.92)	1.78	4.95
PKADD at stance (°) Abduction (+), Adduction (-)	-3.27±1.54	-3.74±1.71	0.76 (0.46-0.90)	0.80	2.23
PKABD at stance (°) Abduction (+), Adduction (-)	2.48±2.30	2.42±2.08	0.71 (0.38-0.88)	1.18	3.27
Knee_ROM_Y at stance (°)	5.76±1.91	6.16±2.00	0.86 (0.66-0.94)	0.73	2.03
PKIR at stance (°) Internal rotation (+), External rotation (-)	2.27±5.60	1.82±4.45	0.89 (0.73-0.96)	1.67	4.62
PKER at stance (°) Internal rotation (+), External rotation (-)	-14.27±6.20	-14.50±4.48	0.86 (0.67-0.95)	2.00	5.54
Knee_ROM_Z at stance (°)	16.54±4.71	16.32±4.14	0.92 (0.79-0.97)	0.99	2.74

Abbreviation: peak knee flexion angle at initial contact= PKF at IC, peak knee flexion angle at early stance phase=PKF at ES, knee sagittal plane ROM at stance phase= Knee_ROM_X at SP, peak knee adduction angle at stance phase= PKADD at SP, peak knee abduction angle at stance phase= PKABD at SP, knee frontal plane ROM at stance phase= Knee_ROM_Y at SP, peak knee internal rotation angle at stance phase= PKIR at SP, peak knee External rotation angle at stance phase= PKER at SP, pnee transverse plane ROM at stance phase= Knee_ROM_Z at SP.

Table 3-19 The between sessions test–retest reliability measures of kinetic variables (Mean±SD) in stance during gait for medial knee OA participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
KFM (Nm/(BW*Ht) %) Flexion (+), Extension (-)	2.96±0.97	3.01±1.08	0.91 (0.76-0.96)	0.31	0.85
KEM (Nm/(BW*Ht) %) Flexion (+), Extension (-)	-1.20±0.48	-1.35±0.42	0.69 (0.34-0.87)	0.25	0.69
EKAM1 (Nm/(BW*Ht) %) Adduction (+), Abduction (-)	3.01±0.50	3.13±0.47	0.97 (0.92-0.98)	0.08	0.23
EKAM2 (Nm/(BW*Ht) %) Adduction (+), Abduction (-)	2.26±0.68	2.27±0.63	0.97 (0.93-0.99)	0.11	0.31
KAAI (Nm · s/(BW *Ht)%)	1.19±0.30	1.22±0.33	0.95 (0.86-0.98)	0.07	0.20
KIRM (Nm/(BW*Ht) %) Internal rotation (+), External rotation (-)	0.86±0.30	0.92±0.28	0.91 (0.77-0.97)	0.09	0.24
KERM (Nm/(BW*Ht) %) Internal rotation (+), External rotation (-)	-0.42±0.17	-0.48±0.21	0.74 (0.43-0.89)	0.10	0.27
1st GRF (BW)	1.04±0.04	1.05±0.04	0.85 (0.65-0.94)	0.02	0.04
2nd GRF (BW)	1.07±0.03	1.07±0.03	0.92 (0.79-0.97)	0.01	0.02

Abbreviation: peak knee flexion moment= KFM, peak knee extension moment= KEM, knee adduction angular impulse=KAAI, peak knee internal rotation moment=KIRM, peak knee external rotation moment=KERM, first peak of ground reaction force=1st GRF, second peak of ground reaction force=2nd GRF

Table 3-20 The between sessions test–retest reliability measures of muscle co-contraction variables (Mean±SD) (expressed as % MVIC) in stance during gait for medial knee OA participants

Variables	Test	Retest	ICC (95% IC)	SEM	MDC
VL/BF Early stance	28.46±13.95	25.66±12.90	0.86 (0.66-0.95)	5.02	13.92
VL/BF Mid stance	9.20±5.07	8.31±4.04	0.89 (0.71-0.96)	1.51	4.19
VL/BF Late stance	4.72±2.68	3.85±2.02	0.70 (0.34-0.88)	1.29	3.57
VL/LG Early stance	11.97±7.80	10.40±6.07	0.68 (0.31-0.87)	3.92	10.87
VL/LG Mid stance	9.94±4.32	10.15±4.43	0.87 (0.67-0.95)	1.58	4.38
VL/LG Late stance	5.24±3.47	4.41±3.63	0.84 (0.62-0.94)	1.42	3.94
VM/ST Early stance	23.28±8.31	22.88±8.36	0.80 (0.53-0.92)	3.73	10.33
VM/ST Mid stance	8.77±5.46	8.04±5.37	0.85 (0.64-0.94)	2.10	5.82
VM/ST Late stance	6.73±4.29	6.25±3.98	0.85 (0.63-0.94)	1.60	4.44
VM/MG Early stance	11.78±3.94	10.88±3.88	0.82 (0.56-0.93)	1.66	4.60
VM/MG Mid stance	8.26±5.34	8.46±5.71	0.90 (0.74-0.96)	1.75	4.84
VM/MG Late stance	7.18±4.62	6.19±2.92	0.84 (0.60-0.94)	1.51	4.18
TA/MG Early stance	11.35±5.59	11.93±6.84	0.68 (0.31-0.87)	3.51	9.74
TA/MG Mid stance	20.53±10.01	18.81±9.69	0.92 (0.80-0.97)	2.79	7.72
TA/MG Late stance	7.65±4.73	7.77±3.47	0.80 (0.54-0.92)	1.83	5.08

3.10.10 Discussion

The aim of the test-retest reliability study for individuals with medial knee OA was to examine the reliability of biomechanical outcomes, which would be used in the clinical and biomechanical effects of TCM in individuals with medial knee OA study. Additionally, to calculate the SEM and MDC for each outcome among individuals with medial knee OA. This study was made to make sure that all the changes, which would be monitored after the six weeks of TCM treatments for individuals with medial knee OA were caused by the interventions rather than the measurement error.

Generally, the results of ICC for between-days temporal-spatial, kinematic, kinetic,

GRF, and muscle co-contraction variables were good to excellent in walking (0.68 to 0.98) which were very similar to the previous study (Ford et al., 2007, Hubley-Kozey et al., 2013, Ferber et al., 2002). Interestingly, most of between days ICC results were good (ICC>0.75), with 12 out of 38 variables were in excellent reliability (ICC>0.90). Therefore, the high ICC results indicated that the marker and electrode placement application method achieved a good accuracy and low measurement error.

The reliability of the temporal-spatial variables had been reported by some previous studies (Kadaba et al., 1989, Feber et al., 2002). Kadaba et al. (1989) reported high reliability of the temporal-spatial variables which was very similar to the current study, however, the reliability of temporal-spatial variables was evaluated by the coefficient of variation (CV) which was defined as the ratio of the SD to the mean value, thus, direct comparison between Kadaba's and current study could not be made. Ferber et al., (2002) also reported excellent reliability (ICC=0.88) in temporal-spatial variables, however, the speed in that study was the running speed which was much higher than the current study.

The reliability of kinematic and kinetic results can be influenced by many factors such as marker placement and static trial alignment (Ferber et al., 2002; Ford et al., 2007; Manal et al., 2000). Kadaba et al. (1989) demonstrated that the variability gait patterns might be caused by the marker's reapplication, however, the current study showed higher ICC in both kinetic and kinematic data, which indicated that the good consistency in marker placement by the investigator. Ford et al. (2007) also reported most of the kinematic and kinetic variables had excellent to good reliability during the dynamic condition, however, the participants in that study were young athletes which were quite from the current study.

Muscle co-contraction reliability was good to excellent (ICC>0.80) for most of the paired muscles, except VL/BF in late stance (0.70), VL/LG in early stance (0.68), and TA/MG in early stance (0.68), where the ICC was fair. One previous study (Hubley-

Kozey et al., 2013) reported the ICC for muscle co-contraction in individuals with medial knee OA, which showed good to excellent reliability of the muscle co-contraction (ICC from 0.76 to 0.89). However, a direct comparison could not be made as the muscle co-contraction reported in Hubley-Kozey's study (Hubley-Kozey et al., 2013) was the muscle co-contraction in the whole stance phase rather than the three sub-phases of stance in the current study.

The current study provides reference values for SEM and MDC for biomechanical outcomes among individuals with medial knee OA, which might be useful for evaluating the biomechanical changes after receiving interventions and helping to further understand the biomechanical effect of TCM in individuals with medial knee OA. Furthermore, to minimize the errors which might be caused by wearing different shoes, participants in this study were asked to wear the same type of standard shoes, which has not been reported in previous studies, thus, the reliability of the biomechanical variables, SEM, and MDC might be more reliable.

Although the reliability of the temporal-spatial, kinematic, kinetic, GRF, and muscle co-contraction variables were consistent with several previous studies (Kadaba et al., 1989, Feber et al., 2002, Ford., et al., 2007). Same as previous studies, there were still some limitations in the current study. Firstly, the generalisability of results was restricted to similar gait analysis system settings, marker location, and the investigators' ability to marker placement. Secondly, the time between sessions was relatively short (one week), which might influence the results due to the familiarisation effect.

3.10.11 Conclusion

In conclusion, the temporal-spatial, kinematic, kinetic, GRF, and muscle co-contraction variables were quite repeatable in this group of individuals with knee OA walking at their natural speed. Therefore, it can be used to evaluate between-days intervention effects.

3.11 Generic methods for the TCM study

3.11.1 Introduction

The study was designed to fill the gap in the literature concerning the clinical and biomechanical effects of the chosen TCM treatments in individuals with knee OA. Three TCM therapies and a control group with neutral flat insole were included in the study, which were grouped as follows:

Experimental group 1: CH

Experimental group 2: AT

Experimental group 3: CM

Control group: CN

The following sections introduce the generic features of the design of the clinical studies, which included the determination of the clinical questions, hypothesis of the study, eligibility assessment of the participants, sample size, randomization, selection of interventions, and determination of the assessment methods for both clinical and biomechanical effects.

The treatment protocols of three chosen TCM therapies were strictly defined and applied in the treatment protocol of Shuguang Hospital, and the protocol of neutral insoles was based on the previous study (Ashraf et al., 2014). The details of the protocol, procedure, and the precaution of the TCM treatments and neutral insole were addressed in the following chapters.

3.11.2 Study design

The purpose of this study was to assess not only the clinical effect (WOMAC scale) but also the biomechanical effect (kinetics, kinematics, GRF, and muscle co-contraction of the knee) of the chosen TCM interventions, (CH, AT, and CM). The results of the study may help to prove the clinical and biomechanical effects of the chosen interventions and reveal the biomechanical mechanism of the chosen TCM treatments in the

management of knee OA.

3.11.3 Hypotheses of the study

1. To determine whether TCM treatments reduce the WOMAC (pain, stiffness, function, and total) scales over a period of six weeks when compared with the baseline and neutral flat insole.

Hypothesis 1: The WOMAC (pain, stiffness, function, and total) scales in TCM groups are improved after receiving six-week treatments when compared with the baseline and six-week CN.

2. To determine whether TCM treatments reduce the EKAM over a period of six weeks when compared with the baseline and neutral flat insole.

Hypothesis 2: The EKAM in TCM groups are reduced after receiving six-week treatments when compared with the baseline and six-week CN.

3. To determine whether TCM treatments reduce the muscle co-contraction over a period of six weeks when compared with the baseline and neutral flat insole.

Hypothesis 3: The muscle co-contraction in TCM group are reduced after receiving six-week treatments when compared with the baseline and six-week CN.

3.11.4 Methods

3.11.4.1 Recruitment

Participants who met the eligibility criteria of the study were recruited from the Shuguang Hospital.

Individuals aged 40 to 70 years old who had been diagnosed with medial knee OA were eligible. Diagnosis of knee OA was completed by a designated doctor with regards to the ACR criteria for the classification and reporting of OA of the knee joint (Hochberg et al., 1995).

3.11.4.2 Eligibility criteria for inclusion and exclusion

The eligibility criteria for inclusion in the study were as follows:

① At an age between 40 and 70 years;

② Medial knee OA diagnosed by a clinician;

③ Having knee pain and did not undergone any treatment for the last 2 months;

④ Could walk independently at least 200 meters without any help;

⑤ Participants did not have any other musculoskeletal or neurological diseases which may affect gait pattern.

⑥ Participants had at least one smartphone with Apple IOS systems or Google Android system

The exclusion criteria for participants

① Participants did not meet the inclusion criteria;

② Participants were unwilling to be randomised in the intervention groups.

3.11.4.3 Sample size

The calculation of the sample size was based on the mean value and the SD of WOMAC score (primary outcome) of a previous four-arm RCT study (Ao, Guo & Wu. 2017), power of 0.80 and alpha level of 0.05, through G*Power Software, version 3.1.97 (Franz Faul, Universitat Kiel, Germany). We estimated that twelve participants were needed in each group. To allow for a 20 % drop-out rate, we aimed to include fifteen participants in each group. Moreover, a previous knee OA study (Braghin et al., 2019) also showed sample size of sixty participants (fifteen for each group) was determined to be sufficient to achieve the pragmatic purpose of the study. Thus, sixty participants (fifteen for each group) were recruited for the current study.

3.11.4.4 Randomization

This was a RCT study involving four parallel groups, which investigated the short-term (6 weeks) clinical and biomechanical effects of TCM treatments in individuals with

medial knee OA during walking. After informed consent had been obtained from all participants, they were asked to contribute baseline data before they were randomly allocated to one of parallel intervention groups which included (CH, AT, CM), and CN group. A statistician in Shuguang Hospital determined the computer-generated randomization sequence and the treatments were assigned according to the randomization with the use of sealed envelopes.

3.11.4.5 Experimental groups

Experimental group 1: CH

Experimental group 2: AT

Experimental group 3: CM

3.11.4.5.1 CH group

The chosen CH patch treatment for this study was FNZG (China State Food and Drug Administration (SFDA) approval no. Z10970019, Jiangsu Nanxing Pharmaceutical Co., Ltd.). The size of each FNZG was 10 cm* 13 cm. (The details of the protocol, treatments selection criteria, procedure, and precaution of the CH patch for this study were addressed in chapter 4, please see **4.4.7 CH group**).

3.11.4.5.2 AT group

The acupuncture intervention was strictly defined and applied in the treatment protocol of Shuguang Hospital. The acupoints were performed on participants in the AT group with nine needle insertions per affected side per session (30 minutes) using 0.25 × 25 mm disposable stainless-steel needles (Tianjin, China). These acupoints included: Yanglinquan [GB34], Yinlinquan [SP 9], Zusanli [ST36], Taixi [KI3], Sanyinjiao [SP6], Xiyan [EX-LE5] (two points), Hegu [LI4], and Fenglung [ST40]. (The details of the protocol, treatments selection criteria, procedure, and precaution of the AT for this study were addressed in chapter 4, please see **4.4.8 AT group**).

3.11.4.5.3 CM group

The CM intervention was strictly defined and applied in the treatment protocol of Shuguang Hospital. Muscles on the thigh and shank massaged by CM (Tui Na) doctor included: VL, VM, BF, ST, MG, LG, and AT. (The details of the protocol, procedure, treatments selection criteria, and precaution of the CM for this study were addressed in chapter 4, please see **4.4.9 CM group**).

3.11.4.6 Control group

The neutral flat insole (Aptonia, Taiwan, China) was used in this study for the no-treatment CN group. (The details of the protocol, procedure, and precaution of the CN for this study were addressed in chapter 4, please see **4.4.10 CN group**).

3.11.4.7 Duration of the TCM treatments

Some researchers reported difference duration of the TCM treatments (Wang et al., Liu & Jiang, Perlman et al., 2012, Chen et al., 2013, Wang et al., 2020), however, based on the CH, AT, and CM protocol for knee OA in Shuguang Hospital, one course of treatment was three weeks, for individuals with knee OA, at least two courses were needed. Therefore the duration of the treatments in TCM studies was six weeks.

3.11.4.8 Research environment

Participants' data collection was conducted in gait analysis lab in Shuguang Hospital.

3.11.4.8.1 Gait analysis and sEMG system

A sixteen-camera (VICON MX T40 series, VICON, UK) three-dimensional motion analysis system (NEXUS 1.8.5, VICON, UK) with a sampling rate of 100 Hz, and with four integrated force plates (BP400600, AMTI, USA) with a sampling rate of 1000 Hz were used to collect kinematic and kinetic data during walking gait. A sixteen-channel wireless sEMG system (TeleMyo 2400T DTS, Noraxon USA Inc., Scottsdale, AZ, USA) with a sampling rate of 1500 Hz was synchronized with the VICON system to collect surface sEMG signals. (For more details about the gait analysis and sEMG systems please see **3.2.1 Gait analysis system** and **3.2.2 sEMG system**)

3.11.4.8.2 Marker placement and sEMG sensor placement

Forty-four retro-reflective markers (14mm) were used in the study. Twenty-four attached on bony prominences with the self-adhesive tapes of each subject's lower limbs at the ASIS, PSIS, Iliac crest, greater trochanter, medial epicondyles, lateral epicondyles, Calcaneus, lateral malleolus, medial malleolus, 1st, 2nd and 5th metatarsal head the tuberosity of the calcaneus (heel) landmarks. Another twenty markers were used to form five marker clusters which were placed on each thigh and shank, with one on the pelvis. To minimize the errors which might be caused by wearing different shoes, participants in this study were asked to wear the same type of standard shoes (Huili, Shanghai Huili Footwear Co. Ltd, China, http://www.warriorshoes.com) which were offered by the investigator during the gait test (Figure 3-9).

The Noraxon Dual sEMG Electrodes (Noraxon, USA, Inc) were attached to the bilateral VL, VM, BF, ST, MG, LG, TA muscles. (Hodges et al., 2016, Al-Khlaifat et al., 2016, Jones et al., 2018, Child et al., 2004). The placement of the selected electrodes followed the SENIAM website guidelines (seniam.org). (For more details please see **3.4.2sEMG sensors placement and skin preparation**)

3.11.4.9 Procedure

1. The first visit (week 0)

The participant who met the inclusion criteria had the purpose of the study explained to them and received a participant information sheet. If participants were willing to participate, the investigator further explained the details of the study which included the description of all of the equipment and the testing procedure. After that, they were given time to ask any questions they had before they were given the consent form (Reference number ChiECRCT 20170055 (approved by the China ethics committee of registering clinical trials), HSR1617-173 (approved by the University of Salford)). Each participant was given at least 24 hours to read and sign the consent form before starting the experiment.

Participants were informed that participation in the current study was completely voluntary, and they were free to withdraw from the study at any point of time without any explanation needed to be given. In the event of their withdrawal, the collected data would not be deleted unless they wished for this to happen. The participants were asked to install the Wechat app on their smartphone and asked them to record their daily walking steps via Wechat.

After that, the participants were asked to continue with their daily activities for 7 days without any intervention, and then they were given an appointment at the gait analysis laboratory in the Shuguang Hospital via telephone, Wechat message, or e-mail. (For more details about daily physical activity (daily number of steps) please see **3.7 Daily number of steps**).

2. The second visit (Week1)

Upon attending the gait laboratory, the WOMAC questionnaire (Chinese Version) was completed. After completion of the WOMAC questionnaire, the participants were asked to show the latest seven days walking steps to the investigator, and the mean value of the seven days walking steps were recorded. After that, the participants were asked to wear shorts and a T-shirt and finish the MVIC test. The MVIC data for each muscle was used for normalizing the sEMG data during the walking trials. Considering the participants in the study had varying degrees of OA severity and levels of mobility, the positions for MVIC collection should be easy for them to complete the test without any difficulties. (For more details about the sEMG sensors placement and the MVIC test please see **3.4.2 sEMG sensors placement and skin preparation** and **3.5 Maximal Voluntary Isometric Contraction**)

After finishing the MVIC test, all markers were placed with all electrodes in place, the participants were asked to stand on top of one force platform to perform a static standing trial, after a test trial to confirm that all the markers were able to be obtained by the

VICON system. The participants were asked to walk for a short time to allow adaptation to the test environment and to determine the best starting point from which they would start walking to hit on the force platforms accurately, this helped to ensure the successful walking trials could be completed in a short time. (For more details about the markers placement please see **3.4.1 Marker placement**)

3. The third visit (week 7)

At the third visit, the same steps in the second visit (week 1) were conducted again, following the same order and procedure.

3.11.4.10 Outcome measures

3.11.4.10.1 Primary outcome measures

WOMAC

The WOMAC (pain, stiffness, function, and total) were measured at baseline (week 1) before treatment and after receiving a six-week treatment (week 7). The WOMAC questionnaire (Chinese version) used in this study was rated on a 0-10 numeric rating scale, thus, the total scale range of 0 to 240 points.

EKAM

The EKAM (1st peak of EKAM, 2nd peak of EKAM, and KAAI) were measured at baseline (week 1) before treatment and after receiving a six-week treatment (week 7).

Muscle co-contraction

The muscle co-contraction between VL/BF, VL/LG, VM/ST, VM/MG, TA/MG at three stages (early stance 0–33% of stance, mid-stance 34–67% of stance, and late stance 68–100% of stance) were measured at baseline (week 1) before treatment and after receiving 6-week treatment (week 7).

The equation for calculating the muscle co-contraction

Muscles co-contraction was defined as the average of simultaneous activation of a pair

of agonist and antagonistic muscles and was calculated according to Equation (Rudolph et al., 2001). EMG lower/EMG higher × (EMG lower +EMG higher) *100%The EMG lower was the level of activity in the less active muscle and EMG higher was the level of activity in more active muscle.

The muscle co-contraction between antagonistic muscle pairs in the lower extremity for this study was referred to the previous studies (Hodges et al., 2016, Al-Khlaifat et al., 2016, Jones et al., 2018, Child et al., 2004).

3.11.4.10.2 Secondary outcome measures

Kinematics and kinetics of the knee during stance phase

Peak angles, ROM, and peak joint moments of the knee during stance phase in the sagittal, frontal, and transverse planes were assessed at baseline (week 1) before treatment and after receiving a six-week treatment (week 7).

Temporal-spatial variables

The walking speed, step length, cadence, double support time, stance phase percentage, and the daily number of steps were assessed at baseline (week 1) before treatment, and after receiving a six-week treatment (week 7).

3.11.4.11 Data processing

After collecting ten successful trials, the data was processed by VICON Nexus Software (Version 1.8.5) and Visual 3D software (v 6.01.16) and then exported to Microsoft Excel. Kinetics, kinematics, GRF, and muscle activity data were normalized to the stance phase. (For more detail about biomechanical modelling and computations, data digitizing, and gap interpolation, kinematics, kinetics, and sEMG raw data filtering, please see section 3.6 **Biomechanical modelling and computations** and 3.8 **Data processing**)

3.11.4.12 Statistical analysis

Statistical analysis in the current study was performed by using SPSS ver. 24.0 (IBM, Chicago, IL). A Shapiro–Wilk test was used to determine the normality distribution of data. For data that did not present normal distribution, logarithmic transformation was carried out (de Matos Brunelli Braghin et al., 2019). Paired t-test was used for comparison within the group, one-way analysis of variance (ANOVA) was used to determine if the groups were different at baseline, and after receiving six-week treatment, all values were expressed as mean±SD, a statistically significant difference was defined as p-value＜0.05 (Lee & Dong. 2018).

One-way ANOVA assumes that the groups have the same, or very similar, SD. However, the greater the difference in SD between groups, the greater chance that the conclusion of the test is inaccurate. Therefore, if the SD was hugely different, and the sample sizes of each group were not roughly equal, a Welch test would be used. Running one-way ANOVA in SPSS, the resulting F value and significance level only show whether at least one group in the analysis is different from at least one other. It does not show how many groups, or which groups, differ statistically. Therefore, for data with normal distribution, one-way ANOVA followed by Tukey's post hoc test was used to determine possible differences between groups (Lee & Dong. 2018).

Although the Bonferroni test can also be used to compare different groups at baseline and examine the endpoint of the trial, it is more rigorous than the Tukey test, which tolerates type I errors and is more generous than the very conservative Scheffé's method. However, it has disadvantages, as it is too conservative (with weak statistical power) to detect real differences.

The effect size was calculated with the Cohen-d test by using G*Power (Version 3.1.7) and classified as small (≥0.2 and＜0.5), medium(≥0.5 and＜0.8), and large (≥0.8) (Cohens 1988, Schween et al., 2015).

Chapter 4: Clinical and biomechanical effects of Traditional Chinese medical treatments in individuals with medial knee osteoarthritis

4.1 Introduction

This chapter presents the assessment of the clinical and biomechanical effects of CH, AT, and CM for individuals with medial knee OA. The chapter starts with an introduction and background to the TCM treatments and identifies the gaps in the current knowledge. This is followed by the methods explaining the design of the study, recruitment of the participants, a brief overview of the laboratory, methods, and statistical approach was undertaken. The following section gives detailed results based on a scientific statistical method. This chapter then ends with a discussion and conclusion, where the results are interpreted and compared with those of previous studies.

4.2 Background and the purpose of the TCM study

TCM treatments (e.g., CH, AT, and CM) have been used extensively with knee OA subjects in China due to their effectiveness, usability, safety, and cost (Chen et al., 2016). To date, the clinical effect of the TCM treatments has been widely investigated by some previous studies (He et al., 2019, Kong & Ye. 2019, Xing et al., 2018, Xia et al., 2018, Lu., 2018, Jiao et al., 2018, Zhou et al., 2017, Hu & Xi. 2015, Yang et al., 2015, Liu & Jiang. 2015, Ju et al., 2013, Jiang et al., 2013, Wang et al., 2012, Zhao & Wang. 2008, , Tu et al., 2021, Wang et al., 2020, Lin et al., 2018, Zhang et al., 2016, Helianthi et al., 2016, Ashraf et al., 2014, Hinman et al., 2014, Chen et al., 2013, Jubb et al., 2008, Scharf et al., 2006, Vas et al., 2004, Tukmachi et al., 2004, Berman et al., 1999, Jin et al., 2017, Zhu et al., 2015, Chen et al., 2015, Zheng et al., 2020). However, the effectiveness of TCM treatments (e.g., acupuncture) in the management of knee OA is

affected by many factors, such as selecting of the acupoints, Deqi sensation during treatment, the depth of needle's insertion, the duration of the treatment (Tu et al., 2021, Wang et al., 2020, Lin et al., 2018, Zhang et al., 2016, Helianthi et al., 2016, Ashraf et al., 2014, Hinman et al., 2014, Chen et al., 2013, Jubb et al., 2008, Scharf et al., 2006, Vas et al., 2004, Tukmachi et al., 2004, Berman et al., 1999). Therefore, the results of previous TCM studies were quite different. For these reasons, some western OA guidelines such as OARSI (McAlindon et al., 2014), the EULAR (Fernandes et al., 2013), the NICE (NICE, 2014), the ACR (Kolasinski et al., 2020), and the AAOS (Jevsevar et al., 2013) have not recommended using TCM treatments (e.g. acupuncture) for knee OA yet that means further studies are still needed.

Moreover, most of the previous TCM studies were encountered some methodological deficiencies. For example, longitudinal studies lacked a no-treatment control group which led to lower levels of evidence, and the evaluations of all these studies were based only on subjective variables such as pain scales (e.g., WOMAC, VAS) rather than quantitative biomechanical outcomes. Unfortunately, change in pain in questionnaires may not accurately reflect the biomechanical condition of the OA knees (e.g., loading at the knee during gait), which plays a critical role in the development and progression of knee OA (Jones et al., 2014). Although the treatments of knee OA primarily aim to relieve the pain, improve the functional ability, and joint stiffness (Chen et al., 2016), the relief of the clinical symptoms may not guarantee the slowing of the progression of the disease. Henriksen et al. (2006) showed that knee pain relief was associated with increased EKAM after receiving an intra-articular injection of 10ml lidocaine (1%). Hurwitz et al. (2000) also reported that decreases in pain following treatment of nonsteroidal anti-inflammatory drug (NASID) among individuals with medial knee OA were related to higher loading of the joints (e.g., EKAM). As mechanical loading is critical to the health of the knee joint and the increase and abnormal distribution of the load can speed up the progression of the disease (DeFrate et al., 2019). Therefore, it is necessary to evaluate the biomechanical changes of the knee after receiving treatments in individuals with knee OA. Additionally, the distribution of the loading at the medial

compartment of the knee also depends on the activity of the muscles around the knee. Increased co-contraction of the selected paired muscles around the knee would also lead to the higher loading on the knee joint, which is not reflected by the EKAM (Walter et al., 2010). Some previous studies (Al-Khlaifat et al., 2016, Preece et al., 2016) demonstrated that the relief of the pain was associated with the reduction of muscle co-contraction even though the EKAM was not reduced. Therefore, the changing of the muscle co-contraction around the knee should also be considered as one of the most important variables that target the progression of knee OA (Booij et al., 2020). So far, to our knowledge, no previous study investigated both the clinical and biomechanical effects of the TCM treatments in individuals with knee OA, which led to the relationship between the change of pain and biomechanical variables (e.g., EKAM, muscle co-contraction) after receiving TCM treatments is still unclear. Therefore, there is a need for a study on the clinical and biomechanical effects of the TCM treatments (e.g., CH, AT, and CM).

The purpose of this study was to compare the clinical and biomechanical outcomes of four parallel groups of individuals with knee OA (CH, AT, CM, and CN), which might help to investigate the clinical and biomechanical effects of the selected TCM treatments in the management of the knee OA.

4.3 Aims and hypothesis of the TCM study

The purpose of the TCM study was to achieve a better understanding of the clinical and biomechanical effects of TCM treatments over a 6-week period. The assessment was conducted by comparing both the clinical and biomechanical outcomes of individuals with medial knee OA from four demographically evenly distributed groups.

The aims and hypotheses of the chapter are therefore:

1. To determine whether TCM treatments reduce the WOMAC (pain, stiffness, function, and total) scales over a period of six weeks when compared with the baseline and

neutral flat insole.

Hypothesis 1: The WOMAC (pain, stiffness, function, and total) scales in TCM groups are improved after receiving six-week TCM treatments when compared with the baseline and six-week CN.

2. To determine whether TCM treatments reduce the EKAM over a period of six weeks when compared with the baseline and neutral flat insole.

Hypothesis 2: The EKAM in TCM groups are reduced after receiving six-week TCM treatments when compared with the baseline and six-week CN.

3. To determine whether TCM treatments reduce the muscle co-contraction over a period of six weeks when compared with the baseline and neutral flat insole.

Hypothesis 3: The muscle co-contraction in TCM group are reduced after receiving six-week treatments when compared with the baseline and six-week CN.

4.4 Methods

4.4.1 Participants recruitment

Participants who met the eligibility criteria of the study were recruited from the Shuguang Hospital.

Individuals aged 40 to 70 years old who had been diagnosed with medial knee OA were eligible. Diagnosis of knee OA was completed by a designated doctor with regards to the ACR for the classification and reporting of OA of the knee joint (Hochberg et al., 1995).

The recruited participants went through the study process shown in the following flow chart (Figure 4-1). The process included four treatments and two data collection and two effect assessment tests.

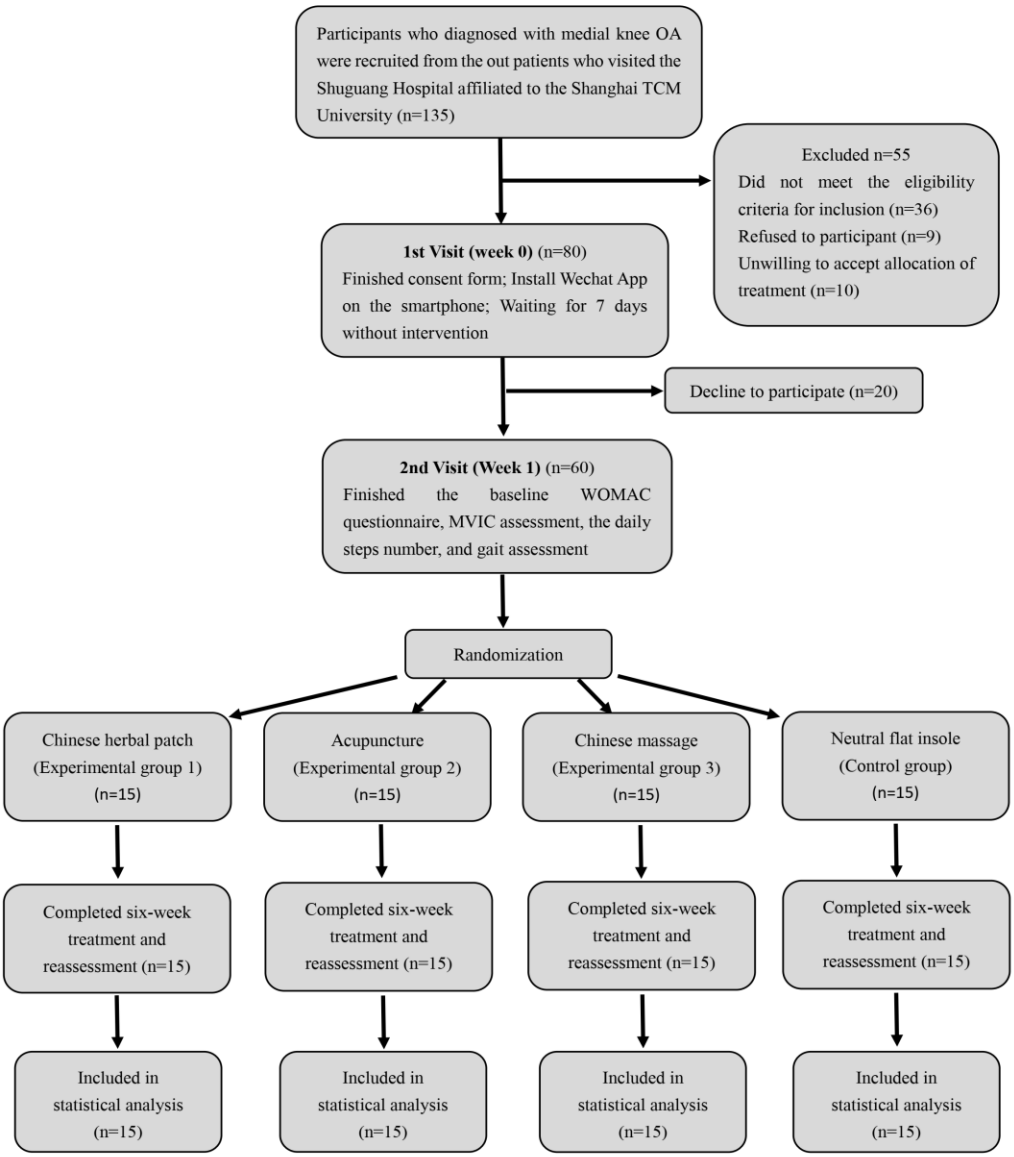


Figure 4-1 Flow of participants through the TCM study

4.4.2 Eligibility criteria for inclusion and exclusion

The eligibility criteria for inclusion in the study were as follows:

1. At an age between 40 and 70 years.
2. Medial knee OA diagnosed by a clinician.
3. Radiologic confirmation of knee OA (Kellgren–Lawrence grade 1 to 3).
4. Having knee pain and not undergone any treatment for the last 2 months.
5. Could walk independently at least 200 metres without any help.
6. Not having any other musculoskeletal or neurological diseases which may affect gait pattern.
7. Having at least one smartphone with Apple IOS systems or Google Android system.

The exclusion criteria for participants were as follows:

1. Not meet the inclusion criteria.
2. Unwilling to be randomised in the intervention groups.

4.4.3 Sample size

Sixty participants who met the eligibility criteria of the study were recruited from the Shuguang Hospital. The calculation of the sample size was based on the mean value and the SD of WOMAC score of a previous four-arm knee OA study (Ao, Guo & Wu. 2017), power of 0.80 and alpha level of 0.05, through G*Power Software, version 3.1.97 (Franz Faul, Universitat Kiel, Germany). (For more details about sample size please see **3.11.4.3 Sample size**).

4.4.4 Randomization

This study involving four groups, which investigated the short-term (6 weeks) effects of CH patches, AT, and CM in individuals with medial knee OA during walking. After informed consent had been obtained from all participants, they were randomly allocated to the CH, AT, CM, and CN groups. A statistician in Shuguang Hospital determined the computer-generated randomization sequence and the treatments were assigned according to the randomization with the use of sealed envelopes.

4.4.5 Research environment

Some of the data such as daily walking steps and pain feedback were collected in the living environment of the participants. The assessment tests were conducted in the gait analysis lab in Shuguang Hospital. (For more details about the gait analysis and sEMG system, please see **3.2.1 Gait analysis system** and **3.2.2 sEMG system**)

4.4.6 The procedure of the TCM study

4.4.6.1 The first visit (week 0)

The participants who met the eligibility criteria of the study had the purpose of the study explained to them and received a participant information sheet. If participants were willing to participate, the investigator further explained the details of the study which included the description of all the equipment and the testing procedure. After that, they were given time to ask any questions they had before they were given the consent form (Reference number ChiECRCT 20170055 (approved by the China ethics committee of registering clinical trials), HSR1617-173 (approved by the University of Salford)). Each participant was given at least 24 hours to read and sign the consent form before starting the experiment.

Participants were informed that participation in the current study was completely voluntary, and they were free to withdraw from the study at any point of time without any explanations. In the event of their withdrawal, the collected data would not be deleted unless they wished for this to happen. The participants were asked to install the Wechat app on their smartphone and asked them to record their daily walking steps via Wechat.

After that, the participants were asked to continue with their daily activities for 7 days, and then an appointment was made for them to come to the gait analysis laboratory in the Shuguang Hospital via telephone, Wechat message, or e-mail. (For more details about daily physical activity (daily number of steps) please see **3.7 Daily number of**

steps)

Moreover, the participants were informed that during the six-week treatment, when they experienced intolerable pain, ibuprofen sustained-release capsules were administrated as rescue medication, however, once they used rescue medication their data would be excluded.

4.4.6.2 The second visit (week 1)

Upon attending the gait laboratory, the WOMAC questionnaire (Chinese Version) was completed. After completion of the WOMAC questionnaire, the participants were asked to return the signed consent form and transfer the latest seven days' daily number of steps and diaries to the investigator and the mean value of the seven days' daily number of steps was recorded. After that, the participants were asked to wear a pair of shorts and a T-shirt for the test setup. The EMG sensors were placed and then the MVIC test would be conducted. The MVIC data for each muscle was used for normalizing the sEMG data during the walking trials. Considering the participants in the study had varying degrees of OA severity and levels of mobility, the positions for MVIC collection were particularly considered so each participant could get in the position and complete the test without any difficulties. (For more details about the sEMG sensors placement and the MVIC test were described in **3.4.2 sEMG sensors placement and skin preparation** and **3.5 Maximal voluntary isometric contraction**).

After finishing the MVIC test, the retro-reflective markers were attached to the participants' skin over bony landmarks on both lower limbs, with all electrodes in place, and then the participants were asked to stand on top of one force platform to perform a static standing trial, after a test trial to confirm that all the markers were able to be obtained by the VICON system. The participants were asked to walk for a short time to allow adaptation to the test environment and to determine the best starting point from which the participants would start walking to hit on the force platforms accurately, this helped to ensure the successful walking trials could be completed in a short time. (For

more details about the markers placement and successful trial please see **3.4.1 Marker placement and 3.9.5.2 The monitoring of walking trials quality**).

The participants were asked to walk on an 8.5-metre long walkway at their self-selected speed. All participants were asked to perform the walking tests until ten successful walking trials were achieved. To minimize the errors which might be caused by wearing different shoes, the participants were asked to wear the same type of standard shoes (Huili, Shanghai Huili Footwear Co. Ltd, China, http://www.warriorshoes.com) which were offered by the investigator during the gait test.

4.4.6.3 The third visit (week 7)

After completing the last treatment (for the CN group after using the insole for six weeks), the participants were advised to start to collect data and make diaries for 7-day before coming to the gait lab for the second assessment.

At the third visit, the same steps in the second visit (week 1) were conducted again, following the same order and procedure.

4.4.6.4 The other recorded data

The daily number of steps data was measured over a mean period of seven days by the smartphone. The daily number of steps data was recorded by the participants themselves and followed the rules: (1) carrying the smartphone during their physical activities, especially outdoor activities; (2) maintain their normal physical activities.

4.4.7 CH group

4.4.7.1 The CH patch protocol and treatments selection criteria

The participants in the CH group underwent treatment seven days per week for six weeks. The chosen CH patch for this study was FNZG (SFDA approval no. Z10970019, Jiangsu Nanxing Pharmaceutical Co., Ltd.). The main active ingredients of FNZG includes Hypaconitine ($C_{33}H_{45}NO_{10}$) and Eugenol ($C_{10}H_{12}O_2$), which were

extracted mainly from raw Rhizoma Arisaematis (Sheng Tiannanxing), raw Radix Aconiti (Sheng Chuanwu), Flos Caryophylli (Dingxiang), Cortex Cinnamomi (Rougui), Radix Angelicae Dahuricae (Baizhi), Herba Asari (Xixin), Rhizoma Chuanxiong (Chuanxiong), Radix Cynanchi Pan- icuclati (Xuchangqing), processed Olibanum (Zhi Ruxiang), processed Myrrha (ZhiMoyao), Camphora (Zhangnao), and Borneolum Syntheticum (Bingpian). The size of each FNZG was 10 cm* 13 cm (Figure 4-2). The protocol of the CH patch in the current study was strictly defined and applied in the treatment protocol of Shanghai Shuguang Hospital.

The rationale for using FNZG is that the clinical effectiveness of the FNZG has been proved by some previous studies (Wang et al., 2008, Jiang et al., 2013, Zhao & Wang et al. 2008). Wang et al. (2008) found that the FNZG showed significant improvement in pain symptoms when compared with the baseline. Jiang et al. (2013) demonstrated that the FNZG showed significant improvement in VAS when compared with the placebo patch. Zhao & Wang. (2008) reported that after receiving a six-week treatment, the FNZG group showed significant improvements in WOMAC pain, stiffness, function, and total scales when compared with the placebo patch group. However, no previous study investigated both the clinical and biomechanical effects of the FNZG, therefore, the FNZG has been selected for the current study.

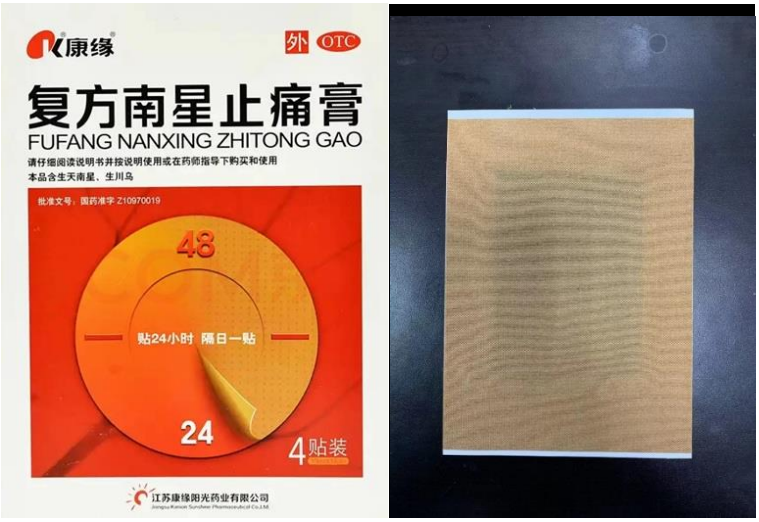


Figure 4-2 The package and outlook of the FNZG herbal patch (The CH patch used in the CH group)

4.4.7.2 CH patch usage

A designated doctor with a minimum of three years of clinical experience in the Institute of Orthopedics & Traumatology, Shanghai Academy of Traditional Chinese Medicine Department of Orthopedics & Traumatology, Shuguang Hospital gave the FNZG herbal patches to the participants and showed them how to use the FNZG patches.

Participants were required to apply the FNZG to cover the affected knees each day and remove it 24 hours after application, which was similar to the previous study (Xing et al., 2018). For participants with bilateral OA, both knees were treated (Berman et al., 2004), but only the data of the more symptomatic limb was evaluated (Sawada et al., 2017). The time of FNZG application and removal was recorded daily in a diary for compliance purposes.

