The effects of rotational knee exercises on alignment, kinematics and medial meniscal extrusion in patients with knee osteoarthritis

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High validity of measuring the width and volume of medial meniscal extrusion three-dimensionally using an MRI-derived tibial model was accepted by *Journal of Experimental Orthopaedics*

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LIST OF ABBREVIATIONS

2D	two-dimensional
3D	three-dimensional
ACL	anterior cruciate ligament
ADL	activities of daily living
ANOVA	analysis of variance
BMI	body mass index
BW	body weight
CI	confidence interval
COP	center of pressure
CT	computed tomography
HR	hazard ratio
HT	height
ICC	interclass correlation coefficient
KAM	external knee adduction moment
KL	Kellgren-Lawrence
KOA	knee osteoarthritis
MM	medial meniscus
MME	medial meniscal extrusion
MMPRT	medial meniscus posterior root tear
MRI	magnetic resonance imaging
OAI	Osteoarthritis Initiative
OR	odds ratio
QOL	quality of life
RCT	randomized controlled trial
RRR	Rotation Restoration and Realignment
TKA	Total knee arthroplasty
US	United States
US	ultrasonography
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WORMS	Whole-Organ Magnetic Resonance Imaging Score

ABSTRACT

Knee osteoarthritis (KOA) is a common musculoskeletal disease that causes difficulties in activities of daily living. Prevalence of radiographic and symptomatic KOA in 2010 in the world was 3.8 [3.6, 4.1]%. Prevalence of KOA rises with age. In addition, increase of populations aged over 60 years old is expected. The number of populations globally aged over 60 years old was estimated to be 962 million in 2017 and would grow at a rate of about 3% per year. The number of patients suffered from KOA will increase in the future. Therefore, development of methods for preventing and treating KOA is a pressing need. One of evidenced-based methods for treating KOA is an exercise therapy. Effects of the exercise programs on KOA were reducing knee pain and improving physical functions. On the other hand, biomechanical risk factors for KOA progression involve varus knee alignment, medial meniscal extrusion (MME), and external knee adduction moment (KAM). However, effects of the exercise programs on biomechanical risk factors have not been understood. Therefore, the objectives of this study were to determine effects of an exercise therapy to improve 6 degrees-of-freedom knee alignment, to reduce MME, and/or to reduce KAM and symptoms.

A randomized controlled trial (RCT) was conducted in this study. Two interventions were applied to orthopaedic outpatients in a local rehabilitation hospital; a leg press activity with tibial internal rotation (Rotation Restoration and Realignment (RRR) program) and conventional exercise program without tibial internal rotation. The RCT showed that both the RRR program and conventional exercise program did not show significant difference in knee kinematics during stepping activity and the MME volume and MME width. Effects of the RRR program on knee kinematics, the MME volume or MME are not clear in patients with mild and moderate medial KOA. On the other hand, the RCT showed that both the RRR and conventional exercise programs improved knee pain, joint stiffness, and physical function in patients with mild and moderate medial KOA. 2nd KAM reduction by 13.2% in the RRR program was observed, which may be clinically significant in some patients. The RRR program with tibial internal rotation exercise

improves knee pain, joint stiffness, and disabilities in patients with mild and moderate medial KOA.

In conclusions, the exercise program with tibial internal rotational exercise is effective on improvement of knee pain, joint stiffness, and physical function in patients with mild and moderate medial KOA. Clinical significance of this study would be that the RRR program involving tibial internal rotation during a leg press activity is safe and effective on the symptoms of KOA. However, the biomechanical effects of the RRR program on the knee remains unanswered. Development of more effective exercise program to reduce KAM and improve knee kinematics would have social and clinical value to contribute to prevent KOA progression. Further studies on effects of the RRR program on knee kinematics and kinetics should be conducted.

CHAPTER 1

Specific Aims

Knee osteoarthritis (KOA) is a common musculoskeletal disease causing difficulties in activities of daily living. Prevalence of radiographic and symptomatic KOA in 1990 and 2010 in the world was (mean [95% confidence interval]) 3.8 [3.6, 4.0]% and 3.8 [3.6, 4.1]%, respectively [1]. Prevalence of KOA rises with age[2]. In addition, increase of populations aged over 60 years old is expected. The number of populations globally aged over 60 years old was estimated to be 962 million in 2017 and would grow at a rate of about 3% per year[3]. The number of patients suffered from KOA will increase in the future. Therefore, development of methods for preventing and treating KOA is a pressing need.

One of evidenced-based methods for treating KOA is an exercise therapy. Several kinds of exercise programs were recommended in various national or international guidelines[4-7]. Effects of the exercise programs on KOA were reducing knee pain and improving physical functions[8, 9]. On the other hand, biomechanical risk factors for KOA progression involve varus knee alignment[10, 11], medial meniscal extrusion (MME)[12, 13], and external knee adduction moment (KAM)[14, 15]. However, effects of the exercise programs on biomechanical risk factors have not been understood. The objective of this study were to determine effects of an exercise therapy to improve 6 degrees-of-freedom knee alignment, to reduce MME, and/or to reduce KAM and symptoms.

Abnormal knee alignment and kinematics may induce excessive stress onto the medial compartment of the femorotibial joint. External rotation, adduction, and posterior translation of the tibia were observed during squat activities in patients with moderate and severe KOA[16]. Adduction and lateral translation of the tibia were observed during stationary stepping activities in patients with severe KOA[17,

[18]. Lever arm of the knee joint in patients with KOA became longer than healthy adults[19]. In addition, KAM in patients with KOA became higher than healthy adults[19-21]. Adduction and lateral translation of the tibia may induce elongation of the lever arm, increase KAM, and worsen MME by pushing the medial meniscus medially. In previous studies, an exercise program with tibial internal rotation immediately reduced the visual distance between the medial femoral condyles in patients with Kellgren-Laurence (KL) grade I to III[22, 23]. Repeated contraction of the medial hamstrings may induce medialization of the tibia and improve adduction and external rotation position of the tibia, while quadriceps training may restore posterior translation of the tibia.

Hypotheses of this research project were that the exercise program with tibial internal rotation would reduce adduction, lateral and posterior translation of the tibia, MME, KAM and symptoms. In order to test these hypotheses, the measurement methods will be validated, and test the hypotheses using a randomized controlled study measuring knee alignment and kinematics, MME, and KAM before and after intervention between randomly allocated two exercise groups. To determine effects of exercise therapies on biomechanical risk factors for KOA would contribute development of methods for treating KOA.

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CHPTER 2

Literature Review

Introduction

Knee osteoarthritis (KOA) is a common musculoskeletal disease. KOA causes knee pain and difficulties in activities of daily living. In addition, effects of KOA on mental disorders[1-3] and internal medical diseases[4] have been focused. Prevalence of KOA increases with age[5]. Number of aged people was estimated to increase in the world for decades. These findings suggest that number of patients with KOA will rise in the future, and that impact of KOA on the society will become larger. Therefore, development of preventing and treating methods of KOA is a pressing need.

One of evidenced-based methods for treating KOA is an exercise therapy. Several kinds of exercise programs were recommended in various national or international guidelines[6-9]. Effects of the exercise programs on KOA were reducing knee pain and improving physical functions[10, 11]. On the other hand, biomechanical risk factors for KOA progression involve varus knee alignment[12, 13], medial meniscal extrusion (MME)[14, 15], and external knee adduction moment (KAM)[16, 17]. However, effects of the exercise programs on biomechanical risk factors have not been understood. Therefore, the objective of this review was to determine necessity for developing an exercise program to improve 6 degrees-of-freedom knee alignment, to reduce MME, and/or to reduce KAM and symptoms.

Epidemiology

Prevalence of symptomatic and radiographic KOA in 1990 and 2010 in the world were 3.8 [95% confidence interval 3.6, 4.0]% and 3.8 [3.6, 4.1]%, respectively[18]. The lowest prevalence in 2010 was in South Asia region; 1.8 [1.4, 2.3] % for males and 3.1 [2.5, 3.9]% for females. The highest prevalence was in Pacific Asia, high-income, region; 4.4 [3.5, 5.5]% for males and 7.5 [5.9, 9.3]% for females. The total number of symptomatic radiographic KOA in the United States (US) in 2011-2012 was estimated to be 15.1 [13.6, 16.8] million in 2011–2012, accounting for 7.3% of the total US population[19]. That of advanced symptomatic KOA, in other words Kellgren-Lawrence (KL)[20] grade III or IV, was estimated to be 8.6 [7.8, 9.6] million, accounting for 4.2% of the total US population[19]. The estimated number of patients with symptomatic and radiographic KOA in Japan was 7.8 million based on the epidemiological study published in 2009[21]. The number of people with symptomatic and radiographic KOA in 2017 was estimated to be 263 [233, 299] billion in the world[22]. Therefore, KOA delivers a high impact to our society.

Prevalence of KOA rises with aging. Prevalence of radiographic KOA in 54-59, 60-69, and 70-79 years old in Japan were 2.7%, 10.9%, and 16.8% for males, and 16.7%, 27.7%, and 43.9% for females in a Japanese epidemiological survey[5]. Prevalence of radiographic KOA in 60-69, 70-79, ≥ 80 years old in the US were 27.4 [21.6, 33.2]%, 33.5 [26.4, 40.5]%, 40.7 [35.0, 46.3]% for males, and 35.2 [29.4, 40.9]%, 44.6 [38.1, 51.1]%, 55.6 [46.7, 64.5]% for females in a national epidemiological survey conducted between 1988 and 1994[23]. In addition, populations aged over 65 years old (elderly population) was estimated to increase from 532 million in 2010 to 612 million in 2015[24]. The number of elderly population would increase in all the regions and would be reportedly more than double in the World between in 2019 and in 2050[25]. Therefore, considering that KOA is a progressive musculoskeletal disease, the number of patients including asymptomatic KOA would increase in our aging society.