4.4.7.3 The precautions for the CH group

A written precaution for the CH group was provided to the participants by the doctor before they started the treatment:

(1) The participants were advised to have a shower before applying the FNZG to the affected part; (2) two pieces of the FNZG patch would be used to cover both medial and lateral sides of the affected knee; (3) if the participants were allergic to FNZG, they were advised to stop using it immediately, which included the skin allergic to the FNZG patch; (4) the participants were advised not to take any other medications (e.g., paracetamol, NSAIDs, corticosteroid injections, and tramadol) whilst they were taking part in the study unless the participants experienced intolerable pain. They were advised to make a report to the investigator once they did (Their data would be excluded from the analysis and extra participants would be recruited).

4.4.8 AT group

4.4.8.1 The AT protocol and treatments selection criteria

Participants in the AT group underwent a 30 minutes session of acupuncture therapy

twice per week for six weeks. The acupoints were performed on participants in the AT group with nine needle insertions per patient per session (30 minutes) using 0.25 × 25 mm disposable stainless-steel needles (Tianjin, China) (Figure 4-3). These points were on the affected side, which included: Yanglinquan [GB34], Yinlinquan [SP9], Zusanli [ST36], Taixi [KI3], Sanyinjiao [SP6], Xiyan [EX-LE5] (two points), Hegu [LI4], and Fenglung [ST40] (Table 4-1, Figure 4-4). The selection of the acupoints was strictly defined and applied in the treatment protocol of Shanghai Shuguang Hospital, which was also recommended by the Diagnosis and management of knee osteoarthritis: Chinese medicine expert consensus (Chen et al., 2015).

The same points were treated for each affected leg. For participants with bilateral medial knee OA, both sides were treated (Berman et al., 2004), but only the data of the more symptomatic limb was evaluated (Sawada et al., 2017). The depth of needle insertion varied with the thickness of the skin and subcutaneous fatty tissues at the site of the acupuncture points (approximately 10 to 15mm). The needles were rotated by an acupuncturist with the index finger and thumb in an alternating clockwise and counterclockwise at the rate of three to five rotations per second to determine the patient's sensation of Deqi to make sure the needles were performed correctly (Vas et al., 2004).

The rationale for using AT is that the clinical effectiveness of AT has been proved by some previous studies (Witt et al., 2005, Jubb et al, 2008, Lansdown et al., 2009). Witt et al. (2005) indicated that after receiving three-month treatment, the AT group showed significant clinical improvements when compared with the control group (sham acupuncture with no non-penetrating). Jubb et al. (2008) also reported that the AT achieved significant symptomatic (WOMAC) improvements in individuals with knee OA in comparison with the baseline. Lansdown et al. (2009) also demonstrated that the AT could significantly improve the pain after having a three-month intervention. Although AT has been proved to be effective in the management of clinical symptoms caused by knee OA, less study investigated short-term biomechanical effects of the AT,

therefore, the AT has been selected for the current study.

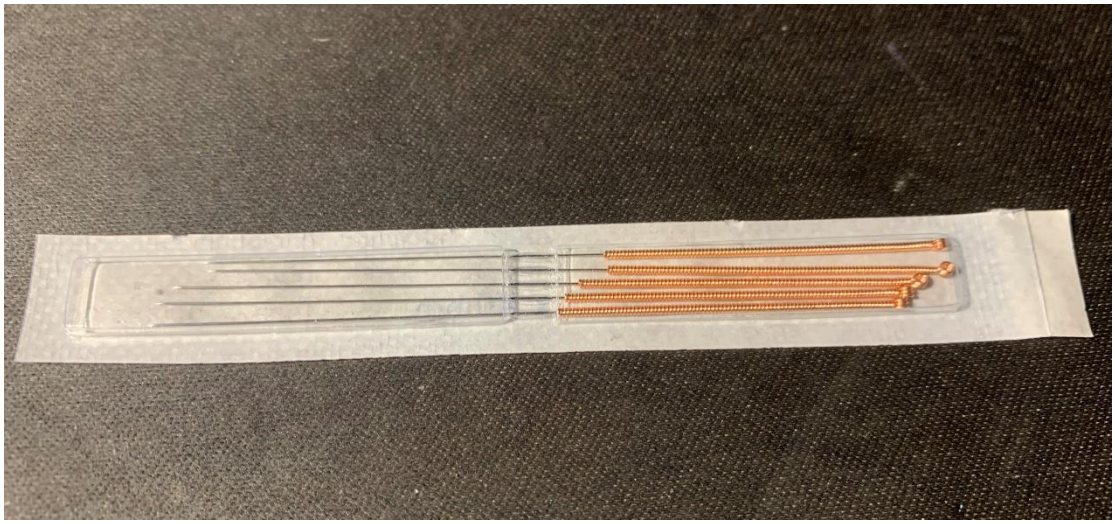


Figure 4-3 The needles for AT group in the current study, 0.25 × 25 mm disposable stainless-steel needles (Tianjin, China)

Table 4-1 The position of the acupuncture points for AT group

The positions of the acupuncture points	
Yanglinquan [GB34]	Located at the depression below the anterior fibular head of the lateral calf.
Yinlinquan [SP9]	Located at the lower border of the medial condyle of the tibia, in the depression between the posterior border of the tibia and gastrocnemius muscle
Zusanli [ST36]	Located at outer sides of both legs. The width of four fingers of the recipient's finger below the lower border of the knee cap and 1 finger width away from the shin bone.
Taixi [KI3]	Located at in the depression midway between the tip of the medial malleolus and the attachment of the Achilles tendon, level with the tip of the medial malleolus.
Sanyinjiao [SP6]	Located at the width of four fingers of the recipient's finger above the tip of the medial malleolus.
Xiyan [EX-LE5]	Located at in the depression on both sides of the patellar ligament when the kneels flexed
Hegu [LI4]	Located at the dorsum of the hand, between the 1st and 2nd metacarpal bone
Fenglung [ST40]	Located at about 2.5 times of the width of four finger of the recipient's finger superior to the tip of the external malleolus.

The number in the bracket. (e.g., [GB34]) represents the international code of the acupoint.

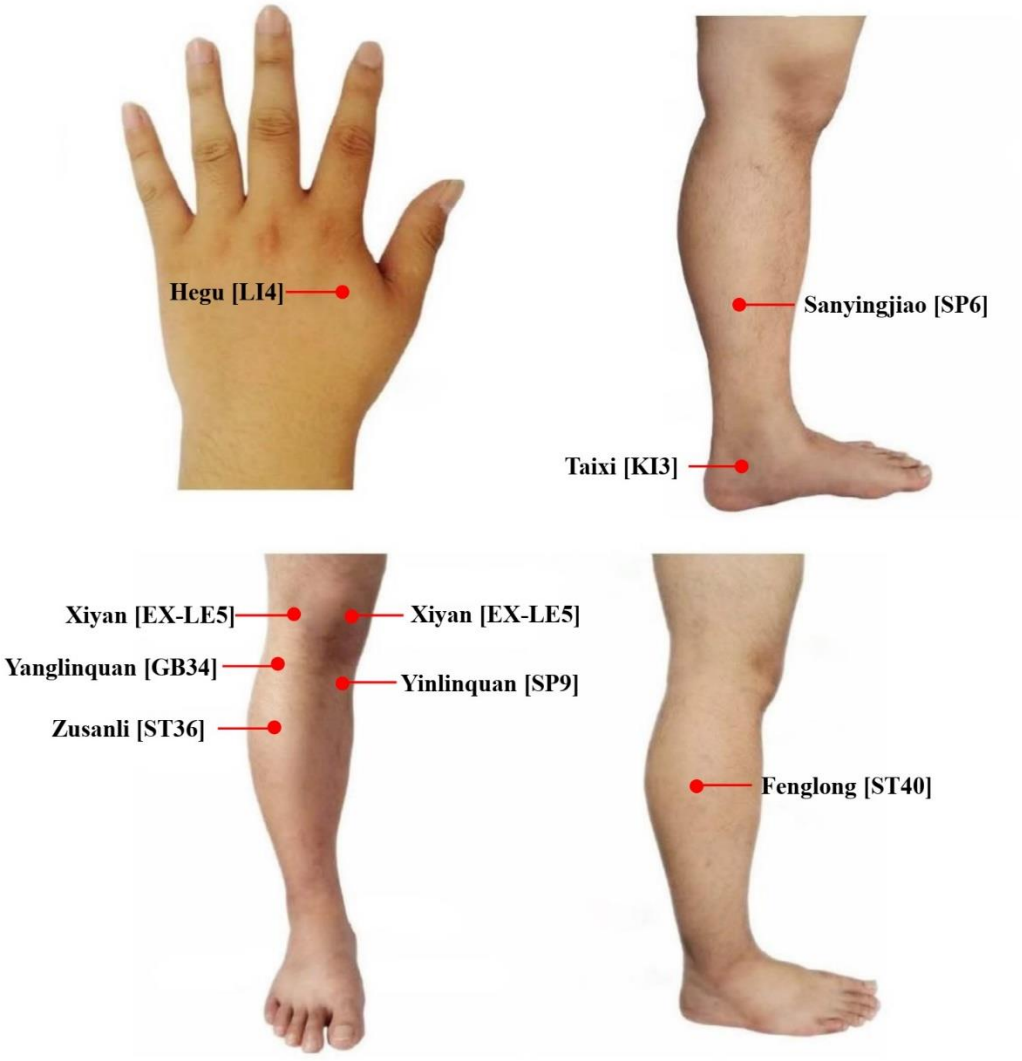


Figure 4-4 Acupoints used in the AT group

4.4.8.2 Acupuncture procedure

Upon attending the treatment room in Shuguang Hospital, the acupuncturist explained the details and precautions of AT to the participants. After that, the participants were asked to lay down comfortably on a bed, and exposure the skin of affected knees to the acupuncturist. The acupuncturist cleaned the skin of the affected knees with 75% alcohol and inserted the needles into the acupoints. The depth of needle insertion varied with the thickness of the skin and subcutaneous fatty tissues at the site of the acupuncture points (approximately 10 to 15mm). The needles were rotated by an

acupuncturist with the index finger and thumb in an alternating clockwise and counterclockwise at the rate of three to five rotations per second to determine the patient's sensation of Deqi to make sure the needles were performed correctly (Vas et al., 2004) (Figure 4-5). The time of needle retaining was 30 minutes. After receiving AT, the acupuncturist removed all the needles and cleaned the skin of the participants' affected knees with 75% alcohol again. The participants were asked to have a rest in the treatment room for 20 minutes to see if they felt any uncomfortable such as dizziness, nausea, or vomiting. If not, they would be given an appointment for the next treatment. If the participants felt discomfort after treatment the acupuncturist would give them further checks.

Figure 4-5 The graphic showed the knee OA participant who was receiving AT

4.4.8.3 The precautions for the AT group

A written precaution for the AT group was provided to the participants by the designated doctor before they started the treatment:

(1) the participants should not undergo AT on an empty stomach; (2) the participants should report to the doctor or investigator immediately when they felt discomfort such as dizziness, nausea, or vomiting during AT; (3) the acupuncture point cannot be washed within 8 hours after treatment; (4) the participants should not take any other treatment during the six weeks of AT.

Participants in the AT group underwent acupuncture treatment twice per week for six weeks, and the time interval between the two AT sessions was at least 48 hours. A notebook was used to record the attendance of the visit during six-week treatment. The acupuncture therapy was performed by a well-qualified acupuncturist doctor with a minimum three-year clinical experience in the Institute of Orthopedics & Traumatology, Shanghai Academy of Traditional Chinese Medicine Department of Orthopaedics & Traumatology, Shuguang Hospital.

4.4.9 CM group

4.4.9.1 The CM protocol and treatments selection criteria

The participants in the CM group underwent a 30 minutes session of CM therapy twice per week for six weeks. CM therapy was performed by a qualified CM (Tui Na) doctor with a minimum three-year clinical experience in the Institute of Orthopedics & Traumatology, Shanghai Academy of Traditional Chinese Medicine Department of Orthopedics & Traumatology, Shuguang Hospital. The protocol of the CM therapy in the current study was strictly defined and applied in the treatment protocol of Shanghai Shuguang Hospital. Muscles on the thigh and shank massaged by CM (Tui Na) doctor included: VL, VM, BF, ST, MG, LG, and TA. Each affected side underwent the same intervention. For participants with bilateral medial knee OA, both sides were treated, but only the data of the more symptomatic side was evaluated.

The rationale for using CM is that the clinical effectiveness of the CM has been proved by some previous studies (Zhu et al., 2015, Yu & Gong. 2018, Chen et al., 2021). Zhu et al., 2015 (2015) reported that two-week CM showed significant improvements in

clinical symptoms caused by knee OA when compared with the baseline. One meta-analysis (Yu & Gong. 2018) indicated that the CM could offer symptomatic improvements for individuals with medial knee OA. The latest RCT study (Chen et al., 2021) indicated that the six-week CM showed significant improvement in clinical symptoms when compared with physical therapy. Although CM has been proved to be effective in the management of clinical symptoms caused by knee OA, less study investigated short-term biomechanical effects (e.g., knee loading, muscle co-contraction) of the CM, which lead to the research gap of the current study. Therefore, the CM has been selected for the current study.

4.4.9.2 CM procedure

Upon attending the treatment room in Shuguang hospital, the CM (Tui Na) doctor explained the details and precautions for CM to the participants. After that, the participants were asked to lay down on the bed, and exposure the skin of affected knees to the CM doctor. The CM doctors operated rolling manipulation on the affected side VL, VM, BF, ST, MG, LG, and TA for 10 minutes (Figure 4-6). After that, the CM doctor operated grasping manipulation on the affected side VL, VM, BF, ST, MG, LG, and TA for another 15 minutes (Figure 4-7). At the end of the treatment, the CM doctor operated rubbing manipulation around the affected knee until the participants sensed warmth (Figure 4-8). During the CM, the participants should feel mild to moderate soreness and distension.

After receiving the CM therapy, the participants were asked to have a rest in the treatment room for 20 minutes to see if they felt any uncomfortable such as dizziness, nausea, or vomiting. If not, they would be given an appointment for the next treatment. If the participants felt discomfort after treatment the CM doctor would give them further checks.

Figure 4-6 The doctor was operating rolling manipulation on the muscles around participant's affected knee

Figure 4-7 The doctor was operating grasping manipulation on the muscles around participant's affected knee

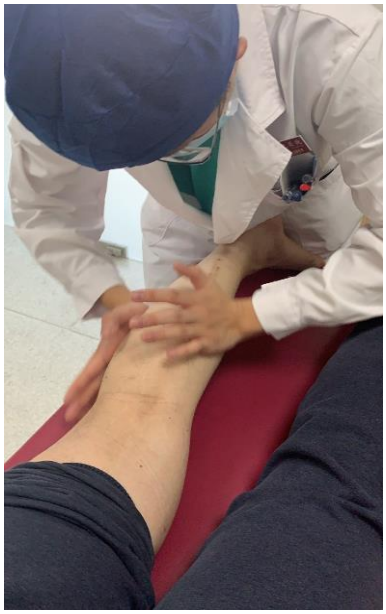


Figure 4-8 The doctor was operating rubbing manipulation around participants affected knee

4.4.9.3 The precautions for the CM group

A written precaution for the CM group was provided to the participants by the designated doctor before they started the treatment:

(1) The participants should not undergo CM on an empty stomach; (2) the participants should report to the doctor or investigator immediately when they felt discomfort such as dizziness, nausea, or vomiting during CM; (3) the participants should not take any other treatment during the six weeks of CM.

Participants in the CM group underwent CM treatment twice per week for six weeks, and the time interval between the two CM sessions was at least 48 hours. A notebook was used to record the attendance of the visit during the six-week treatment. The CM therapy was performed by a well-qualified CM doctor with a minimum three-year clinical experience in the Institute of Orthopaedics & Traumatology, Shanghai Academy of Traditional Chinese Medicine Department of Orthopaedics & Traumatology, Shuguang Hospital.

4.4.10 CN group

4.4.10.1 The CN protocol and treatments selection criteria

To strengthen the validity and credibility of the results and enable the improvements to be attributed to the intervention itself, the design of a control group is critical to the research (Kinser & Robins). Based on the suggestion of the Food and Drug Administration (FDA) the no-treatment control group is suitable to use when the study results are objective and cannot be influenced by the lack of blinding. Most of the outcomes of the current study were quantified objective variables such as kinetic, kinematic, muscle co-contraction, and temporal-spatial parameters, therefore, neutral (flat) insoles were used in this study as a no-treatment control. The participants in the CN group were instructed to use the neutral insole (Aptonia, Taiwan, China) in their shoes and wear them for a minimum of 8 hours per day for six-week (Figure 4-9).

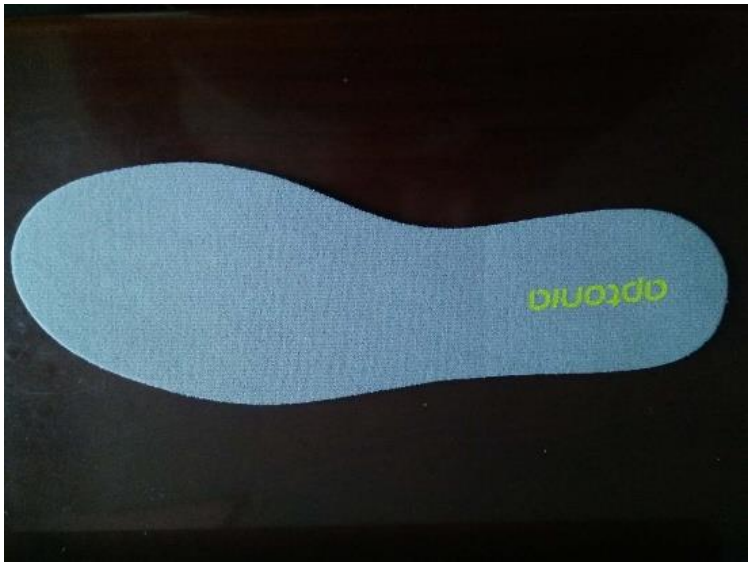


Figure 4-9 The neutral insole (Aptonia, Taiwan, China) which was used in the control group

4.4.10.2 Neutral (flat) insole usage

Upon attending the treatment room in Shuguang Hospital, the investigator explained the details and precautions for neutral insoles to the participants. After that, a designated doctor gave the neutral insole to the participants and showed them how to use the neutral insoles. The hours of using neutral insoles were recorded daily in a diary for

compliance purposes.

4.4.10.3 The precautions for the CN group

(1) The participants should report to the doctor or investigator immediately when they felt discomfort during wearing flat insoles. (2) The participants should not take any other medications (e.g., paracetamol, NSAIDs, corticosteroid injections, and tramadol) whilst they were taking part in the study unless the participants experienced intolerable pain. They were advised to make a report to the investigator once they did. (Their data would be excluded from the analysis, and extra participants would be recruited).

4.4.10.4 The treatments for the CN group after the study

As the participants in the CN group were treated with neutral flat insoles in this study, the investigators would offer one of TCM treatments (CH patch, AT, or CM) to these participants after they finished the study.

4.4.11 Participant's compliance

All the participants were asked to keep a diary on their symptoms and activities during the treatment and use their mobile phones to record their daily number of steps. The information was a report of the effect and compliance of the treatment.

4.4.12 Data processing and analysis of the TCM study

The mobile recorded daily activity data, the completed WOMAC forms, and the diaries were summarized in Microsoft Word and Excel for further analysis. The biomechanical outcomes and muscle activity data processed with Vicon Nexus Software (Version 1.8.5) and Visual 3D software (v 6.01.16) from each assessment gait test, which were performed in gait lab with a minimum of ten successful trials, were exported to Microsoft Excel for further analysis. The kinematics, kinetics, GRF, and muscle activity data were normalised to the stance phase. (For more detail about biomechanical modelling and computations, data digitizing, and gap interpolation, kinematics, kinetics, and sEMG raw data filtering, please see section 3.6 **Biomechanical modelling and**

computations and **3.8 Data processing**)

4.4.13 Outcome measures

These following outcome measures enabled the investigator to test hypotheses 1, 2, and 3 concerning the effect of TCM treatments on clinical, biomechanical outcomes, and muscle co-contraction variables.

4.4.13.1 The primary outcome measures

- ***WOMAC***

The WOMAC (pain, stiffness, function, and total) were measured at baseline (week 1) before treatment and after receiving a six-week treatment (week 7). The WOMAC questionnaire (Chinese version) used in this study was rated on a 0-10 numeric rating scale for every subscale, thus, the total scale range of 0 to 240 points.

- ***EKAM***

The EKAMs (1st peak of EKAM, 2nd peak of EKAM, and KAAI) were measured at baseline (week 1) before treatment and after receiving a six-week treatment (week 7).

- ***Muscle co-contraction***

The muscle co-contraction between VL/BF, VL/LG, VM/ST, VM/MG, TA/MG at three stages (early stance 0–33% of stance, mid-stance 34–67% of stance, and late stance 68–100% of stance) were measured at baseline (week 1) before treatment and after receiving 6-week treatment (week 7).

- ***The equation for calculating the muscle co-contraction***

Muscles co-contraction was defined as the average of simultaneous activation of a pair of agonist and antagonistic muscles and was calculated according to Equation (Rudolph et al., 2001).

EMG lower/EMG higher × (EMG lower +EMG higher) *100%

The EMG lower was the level of activity in the less active muscle and EMG higher was

the level of activity in more active muscle.

The muscle co-contraction between antagonistic muscle pairs in the lower extremity for this study was referred to the previous studies (VL v.s. BF, VM v.s. ST, VL v.s. LG, VM vs. MG, and TA v.s. MG) (Hodges et al., 2016, Al-Khlaifat et al., 2016, Jones et al., 2018, Child et al., 2004).

4.4.13.2 The secondary outcome measures

- ***Kinematics and kinetics of the knee during stance phase***

Peak angles, ROM, and peak joint moments of the knee during stance phase in the sagittal, frontal, and transverse planes were assessed at baseline (week 1) before treatment and after receiving a six-week treatment (week 7).

- ***Temporal spatial variables***

The walking speed, step length, cadence, double support time, stance phase percentage, and the daily number of steps were assessed at baseline (week 1) before treatment, and after receiving a six-week treatment (week 7).

4.4.14 Statistical analyses

Statistical analysis in the current study was performed using SPSS ver. 24.0 (IBM, Chicago, IL) and a Shapiro–Wilk test was used to determine the normality distribution of data. A paired t-test was used for comparison within the group, all values were expressed as Mean±SD, a statistically significant difference was defined as p-value≤0.05. One-way ANOVA followed by Tukey's post hoc test was used to determine possible differences between groups was used to determine if the groups were different at baseline, and after 6 weeks' use of the intervention, a statistically significant difference was defined as P-value<0.05 (de Matos Brunelli Braghin et al., 2019). The effect size was calculated with the Cohen-d test by using GPOWER (Version 3.1.7) and classified as small (≥0.2 and＜0.5), medium(≥0.5 and＜0.8), and large (≥0.8) (Cohens, 1988, Schween et al., 2015). (For more details, please check **3.11.4.12 Statistical**

analyses)

4.5 Results

Demographic details were described in Table 4-2 with data showed no significant difference between the CH, AT, CM, and CN groups in terms of age, height, body mass, and body mass index. The sixty participants were randomly assigned to the CH, AT, CM, and CN groups (Figure 4-1). No adverse event was detected, and no participant dropped out or reported using rescue medicine during the study.

Table 4-2 The demographic data (Mean±SD) and knee condition scales of the CH, AT, CM, and CN groups

Variable	CN (n=15)	CH (n=15)	AT (n=15)	CM (n=15)	P
Age (years)	61.67±6.40	61.87±6.12	60.27±5.98	61.33±6.16	0.90
Height (m)	1.60±0.06	1.61±0.05	1.61±0.06	1.62±0.06	0.82
Body Mass (kg)	61.99±7.45	62.78±8.95	63.37±6.22	65.39±15.32	0.97
Body mass index (kg/m²)	24.27±3.09	24.26±2.74	24.53±2.76	24.74±4.04	0.98
Total number (male, female)	male=3, female=12	male=4, female=11	male=2, female=13	male=2, female=13	
KL grade of knee OA	grade 2=12, grade 3=3	grade 2=11, grade 3=4	grade 2=12, grade 3=3	grade 2=10, grade 3=5	
Unilateral pain	8	7	8	9	
Bilateral pain	7	8	7	6	

4.5.1 Primary outcomes

WOMAC: The baseline data indicated that the WOMAC scores between the CH, AT, CM, and CN groups had no significant difference (P>0.05). The data from the assessment post six-week treatment indicated that the six-week CN still had no significant differences in WOMAC pain, stiffness, function, and total score when compared with the baseline (P>0.05). However, the data from the CH, AT, and CM groups at the assessment post six-week treatment demonstrated some improvements in WOMAC scores in comparison with the baseline. The changes were also identified in comparison with the data of CN collected after six-week (Table 4-3, Figure 4-10 A, B, C, and D).

After six-week treatment period, the participants in the CH group achieved 14.0% reduction in WOMAC pain (P=0.03, Cohen's d= 0.42), 17.5% reduction in stiffness

(P=0.15, Cohen's d=0.43), 9.3% reduction in function (P=0.54, Cohen's d=0.27), and 11.2% reduction in total scores (P=0.03, Cohen's d=0.40) in comparison with the baseline. However, only the reduction in WOMAC pain and total were statistically significant (P<0.05), the other changes were not statically significant (P>0.05). Small in-group effect sizes were observed in WOMAC pain, stiffness, function, and total (Table 4-3, Figure 4-10 A, B, C, and D).

The six-week AT achieved 39.1% reduction in WOMAC pain (P=0.00, Cohen's d=1.12), 41.0% reduction in WOMAC stiffness (P=0.00, Cohen's d=1.11), 26.7% reduction in WOMAC function (P=0.00, Cohen's d=1.24), and 30.9% reduction in WOMAC total (P=0.00, Cohen's d=1.54) in comparison with the baseline, the reduction were statistically significant (P<0.05). Large in-group effect sizes were observed in WOMAC pain, stiffness, function, and total (Table 4-3, Figure 4-10 A, B, C, and D).

The six-week CM achieved 33.2% reduction in WOMAC pain (P=0.00, Cohen's d=1.23), 47.3% reduction in WOMAC stiffness (P=0.00, Cohen's d=0.71), 24.8% reduction in WOMAC function (P=0.00, Cohen's d=1.23), and 28.7% reduction in WOMAC total (P=0.00, Cohen's d=1.02) in comparison with the baseline, the reduction were also statistically significant (P<0.05). Large in-group effect sizes were observed in WOMAC pain, function, and total, and medium in-group effect size was observed in WOMAC stiffness (Table 4-3, Figure 4-10 A, B, C, and D).

In comparison with the six-week CN, the participants in six-week CH achieved 4.3% reduction in WOMAC pain (P=0.76, Cohen's d=0.11), 5.8% reduction in stiffness (P=0.74, Cohen's d=0.13), 13.2% reduction in function (P=0.29, Cohen's d=0.39), and 10.6% reduction in total (P=0.34, Cohen's d=0.35), however, the changes were not statically significant (P>0.05). Small between-group effect sizes were observed in WOMAC pain, stiffness, function, and total (Table 4-3, Figure 4-10 A, B, C, and D).

In comparison with the six-week CN the participants in six-week AT achieved 33.6% reduction in WOMAC pain (P=0.01, Cohen's d=1.24), 34.3% reduction in WOMAC stiffness (P=0.01, Cohen's d=1.19), 28.2% reduction in WOMAC function (P=0.01, Cohen's d=1.02), and 29.9% reduction in WOMAC total (P=0.00, Cohen's d=1.19), the changes were aslo statistically significant (P<0.05). Large between-group effect sizes were also observed in WOMAC pain, stiffness, function, and total (Table 4-3, Figure 4-10 A, B, C, and D).

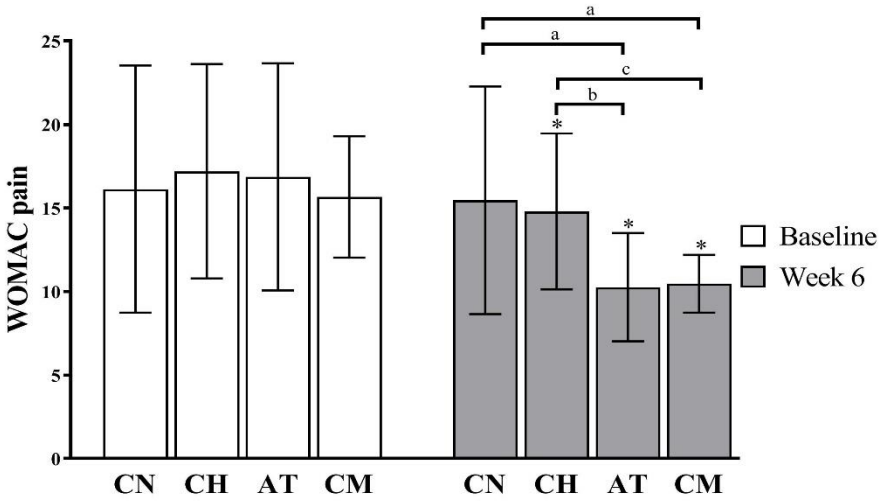
In comparison with the six-week CN, the participants in six-week CM achieved 32.3% reduction in WOMAC pain (P=0.01, Cohen's d=1.00), 43.0% reduction in WOMAC stiffness (P=0.00, Cohen's d=1.33), 29.2% reduction in WOMAC function (P=0.01, Cohen's d=1.09), and 30.9% reduction in WOMAC total (P=0.00, Cohen's d=1.28), the changes were statistically significant (P<0.05). Large between-group effect sizes were observed in WOMAC pain, stiffness, function, and total (Table 4-3, Figure 4-10 A, B, C, and D).

The reduction of WOMAC scores were found in pain (30.6%, P=0.01, Cohen's d=1.12), stiffness (30.2%, P=0.04, Cohen's d=0.70), function (17.2%, P=0.15 Cohen's d=0.51), total (21.5%, P=0.03 Cohen's d=0.81) in six-week AT when compared with the six-week CH. Moreover, in comparison with the CH group at post-treatment, the six-week CM showed reduction in WOMAC pain (29.26%, P=0.01, Cohen's d=1.23), stiffness (39.5%, P=0.01 Cohen's d=0.93), function (18.4%, P=0.12 Cohen's d=0.57), and total (22.7%, P=0.02 Cohen's d=0.88). Except the WOMAC function, the other improvements were statistically significant (P<0.05). Medium to large effect sizes were observed in WOMAC pain, stiffness, function, and total between groups. However, there was no significant difference between the six-week AT and six-week CM in WOMAC pain, stiffness, function, and total (P>0.05) (Table 4-3, Figure 4-10 A, B, C, and D).

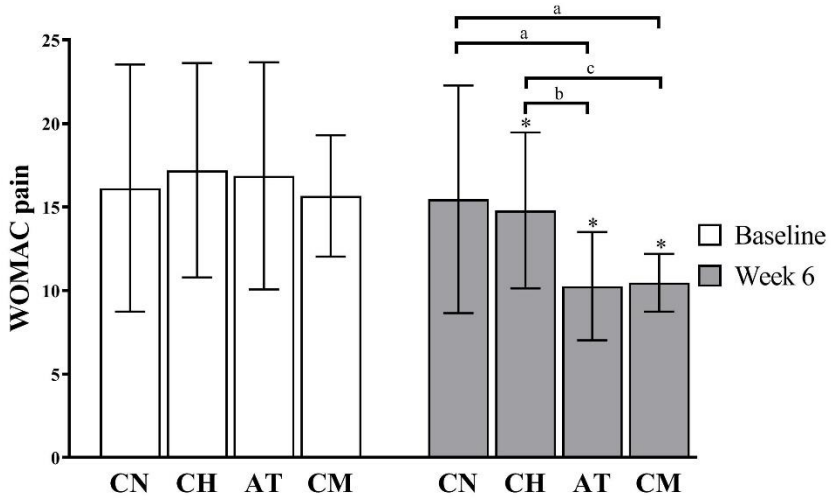
Table 4-3 The WOMAC scores (Mean±SD) of the CN, CH, AT, and CM groups

Outcome Measure		CN (n=15)	CH (n=15)	AT (n=15)	CM (n=15)
WOMAC pain	Baseline	16.13±7.40	17.20±6.42	16.87±6.80	15.67±3.64
	Week 6	15.47±6.81	14.80±4.66*[b,c]	10.27±3.24*[a]	10.47±1.73*[a]
WOMAC stiffness	Baseline	4.93±1.94	5.33±1.72	5.20±2.21	5.07±3.03
	Week 6	4.67±1.84	4.40±2.41[b,c]	3.07±1.22*[a]	2.66±1.05*[a]
WOMAC function	Baseline	47.73±15.16	44.40±14.58	45.47±9.47	43.73±12.03
	Week 6	46.40±15.13	40.27±15.98	33.33±10.11*[a]	32.87±8.90*[a]
WOMAC total	Baseline	68.80±21.38	66.93±17.26	67.53±15.10	64.47±14.33
	Week 6	66.53±20.57	59.47±19.48*[b,c]	46.67±11.20*[a]	46.00±9.42*[a]

*: P<0.05 when a treatment group was compared with baseline (intragroup evaluation).
[a]: P<0.05 when a treatment group was compared with six-week CN (intergroup evaluation).
[b]: P<0.05 when six-week CH was compared with six-week AT (intergroup evaluation).
[c]: P<0.05 when six-week CH was compared with six-week CM (intergroup evaluation).



(A) Mean (SD) WOMAC pain



(B) Mean (SD) WOMAC stiffness

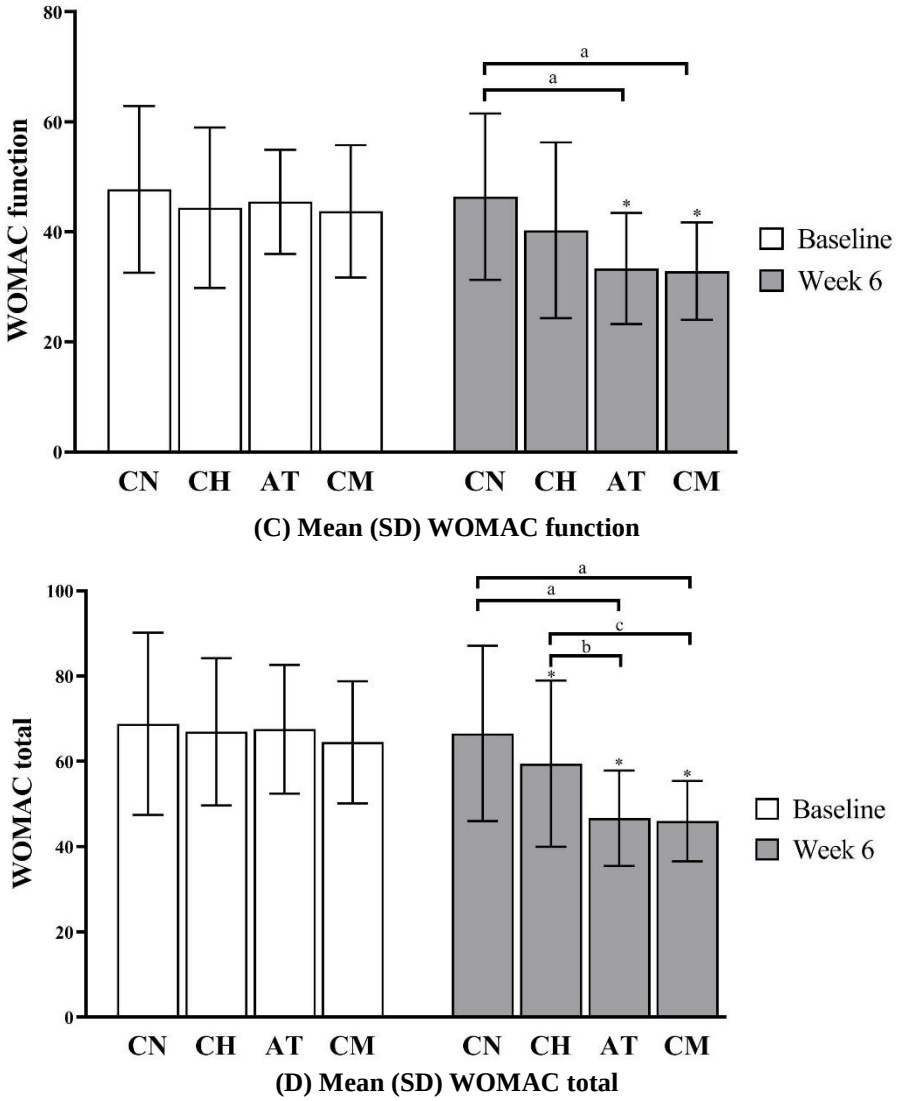


Figure 4-10 The pre- and post-treatment WOMAC scores of the CN, CH, AT and CM groups

Mean (SD) WOMAC scores for (A) pain, (B) stiffness, (C) function, and (D) total. CN=control group, CH=Chinese herbal patch group, AT= acupuncture group, CM= Chinese massage group. The baseline data were showed in white, and the six-week data were showed in grey. *: P<0.05 when a treatment group was compared with baseline (intragroup evaluation). [a]: P<0.05 when a treatment group was compared with six-week CN (intergroup evaluation). [b]: P<0.05 when six-week CH was compared with six-week AT (intergroup evaluation). [c]: P<0.05 when six-week CH was compared with six-week CM (intergroup evaluation).

EKAM: The baseline data indicated that the dynamic knee load in the frontal plane between the CN, CH, AT, and CM groups had no statistically significant difference in terms of the 1st, 2nd peak of EKAM (i.e., EKAM1 and EKAM2), and KAAI (P>0.05). The data from the assessment post six-week treatment indicated that dynamic knee load in the CN group had little difference in terms of EKAM and KAAI. However, the data from the CH, AT, and CM groups at the assessment post six-week treatment

demonstrated some increase in the dynamic knee load in the frontal plane in comparison with the baseline. The changes were also identified in comparison with the data of CN collected after six-week (Table 4-4, Figure 4-11 A, B, and C, Figure 4-12).

After six-week treatment period, the participants in the CH group achieved 2.1% increase in EKAM1 (P=0.27, Cohen's d=0.1), 1.4% in EKAM2 (P=0.71, Cohen's d=0.05), and 7.4% increase in KAAI (P=0.44, Cohen's d=0.07) in comparison with the baseline. However, the changes were not statically significant (P>0.05). Small in-group effect sizes were observed in EKAM1, EKAM2, and KAAI (Table 4-4, Figure 4-11 A, B, and C, Figure 4-12).

The six-week AT achieved 13.6% increase in EKAM1 (P=0.00, Cohen's d=0.58), 11.2% increase in EKAM2 (P=0.08, Cohen's d=0.35), and 8.8% increase in KAAI (P=0.00, Cohen's d=0.33) in comparison with the baseline. Except EKAM2, the increase were significant (P<0.05). Medium in-group effect size was observed in EKAM1, and small effect sizes were observed in EKAM2 and KAAI (Table 4-4, Figure 4-11 A, B, and C, Figure 4-12).

After six-week treatment, the CM group achieved 3.4% increase in EKAM1 (P=0.09, Cohen's d=0.14), 1.8% increase in EKAM2 (P=0.76, Cohen's d=0.05), 1.7% increase in KAAI (P=0.38, Cohen's d=0.07) in comparison with the baseline. However, the changes were not statically significant (P>0.05). Small in-group effect sizes were observed in EKAM1, EKAM2, and KAAI (Table 4-4, Figure 4-11 A, B, and C, Figure 4-12).

In comparison with the data of CN collected after six-week, the CH group achieved 2.7% reduction in EKAM1(P=0.69, Cohen's d=0.14), 4.9% reduction in EKAM2 (P=0.64, Cohen's d=0.17), and 3.4% reduction in KAAI (P=0.68, Cohen's d=0.14), however, no statistically significant difference was found between groups (P>0.05). Small between-group effect sizes were observed in EKAM1, EKAM2, and KAAI (Table 4-4, Figure

4-11 A, B, and C, Figure 4-12).

The increase in EKAM were found in six-week AT and CM groups in comparison with the CN group at week six. Compared with the six-week CN, the six-week AT showed 12.2% increase in EKAM1 (P=0.09, Cohen's d=0.65), 13.2% increase in EKAM2 (P=0.22, Cohen's d=0.47), 5.7% increase in KAAI (P=0.54, Cohen's d=0.24), even though the changes were not statistically significant (P>0.05). Medium between-group effect size was observed in EKAM1 and small effect sizes were observed in EKAM2 and KAAI (Table 4-4, Figure 4-11 A, B, and C, Figure 4-12).

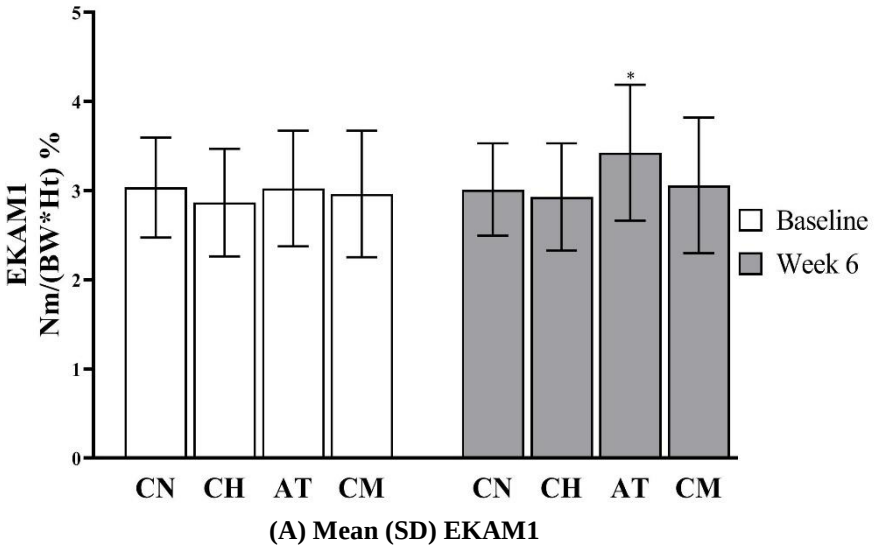
Compared with the six-week CN, the six-week CM showed 1.7% increase in EKAM1 (p=0.85, Cohen's d=0.08), 3.1% increase in EKAM2 (p=0.91, Cohen's d=0. 04), 0.9% increase in KAAI (p=0.91, Cohen's d=0.04), even though the changes were not statistically significant (P>0.05). Small between-group effect sizes were observed in EKAM1, EKAM2, and KAAI. (Table 4-4, Figure 4-11 A, B, and C, Figure 4-12).

The increase in EKAM was also found in AT group in comparison with the CH and CM group at week six. Compared with the six-week CH, the six-week AT showed 17.1% increase in EKAM1 (P=0.282, Cohen's d=0.73), 21.1% increase in EKAM2 (P=0.66, Cohen's d=0.58), and 9.7% increase in KAAI (P=1.00, Cohen's d=0.35). Moreover, the increase in EKAM were also found in EKAM1 (12.1%, P=0.83, Cohen's d=0.49), EKAM2 (11.7%, P=1.00 Cohen's d=0.33), and KAAI (5.1%, P=1.00 Cohen's d=0.20) in six-week AT when compared with the six-week CM. Small to medium effect sizes were observed in EKAM1, EKAM2, and KAAI between groups. However, there was no significant difference between the six-week CH, AT, and CM in EKAM1, EKAM2, and KAAI (P>0.05) (Table 4-4, Figure 4-11 A, B, and C, Figure 4-12).

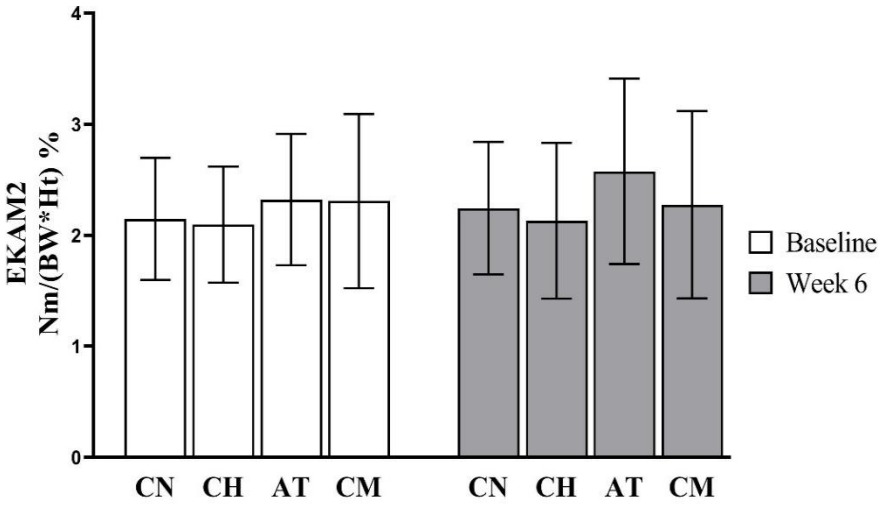
Table 4-4 The EKAM variables (Mean±SD) of the CH, AT, CM and CN groups

Outcome Measure		CN (n=15)	CH (n=15)	AT (n=15)	CM (n=15)
EKAM1	Baseline	3.03±0.56	2.87±0.60	3.02±0.65	2.96±0.71
Nm/(BW*Ht) %	Week 6	3.01±0.52	2.93±0.60	3.43±0.76*	3.06±0.76
EKAM2	Baseline	2.15±0.55	2.10±0.52	2.32±0.59	2.27 ±0.84
Nm/(BW*Ht) %	Week 6	2.24±0.60	2.13±0.70	2.58±0.84	2.31±0.79
KAAI	Baseline	1.13±0.28	1.11±0.27	1.14±0.29	1.16±0.29
Nm · s/(BW *Ht)%	Week 6	1.17±0.26	1.13±0.31	1.24±0.31*	1.18±0.29

*: P<0.05 when a treatment group was compared with baseline (intragroup evaluation).



(A) Mean (SD) EKAM1



(B) Mean (SD) EKAM2

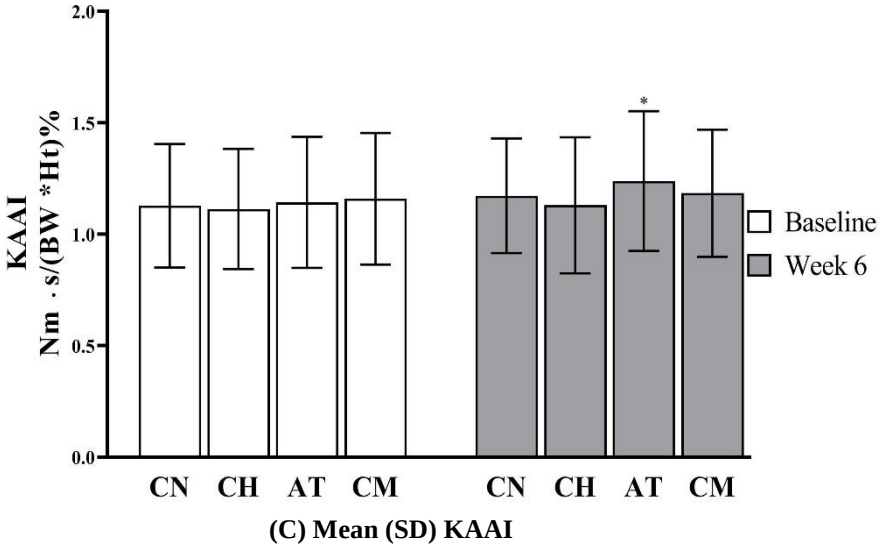


Figure 4-11 The pre- and post-treatment EKAM1, EKAM2, and KAAI of the CN, CH, AT and CM groups

Mean (SD) for (A) EKAM1, (B) EKAM2, and (C) KAAI. CN=control group, CH=Chinese herbal patch group, AT=acupuncture group, CM=Chinese massage group. The baseline data were showed in white, and the six-week data were showed in grey. *: P<0.05 when a treatment group was compared with baeline (intragroup evaluation)

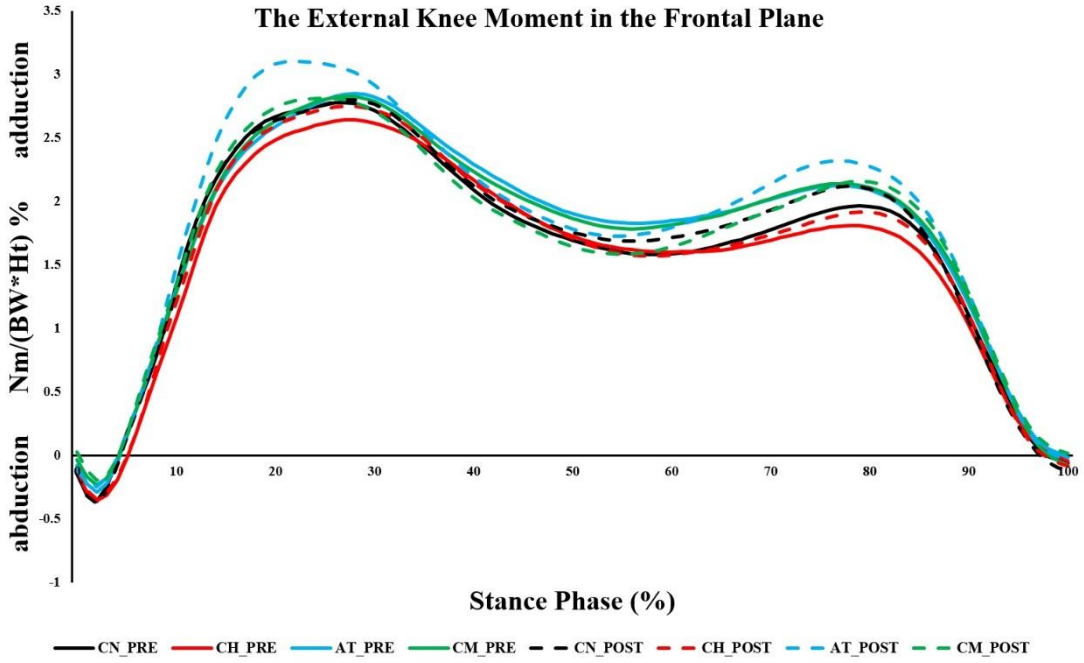


Figure 4-12 The pre- and post-treatment EKAM of the CN, CH, AT, and CM groups

CN_PRE=CN group at baseline, CN_POST= six-week CN group, CH_PRE=CH group at baseline, CH_POST= six-week CH group, AT_PRE=AT group at baseline, AT_POST=six-week AT group, CM_PRE=CM group at baseline, CM_POST=CM group after receiving six-week treatment. The black solid line was the mean of the baseline of the control group (CN_PRE). The red solid line was the mean of the baseline of the Chinese patch group (CH_PRE). The blue solid line was the mean of the baseline of the acupuncture group (AT_PRE). The green solid line was the mean of the baseline of the Chinese massage group (CM_PRE). The black dash line was the mean of the six-week control group (CN_POST). The red dash line was the mean of the six-week Chinese patch group (CH_POST). The blue dash line was the mean of the six-week acupuncture group (AT_POST). The green dash line was the mean of the six-week Chinese massage group (CM_POST).

Muscle co-contraction: The baseline data indicated that muscle activity around the knee between the CN, CH, AT and CM groups had no statistically significant difference in terms of muscle co-contraction (P>0.05). The data from the six-week assessment still indicated no difference in the above parameters in the CN group (P>0.05), however, the data from the CH, AT, and CM groups at the assessment post six-week treatment demonstrated some improvements in muscle co-contraction in comparison with the baseline. The changes were also identified in comparison with the data of CN collected after six-week (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

After six-week treatment period, the reduction of co-contraction were found at early stance VL/BF (2.1%, P=0.75, Cohen's d=0.03), early stance VM/ST (2.6%, P=0.62, Cohen's d=0.05), mid-stance VM/ST (11.5%, P=0.20, Cohen's d=0.21), early stance VM/MG (5.3%, P=0.57, Cohen's d=0.10), mid-stance VM/MG (0.2%, P=0.98, Cohen's d=0.00), mid-stance TA/MG (1.34%, P=0.94, Cohen's d=0.02), and late stance TA/MG (3.6%, P=0.69, Cohen's d=0.09) in the CH group when compared with the baseline. However, no statistically significant difference was found (P>0.05). Small in-group effect sizes were observed in all muscle co-contraction variables (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

After six-week treatment, the reduction of muscle co-contraction were found at early stance VL/BF (10.8%, P=0.27, Cohen's d=0.18), mid-stance VL/BF (22.7%, P=0.22, Cohen's d=0.29), late stance VL/BF (21.0%, P=0.31, Cohen's d=0.37), early stance VL/LG (14.8%, P=0.38, Cohen's d=0.07), mid-stance VL/LG (15.4%, P=0.27, Cohen's d=0.25), late stance VL/LG (15.9%, P=0.21, Cohen's d=0.24), early stance VM/ST (10.5%, P=0.52, Cohen's d=0.23), mid-stance VM/ST (16.6%, P=0.21 , Cohen's d=0.42), late stance VM/ST (14.6%, P=0.16, Cohen's d=0.39), early stance VM/MG (6.2%, P=0.63, Cohen's d=0.18), mid-stance VM/MG (19.6%, P=0.42, Cohen's d=0.26), late stance VM/MG (22.20%, P=0.25, Cohen's d=0.45), early stance TA/MG (4.1%, P=0.76, Cohen's d=0.09), mid-stance TA/MG (16.8%, P=0.22, Cohen's d=0.29),

and late stance TA/MG (4.0%, P=0.78, Cohen's d=0.08) in the AT group when compared with the baseline, however, no statistically significant difference was found (P>0.05). Small in-group effect sizes were observed in all muscle co-contraction variables (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

After six-week treatment, the reduction of co-contraction were found at early stance VL/BF (17.5%, P=0.27, Cohen's d=0.39), mid-stance VL/BF (20.8%, P=0.13, Cohen's d=0.41), late stance VL/BF (16.3%, P=0.44, Cohen's d=0.22), early stance VL/LG (22.8%, P=0.21, Cohen's d=0.33), mid-stance VL/LG (24.5%, P=0.14, Cohen's d=0.37), late stance VL/LG (17.2%, P=0.24, Cohen's d=0.27), early stance VM/ST (44.4%, P=0.00, Cohen's d=1.00), mid-stance VM/ST (31.5%, P=0.10 , Cohen's d=0.66), late stance VM/ST (30.0%, P=0.03, Cohen's d=0.75), early stance VM/MG (13.8%, P=0.41, Cohen's d=0.29), mid-stance VM/MG (22.5%, P=0.12, Cohen's d=0.33), late stance VM/MG (31.4%, P=0.12, Cohen's d=0.63), early stance TA/MG (23.2%, P=0.11, Cohen's d=0.58), mid-stance TA/MG (11.7%, P=0.49, Cohen's d=0.21), and late stance TA/MG (23.7%, P=0.14, Cohen's d=0.35) in the CM group when compared with the baseline. However, only the reduction in early and mid-stance VM/ST were statistically significant (P<0.05), the other changes were not statically significant (P>0.05). Large in-group effect sizes were observed in early stance VM/ST, medium in-group effect sizes were observed in mid-stance VM/ST and late stance VM/MG, and small in-group effect sizes were observed in other co-contraction variables (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

The reduction of knee muscle co-contractions were also found in six-week CH, AT, and CM in comparison with the CN group at week six. Compared with the six-week CN, the six-week CH showed 4.6% decrease in early stance VL/BF (P=0.84, Cohen's d=0.08), 4.0% decrease in mid-stance VL/LG (P=0.92, Cohen's d=0.07), 13.4% decrease in early stance VM/ST (P=0.36, Cohen's d=0.34), 21.0% decrease in mid-stance VM/ST (P=0.26, Cohen's d=0.42), 18.1% decrease in early stance VM/MG (P=0.33, Cohen's d=0.36), and 8.3% decrease in late stance VM/MG (P=0.73, Cohen's

d=0.13). However, no statistically significant difference was found between groups (P>0.05). Small between-group effect sizes were observed in all muscle co-contraction variables (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

Compared with the six-week CN, the six-week AT showed 10.9% decrease in early stance VL/BF (P=0.55, Cohen's d=0.22), 3.1% decrease in mid-stance VL/BF (P=0.92, Cohen's d=0.03), 15.6% decrease in late stance VL/BF (P=0.38, Cohen's d=0.30), 0.3% decrease in early stance VL/LG (P=0.96, Cohen's d=0.00), 2.5% decrease in mid-stance VL/LG (P=0.89, Cohen's d=0.03), 17.3% decrease in early stance VM/ST (P=0.19, Cohen's d=0.49), 23.1% decrease in mid-stance VM/ST (P=0.16 , Cohen's d=0.52), 17.8% decrease in late stance VM/ST (P=0.27, Cohen's d=0.41), 20.6% decrease in early stance VM/MG (P=0.23, Cohen's d=0.45), 18.7% decrease in mid-stance VM/MG (P=0.47, Cohen's d=0.27), 20.2%, decrease in late stance VM/MG (P=0.39, Cohen's d=0.32), 4.11% decrease in early stance TA/MG (P=0.77, Cohen's d=0.11), and 19.0% decrease in mid-stance TA/MG (P=0.48, Cohen's d=0.26). However, no statistically significant difference was found between groups (P>0.05). Medium between-group effect size was observed in VM/ST in mid-stance and small between-group effect sizes were observed in other muscle co-contraction variables (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

The reduction of knee muscle co-contractions were also found at early stance VL/BF (22.3%, P=0.19, Cohen's d=0.49), mid-stance VL/BF (28.9%, P=0.23, Cohen's d=0.45), early stance VL/LG (21.6%, P=0.38, Cohen's d=0.36), mid-stance VL/LG (21.5%, P=0.54, Cohen' s d=0.32), early stance VM/ST (47.3%, P=0.00, Cohen's d=1.97), mid-stance VM/ST (42.7%, P=0.01 , Cohen's d=1.00), late stance VM/ST (37.8%, P=0.02 Cohen's d=0.88), early stance VM/MG (29.4%, P=0.10, Cohen's d=0.63), mid-stance VM/MG (29.5%, P=0.16, Cohen's d=0.53), late stance VM/MG (36.5%, P=0.13, Cohen's d=0.58), early stance TA/MG (16.4%, P=0.22, Cohen's d=0.46), mid-stance TA/MG (34.2%, P=0.18, Cohen's d=0.49), and late stance TA/MG (8.7%, P=0.59, Cohen's d=0.20) in the CM group in comparison with the CN group after six week

treatment. However, only the reduction in early, and mid- stance VM/ST were statistically significant (P<0.05), the other changes were not statically significant (P>0.05). Large between-group effect sizes were observed in early, mid-, and late stance VM/ST, medium between-group effect sizes were observed in early, mid-, and late stance VM/MG, and small between-group effect sizes were observed in other co-contraction variables (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

The decrease in muscle co-contraction were also found in CM group in comprasion with the CH and AT groups at week six. Compared with the six-week CH, the six-week CM showed 18.5% decrease in early stance VL/BF (P=0.37, Cohen's d=0.31), 33.3% decrease in mid-stance VL/BF (P=0.21, Cohen's d=0.57), 16.9% decrease in late stance VL/BF (P=0.33, Cohen's d=0.33), 24.0% decrease in early stance VL/LG (P=0.21, Cohen's d=0.51), 18.2% decrease in mid-stance VL/LG (P=0.46, Cohen's d=0.32), 15.9% decrease in late stance VL/LG (P=0.43, Cohen's d=0.32), 39.1% decrease in early stance VM/ST (P=0.01, Cohen's d=0.99), 27.5% decrease in mid-stance VM/ST (P=0.06, Cohen's d=0.54), 47.3% decrease in late stance VM/ST (P=0.01, Cohen's d=1.19), 14.2% decrease in early stance VM/MG (P=0.50, Cohen's d=0.26), 34.5% decrease in mid-stance VM/MG (P=0.16, Cohen's d=0.50), 30.8% decrease in late stance VM/MG (P=0.17, Cohen's d=0.63), 24.5% decrease in early stance TA/MG (P=0.14, Cohen's d=0.47), 29.4% decrease in mid-stance TA/MG (P=0.22, Cohen's d=0.60), and 18.3% decrease in mid-stance TA/MG (P=0.24, Cohen's d=0.43). However, only the reduction in early and late stance VM/ST were statistically significant (P<0.05), the other changes were not statically significant (P>0.05). Large between-group effect sizes were observed in early stance VM/ST, and medium to small between-group effect sizes were observed in other co-contraction variables (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

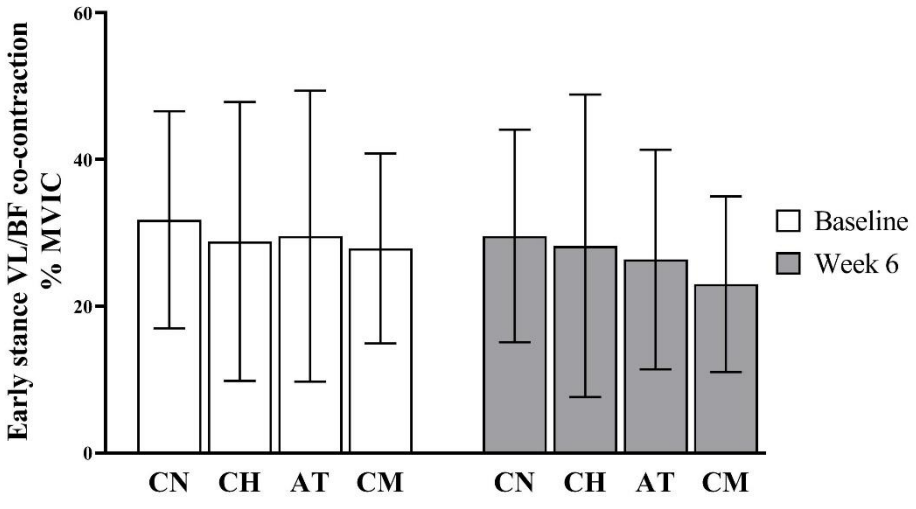
Compared with the six-week AT, the six-week CM showed 12.8% decrease in early stance VL/BF (P=0.56, Cohen's d=0.25), 26.7% decrease in mid-stance VL/BF (P=0.36,

Cohen's d=0.35), 21.3% decrease in early stance VL/LG (P=0.29, Cohen's d=0.41), 19.6% decrease in mid-stance VL/LG (P=0.42, Cohen's d=0.28), 10.6% decrease in late stance VL/LG (P=0.62, Cohen's d=0.15), 36.2% decrease in early stance VM/ST (P=0.02, Cohen's d=1.01), 25.6% decrease in mid-stance VM/ST (P=0.21, Cohen's d=0.61), 24.4% decrease in late stance VM/ST (P=0.33, Cohen's d=0.56), 11.6% decrease in early stance VM/MG (P=0.59, Cohen's d=0.23), 13.3% decrease in mid-stance VM/MG (P=0.68, Cohen's d=0.16), 20.5% decrease in late stance VM/MG (P=0.42, Cohen's d=0.37), 12.8% decrease in early stance TA/MG (P=0.50, Cohen's d=0.30), 18.7% decrease in mid-stance TA/MG (P=0.50, Cohen's d=0.35), and 25.16% decrease in mid-stance TA/MG (P=0.08, Cohen's d=0.63). However, only the reduction in early stance VM/ST were statistically significant (P<0.05), the other changes were not statically significant (P>0.05). Large between-group effect sizes were observed in early stance VM/ST, and medium to small between-group effect sizes were observed in other co-contraction variables. There was no significant difference between the six-week CH and AT in muscle co-contraction (P>0.05) (Table 4-5, Figure 4-13 A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O).

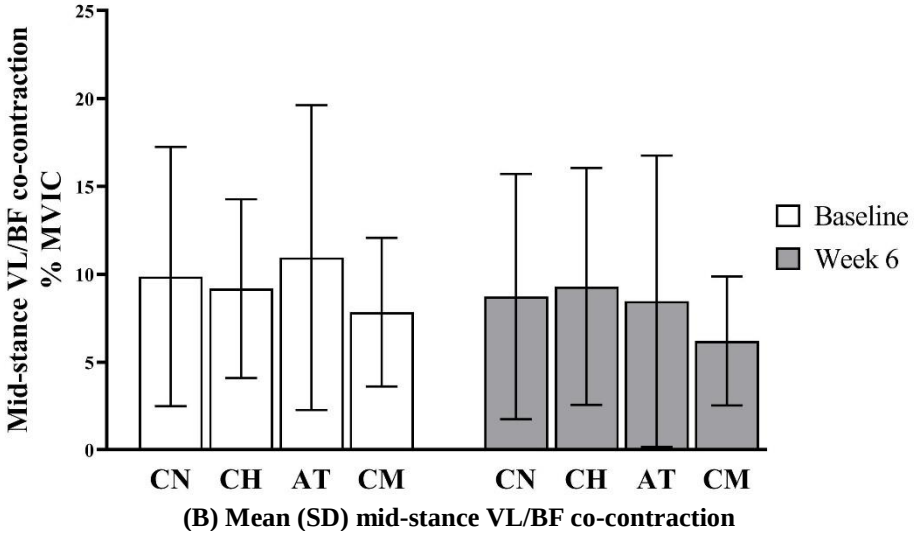
Table 4-5 The muscle co-contraction variables (Mean±SD) (expressed as % MVIC) of the CN, CH, AT, and CM groups

Outcome Measure		CN (n=15)	CH (n=15)	AT (n=15)	CM (n=15)
VL/BF (early stance)	Baseline	31.77±14.81	28.84±19.01	29.55±19.83	27.89±12.95
	Week 6	29.59±14.49	28.23±20.63	26.36±14.97	23.00±11.97
VL/BF (mid-stance)	Baseline	9.87±7.38	9.18±5.10	10.95±8.68	7.84±4.23
	Week 6	8.73±6.99	9.31±6.74	8.47±8.30	6.21±3.67
VL/BF (late stance)	Baseline	5.23±2.97	5.67±3.62	5.42±3.57	6.31±5.23
	Week 6	5.07±3.08	6.35±3.12	4.28±2.15	5.28±3.28
VL/LG (early stance)	Baseline	15.12±10.56	13.60±6.87	15.97±12.39	13.87±10.87
	Week 6	13.65±9.11	14.10±5.98	13.61±6.80	10.71±7.30
VL/LG (mid-stance)	Baseline	13.61±9.91	12.27±5.10	14.78±8.69	13.30±9.57
	Week 6	12.79±9.14	12.28±5.91	12.48±9.35	10.04±7.81
VL/LG (late stance)	Baseline	5.50±4.64	6.20±3.25	7.40±5.16	6.73±4.56
	Week 6	4.76±3.09	6.62±2.44	6.23±4.56	5.57±4.03
VM/ST (early stance)	Baseline	26.64±9.68	24.06±13.92	24.99±11.87	25.65±12.73
	Week 6	27.08±8.39	23.44±12.55[c]	22.38±10.71[d]	14.27±3.71*,[a]
VM/ST (mid-stance)	Baseline	5.84±2.08	6.34±3.68	6.56±2.75	5.94±2.73
	Week 6	7.10±3.68	5.61±3.42	5.47±2.40	4.07±2.20*,[a]
VM/ST (late stance)	Baseline	5.39±2.89	6.30±2.42	5.81±2.10	5.37±2.68
	Week 6	6.04±2.98	7.14±3.43[c]	4.97±2.22	3.76±2.11
VM/MG (early stance)	Baseline	18.63±9.31	17.12±9.28	16.77±11.24	16.21±7.35
	Week 6	19.81±10.51	16.22±9.40	15.73±7.58	13.98±7.82
VM/MG (mid-stance)	Baseline	8.27±6.77	10.57±9.56	9.90±6.78	8.91±6.59
	Week 6	9.81±5.85	10.55±8.84	7.97±7.74	6.91±5.15
VM/MG (late stance)	Baseline	7.26±7.93	7.04±4.07	9.08±4.81	8.19±4.26
	Week 6	8.85±6.90	8.12±4.08	7.07±3.95	5.62±3.91
TA/MG (early stance)	Baseline	16.14±5.31	16.97±9.21	16.37±7.51	17.82±7.73
	Week 6	16.37±5.29	18.14±11.84	15.70±7.08	13.69±6.26
TA/MG (mid-stance)	Baseline	15.74±11.84	14.23±7.09	14.65±9.10	11.22±6.53
	Week 6	15.05±13.52	14.04±8.03	12.19±7.46	9.91±5.56
TA/MG (late stance)	Baseline	6.01±2.65	7.59±2.43	8.33±4.70	7.84±6.16
	Week 6	6.55±2.80	7.32±3.15	7.99±3.37	5.98±3.02

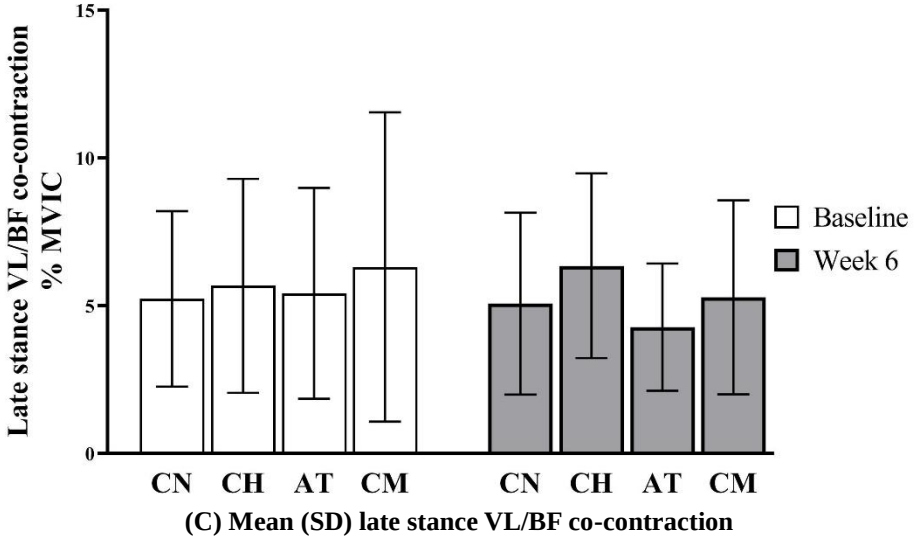
*: P<0.05 when a treatment group was compared with baseline (intragroup evaluation).
[a]: P<0.05 when a treatment group was compared with six-week CN (intergroup evaluation).
[c]: P<0.05 when six-week CH was compared with six-week CM (intergroup evaluation).
[d]: P<0.05 when six-week AT was compared with six-week CM (intergroup evaluation).



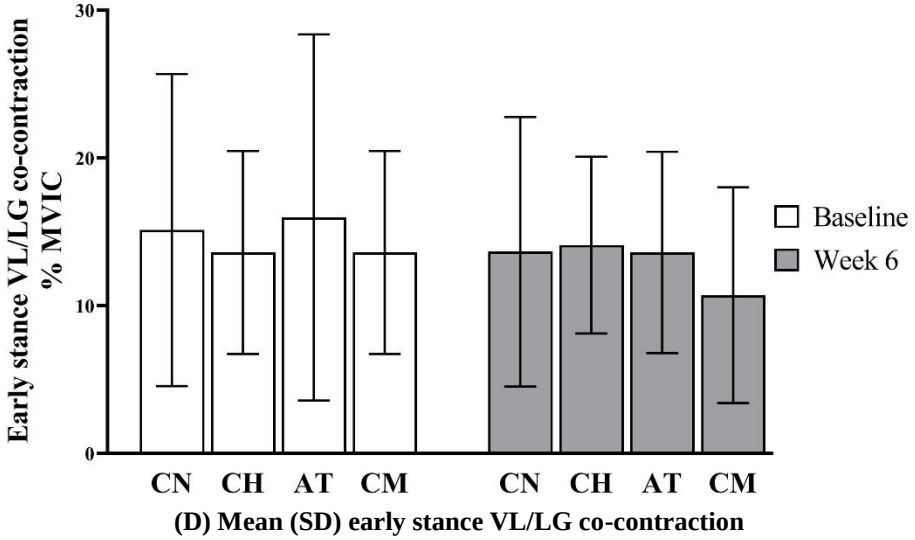
(A) Mean (SD) early stance VL/BF co-contraction



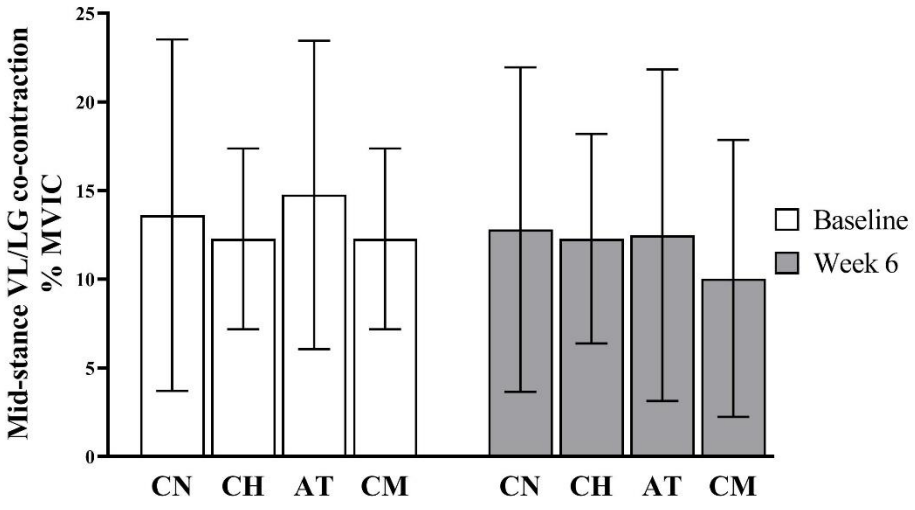
(B) Mean (SD) mid-stance VL/BF co-contraction



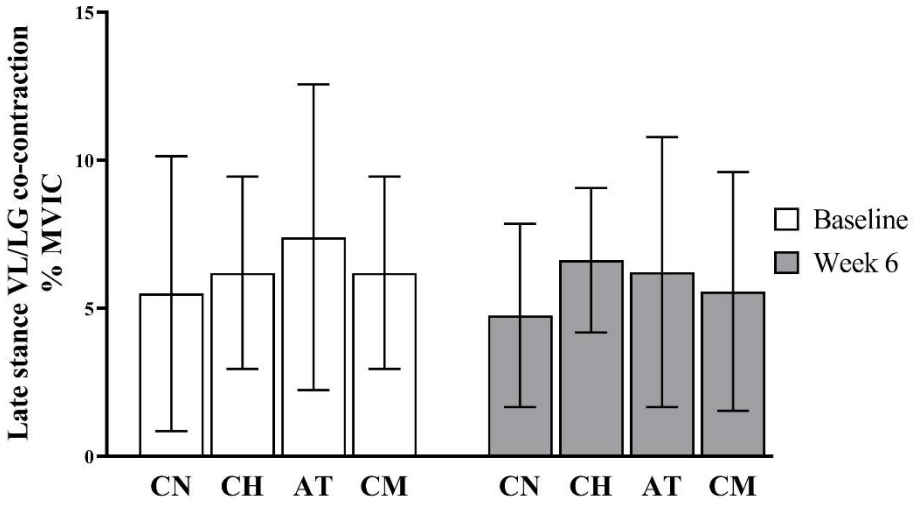
(C) Mean (SD) late stance VL/BF co-contraction



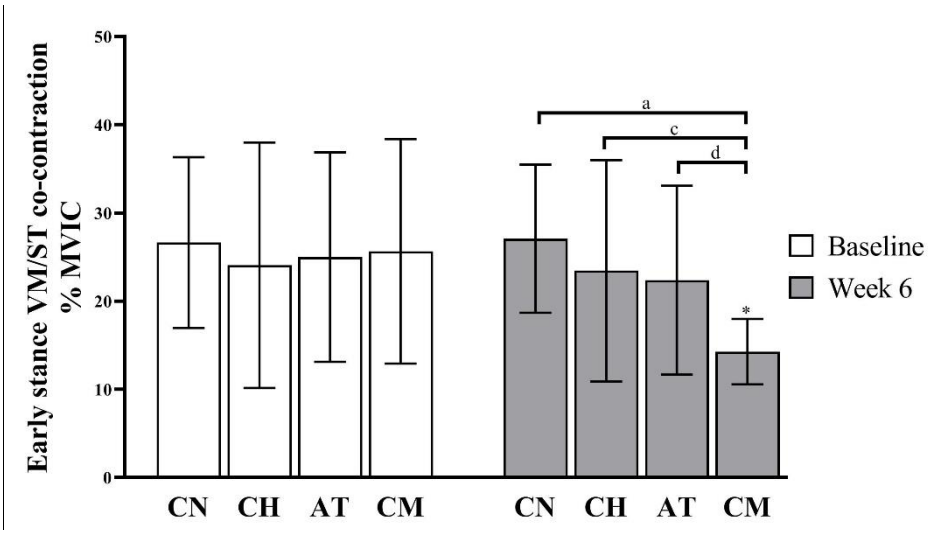
(D) Mean (SD) early stance VL/LG co-contraction



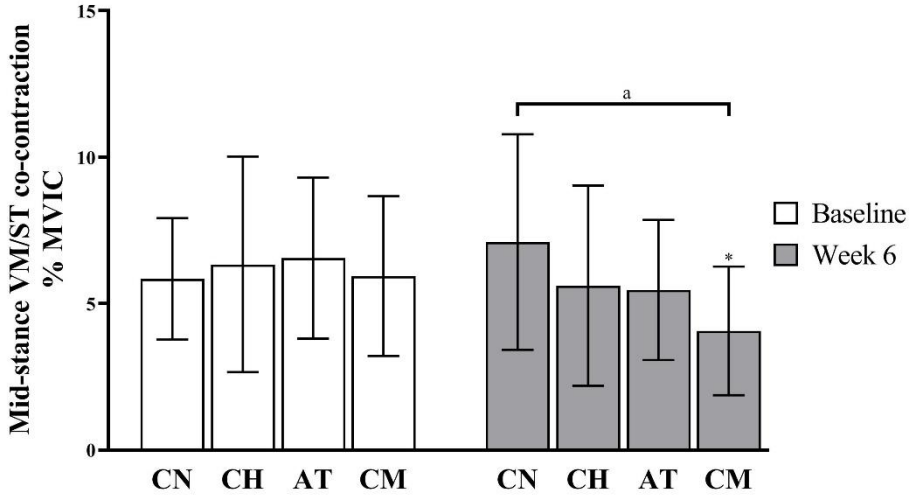
(E) Mean (SD) mid-stance VL/LG co-contraction



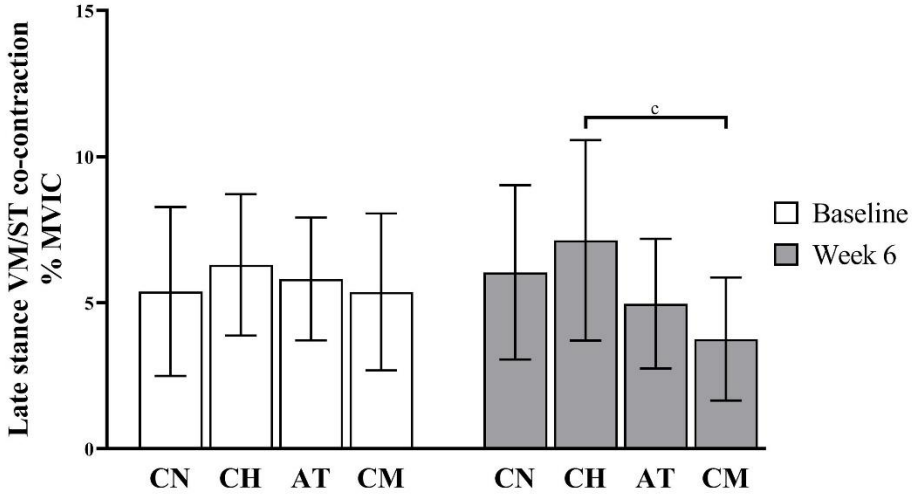
(F) Mean (SD) late stance VL/LG co-contraction



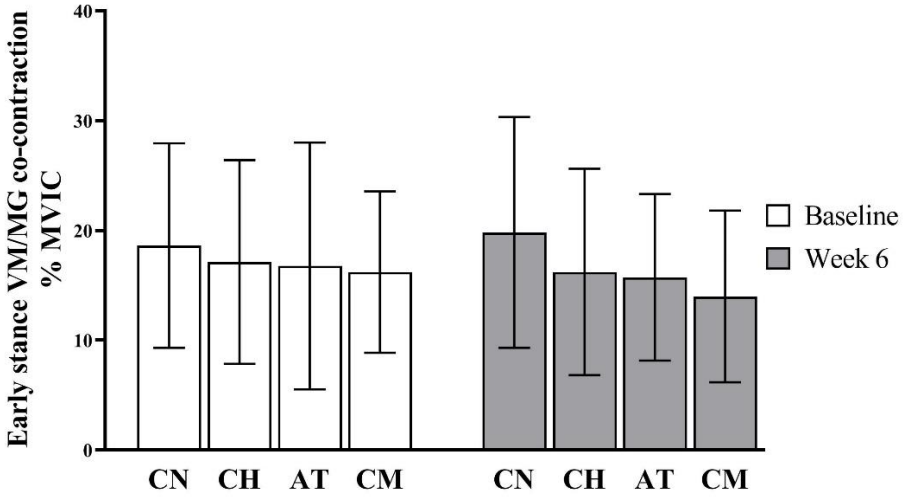
(G) Mean (SD) early stance VM/ST co-contraction



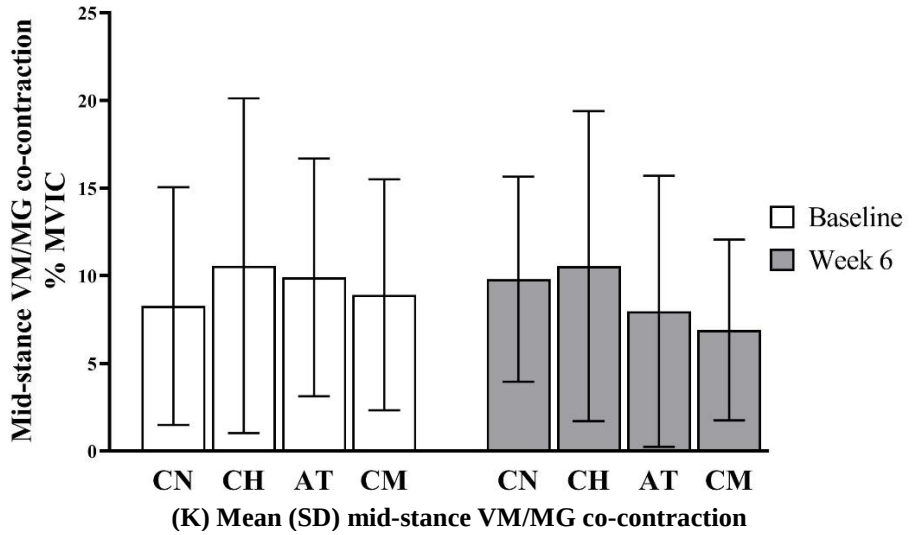
(H) Mean (SD) mid-stance VM/ST co-contraction



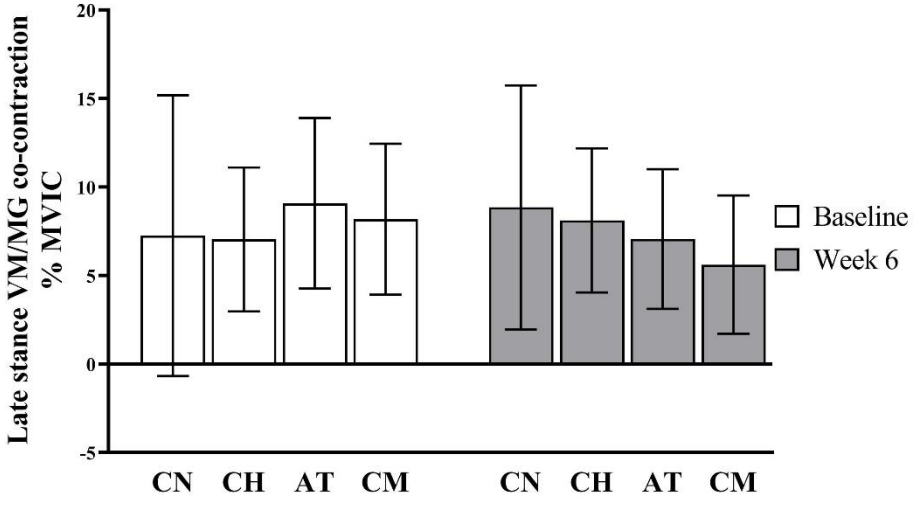
(I) Mean (SD) late stance VM/ST co-contraction



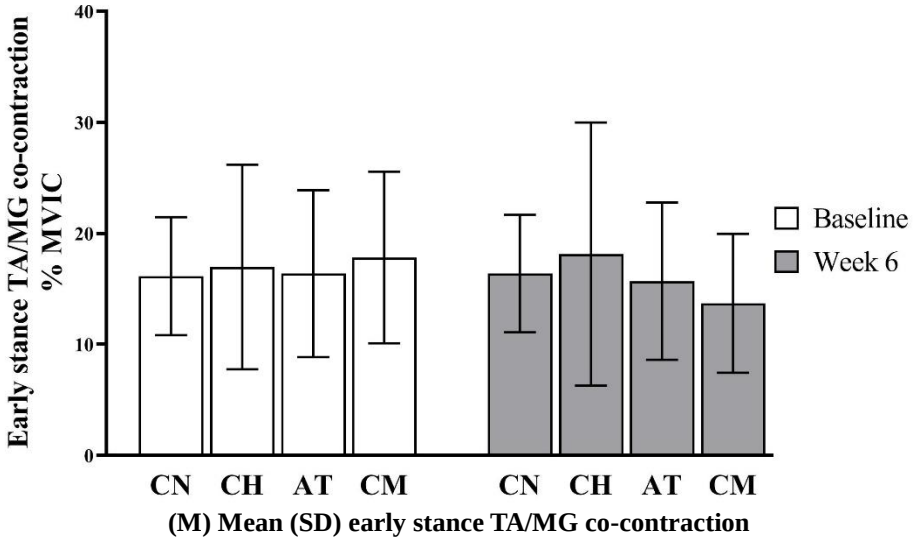
(J) Mean (SD) early stance VM/MG co-contraction



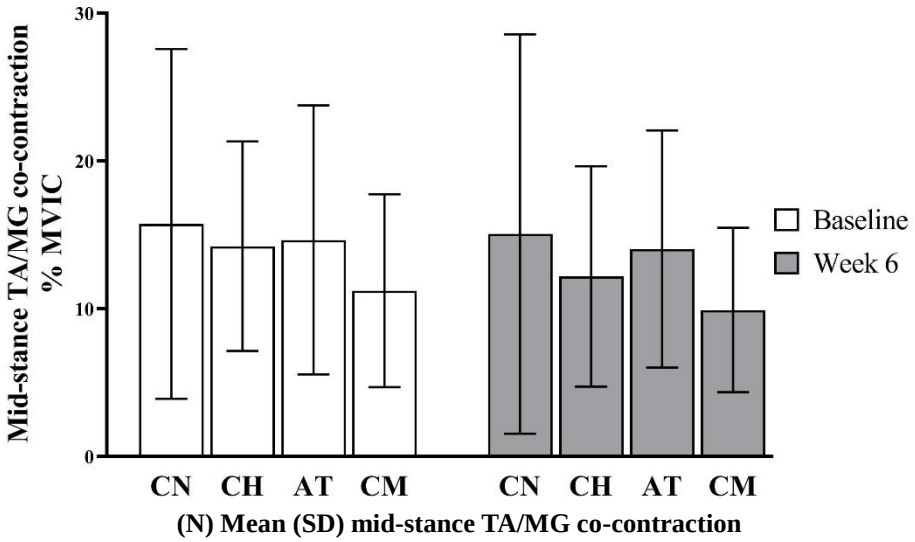
(K) Mean (SD) mid-stance VM/MG co-contraction



(L) Mean (SD) late stance VM/MG co-contraction



(M) Mean (SD) early stance TA/MG co-contraction



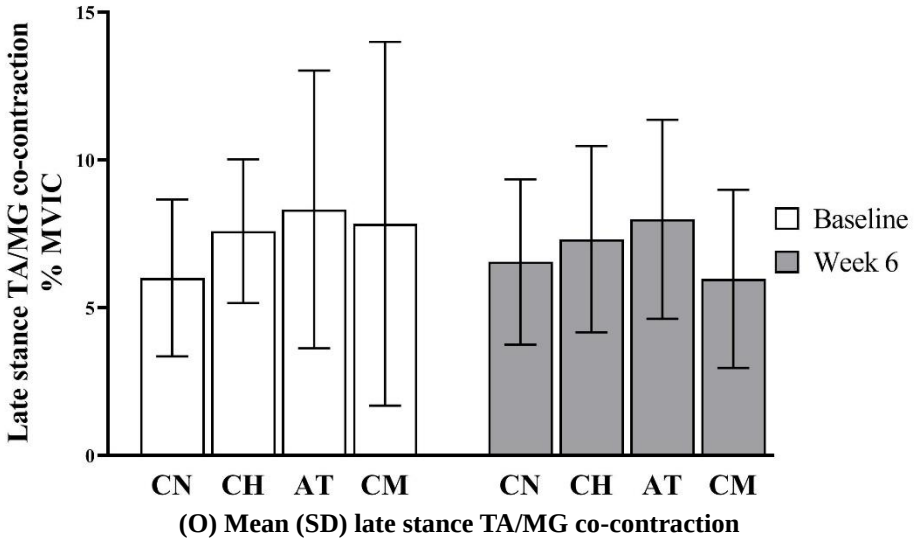


Figure 4-13 The pre- and post-treatment muscle co-contraction of the CN, CH, AT, and CM groups

Mean (SD) muscle co-contraction for (A) early stance VL/BF, (B) mid-stance VL/BF, (C) late stance VL/BF, (D) early stance VL/LG, (E) mid-stance VL/LG, (F) late stance VL/LG, (G) early stance VM/ST, (H) mid-stance VM/ST, (I) late stance VM/ST, (J) early stance VM/MG, (K) mid-stance VM/MG, (L) late stance VM/MG, (M) early stance TA/MG, (N) mid-stance TA/MG, and (O) late stance TA/MG. CN=control group, CH=Chinese herbal patch group, AT=acupuncture group, CM=Chinese massage group. The baseline data were showed in white, and the six-week data were showed in grey. *: $P<0.05$ when a treatment group was compared with baseline (intragroup evaluation). [a]: $P<0.05$ when a treatment group was compared with six-week CN (intergroup evaluation). [c]: $P<0.05$ when six-week CH was compared with six-week CM (intergroup evaluation). [d]: $P<0.05$ when six-week AT was compared with six-week CM (intergroup evaluation).