Social and economic burden from KOA is high. According to the publication about the cost in 2012, monthly medical cost per person with KOA was mean €149, and monthly producibility cost was mean €722 [26]. According to the systematic review on direct and indirect cost per year of hip or knee osteoarthritis, mean direct and indirect cost were €9,500 and €4,400 per person, respectively[27]. Direct cost with and without a surgical operation was €6,700 and €10,800, respectively[27]. The estimated number of total knee arthroplasty (TKA) in the US was 1,5 [1,4, 1,7] million in 2020, and 3,5 [2,9, 4,1] million in 2030[28]. In addition, medical cost of osteoarthritis and rheumatoid diseases also was higher with age [29]. Individual/social economic burden of treating KOA would increase in association with rising number of patients with KOA in the future.

Risk Factors of Knee Osteoarthritis

Systemic Factors

Age

Association of aging with progression of KOA has been indicated. According to a population-based, longitudinal prospective study named the Johnston County Osteoarthritis Project, lifetime risk of KOA (namely Kellgren-Lawrence (KL) grade ≥ II) by 85 years old was 44.7 [40.0, 49.3]%[30]. A systematic review on the onset of KOA showed that older age was a risk factor[31]. When 60 years old is set at the cut-off line, odds ratio (OR) of KL grade ≥ II in Japan was 1.31 [1.15, 1.40], OR of KL grade ≥ III was

1.25 [1.13, 1.39], indicating the older age is a risk factor [32]. In a cross-sectional study on risk factors in Wuchuan County, Inner Mongolia, persons of 50–52.5, 52.5–59, 60–69 years old had lower risk for medial compartment KOA with OR of 0.037 [0.017, 0.082], 0.089 [0.047, 0.17], 0.39 [0.22, 0.70], respectively, compared with persons over 70 years old[33]. KOA is associated with aging, with greater cumulative knee joint damage and limited repairability of joint degradation involving damages of the bone, cartilage, meniscus, and ligaments.

Sex

Female sex is a risk factor of progression of KOA. A systematic review on onset of KOA showed that OR of females having KOA was 1.84 [1.32, 2.55] in individuals older than 50 years [31]. However, lifetime risk of symptomatic KOA graded as KL ≥ II for males and females were 39.8 [32.2, 47.3]% and 46.8 [41.2, 52.5]%, respectively, with no significant difference [30]. In addition, OR for females among KL grade ≥ III was 1.42 [0.88, 2.29][32]. Female sex is a risk factor of progression of KOA and may not be a risk factor of end-stage KOA.

Body Weight

Overweight and obesity are risk factors of KOA. Lifetime risk (below 85 years old) of KOA graded as KL ≥ II for normal weight individuals (body mass index (BMI) < 25 kg/m^2), overweight individuals (BMI between 25–30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were 30.2 [23.0, 37.4]%, 46.9 [39.3, 54.5]%, and 60.5 [53.0, 68.1]%, respectively, with significant difference[30]. OR of KOA onset for overweight compared to normal weight was 2.18 [1.86, 2.55], and OR for obesity compared to normal weight was 2.63 [2.28, 3.05][31]. Therefore, excessive body weight is the risk factor for KOA, which may affect biomechanical factors such as knee joint load and external knee adduction moment (KAM).

Physical Activities

Physical activities are associated with development of KOA. Moderate activity level (activity duration 150 minutes/week), compared with inactive level (< 10 minutes/week), was not a risk factor for KOA development with hazard ratio (HR) of 1.52 [0.68, 3.40]. Similarly, meeting with physical activity guideline of Department of Health and Human Services in US not a risk factor for development of radiographic KOA with HR of 1.20 [0.92, 1.56] as well as for symptomatic KOA with HR of 1.24 [0.87, 1.76] [34]. Therefore, moderate activities are not associated with KOA. On the other hand, meeting with that guideline had significant association with joint space narrowing with HR of 1.42 [1.10, 1.82][34]. In addition, longer time of physical activity over 300 minutes/week had significant association with joint space narrowing with HR of 1.97 [1.20, 3.26] [34]. A systematic review on occupational exposure to knee loading concluded that longer cumulative exposure to kneeling and squatting during working was risk factor for KOA with moderate quality evidence[35]. Therefore, low or moderate activity would not increase the risk of KOA and increase the risk of joint space narrowing, while longer physical activity would increase the risk of KOA.

Local Risk Factors

Knee Pain

Prevalence of knee pain among <40, 40-49, 50-59, 60-69, 70-79, ≥80 years old was 10.2%, 13.2%, 13.7%, 24.9%, 29.6%, 35.0%, 38.6% in males, and 6.6%, 13.1%, 21.5%, 36.4%, 37.1%, 36.8%, 42.9% in females, respectively, in a large cohort study called the LOCOMO study[36]. Prevalence of knee pain among patients with KOA of KL grade 0 or I were about 10% in males and about 20% in females[37]. On the other hand, knee pain at baseline was a risk factor of KL grade ≥ III after 3.3 year-follow-up with OR of 2.54 [1.52, 4.00])[32]. A systematic review on factors for KOA progression concluded that knee pain at baseline was associated with KOA progression with OR 2.38 or [1.74, 3.27][38]. Knee pain is a risk factor for KOA progression.

Knee Alignment

Knee varus alignment can lead to greater knee loading. In early stage KOA of KL grade 0 or I, knee with varus alignment did not have significant association with KOA progression after 18-month follow-up with OR of 2.50 [0.67, 9.39], compared with knee without varus alignment[39]. On the other hand, varus alignment had significant association with KOA progression after 6.6-year follow-up with OR of 2.06 [1.28, 3.32] compared with normal alignment[40]. A longitudinal cohort study over 21 years including individuals aged mean 49 (range: 40-65) years at baseline showed that lower tibial plateau angle relative to the longitudinal axis of the tibia in the frontal plane was associated with advanced KOA with OR of 1.15 [1.04, 1.24][41]. In moderate stage KOA, knee with varus alignment had significant association with KOA progression after 18-month follow-up with OR of 4.12 [1.92, 8.82] for KL grade II and 10.96 [3.10, 38.77] for KL grade III [39]. Varus knee alignment at baseline was a risk factor for increase of bone marrow lesion in the medial compartment with relative ratio 1.5 [1.2, 1.9][42]. Therefore, knee varus alignment is a risk factor for KOA progression and the progression rate is accelerated after KL grade II.

History of Knee Injuries

Association between history of some kinds of knee injuries and incidence of KOA have been investigated. In a large prospective cohort study, lifetime risk of incidence of KOA in persons with and without history of knee injury was 56.8 [48.4, 65.2]% and 42.3 [37.2, 47.4]% respectively[30]. A systematic review on risk factors for KOA showed that previous knee injury was associated with onset of KOA with OR of 3.86 [2.61, 5.70][31]. In a systematic review on risk factors for KOA after anterior cruciate ligament (ACL) injury, isolated ACL injury, meniscal injury, and combined ACL and meniscal injury were associated with development of KOA with OR of 4.2 [2.2, 8.0], 6.3 [3.8, 10.5], and 6.4 [4.9, 8.3], respectively[43]. On the other hand, a cross-sectional study in Inner Mongolia showed that absence of knee injury was not associated with incident medial compartment KOA with OR of 0.52 [0.24, 1.10] and reduced the risk of incidence of KOA with medial and lateral compartment KOA combined with OR of 0.43 [0.23, 0.81][33]. It is noteworthy that the study sample was limited to people in the agricultural community requiring strenuous physical activities. Therefore, history of knee injury may be a risk factor for incident KOA.

Medial Meniscal Tear

Prevalence of medial meniscal tear in 50–59, 60–69, > 70 years old without radiographic KOA were 17, 24, 36%, respectively44.

Osteophytes

Osteophyte is one of characteristics used in diagnosis and evaluation of KOA progression. In a cross-sectional study on relationship between osteophytes and KOA progression, femoral osteophyte grading, tibial osteophyte grading, and joint space narrowing were associated with increase of area of the medial tibial plateau[45]. 74% of participants aged 50 years old without radiographic deformity (KL grade 0) had osteophytes detected in the tibiofemoral compartment using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) grading in the Framingham Osteoarthritis Study[44]. In addition, Hada et al. [46] showed that 98% of participants in KL 0, I, or II had osteophytes in the medial compartment using T2 mapping. In a longitudinal study on risk factors for development of KOA using the Osteoarthritis Initiative (OAI) database, osteophytes formation of femoral intercondylar notch graded as mild and moderate size using WORMS in patients with KL grade 0 or I was associated with progression to KL grade II in 48-month follow-up with OR of 9.41 [2.06, 43.06] and 9.8 [2.76, 4.85], respectively[47]. In addition, osteophyte score detected by WORMS in patients with KL grade IV was associated with receiving TKA in 6-month follow-up[48]. Therefore, osteophytes formation is a risk factor for progression of KOA.

Muscle Strength

Quadriceps strength may be associated with onset or progression of KOA. Talago et al.[49] conducted a longitudinal study and reported weakness of the quadriceps was associated with incidence of KOA in both females (mean 64 years) and males (mean 65 years) with OR of 2.41 [1.10, 5.31] and 2.77 [1.05, 7.31], respectively. In the same study, quadriceps weakness was not associated with progression of KOA in both females and males with OR of 1.04 [0.39, 2.80] and 2.81 [0.53, 14.90], respectively[49]. Therefore, weakness of the quadriceps may be a risk factor for incidence of KOA, but not for progression of KOA.

External Knee Adduction Moment

KAM during gait in patient with KOA has been investigated. Miyazeki et al. [16] reported, in a six-year longitudinal study on progression of KOA, 1% increase of KAM was associated with progression of KOA with OR of 6.46 [2.40, 17.45] at 6-year follow-up. Chang et al. [17] performed a prospective cohort study on progression of KOA with KL grade ≥ II. Greater peak KAM at baseline was associated with increase of bone marrow lesion (BML) in the medial femoral and tibial condyles with OR of 2.20 [1.12, 4.38]. OR became higher to 3.29 [1.46, 7.41] with the dependent variable of medial tibial condyle only. In addition, higher KAM impulse at baseline was also associated with cartilage thickness loss at 2-year follow-up with OR of 3.38 [1.33, 5.42]. Kean et al.[50] concluded that KAM impulse was more sensitive than peak KAM to distinguish between KL grades and between severity of malalignment than peak KAM. Therefore, greater peak KAM and KAM impulse are risk factors for progression of KOA.