4.5.2 Secondary outcomes

Temporal and Spatial parameters: At baseline assessment, the temporal-spatial gait parameters and daily activity (i.e., walking speed, step length, cadence, double support time, stance phase percentage in a gait cycle, and the daily number of steps) showed no differences between the CN, CH, AT, and CM groups ($P>0.05$). The data from the six-week assessment still indicated no difference in the above parameters in the CN group

(P>0.05), however, the data from the CH, AT, and CM groups at the assessment post six-week treatment demonstrated some improvements in temporal and spatial parameters in comparison with the baseline. The changes were also identified in comparison with the data of CN collected after six-week (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

After six-week treatment, the participants in the CH group achieved 6.9% increase in walking speed (P=0.10, Cohen's d=0.43), 5.6% increase in step length (P=0.12, Cohen's d=0.42), 2.5% increase in cadence (P=0.14, Cohen's d=0.32), and 2.6% increase in daily number of steps (P=0.18, Cohen's d=0.17). The changes in double support time and stance phase percentage were unrecognized in comparison with the baseline. However, none of the above-mentioned changes was statistically significant (P>0.05). Small in-group effect sizes were observed in all temporal-spatial variables (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

After six-week treatment, the participants in the AT group achieved 15.3% increase in walking speed (P=0.00, Cohen's d=1.09), 9.3% increase in step length (P=0.00, Cohen's d=0.90), 5.0% increase in cadence (P=0.02, Cohen's d=0.54), 16.7% reduction in double support time (P=0.01, Cohen's d=0.80), 0.7% reduction stance phase percentage (P=0.11, Cohen's d=0.25), and 7.8% increase in daily number of steps (P=0.01, Cohen's d=0.53) in comparison with the baseline. Except stance phase percentage, the other improvements were statistically significant (P<0.05). Large in-group effect sizes were observed in walking speed, step length, and double support time, medium in-group effect sizes were observed in cadence and the daily number of steps, and small in-group effect size was observed in stance phase percentage (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

After six-week treatment, the participants in the CM group achieved 8.9% increase in walking speed (P=0.01, Cohen's d=0.65), 7.3% increase in step length (P=0.00, Cohen's d=0.80), 2.9% increase in cadence (P=0.17, Cohen's d=0.32), and 6.4%

increase in daily number of steps (P=0.04, Cohen's d=0.39) in comparison with the baseline. However, the difference in double time and stance phase percentage were unrecognizable. The increase in walking speed, step length, and the daily number of steps were statistically significant (P<0.05). Large in-group effect size was observed in step length, medium in-group effect size was observed in walking speed, and small in-group effect sizes were observed in other temporal-spatial variables (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

In comparison with the six-week CN, the six-week CH achieved 6.9% increase in walking speed (P=0.14, Cohen's d=0.56), 1.8% increase in step length (P=0.60, Cohen's d=0.17), 4.5% increase in cadence (P=0.08, Cohen's d=0.64), and 4.6% increase in daily number of steps (P=0.43, Cohen's d=0.29). The changes in stance phase percentage (P=0.45, Cohen's d=0.00) and double support time were unrecognized (P=0.45, Cohen's d=0.14). Nevertheless, the above identified improvements were not statistically significant (P>0.05). Medium between-group effect sizes were observed in walking speed and cadence. Small between-group effect sizes were observed in other temporal-spatial variables (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

In comparison with the CN group at post-treatment, the six-week AT showed 10.8% increase in walking speed (P=0.01, Cohen's d=0.91), 5.4% increase in step length (P=0.10, Cohen's d=0.54), 3.9% increase in cadence (P=0.12, Cohen's d=0.60), and 16.7% reduction in double support time (P=0.07, Cohen's d=1.00) with only the reduction in stance phase percentage unrecognized while the 9.4% increase in daily number of steps (P=0.08, Cohen's d=0.66) being recorded. Nevertheless, the above identified improvements were not statistically significant (P>0.05) except walking speed (P<0.05). Large between-group effect sizes were observed in walking speed and double support time, medium between-group effect sizes were observed in step length, cadence, and the daily number of steps, small between-group effect size was observed in stance phase percentage (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

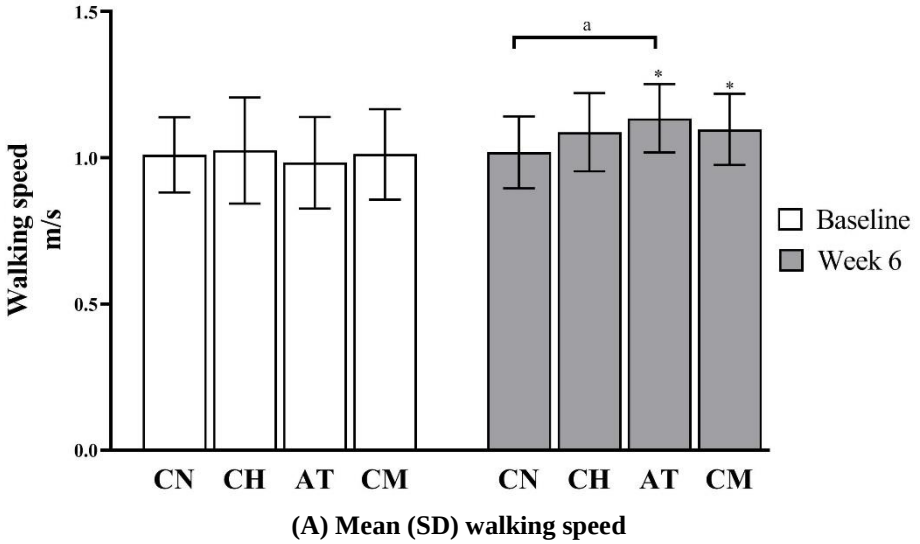
In comparison with the CN group at post-treatment, the six-week CM group showed 7.8% increase in walking speed (P=0.08, Cohen's d=0.67), 5.4% increase in step length (P=0.13, Cohen's d=0.54), 3.2% increase in cadence (P=0.27, Cohen's d=0.41), with the reduction in double support time and stance phase percentage unrecognized while the 8.2% increase in the daily number of steps (P=0.21, Cohen's d=0.47) being recorded. Nevertheless, the above identified improvements were not statistically significant (P>0.05). Medium between-group effect sizes were observed in walking speed and step length, and small between-group effect sizes were observed in other temporal-spatial variables (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

The improvement in temporal-spatial variables were also found in AT group in comparison with the CH and CM groups at week six. Compared with the six-week CH, the six-week AT showed 3.7% increase in walking speed (P=0.45, Cohen's d=0.32), 3.5% increase in step length (P=0.68, Cohen's d=0.36), and 4.6% increase in daily number of steps (P=0.39, Cohen's d=0.38), and 16.7% decrease in double support time (P=0.33, Cohen's d=0.78). However, no change was found statically significant (P>0.05). Small to medium between-group effect sizes were observed in all temporal-spatial variables. Compared with the six-week CM, the six-week AT showed 2.7% increase in walking speed (P=0.45, Cohen's d=0.25), 1.1% increase in the daily number of steps (P=0.83, Cohen's d=0.08). However, no change was found statically significant (P>0.05). Small between-group effect sizes were observed in all temporal-spatial variables. There was no significant difference between the six-week CH and CM in temporal-spatial variables (P>0.05) (Table 4-6, Figure 4-14 A, B, C, D, E, and F).

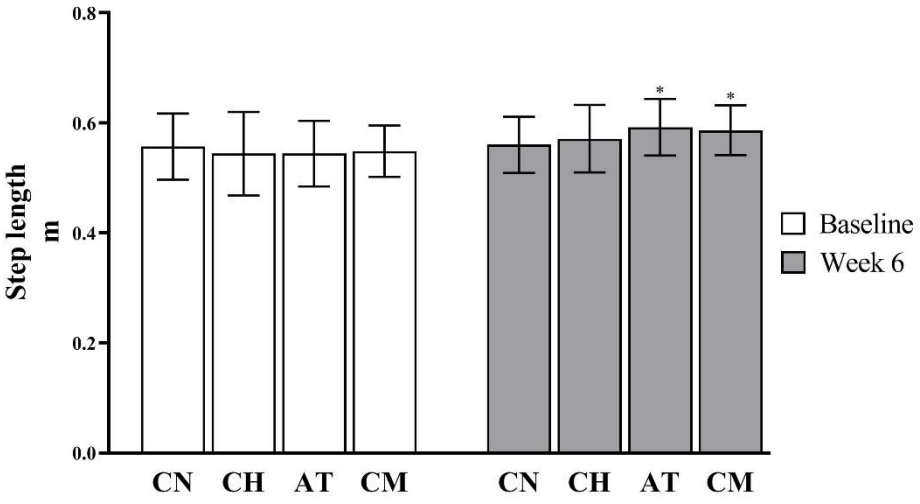
Table 4-6 The temporal-spatial variables (Mean±SD) of the CN, CH, AT, and CM groups

Outcome Measure		CN (n=15)	CH (n=15)	AT (n=15)	CM (n=15)
Walking speed(m/s)	Baseline	1.01±0.13	1.02±0.18	0.98±0.15	1.01±0.15
	Week 6	1.02±0.12	1.09±0.13	1.13±0.12*,[a]	1.10±0.12*
Step length (m)	Baseline	0.55±0.06	0.54±0.08	0.54±0.06	0.55±0.05
	Week 6	0.56±0.06	0.57±0.06	0.59±0.05*	0.59±0.05*
Cadence (steps/min)	Baseline	108.47±10.34	110.73±9.80	107.53±11.35	109.00±10.87
	Week 6	108.67±8.41	113.53±6.62	112.87±5.80*	112.13±8.29
Double support time(s)	Baseline	0.12±0.03	0.12±0.03	0.12±0.03	0.12±0.03
	Week 6	0.12±0.02	0.12±0.03	0.10±0.02*	0.12±0.01
Stance phase	Baseline	60.52±1.54	61.10±2.68	60.93±1.59	60.51±1.70
percentage (%)	Week 6	60.48±2.06	60.20±1.81	60.48±1.96	60.75±1.71
Daily number of steps	Baseline	3708.33±656.13	3692.67±645.61	3679.27±613.30	3685.80±543.48
(steps/day)	Week 6	3624.93±605.37	3790.20±511.31	3965.87±412.13*	3922.53±665.73*

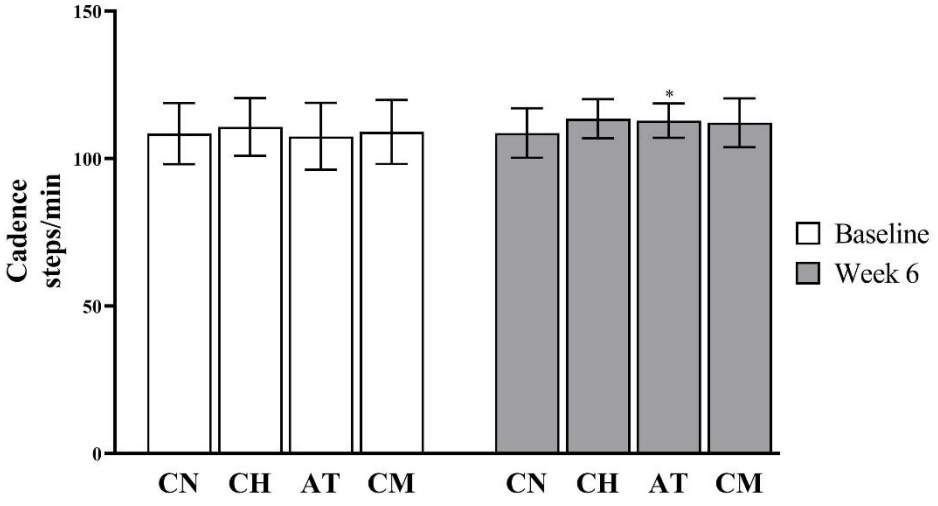
*: P<0.05 when a treatment group was compared with baseline (intragroup evaluation).
[a]: P<0.05 when a treatment group was compared with six-week CN (intergroup evaluation).



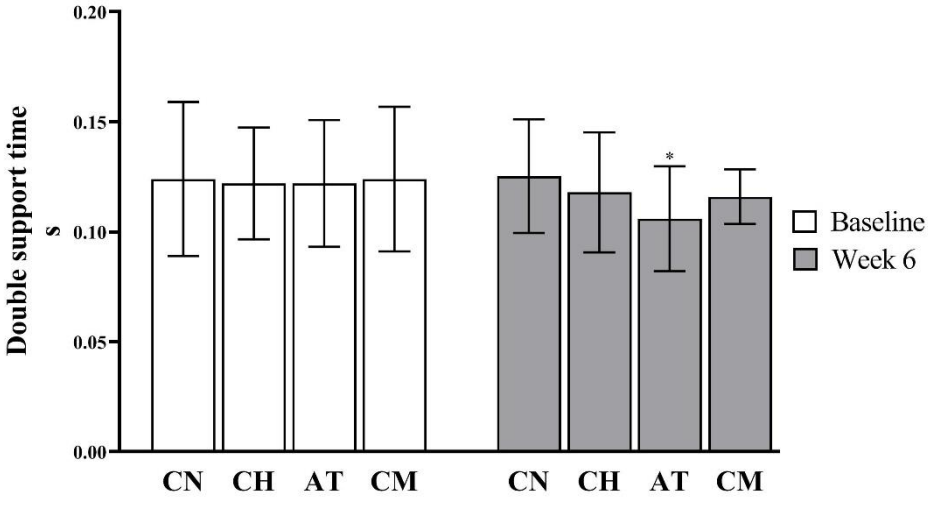
(A) Mean (SD) walking speed



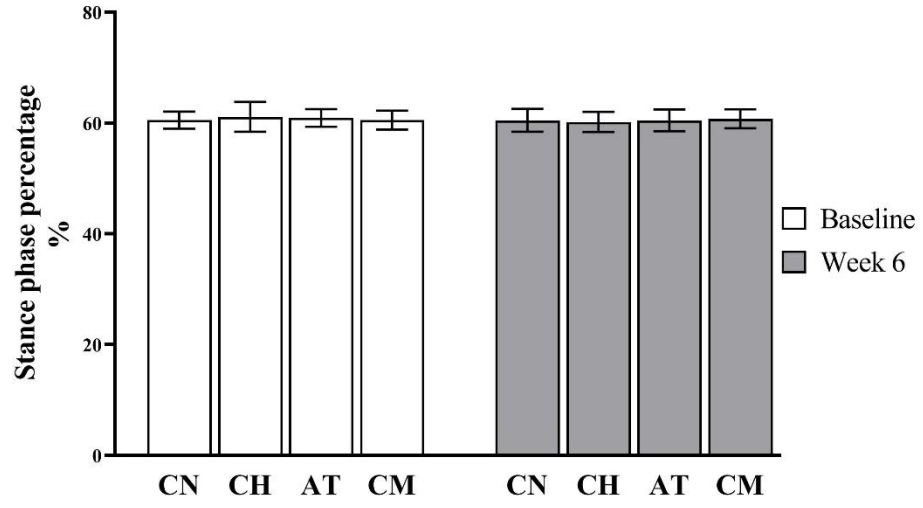
(B) Mean (SD) step length



(C) Mean (SD) cadence



(D) Mean (SD) double support time



(E) Mean (SD) stance phase percentage

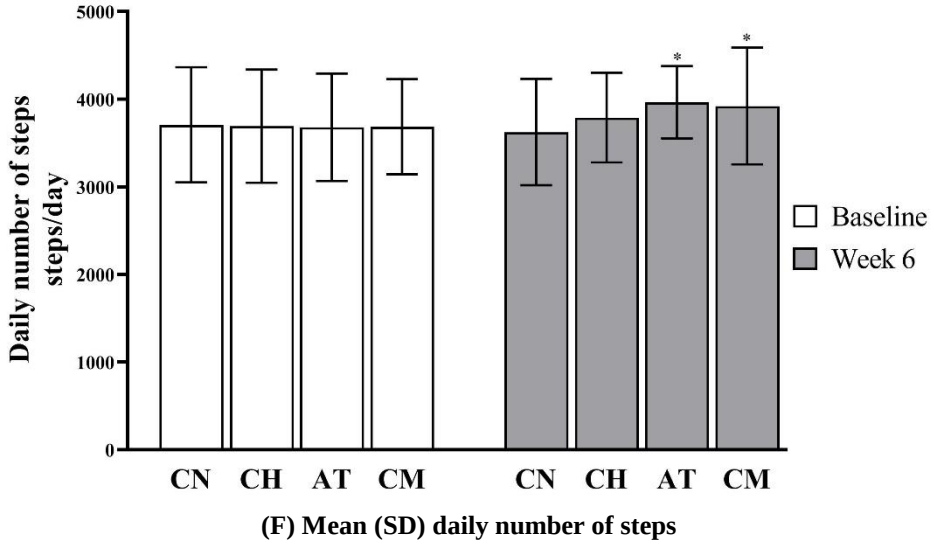


Figure 4-14 The pre- and post-treatment temporal-spatial variables of the CN, CH, AT, and CM groups

Mean (SD) for (A) walking speed, (B) step length, (C) cadence, (D) double support time, (E) stance phase percentage, (F) daily number of steps. CN=control group, CH=Chinese herbal patch group, AT=acupuncture group, CM=Chinese massage group. The baseline data were showed in white, and the six-week data were showed in grey. *: P<0.05 when a treatment group was compared with baseline (intragroup evaluation). [a]: P<0.05 when a treatment group was compared with six-week CN (intergroup evaluation).

Knee joint kinematic outcomes: At baseline assessment, the knee joint kinematic outcomes(i.e., peak knee joint angle and knee joint ROM during stance phase in the sagittal, frontal, and transverse planes) showed no differences between the CN, CH, AT, and CM groups (P>0.05). The data from the post six-week assessment still indicated no difference in the above parameters in the CN group, however, the data from the CH, AT, and CM groups at the assessment post six-week treatment demonstrated some improvements in the kinematic parameters in comparison with the baseline, which were also identified in the data of CN collected after six-week (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

After six-week treatment, in comparison with the baseline, the CH group achieved 5.1% and 11.6% increase in knee joint ROM during stance phase in the sagittal (P=0.27, Cohen's d=0.14) and transverse plane (P=0.30, Cohen's d=0.29), which were accompanied with 0.6%, 25.8%, and 40.4% increase in knee flexion angle at early stance phase (P=0.89, Cohen's d=0.03), peak knee abduction angle during stance phase

(P=0.16, Cohen's d=0.24) and knee internal rotation angle during stance phase (P=0.10, Cohen's d=0.52). Meanwhile, 0.4% reduction in knee flexion angle at initial contact (P=0.97, Cohen's d=0.01), 23.3% reduction in knee adduction angle (P= 0.16, Cohen's d=0.25), and 0.6% reduction in knee joint ROM during stance phase in the frontal plane (P=0.93, Cohen's d=0.01) was found. However, no change was found statically significant (P>0.05). Medium in-group effect size was observed in peak knee internal rotation angle, and small in-group effect sizes were observed in other kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

After six-week treatment, in comparison with the baseline, the AT group achieved 18.1% and 9.1% increase in knee joint ROM during stance phase in the sagittal (P=0.00, Cohen's d=0.90) and transverse planes (P=0.15, Cohen's d=0.22), which were accompanied with 3.3%, 4.7%, 41.4%, and 2.5% increase in peak knee flexion angle during early stance phase (P=0.59, Cohen's d=0.08), peak knee abduction angle (P=0.77, Cohen's d=0.04), peak knee internal rotation angle (P=0.27, Cohen's d=0.22), and peak knee external rotation angle during stance phase (P=0.96, Cohen's d=0.01). Meanwhile, 8.5% decrease in knee flexion angle at initial contact (P=0.52, Cohen's d=0.11), 21.5% (P=0.14, Cohen's d=0.21) decrease in peak knee adduction angle, and 10.1% decrease in knee joint ROM during stance phase in the frontal plane (P=0.39, Cohen's d=0.28) were found. However, only the increase in knee joint ROM during stance phase in the sagittal plane was statistically significant (P<0.05), the other changes were not statically significant (P>0.05). Large in-group effect size was observed in knee joint ROM during stance phase in the sagittal plane, and small in-group effect sizes were observed in other kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

After six-week treatment, in comparison with the baseline, the CM group achieved 15.1%, 2.0%, and 9.6% increase in knee joint ROM during stance phase in the sagittal (P=0.00, Cohen's d=0.99), frontal (P=0.91, Cohen's d=0.04), and transverse planes

(P=0.43, Cohen's d=0.28), which were accompanied with 6.6%, 14.9%, and 16.2% increase in peak knee flexion angle during early stance (P=0.34, Cohen's d=0.22), peak knee abduction angle (P=0.64, Cohen's d=0.12), and peak knee external rotation angle (P=0.34, Cohen's d=0.25) during stance phase. Meanwhile, 10.8% decrease in knee flexion angle at initial contact (P=0.60, Cohen's d=0.19), 15.9% decrease in peak knee adduction angle (P=0.36, Cohen's d=0.19), 4.5% decrease in peak knee internal rotation angle (P=0.91, Cohen's d=0.03) during stance phase were found. However, only the increase in knee joint ROM during stance phase in the sagittal plane was statistically significant (P<0.05), the other changes were not statically significant (P>0.05). Large in-group effect size was observed in knee joint ROM in the sagittal plane, and small in-group effect sizes were observed in other kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

In comparison with the data of CN collected after six-week, the above-mentioned changes were found slightly different. The participants in the CH group achieved 1.5% increase in knee joint ROM during stance phase in the sagittal plane (P=0.84, Cohen's d=0.08), while 7.3% and 9.6% reduction in knee joint ROM during stance phase in the frontal (P=0.61, Cohen's d=0.19) and transverse planes (P=0.46, Cohen's d=0.28), which were accompanied with 18.2% increase in knee flexion angle at initial contact (P=0.33, Cohen's d=0.36), 2.0% increase in peak knee flexion angle in early stance (P=0.83, Cohen's d=0.07), and 27.5% increase in knee abduction angle during stance phase (P=0.91, Cohen's d=0.24). Meanwhile, 23.3% reduction in peak knee adduction angle (P=0.31, Cohen's d=0.38), 23.8% reduction in peak knee external rotation angle (P=0.14, Cohen's d=0.55) and 31.3% increase in peak knee internal rotation during stance phase (0.39, Cohen's d=0.32) were found. However, the changes were not statically significant (P>0.05). Medium between-group effect size was found in peak knee external rotation angle, and small between-group effect sizes were observed in other kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

In comparison with the data of CN collected after six-week, the participants in the AT group achieved 16.8% increase in knee joint ROM during stance phase in the sagittal plane (P=0.02, Cohen's d=0.92), while 10.4% and 4.5% reduction in knee joint ROM during stance phase in the frontal (P=0.45, Cohen's d=0.28) and transverse planes (P=0.46, Cohen's d=0.11) were found, which were accompanied with 0.9% and 6.5% increase in max knee flexion angle at early stance phase (P=0.94, Cohen's d=0.03) and peak knee abduction angle during stance phase (P=0.89, Cohen's d=0.05), and 8.4% reduction in peak knee internal rotation angle during stance phase (P=0.39, Cohen's d=0.07). Meanwhile, 7.6% decrease in knee flexion angle at initial contact (P=0.76, Cohen's d=0.11), 22.9% decrease in peak knee adduction (P=0.56, Cohen's d=0.22), and 1.8% reduction in peak knee external rotation angle during stance phase (P=0.14, Cohen's d=0.04) were found. However, no above changes were statically significant (P>0.05). Large between-group effect size was observed in knee joint ROM during stance phase in the sagittal plane and small between-group effect sizes were observed in other kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

Comparing with the data of CN collected after six-week, the participants in the CM group achieved 16.8% increase in knee joint ROM during stance phase in the sagittal plane (P=0.02, Cohen's d=1.04), while 2.6% and 12.8% reduction in knee joint ROM during stance phase in the frontal (P=0.85, Cohen's d=0.07), and transverse planes (P=0.35, Cohen's d=0.35) were found, which were accompanied with 25.7% decrease in knee flexion angle at initial contact (P=0.20, Cohen's d=0.52), 10.2% reduction in peak knee flexion angle in early stance (P=0.30, Cohen's d=0.39). Meanwhile, 22.1% decrease in peak knee adduction angle (P=0.49, Cohen's d=0.25), 3.4% decrease in peak knee internal rotation angle (P=0.94, Cohen's d=0.03), and 14.1% decrease in peak knee external rotation angle (P=0.41, Cohen's d=0.30) during stance phase were found. However, no above changes were statically significant (P>0.05). Large between-group effect size was observed in knee joint ROM during stance phase in the sagittal plane, medium between-group effect size was observed in knee flexion angle at initial

contact, and small between-group effect sizes were observed in other kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

The changes in kinematic variables were also found in the CM group in comparison with the CH and AT groups at week six. Compared with the six-week CH, the six-week CM achieved 37.1% decrease in knee flexion angle at initial contact (P=0.20, Cohen's d=1.14), 11.9% decrease in peak knee flexion angle in early stance (P=0.68, Cohen's d=0.53), 6.5% decrease in knee abduction angle (P=0.99, Cohen's d=0.07), 26.4% decrease in knee internal rotation angle (P=0.85, Cohen's d=0.33), and 2.0% decrease in knee joint ROM during stance phase in the transverse plane (P=0.99, Cohen's d=0.05). Moreover, the six-week CM showed 15.0% increase in knee joint ROM during stance phase in the sagittal plane (P=0.15, Cohen's d=0.86), 16.3% increase in knee adduction angle (P=0.99, Cohen's d=0.17), 5.2% increase in knee joint ROM during stance phase in the frontal plane (P=1.00, Cohen's d=0.12), and 12.7% increase in knee external rotation angle (P=0.93, Cohen's d=0.23). However, no above changes were statically significant (P>0.05). Large to small between-group effect sizes were observed in all kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

Compared with the six-week AT, the six-week CM achieved 19.5% decrease in knee flexion angle at initial contact (P=0.84, Cohen's d=0.30), 11.0% decrease in peak knee flexion angle in early stance (P=0.73, Cohen's d=0.34), 12.4% decrease in knee external rotation angle (P=0.88, Cohen's d=0.27), and 8% decrease in knee joint ROM during stance phase in the transverse plane (P=0.88, Cohen's d=0.23). Moreover, the six-week CM showed a 1% increase in knee adduction angle (P=1.00, Cohen's d=0.01), 11.9% increase in knee abduction angle (P=0.99, Cohen's d=0.10), 8.8% increase in knee joint ROM during stance phase in the frontal plane (P=0.94, Cohen's d=0.21), and 5.5% increase in knee internal rotation angle (P=0.99, Cohen's d=0.04) when compared with six-week AT. However, no above changes were statically significant (P>0.05). Small

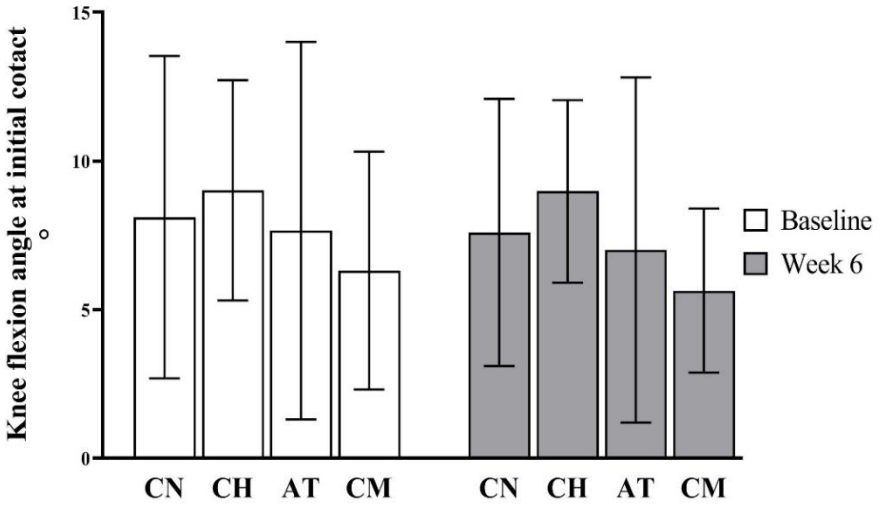
between-group effect sizes were observed in all kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

Compared with the six-week CH, the six-week AT showed 21.9% decrease in knee flexion angle at initial contact (P=0.59, Cohen's d=0.42), 1% decrease in peak knee flexion angle in early stance (P=1.00, Cohen's d=0.05), 16.4% decrease in knee abduction angle during stance phase (P=0.97, Cohen's d=0.19), 3.3% decrease in knee joint ROM during stance phase in the frontal plane (P=1.00, Cohen's d=0.08), and 30.2% decrease in knee internal rotation angle (P=0.79, Cohen's d=0.40). Moreover, the six-week AT showed a 15.1% increase in knee joint ROM during stance phase in the sagittal plane (P=0.11, Cohen's d=0.78), 15.2% increase in knee adduction angle (P=0.99, Cohen's d=0.11), 28.6% increase in knee external rotation angle (P=0.54, Cohen's d=0.52), and 6.5% increase in knee joint ROM during stance phase in the transverse plane (P=0.63, Cohen's d=0.17). However, no above changes were statically significant (P>0.05). Small between-group effect sizes were observed in all kinematic variables (Table 4-7, Figure 4-15, A, B, C, D, E, F, G, H, and I, Figure 4-16 A, B, and C).

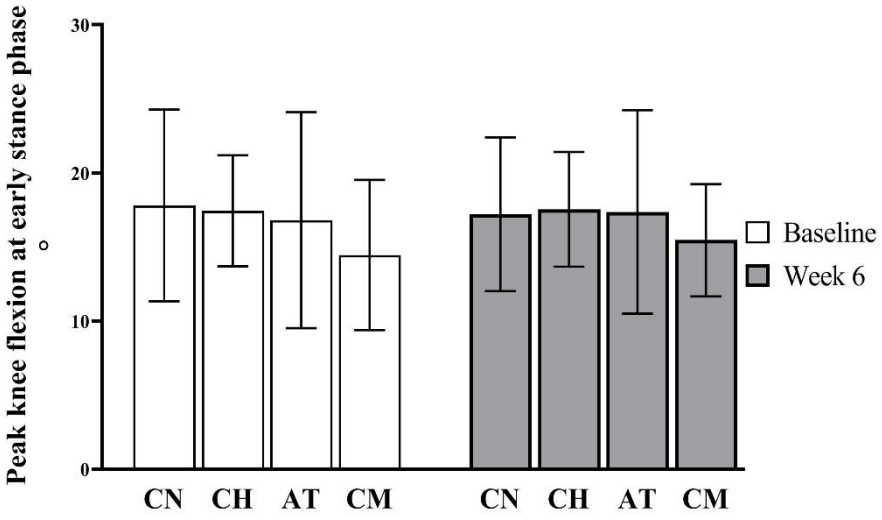
Table 4-7 The kinematic variables (Mean±SD) of the CN, CH, AT, and CM groups

Outcome Measure		CN (n=15)	CH (n=15)	AT (n=15)	CM (n=15)
PKF at IC (°)	Baseline	8.11±5.43	9.01±3.70	7.66±6.35	6.32±3.99
Flexion (+), Extension (-)	Week 6	7.59±4.49	8.97±3.07	7.01±5.81	5.64±2.76
PKF at ES (°)	Baseline	17.80±6.47	17.44±3.74	16.81±7.29	14.45±5.07
Flexion (+), Extension (-)	Week 6	17.20±5.19	17.54±3.87	17.36±6.87	15.45±3.79
Knee_ROM_X at SP (°)	Baseline	36.52±7.39	36.03±9.81	36.90±7.68	37.85±6.31
	Week 6	37.30±7.01	37.87±7.99	43.57±6.58*	43.56±4.86*
PKADD at SP (°)	Baseline	-4.65±4.19	-3.43±2.88	-3.86±3.89	-3.64±3.31
Abduction (+), Adduction (-)	Week 6	-3.93±4.16	-2.63±2.55	-3.03±4.18	-3.06±2.49
PKABD at SP (°)	Baseline	1.94±4.37	2.95±3.39	2.96±4.18	3.02±2.81
Abduction (+), Adduction (-)	Week 6	2.91±3.61	3.71±3.03	3.10±3.43	3.47±4.10
Knee_ROM_Y at SP(°)	Baseline	6.58±3.13	6.38±3.49	6.82±2.50	6.54±4.04
	Week 6	6.84±2.60	6.34±2.74	6.13±2.43	6.67±2.61
PKIR at SP (°)	Baseline	3.40±5.49	3.89±3.42	2.63±5.47	4.21±5.46
Inter rotation (+), Exter rotation (-)	Week 6	4.16±5.24	5.46±2.42	3.81±5.36	4.02±5.65
PKER at SP (°)	Baseline	-11.45±6.91	-9.17±4.11	-11.68±5.89	-8.84±5.99
Inter rotation (+), Exter rotation (-)	Week 6	-11.96±5.66	-9.11±4.60	-11.72±5.41	-10.27±5.44
Knee_ROM_Z at SP (°)	Baseline	14.85±5.79	13.06±4.63	14.31±5.19	13.04±3.32
	Week 6	16.12±5.43	14.58±5.76	15.53±5.73	14.29±5.06

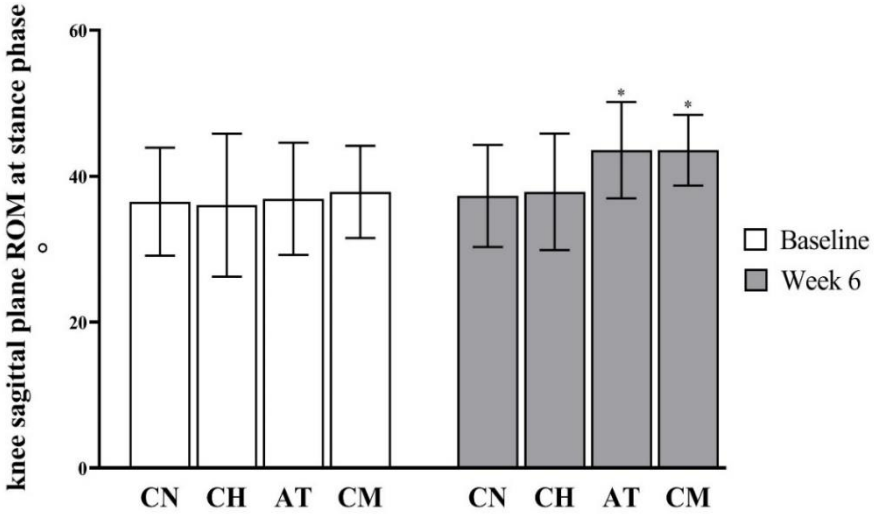
Abbreviation: peak knee flexion angle at initial contact= PKF at IC, peak knee flexion angle at early stance phase=PKF at ES, knee sagittal plane ROM at stance phase= Knee_ROM_X at SP, peak knee adduction angle at stance phase= PKADD at SP, peak knee abduction angle at stance phase= PKABD at SP, knee frontal plane ROM at stance phase= Knee_ROM_Y at SP, peak knee internal rotation angle at stance phase= PKIR at SP, peak knee External rotation angle at stance phase= PKER at SP, pnee transverse plane ROM at stance phase= Knee_ROM_Z at SP.
+ = positive, - = negative
*: P<0.05 when a treatment group was compared with baseline (intragroup evaluation).



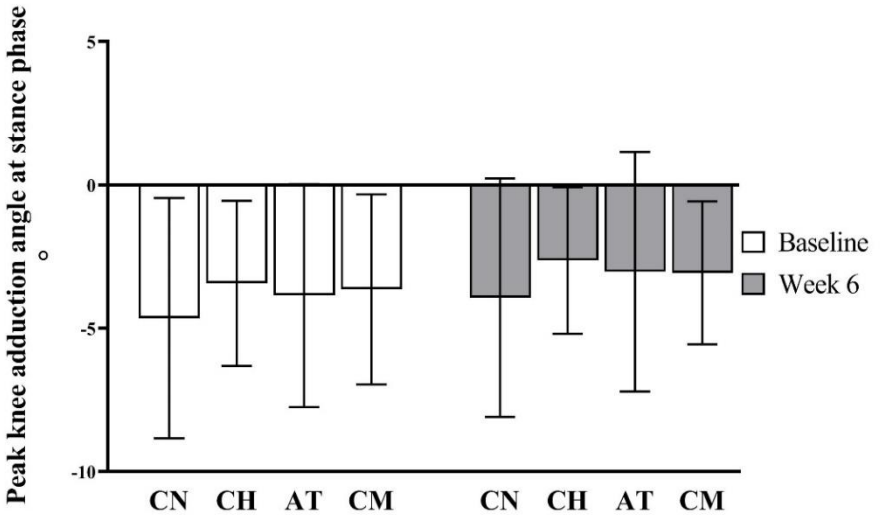
(A) Mean (SD) knee flexion angle at initial contact



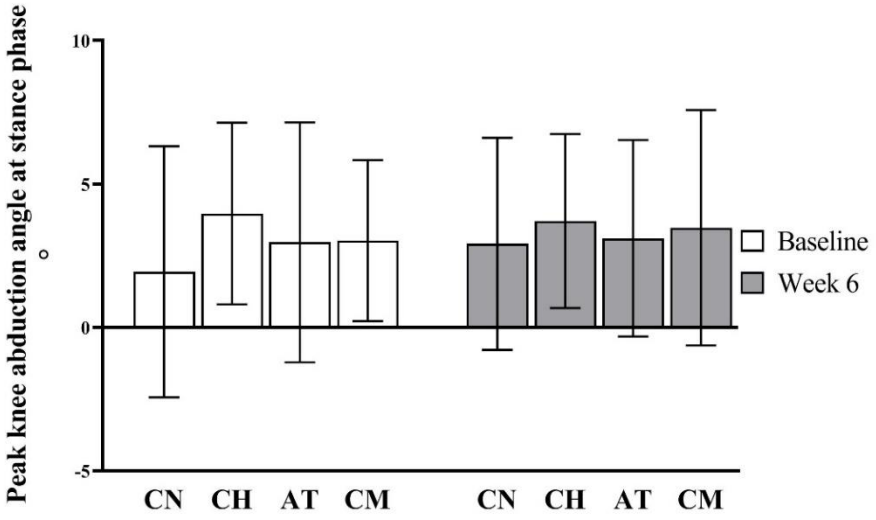
(B) Mean (SD) peak knee flexion at early stance phase



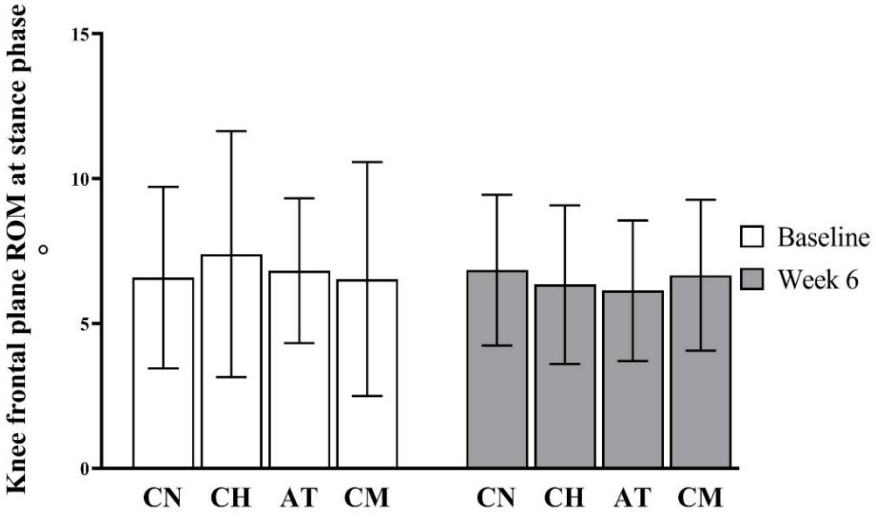
(C) Mean (SD) knee sagittal plane ROM at stance phase



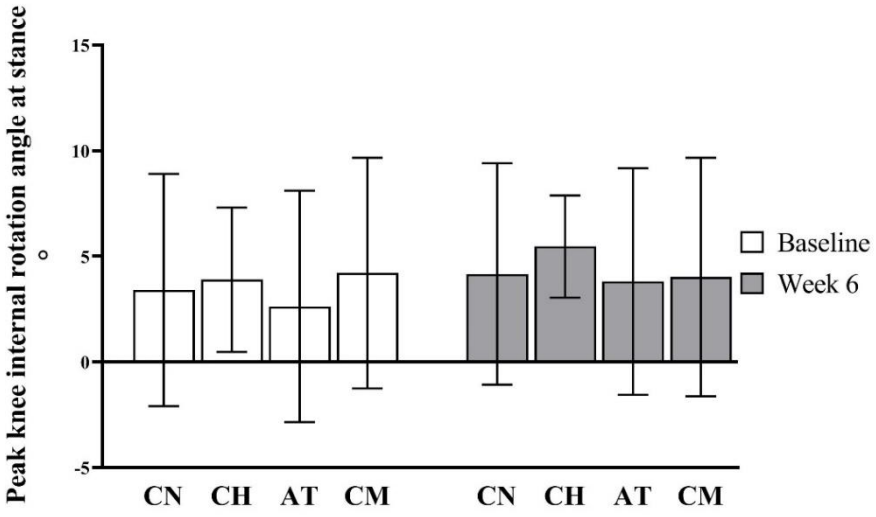
(D) Mean (SD) peak knee adduction angle at stance phase



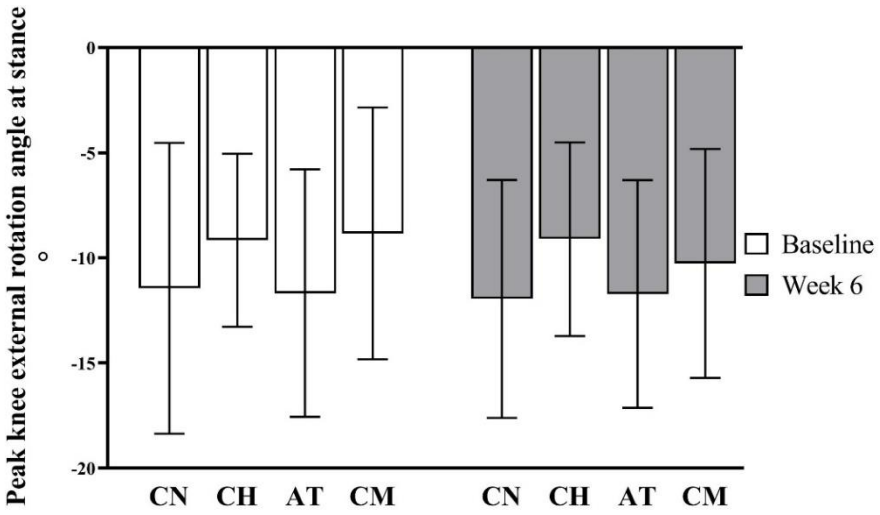
(E) Mean (SD) peak knee abduction angle at stance phase



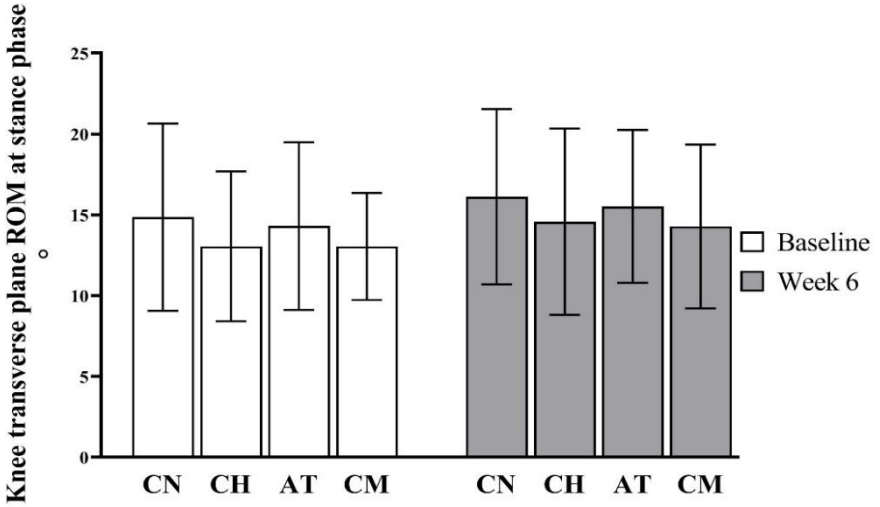
(F) Mean (SD) knee frontal plane ROM at stance phase



(G) Mean (SD) peak knee internal rotation angle at stance phase



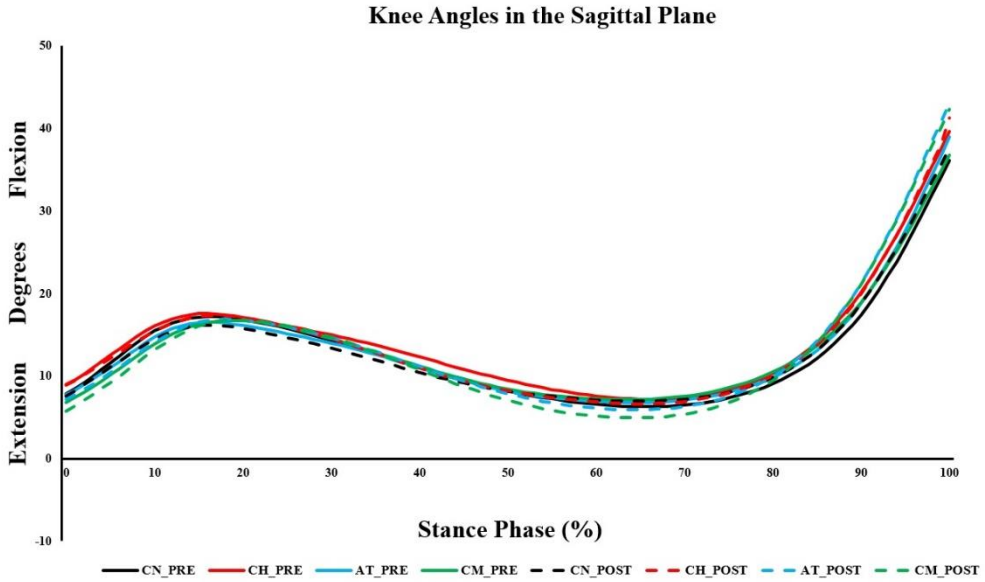
(H) Mean (SD) peak knee external rotation angle at stance phase



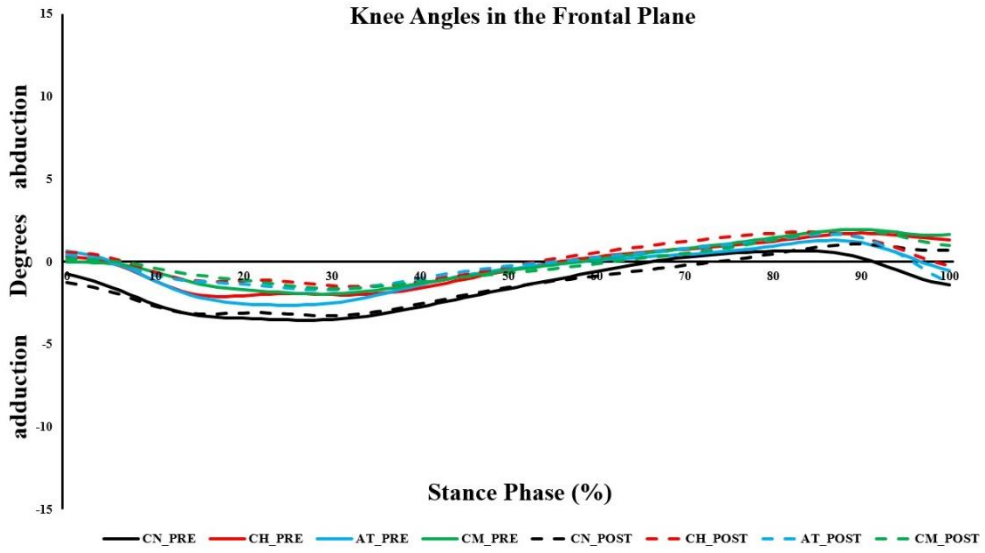
(I) Mean (SD) knee tansverse plane ROM at stance phase

Figure 4-15 The pre- and post-treatment kinematic variables of the CN, CH, AT, and CM groups

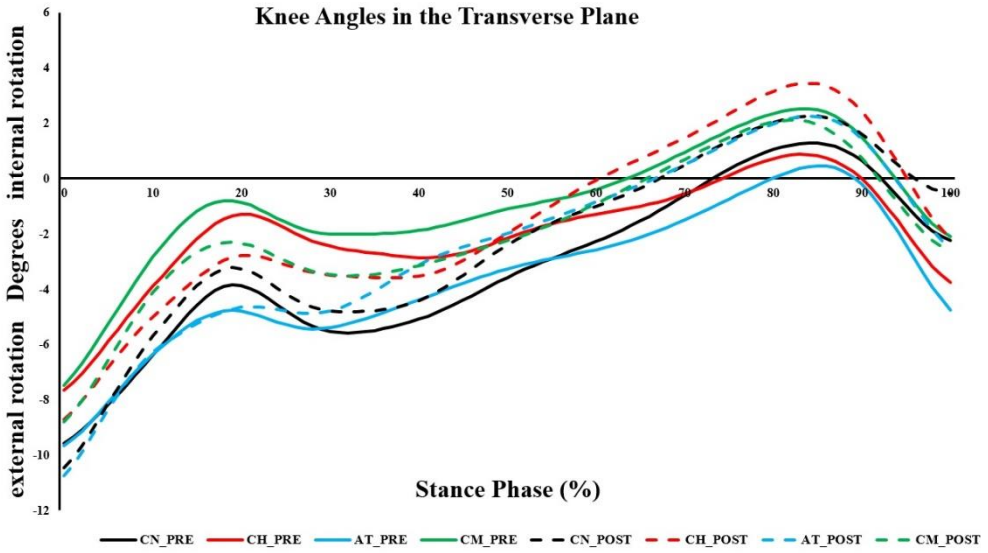
Mean (SD) for (A) knee flexion angle at initial contact, (B) peak knee flexion at early stance phase, (C) knee sagittal plane ROM at stance phase, (D) peak knee adduction angle at stance phase, (E) peak knee abduction angle at stance phase, (F) knee frontal plane ROM at stance phase, (G) peak knee internal rotation angle at stance phase, (H) peak knee external rotation angle at stance phase, (I) knee tansverse plane ROM at stance phase. CN=control group, CH=Chinese herbal patch group, AT=acupuncture group, CM=Chinese massage group. The baseline data were showed in white, and the six-week data were showed in grey. *: $P<0.05$ when a treatment group was compared with baseline (intragroup evaluation).



(A) The pre- and post-treatment knee joint angles in the sagittal plane of the CN, CH, AT, and CM groups



(B) The pre- and post-treatment knee joint angles in the frontal plane of the CN, CH, AT, and CM groups



(C) The pre- and post-treatment knee joint angles in the transverse plane of the CN, CH, AT, and CM groups

Figure 4-16 The pre- and post-treatment knee joint angles in the sagittal, frontal and transverse planes of the CN, CH, AT, and CM groups

(A) The pre- and post-treatment knee joint angles in the sagittal plane of the CN, CH, AT, and CM groups, (B) The pre- and post-treatment knee joint angles in the frontal plane of the CN, CH, AT, and CM groups, (C) The pre- and post-treatment knee joint angles in the transverse plane of the CN, CH, AT, and CM groups. CN_PRE=CN group at baseline, CN_POST= six-week CN group, CH_PRE=CH group at baseline, CH_POST= six-week CH group, AT_PRE=AT group at baseline, AT_POST=six-week AT group, CM_PRE=CM group at baseline, CM_POST=CM group after receiving six-week treatment. The black solid line was the mean of the baseline of the control group (CN_PRE). The red solid line was the mean of the baseline of the Chinese patch group (CH_PRE). The blue solid line was the mean of the baseline of the acupuncture group (AT_PRE). The green solid line was the mean of the baseline of the Chinese massage group (CM_PRE). The black dash line was the mean of the six-week control group (CN_POST). The red dash line was the mean of the six-week Chinese patch group (CH_POST). The blue dash line was the mean of the six-week acupuncture group (AT_POST). The green dash line was the mean of the six-week Chinese massage group (CM_POST).

Knee joint kinetic outcomes: At baseline assessment, the other knee joint kinetic outcomes (i.e., knee moment during stance phase in the sagittal, and transverse planes) showed no differences between the CN, CH, AT, and CM groups ($P>0.05$). The data from the post six-week assessment still indicated no difference in the above parameters in the CN group, however, the data from the CH, AT, and CM groups at the assessment post six-week treatment demonstrated some improvements in the kinetic parameters in comparison with the baseline, which were also seen in the data of CN collected after six-week (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

The data from the CH, AT, and CM groups at the assessment post six-week treatment demonstrated some improvements in the kinetic parameters in comparison with the

baseline, which were also seen in the data of CN collected after six-week. After the six-week treatment, in comparison with the baseline, the participants in the CH group achieved 13.3%, 1.3%, and 1.5% increase in the peak knee flexion (P=0.18, Cohen's d=0.30), internal rotation (P=0.96, Cohen's d=0.03), and external rotation moment (P=0.83, Cohen's d=0.03), which were accompanied with 3.8% reduction in knee extension moment (P=0.52, Cohen's d=0.10). Meanwhile, 1.0% and 0.9% increase in 1st peak GRF (P=0.51, Cohen's d=0.20) and 2nd peak GRF (P=0.18, Cohen's d=0.15 were found. However, no above changes were statically significant (P>0.05). Small in-group effect sizes were observed in all the kinetic and GRF variables (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

The data from the AT group at the assessment post six-week treatment demonstrated some improvements in the kinetic parameters in comparison with the baseline, which were also seen in the data of CN collected after six-week. After six-week treatment, in comparison with the baseline the participants in the AT group achieved 8.8%, 6.5%, 11.5% and 15.2% increase in the peak knee flexion (P=0.28, Cohen's d=0.17), extension (P=0.39, Cohen's d=0.13), internal rotation (P=0.10, Cohen's d=0.22) and external rotation (P=0.06, Cohen's d=0.36) moment even though the changes were not statistically significant (P>0.05). Meanwhile, 7.6% and 2.8% increase in 1st peak GRF (P=0.00, Cohen's d=1.13) and 2nd peak GRF (P=0.01, Cohen's d=0.50) were found and the difference were significant (P<0.05). Large in-group effect size was observed in first peak of GRF, medium in-group effect size of 0.50 was observed in second peak of GRF, and small in-group effect size were observed in other kinetic variables (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

After six-week treatment, in comparison with the baseline, the participants in the CM group achieved 17.3%, 14.0%, 12.3% and 13.4% increase in the peak knee flexion (P=0.92, Cohen's d=0.04), extension (P=0.37, Cohen's d=0.32), internal rotation (P=0.33, Cohen's d=0.38) and external rotation (P=0.08, Cohen's d=0.63) moment, even though the changes were not statistically significant (P>0.05). Meanwhile, 5.8%

and 1.0% increase in 1st peak GRF (P=0.00, Cohen's d=1.08) and 2nd peak GRF (P=0.19, Cohen's d=0.20) were found. However, only the increase in 1st peak GRF was significant (P<0.05). Large in-group effect size was observed in 1st GRF, and small in-group effect sizes were observed in other kinetic variables and 2nd GRF (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

In comparison with the data of CN collected after six-week, the above-mentioned changes were found slightly different. In comparison with the data of CN collected after the six-weeks, the CH group achieved 9.0%, 21.4%, 1.0%, and 1.9% increase in the knee extension moment (P=0.60, Cohen's d=0.19), knee external rotation moment (P=0.30, Cohen's d=0.37), 1st peak GRF (P=0.75, Cohen's d=0.15), and 2nd peak GRF (P=0.24, Cohen's d=0.35). Meanwhile, 8.3% reduction in knee flexion moment (0.60, Cohen's d=0.19) and 17.0% reduction in knee internal rotation moment (Cohen's d=0.0.20, Cohen's d=0.46) were found. However, the changes were not statically significant (P>0.05). Small between-group effect sizes were observed in all the kinetic and GRF variables (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

In comparison with the data of CN collected after six-week, the AT group achieved 7.5%, 1.4%, 3.2%, 35.7%, 7.6%, and 2.8% increase in the peak knee flexion (P=0.68, Cohen's d=0.15), extension (P=0.99, Cohen's d=0.03), internal rotation (P=0.84, Cohen's d=0.07), and external rotation moment (P=0.07, Cohen's d=0.69), 1st peak GRF (P=0.01, Cohen's d=1.23), and 2nd peak GRF (P=0.11, Cohen's d=0.58). However, except 1st peak GRF (P<0.05) the other improvements were not statistically significant (P>0.05). Large between-group effect size was observed in first peak of GRF, medium between-group effect size were observed in second peak of GRF and peak external rotation moment, and small between-group effect size were observed in other kinetic variables (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

In comparison with the data of CN collected after the six-week, the six-week CM achieved 12.4%, 35.7%, 3.8%, and 1.9% increase in the peak knee extension (P=0.37, Cohen's d=0.32) and external rotation moment (P=0.08, Cohen's d=0.63), 1st peak GRF(P=0.13, Cohen's d=0.66), and 2nd peak GRF (P=0.10, Cohen's d=0.44). Meanwhile, 1.7% and 12.8% decrease in peak knee flexion (P=0.92, Cohen's d=0.04) and knee internal rotation moment were found (P=0.33, Cohen's d=0.38). However, no above changes were statically significant (P>0.05). Medium between-group effect size was observed in 1st GRF, and small between-group effect sizes were observed in other kinetic variables and 2nd GRF (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

The changes in kinetic variables were also found in AT group in comparison with the CH and CM groups at week six. Compared with the six-week CH, the six-week AT showed 15.8% increase in knee flexion (P=0.76, Cohen's d=0.34), 24.4% increase in knee internal rotation (P=0.45, Cohen's d=0.47), 11.8% increase in knee external rotation (P=0.90, Cohen's d=0.28), 6.6% increase in 1st peak GRF (P=0.03, Cohen's d=1.17), and 0.92% increase 2nd peak GRF (P=1.00, Cohen's d=0.15). Meanwhile, 7.0% decrease in knee extension moment (P=0.95, Cohen's d=0.17) was found. However, except the increase in 1st peak GRF was statistically significant (P<0.05), the other changes were not statically significant (P>0.05). The large between-group effect size was observed in 1st GRF, and small between-group effect sizes were observed in other kinetic variables and 2nd GRF (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

Compared with the six-week CM, the six-week AT showed 9.3% increase in knee flexion (P=0.94, Cohen's d=0.20), 18.3% increase in knee internal rotation moment (P=0.69, Cohen's d=0.39), 3.7% increase in 1st peak GRF (P=0.36, Cohen's d=0.72), and 0.92% increase 2nd peak GRF (P=1.00, Cohen's d=0.18). Meanwhile, 9.7% decrease in knee extension moment (P=0.86, Cohen's d=0.29) was found. However, no above changes were statically significant (P>0.05). The small between-group effect size

was observed in all the kinetic variables, 1st GRF, and 2nd GRF (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

Compared with the six-week CH, the six-week CM showed 7.2% increase in knee flexion (P=0.98, Cohen's d=0.18), 3.1% increase in knee extension (P=0.99, Cohen's d=0.09), 5.1% increase in knee internal rotation (P=0.98, Cohen's d=0.13), 11.8% increase in knee external rotation moment (P=0.88, Cohen's d=0.26) and 3.7% increase in 1st peak GRF (P=0.58, Cohen's d=0.54). However, no above changes were statically significant (P>0.05). The medium between-group effect size was observed in 1st peak GRF and small effect sizes were observed in other kinetic variables and 2nd GRF (Table 4-8, Figure 4-17 A, B, C, D, E, and F, Figure 4-18 A and B, Figure 4-19).

Table 4-8 The kinetic variables (Mean±SD) of the CN, CH, AT, and CM groups

Outcome Measure		CN (n=15)	CH (n=15)	AT (n=15)	CM (n=15)
KFM (Nm/(BW*Ht)%)	Baseline	2.46±1.35	1.95±0.79	2.38±1.24	2.02±0.87
Flexion (+), Extension (-)	Week 6	2.41±1.15	2.21±0.93	2.59±1.27	2.37±0.89
KEM (Nm/(BW*Ht)%)	Baseline	-2.12±1.04	-2.38±0.98	-2.00±0.98	-2.07±0.73
Flexion (+), Extension (-)	Week 6	-2.10±0.98	-2.29±0.89	-2.13±0.97	-2.36±0.60
KIRM (Nm/(BW*Ht)%)	Baseline	0.94±0.38	0.77±0.27	0.87±0.45	0.73±0.35
Inter rotation (+), Exter rotation (-)	Week 6	0.94±0.35	0.78±0.34	0.97±0.46	0.82±0.28
KERM (Nm/(BW*Ht)%)	Baseline	-0.51±0.28	-0.67±0.27	-0.66±0.31	-0.67±0.30
Inter rotation (+), Exter rotation (-)	Week 6	-0.56±0.33	-0.68±0.32	-0.76±0.24	-0.76±0.30
1st GRF (BW)	Baseline	1.05±0.07	1.05±0.05	1.05±0.06	1.03±0.06
	Week 6	1.05±0.07	1.06±0.06[b]	1.13±0.06*[,a]	1.09±0.05*
2nd GRF (BW)	Baseline	1.06±0.05	1.07±0.06	1.06±0.06	1.07±0.05
	Week 6	1.06±0.04	1.08±0.07	1.09±0.06*	1.08±0.05

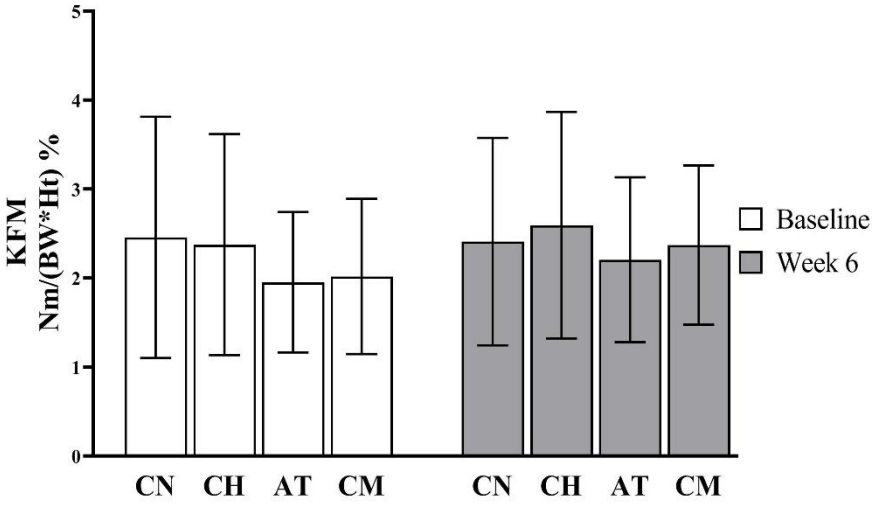
Abbreviation: peak knee flexion moment=KFM, peak knee extension moment=KEM, knee adduction angular impulse=KAAI, peak knee internal rotation moment=KIRM, peak knee external rotation moment=KERM, first peak of ground reaction force=1st GRF, second peak of ground reaction force=2nd GRF

+ = positive, - = negative

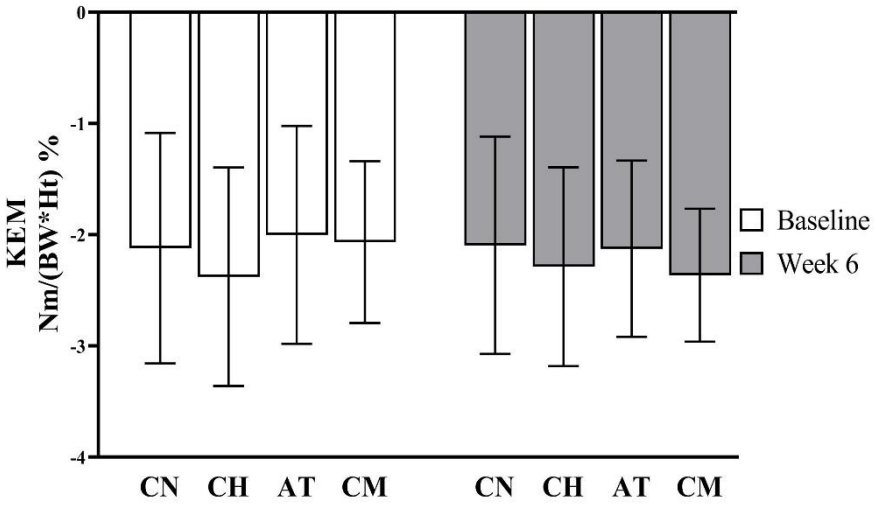
*: P<0.05 when a treatment group was compared with baseline (intragroup evaluation).

[a]: P<0.05 when a treatment group was compared with six-week CN (intergroup evaluation).

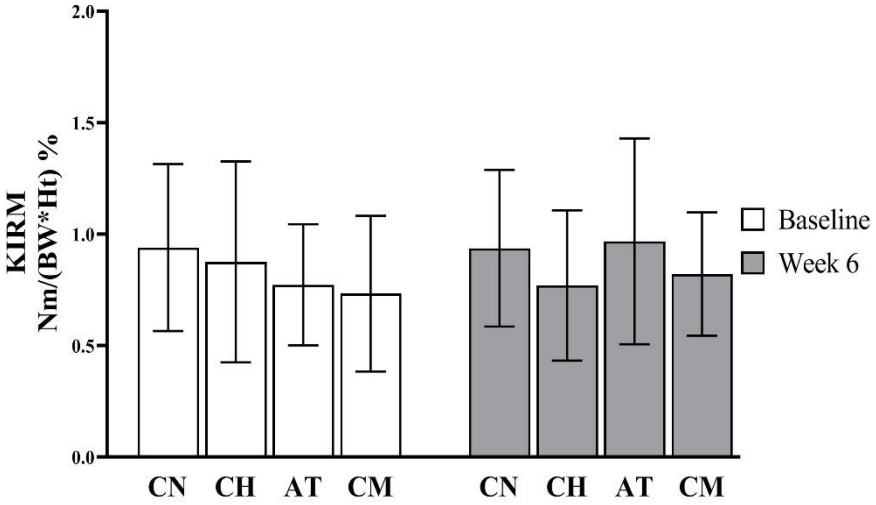
[b]: P<0.05 when six-week CH was compared with six-week AT (intergroup evaluation).



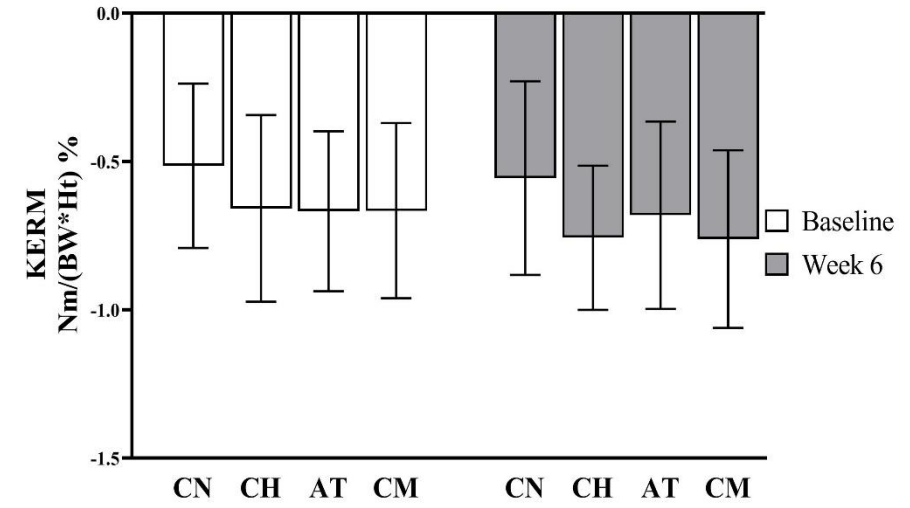
(A) Mean (SD) knee flexion moment



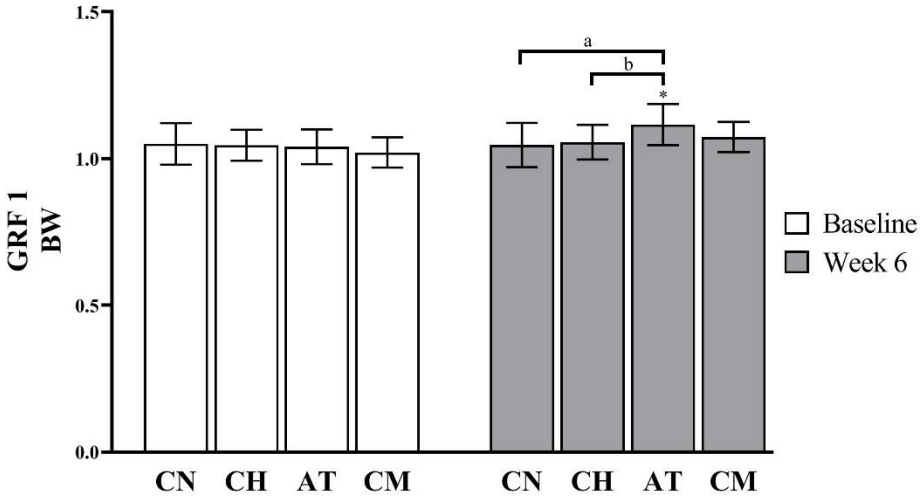
(B) Mean (SD) knee extension moment



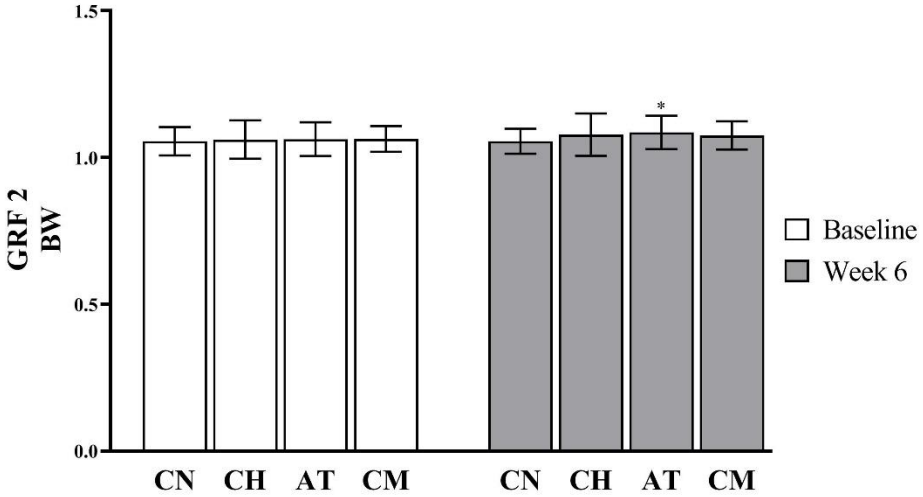
(C) Mean (SD) knee internal rotation moment



(D) Mean (SD) knee external rotation moment



(E) Mean (SD) 1st peak GRF

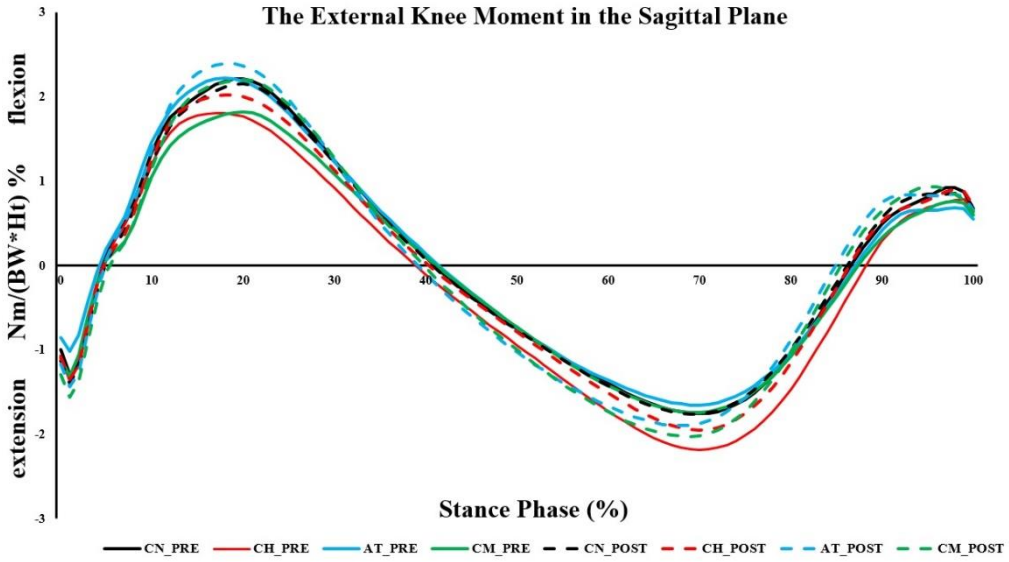


(F) Mean (SD) 2nd peak GRF

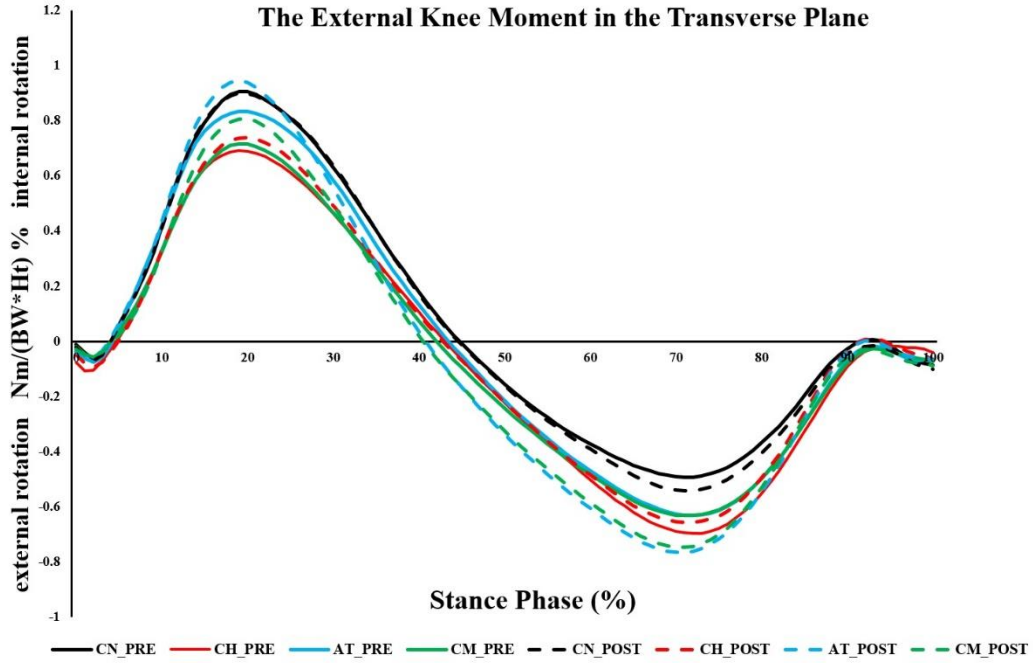
Figure 4-17 The pre- and post-treatment kinetic variables of the CN, CH, AT, and CM groups

Mean (SD) for (A) knee flexion moment, (B) knee extension moment, (C) knee internal rotation moment, (D) knee external rotation moment, (E) 1st peak GRF, (F) 2nd peak GRF. CN=control group, CH=Chinese herbal patch group, AT=acupuncture group, CM=Chinese massage group. The baseline data were showed in white, and the six-week data were showed in grey.*: P<0.05 when a treatment group was compared with baseline (intragroup evaluation). [a]: P<0.05 when a treatment group was compared with six-

week CN (intergroup evaluation). [b]: P<0.05 when six-week CH was compared with six-week AT (intergroup evaluation).



(A) Mean (SD) knee joint moment in sagittal plane



(B) Mean (SD) knee joint moment in transverse plane

Figure 4-18 The pre- and post-treatment external knee joint moment in the sagittal and transverse planes of the CN, CH, AT, and CM groups

(A) The pre- and post-treatment external knee joint moment in the sagittal plane of the CN, CH, AT, and CM groups, (B) The pre- and post-treatment external knee joint moment in the transverse plane of the CN, CH, AT, and CM groups. CN_PRE=CN group at baseline, CN_POST= six-week CN group, CH_PRE=CH group at baseline, CH_POST= six-week CH group, AT_PRE=AT group at baseline, AT_POST=six-week AT group, CM_PRE=CM group at baseline, CM_POST=CM group after receiving six-week treatment. The black solid line was the mean of the baseline of the control group (CN_PRE). The red solid line was the mean of the baseline of the Chinese patch group (CH_PRE). The blue solid line was the mean of the baseline of the acupuncture group (AT_PRE). The green solid line was the mean of the baseline of the Chinese massage group (CM_PRE). The black dash line was the mean of the six-week control group (CN_POST). The red dash line was the mean of the six-week Chinese patch group (CH_POST). The blue dash line was the mean of the six-week acupuncture group (AT_POST). The green dash line was the mean of the six-week Chinese massage group (CM_POST).

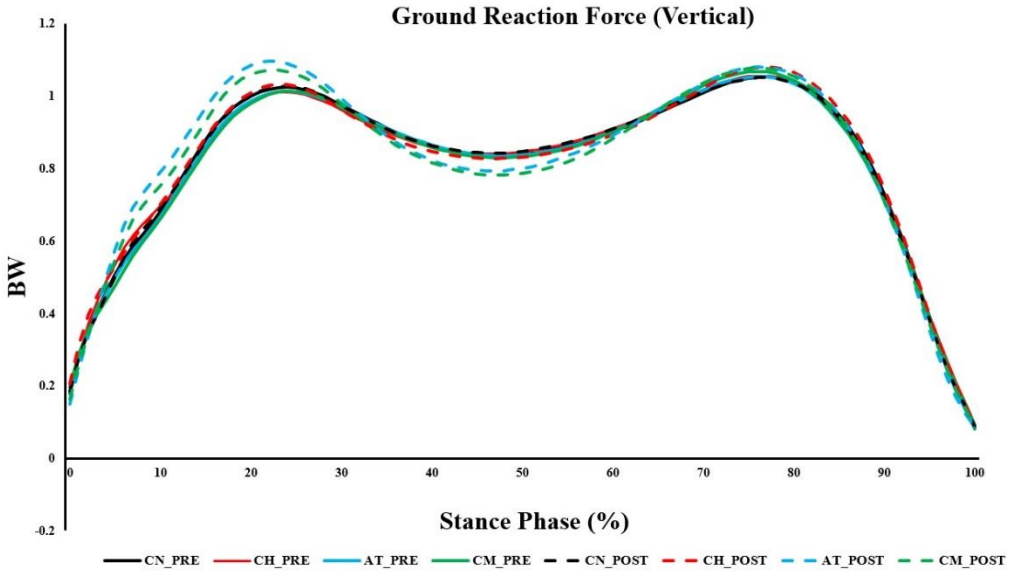


Figure 4-19 The pre- and post-treatment ground reaction force (vertical) of the CN, CH, AT, and CM groups

CN_PRE=CN group at baseline, CN_POST= six-week CN group, CH_PRE=CH group at baseline, CH_POST= six-week CH group, AT_PRE=AT group at baseline, AT_POST=six-week AT group, CM_PRE=CM group at baseline, CM_POST=CM group after receiving six-week treatment. The black solid line was the mean of the baseline of the control group (CN_PRE). The red solid line was the mean of the baseline of the Chinese patch group (CH_PRE). The blue solid line was the mean of the baseline of the acupuncture group (AT_PRE). The green solid line was the mean of the baseline of the Chinese massage group (CM_PRE). The black dash line was the mean of the six-week control group (CN_POST). The red dash line was the mean of the six-week Chinese patch group (CH_POST). The blue dash line was the mean of the six-week acupuncture group (AT_POST). The green dash line was the mean of the six-week Chinese massage group (CM_POST).

Chapter 5: Discussion

TCM treatments (e.g., CH, AT, and CM) have been widely advertised for the management of knee OA, as it has been proved to be very effective in relieving the pain. Although previous studies (He et al., 2019, Kong & Ye. 2019, Xing et al., 2018, Xia et al., 2018, Lu., 2018, Jiao et al., 2018, Zhou et al., 2017, Hu & Xi. 2015, Yang et al., 2015, Liu & Jiang. 2015, Ju et al., 2013, Jiang et al., 2013, Wang et al., 2012, Zhao & Wang. 2008, , Tu et al., 2021, Wang et al., 2020, Lin et al., 2018, Zhang et al., 2016, Helianthi et al., 2016, Ashraf et al., 2014, Hinman et al., 2014, Chen et al., 2013, Jubb et al., 2008, Scharf et al., 2006, Vas et al., 2004, Tukmachi et al., 2004, Berman et al., 1999, Jin et al., 2017, Zhu et al., 2015, Chen et al., 2015, Zheng et al., 2020) proved that the TCM treatments could be very safe, cheap, and effective treatments in the management of knee OA. However, the effect of the TCM treatments is still controversial. Moreover, most of the previous studies investigating TCM treatments have primarily concentrated on the clinical effect (e.g., pain, stiffness, and function) rather than the biomechanical changes (e.g., EKAM, KAAI, knee joint angles, and muscle co-contraction) over a period. Whilst pain and functional changes have been demonstrated, it is not currently known if the changes in pain and function seen following TCM results in changes in the loading at the knee. So far, less study has reported the biomechanical effectiveness of TCM in individuals with knee OA and reported the gait patterns changing after having the TCM treatments in individuals with knee OA, moreover, none of these studies reported the muscle activation patterns changes during gait, which also play an important role in the progression of the disease. Therefore, it was still hard to draw firm conclusion due to the quality of the previous research. This study was designed to investigate the clinical and biomechanical effects of TCM treatments after a period of 6 weeks. The results could help to enable the investigator to understand the short-term clinical and the biomechanical effects of the selected TCM treatments (i.e., CH, AT, and CM) on knee OA, which contributed to the literature of the field with novel data.

At baseline, there was no significant difference between the CN, CH, AT, and CN groups in demographic characteristics, WOMAC scale, EKAM, or muscle co-contraction. Sixty participants with medial compartment knee OA were enrolled in this study: fourty-nine females and eleven males, the percentage of female was 81.7%. The mean age was 61.33±6.03 years, the mean height was 1.61±0.06 m, the mean mass was 62.87±8.27kg, and the mean BMI was 24.28±2.79 kg/m². As anticipated, the percentage of female in the current study was very similar to the previous knee OA studies (Wang et al., 2020, Tu et al., 2021) where the percentage of female was 82.1% and 78.8%, respectively. The current study age (61.77±6.15 years) and the BMI (24.26±2.87 kg/m²) was also comparable with the previous studies (Tu et al., 2021, Wang et al., 2020), where the age were 62.8 years and 59.31 years, and the BMI were 25.5 kg/m² and 25.59 kg/m², respectively.

Previous studies (Tu et al., 2021, Wang et al., 2020, Lin et al 2018, Hinman et al., 2014) showed that the baseline WOMAC pain in knee OA was from 5.8 to 7.8, which were quite different from the current study (16.47±6.10), the reason for that can be explained by the WOMAC questionnaire used in the current study was rated on a 0-10 numeric rating scale rather than the 0-4 numeric rating scale. Moreover, the latest TCM study (Ying et al., 2018) which used a 0-10 numeric rating scale WOMAC questionnaire showed that the baseline WOMAC pain in individual with knee OA was 17.49, and the result was very similar to the current study. Therefore, the current population in this study recorded a baseline of 16.67 for WOMAC pain was consistent with some previous studies.

The mean of EKAM1 and KAAI at baseline were 2.97±0.62 Nm/(BW*Ht)% and 1.14±0.28 Nm · s/(BW *Ht)%, which were similar to that from the latest study (Hart et al., 2020), where the EKAM1 was 3.21 Nm/(BW*Ht)%. Some studies (Schween et al., 2015, Hinman et al., 2008) reported higher EKAM1 (4.9 Nm/(BW*Ht)%, 3.6 Nm/(BW*Ht)%, respectively) when compared with the current study, the reason for

that might be explained by higher walking speed or difference in demographic characteristics (i.e., the percentage of female participants). Additionally, the KAAI in the current study was also very similar to that in a previous study (Kean et al., 2012) where the mean KAAI for individuals with mild medial compartment knee OA was 1.2 Nm · s/(BW *Ht)%.

The baseline early stance muscle co-contraction (VL/BF: 29.51±16.52, VL/LG: 14.57±9.29, VM/ST: 25.34±11.88, VM/MG: 17.39±9.05) from the current study were similar to Lewek's study (Lewek et al., 2006), where the early stance VL/BF, VL/LG, VM/MG were 25.5, 16.4, and 16.0, respectively. Additionally, the early stance VL/LG and VM/MG muscle co-contraction (17.3, 12.7, respectively) reported by Jones et al. (2018) were also very similar to the current study. The latest study (Preece & Alghamdi, 2021) showed higher VL/BF, VL/LG, VM/MG, and VM/ST co-contraction (37±17, 38±19, 33±15, 30±15, respectively) when compared with the current study, the reason can be explained by the study focused on the 15-25% stance muscle co-contraction, and the equation which they used to calculate the muscle co-contraction was equal to agonist plus antagonistic. Previous studies (Al-Khlaifat et al., 2016, Preece et al., 2016) also showed greater muscle co-contraction indices when compared with the current study, this might be explained by the slower walking speed in the current study (1.02m/s), or the difference in muscle strength, balance, pain catastrophizing, and so on.

Therefore, the baseline data for the percentage of female, age, BMI, WOMAC scale, EKAM, KAAI, and muscle co-contraction were agreed with previous literature. This indicates that the current study populations were similar to other studies populations with knee OA.