Varus Thrust

Varus thrust during gait is one of signs observed in patients with KOA. Omori et al.[51] found that, in a cross-sectional study with large cohort, presence of varus thrust during gait without instructions was associated with presence of KOA with KL grade ≥ II in both females and males with OR of 2.61 [1.92, 3.54] and 1.88 [1.33, 2.66], respectively. Chang et al.[52] found presence of varus thrust in patients with KL grade ≥ II was associated with progression of KOA at 18-month follow-up with OR of 3.96 [2.11, 7.43]. Sharma et al.[53] showed presence of varus thrust in patients with KL grade < II was not associated with incidence of KOA and narrowing of the medial joint space at 12-month follow-up with OR of 1.09 [0.86, 1.37] and 0.98 [0.73, 1.32], respectively. However, presence of varus thrust in patients with KL grade ≥ II was associated with joint space narrowing in the medial compartment with OR of 1.49 [1.20, 1.83]. Therefore, presence of varus thrust may be a risk factor for progression of KOA in patients with moderate KOA.

Crepitus

Presence of crepitus (rarely, sometimes, often, and always) in individuals with KL grade < II was associated with incidence of KOA with KL grade ≥ II at 4-year follow-up with OR of 1.5 [1.1, 2.0], 1.5 [1.2, 1.9], 2.2 [1.6, 3.0], and 3.8 [2.5, 5.7], respectively. Therefore, presence of crepitus may be associated with progression of KOA.

Biomechanics of KOA

Medial Meniscal Extrusion

The medial meniscus (MM) plays a crucial role in absorbing load, adapting knee compatibility between the femur and tibia, and providing distribution of load. MM is attached to the tibia by the coronary ligament. MME may reportedly occur by medial meniscus posterior root tear[54-56]. However, medial meniscus posterior root tear did not accompany with medial KOA[46, 57]. MME width in patients with KOA was greater than that in healthy controls[58]. In addition, MME width measured using the ultrasonography increased with progression of KL grades[59]. Knee kinematics in patients with medial KOA showed tibial external rotation, knee adduction, and tibial posterior translation[60, 61]. In addition, stationary stepping activity in patients with end-stage KOA immediately before total knee arthroplasty showed tibial lateral translation and adduction[62]. Knee adduction may induce the MME by pushing out the MM from the joint space between the femur and tibia. On the other hand, tibial lateral translation may induce the MME by the medial femoral condyle pushing the MM out of the medial tibial plateau.

MME is a common sign with KOA. Prevalence of MME was 44.2% in subjects who had risk factors for KOA aged mean 62.3 ± 8.0 [57]. In the same study, comorbidity of MME and medial meniscal posterior root tear (MMPRT) in the patient with KL grade I and II were 0.1% and 2.4%, respectively. Patients with KL grade 0, I, or II had MME distance of mean 3.0 ± 1.6 mm and none of them had MMPRT[46]. Therefore, MME could occur without MMPRT. MME distance in symptomatic and asymptomatic KOA assessed by coronal MRI were 5.1 ± 3.2 mm and 2.8 ± 2.1 mm, respectively, with a significant difference[63]. In symptomatic KOA, MME distances in several slices in coronal MRI images were correlated with medial joint space narrowing with correlation coefficients of range 0.50 to 0.54 for males and 0.57 to 0.64 for females. Therefore, it is obvious that MME is associated with deformity of KOA based on the cross-sectional studies.

Longitudinal studies have investigated on the association of MME with incidence and progression of KOA. Presence of MME in patients with KOA was associated with increase of bone marrow lesions and bone cysts in the tibiofemoral compartment after 2-year follow-up with OR of 3.3 [1.2, 0.1] and 6.8 [2.0, 23.8], respectively[64]. Presence of MME on coronal MRI in patients with KL grade 0 or I was associated with development of KOA with KL grade ≥ II after 2-year follow-up with OR of 3.03 [1.40, 6.53][65]. Presence of MME in patients with KOA was associated with cartilage loss after 30-month follow-up with OR of 2.92 [1.62, 5.26][66]. Presence of MME in patients with KOA, in which 77% of participants were KL grade ≥ II, was associated with cartilage loss after 30-month follow-up with OR of 2.4 [1.1, 5.0][14]. In a 10-year longitudinal study, presence of MME was associated with radiographic morphological change such as joint space narrowing and osteophyte formation with OR of 2.3 [1.1, 4.6][67]. In addition, when the MME distance of 5.5 mm was set as a cut-off, patients with KL grade III or IV and MME of ≥ 5.5 mm had greater risk for rapid progression of KOA after 3-year follow-up with OR of 3.7 [1.8, 7.7][68]. Therefore, MME is a risk factor of development and progression of KOA.

Kinematics

Knee kinematics in patients with medial KOA has been analyzed in various activities such as knee extension–flexion without loading, squatting, stepping activity, and gait. In knee extension–flexion activity, Ikuta et al.[69] showed that tibial external rotation in patients with KL grade III/IV was greater than that in patients with KL grade 0/I, that tibial adduction in patients with KL grade IV was greater than that with other grades, and that tibial posterior translation in patients with KL grade III/IV was greater than that with grade 0/I/II. Knees with KL grade III or IV immediately before TKA displayed tibial external rotation from maximum extension to 90° flexion that was opposite to the normal kinematics called screw home movement[70]. Therefore, characteristics of knee kinematics under unloading condition with medial KOA may be tibial adduction, posterior translation, and external rotation.

In squatting activity, KOA displayed abnormal kinematics. Saari et al.[60] showed that, from knee 50° to 20° flexion, KOA group including wide range of disease stages showed greater tibial external rotation and adduction positions than the controls without external rotation movement and the amount of tibial anterior translation during knee extension was significantly greater in the controls with average of 10 mm than KOA with that of 6.5 mm. Ikuta et al. [69] showed tibial external rotation with KL I in low flexion range during the flexion phase of squatting was smaller than that with KL III and IV. Tibial adduction with KL IV was the largest in all grades during flexion or extension, and that with KL III was second to KL grade IV. In addition, tibial posterior translation with KL grade III and IV was greater than that with KL grade 0, I, and II. Zeighami et al.[71] showed knees with KL grade IV before TKA displayed greater tibial lateral translation and adduction position than healthy knees, but tibial rotation was not significantly different. Therefore, characteristics of knee kinematics in squatting activities may be tibial external rotation, adduction, posterior translation, and they may increase with progression of KOA.

In a stepping activity, magnitude of tibial internal rotation from full extension to 30° flexion was not significantly different between knees with KL grade III or IV and healthy knees, 5.2 ± 5.1° and 7.2 ± 4.6°, respectively[72]. On the other hand, Hoshi et al.[73] showed that tibial adduction and lateral translation with KL grade III or IV during the loading phase was greater than that during the unloading. However, tibial internal rotation was not different between the loading and unloading phases. Hamai et al.[62] showed that tibia displayed the maximum of 6° varus alignment in knees with KL grade III or IV before TKA and -2° varus in healthy knees during stepping. Tibial lateral translation in OA was significantly greater than healthy knees from terminal stance (heel-off) and midswing (maximum knee flexion). Therefore, characteristics of knee kinematics in stepping activities may be tibial adduction and lateral translation.

Gait analysis for KOA was performed using stereoradiography during treadmill gait. Farrokhi et al.[74] reported that joint excursion of knee flexion and internal rotation in KOA and the control group were 9.7 ± 3.4° and 17.4 ± 4.7°, and 7.4 ± 2.2° and 4.7 ± 1.2°, respectively, with a significant difference.

In addition, joint excursion of adduction in KOA was greater than in the control group with -1.0 ± 0.5° and -2.2 ± 0.7°, respectively, with a significant difference. On the other hand, joint excursion of tibial lateral translation in KOA was greater than that in the control group, but there was no significant difference, 1.2 ± 0.3 mm and -1.2 ± 0.7 mm, respectively. Therefore, characteristics of knee kinematics during the loading phase of gait may be tibial adduction, internal rotation, and extension [74].

Contact kinematics have been analyzed using accurate stereoradiography. Farrokhi et al.[75] analyzed tibiofemoral joint contact mechanics and found peak and mean angular velocity of knee adduction in patients with KOA were higher than those of the controls. In addition, total length of contact path in the medial compartment in KOA with and without self-reported instability were 9.5 ± 4.6 mm and 5.2 ± 2.0 mm, respectively. Furthermore, average velocity of the contact point in the medial compartment was significantly faster in KOA with self-reported instability than without self-reported instability. Therefore, the patients with self-reported instability during gait may accompany with longer and faster excursion of the contact point in the medial tibiofemoral joint than patients without self-reported instability.

Kinetics

Analyses on KAM during gait involve peak value and integrated value of the KAM impulse as outcomes. Mundermann et al.[76] found that 1st peak KAM of severe KOA (KL grade ≥ III; mean age, 65.0 years) during gait at self-selected speed was significantly higher than age matched control by 27.9%, while that of less severe KOA (KL grade ≤ II; mean age, 65.2 years) was significantly higher than age-matched controls by 11.4%. Hunt et al.[77] reported that peak magnitude of KAM (%body weight*height) of affected side and contralateral side during walking were 3.65 ± 1.23 and 3.25 ± 1.03, respectively ($p < 0.001$). Foroughi et al.[78] published a systematic review on association of KAM with biomechanical variables, and concluded that KAM increased with severity of KOA and with growing varus knee alignment. Therefore, peak magnitude of KAM with KOA is higher than that with normal knee.

Lever arm in calculating KAM have been studied. Hunt et al.[77] frontal plane lever arms of affected side with medial KOA and contralateral side during walking (%height) were 2.96 ± 0.93 and 2.46 ± 0.82, respectively ($p < 0.001$). However, peak magnitude of ground reaction force (normalized by body weight) was 1.06 ± 0.07 and 1.09 ± 0.07, respectively ($p < 0.001$). Therefore, peak magnitude of KAM with KOA is higher than that with normal knee.

Effectiveness of therapies

Non-specific Exercises

Many studies suggested that quadriceps contraction below 70° knee flexion induce anterior translation of the tibia[79, 80]. Bennell et al.[81] reported that both neuromuscular exercise and quadriceps strengthening exercise for 12 weeks improved knee pain and physical function, with no significant between-group difference. Foroughi et al.[82] reported that progressive resistance training to lower extremity muscles with high intensity for six months improved knee pain, joint stiffness, and physical function. On the other hand, Sled et al.[83] reported that hip adduction muscle strengthening improved knee pain, but did not improve joint stiffness.

Gait Training

KAM during gait was greater in patients with medial KOA[83, 84]. Real-time biofeedback with emphasis on the foot progression with external rotation decreased pain scale by mean 28.4% and total score by 28.5% of the WOMAC[85]. Gait retraining program designed to reduce KAM for six weeks decreased pain scale by mean 49% and total score by 42% of the WOMAC[86]. Gait training to reduce KAM may be effective. Gait training program often employed “toe-out” which meant external rotation angle of the feet. Patients with KOA demonstrate abnormal rotational kinematics as Saari et al.[60] reported. On the other hand, Wheeler et al.[87] showed that most of participants (14/16 healthy subjects) answered that gait modification with toe-in (or foot in internal rotation) was effective. This may suggest that restoring normal rotational kinematics have an effect to reduce KAM in patients with KOA.

Specific Exercises

A few studies showed that an exercise program had an effect on biomechanical factors. Thorp et al.[88] reported that exercise program with strengthening of hip abductors, hamstrings, and quadriceps for 4 weeks reduced by about 9% of peak KAM during gait. This study had a limitation of small number of participants. In addition, Thorstensson et al.[89] reported that exercise program to improve muscle strengthening and neuromuscular control of the lower extremity for 8 weeks reduced peak KAM during one-leg raise, but did not reduce KAM during gait. Hanada et al.[90] showed that an exercise program designed to restore knee rotational kinematics improved time of 10-m walking, timed-up and go test, knee pain during gait at post-intervention.

Conclusions

Number of patients with KOA would increase, and social and economic burden of KOA is estimated to become larger in the future. Systemic risk factors of KOA were higher age, female sex, obesity. Local risk factors of KOA were knee pain, varus knee alignment, history of knee injury, KAM during gait, varus thrust, and MME. Kinematics of patients with medial KOA demonstrated tibial adduction and lateral translation. KAM increased with progression of KOA and with greater varus angle. A few studies showed that KAM during gait reduced after gait training. However, an effective exercise program to reduce KAM, improve kinematics and alignment has not been developed so far. Development of effective exercise program on biomechanical factors of KOA would have social and clinical significance in treatment of KOA.

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CHAPTER 3

High validity of measuring the width and volume of medial meniscal extrusion three-dimensionally using an MRI-derived tibial model

Introduction

Medial meniscal extrusion (MME), with or without meniscal injury, is an important marker of knee osteoarthritis (KOA) progression. Both Kawaguchi et al.[1] and Yanagisawa et al.[2]demonstrated that MME width was greater in patients with higher Kellgren-Lawrence (KL) grades. In addition, the Multicenter Osteoarthritis (MOST) study found that the presence of MME predicted cartilage loss after thirty months with odds ratios of 2.02 and 3.62 for slow cartilage loss and fast cartilage loss, respectively[3]. Accurate MME measurements would be important for evaluating the efficacy of interventions as well as KOA progression[4]. Although many studies support the association between KOA progression and MME width, the method of MME measurement utilized only a two-dimensional (2D) MRI slice, which might not have measured the greatest extrusion width. Furthermore, validation studies for this method are lacking.

Our ability to assess the MME and osteophytes around the tibial plateau three-dimensionally may be limited. To improve longitudinal assessments of changes in MME volume and width, effects of the osteophytes should be eliminated. Therefore, Computed tomography (CT) could represent a valid alternative since CT demonstrates sharp bone contours and allows automatic or semi-automatic segmentation in a reproducible manner[5, 6]. In addition, CT had higher ability to detect bony erosions than MRI[7]. For example, two previous studies concluded that both CT-derived bone model and MRI-derived model provide highly accurate data[8, 9]. On the other hand, White et al.[10] used a digital caliper to determine that the CT-derived model was 0.9% larger and the MRI-derived model was 3.5% smaller than direct measurements of the femur and tibia, concluding that the MRI-derived model would not offer a feasible alternative to the CT-derived model due to size inaccuracies[10]. Moreover, detecting the contours of osteophytes around the tibial plateau yields greater error on MRI because these structures demonstrate a gradual histological appearance on MRI[11]. Therefore, questions remain as to whether the MRI-derived model provides accurate contour information in KOA and whether conventional 2D measurements of MME width is valid and reliable as compared with three-dimensional (3D) measurement.

In fact, the contour of the tibial plateau serves as a reference point for measuring MME. Several studies chose the outermost margin of the tibial plateau as the reference after researchers manually excluded any osteophytes[4, 12, 13]. However, this method may involve measurement bias due the subjective judgments involved in excluding osteophytes. 2D measurements of MME largely depend on whether the particular MRI slice used for the measurement reflects the true maximal MME width, while 3D measurement of MME using common coordinate systems allows researchers to obtain true volume data that is not biased by slice selection and/or knee position during scanning.

This study aimed to determine: 1) whether there are morphological differences between CT- and MRI-derived tibial plateau models, 2) whether measuring MME volume and width on MRI-derived tibial models is as accurate as measurements using CT-derived tibial models. The hypotheses of this study were: 1) volume and area of the CT-derived tibial plateau would be larger than those derived from MRI; and 2) MME width measured on 2D MRI slices is inaccurate compared with 3D measurement on CT-derived tibial models combined with MRI-derived meniscal models.

Methods

This was a cross-sectional study based on image data obtained as baseline data in a randomized controlled trial (RCT) investigating the effect of exercise therapy in patients with KOA. This RCT was approved by the institutional review board of Hiroshima Prefectural Rehabilitation Center and Hiroshima International University (approval number: 19-029). Participants of this study were recruited from patients consulting the Department of Orthopaedics at Hiroshima Prefectural Rehabilitation Center. Informed consent was obtained from each of the individual participant included in this study in accordance with the Helsinki Declaration.

Inclusion criteria were Japanese aged from fifty to eighty years old, primary KOA, and KL grade from 1 to 3. Exclusion criteria were valgus KOA, secondary KOA, a history of knee surgery or knee injury, a history of other somatic diseases that could pose a risk, mental disorders, and communication difficulty. 327 patients were assessed for eligibility and 39 patients met the criteria. Ten subjects in this study were selected based on the additional procedure to choose three or four patients randomly from the stratified pools of patients based on the KL grade 1-3.

CT images were obtained using a clinical X-ray CT scanner (Aquilion TSX-101A, Toshiba Medical Systems, Japan). CT scan was taken using axial slices, kilovoltage: 120 kVp, tube current: 70 mA, exposure time: 500 ms, exposure: 70 mAs, slice thickness: 0.50 mm, sampling 150 × 150 mm in-plane sampling, and imaging matrix: 512 × 512. MRI images were obtained using a 1.5 Tesla MRI (MAGNETOM Aera, Siemens, Germany), and knee coil (Tx/Rx 15-Channel Knee Coil, Siemens, Germany). MRI were obtained as coronal slices of proton density sequences, slice thickness: 2.0 mm, intersection gap: 0 mm, slice resolution: 180 × 180 mm, imaging matrix: 384 × 384, TE time: 11 ms, TR time: 3810 ms. Participants were in the supine position with the foot elevated so that the examined knee was fully extended.

Manual segmentation was utilized to differentiate osteophytes and the other tissues using 3D modeling software (3D-DOCTOR, Able Software Corp. Lexington, MA). Geometric bone models and medial meniscus (MM) models were created by segmenting the exterior cortical bone edges and MM edges. Created 3D models were converted to polygonal surface models. Smoothing was applied using a reverse engineering software (Geomagic Studio, Geomagic Inc., Research Triangle Park, NC).

A tibial coordinate system was embedded on the CT-derived tibia, which then was best-fitted to the MRI-derived tibia in order to share a common local coordinate system. A single experienced researcher embedded the local tibial coordinate system onto the CT-derived tibial models using commercial software (3D-Aligner, GLAB Corp., Higashihiroshima, Japan). On the CT-derived model, a virtual rectangle parallel to the tibial plateau plane was fitted onto the tibial plateau contours at the top of the fibular notch of the tibia in order to avoid osteophytes on the osteoarthritic tibial plateau[14]. Four sides of the rectangle were fitted onto the tangent of the posterior contours of the medial and lateral tibial condyles, the medial and lateral tangents of the medial and lateral tibial condyles, and the anterior tangent of the medial tibial condyle[14]. Then, the fitted rectangle was transferred superiorly to the bottom of the medial tibial plateau (Figure 1). The origin of the tibial local coordinate system was defined as the center of the rectangle, and medial/lateral (Z) axes and anteroposterior (X) axes were defined as two axes of the rectangle. The superior/inferior (Y) axis was defined as the cross product of the X- and Z-axes. Intra-researcher errors of the OA tibia on the X-, Y-, and Z-axis were (translation/rotation) 0.56 [0.22, 0.91] mm/0.86 [0.32, 1.40]°, 0.15 [0.08, 0.23] mm/0.39 [0.28, 0.50]°, and 0.21 [0.03, 0.40] mm/0.78 [0.28, 1.28]°, respectively[15]. The local tibial coordinate system of the MRI-derived model was embedded using the iterative closest point algorithm in Geomagic Studio.