5.1 Primary outcomes

5.1.1 Effect of the TCM treatments on WOMAC scales

5.1.1.1 Effect of the CH on WOMAC scales

The primary purpose of the treatment in the management of knee OA is to improve the clinical symptoms (Zhao et al., 2016, Wang et al., 2015, Jiang et al., 2014, Wang et al., 2014, Zhou et al., 2014). It has been demonstrated that the CH patch is effective in pain relief in individuals with knee OA (He et al., 2019, Xing et al., 2018, Xia et al., 2018, Ju et al., 2013). The results of the current study showed that six-week of CH provided symptomatic improvements in WOMAC pain and total when compared with the baseline (14.0% reduction in pain and 11.2% reduction in total), which were in agreement in general to previous studies (Xia et al., 2018, Zhou et al., 2017, Hu & Xi, 2015, Yang et al., 2015, Zhao & Wang, 2008). Ying et al. (2018) reported that after receiving two-week treatment, the CH patch showed significant improvements in clinical symptoms when compared with the baseline, where the reduction of WOMAC pain and total were 27.5% and 20.0%, respectively, which were very close to the current study. Xing et al. (2018) found that the CH patch achieved significant symptomatic improvements in individuals with knee OA in comparison with the baseline after receiving middle-term (24 weeks) CH patch treatment, where the reduction of the WOMAC pain, stiffness, function, and total were 70.5%, 41.3%, 49.5%, and 55.2%, respectively, which were much higher than the current study, the reason can be explained by the duration of the treatment of that study was quite different from the current study. Interestingly, in the current study, the reduction of WOMAC pain in six-week CH was higher than 12% when compared with baseline, which indicated that the improvements in clinical symptoms were caused by the treatment itself rather than the measurement error, as previous study (Angst et al., 2001) demonstrated that effects larger than 12% of baseline score can be detected as MDC. Although the CH group in the current study showed significant improvements in WOMAC pain and total when compared with the baseline, the effect size was small, and no significant difference was found between the six-week CH and CN, this might be due to the small sample size.

No significant change was found in WOMAC in six-week CH in comparison with the six-week CN, however, the six-week CH showed a slight trend toward reduced WOMAC when compared with the six-week CN. The results indicated that long-term CH might be helpful to improve the clinical symptoms further, as one previous study (Wang et al., 2012) also indicated that the short-term CH did not show significant improvement in clinical symptoms in comparison with the control group, even though it could significantly improve the symptom of fear of coldness which could be regarded as a useful treatment for knee OA.

Previous studies showed that the CH patch could significantly improve the clinical symptoms, however, most of them have some limitations. In Lu's study (Lu et al., 2018), the CH patch demonstrated a statistical improvement in WOMAC which was very similar to the current study, however, no effect size of the difference was reported, which might lead to the clinical effectiveness of the CH patch was still unclear. Zhao & Wang. (2008) showed that the FNZG showed significant improvements in WOMAC pain (18.7%), stiffness (10.5%), function (10.8%), and total (11.6%) when compared with the baseline, which was also very similar to the current study, however, they failed to include the control group without real treatment, which might lead low validity and credibility of the results. Wang et al. (2012) reported that FNZG did not perform any better than the placebo patch, the reason can be explained by the individuals with knee OA only receiving one-week treatment, as the purpose of Wang's study was to assess the very short-term efficacy and safety of the CH patch.

This short-term TCM study avoided the shortcomings of the previous studies as follows: firstly, the duration of CH patch was six weeks rather than one to three weeks that reported by some previous studies (He et al., 2019, Xia et al., 2018, Lu., 2018, Jiao et al., 2018, Yang et al., 2015, Ju et al., 2013, Wang et al., 2012), which examined the clinical effect of CH patch for a longer duration. Secondly, the control group without real treatment was included in the current study which can help to further understand the clinical effect of the CH patch after receiving six-week treatment. Finally, the effect

size and the MDC were reported in the current study, which can help to further reveal the true effect of the CH patch in the management of knee OA.

5.1.1.2 Effect of the AT on WOMAC scales

After six-week treatment, the AT group achieved significant reduction in WOMAC pain, stiffness, function, and total scores in comparison with the baseline with all large effect sizes. The same effect was identified in comparison with the CN group at week six with also all large effect sizes. Moreover, our observed in-group and between-group difference (WOMAC pain) were bigger than the MDC (12% from the baseline) that reported in previous studies (Hinman et al., 2014, Angst et al., 2001) which indicated that the improvement in WOMAC pain was caused by the treatment itself rather than the measurement error or other factors.

The results indicated that the AT could offer symptomatic improvements for individuals with medial knee OA, which were very similar to some previous studies (Berman et al., 2004, Witt et al., 2005, Jubb et al, 2008, Lansdown et al., 2009, Shen et al., 2009, Lu, et al., 2010, Liu et al., 2017, Wang et al., 2017). Witt et al. (2005) indicated that after receiving three-month treatment, the AT showed significant clinical improvements (37.6% reduction in WOMAC pain, 32.9% in WOMAC stiffness, 33.1% in WOMAC function, and 33.8% in WOMAC total) when compared with the control group (sham acupuncture with no non-penetrating) which was very similar to the current study where the reduction in WOMAC pain, stiffness, function, and total were 33.6%, 34.3%, 28.2%, and 29.9% respectively. Jubb et al. (2008) also reported that the AT achieved significant symptomatic (WOMAC) improvements in individuals with knee OA in comparison with the baseline, which was also very similar to the current study. However, there was no significant difference between the AT group and control group (sham acupuncture with no real insertion) after receiving 9-week treatment, the reason for that can be explained by the AT group in that study underwent electrical stimulation during treatment, therefore, the clinical improvements in the AT group might be caused by electrical stimulus rather than the penetration of the needles. Lansdown et al. (2009)

also demonstrated that the AT could significantly improve the pain after having a three-month intervention (45.2% reduction in WOMAC pain, 37.1% in WOMAC stiffness, 38.7% in WOMAC function, and 39.5% in WOMAC total). However, the reduction percentage of WOMAC subscales and total in Lansdown's study (Lansdown et al., 2009) were higher than the current study, the reason might be caused by the longer duration of the treatment in their study (three months) when compared with the current study (six weeks). Moreover, both Shen et al. (2009) and Spaeth et al. (2013) showed that the AT group showed better clinical outcomes when compared with the control group, which was also in agreement with the current study. The results of this study have fully accepted the hypothesis that the WOMAC scales (pain, stiffness, function, and total) in AT group were improved after receiving a six-week AT when compared with the baseline and six-week CN, and contributed to the literature in highlighting the clinical effect of AT.

Although previous researchers have studied the effect of AT in individuals with knee OA, no consensus on the effect of AT in the field has been formed. Among previous reports, some studies concluded that no effect of AT on knee OA could be identified. Hinman et al. (2014) and Chen et al. (2013) reported that AT failed to offer clinical improvements in individuals with knee OA when compared with the sham acupuncture, which was as same as some other studies (Foster et al., 2007, Yurtkuran et al., 2007, Scharf et al., 2006, Grotle 2011, Soni et al., 2012, Chen et al., 2013). However, by comparing their reports, some limitations in these studies could be identified. For example, Yurtkuran's study (Yurtkuran et al., 2007) adopted the dose of the AT that was less than the recommendation by a previous study (Walt, 2004), which might be resulted in the uncertain effectiveness of AT. Lansdown et al. (2009) failed to consider the subjects' preferences which might lead to the bias of the results, as the subjects who were allocated to the usual care might have been more negative about the experience during treatment. The results from another two studies by Shen et al. (2009) and Spaeth et al. (2013) might also have some limitations due to the higher drop rate. Scharf et al. (2006) failed to offer the monitoring of the predefined AT schemes which might also

lead to the bias of the results. Moreover, some of the studies (Grotle. 2011, Soni et al., 2012) did not consider the typical AT sensation of Deqi which might lead to the unsatisfied clinical effect of the AT due to inadequate needle insertion depth. These potential limitations might be the reasons that AT failed to show clinical improvements in individuals with knee OA. Additionally, inconsistencies in the numbers and locations of acupuncture points have been found in some previous acupuncture studies, which could have failed in identifying the effect on the clinical symptoms.

This short-term TCM study avoided the shortcomings of the previous studies as follows: firstly, the Deqi sensation was considered in the current study. Secondly, the selection of acupuncture points and the dose of the AT were strictly defined and applied in the treatment protocol of Shuguang Hospital. Thirdly, the procedure of the AT was strictly performed by a well-qualified acupuncturist doctor with a minimum three-year clinical experience. Fourthly, the effect size was reported in the current study, which can help to reveal the true effect of acupuncture in the management of knee OA. Finally, we compared the in-group and between-group difference (WOMAC pain) with the MDC from previous studies. The results indicated that the improvement in WOMAC pain was caused by the AT itself rather than the measurement error. Therefore, the clinical symptoms (WOMAC) results of six-week AT might be more reliable.

5.1.1.3 Effect of the CM on WOMAC scales

It has been demonstrated that massage is effective in pain relief in individuals with knee OA (Pehlivan & Karadakovan, 2019, Perlman et al., 2018, Zhu et al., 2016, Zhu et al., 2015, Zhou et al., 2012). The results of the current study showed that six-week of CM provided statistical improvements in WOMAC subscales and total score when compared with the baseline (33.2% reduction in pain, 47.3% reduction in stiffness, 24.8% reduction in function, and 28.7% reduction in WOMAC total) and six-week CN (32.3% reduction in pain, 43.0% reduction in stiffness, 29.2% reduction in function, and 30.9% reduction in WOMAC total) with medium to large effect sizes, which were in agreement in general to previous studies (Pehlivan & Karadakovan, 2019, Perlman et

al., 2018, Zhu et al., 2015, Atkins, et al., 2013, Efe Arslan et al., 2018). Moreover, our observed in-group and between-group differences (WOMAC pain) were bigger than the MDC (12% from the baseline) that reported in previous studies (Hinman et al., 2014, Angst et al., 2001) which indicated that the improvement in WOMAC pain was caused by the treatment itself rather than the measurement error.

Pehlivan & Karadakovan. (2019) demonstrated that after receiving three-week treatment, the massage group showed significant improvements in clinical symptoms when compared with the control group, where the reduction of WOMAC pain and function were 29.3% and 44.0%, respectively, which were very similar to the current study. Efe Arslan et al. (2018) also reported that the massage group achieved significant symptomatic improvements in individuals with knee OA in comparison with the control group after receiving short-term (3 weeks) treatment, where the reduction of the WOMAC pain, stiffness, function, and total were 47.8%, 41.1%, 39.4%, and 41.2%, respectively, which were also very close to the current study. Zhu et al. (2015) proved that the CM could significantly decrease the WOMAC pain (16.7%), stiffness (33.3%), function (10.6%), and total (31.5%) after receiving a two-week of intervention. Perlman et al. (2018) reported that the eight-week massage therapy showed significant improvements in clinical symptoms when compared with the control group, however, the reduction of WOMAC pain (10.98) in their study was quite different from the current study (5.00), this might be explained by the WOMAC subscales assess dimensions of pain in their study was rated on 0 to 100 visual analog scale, rather than the WOMAC pain rated on a 0-10 numeric rating scale in the current study. The results of this study have fully accepted the hypothesis that The WOMAC (pain, stiffness, function, and total) scales in the CM group were improved after receiving a six-week CM when compared with the baseline and six-week CN.

Although previous studies showed that the massage could significantly improve the clinical symptoms, most of them have some limitations. In Zhu's study (Zhu et al., 2015), the CM demonstrated statistical improvement in WOMAC scales which was

very similar to the current study, however, the effect size of the WOMAC difference in their study were quite small (from 0.08 to 0.31), which might lead to the clinical effectiveness of the massage was still unclear. In the current study, the CM group showed significant improvements in clinical symptoms with medium to large effect size which indicated that the results might be more reliable. Additionally, the individuals with knee OA in Zhu's study only underwent two-week treatment, which made the short-term (e.g., six-week) effectiveness of the CM had not been identified. Moreover, they failed to include the control group for the study, therefore, the investigation was urgently needed to identify the clinical improvement of CM when compared with the control group without real treatment. Efe Arslan et al. (2018) reported that the CM showed statistical reduction in WOMAC pain, stiffness, and function, however, such marked symptomatic improvements in the aromatic oils massage group might be a result of the combination of blending oils and massage during treatment, as the aromatic oils were reported to have effectiveness in improving muscle tension, pain perception and anxiety status (Buckle. 2001). Atkins & Eichler. (2013) reported that the self-massage could also statistically decrease WOMAC pain (45.3%), stiffness (38.6%), and function (44.2%) when compared with the waitlist group. However, the study included an unsupervised self-massage intervention, which led to the uncertain effectiveness of this intervention.

This short-term TCM study avoided the shortcomings of the previous studies as follows: firstly, the CM treatment was strictly given by the experienced doctor with a minimum three-year clinical experiences. Secondly, the control group without real treatment was included in the current study, which can help to further understand the clinical effect of the CM after receiving six-week treatment. Thirdly, the effect size and MDC were reported in the current study, which can help to reveal the true effect of the CM in the management of knee OA. Finally, our observed between-group difference (WOMAC pain) was bigger than the MDC (12% from the baseline) that reported in previous studies (Hinman et al., 2014, Angst et al., 2001), which indicated that the improvement in WOMAC pain was caused by the treatment itself rather than the measurement error.

Therefore, the clinical symptoms (WOMAC) results of this study might be more reliable.

5.1.1.4 Comparison of WOMAC scales between CH, AT, and CM

The six-week CH showed significant improvement in WOMAC pain and total when compared with the baseline, which was very similar to some previous studies (Ying et al., 2018, Xing et al., 2018, Lu et al., 2018). Both the six-week AT and CM groups achieved significant reduction in WOMAC pain, stiffness, function, and total scores in comparison with the six-week CH group. The reason might be explained by the duration of the treatment, as one previous study (Wang et al., 2012) also demonstrated that the short-term CH did not show significant improvement in WOMAC scales in comparison with the control group, even though it could significantly improve the symptom of fear of coldness. However, previous acupuncture studies (Liu et al., 2017, Lu et al., 2012) showed immediate effects of AT on clinical symptoms. Moreover, one study reported that even two-week CM could significantly improve the WOMAC scales in individuals with knee OA (Zhu et al., 2015). Therefore, the results indicated that the AT and CM might be more effective in improving the clinical symptoms in short term in comparison with CH. No significant change was found in WOMAC pain, stiffness, function, and total between six-week AT and CM, which indicated that the short-term AT and CM achieved similar clinical effects in the management of knee OA.

5.1.2 Effect of the TCM treatments on EKAM

5.1.2.1 Effect of the CH on EKAM

It is very natural to speculate some variations in biomechanical variables based on the significant effect in clinical symptoms such as pain, which have not been thoroughly studied in the past. The current study has achieved some results that could improve the understanding of the effect of the CH on EKAM. To our knowledge, this is the first study that has investigated both the clinical and biomechanical effects of CH patch in individuals with medial knee OA, therefore, no previous studies are available to compare with the results of the current study. The results from the six-week assessment

demonstrated slight trend towards higher EKAM from baseline with all small effect sizes, additionally, our observed in-group and between-group differences in EKAM1, EKAM2, and KAAI were smaller than the MDC in the test-retest reliability study. After the six-week treatment, the slight trend towards higher EKAM1, EKAM2, and KAAI in comparison with the baseline indicated that the participants in the CH group could walk more dynamically with an increased walking speed and step length due to the reduction in pain. Although the six-week CH showed higher EKAM1, EKAM2, and KAAI when compared with the six-week CN, no significant difference between groups in the above variables was found.

The EKAM is the variable that received the most attention in evaluating the biomechanical changes in individuals with knee OA (Favre et al., 2016). It has been widely reported to play a critical role in the progress of knee OA (Sharma et al., 1998, Hunt et al., 2006, Sharma et al., 2001). It was not surprising to achieve the results that the six-week CH demonstrated slight trend towards higher EKAM1, EKAM2, and KAAI after a six-week treatment period due to the relief of pain. However, in comparison with the six-week CN, the six-week CH showed smaller EKAM1, EKAM2, and KAAI, this can be explained by the CH group had smaller EKAM1, EKAM2, and KAAI at baseline, which led to the smaller EKAM relative variables after receiving six-week treatment. Hunt et al. (2006) also suggested that the changes of kinetic variables have been associated with changes in temporal-spatial variables. Thorp et al. (2007) indicated that the peak of the EKAM was positively associated with the pain intensity, the symptomatic individual with mild radiographic knee OA (K/L grade 2) showed significant higher EKAM when compared with the asymptomatic counterparts, however, there was no difference in EKAM between the asymptomatic knee OA and normal subjects. It was understandable that changes in biomechanical variables resulting from the increase of walking speed were due to the relief of pain.

Ideally, it is expected that the dynamic knee joint alignment and muscle functions could be systematically improved, so the biomechanical risk factors could be lowered.

Although the recovery of dynamic walking of the individuals with knee OA could be simply regarded as a positive effect of CH patch, the trend towards higher EKAM1, EKAM2, and KAAI could be indicators of an increase in knee loading and risks of further damage to the joint cartilage (Brisson et al., 2017). Therefore, the outcome should be welcomed with caution if the CH patch only functioned in terms of pain reduction. In summary, the hypothesis was fully rejected as the six-week CH patch did not significantly decrease the EKAM1, EKAM2, and KAAI when compared with baseline and the six-week CN.

5.1.2.2 Effect of the AT on EKAM

The results from the six-week AT demonstrated some increase in EKAM when compared with the baseline, which were also identified in comparison with the data of the six-week CN group. After the six-week treatment, the trend towards higher EKAM1, EKAM2, and KAAI in comparison with the baseline indicated that the participants in AT group could walk more dynamically with an increased walking speed and step length due to the reduction in pain. Although the six-week AT showed significantly higher EKAM1, and KAAI when compared with baseline, no significant difference in EKAM1 and KAAI between groups in the above variables were found. Medium in-group effect size of 0.58 was observed in EKAM1 and our observed in-group difference in EKAM1 was larger than the MDC of EKAM1 (0.23) in the test-retest reliability study. Therefore, the in-group difference in EKAM1 was likely to have practical importance. However, only small in-group effect size of 0.33 was observed in the KAAI and our observed in-group difference in KAAI was smaller than the MDC of KAAI (0.20) in the test-retest reliability study. Therefore, the in-group difference in KAAI was unlikely to have practical importance.

The results of the AT group from the current study showed significantly higher EKAM1 and KAAI when compared with the baseline which was generally in agreement with the previous studies (Lu et al., 2010, Liu et al., 2017), and improved the understanding of the treatment effect with a six-week post-treatment effect. However, Lu et al. (2010)

focused on only the immediate effect of acupuncture on EKAM with only three successful gait trials before and after the treatment being recorded, which might influence the accuracy of the data. Instead of focusing on the short-term biomechanical effects, another study (Liu et al., 2017) also only investigated the immediate effect of AT and reported the changes of the EKAM after receiving the acupuncture, which led to the short-term effect of AT on EKAM is still unclear. Therefore, this is the first study to investigate the changes in EKAM during level gait after receiving short-term (6 weeks) AT.

It was not surprising that AT group demonstrated trend towards higher EKAM1, EKAM2, and KAAI after six-week treatment when compared with the baseline, which was accompanied with significant increase in walking speed, step length, and GRF due to the pain reduction. Hunt et al. (2006) also suggested that the changes of kinetic variables were associated with changes in temporal-spatial variables. Thorp et al. (2007) also indicated that the peak of the EKAM was positively associated with the pain intensity, the symptomatic individual with mild radiographic knee OA (K/L grade 2) showed significant higher EKAM when compared with the asymptomatic counterparts, however, there was no difference in EKAM between asymptomatic and the normal subjects. It was understandable that changes in biomechanical variables resulting from the increase in walking speed were due to the relief of pain symptom.

Although the recovery of knee OA individuals' dynamic walking could be simply regarded as a positive effect of AT, the trend towards higher EKAM and KAAI could be indicators of increase in knee loading and risks of further damage to the joint cartilage (Brisson et al., 2017). Therefore, the outcome should be welcomed with caution if the AT only functioned in terms of pain reduction. Ideally, it is expected that the dynamic leg alignment, muscle functions could be systematically improved so the biomechanical risk factors could be lowered. In summary, the hypothesis was fully rejected, as six-week AT showed higher EKAM when compared with the baseline and six-week CN.

5.1.2.3 Effect of the CM on EKAM

To our knowledge, this is the first study that has investigated both the clinical and biomechanical effects of CM in individuals with medial knee OA, therefore, no previous studies were available to compare with the results of this study. After six-week treatment, the CM showed trend towards higher EKAM1, EKAM2, and KAAI in comparison with the baseline indicated that the participants in the CM group could walk more dynamically with increased walking speed and step length due to the reduction in pain. Although the six-week CM showed higher EKAM1, EKAM2, and KAAI when compared with the six-week CN, no significant difference between groups in the above variables was found.

It was not surprising to achieve the results that six-week CM demonstrated trend towards higher EKAM1, EKAM2, and KAAI after six-week treatment when compared with the baseline, which were accompanied with the significant increase in walking speed, step length, and GRF due to the relief of pain. However, medium in-group effect sizes were observed in EKAM1, EKAM2, and KAAI, and our observed in-group difference was smaller than the MDC of EKAM1, EKAM2, and KAAI in the test-retest reliability study. Therefore, the in-group difference in EKAM was unlikely to have practical importance.

Both Lu et al. (2010) and Liu et al. (2016) reported that the increase of loading after receiving TCM treatment, the possible mechanism may be that the TCM treatment could reduce the co-contraction of the muscles around the knee, which in turn leads to the reduction of the pain and increased walking speed and GRF. Hunt et al. (2006) also suggested that the changes of kinetic variables were associated with changes in temporal-spatial variables. Thorp et al. (2007) indicated that the peak of the EKAM was positively associated with the pain intensity, the symptomatic individuals with mild radiographic knee OA (K/L grade 2) showed significant higher EKAM when compared with the asymptomatic counterparts, however, there was no difference in EKAM

between the asymptomatic knee OA and the normal subjects. It was understandable that changes in biomechanical variables resulted from the increased walking speed were due to pain relief. For asymptomatic individuals with light or moderate knee OA, the biomechanical changes might not be detectable.

Ideally, it is expected that the dynamic knee joint alignment, muscle functions could be systematically improved, so the biomechanical risk factors could be lowered. Although the recovery of dynamic walking of the individuals with knee OA could be simply regarded as a positive effect of CM, trend towards higher EKAM1, EKAM2, and KAAI could be indicators of increased knee loading and risks of further damage to the joint cartilage (Brisson et al., 2017). Therefore, the outcome should be welcomed with caution if the CM only functioned in terms of pain reduction. In summary, the hypothesis was fully rejected as the six-week CM did not show the reduction of EKAM when compared with the baseline and six-week CN group.

5.1.2.4 Comparison of EKAM between CH, AT, and CM

Both six-week AT and CM showed trend towards higher EKAM1, EKMA2, and KAAI in comparison with the six-week CH. The reason could be explained by the significant improvement in clinical symptoms (WOMAC pain, stiffness, function, and total) which led to higher walking speed during gait. As one previous study (Landary et al., 2006) suggested that increase in the magnitude of EKAM was associated with an increase in temporal-spatial variables such as walking speed in individuals with knee OA. Therefore, it was understandable that the change in EKAM resulting from the increase of walking speed was due to the relief of pain. As both six-week AT and CM showed significant improvement in WOMAC pain in comparison with the six-week CH. Although, the six-week AT also showed higher EKAM and KAAI when compared with the six-week CM, however, no significant change was found. This reason might be explained by the higher EKAM in the baseline AT in comparison with the CM.

5.1.3 Effect of the TCM treatments on muscle co-contraction

5.1.3.1 Effect of the CH on muscle co-contraction

The distribution of the loading at the medial compartment of the knee depends on two main factors: the EKAM and the muscle force to support coordination and stability of the knee (Lewek et al., 2004), and the coordination of activity of muscle around the knee has been reported as a determinant of knee loading. To compensate for the knee joint laxity during daily activities, the individuals with self-reported knee instability usually show increased knee muscle co-contraction (Schmitt & Rudolph, 2008). Although the increased muscle co-contraction can help to enhance the joint protection in the short term (Lewek et al., 2004), it also increases the joint mechanical loading during gait (Schipplein & Andriacchi, 1991, Lloyd & Buchanan, 2001), and then leads to the acceleration of the cartilage volume loss. Increased co-contraction of the selected paired muscles around the knee would lead to the higher loading on the knee joint, which is not reflected by the EKAM (Walter et al., 2010), and then increased the likelihood of undergoing TKA at the five-year follow-up (Hubley-Kozey et al., 2013). Hatfield et al. (2021) found that the knee OA individual who advanced to the TKA had higher magnitudes and more prolonged co-contraction in comparison with those who did not advance to TKA, therefore, the changing of the muscle co-contraction around the knee should be considered as one of the most important variables that target the progression of knee OA (Booij et al., 2020).

To our knowledge, this is the first study that has investigated both the clinical and biomechanical effects of CH patch in individuals with medial knee OA, therefore, no previous studies are available to compare with the results of this study. The data from the CH group demonstrated some muscle co-contraction changes after a six-week treatment period in comparison with the baseline, which was also confirmed when compared with the data of CN after six-week. After a six-week treatment period, the results of the CH group showed that most of the medial paired muscles (VM/ST, VM/MG) achieved 0.2% to 11.5% reduction in co-contraction at early, mid-, and late stance in comparison with the baseline with small effect sizes. The medial co-

contraction reductions were also confirmed in comparison with the CN group at week six, which were from 8.3% to 21.0% with small effect size. Additionally, our observed in-group and between-group differences in muscle co-contraction were smaller than the MDC in the test-retest reliability study.

Although no statistically significant improvement in muscle co-contraction was found, most of the selected medial muscle showed decreased activity during walking after receiving six-week CH treatment, this might be partially explained by the increase in muscle strength due to the reduction of the pain (Al-Khlaifat et al., 2016). Furthermore, Ramsey et al. (2007) reported that the reduction of muscle co-contraction was associated with the increase of the knee stability, as the knee stability scored better in the neutral position, which indicated that the decreased knee adduction angle during gait was associated with the improvement of the muscle co-contraction, as the main purpose of the increased muscle co-contraction in individuals with knee OA during dynamic condition is to support coordination and stability of the knee (Lewek et al., 2004). Interestingly, the current study also showed the reduction of knee adduction angle after receiving six-week CH when compared with the baseline (23.3%) and six-week CN (33.1%) which indicated that the reduction of muscle co-contraction might have a relationship with that the improvement of the joint alignment during gait. Interestingly, Hinman et al. (2008) demonstrated that therapeutic taping around the knee could help to relieve the pain by improving the alignment of the knee and unloading soft tissues around the joint. In the current study, the FNZG was applied to the area around the knee, which might act as the knee tape for unloading the soft tissues and improving joint alignment (Wang et al., 2012).

5.1.3.2 Effect of the AT on muscle co-contraction

To our knowledge, this is the first study to investigate the changes in muscle co-contraction during gait after receiving short-term AT, therefore, no previous studies are available to compare with the results of this study. The data from the AT group demonstrated some muscle co-contraction changes after six-week treatment in

comparison with the baseline, which were also confirmed compared with the data of CN after six-week. After six-week treatment, the results of the AT group showed that all pairs of muscles showed reduction in muscle co-contraction (from 4% to 22%) at the early, mid-, and late stance in comparison with the baseline. The co-contraction reductions were also confirmed in comparison with the CN group at week six, which were from 3% to 20% except the VL/LG and TA/MG in late stance. However, the difference in muscle co-contraction between the two groups did not reach statistical significance at week six. Medium between-group effect size was observed in mid-stance VM/ST co-contraction, and small between-group effect sizes were observed in other muscle co-contraction variables. Moreover, our observed in-group and between-group difference were less than the MDC of muscle co-contraction.

Although statistically insignificant, most of the selected muscles showed slight trend towards decreased activity during walking after the AT, this might be partially explained by the increase stability of the knee due to the reduction of the pain (Hodges et al., 2016). Ramsey et al. (2007) demonstrated that muscle co-contraction can be reduced by improving the knee instability, as the knee stability scored better in the neutral position, which indicated that the decreased knee adduction angle during gait was associated with improvements of the muscle co-contraction, as the main purpose of the increased muscle co-contraction in individuals with knee OA during dynamic condition is to support coordination and stability of the knee (Lewek et al., 2004). Interestingly, the current study also showed the reduction of knee adduction angle after receiving six-week AT when compared with baseline (21.5%) and the six-week CN (22.9%) which indicated that the reduction of muscle co-contraction might have a relationship with that.

Some previous studies demonstrated that the reduction of joint contact force and pain symptom (Preece et al., 2016, Hodges et al., 2016, Lewek et al., 2004) were associated with decreased medial muscle co-contraction, however, Al-Khlaifat et al. (2016) demonstrated that the reduction of the pain was also associated with the lateral muscle

co-contraction (VL/BF). The current study showed slight trend towards reduced medial and lateral co-contraction after receiving six-week AT, the reason for that might be the selected acupoints included both medial and lateral sides.

5.1.3.3 Effect of the CM on muscle co-contraction

The data from the CM group demonstrated some muscle co-contraction changes after six-week treatment in comparison with the baseline, which were also confirmed when compared with the data of CN after six-week. After six-week treatment, reduction in muscle co-contraction in the CM group ranged from 11.7% to 44.4% in comparison with the baseline, with the reduction in early and mid-stance VM/ST co-contraction were significant with medium to large effect size. Moreover, our observed in-group and between-group difference in early stance VM/ST co-contraction were larger than the MDC of early stance VM/ST (10.33) in the test-retest reliability study. Therefore, the in-group difference in early stance VM/ST was likely to have practical importance. However, our observed in-group and between-group difference in mid-stance VM/ST were smaller than MDC of mid-stance VM/ST (5.82) in the test-retest reliability study. Therefore, the in-group difference in mid-stance VM/ST was unlikely to have practical importance.

The reduction of muscle co-contraction was also confirmed in comparison with the CN group at week six, which ranged from 8.7% to 47.3%, except the VL/BF and VL/LG in late stance. Moreover, the reduction in early and mid-stance VM/ST co-contraction in the six-week CM group was still significant when compared with the six-week CN.

Although only the reduction of early and mid-stance VM/ST co-contraction were statistically significant, most of the selected muscle showed decreased activity during walking after the CM, this might be partly explained by the increase in stability of the knee due to the reduction of the pain (Hodges et al., 2016). Ramsey et al. (2007) demonstrated that the reduction of muscle co-contraction was associated with the increase of the knee stability, as the knee stability scored better in the neutral position,

which indicated that the decreased knee adduction angle during gait was associated with the improvement of the muscle co-contraction, as the main purpose of the increased muscle co-contraction in individuals with knee OA during dynamic condition is to support coordination and stability of the knee (Lewek et al., 2004). Interestingly, the current study also showed the reduction of knee adduction angle after receiving six-week CM when compared with baseline (15.93%) and the six-week CN (22.14%) which indicated that the reduction of muscle co-contraction might have a relationship with that.

Furthermore, the reduction of the muscle co-contraction was associated with the reduction of the pain during walking, which was agreed with some previous studies (Al-Khlaifat et al., 2016, Preece et al., 2016). Previous studies demonstrated that the reduction of joint contact force and pain symptoms were associated with decreased medial muscle co-contraction (Preece et al., 2016, Hodges et al., 2016, Lewek et al., 2004) or bias of muscle activation to lateral muscles (Hodges et al., 2016, Hedien et al., 2009, Hubley-Kozey et al., 2006), however, Al-Khlaifat et al. (2016) showed that the reduction of the pain was also associated with the reduction of lateral muscle co-contraction. The current study showed that both medial and lateral co-contraction were decreased after receiving six-week CM, the reason for that might be explained by the CM covered both medial and lateral sides paired muscles around the knee. Although Cruz-Montecinos et al. (2015) showed that the reduction of the pain was associated with the increased lateral muscle co-contraction, as this could help to generate an internal abduction moment and reduce the loading (EKAM) at the medial compartment of the knee. However, the individuals with knee OA in Cruz-Montecinos's study (Cruz-Montecinos et al., 2015) only receiving one session treatment, which leads to the results may not be reliable. Interestingly, the bias towards lateral muscle co-contraction was also found in six-week CM due to the significant reduction in the medial muscle co-contraction, therefore, the mechanisms of the CM in the management of knee OA might also correlate with this. Al-Khlaifat et al. (2016) showed that the improvement of pain symptoms was associated with the reduction of medial and lateral muscle co-

contraction with only the lateral muscle co-contraction (BF/VL) reached a significant level. However, Preece et al. (2016) reported that the reduction of the pain was associated with the reduction of medial and lateral muscle co-contraction with only medial co-contraction reached a significant level. The reason for that can be explained by the different motions between the self-design exercise and the Alexander Technique programme.

Trend towards decreased muscle co-contraction were found in most of the selected paired muscles in the CM group after receiving six-week treatment. However, only the early, mid-, and late stance VM/ST co-contraction reached statistical significance when compared with the six-week CN. The possible reasons for the results of the current study might be explained as follows: firstly, the walking speed in the six-week CM group was higher when in comparison with the CM baseline and the six-week CN, which might lead to the reduction of muscle co-contraction was not significant as there is a positive correlation between the walking speed and muscle co-contraction (Zeni et al., 2010). Secondly, the duration of the intervention was only six weeks, which may also affect the results.

5.1.3.4 Comparison of muscle co-contraction between CH, AT, and CM

The CM demonstrated statistically significant reduced muscle co-contraction in early stance MV/ST and mid-stance MV/ST after six-week treatment when compared with the CH and AT. The results indicated that the CM was more effective in improving the medial muscle co-contraction in short term in comparison with the CH and AT, which might lead to lower knee contact force during gait. The AT showed significant improvement in clinical symptoms in comparison with the CH after receiving six-week treatment, however, no significant change was found in muscle co-contraction between six-week AT and CH. Therefore, the results indicated that the CM might be more effective in improving the muscle co-contraction in short term in comparison with the CH and AT.

5.2 Secondary outcomes

5.2.1 Effect of the TCM treatments on temporal spatial variables

5.2.1.1 Effect of the CH on temporal-spatial variables

Due to pain sensation, individuals with knee OA usually show significant reduction of temporal-spatial parameters such as: walking speed, step length during gait (Ismailidis et al., 2020, Mills et al., 2013, Gyory et al., 1976, Stauffer et al., 1997, Messier et al., 1992, Brinkmann et al., 1985). This is typically a compensation to reduce the loads on the knee with a corresponding reduction in the GRF (Stansfield et al., 2001), which could not only help to reduce the loading of the knee but also increase the stability of the lower limb during gait (Andriacchi et al., 1982). The magnitude of walking speed, step length, cadence, double support time, stance phase percentage in the current study was very similar to the previous studies (Turcot et al., 2013, da Da Silva et al., 2012), which indicated that the results were reliable.

To our knowledge, this is the first study that has investigated both the clinical and biomechanical effects of CH in individuals with medial knee OA, therefore, no previous study was available to compare with the results of this study. In comparison with the baseline, the CH group achieved some improvements in the temporal-spatial gait parameters and the daily number of steps after receiving six-week treatment, which were also identified in data of CN collected after six-week, except the cadence the other changes displayed small effect sizes. However, no significant difference was found when compared with baseline and six-week CN. Additionally, our observed in-group and between-group differences in temporal-spatial variables were smaller than the MDC. The improvement of the temporal-spatial variables can be explained by the reduction of the pain and the decrease of the medial muscle co-contraction, as the individuals with knee OA usually show significant reduction of temporal-spatial parameters such as: walking speed, step length during gait to decrease the mechanical loading during the dynamic condition.

A low level of physical activity was prevalent among the individuals with knee OA (Paxton et al., 2015, Harding et al., 2014), a previous study (Lee et al., 2013) reported that over 20% of the knee OA individuals showed physical inactivity. Therefore, any treatments that could help OA individuals recover or maintain a certain amount of physical activity would be regarded as effective. Although self-reported data such as WOMAC scores have been widely used as the primary outcomes of in the previous studies (Berman et al., 2004, Witt et al., 2005, Jubb et al, 2008, Lansdown et al., 2009), the data could be biased due to pain experience and collecting the data of the physical activity during a fixed period before and after the interventions could improve the assessment to the outcomes, which could make the evaluation more objective and reasonable (Daugaard et al., 2018).

The results from the assessment post six-week treatment demonstrated some increase from baseline, which were also identified in comparison with the data of CN collected after six-week. After a six-week treatment period, the increase in the daily number of steps in comparison with the baseline indicated that the participants had increased daily activity (walking steps) due to the reduction in pain. However, there were no significant differences in daily walking steps between the CH and CN group at week six. When the pain relief was successfully achieved, the daily activities of the knee OA individuals should be gradually recovered to a level that is similar to the age-matching healthy counterparts, which may be well proved in future further follow-up studies and longer time of data collection might be needed.

5.2.1.2 Effect of the AT on temporal-spatial variables

In comparison with the baseline, the AT group achieved some improvements in the temporal-spatial gait parameters and the daily number of steps after six-week treatment, which were also recognizable in comparison with the data of CN collected after six-week.

The participants in the AT group achieved improvements in their mobility because of

the increase in walking speed, step length, cadence, daily walking steps, and a reduction in double support time and stance phase percentage. Except cadence, stance phase percentage, the other improvements were statistically significant. The improvements in temporal-spatial variables were also identified in comparison with the data of CN collected after six-week, however, except walking speed the other improvements were not statistically significant. Medium in-group effect sizes were observed in cadence and the daily number of steps. Large in-group effect sizes were observed in walking speed, step length, and double support time. Our observed in-group differences in cadence, double support time, and the daily number of steps were larger than the MDC (3.50, 0.01, and 188.98, respectively) in the test-retest reliability study. Therefore, in-group differences in cadence, double support time, and the daily number of steps were likely to have practical importance. However, our observed in-group difference in step length was smaller than MDC (0.04). Therefore, the in-group difference in step length was unlikely to have practical importance.

The outcome of the current study was in agreement with some previous studies (Lu et al., 2010, Liu et al., 2017). Lu et al. (2010) reported that compared with the baseline the AT showed 2% improvement in walking speed due to the relieving of the pain, and Liu et al. (2017) demonstrated that the improvement of walking speed was over 18%. In the current study, the AT group showed significant improvement in walking speed when compared with the six-week CN and baseline, which was very similar to Liu et al. (2017). The improvement in walking speed between Lu et al. (2010) and the current study were quite different, this can be explained by several factors such as the duration of the treatment and the slower walking speed in Lu's study at the baseline. Additionally, statistical improvements in step length, cadence, and double support time were also found in the six-week AT when compared with the baseline which indicated that the restriction of daily activity had been improved, but no significant difference in stance phase percentage was found between groups.

It is well documented that individuals with knee OA have reduced physical activity

(Paxton et al., 2015, Harding et al., 2014). One previous study (Lee et al., 2013) reported that over 23% of knee OA individuals showed physical inactivity. Therefore, any treatments that could help OA individuals recover or maintain a certain amount of physical activity would be regarded as effective. Although self-reported data such as WOMAC scores have been widely used as the primary outcomes of in the previous studies (Berman et al., 2004, Witt et al., 2005, Jubb et al, 2008, Lansdown et al., 2009), the data could be biased due to pain experience and collecting the data of the physical activity during a fixed period before and after the interventions could improve the assessment to the outcomes, which could make the evaluation more objective and reasonable (Daugaard et al., 2018).

The results from the assessment post six-week treatment demonstrated some increase from baseline, which were also identified in comparison with the data of CN collected after six-week. After six-week treatment, the increase of the daily number of steps in comparison with the baseline indicated that the participants had an improved function due to the reduction in pain. However, there were no significant differences in the daily number of steps between the AT and CN group at week six. When the pain relief was successfully achieved, the daily activities of the knee OA individuals should be gradually recovered to a level that is similar to the age-matching healthy counterparts, which may be well proved in future further follow-up studies and longer time of data collection might be needed. Although the increase of the daily number of steps can be regarded as a positive clinical effect of the AT in the management of knee OA, the increase of walking steps could be an indicator of an increase in knee loading and risks of further damage to the joint cartilage (Brisson et al., 2017). Therefore, the outcome should be welcomed with caution.

5.2.1.3 Effect of the CM on temporal-spatial variables

In comparison with the baseline, the CM group achieved some improvements in the temporal-spatial gait parameters and daily walking steps after six-week treatment, which were also identified in the data of CN collected after six-week. After receiving

six-week treatment the CM group achieved improvement in mobility due to the increase in walking speed, step length, cadence, and daily walking steps. However, no significant difference was found between the six-week CM group and the six-week CN group. Large in-group effect size was observed in step length, medium in-group effect size was observed in walking speed, and small in-group effect sizes were observed in other temporal-spatial variables. Our observed in-group difference in step length and the daily number of steps were larger than the MDC (0.04 and 188.98, respectively) in the test-retest reliability study. Therefore, in-group differences in walking speed, step length, and the daily number of steps were likely to have practical importance.

The outcome of the current study conformed to the previous study (Zhu et al., 2015), which showed that after receiving two-week CM, the individuals with knee OA showed 5.0% increase in walking speed and 2.7% in step length due to the relief of the pain. The reduction of the pain scale can be explained by the reduction of the medial muscle co-contraction (VM/ST), which led to lower medial contact force during gait. Additionally, a statistical improvement in step length was also found in the six-week CM group when compared with the baseline, which indicated that the restriction of daily activity had been improved. However, no significant difference in cadence, double support time, stance phase percentage were found between groups.

Individuals with knee OA often are physically inactive (Paxton et al., 2015, Harding et al., 2014). One previous study (Lee et al., 2013) reported that over 20% of knee OA individuals showed physical inactivity. Therefore, any treatments that could help OA individuals recover or maintain a certain amount of physical activity would be regarded as effective. Although self-reported data such as WOMAC scores have been widely used as the primary outcomes in previous studies (Berman et al., 2004, Witt et al., 2005, Jubb et al, 2008, Lansdown et al., 2009), the data could be biased due to pain experience, and collecting the data of the physical activity during a fixed period before and after the interventions could improve the assessment to the outcomes, which could make the evaluation more objective and reasonable (Daugaard et al., 2018).

The results from the assessment post-six-week treatment demonstrated some increase from baseline, which were also identified in comparison with the data of CN collected after six-week. After six-week treatment, the increase of daily walking steps in comparison with the baseline indicated that the participants had better joint function due to the reduction in pain. However, there was no significant difference in daily walking steps between the CM and CN group at week six. When the pain relief was successfully achieved, the daily activities of the knee OA individuals should be gradually recovered to a level that is similar to the age-matching healthy counterparts, which may be well proved in future further follow-up studies and longer time of data collection might be needed. However, the increase of walking steps could be an indicator of an increase in knee loading during daily activity and risks of further damage to the joint cartilage (Brisson et al., 2017). Therefore, the outcome should be welcomed with caution.

5.2.1.4 Comparison of temporal-spatial variables between CH, AT, and CM

The six-week AT and CM demonstrated trend towards increased walking speed, step length, and the daily number of steps after six-week treatment when compared with the six-week CH. The reason could be explained by the significant improvement in clinical symptoms (WOMAC pain, stiffness, function, and total) which led to increased walking speed and improved daily activity. As previous studies (Tani et al., 2018, Astephen et al., 2008) indicated that the increased walking speed and step length were associated with the decrease of pain symptoms in individuals with knee OA. Therefore, it was understandable that the changes in walking speed, step length, and the daily number of steps were due to the relief of pain. Although the AT and CM significantly improved the clinical symptoms, improved walking speed, step length, and the daily number of steps in comparison with six-week CH, no significant improvement in temporal-spatial variable between groups was found. Therefore, a long-term study might be needed to clarify the difference in temporal-spatial variables.

5.2.2 Effect of the TCM treatments on other kinematic outcomes of the knee joint during the stance phase

5.2.2.1 Effect of the CH on other kinematic outcomes of the knee joint during the stance phase

As mentioned above, the CH achieved significant improvements in some clinical outcomes and temporal-spatial variables, to investigate the effect of changes in kinematic data during gait would help understand the correlations between them, thus, there was a critical need to understand the mechanical effects of the CH during gait. The knee joint angular movement is one of the key kinematic variables that reflects the joint mobility, we have good reasons to assume that the joint kinematic variables would show some changes when WOMAC stiffness and other clinical outcomes were found improved.