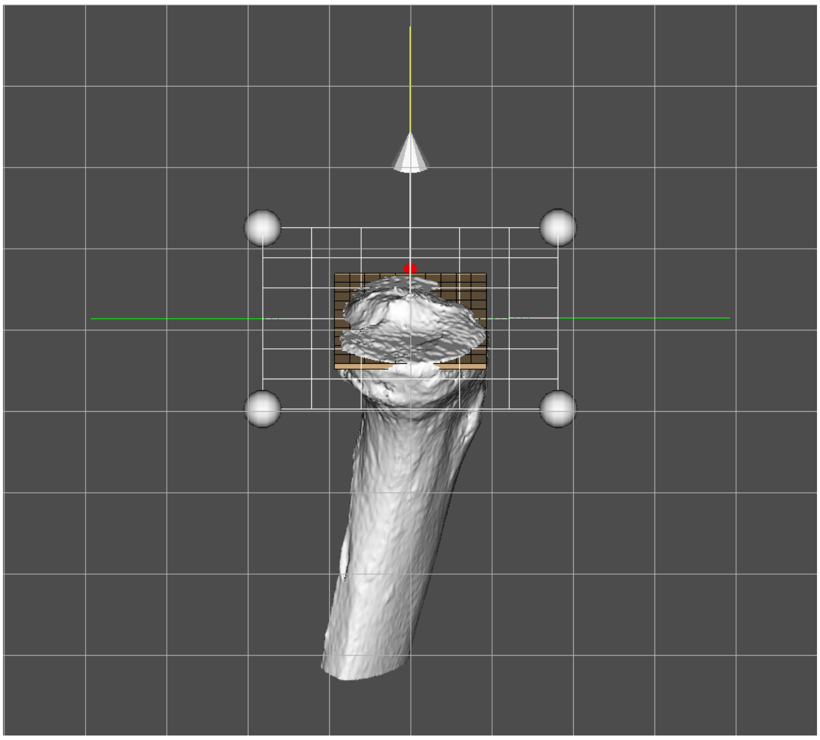

Figure 1.A local coordinate system of the tibia using the CT-derived tibial model. Tibial coordinate system was embedded using a virtual rectangle fitted onto the tibial cross section at the top of the fibular notch level. Then, the fitted rectangle was translated superiorly to the bottom of the medial and lateral tibial plateaus.

Surface differences and volume of the medial tibial plateau model were calculated using Geomagic Studio. A model of the medial tibial plateau was created by cutting the original tibial bone model at the level of 10.0 mm inferior to the origin parallel to the ZX plane and at the original XY plane (Figure 2). The osteophytes were visually observed, and the obvious protrusion of bone were recognized as an osteophyte. The contour of the plane 10.0 mm below the tibial plateau plane was observed and bony protrusion was recognized as osteophyte at the observed plane. Cross-sectional model was a cross-section of the medial tibial plateau model at the level of 10.0 mm inferior to the origin parallel to the ZX plane (Figure 3). Then, the contour of the cross-sectional model was thickened superiorly for 30.0 mm to create a thickened cross-sectional model. MME volume was defined as the volume of the MM model outside the thickened cross-sectional model (Figure 4). MME width was the distance of MME outside the thickened model on the Z-axis (Figure 5).

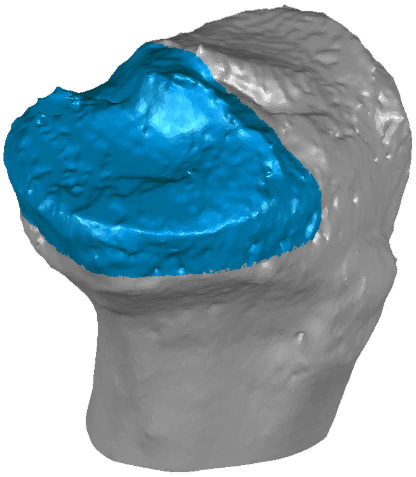

Figure 2. Model of the medial tibial plateau.
The medial plateau model (blue) and the tibial model (gray) is shown. The medial tibial model is created by cutting the original tibial bone model at the level of 10.0 mm inferior to the tibial plateau (the ZX plane) and the original XY plane.

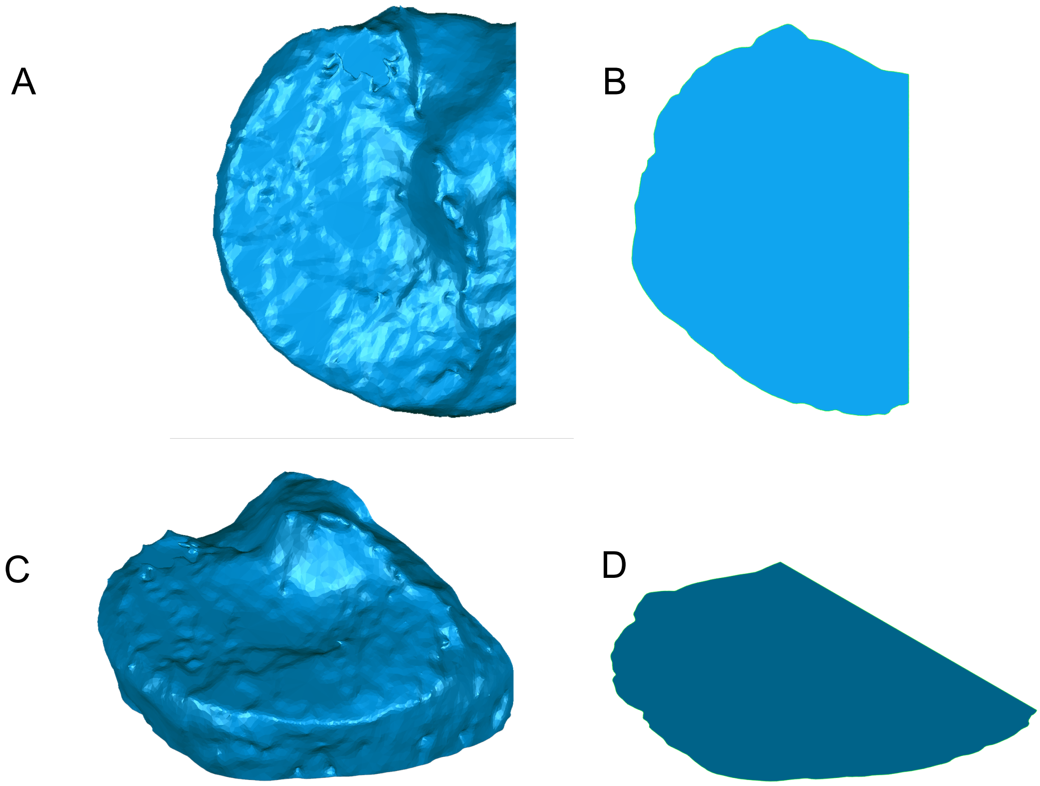

Figure 3. Cross-sectional model of the medial tibial plateau.
Cross-sectional model is a cross-section of the medial tibial plateau model at the level of 10.0 mm inferior to the origin parallel to the ZX plane. A. Axial view of the medial tibial plateau model. B. Axial view of the cross-sectional model of the medial tibial plateau. C. Anteromedial view of the medial tibial plateau model. D. Anteromedial view of the cross-sectional model of the medial tibial plateau.

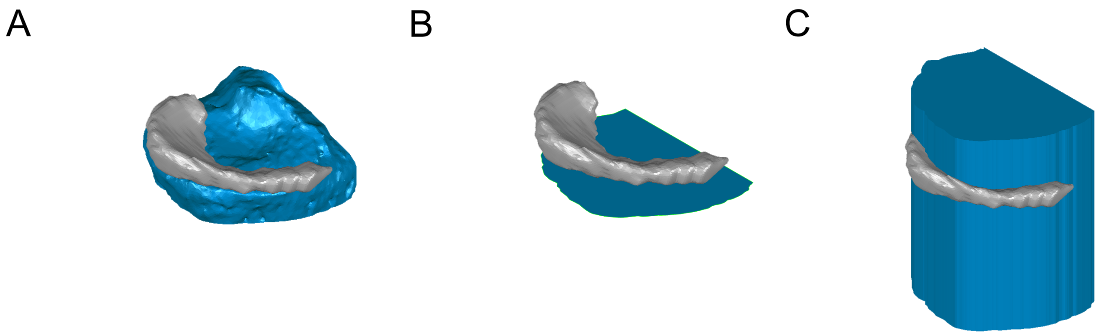

Figure 4. Volume of the medial meniscal extrusion (MME) model.
The medial meniscus is shown in gray color. A. The medial meniscus (gray) and the medial tibial plateau model (blue). B. The medial meniscus (gray) and the cross-sectional model of the medial tibial plateau (blue). C. MME model (gray) and the thickened cross-sectional model. The MME volume is defined as the volume of the medial meniscus model outside the thickened cross-sectional model.

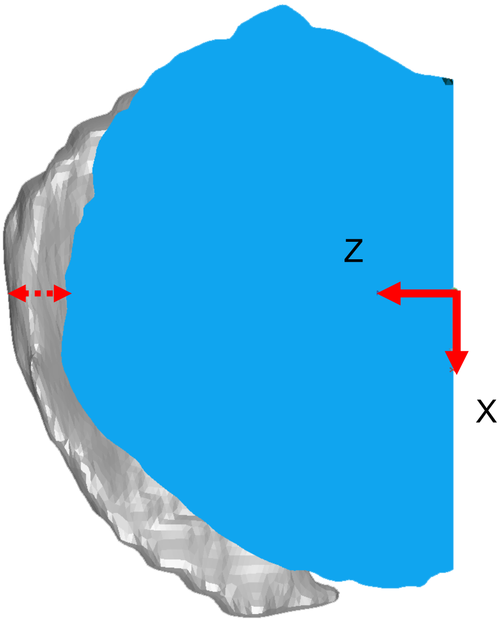

Figure 5. Width of the medial meniscal extrusion (MME) model.
The MME model (gray) and the thickened cross-sectional model are shown from the axial view. The MME width is the distance from the outer edge of the thickened model to the outer edge of the medial meniscus model through the Z-axis.

2D MME width was measured using image processing software (ImageJ 1.50i, Wayne Rasband, USA). 2D MME width was defined as the distance from the most extruded edge of the medial meniscus to the edge of the medial tibial plateau[16]. The coronal slice showing the greatest area of the medial tibial spine was selected. The tibial reference point for 2D MME width was the edge of the bony contour of the tibial plateau without an osteophyte. A vertical line connecting the femur and the reference point was drawn (Figure 6). A single observer performed measurements of the 2D MME width, MME volume, and MME width to assess intra-researcher reproducibility using interclass correlation coefficient (ICC). These measurements were conducted twice for eight subjects at an interval of one week.