To our knowledge, this is the first study that has investigated both the clinical and biomechanical effects of CH in individuals with medial knee OA, therefore, no previous studies are available to compare with the results of this study. Same as the other measured parameters, the kinematic data of the measured knee joint, (i.e., peak knee joint angles and knee joint ROM) during stance in the sagittal, frontal, and transverse planes showed no differences between CH and CN groups at the baseline. After a six-week treatment period, the CH group achieved the relative-to-baseline increase in knee joint ROM in the sagittal plane during stance phase, which was accompanied with the decreased in knee flexion angle at initial contact and peak knee adduction angle during stance phase and increased knee flexion angle at early stance, except peak knee internal rotation angle, the other changes displayed small effect sizes, additionally, our observed in-group and between-group differences in kinematic variables were smaller than the MDC. Some of these changes in comparison with the CN group after six-week were confirmed as well. However, no statically significant difference was found. The changes of gait parameters in knee OA individuals have been widely reported, as the elucidation of the kinematics role in the progression of knee OA could help to develop interventions that can delay the progress of the disease. Astephen et al. (2008 a)

reported that compared with the asymptomatic subjects, the individuals with knee OA showed significantly decreased knee flexion angle at early stance phase as the reduction of the knee flexion angles were positively correlated with the knee flexion moment, which could help to reduce the loading during the stance phase. Kawaji et al. (2019) also reported that the increase in knee flexion angle at early stance was associated with the higher knee loading, as at the initial contact the vector of the GRF is anterior to the knee. Next, as the increase of knee flexion angle the GRF vector moves posterior to the knee, the external knee moment in the sagittal plane changes from extension to flexion. When there is an increased knee flexion at initial contact, the position of the GRF vector moves to the posterior of the knee earlier, which leads to the knee flexion moment occurs earlier, thereby increasing the knee loading. The result of the study showed that the CH group showed decreased knee flexion angle at initial contact when compared with the baseline, which could be simply regarded as a positive effect of six-week CH, as higher knee flexion at initial contact may lead to the knee flexion moment to begin earlier, thereby increasing the loading of the knee joint (Kawaji et al., 2019). Although the knee flexion angle at initial contact in the six-week CH patch was higher when compared with the six-week CN, this might be partially explained higher knee flexion angle at initial contact at baseline in the CH group when compared with the CN group.

The decreased knee adduction angle was also found in the six-week CH when compared with the baseline and six-week CN, which indicated that the knee stability might be improved during stance phase by the CH due to the improvements of clinical symptoms and the decreased medial muscle co-contraction, as mentioned before, the greater muscle co-contraction around the knee is due to the instability of the joint during the dynamic condition, thus, the decreased knee adduction angle can partially explain the decrease of the muscle co-contraction after receiving six-week CH, this might be explained by the FNZG acted as the knee tape for unloading the soft tissues and improving joint alignment (Wang et al., 2012). Hinman et al. (2008) showed that the tape around the knee could help to relieve the pain by improving the alignment of the knee which led to lower mechanical loading at the knee during gait. In the current study,

the FNZG covered the pain area around the knee which might act as the knee tape, therefore, the improvement of pain symptoms might have a relationship with that.

The six-week CH showed increased internal rotation and decreased external rotation angle during stance phase when compared with the baseline, however, compared with the six-week CN the external rotation angle was decreased. Although Fukaya et al. (2015) indicated that the increased internal rotation angle during the loading response phase was associated with increased knee adduction degree which leads to higher loading at the knee during gait, in the current study, due to the FNZG around the knee the alignment of the knee has been improved, therefore, the higher internal movement of the knee in the current study may not influence the loading at the medial compartment of the tibia and absorbing the loading during stance phase.

Although no significant improvement in knee flexion angles at initial contact and early stance phase was found after a six-week CH, knee joint ROM during stance phase in the sagittal plane was improved, which indicated that the improvements of the symptoms were associated with the kinematics variables.

5.2.2.2 Effect of the AT on other kinematic outcomes of the knee joint during the stance phase

As mentioned above, the AT achieved significant improvements in some clinical outcomes and temporal-spatial variables. To investigate the effect of changes in kinematic data during gait would help understand the correlations between them, thus, there was a critical need to understand the mechanical effects of the AT during gait.

The knee joint angular movement is one of the key kinematic variables that reflect joint mobility, we have good reasons to assume that the joint kinematic variables would show some changes when clinical outcomes were found improved. Same as the other measured parameters, the kinematic data of the measured knee joint (i.e., peak knee joint angle and knee joint ROM in the sagittal, frontal, and transverse planes) showed

no differences between the AT and CN groups at the baseline.

After six-week treatment, the AT group achieved the relative-to-baseline increase in knee joint ROM in the sagittal and transverse planes during stance, which were accompanied with decreased in peak knee flexion angle in early stance and peak knee adduction angle during stance phase. These changes in comparison with the CN group after six-week were confirmed as well. However, only the increase in knee joint ROM in the sagittal plane was statistically significant with large effect size, the other changes were not statically significant. Interestingly, our observed in-group and between-group differences in knee joint ROM in the sagittal during stance phase were larger than the MDC (4.95) in the test-retest reliability study, therefore, the improvement in ROM of knee joint in the sagittal plane might be caused by the AT rather than the measurement error.

The changes of gait parameters in knee OA individuals have been widely reported, as the elucidation of the kinematics role in the progression of knee OA could help to develop interventions that can delay the progress of the disease. Astephen et al. (2008 a) reported that compared with the asymptomatic subjects, the knee OA individuals showed significantly decreased knee flexion angles at the early stance phase as the reduction of the knee flexion angles at the early stance phase were positively correlated with the knee flexion moment, which could help to reduce the loading during the stance phase. Kawaji et al. (2019) also reported that an increase in knee flexion angle at early stance was associated with the higher knee loading, as at the initial contact the vector of the GRF is anterior to the knee. Next, as the increase of knee flexion angle the GRF vector moves posterior to the knee, and then the external knee moment changes from extension to flexion. When there is an increased knee flexion at initial contact, the position of the GRF vector moves to the posterior of the knee earlier, which leads to the knee flexion moment occurs earlier, thereby increasing the knee loading. The result of the study showed that the AT group showed decreased knee flexion angle at initial contact and increased knee joint ROM in the sagittal plane when compared with the

baseline and the six-week CN, which could be simply regarded as a positive effect of six-week AT, as higher knee flexion at initial contact may lead to the knee flexion moment to begin earlier, thereby increasing the loading (Kawaji et al., 2019). Although the six-week AT showed increased knee flexion moment, this could be explained by the improvement of the pain symptom, which led to higher walking speed and increased vertical GRF. However, the increased knee flexion moment might lead to a higher medial contact force (Walter et al., 2010). Therefore, the outcome should be welcomed with caution if the AT only functioned in terms of pain reduction.

The decreased knee adduction angle and decreased knee joint ROM in the frontal plane were also found in the six-week AT when compared with the baseline and six-week CN, which indicated that the knee stability might be improved during gait by the AT due to the improvement of clinical symptoms, as mentioned before, the greater muscle co-contraction around the knee is due to the instability of the joint during the dynamic condition, thus, the decreased knee adduction degree and knee joint ROM in the frontal plane can partially be explained by the decrease of the muscle co-contraction after receiving six-week AT.

The six-week AT showed increased internal rotation and external rotation angle when compared with the baseline, however, compared with the six-week CN both internal rotation and external rotation angle were decreased. Although Fukaya et al. (2015) indicated that the increased internal rotation angle during the initial stance phase was associated with increased knee adduction degree, in the current study the increased knee internal rotation degree was associated with the decreased knee adduction angle, the reason for that can be explained by the participants in Fukaya's (Fukaya et al., 2015) study were the individuals with severe medial knee OA or the difference in demographic characteristics (e.g. the percentage of female participants).

Although no significant improvement in knee flexion angles at initial contact and early stance phase was found after a six-week intervention, knee joint ROM in the sagittal

plane in the stance phase was markedly improved, which indicated that the improvement of the symptoms were associated with the kinematics variables.

5.2.2.3 Effect of the CM on other kinematic outcomes of the knee joint during the stance phase

The CM achieved significant improvements in some clinical outcomes and temporal-spatial variables. To investigate the effect of changes in kinematic variables during gait would help understand the correlations between them. Therefore, there was a critical need to understand the mechanical effects of the CM during gait.

The knee joint angular movement is one of the key kinematic variables that reflect joint mobility, we have good reasons to assume that the joint kinematic variables would show some changes when WOMAC stiffness and other clinical outcomes were found to be improved. Same as the other measured parameters, the kinematic data of the measured knee joint (i.e., peak knee joint angle and knee joint ROM in the sagittal, frontal, and transverse planes) showed no differences between the CM and CN groups at the baseline. After six-week treatment, the CM group achieved the relative-to-baseline increase in knee joint ROM in the sagittal, frontal, and transverse planes during stance phase, which were accompanied with decreased peak knee adduction angle and peak knee flexion angle in early stance. Some of these changes in comparison with the CN group after six-week were confirmed as well. However, only the increase in knee joint ROM in the sagittal plane was statistically significant with large effect size, the other changes were not statically significant. Interestingly, our observed in-group and between-group differences in the knee joint ROM in the sagittal plane during stance phase were larger than the MDC (4.95) in the test-retest reliability study, therefore, the improvement in knee joint ROM in the sagittal plane might be caused by the treatment itself rather than the measurement error.

The changes of gait parameters in knee OA individuals have been widely reported, as the elucidation of the kinematic role in the progression of knee OA could help to

develop interventions that can delay the progress of the disease. Astephen et al. (2008 a) reported that compared with the asymptomatic subjects, the knee OA subjects showed significantly decreased knee flexion angles, as the reduction of the knee flexion angles at the early stance phase were positively correlated with the knee flexion moment, which could help to reduce the loading during the stance phase. Kawaji et al. (2019) also demonstrated that the increased knee flexion angle during early stance was associated with the higher knee loading. As at the initial contact, the vector of the GRF is anterior to the knee. Due to the increase of knee flexion angle, the GRF vector moves posterior to the knee, the external knee moment in the sagittal plane changes from extension to flexion. When there is an increased knee flexion at initial contact, the position of the GRF vector moves to the posterior of the knee earlier, which leads to the knee flexion moment occurs earlier, thereby increasing the knee loading. The result of the current study demonstrated that the CM group showed decreased knee flexion angle at initial contact when compared with the baseline and the six-week CN, which could be simply regarded as a positive effect of six-week CM, as higher knee flexion at initial contact may lead to the knee flexion moment to begin earlier, thereby increasing the loading (Kawaji et al., 2019). Although the six-week CM showed increased knee flexion moment in comparison with the baseline, this might be due to the improvement of the pain symptom, which led to higher walking speed and increased vertical GRF.

The increased knee abduction and decreased knee adduction angle were also found in the six-week CM when compared with the baseline and six-week CN, which indicated that the knee stability might be improved during gait by the CM due to the improvements of clinical symptoms, and reduction in medial co-contraction, as mentioned before, the greater muscle co-contraction around the knee is due to the instability of the joint during the dynamic condition, thus, the decreased knee adduction degree can partly explain the decrease of the muscle co-contraction after receiving six-week CM.

The six-week CM showed decreased internal rotation and increased external rotation

angle when compared with the baseline, however, in comparison with the six-week CN, both internal rotation and external rotation angles were decreased. The decreased internal rotation angle can be regarded as a positive effect of the CM as it was associated with decreased knee adduction angle during stance. Fukaya et al. (2015) reported that the increased internal rotation angle during the loading response phase was associated with increased knee varus degree which leads to higher loading at the knee during gait. Therefore, the slower internal movement of the knee may help to decrease the contact force at the medial compartment of the knee, and making it easier to absorb the loading during gait.

Although no significant improvement in knee flexion angles at initial contact and early stance phase was found after a six-week intervention, knee joint ROM in the sagittal plane during stance phase was markedly improved, which indicated that the improvement of the symptoms was associated with the kinematic variables.

5.2.2.4 Comparison of other kinematic outcomes of the knee joint during the stance phase between CH, AT, and CM

The six-week AT and CM demonstrated trend towards increased knee joint ROM in the sagittal plane during the stance phase when compared with the six-week CH. The reason could be explained by the significant improvement in clinical symptoms (WOMAC pain, stiffness, function, and total), as there is a negative correlation between the knee joint ROM in the sagittal plane and pain symptoms (Astephen et al., 2008). Moreover, the six-week CM showed reduced knee flexion angle at the early stance in comparison with the six-week CH and six-week AT. The results indicated that CM might be helpful to reduce the loading at the knee during the early stance phase, as the previous study (Kawaji et al., 2019) demonstrated that the increase of knee flexion angle leads to the knee flexion moment occurring earlier and then leads to higher knee loading during gait. Although the AT and CM significantly improved the clinical symptoms and tendency to improve the kinematic variables in comparison with the six-week CH, no significant improvement in knee joint kinematic variable was found, this

might be due to OA severity level, sample size, and the duration of the treatment. Therefore long-term study might be needed to clarify the difference in kinematic variables between TCM treatments.

5.2.3 Effect of the TCM treatments on other kinetic outcomes of the knee joint during the stance phase

5.2.3.1 Effect of the CH on other kinetic outcomes of the knee joint during the stance phase

Since EKAM played a critical role in predicting the loading at the knee joint and represented about 60% loading in the medial compartment (Manal et al., 2015), it was singled out and assessed as a primary outcome. The other kinetic variables that represented about 20% of knee loading were calculated and presented as well in the current study, which were represented by the knee flexion moment and internal rotation moment. Walter et al. (2010) demonstrated that the reduction of EKAM cannot guarantee the reduction of the contact force in the medial compartment of the knee, the reason for that can be explained by the increased knee flexion moment during stance phase. When these knee moment components were analyzed together with EKAM, the assessment of the biomechanical effect of CH would be more comprehensive (Manal et al., 2015, Walter et al., 2010). The negative relationship between the knee internal rotation moment and the severity of knee OA has also been reported (Astephen et al., 2008a), thus the improvements of the clinical symptoms might influence the kinetics of the knee at the sagittal and transverse planes.

Compared with the baseline, the six-week CH showed increased knee flexion moment, this can be explained by the increased knee flexion degree at early stance due to the improved pain symptoms, increased walking speed, and vertical GRF. Creaby et al. (2013) showed that the greater knee flexion excursion was associated with increased knee flexion moment and higher vertical GRF. Some studies (Huang et al., 2008, Astephen et al., 2008 a, Deluzio et al., 2007) indicated that the individual with knee OA showed significant smaller knee flexion moment when compared with the healthy

counterpart as the individuals with knee OA adopts a gait pattern to increase the joint stability and to relieve the pain during gait (Heiden et al., 2009, Astephen et al., 2008a), and to develop a walking gait pattern to prevent the progression of the disease (Favre et al., 2016). In the current study, no comparison study against the healthy individuals was performed and no serious knee OA individuals (KL=4) were included, therefore, no contrast to healthy individuals was achieved. Interestingly, the six-week CH showed a smaller knee flexion moment in comparison with the six-week CN, this can partially be explained by the higher knee flexion moment in the CN group at the baseline. The increase identified in the knee flexion moment and knee extension moment after receiving a six-week CH indicated the load-bearing ability of the affected knee was improved even though the changes were yet statistically significant.

At baseline both the CH and CN groups showed smaller magnitude of 1st peak of GRF when compared with the 2nd peak of GRF which was very similar to the previous studies (Messier., 1994, Tang et al., 2005), the reason for that can be attributed to the knee OA individuals attempt to reduce the stress placed on the affected knee. Increases in the first and the second peak of GRF were found in the six-week CH when compared with the baseline. The changes were also found in comparison with six-week CN, which was a 1.0% increase in 1st peak of GRF, and the increase was associated with the pain relief and the increased walking speed, which was in agreement with Tang et al. (2005), that study also demonstrated that the individuals with knee OA showed improvements in first and the second peak of GRF due to the improvement of the pain symptom and the walking ability (e.g., walking speed).

Astephen et al. (2008a) demonstrated that the peak internal knee rotation moment in individuals with mild to severe knee OA ranged from 0.73 to 1.12 Nm/(Bw*Ht) % which was very close to the current study. The CH group achieved some improvements after a six-week treatment period in the kinetic parameters in comparison with the baseline. The increase in comparison with baseline in the knee flexion moment, the peak internal rotation moment, and the peak external rotation moment during stance

phase were confirmed. In comparison with the CN after six-week, the increase of knee extension moment and knee external rotation moment were confirmed. The increase in moments could be due to the increase in walking speed and walking step length, the increase in knee joint mobility that resulted in increased moment arm, or the higher moment at the baseline. The increase in knee joint moments demonstrated the recovery of the dynamic walking pattern, which were positive effect indicators, but they also indicated a potential increase in knee loading that might raise the risk of further damage. Therefore, it was important to let the knee OA individuals understand the treatment effect at the end of the study, which was done in the completion of the study. Although the CH significantly improved the clinical symptoms in individuals with knee OA, no significant improvement in knee joint moment was found, this might be due to OA severity level, sample size, and treatment term length.

The CH was aimed to reduce the pain and recover the dynamic walking pattern for individuals with knee OA. If the dynamic knee joint alignment could be improved, it is possible to expect reductions in knee moments while the walking speed is maintained. Based on what was achieved from this study, such effects were not confirmed. This could be a focus for future studies with a longer-term.

5.2.3.2 Effect of the AT on other kinetic outcomes of the knee joint during the stance phase

Compared with the baseline and six-week CN, the six-week AT showed increased knee flexion moment, this can be explained by the increased knee flexion degree at early stance due to the improved pain symptom, increased walking speed, and vertical GRF, as Creaby et al. (2013) showed that the greater knee flexion excursion was associated with increased knee flexion moment and higher vertical GRF. Some studies (Huang et al., 2008, Astephen et al., 2008, Deluzio et al., 2007) indicated that the individual with knee OA showed significant smaller knee flexion moment when compared with the healthy counterpart as the individuals with knee OA adopts a gait pattern to increase the joint stability and to relieve the pain during gait (Heiden et al., 2009, Astephen et

al., 2008a) and to develop a walking gait pattern to prevent the progression of the disease (Favre et al., 2016). In the current study, no comparison study against the healthy individuals was performed and no serious knee OA individuals (KL=4) were included, therefore, no contrast to health group results was achieved. The increase identified in the knee flexion moment and knee extension moment after receiving a six-week AT indicated the load-bearing ability of the affected knee was improved even though the changes were yet statistically significant.

At baseline both the AT and CN groups showed the smaller magnitude of the first peak of GRF when compared with the second peak of GRF which were very similar to the previous studies (Messier., 1994, Tang et al., 2005), the reason for that can be attributed to the individuals with knee OA attempted to reduce the stress placed on the affected knee. Significantly increased in the first and the second peak of GRF with medium to large effect sizes were found in six-week AT when compared with the baseline. Our observed in-group difference in the 1st GRF and 2nd GRF were larger than the MDC (0.04 and 0.02, respectively) in the test-retest reliability study. Therefore, the in-group difference in the 1st GRF and 2nd GRF were likely to have practical importance. The increase in GRF was also identified in comparison with the data of CN collected after six-week, however, only the increase in the 1st peak of GRF was statistically significant with a large effect size. Moreover, our observed between-group difference in the 1st GRF was larger than the MDC (0.04) in the test-retest reliability study. Therefore, the between-group difference in the 1st GRF was also likely to have practical importance. The increase in vertical GRF was associated with the pain relief and the higher walking speed, which was in agreement with Tang et al. (2005), whose study also demonstrated that individuals with knee OA showed significant improvements in the first and second peak of GRF due to the improvement of the pain symptom and the walking ability (e.g., walking speed).

Astephen et al. (2008a) demonstrated that the peak internal knee rotation moment in individuals with mild to severe knee OA ranged from 0.73 to 1.12 Nm/(Bw*Ht) %

which was very close to the current study. The AT group achieved some improvements after six-week treatment in the kinetic parameters in comparison with the baseline, which was also seen in the data of CN collected after six-week. The increase in comparison with baseline in knee flexion moment, peak extension moment, peak internal rotation moment, and peak external rotation moment at stance were confirmed. In comparison with the CN after six-week, similar increases were confirmed. The increase in moments could be due to either the increase in walking speed and walking step length or the increase in knee joint mobility that resulted in increased moment arm. The increase in knee joint moments demonstrated the recovery of the dynamic walking pattern, which were positive effect indicators, however, they also indicated a potential increase in knee loading that might raise the risk of further damage. Therefore, it was important to let the participants understand the treatment effect at the end of the study, which was done in the completion of the study. Although the AT significantly improved the clinical symptoms in individuals with knee OA, no significant improvement in knee joint moment was found, this might be due to OA severity leveland the duration of the treatment.

The AT was aimed to reduce the pain and recover the dynamic walking pattern for individuals with knee OA. If the dynamic knee joint alignment could be improved, it is possible to expect reductions in knee moments while the walking speed is maintained. Based on what was achieved from this study, such effects were not confirmed that could be due to varied reasons. This could be a focus for future studies with a long-term.

5.2.3.3 Effect of the CM on other kinetic outcomes of the knee joint during the stance phase

Compared with the baseline the six-week CM showed increased knee flexion moment, this can be explained by the increased knee flexion degree at early stance due to the improved pain symptoms, increased walking speed, and vertical GRF, as Creaby et al. (2013) showed that the greater knee flexion excursion was associated with increased knee flexion moment and higher vertical GRF. Previous studies (Huang et al., 2008,

Astephen et al., 2008, Deluzio et al., 2007) indicated that individuals with knee OA showed significant smaller knee flexion moment when compared with the healthy counterpart, as the individuals with knee OA adopt a gait pattern to increase the joint stability and to relieve the pain during gait (Heiden et al., 2009, Astephen et al., 2008a) and to develop a walking gait pattern to prevent the progression of the disease (Favre et al., 2016). In the current study, no comparison study against the healthy individuals was performed and no serious knee OA individuals (KL=4) were included, therefore, no contrast to healthy individuals results was achieved. Interestingly, the six-week CM showed a smaller knee flexion moment in comparison with the six-week CN, this can be explained by the higher knee flexion moment in the CN group at the baseline.

The increase identified in the knee flexion moment and knee extension moment after receiving a six-week CM indicated the load-bearing ability of the affected knee was improved even though the changes were yet statistically significant.

At baseline both the CM and CN groups showed smaller first peak of GRF when compared with the second peak of GRF, which was very similar to the previous studies (Messier., 1994, Tang et al., 2005), the reason for that can be attributed to the subjects' attempt to reduce the stress placed on the affected knee. The increase of first peak of GRF was found in the six-week CM when compared with the baseline. The improvement was also identified in comparison with six-week CN, moreover, the increase was associated with the relief of pain and the higher walking speed, which was in agreement with Tang et al. (2005), whose study also demonstrated that individuals with knee OA showed significant improvements in first and second peak of GRF due to the improvement of the pain symptom and the walking ability (e.g. walking speed).

Astephen et al. (2008a) demonstrated that the peak internal knee rotation moment in individuals with mild to severe knee OA ranged from 0.73 to 1.12 Nm/(Bw*Ht) % which was very close to the current study. The CM group achieved some improvements after six-week treatment in the kinetic parameters in comparison with the baseline. In

comparison with the baseline, higher knee flexion moment, knee extension moment, knee internal rotation moment, and knee external rotation moment at stance were confirmed. In comparison with the CN after six-week, the increase of knee extension moment and knee external rotation moment were confirmed. The increase in moments could be due to the increase in walking speed and walking step length, the increase in knee joint mobility that resulted in increased moment arm, or the higher moment at the baseline. The increase in knee joint moments demonstrated the recovery of the dynamic walking pattern, which were positive effect indicators, however, these changes also indicated a potential increase in knee loading that might raise the risk of further damage. Therefore, it was important to let the individuals with knee OA understand the treatment effect at the end of the study. Although the CM significantly improved the clinical symptoms in individuals with knee OA, no significant improvement in knee joint moment was found, this might be due to OA severity level and treatment term length.

The CM was aimed to reduce the pain and recover the dynamic walking pattern for individuals with knee OA. If the dynamic knee joint alignment could be improved, it is possible to expect reductions in knee moments while the walking speed is maintained. Based on what was achieved from this study, such effects were not confirmed that could be due to varied reasons. This could be a focus for future studies with a longer-term.

5.2.3.4 Comparison of other kinetic outcomes of the knee joint during the stance phase between CH, AT, and CM

The six-week AT and CM demonstrated trend towards increased knee flexion moment, knee internal rotation moment, knee external rotation moment, the first peak of GRF, and the second peak of GRF in comparison with six-week CH. The increased in knee flexion moment in six-week AT and CM can be explained by the increased knee flexion degree at early stance due to the improved pain symptom, increased walking speed, and vertical GRF, as Creaby et al. (2013) showed that the greater knee flexion excursion was associated with increased knee flexion moment and higher vertical GRF. At baseline both the CH, AT, and CN groups showed the smaller magnitude of the first

peak of GRF when compared with the second peak of GRF which was very similar to Tang's study (Tang et al., 2005), the reason for that can be attributed to the individuals with knee OA attempted to reduce the stress placed on the affected knee. Increased in the first peak of GRF was found in six-week AT and CM when compared with the six-week CH, moreover, the difference in the first peak of GRF between six-week AT and CH reached a significant level. The increase in vertical GRF was associated with pain relief and higher walking speed. Although the AT and CM significantly improved the clinical symptoms in individuals with knee OA, no significant improvement in knee joint moment and GRF was found, this might be due to OA severity level and the duration of the treatment. Therefore long-term study might be needed to clarify the difference in kinetics variables between TCM treatments.

5.3 Conclusion

This study aimed to confirm the short-term clinical and biomechanical effects of CH, AT, and CM in individuals with medial knee OA. The results demonstrated that both CH, AT, and CM could significantly improve the pain symptoms after receiving six-week treatment in comparison with the baseline. Moreover, the six-week AT and CM showed significant improvement in WOMAC pain, function, stiffness, and total in comparison with the six-week CN and CH, which indicated that the AT and CM might be more effective in the management of clinical symptoms caused by medial knee OA in the short term when compared with CH. Additionally, the improvements in clinical symptoms were associated with the changes in EKAM and muscle co-contraction. Both the CH, AT, CM showed a trend toward increased EKAM and KAAI in comparison with the baseline. A trend toward decreased medial muscle co-contraction was found in six-week CH, AT, and CM when compared with the baseline. Moreover, significantly decreased early and mid-stance VM/ST co-contraction were found in six-week CM when compared with the CN, CH, and AT, which indicated that the CM might help to reduce the loading at the knee during gait.

In conclusion, the results of this study confirmed the short-term clinical and biomechanical effects of CH, AT, and CM. However, a long-term study may be needed to provide more results to clarify the issues like some statistically insignificant variations.

Chapter 6 General conclusion and future study

6.1 General conclusion

This study aimed to identify the clinical and biomechanical effects of the CH, AT, and CM in comparison with a control group with the neutral flat insole, where the results could help to improve the understanding of both clinical and biomechanical effects and the possible underlying mechanism of the different TCM therapies in the management of knee OA.

In chapter two, the full background of knee OA and the relative research literature including the disease impact, the development, and the effect assessment of different treatments methods were reviewed. The review also included the incidence and global prevalence of OA and risk factors that may influence the progression of the OA. A section followed exploring the clinical assessment of OA, with a specific focus on knee and medial knee OA. Following this, the biomechanics of knee OA and in particular the EKAM and their correlations with OA progression were discussed. The second part of this chapter presented an overview of the current treatment options available for individuals with medial knee OA. Following this, current TCM treatments were reviewed and critiqued. This chapter concluded by formulating the hypotheses and aims of the study: to investigate both the clinical and biomechanical effects of TCM treatments in the management of medial knee OA.

In chapter three, the study methods were established, and test-retest reliability studies were conducted on healthy individuals and individuals with medial knee OA. The reliability studies were conducted to investigate the consistency of the instruments used to measure the biomechanical outcomes. This was to ensure that changes observed in the variables of interest were caused by the treatment itself and not by measurement error (e.g., markers and sensors placement, system operation, data procession, and computation). The test-retest reliability studies results revealed good to excellent data

reliability for most biomechanical outcomes.

In chapters four, the TCM study was conducted to determine whether three selected TCM groups reduced the WOMAC scales (pain, stiffness, function, and total), EKAM, and muscle co-contraction over a period of six weeks when compared with the baseline and no-treatment control group. The results demonstrated that both CH, AT, and CM significantly improved WOMAC pain and total in comparison with baseline after receiving six-week treatments. Moreover, the six-week AT and CM showed significant improvement in WOMAC pain, stiffness, function, and total in comparison with the baseline line, six-week CN, and CH. Therefore, the results indicated that the AT and CM might be more effective in improving the clinical symptoms in short term in comparison with CH. The AT and CM demonstrated trend toward higher EKAM1, EKAM2, and KAAI after six-week treatment when compared with the CH and CN. The reason could be explained by the significant improvement in clinical symptoms which led to higher walking speed, step length during gait. These changes demonstrated the recovery of the dynamic walking gait pattern as EKAM and other moment components are positively proportional to walking speed. However, these changes could also mean an increase in the risks of potential damage as the knee joint forces are positively proportional to EKAM and other moment components. Interestingly, most of the selected paired muscles in six-week CH, AT, and CM showed trend towards reduced co-contraction in comparison with the baseline. Moreover, the six-week CM demonstrated statistically significant reduced muscle co-contraction in early stance MV/ST and mid-stance MV/ST after six-week treatment when compared with the six-week CN, CH, and AT. The results indicated that the CM was more effective in improving the medial muscle co-contraction in short term in comparison with the CH and AT, which might lead to lower knee contact force during gait. Both the AT and CM showed significantly increased knee joint ROM in the sagittal plane in comparison with the baseline, which indicated that improvement of the symptoms was associated with the kinematics variables.

In conclusion, the results of this study confirmed the short-term clinical and biomechanical effects of CH, AT, and CM, which could further help to understand their potential biomechanical mechanism in the management of knee OA. However, a long-term study may be needed to provide more results to clarify the issues like some statistically insignificant variations.

6.2 The novelties of the study

No previous study has investigated both the clinical and biomechanical effects of the CH, AT, and CM in individuals with medial knee OA. Therefore, the original conrtributions of this study include:

(1) Investigating the short-term (six weeks) effect of three selected TCM treatments on all measures of the loading on the knee joint (EKAM and KAAI) and its relationship with clinical symptoms.

(2) Investigating the short-term (six weeks) effect of three selected TCM treatments on co-contraction of knee antagonist muscles in medial knee OA and its relationship with clinical symptoms.

(3) Investigating the short-term (six weeks) effect of three selected TCM treatments on daily activity and its relationship with clinical symptoms.

(4) Testing the reliability of gait and sEMG data in healthy individuals and individuals with medial knee OA.

Overall, this is the first study to explore both the clinical and biomechanical effects of CH, AT, and CM in individuals with medial knee OA, which could help to further understand the short-term (six weeks) clinical and biomechanical effects of the CH, AT, and CM in the management of medial knee OA. This study will therefore add much

knowledge to the current literature concerning the effects of TCM treatments in the management of medial knee OA.

6.3 The limitations of the study

To our knowledge this is the first study that investigated both the clinical and biomechanical effects of three selected TCM treatments in individuals with medial knee OA, however, we should notice that we faced some limitations during the study as follows:

(1) Firstly, the investigator who assessed clinical outcomes was not blinded by the interventions.

(2) The immediate biomechanical effects of TCM treatments were not evaluated.

(3) In the current study, the treatments were conducted over 6 weeks. However, it is not known if a long period (e.g., six months or twelve months) would show better results.

(4) Due to the time and budget limitation, the effects of TCM treatments on structural changes have not been investigated in the current study.

(5) The monitoring of daily activity is very important, as the increased daily activity may lead to more loading. Although the current study record the daily activity, the equipment used in this study was based on mobile phone step tracking, which was not validated due to several reasons, for example, the participants might not always keep the mobile phone with them during daily activity, and the accuracy of the equipment might not be precise enough.

6.4 Future study

In chapter four, both the AT and CM groups showed significant improvements in clinical symptoms when compared with the baseline and the six-week CN. The reduction of pain symptoms was associated with increased walking speed. Although the increase in walking speed can be regarded as a positive effect of the TCM treatments. However, the increased walking speed involved a higher knee flexion moment, EKAM,

and KAAI, which indicated higher medial contact force at the knee during the dynamic condition. Chehab et al. (2014) demonstrated that the EKAM has a great influence on the femoral cartilage, and the knee flexion moment has a great influence on the tibial cartilage. Therefore, the increased knee flexion moment, EKAM, and KAAI caused by the improvement of clinical symptoms might lead to the further development and progression of knee OA in long term. Such biomechanical variables could be a focus in future studies.

The biomechanical treatment such as LWI has been widely reported to decrease the EKAM in individuals with medial knee OA by shifting the COP more laterally and therefore reducing the perpendicular distance between the centre of the knee joint and the GRF at the frontal plane (knee joint moment lever arm on the frontal plane) (Jones et al., 2013, Reeves & Bowling. 2011). Unfortunately, some previous studies (Bennell et al., 2011, Campos et al., 2014, Baker et al., 2007) showed that the LWI failed to provide the symptomatic benefits when compared with flat control insoles in individuals with knee OA. A meta-analysis (Parkes et al., 2013) also indicated that compared with the neutral insole the LWI did not show a significant or clinically important association. Interestingly, the current study demonstrated that in comparison with the neutral insole both short-term AT and CM were very effective in the management of the clinical symptoms caused by knee OA, however, the knee joint loading increased during dynamic condition due to the relief of the clinical symptoms, thus, the combined treatment (e.g., AT plus LWI, or CM plus lLWI) might be a good option in the management of knee OA, which can not only improve the clinical symptoms but also decrease the loading at the knee.

In the current study, the TCM treatments were conducted over 6 weeks, and it is not known if a longer period (e.g., six months or twelve months) would provide better results. Therefore, future studies should investigate the effects of longer intervention periods to investigate if the pain and muscle co-contraction could be reduced by TCM treatments further.

Due to the time and budget limitation, the effect of TCM treatments on structural changes has not been investigated in the current study. The ultimate therapeutic goals in TCM treatment are not only to improve the clinical symptom and function ability but also to delay the progression and the development of the disease. For that reason, structural changes such as cartilage changes should be included as an outcome in the future study.

In summary, regarding the TCM treatments in the management of knee OA, this study is only the start in this area, and future studies are needed to investigate more in the effect of TCM treatments longitudinally with a larger sample. The future study could be an RCT study that investigates the effects of combined treatments (e.g., AT, LWI, and AT plus LWI) which can help to investigate the clinical and biomechanical effects of combined treatments in the management of knee OA.

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Appendix 1

Ethical approval 1

Research, Enterprise and Engagement
Ethical Approval Panel

Research Centres Support Team
G0.3 Joule House
University of Salford
M5 4WT

T +44(0)161 295 2280

www.salford.ac.uk/

9 January 2018

Dear Min,

RE: ETHICS APPLICATION–HSR1617-173–'The Assessment of the Effect of the Traditional Chinese Medicine and lateral wedge insole treatments to medial Knee Osteoarthritis.'

Based on the information you provided I am pleased to inform you that application HSR1617-173 has been approved.

If there are any changes to the project and/or its methodology, then please inform the Panel as soon as possible by contacting Health-ResearchEthics@salford.ac.uk

Yours sincerely,

Sue McAndrew
Chair of the Research Ethics Panel

Appendix 2

Ethical approval 2

中国注册临床试验伦理审查委员会
China Ethics Committee of Registering Clinical Trials
地址：四川大学华西医院、中国四川省成都市国学巷37号行政楼八角亭2092室
Address:West China Hospital, Sichuan University, No.37, Guo Xue Xiang, Chengdu, Sichuan, China
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中国注册临床试验伦理委员会

伦 理 审 查 报 告

研究题目：膝骨关节炎中医药综合外治法的随机对照研究
申请审查人：张旻/郑显新　　电话：18616986987
申请审查单位：上海中医药大学附属曙光医院
伦理审查文号：ChiECRCT 20170055

本伦理委员会按照中华人民共和国卫计委（原卫生部）《涉及人的生物医学研究伦理审查办法（试行）》（卫科教发〔2007〕17号）、《赫尔辛基宣言v.08》和《涉及人的生物医学研究国际伦理指南》对上海中医药大学附属曙光医院张旻/郑显新教授提交伦理审查的临床试验“膝骨关节炎中医药综合外治法的随机对照研究”进行审查，报告如下：

本伦理委员会评审专家独立审查后认为：该试验采用针灸+推拿+敷贴+矫形鞋垫中医药综合外治法与传统牵引治疗+安慰剂敷贴进行对照，评估中医药综合外治法治疗膝骨关节炎的疗效，不会增加受试者的安全风险；知情同意过程合理、充分；采用随机对照设计，可达到研究目的。

综上，该研究符合医学研究伦理，同意实施研究。

请研究者注意：

1. 本委员会审查专家提出了一些修改意见，请研究团队据此将研究计划修改后发回备案；
2. 每年应向本委员会提交书面进度报告；如有严重不良反应发生需向本委员会报告，以决定是否需中止试验。

申　明

中国注册临床试验伦理审查委员会是公益性独立机构伦理委员会，只负责审查临床试验的伦理学原则和研究设计的科学性，对是否可实施该临床试验提出建议，并要求临床试验在中国临床试验注册中心注册。

Appendix 3

WOMAC questionnaire

WOMAC pain	
Walking	
Climbing stairs	
Sleeping at night	
Resting	
Standing	
WOMAC stiffness	
In morning	
Occurring during the day	
WOMAC function	
Descending stairs	
Ascending stairs	
Rising from sitting	
Standing	
Bending to the floor	
Walking on flat	
Getting in/out of a car	
Going shopping	
Putting on socks	
Rising form bed	
Taking off socks	
Lying in bed	
Getting in/out of bath	
Sitting	
Getting on/off toilet	
Heavy domestic duties	
Light domestic duties	

The WOMAC measures three separate dimensions:
1) Pain (5 question) every question rate from 0-10, higher scores indicate worse pain, stiffness, and functional limitations.

2) Stiffness (2 questions) every question rates from 0-10, higher scores indicate worse pain, stiffness, and functional limitations.

3) Function (17 questions) every question rates from 0-10, higher scores indicate worse pain, stiffness, and functional limitations.

Appendix 4

Normality test results

One-Sample Kolmogorov-Smirnov Test

group			age	height	weight	BMI
1	N		15	15	15	15
	Normal Parameters[a]	Mean	61.6667	1.5993	61.9880	24.2727
		Std. Deviation	6.39940	.06273	7.44716	3.08745
	Most Extreme Differences	Absolute	.150	.154	.185	.179
		Positive	.091	.154	.131	.179
		Negative	-.150	-.132	-.185	-.084
	Kolmogorov-Smirnov Z		.581	.598	.718	.695
	Asymp. Sig. (2-tailed)		.888	.867	.681	.720
2	N		15	15	15	15
	Normal Parameters[a]	Mean	60.2667	1.6100	63.3707	24.5253
		Std. Deviation	5.98172	.06188	6.22215	2.76096
	Most Extreme Differences	Absolute	.152	.173	.117	.161
		Positive	.102	.173	.101	.137
		Negative	-.152	-.173	-.117	-.161
	Kolmogorov-Smirnov Z		.590	.671	.454	.622
	Asymp. Sig. (2-tailed)		.877	.759	.986	.834
3	N		15	15	15	15
	Normal Parameters[a]	Mean	61.8667	1.6067	62.7787	24.2553
		Std. Deviation	6.11633	.04995	8.94902	2.73490
	Most Extreme Differences	Absolute	.197	.127	.128	.174
		Positive	.183	.119	.084	.114
		Negative	-.197	-.127	-.128	-.174
	Kolmogorov-Smirnov Z		.763	.490	.495	.674
	Asymp. Sig. (2-tailed)		.606	.970	.967	.755
4	N		15	15	15	15
	Normal Parameters[a]	Mean	61.3333	1.6193	63.3553	24.0460
		Std. Deviation	6.16055	.05775	1.0597E1	2.81983
	Most Extreme Differences	Absolute	.212	.229	.180	.181
		Positive	.140	.229	.180	.181
		Negative	-.212	-.115	-.138	-.161
	Kolmogorov-Smirnov Z		.820	.886	.697	.699
	Asymp. Sig. (2-tailed)		.512	.413	.717	.712

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			pain	stiffness	function	total
1	N		15	15	15	15
	Normal Parameters[a]	Mean	16.1333	4.9333	47.7333	68.8000
		Std. Deviation	7.39562	1.94447	1.5158E1	2.1384E1
	Most Extreme Differences	Absolute	.167	.173	.253	.192
		Positive	.167	.173	.253	.192
		Negative	-.108	-.123	-.150	-.123
	Kolmogorov-Smirnov Z		.648	.671	.978	.745
	Asymp. Sig. (2-tailed)		.796	.759	.294	.636
2	N		15	15	15	15
	Normal Parameters[a]	Mean	16.8667	5.2000	45.4667	67.5333
		Std. Deviation	6.80196	2.21037	9.47076	1.5103E1
	Most Extreme Differences	Absolute	.139	.108	.153	.165
		Positive	.139	.107	.153	.165
		Negative	-.110	-.108	-.151	-.089
	Kolmogorov-Smirnov Z		.539	.418	.591	.640
	Asymp. Sig. (2-tailed)		.934	.995	.876	.807
3	N		15	15	15	15
	Normal Parameters[a]	Mean	17.2000	5.3333	44.4000	66.9333
		Std. Deviation	6.41650	1.71825	1.4583E1	1.7264E1
	Most Extreme Differences	Absolute	.210	.223	.104	.132
		Positive	.210	.216	.095	.103
		Negative	-.131	-.223	-.104	-.132
	Kolmogorov-Smirnov Z		.814	.864	.403	.511
	Asymp. Sig. (2-tailed)		.521	.444	.997	.956
4	N		15	15	15	15
	Normal Parameters[a]	Mean	15.6667	5.0667	43.7333	64.4667
		Std. Deviation	3.63842	3.03472	1.2032E1	1.4332E1
	Most Extreme Differences	Absolute	.106	.219	.222	.182
		Positive	.106	.219	.222	.182
		Negative	-.083	-.166	-.113	-.111
	Kolmogorov-Smirnov Z		.411	.847	.859	.704
	Asymp. Sig. (2-tailed)		.996	.470	.452	.704

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			pain	stiffness	function	total
1	N		15	15	15	15
	Normal Parameters[a]	Mean	15.4667	4.6667	46.4000	66.5333
		Std. Deviation	6.81245	1.83874	1.5131E1	2.0566E1
	Most Extreme Differences	Absolute	.142	.175	.197	.195
		Positive	.142	.175	.197	.195
		Negative	-.070	-.116	-.139	-.126
	Kolmogorov-Smirnov Z		.549	.677	.764	.756
	Asymp. Sig. (2-tailed)		.924	.749	.604	.617
2	N		15	15	15	15
	Normal Parameters[a]	Mean	10.2667	3.0667	33.3333	46.6667
		Std. Deviation	3.23964	1.22280	1.0111E1	1.1197E1
	Most Extreme Differences	Absolute	.177	.208	.188	.221
		Positive	.177	.208	.188	.221
		Negative	-.170	-.177	-.094	-.153
	Kolmogorov-Smirnov Z		.684	.807	.729	.858
	Asymp. Sig. (2-tailed)		.737	.532	.663	.454
3	N		15	15	15	15
	Normal Parameters[a]	Mean	14.8000	4.4000	40.2667	59.4667
		Std. Deviation	4.66292	2.41424	1.5979E1	1.9478E1
	Most Extreme Differences	Absolute	.150	.186	.107	.108
		Positive	.132	.186	.107	.108
		Negative	-.150	-.160	-.086	-.096
	Kolmogorov-Smirnov Z		.580	.719	.413	.418
	Asymp. Sig. (2-tailed)		.890	.679	.996	.995
4	N		15	15	15	15
	Normal Parameters[a]	Mean	10.4667	2.6667	32.8667	46.0000
		Std. Deviation	1.72654	1.04654	8.89516	9.41883
	Most Extreme Differences	Absolute	.221	.205	.183	.138
		Positive	.136	.205	.183	.138
		Negative	-.221	-.165	-.139	-.084
	Kolmogorov-Smirnov Z		.857	.792	.709	.534
	Asymp. Sig. (2-tailed)		.455	.556	.696	.938

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			EKAM1	EKAM2	KAAI
1	N		15	15	15
	Normal Parameters[a]	Mean	3.0353	2.1473	1.1280
		Std. Deviation	.56057	.55007	.27695
	Most Extreme Differences	Absolute	.130	.132	.115
		Positive	.121	.132	.079
		Negative	-.130	-.107	-.115
	Kolmogorov-Smirnov Z		.503	.511	.447
	Asymp. Sig. (2-tailed)		.962	.957	.988
2	N		15	15	15
	Normal Parameters[a]	Mean	3.0240	2.3213	1.1433
		Std. Deviation	.64840	.59165	.29400
	Most Extreme Differences	Absolute	.163	.161	.162
		Positive	.163	.161	.123
		Negative	-.072	-.097	-.162
	Kolmogorov-Smirnov Z		.631	.623	.628
	Asymp. Sig. (2-tailed)		.820	.833	.825
3	N		15	15	15
	Normal Parameters[a]	Mean	2.8660	2.0960	1.1133
		Std. Deviation	.60406	.52326	.26986
	Most Extreme Differences	Absolute	.122	.114	.194
		Positive	.122	.114	.194
		Negative	-.115	-.112	-.147
	Kolmogorov-Smirnov Z		.473	.442	.752
	Asymp. Sig. (2-tailed)		.979	.990	.624
4	N		15	15	15
	Normal Parameters[a]	Mean	2.9633	2.3080	1.1593
		Std. Deviation	.70995	.78485	.29548
	Most Extreme Differences	Absolute	.196	.162	.154
		Positive	.196	.162	.153
		Negative	-.153	-.092	-.154
	Kolmogorov-Smirnov Z		.759	.628	.595
	Asymp. Sig. (2-tailed)		.612	.825	.871

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			EKAM1	EKAM2	KAAI
1	N		15	15	15
	Normal Parameters[a]	Mean	3.0127	2.2440	1.1727
		Std. Deviation	.51765	.59698	.25725
	Most Extreme Differences	Absolute	.190	.156	.104
		Positive	.124	.156	.104
		Negative	-.190	-.108	-.103
	Kolmogorov-Smirnov Z		.737	.604	.403
	Asymp. Sig. (2-tailed)		.649	.859	.997
2	N		15	15	15
	Normal Parameters[a]	Mean	3.4260	2.5760	1.2387
		Std. Deviation	.76193	.83592	.31373
	Most Extreme Differences	Absolute	.087	.118	.194
		Positive	.087	.104	.119
		Negative	-.080	-.118	-.194
	Kolmogorov-Smirnov Z		.339	.455	.750
	Asymp. Sig. (2-tailed)		1.000	.986	.626
3	N		15	15	15
	Normal Parameters[a]	Mean	2.9300	2.1313	1.1300
		Std. Deviation	.60165	.70134	.30533
	Most Extreme Differences	Absolute	.186	.158	.210
		Positive	.186	.158	.162
		Negative	-.109	-.129	-.210
	Kolmogorov-Smirnov Z		.722	.614	.813
	Asymp. Sig. (2-tailed)		.675	.846	.522
4	N		15	15	15
	Normal Parameters[a]	Mean	3.0587	2.2740	1.1840
		Std. Deviation	.75995	.84334	.28553
	Most Extreme Differences	Absolute	.259	.124	.175
		Positive	.259	.124	.175
		Negative	-.147	-.122	-.117
	Kolmogorov-Smirnov Z		1.003	.481	.678
	Asymp. Sig. (2-tailed)		.267	.975	.748

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			TA_MG_E	TA_MG_M	TA_MG_L
1	N		15	15	15
	Normal Parameters[a]	Mean	16.3700	15.0500	6.5507
		Std. Deviation	5.29232	13.51726	2.79676
	Most Extreme Differences	Absolute	.141	.275	.150
		Positive	.141	.275	.150
		Negative	-.087	-.188	-.108
	Kolmogorov-Smirnov Z		.546	1.066	.583
	Asymp. Sig. (2-tailed)		.927	.206	.886
2	N		15	15	15
	Normal Parameters[a]	Mean	15.6967	12.1907	7.9900
		Std. Deviation	7.08019	7.45541	3.36842
	Most Extreme Differences	Absolute	.179	.186	.161
		Positive	.124	.186	.161
		Negative	-.179	-.131	-.119
	Kolmogorov-Smirnov Z		.693	.720	.623
	Asymp. Sig. (2-tailed)		.722	.677	.833
3	N		15	15	15
	Normal Parameters[a]	Mean	18.1360	14.0380	7.3180
		Std. Deviation	11.84133	8.03084	3.15138
	Most Extreme Differences	Absolute	.169	.212	.248
		Positive	.169	.212	.248
		Negative	-.100	-.127	-.164
	Kolmogorov-Smirnov Z		.654	.821	.960
	Asymp. Sig. (2-tailed)		.786	.511	.315
4	N		15	15	15
	Normal Parameters[a]	Mean	13.6913	9.9053	5.9767
		Std. Deviation	6.25533	5.55937	3.01799
	Most Extreme Differences	Absolute	.166	.214	.082
		Positive	.166	.214	.073
		Negative	-.134	-.117	-.082
	Kolmogorov-Smirnov Z		.641	.828	.319
	Asymp. Sig. (2-tailed)		.805	.499	1.000

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			TA_MG_E	TA_MG_M	TA_MG_L
1	N		15	15	15
	Normal Parameters[a]	Mean	16.1367	15.7387	6.0073
		Std. Deviation	5.31517	11.83722	2.65393
	Most Extreme Differences	Absolute	.158	.186	.174
		Positive	.158	.186	.174
		Negative	-.124	-.152	-.081
	Kolmogorov-Smirnov Z		.611	.719	.673
	Asymp. Sig. (2-tailed)		.850	.679	.755
2	N		15	15	15
	Normal Parameters[a]	Mean	16.3727	14.6520	8.3247
		Std. Deviation	7.51457	9.10105	4.69866
	Most Extreme Differences	Absolute	.138	.126	.155
		Positive	.138	.124	.155
		Negative	-.135	-.126	-.107
	Kolmogorov-Smirnov Z		.534	.488	.602
	Asymp. Sig. (2-tailed)		.938	.971	.862
3	N		15	15	15
	Normal Parameters[a]	Mean	16.9633	14.2240	7.5900
		Std. Deviation	9.21376	7.08957	2.43111
	Most Extreme Differences	Absolute	.137	.154	.149
		Positive	.137	.154	.149
		Negative	-.080	-.104	-.103
	Kolmogorov-Smirnov Z		.532	.596	.579
	Asymp. Sig. (2-tailed)		.940	.870	.891
4	N		15	15	15
	Normal Parameters[a]	Mean	17.8207	11.2193	7.8387
		Std. Deviation	7.73324	6.53415	6.15670
	Most Extreme Differences	Absolute	.159	.223	.331
		Positive	.144	.223	.331
		Negative	-.159	-.164	-.233
	Kolmogorov-Smirnov Z		.615	.863	1.281
	Asymp. Sig. (2-tailed)		.844	.446	.075

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VL_BF_E	VL_BF_M	VL_BF_L
1	N		15	15	15
	Normal Parameters[a]	Mean	31.7687	9.8740	5.2307
		Std. Deviation	14.80881	7.38134	2.97093
	Most Extreme Differences	Absolute	.093	.256	.249
		Positive	.093	.256	.249
		Negative	-.082	-.171	-.150
	Kolmogorov-Smirnov Z		.361	.993	.966
	Asymp. Sig. (2-tailed)		.999	.277	.309
2	N		15	15	15
	Normal Parameters[a]	Mean	29.5547	10.9533	5.4160
		Std. Deviation	19.83080	8.68113	3.56865
	Most Extreme Differences	Absolute	.192	.245	.294
		Positive	.192	.245	.294
		Negative	-.153	-.154	-.190
	Kolmogorov-Smirnov Z		.744	.948	1.138
	Asymp. Sig. (2-tailed)		.638	.329	.150
3	N		15	15	15
	Normal Parameters[a]	Mean	28.8420	9.1827	5.6727
		Std. Deviation	19.01639	5.09414	3.62030
	Most Extreme Differences	Absolute	.220	.140	.205
		Positive	.220	.140	.205
		Negative	-.137	-.093	-.166
	Kolmogorov-Smirnov Z		.851	.543	.793
	Asymp. Sig. (2-tailed)		.464	.929	.555
4	N		15	15	15
	Normal Parameters[a]	Mean	27.8867	7.8407	6.3093
		Std. Deviation	12.94609	4.22987	5.23353
	Most Extreme Differences	Absolute	.231	.190	.355
		Positive	.231	.190	.355
		Negative	-.125	-.117	-.235
	Kolmogorov-Smirnov Z		.895	.737	1.374
	Asymp. Sig. (2-tailed)		.399	.649	.046

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VL_BF_E	VL_BF_M	VL_BF_L
1	N		15	15	15
	Normal Parameters[a]	Mean	29.5880	8.7347	5.0700
		Std. Deviation	14.49121	6.98681	3.07920
	Most Extreme Differences	Absolute	.206	.285	.187
		Positive	.206	.285	.187
		Negative	-.115	-.215	-.126
	Kolmogorov-Smirnov Z		.797	1.105	.724
	Asymp. Sig. (2-tailed)		.548	.174	.671
2	N		15	15	15
	Normal Parameters[a]	Mean	26.3567	8.4653	4.2780
		Std. Deviation	14.96832	8.30180	2.15202
	Most Extreme Differences	Absolute	.150	.272	.216
		Positive	.150	.272	.216
		Negative	-.100	-.220	-.155
	Kolmogorov-Smirnov Z		.580	1.052	.838
	Asymp. Sig. (2-tailed)		.889	.218	.484
3	N		15	15	15
	Normal Parameters[a]	Mean	28.2320	9.3107	6.3507
		Std. Deviation	20.63089	6.74451	3.12229
	Most Extreme Differences	Absolute	.264	.264	.140
		Positive	.264	.264	.140
		Negative	-.209	-.161	-.088
	Kolmogorov-Smirnov Z		1.021	1.022	.541
	Asymp. Sig. (2-tailed)		.248	.248	.931
4	N		15	15	15
	Normal Parameters[a]	Mean	23.0007	6.2060	5.2827
		Std. Deviation	11.97200	3.66725	3.28555
	Most Extreme Differences	Absolute	.198	.173	.259
		Positive	.198	.173	.259
		Negative	-.107	-.106	-.106
	Kolmogorov-Smirnov Z		.766	.671	1.004
	Asymp. Sig. (2-tailed)		.601	.759	.266

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VL_LG_E	VL_LG_M	VL_LG_L
1	N		15	15	15
	Normal Parameters[a]	Mean	15.1180	13.6087	5.4953
		Std. Deviation	10.56174	9.90909	4.64105
	Most Extreme Differences	Absolute	.224	.176	.225
		Positive	.224	.176	.225
		Negative	-.175	-.144	-.199
	Kolmogorov-Smirnov Z		.866	.681	.870
	Asymp. Sig. (2-tailed)		.441	.743	.436
2	N		15	15	15
	Normal Parameters[a]	Mean	15.9687	14.7533	7.4040
		Std. Deviation	12.38879	8.69497	5.16147
	Most Extreme Differences	Absolute	.264	.233	.278
		Positive	.264	.233	.278
		Negative	-.160	-.200	-.168
	Kolmogorov-Smirnov Z		1.021	.902	1.078
	Asymp. Sig. (2-tailed)		.249	.390	.196
3	N		15	15	15
	Normal Parameters[a]	Mean	13.5980	12.2673	6.2013
		Std. Deviation	6.87098	5.09925	3.24484
	Most Extreme Differences	Absolute	.239	.137	.174
		Positive	.239	.105	.174
		Negative	-.128	-.137	-.109
	Kolmogorov-Smirnov Z		.924	.529	.676
	Asymp. Sig. (2-tailed)		.360	.943	.751
4	N		15	15	15
	Normal Parameters[a]	Mean	13.8667	13.3013	6.7340
		Std. Deviation	10.86892	9.57016	4.55981
	Most Extreme Differences	Absolute	.310	.305	.294
		Positive	.310	.305	.294
		Negative	-.200	-.170	-.187
	Kolmogorov-Smirnov Z		1.201	1.182	1.139
	Asymp. Sig. (2-tailed)		.111	.122	.149

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VL_LG_E	VL_LG_M	VL_LG_L
1	N		15	15	15
	Normal Parameters[a]	Mean	13.6520	12.7927	4.7573
		Std. Deviation	9.11487	9.14504	3.09294
	Most Extreme Differences	Absolute	.175	.167	.184
		Positive	.175	.164	.184
		Negative	-.147	-.167	-.161
	Kolmogorov-Smirnov Z		.677	.646	.713
	Asymp. Sig. (2-tailed)		.748	.798	.690
2	N		15	15	15
	Normal Parameters[a]	Mean	13.6067	12.4760	6.2267
		Std. Deviation	6.80458	9.35110	4.55951
	Most Extreme Differences	Absolute	.170	.219	.249
		Positive	.125	.219	.249
		Negative	-.170	-.164	-.140
	Kolmogorov-Smirnov Z		.660	.849	.965
	Asymp. Sig. (2-tailed)		.777	.467	.310
3	N		15	15	15
	Normal Parameters[a]	Mean	14.0993	12.2787	6.6213
		Std. Deviation	5.98101	5.90874	2.43998
	Most Extreme Differences	Absolute	.143	.105	.206
		Positive	.143	.105	.206
		Negative	-.087	-.066	-.118
	Kolmogorov-Smirnov Z		.556	.407	.797
	Asymp. Sig. (2-tailed)		.917	.996	.549
4	N		15	15	15
	Normal Parameters[a]	Mean	10.7087	10.0393	5.5700
		Std. Deviation	7.29491	7.81036	4.02683
	Most Extreme Differences	Absolute	.246	.200	.208
		Positive	.246	.200	.208
		Negative	-.194	-.128	-.129
	Kolmogorov-Smirnov Z		.953	.774	.804
	Asymp. Sig. (2-tailed)		.324	.587	.537

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VM_MG_E	VM_MG_M	VM_MG_L
1	N		15	15	15
	Normal Parameters[a]	Mean	18.6287	8.2687	7.2553
		Std. Deviation	9.31352	6.78041	7.92825
	Most Extreme Differences	Absolute	.145	.243	.332
		Positive	.145	.243	.332
		Negative	-.109	-.223	-.252
	Kolmogorov-Smirnov Z		.562	.942	1.287
	Asymp. Sig. (2-tailed)		.910	.337	.073
2	N		15	15	15
	Normal Parameters[a]	Mean	16.7700	9.9060	9.0827
		Std. Deviation	11.24024	6.77988	4.81439
	Most Extreme Differences	Absolute	.333	.252	.239
		Positive	.333	.252	.239
		Negative	-.170	-.185	-.139
	Kolmogorov-Smirnov Z		1.290	.976	.924
	Asymp. Sig. (2-tailed)		.072	.296	.360
3	N		15	15	15
	Normal Parameters[a]	Mean	17.1167	10.5687	7.0427
		Std. Deviation	9.28205	9.55411	4.06971
	Most Extreme Differences	Absolute	.154	.221	.188
		Positive	.154	.221	.188
		Negative	-.143	-.191	-.180
	Kolmogorov-Smirnov Z		.597	.856	.729
	Asymp. Sig. (2-tailed)		.869	.456	.662
4	N		15	15	15
	Normal Parameters[a]	Mean	16.2073	8.9120	8.1860
		Std. Deviation	7.34840	6.58568	4.25919
	Most Extreme Differences	Absolute	.145	.242	.260
		Positive	.125	.242	.260
		Negative	-.145	-.195	-.124
	Kolmogorov-Smirnov Z		.560	.937	1.007
	Asymp. Sig. (2-tailed)		.913	.343	.262

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VM_MG_E	VM_MG_M	VM_MG_L
1	N		15	15	15
	Normal Parameters[a]	Mean	19.8140	9.8047	8.8513
		Std. Deviation	10.51004	5.84974	6.89627
	Most Extreme Differences	Absolute	.201	.165	.271
		Positive	.201	.165	.271
		Negative	-.106	-.135	-.179
	Kolmogorov-Smirnov Z		.779	.638	1.048
	Asymp. Sig. (2-tailed)		.579	.810	.222
2	N		15	15	15
	Normal Parameters[a]	Mean	15.7253	7.9700	7.0673
		Std. Deviation	7.58288	7.73678	3.94697
	Most Extreme Differences	Absolute	.157	.285	.207
		Positive	.145	.285	.207
		Negative	-.157	-.226	-.134
	Kolmogorov-Smirnov Z		.608	1.105	.800
	Asymp. Sig. (2-tailed)		.854	.174	.544
3	N		15	15	15
	Normal Parameters[a]	Mean	16.2167	10.5473	8.1153
		Std. Deviation	9.39795	8.83842	4.07579
	Most Extreme Differences	Absolute	.136	.246	.142
		Positive	.129	.246	.134
		Negative	-.136	-.180	-.142
	Kolmogorov-Smirnov Z		.526	.951	.550
	Asymp. Sig. (2-tailed)		.945	.326	.923
4	N		15	15	15
	Normal Parameters[a]	Mean	13.9813	6.9060	5.6187
		Std. Deviation	7.81881	5.15261	3.91117
	Most Extreme Differences	Absolute	.167	.269	.228
		Positive	.167	.269	.228
		Negative	-.078	-.143	-.182
	Kolmogorov-Smirnov Z		.646	1.042	.883
	Asymp. Sig. (2-tailed)		.799	.228	.417

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VM_ST_E	VM_ST_M	VM_ST_L
1	N		15	15	15
	Normal Parameters[a]	Mean	26.6400	5.8440	5.3873
		Std. Deviation	9.68308	2.07473	2.89032
	Most Extreme Differences	Absolute	.116	.133	.182
		Positive	.116	.133	.182
		Negative	-.076	-.111	-.107
	Kolmogorov-Smirnov Z		.449	.515	.703
	Asymp. Sig. (2-tailed)		.988	.953	.706
2	N		15	15	15
	Normal Parameters[a]	Mean	24.9953	6.5560	5.8147
		Std. Deviation	11.87103	2.75136	2.10082
	Most Extreme Differences	Absolute	.200	.168	.206
		Positive	.200	.168	.206
		Negative	-.104	-.106	-.110
	Kolmogorov-Smirnov Z		.775	.650	.797
	Asymp. Sig. (2-tailed)		.586	.792	.549
3	N		15	15	15
	Normal Parameters[a]	Mean	24.0613	6.3387	6.2953
		Std. Deviation	13.92063	3.67835	2.42160
	Most Extreme Differences	Absolute	.211	.258	.229
		Positive	.211	.258	.229
		Negative	-.140	-.171	-.133
	Kolmogorov-Smirnov Z		.818	1.001	.886
	Asymp. Sig. (2-tailed)		.516	.269	.413
4	N		15	15	15
	Normal Parameters[a]	Mean	25.6460	5.9420	5.3700
		Std. Deviation	12.73081	2.73199	2.68304
	Most Extreme Differences	Absolute	.256	.129	.153
		Positive	.256	.129	.142
		Negative	-.124	-.079	-.153
	Kolmogorov-Smirnov Z		.992	.500	.591
	Asymp. Sig. (2-tailed)		.279	.964	.876

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			VM_ST_E	VM_ST_M	VM_ST_L
1	N		15	15	15
	Normal Parameters[a]	Mean	27.0793	7.1027	6.0420
		Std. Deviation	8.39481	3.68183	2.98125
	Most Extreme Differences	Absolute	.161	.136	.212
		Positive	.161	.136	.212
		Negative	-.155	-.111	-.133
	Kolmogorov-Smirnov Z		.625	.527	.823
	Asymp. Sig. (2-tailed)		.829	.944	.507
2	N		15	15	15
	Normal Parameters[a]	Mean	22.3820	5.4660	4.9667
		Std. Deviation	10.70716	2.39467	2.21879
	Most Extreme Differences	Absolute	.162	.141	.218
		Positive	.162	.141	.218
		Negative	-.098	-.087	-.153
	Kolmogorov-Smirnov Z		.626	.547	.846
	Asymp. Sig. (2-tailed)		.829	.926	.472
3	N		15	15	15
	Normal Parameters[a]	Mean	23.4420	5.6147	7.1373
		Std. Deviation	12.55185	3.41926	3.43331
	Most Extreme Differences	Absolute	.330	.263	.152
		Positive	.330	.263	.135
		Negative	-.119	-.208	-.152
	Kolmogorov-Smirnov Z		1.279	1.019	.591
	Asymp. Sig. (2-tailed)		.076	.251	.877
4	N		15	15	15
	Normal Parameters[a]	Mean	14.2747	4.0667	3.7593
		Std. Deviation	3.70518	2.19988	2.10659
	Most Extreme Differences	Absolute	.094	.127	.229
		Positive	.094	.127	.229
		Negative	-.078	-.113	-.125
	Kolmogorov-Smirnov Z		.364	.491	.889
	Asymp. Sig. (2-tailed)		.999	.969	.409

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			steps
1	N		15
	Normal Parameters[a]	Mean	3.7083E3
		Std. Deviation	6.5612E2
	Most Extreme Differences	Absolute	.237
		Positive	.237
		Negative	-.159
	Kolmogorov-Smirnov Z		.919
	Asymp. Sig. (2-tailed)		.367
2	N		15
	Normal Parameters[a]	Mean	3.6793E3
		Std. Deviation	6.1330E2
	Most Extreme Differences	Absolute	.192
		Positive	.192
		Negative	-.178
	Kolmogorov-Smirnov Z		.744
	Asymp. Sig. (2-tailed)		.637
3	N		15
	Normal Parameters[a]	Mean	3.6927E3
		Std. Deviation	6.4560E2
	Most Extreme Differences	Absolute	.167
		Positive	.132
		Negative	-.167
	Kolmogorov-Smirnov Z		.647
	Asymp. Sig. (2-tailed)		.796
4	N		15
	Normal Parameters[a]	Mean	3.6858E3
		Std. Deviation	5.4347E2
	Most Extreme Differences	Absolute	.187
		Positive	.168
		Negative	-.187
	Kolmogorov-Smirnov Z		.725
	Asymp. Sig. (2-tailed)		.669

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			steps
1	N		15
	Normal Parameters[a]	Mean	3.6249E3
		Std. Deviation	6.0537E2
	Most Extreme Differences	Absolute	.178
		Positive	.178
		Negative	-.161
	Kolmogorov-Smirnov Z		.691
	Asymp. Sig. (2-tailed)		.727
2	N		15
	Normal Parameters[a]	Mean	3.9659E3
		Std. Deviation	4.1213E2
	Most Extreme Differences	Absolute	.170
		Positive	.102
		Negative	-.170
	Kolmogorov-Smirnov Z		.659
	Asymp. Sig. (2-tailed)		.779
3	N		15
	Normal Parameters[a]	Mean	3.7902E3
		Std. Deviation	5.1130E2
	Most Extreme Differences	Absolute	.161
		Positive	.161
		Negative	-.133
	Kolmogorov-Smirnov Z		.622
	Asymp. Sig. (2-tailed)		.834
4	N		15
	Normal Parameters[a]	Mean	3.9225E3
		Std. Deviation	6.6573E2
	Most Extreme Differences	Absolute	.170
		Positive	.132
		Negative	-.170
	Kolmogorov-Smirnov Z		.658
	Asymp. Sig. (2-tailed)		.779

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			speed	S_length	Cadence	SPper	DSper
1	N		15	15	15	15	15
	Normal Parameters[a]	Mean	1.0099	.5548	1.0847E2	60.5180	10.9907
		Std. Deviation	.12928	.06015	1.0343E1	1.53667	3.03192
	Most Extreme Differences	Absolute	.125	.099	.090	.136	.260
		Positive	.078	.099	.090	.083	.260
		Negative	-.125	-.095	-.067	-.136	-.115
	Kolmogorov-Smirnov Z		.485	.382	.347	.527	1.008
	Asymp. Sig. (2-tailed)		.973	.999	1.000	.944	.261
2	N		15	15	15	15	15
	Normal Parameters[a]	Mean	.9817	.5425	1.0753E2	60.9267	10.7547
		Std. Deviation	.15490	.05891	1.1350E1	1.58476	1.74011
	Most Extreme Differences	Absolute	.174	.122	.182	.197	.205
		Positive	.108	.076	.182	.197	.205
		Negative	-.174	-.122	-.119	-.103	-.166
	Kolmogorov-Smirnov Z		.675	.472	.704	.764	.795
	Asymp. Sig. (2-tailed)		.753	.979	.705	.603	.552
3	N		15	15	15	15	15
	Normal Parameters[a]	Mean	1.0238	.5430	1.1073E2	61.0987	11.1473
		Std. Deviation	.18157	.07621	9.80136	2.67845	2.15275
	Most Extreme Differences	Absolute	.225	.114	.139	.269	.199
		Positive	.109	.088	.115	.269	.199
		Negative	-.225	-.114	-.139	-.152	-.110
	Kolmogorov-Smirnov Z		.871	.440	.537	1.042	.770
	Asymp. Sig. (2-tailed)		.433	.990	.935	.227	.594
4	N		15	15	15	15	15
	Normal Parameters[a]	Mean	1.0117	.5493	1.0900E2	60.5120	11.0933
		Std. Deviation	.15379	.04677	1.0869E1	1.69732	2.44299
	Most Extreme Differences	Absolute	.109	.160	.126	.119	.248
		Positive	.109	.144	.126	.119	.248
		Negative	-.101	-.160	-.126	-.096	-.114
	Kolmogorov-Smirnov Z		.423	.621	.490	.459	.961
	Asymp. Sig. (2-tailed)		.994	.836	.970	.984	.314

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			speed	S_length	Cadence	SPper	DSper
1	N		15	15	15	15	15
	Normal Parameters[a]	Mean	1.0175	.5593	1.0867E2	60.4820	11.0320
		Std. Deviation	.12275	.05151	8.41484	2.06207	1.83664
	Most Extreme Differences	Absolute	.156	.154	.141	.198	.113
		Positive	.103	.148	.141	.198	.075
		Negative	-.156	-.154	-.137	-.095	-.113
	Kolmogorov-Smirnov Z		.605	.597	.547	.768	.438
	Asymp. Sig. (2-tailed)		.857	.868	.925	.597	.991
2	N		15	15	15	15	15
	Normal Parameters[a]	Mean	1.1344	.5915	1.1287E2	60.4767	9.8120
		Std. Deviation	.11780	.05179	5.80476	1.96378	1.70606
	Most Extreme Differences	Absolute	.193	.139	.159	.125	.176
		Positive	.141	.139	.159	.125	.176
		Negative	-.193	-.073	-.111	-.101	-.116
	Kolmogorov-Smirnov Z		.746	.540	.617	.484	.684
	Asymp. Sig. (2-tailed)		.634	.932	.841	.973	.738
3	N		15	15	15	15	15
	Normal Parameters[a]	Mean	1.0881	.5701	1.1353E2	60.2040	10.8887
		Std. Deviation	.13266	.06042	6.62103	1.80405	2.11983
	Most Extreme Differences	Absolute	.181	.171	.132	.118	.168
		Positive	.118	.171	.132	.118	.168
		Negative	-.181	-.120	-.076	-.113	-.084
	Kolmogorov-Smirnov Z		.703	.662	.510	.459	.652
	Asymp. Sig. (2-tailed)		.706	.773	.957	.984	.789
4	N		15	15	15	15	15
	Normal Parameters[a]	Mean	1.0977	.5872	1.1213E2	60.7540	10.8887
		Std. Deviation	.12078	.04613	8.28826	1.71070	1.03114
	Most Extreme Differences	Absolute	.117	.151	.146	.186	.127
		Positive	.117	.151	.137	.186	.108
		Negative	-.111	-.124	-.146	-.118	-.127
	Kolmogorov-Smirnov Z		.454	.583	.566	.721	.490
	Asymp. Sig. (2-tailed)		.986	.886	.905	.677	.970

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			PKF_IC	PKF_ES	Knee_ROM_X
1	N		15	15	15
	Normal Parameters[a]	Mean	8.1093	17.8040	36.5160
		Std. Deviation	5.42505	6.46637	7.39135
	Most Extreme Differences	Absolute	.123	.181	.162
		Positive	.106	.126	.122
		Negative	-.123	-.181	-.162
	Kolmogorov-Smirnov Z		.476	.701	.627
	Asymp. Sig. (2-tailed)		.977	.709	.826
2	N		15	15	15
	Normal Parameters[a]	Mean	7.6560	16.8087	36.8980
		Std. Deviation	6.35326	7.29165	7.68431
	Most Extreme Differences	Absolute	.132	.143	.146
		Positive	.132	.143	.119
		Negative	-.114	-.090	-.146
	Kolmogorov-Smirnov Z		.512	.554	.566
	Asymp. Sig. (2-tailed)		.956	.918	.906
3	N		15	15	15
	Normal Parameters[a]	Mean	9.0120	17.4420	36.0287
		Std. Deviation	3.70242	3.74453	9.80751
	Most Extreme Differences	Absolute	.148	.203	.203
		Positive	.148	.114	.110
		Negative	-.104	-.203	-.203
	Kolmogorov-Smirnov Z		.575	.787	.786
	Asymp. Sig. (2-tailed)		.895	.565	.567
4	N		15	15	15
	Normal Parameters[a]	Mean	6.3150	14.4533	37.8508
		Std. Deviation	3.99946	5.06960	6.31241
	Most Extreme Differences	Absolute	.176	.153	.226
		Positive	.169	.153	.114
		Negative	-.176	-.105	-.226
	Kolmogorov-Smirnov Z		.609	.593	.783
	Asymp. Sig. (2-tailed)		.853	.874	.573

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			PKF_IC	PKF_ES	Knee_ROM_X
1	N		15	15	15
	Normal Parameters[a]	Mean	7.5920	17.2040	37.3007
		Std. Deviation	4.49562	5.18818	7.00627
	Most Extreme Differences	Absolute	.145	.145	.136
		Positive	.145	.104	.082
		Negative	-.142	-.145	-.136
	Kolmogorov-Smirnov Z		.561	.560	.528
	Asymp. Sig. (2-tailed)		.911	.913	.943
2	N		15	15	15
	Normal Parameters[a]	Mean	7.0047	17.3653	43.5680
		Std. Deviation	5.80558	6.87002	6.58408
	Most Extreme Differences	Absolute	.185	.132	.154
		Positive	.109	.132	.154
		Negative	-.185	-.122	-.135
	Kolmogorov-Smirnov Z		.718	.511	.598
	Asymp. Sig. (2-tailed)		.682	.957	.867
3	N		15	15	15
	Normal Parameters[a]	Mean	8.9753	17.5380	37.8680
		Std. Deviation	3.07103	3.86788	7.99076
	Most Extreme Differences	Absolute	.187	.208	.196
		Positive	.148	.094	.119
		Negative	-.187	-.208	-.196
	Kolmogorov-Smirnov Z		.725	.806	.759
	Asymp. Sig. (2-tailed)		.669	.534	.613
4	N		15	15	15
	Normal Parameters[a]	Mean	5.6383	15.4520	43.5575
		Std. Deviation	2.75965	3.78732	4.85535
	Most Extreme Differences	Absolute	.105	.094	.151
		Positive	.103	.094	.151
		Negative	-.105	-.088	-.118
	Kolmogorov-Smirnov Z		.363	.365	.522
	Asymp. Sig. (2-tailed)		.999	.999	.948

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			KABD	KADD	Knee ROM Y
1	N		15	15	15
	Normal Parameters[a]	Mean	1.9393	-4.6453	6.5847
		Std. Deviation	4.37525	4.18965	3.13404
	Most Extreme Differences	Absolute	.103	.118	.238
		Positive	.103	.105	.238
		Negative	-.097	-.118	-.142
	Kolmogorov-Smirnov Z		.398	.456	.923
	Asymp. Sig. (2-tailed)		.997	.985	.361
2	N		15	15	15
	Normal Parameters[a]	Mean	2.9633	-3.8573	6.8193
		Std. Deviation	4.02790	3.74988	2.40775
	Most Extreme Differences	Absolute	.238	.100	.152
		Positive	.116	.095	.152
		Negative	-.238	-.100	-.123
	Kolmogorov-Smirnov Z		.920	.386	.587
	Asymp. Sig. (2-tailed)		.366	.998	.881
3	N		15	15	15
	Normal Parameters[a]	Mean	3.9640	-3.4313	7.3960
		Std. Deviation	3.16662	2.87993	4.24774
	Most Extreme Differences	Absolute	.176	.095	.169
		Positive	.176	.092	.169
		Negative	-.125	-.095	-.145
	Kolmogorov-Smirnov Z		.680	.369	.655
	Asymp. Sig. (2-tailed)		.744	.999	.784
4	N		15	15	15
	Normal Parameters[a]	Mean	3.0247	-3.6413	6.5347
		Std. Deviation	2.80762	3.31384	4.03798
	Most Extreme Differences	Absolute	.138	.160	.219
		Positive	.138	.112	.219
		Negative	-.090	-.160	-.185
	Kolmogorov-Smirnov Z		.533	.620	.848
	Asymp. Sig. (2-tailed)		.938	.837	.468

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			KABD	KADD	Knee ROM Y
1	N		15	15	15
	Normal Parameters[a]	Mean	2.9113	-3.9300	6.8413
		Std. Deviation	3.69383	4.15633	2.60365
	Most Extreme Differences	Absolute	.130	.265	.161
		Positive	.107	.155	.161
		Negative	-.130	-.265	-.071
	Kolmogorov-Smirnov Z		.505	1.027	.622
	Asymp. Sig. (2-tailed)		.961	.242	.834
2	N		15	15	15
	Normal Parameters[a]	Mean	3.1043	-3.0258	6.1300
		Std. Deviation	3.30206	4.02367	2.34144
	Most Extreme Differences	Absolute	.258	.229	.129
		Positive	.143	.107	.129
		Negative	-.258	-.229	-.122
	Kolmogorov-Smirnov Z		1.001	.885	.499
	Asymp. Sig. (2-tailed)		.269	.413	.964
3	N		15	15	15
	Normal Parameters[a]	Mean	3.7073	-2.6340	6.3407
		Std. Deviation	3.03152	2.55291	2.73784
	Most Extreme Differences	Absolute	.122	.146	.342
		Positive	.115	.118	.342
		Negative	-.122	-.146	-.211
	Kolmogorov-Smirnov Z		.472	.564	1.326
	Asymp. Sig. (2-tailed)		.979	.908	.060
4	N		15	15	15
	Normal Parameters[a]	Mean	3.4740	-3.0620	6.6647
		Std. Deviation	4.10046	2.49164	2.60677
	Most Extreme Differences	Absolute	.208	.131	.257
		Positive	.208	.131	.257
		Negative	-.135	-.095	-.171
	Kolmogorov-Smirnov Z		.806	.508	.995
	Asymp. Sig. (2-tailed)		.535	.958	.275

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			KIR	KER	Knee ROM Z
1	N		15	15	15
	Normal Parameters[a]	Mean	3.4033	-11.4493	14.8533
		Std. Deviation	5.49250	6.91268	5.79179
	Most Extreme Differences	Absolute	.202	.215	.148
		Positive	.089	.215	.148
		Negative	-.202	-.176	-.113
	Kolmogorov-Smirnov Z		.782	.832	.574
	Asymp. Sig. (2-tailed)		.573	.493	.897
2	N		15	15	15
	Normal Parameters[a]	Mean	2.6273	-11.6793	14.3060
		Std. Deviation	5.47518	5.88638	5.18522
	Most Extreme Differences	Absolute	.139	.160	.274
		Positive	.139	.160	.274
		Negative	-.098	-.145	-.168
	Kolmogorov-Smirnov Z		.539	.621	1.060
	Asymp. Sig. (2-tailed)		.934	.835	.211
3	N		15	15	15
	Normal Parameters[a]	Mean	3.8920	-9.1660	13.0593
		Std. Deviation	3.41604	4.11004	4.63289
	Most Extreme Differences	Absolute	.113	.172	.202
		Positive	.111	.100	.202
		Negative	-.113	-.172	-.115
	Kolmogorov-Smirnov Z		.436	.665	.784
	Asymp. Sig. (2-tailed)		.991	.768	.571
4	N		15	15	15
	Normal Parameters[a]	Mean	4.2053	-8.8360	13.0427
		Std. Deviation	5.45745	5.98809	3.31583
	Most Extreme Differences	Absolute	.177	.151	.167
		Positive	.122	.097	.167
		Negative	-.177	-.151	-.102
	Kolmogorov-Smirnov Z		.687	.585	.645
	Asymp. Sig. (2-tailed)		.733	.883	.799

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			PKF_IC	PKF_ES	Knee_ROM_X
1	N		15	15	15
	Normal Parameters[a]	Mean	4.1640	-11.9560	16.1207
		Std. Deviation	5.24330	5.65644	5.42668
	Most Extreme Differences	Absolute	.203	.179	.130
		Positive	.126	.123	.130
		Negative	-.203	-.179	-.100
	Kolmogorov-Smirnov Z		.787	.695	.502
	Asymp. Sig. (2-tailed)		.565	.720	.963
2	N		15	15	15
	Normal Parameters[a]	Mean	3.8053	-11.7207	15.5247
		Std. Deviation	5.36025	5.41257	4.73129
	Most Extreme Differences	Absolute	.158	.121	.123
		Positive	.122	.121	.123
		Negative	-.158	-.080	-.085
	Kolmogorov-Smirnov Z		.612	.469	.478
	Asymp. Sig. (2-tailed)		.848	.981	.976
3	N		15	15	15
	Normal Parameters[a]	Mean	5.4640	-9.1133	14.5800
		Std. Deviation	2.41625	4.60390	5.75986
	Most Extreme Differences	Absolute	.136	.128	.166
		Positive	.136	.128	.166
		Negative	-.113	-.099	-.123
	Kolmogorov-Smirnov Z		.526	.496	.643
	Asymp. Sig. (2-tailed)		.945	.966	.802
4	N		15	15	15
	Normal Parameters[a]	Mean	4.0167	-10.2693	14.2847
		Std. Deviation	5.64549	5.44134	5.06173
	Most Extreme Differences	Absolute	.110	.199	.132
		Positive	.110	.199	.132
		Negative	-.101	-.171	-.089
	Kolmogorov-Smirnov Z		.425	.771	.512
	Asymp. Sig. (2-tailed)		.994	.592	.956

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			KFM	KEM
1	N		15	15
	Normal Parameters[a]	Mean	2.4580	-2.1227
		Std. Deviation	1.35507	1.03648
	Most Extreme Differences	Absolute	.160	.174
		Positive	.160	.134
		Negative	-.127	-.174
	Kolmogorov-Smirnov Z		.620	.673
	Asymp. Sig. (2-tailed)		.836	.756
2	N		15	15
	Normal Parameters[a]	Mean	2.3767	-2.0027
		Std. Deviation	1.24272	.98000
	Most Extreme Differences	Absolute	.137	.200
		Positive	.137	.079
		Negative	-.077	-.200
	Kolmogorov-Smirnov Z		.529	.776
	Asymp. Sig. (2-tailed)		.942	.584
3	N		15	15
	Normal Parameters[a]	Mean	1.9520	-2.3787
		Std. Deviation	.78919	.98188
	Most Extreme Differences	Absolute	.132	.133
		Positive	.132	.133
		Negative	-.086	-.122
	Kolmogorov-Smirnov Z		.513	.514
	Asymp. Sig. (2-tailed)		.955	.954
4	N		15	15
	Normal Parameters[a]	Mean	2.0180	-2.0680
		Std. Deviation	.87249	.72728
	Most Extreme Differences	Absolute	.132	.141
		Positive	.132	.141
		Negative	-.129	-.086
	Kolmogorov-Smirnov Z		.511	.546
	Asymp. Sig. (2-tailed)		.956	.927

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			KFM	KEM
1	N		15	15
	Normal Parameters[a]	Mean	2.4087	-2.0953
		Std. Deviation	1.16544	.97663
	Most Extreme Differences	Absolute	.201	.139
		Positive	.201	.109
		Negative	-.111	-.139
	Kolmogorov-Smirnov Z		.779	.537
	Asymp. Sig. (2-tailed)		.579	.935
2	N		15	15
	Normal Parameters[a]	Mean	2.5933	-2.1273
		Std. Deviation	1.27305	.79194
	Most Extreme Differences	Absolute	.134	.214
		Positive	.127	.148
		Negative	-.134	-.214
	Kolmogorov-Smirnov Z		.520	.828
	Asymp. Sig. (2-tailed)		.950	.500
3	N		15	15
	Normal Parameters[a]	Mean	2.2060	-2.2893
		Std. Deviation	.92668	.89385
	Most Extreme Differences	Absolute	.158	.220
		Positive	.129	.105
		Negative	-.158	-.220
	Kolmogorov-Smirnov Z		.613	.851
	Asymp. Sig. (2-tailed)		.846	.464
4	N		15	15
	Normal Parameters[a]	Mean	2.3693	-2.3647
		Std. Deviation	.89501	.59747
	Most Extreme Differences	Absolute	.106	.185
		Positive	.106	.133
		Negative	-.096	-.185
	Kolmogorov-Smirnov Z		.411	.715
	Asymp. Sig. (2-tailed)		.996	.686

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			KIRM	KERM
1	N		15	15
	Normal Parameters[a]	Mean	.9393	-.5147
		Std. Deviation	.37446	.27715
	Most Extreme Differences	Absolute	.105	.126
		Positive	.105	.077
		Negative	-.098	-.126
	Kolmogorov-Smirnov Z		.409	.486
	Asymp. Sig. (2-tailed)		.996	.972
2	N		15	15
	Normal Parameters[a]	Mean	.8747	-.6587
		Std. Deviation	.45065	.31471
	Most Extreme Differences	Absolute	.164	.109
		Positive	.164	.077
		Negative	-.111	-.109
	Kolmogorov-Smirnov Z		.637	.423
	Asymp. Sig. (2-tailed)		.812	.994
3	N		15	15
	Normal Parameters[a]	Mean	.7727	-.6680
		Std. Deviation	.27146	.26966
	Most Extreme Differences	Absolute	.150	.136
		Positive	.150	.098
		Negative	-.079	-.136
	Kolmogorov-Smirnov Z		.580	.526
	Asymp. Sig. (2-tailed)		.890	.945
4	N		15	15
	Normal Parameters[a]	Mean	.7327	-.6660
		Std. Deviation	.34950	.29536
	Most Extreme Differences	Absolute	.156	.122
		Positive	.156	.081
		Negative	-.077	-.122
	Kolmogorov-Smirnov Z		.604	.474
	Asymp. Sig. (2-tailed)		.859	.978

a. Test distribution is Normal.

One-Sample Kolmogorov-Smirnov Test

group			KIRM	KERM
1	N		15	15
	Normal Parameters[a]	Mean	.9360	-.5567
		Std. Deviation	.35154	.32640
	Most Extreme Differences	Absolute	.133	.120
		Positive	.133	.076
		Negative	-.127	-.120
	Kolmogorov-Smirnov Z		.517	.466
	Asymp. Sig. (2-tailed)		.952	.982
2	N		15	15
	Normal Parameters[a]	Mean	.9673	-.7573
		Std. Deviation	.46180	.24300
	Most Extreme Differences	Absolute	.140	.129
		Positive	.140	.129
		Negative	-.128	-.116
	Kolmogorov-Smirnov Z		.543	.501
	Asymp. Sig. (2-tailed)		.930	.963
3	N		15	15
	Normal Parameters[a]	Mean	.7693	-.6813
		Std. Deviation	.33687	.31577
	Most Extreme Differences	Absolute	.152	.130
		Positive	.152	.107
		Negative	-.130	-.130
	Kolmogorov-Smirnov Z		.589	.505
	Asymp. Sig. (2-tailed)		.879	.961
4	N		15	15
	Normal Parameters[a]	Mean	.8207	-.7620
		Std. Deviation	.27660	.29960
	Most Extreme Differences	Absolute	.109	.183
		Positive	.065	.151
		Negative	-.109	-.183
	Kolmogorov-Smirnov Z		.421	.707
	Asymp. Sig. (2-tailed)		.994	.699

a. Test distribution is Normal.