Figure 6. Measurement of two-dimensional (2D) medial meniscal extrusion (MME) width. 2D MME width was defined as the distance from the most extruded edge of the medial meniscus to the edge of the medial tibial plateau. The reference point for 2D MME width was the tibial plateau without the osteophyte. A vertical line was drawn connecting the femur and the reference point.

Statistical analysis

Sample size of this study was calculated using a power analysis program (G*Power version 3.1.9.2, Franz Faul, Germany). A power analysis was conducted using the result of the previous study[17]. 0.82 ± 0.62 mm were the surface difference between the CT- and MRI-derived tibial bone models. Effect size was 1.32. Calculations using an effect size of 1.32, $\alpha = 0.05$, and power 0.95

showed that the required sample size was ten.

All variables were tested with Shapiro-Wilk test in order to determine the normality. Mean and 95% confidence interval were used to assess the demographic characteristics. Two-sample t-test was used to test each variable of the CT- and MRI-derived models. Linear regression analysis was carried out in order to test consistency of the medial tibial plateau volume and the cross-sectional area between the CT-derived models and MRI-derived models. Next, linear regression analysis was carried out to test consistency of the MME volume and width between the CT-derived models and MRI-derived models. In both analyses, data from the CT-derived model were dependent variables and data from the MRI-derived model were independent variables. Lastly, linear regression analysis was performed in order to assess the consistency between the 3D MME width and the 2D MME width obtained from an MRI slice. Statistical analysis was performed using commercial software (SPSS Statistics version 21, IBM Corp., Armonk, NY). The level of significance was set at $\alpha = 0.05$.

Results

Age, height, body mass, and body mass index (BMI) of the participants were 69.5 [65.5, 73.5] (mean [95% confidence interval]) years, 157.8 [153.6, 162.1] cm, 61.9 [53.1, 70.8] kg, and 25.1 [20.9, 29.2] kg/m2, respectively (Table 1). Three males and seven females were included; there were three, three, and four participants in KL grades 1, 2 and 3, respectively.

Table 1 Characteristics of the participants

Variable			P-value
Age（years-old）	69.5	[65.5, 73.5]	0.210
Height（cm）	157.8	[153.6, 162.1]	0.090
Weight（kg）	61.9	[53.1, 70.8]	0.086
Body Mass Index（kg/m^2）	25.1	[20.9, 29.2]	0.075
Kellgren-Lawrence grade 1/2/3		3/3/4	

All variables except Kellgren-Lawrence grade are shown as mean [95% confidence interval]. P-value are calculated using Shapiro-Wilk test.

ICC for 2D MME width for intra-researcher agreement was 0.990 [0.971, 0.997]. ICC for measuring the MME volume was 0.998 [0.992, 1.000]. ICC for measuring the MME width was 0.983 [0.924, 0.996].

All the participants had osteophyte in the medial tibial plateau, and none of ten had small osteophytes at 10.0 mm below the tibial plateau plane. All the participants except one could fully extend their knees. One participant with KL grade 3 had flexion angle of 4.5° by calculating with 3D bone models during MRI acquisition. MME volume and MME width using the CT- and MRI-derived tibia, and cross-sectional area of the medial tibial plateau using the CT- and MRI-derived tibia were normally distributed (Table 2). However, volume of the medial tibial plateau using the CT- and MRI-derived tibia were not normally distributed (Table 2).

Table 2 Demographic data of volume and cross-sectional area of the medial tibial plateau models and volume and width of the medial meniscal extrusion

Variable		CT-derived model		MRI-derived model		P value	Effect size	Power
		Representative value	P value	Representative value	P value			
Medial tibial plateau	Volume (mm^3)	13,031 (5,300)	0.013	12,628 (4,373)	0.019	0.912	0.08	0.91
	Cross-sectional area (mm^2)	1,484 [1338, 1630]	0.211	1,493 [1340, 1646]	0.122	0.906	0.04	0.91
Medial meniscal extrusion	Volume (mm^3)	942.6 [597.7, 1287.6]	0.540	916.2 [557.9, 1274.6]	0.569	0.938	0.05	0.91
	Width (mm)	4.2 [1.9, 6.5]	0.242	4.5 [2.2, 6.9]	0.155	0.967	0.12	0.80

Volume of the medial tibial plateau is shown as median (inter-quartile range), and the others are shown as means [95% confidence interval]. P-values of CT- and MRI-derived model are based on the Shapiro-Wilk test.

Minimal and maximal surface differences of the medial tibial plateau between the CT- and MRI-derived models were -0.13 [-0.42, 0.16] mm (mean [95% confident interval]) and 0.23 [-0.10, 0.56] mm, respectively (Table 3, Figure 7). The volume of the medial tibial plateau from the CT- and MRI-derived models were 13,031 (5,300) mm^3 (median (inter-quartile range)) and 12,628 (4,373) mm^3 ($p = 0.912$, $d = 0.08$, power = 0.91), respectively (Table 2). The cross-sectional area of the medial tibial plateau from the CT- and MRI-derived models was 1484 [1338, 1630] mm^3 (mean [95%coefficient interval]) and 1493 [1340, 1646] mm^3 ($p = 0.906$, $d = 0.04$, power = 0.91), respectively. Therefore, there were no significant differences in the volume and cross-sectional area of the medial tibial plateau between the MRI-derived and CT-derived tibial models. Linear regression analysis demonstrated that the volume of the medial tibial plateau of the CT- and MRI-derived models showed a high consistency ($F(1, 9) = 8{,}015$, $p < 0.001$) with adjusted R^2 of 0.999 (Table 4). Linear regression analysis also demonstrated that the cross-sectional area of the medial tibial plateau of the CT- and MRI-derived models showed a high consistency ($F(1, 9) = 32{,}275$, $p < 0.001$) with adjusted R^2 of 1.000 (Table 4).

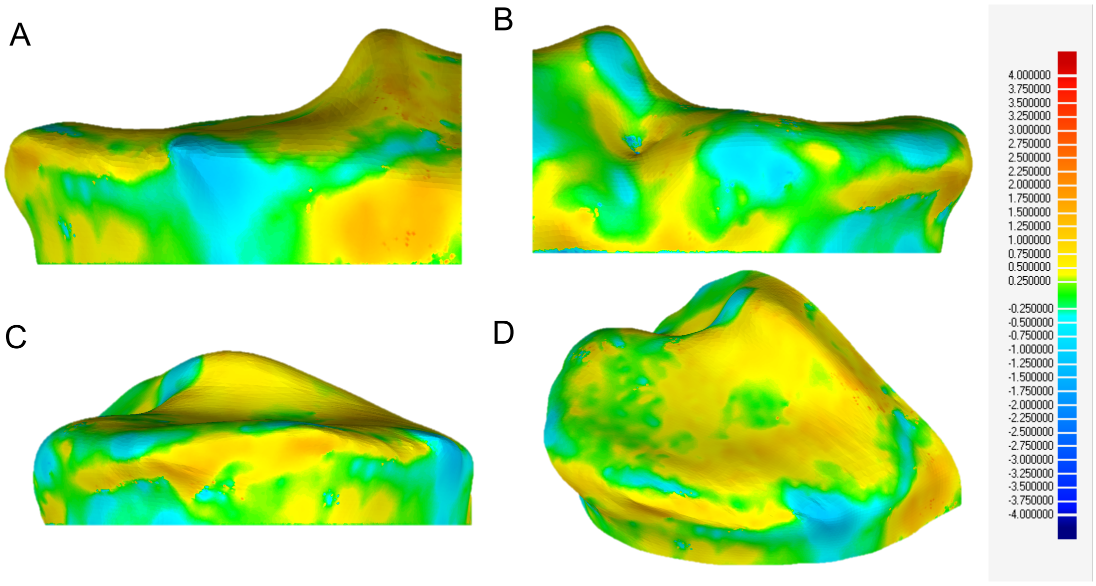

Figure 7. Representative case showing surface differences on medial tibial plateau models. A. Anterior view. B. Posterior view. C. Medial view. D. View from the upwards.

Table 3 Surface difference of the medial tibial plateau models

Participants	KL grade	Surface difference	
1	I	0.09	[-0.15, 0.34]
2	I	0.10	[-0.16, 0.35]
3	I	-0.15	[-0.44, 0.14]
4	II	0.18	[-0.04, 0.40]
5	II	0.00	[-0.29, 0.30]
6	II	0.15	[-0.19, 0.49]
7	III	0.24	[-0.09, 0.57]
8	III	-0.02	[-0.32, 0.27]
9	III	0.20	[-0.09, 0.48]
10	III	-0.05	[-0.33, 0.24]

Surface difference is shown as means [95% confidence interval]
KL grade: Kellgren-Lawrence grade.

Table 4 Models of linear regression analyses and results of coefficients of each analysis

Model			Unstandardized coefficients		Standardized coefficients	t	Significant level
Outcome	Independent variable	Dependent variable	B	Standard error	Beta		
Volume of the medial tibial plateau	CT-derived model	MRI-derived model	0.978	0.011	0.999	89.527	0.000
Cross-sectional area of the medial tibial plateau	CT-derived model	MRI-derived model	1.007	0.006	1.000	179.653	0.000
MME volume	CT-derived model	MRI-derived model	0.983	0.200	0.998	49.932	0.000
MME width	CT-derived model	MRI-derived model	1.063	0.023	0.998	46.107	0.000
MME width	3D model	2D MRI slice	0.963	0.134	0.923	7.183	0.000

MME: medial meniscal extrusion, 3D: three-dimensional, and 2D: two-dimensional.

The MME volumes of the CT- and MRI-derived models were 942.6 [597.7, 1287.6] mm^3 and 916.2 [557.9, 1274.6] mm^3, respectively ($p = 0.938$, $d = 0.05$, power = 0.91) (Table 2). The MME widths of the CT- and MRI-derived tibial models were 4.2 [1.9, 6.5] mm and 4.5 [2.2, 6.9] mm, respectively ($p = 0.967$, $d = 0.12$, power = 0.80). MME width measured on a 2D MRI slice was 5.5 [4.3, 6.7] mm. In addition, linear regression analysis demonstrated that the MME volumes on the CT- and MRI-derived models showed a high consistency ($F(1, 9) = 2{,}493$, $p < 0.001$) with adjusted R^2 of 0.996 (Table 4). Linear regression analysis also demonstrated that the MME width of the CT- and MRI-derived models showed a high consistency ($F(1, 9) = 2{,}126$, $p < 0.001$) with adjusted R^2 of 0.995. Lastly, linear regression analysis demonstrated that MME width on the 2D MRI slices and 3D models had an excellent consistency ($F(1, 9) = 51.6$, $p < 0.001$) with adjusted R^2 of 0.835.

Discussion

The most important findings in this study were that surface differences of the medial tibial plateau ranged from -0.15 [-0.44, 0.14] to 0.24 [-0.09, 0.57], and that there was no significant difference between the MME volume calculated using the CT- and MRI-derived tibial models, and no significant difference between the MME widths calculated using the CT- and MRI-derived tibia. The consistency of the MME volume and the MME was excellent on linear regression analysis. 2D MME width was 5.5 [4.3, 6.7] mm, and the coefficient of determination adjusted R^2 was lower than that of the MME width on CT- and MRI-derived models.

Accurate MME measurement requires accurate contours of the tibial plateau with the longitudinal osteophytes taken into consideration. Neubert et al.[17] showed that surface differences between CT- and MRI-derived models of the entire tibia ranged from 0.45 ± 0.38 mm to 0.83 ± 0.55 mm. The surface of the CT femur-derived femur of sheep were 0.23 mm greater than MRI-derived models[8]. Moro-oka et al.[18] reported that mean surface differences between CT- and MRI-derived models of the femur and tibia were 0.08 mm and 0.14 mm, respectively. The average [95% CI] surface difference of the medial tibial plateau in this study was 0.24 [-0.09, 0.57] in the subject showing the greatest difference. Therefore, surface differences between CT- and MRI-derived models in this study were similar to those found by Rathnayaka et al.[8]. In addition, there was no significant difference in cross-sectional area of the medial tibial plateau between CT- and MRI-derived models. Therefore, the MRI-derived medial tibial plateau model is as accurate as the CT-derived model for measurement of the MME and a difference in the MME width greater than 0.57 mm would be considered reliable.

Longitudinal comparison of the MME requires reasonable management of osteophyte growth over time. Hayeri et al.[19] observed osteophyte formation in the medial and lateral tibial compartments; 16 of 35 knees demonstrated osteophytes around the anterior part of the medial tibial plateau, while 12 of 35 showed osteophytes along the posterior part. Nagaosa et al.[20] observed osteophyte formation with attention to the orientation and found that osteophytes on the medial tibial plateau were oriented medially (73.1%), infero-medially (14.3%), or super-medially (8.4%). Therefore, regions and directions of osteophytes on the medial plateau may vary across patients with knee OA. In addition, Zhu et al.[21] showed that MRI detected osteophytes in 85% of participants, while X-ray image detected only 10% at the baseline. Using T2 mapping, Hada et al.[11] showed that osteophyte width including the cartilage corresponded to the actual measurement of the osteophyte tissue obtained during total knee arthroscopic surgery. Although these difference in detecting osteophytes may affect longitudinal comparisons of the MME, there has not yet been any longitudinal study investigating the effects of osteophyte growth on the accuracy of MME measurement over time. Therefore, the reference point on the tibial side for the measurement of the MME must be a point without osteophytes in order to minimize any bias caused by osteophyte growth. This study selected the reference point at the level of

10.0 mm. By selecting the plane without the effects of osteophyte, this technique can measure the MME more correctly especially in a longitudinal study. Moreover, this technique may allow to measure the morphological changes of the osteophytes. Therefore, the natural course of the biological adaptation can be measured. In the case of patients with greater osteophyte over this reference point, this method would not be adopted.

There has not been a previous study that compared MME measurements obtained from CT- and MRI-derived tibial bone models combined with an MRI-derived MM model. In patients with medial KOA, MME width on 2D MRI measured 4.3 ± 2.5 mm[16]. MME width in patients with KL grade 2 or 3 was reportedly 2.64 ± 1.10 mm when a method of excluding osteophytes was used during the segmentation process [13]. However, the method of identifying the osteophyte contours was not described in detail and there may have been a potential bias in detecting the tibial contour. In the non-weight-bearing knee of patients with KOA, ultrasonographic measurement of the MME was 6.12 ± 2.57 mm[2]. These researchers tried to exclude osteophytes by connecting the medial contour of the cortical bone of the tibia and femur[2]. This method may produce an error on longitudinal measurements of the MME due not only to the 2D method used but also to potential longitudinal changes in the femorotibial lateral translation[22] or lateral translation and adduction[23, 24] of the tibia on the coronal plane. This study measured the MME using a reference point on the contour of the tibial condyle 10 mm below the tibial plateau plane where there was less possibility to influence osteophytes. Since the selected contour was considered unlikely to be affected by the longitudinal growth of the osteophytes, measurement method in this study may be more accurate in measuring the MME displacement from the original meniscal position, not relative the edge of the osteophyte, but from the contour of the young tibial plateau without osteophytes.

In this study, there was no significant difference in MME measurements between the CT- and MRI-derived tibial bone models. However, the average surface difference of 0.24 [-0.09, 0.57] mm at maximum would likely be a source of systematic error and should be taken into consideration when comparing MME measurements between the CT- and MRI-derived tibial bone models. From the above, the MRI-derived tibial models provided reasonably accurate measurements of the MME volume and width after removing the influence of tibial plateau osteophytes. The internal validity of this study was high, and the methods used in this study are available for MME measurement in the early-to-moderate stages of primary medial KOA.

This study has a few limitations. First, the MRI sequences of this study were not specialized for analyzing bone morphology. This study employed a clinical sequence for analyzing medial meniscal disorder. Surface differences were similar to the findings of previous studies. Secondly, this study employed coronal slices in the MRI and the slice pitch was 2.0 mm. This may have affected the anterior or posterior margin of the MM, which can cause some error in volume and lesser extent in distance. Therefore, caution is necessary when comparing data from different studies due to errors caused by the segmentation method on MRI and when comparing 2D and 3D measurements of the MME. Thirdly, manual segmentation of the medial meniscus was done by single researcher. One observer segmentation has an advantage in reducing inter-observer errors, which is desired in a small study with 10 samples. However, it has a limited generalizability. Fourthly, this study applied the level of 10.0 mm as the reference cut point of the tibial plateau model. All the tibia in this study had no visual osteophyte at the level. However, careful attention would be needed when analyzing the MME with greater osteophyte in the tibial plateau.

Conclusions

In conclusion, this study showed that the medial tibial plateau does not demonstrate significant morphological difference between the CT- and MRI-derived models, and that both models can be used as a reference to measure the MME in early-to-moderate medial KOA. This study showed the validity of the MME measurement method using the MRI-derived 3D tibial models after excluding the influence of tibial plateau osteophytes. Further studies are required to determine longitudinal changes in MME after eliminating the effects of osteophyte growth. This study concluded that the morphology of the medial tibial plateau does not demonstrate significant differences between CT- and the MRI-derived models, and that both the CT-derived tibial model and the MRI-derived tibial model can be used as a reference when measuring MME in early-to-moderate medial KOA.

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CHAPTER 4

Effects of an exercise program with tibial internal rotation on the knee kinematics and medial meniscal extrusion in medial osteoarthritis of the knee: A randomized controlled trial

Introduction

Knee osteoarthritis (KOA) is a common musculoskeletal disease with complaints in the daily activities. 3.8% of the population in the world was reportedly symptomatic radiographic KOA[1]. It accounts for 267 million patients with KOA using the number of the world population in 2010. The estimated number of patients with symptomatic radiographic KOA was 7.8 million in Japan based on the publication in 2009[2]. The number of aged people was reportedly 6,118.9 million in 2015, and would increase to 1.295 billion in 2040[3]. Prevalence of KOA became high with aging[1, 2, 4]. Therefore, patients with KOA will increase in the future. Progression of KOA produces changes in knee kinematics. Patients of medial KOA showed the tibial external rotation, adduction, and posterior translation compared with asymptomatic controls using a radiostereometric analysis (RSA) [5]. Patients with severe medial KOA showed the tibial lateral translation and posterior translation compared with the healthy subjects using orthogonal dual fluoroscopic technique[6]. In addition, the medial meniscal extrusion (MME) was considered as one of markers of the early stage of KOA[7, 8]. Presence of MME positively correlated with the femorotibial joint space narrowing compared with absence of MME[9]. The MME width with and without joint space narrowing in the patients with knee pain were 3.4 ± 2.0 mm (mean ± standard deviation) and 1.8 ± 1.3 mm, respectively[10]. Kinematic change of the knee adduction and lateral translation may induce the MME mechanically by pushing the medial meniscus medially from the tibial plateau. Therefore, the abnormal knee kinematics and the MME in KOA should be targeted to delay disease progression.

Changes in knee kinematics in patients with KOA may change a course of disease progression. External rotation, adduction, and posterior translation of the tibia were greater with progression of the Kellgren-Lawrence (KL) grade[11]. Stationary stepping activity in patients with severe KOA showed knee adduction and lateral translation motion in the early stance phase[12, 13]. The knee adduction may affect on joint space narrowing of the femorotibial joint, and contrarily joint space narrowing may induce the knee adduction. Presence of joint space narrowing associated with increasing degree of MME[10]. Boxheimer et al.[14] indicated the association between the greater amount of MME and increased tibial external rotation. The tibia in KOA translated laterally relative to the femur during between 30 and 60° flexion during a squatting activity[6]. Tibial lateral translation is accompanied by medial femoral translation and may induce the medialization of the menial meniscus pushed by the medial femoral condyle during femoral medial translation. Therefore, reducing tibial lateral translation may contribute to prevent and/or reduce the MME. Restoration of normal kinematics in KOA may require an increase of tibial internal rotation as well as tibial anterior and medial translation considering the abnormal kinematics in KOA[5, 6]. To our knowledge, there has been no studies showing the effects of exercise on knee kinematics. Therefore, the objective of this study was to reveal the potential effects of an exercise program designed to induce tibial medial translation on knee kinematics and the MME in individuals with KOA.

Exercise therapy for KOA is recommended by various guidelines[15-18]. Systematic reviews on the exercise therapy on KOA revealed that exercise programs reduced knee pain, and improved physical function[19, 20]. Similarly, a home exercise program reduced knee pain and improved function[21]. The exercise programs with quadriceps contraction have been shown to be effective to reduce pain in KOA[22]. Many studies suggested that quadriceps contraction below 70° knee flexion induce anterior translation of the tibia[23, 24]. Therefore, it is reasonable to believe that quadriceps training can help restoring posterior translation of the tibia in KOA. Abnormal tibial external rotation and lateral translation may be restored by contraction of the medial muscles of the knee. The semitendinosus, gracilis and sartorius attach the pes anserinus and have a moment arm of tibial internal rotation (and medial translation). Accordingly, we can assume that an exercise with activities of the quadriceps and medial muscles may potentially restore abnormal knee kinematics. A leg press activity with tibial internal rotation (Rotation Restoration and Realignment (RRR) program) would be a possibility of achieving the kinematic change.

The hypotheses of this study were that the leg press activity with tibial internal rotation would 1) improve angle of tibial external rotation, adduction, and lateral translation during squatting, and 2) reduce MME after intervention in knee extension in the supine position. To test the hypotheses, a 3D-to-2D registration technique and MRI-derived three-dimensional models of the femur, tibia and medial meniscus were used, and their relative positions in knee extension in the supine position was measured.

Materials and Methods

Design

This study was a single-blinded, randomized controlled trial (RCT). Protocol of this study involved a baseline data acquisition, intervention for three months, and data acquisition after intervention. This RCT was approved by the institutional review boards (IRB's) of Hiroshima Prefectural Rehabilitation Center and Hiroshima International University (approval number: 19-029). Participants of this study was recruited from the patients with KOA of Department of Orthopaedics at Hiroshima Prefectural Rehabilitation Center in Higashihiroshima City. Higashihiroshima City is a medium-sized city with the population of about 185,000 in 2017. Informed consent, approved by the IRB, was obtained from all the individual participants included in this study.

Participants

Inclusion criteria of this study were Japanese aged from fifty to eighty, primary medial KOA, and KL grade I to III. Exclusion criteria were valgus deformity, secondary KOA, history of knee injury or knee surgery, undertaking physical therapy or having a plan to undertake physical therapy at another medical institution, inflammatory diseases (for example rheumatoid arthritis and gout), difficulty in visiting Hiroshima Prefectural Rehabilitation Center regularly, difficulty in undertaking exercise therapy for some reasons, having risks of internal medicine, mental disorders, or communication disorders. Discontinuance criteria were withdrawal request from participants, difficulty in continuing intervention due to worsening of KOA symptoms and/or coexisting illness, apparent lack of compliance, and surgeon’s judgement to abandon the intervention for some reasons.

Allocation and blinding

Participants was randomly allocated to one of the two groups: the RRR group performing tibial internal rotation exercises and control group performing general muscle strengthening exercises. Random allocation stratified by sex using a computer-generated random table was performed in the sequential order of consenting participation. Participants as well as surgeons and radiological technicians for computerized tomography (CT), fluoroscopy, and magnetic resonance imaging (MRI) were blinded from allocation until the outcome assessments were finished.

Intervention was performed by two physical therapists on a one-to-one basis in a room invisible from outside and the participants were not allowed to communicate with each other. Concealing the allocation information for therapists was impossible because contents of exercises were different between the two groups. The interventions for both groups had been documented so that the therapists were required to follow the manuals. The analysis was performed by a single investigator who was blinded until the outcome assessments were finished.

Interventions

Intervention were performed at the single medical institution. A 40 minutes intervention session was given weekly for three months accompanied by home exercises which were given personally and modified at each intervention session considering participants' knee condition and familiarization of exercises to provide gradual load. Both groups used a special leg press device (ReaLine LegPress, GLAB Corporation, Higashihiroshima, Japan), which allows assistive or resistive tibial internal/external rotation, as well as a leg press activity with or without tibial rotation. There are a set of rubber bands on both sides of the foot plate, which allows assistive or resistive tibial internal rotation, as well as resistive leg press exercise with or without tibial internal rotation.

The RRR group performed three exercises (Figure 1); (1) tibial internal-external rotation exercises with the knee at 90° , (2) a leg press activity with tibial maximal internal rotation from 90° to 0° using ReaLine LegPress, and (3) a squat activity with tibial internal rotation (knee-out squat) from 0° to 60° flexion. The knee-out squat was instructed to stand with the feet at shoulder width apart, flex the knee to 60° in neutral position, perform knee-out motion by external rotation of the hip while the feet were maintained in the parallel position, then extend the knees to 0° while maintaining hip external rotation. Manual soft tissue release (inter-structural release: ISR) was given, if necessary, to the increase the tibial internal rotation, which was targeted to the subcutaneous tissue of the popliteal region, the iliotibial tract, the biceps femoris, gastrocnemius, fibular longus, pes anserinus, patellar tendon, and the infrapatellar fat pad. Home exercises consisting of four exercises with the tibial internal rotation: sitting tibial internal rotation exercise with knee flexed, active knee extension exercise with the tibial maximal internal rotation, active knee flexion exercise with the tibial internal rotation, and squat activity with the tibial internal rotation.

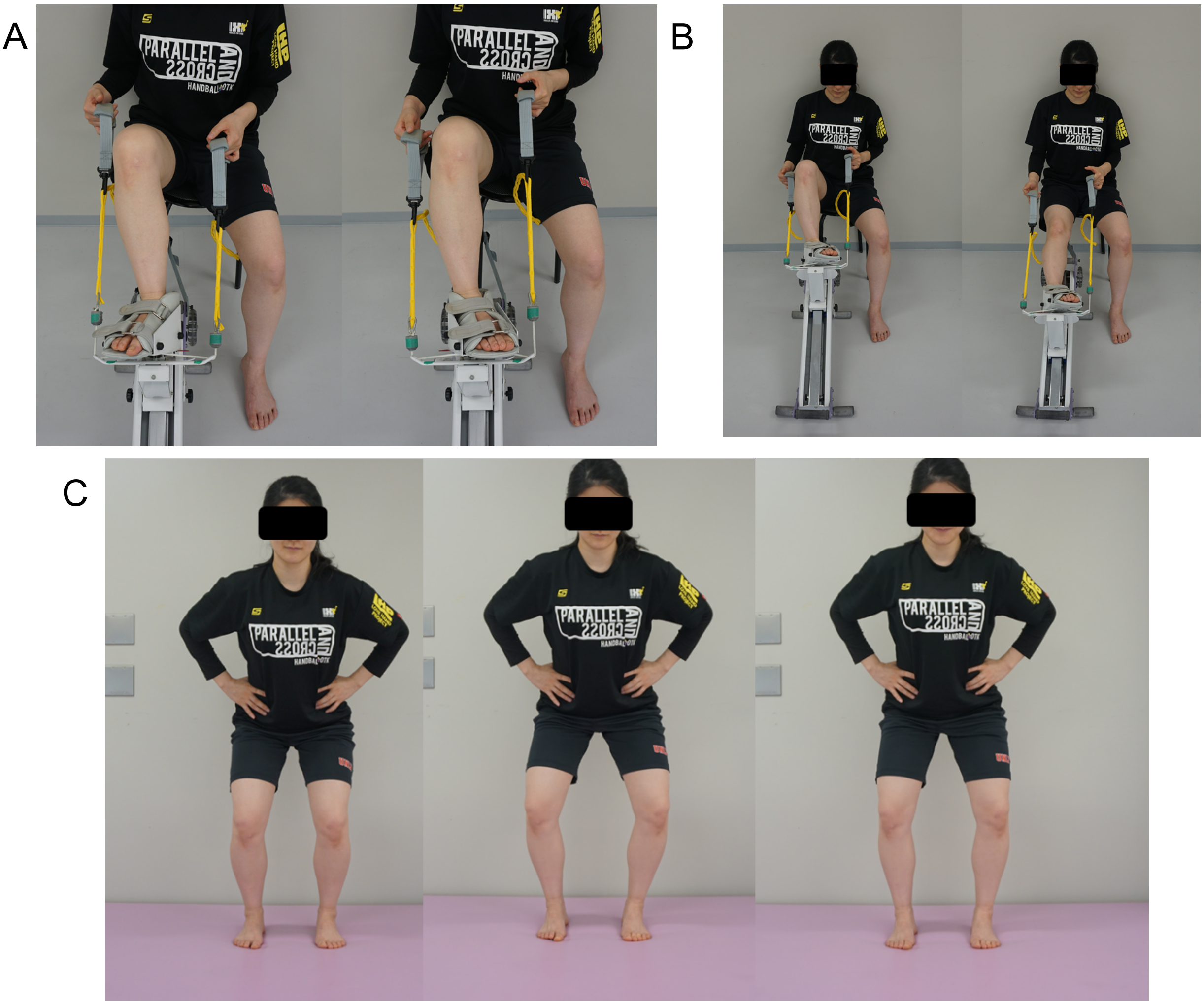

Figure 1. Three exercises of the RRR group.

A. Tibial internal-external rotation exercises with the knee at 90°. B. A leg press activity with tibial maximal internal rotation from 90 ° to 0° using ReaLine LegPress. C. A squat activity with tibial internal rotation (knee-out squat) from 0° to 60° flexion.

The control group performed two exercises (Figure 2); (1) a leg press activity from 90° to 0° with the tibia in neutral internal/external rotation using ReaLine LegPress, and (2) a squat activity without tibial internal/external rotation from 0° to 60° flexion. Home exercises consisting of four exercises: patella setting (the quadriceps activation), bridge (the gluteus major and hamstrings activation), isometric hip adduction (the hip adductors activation), and squat.

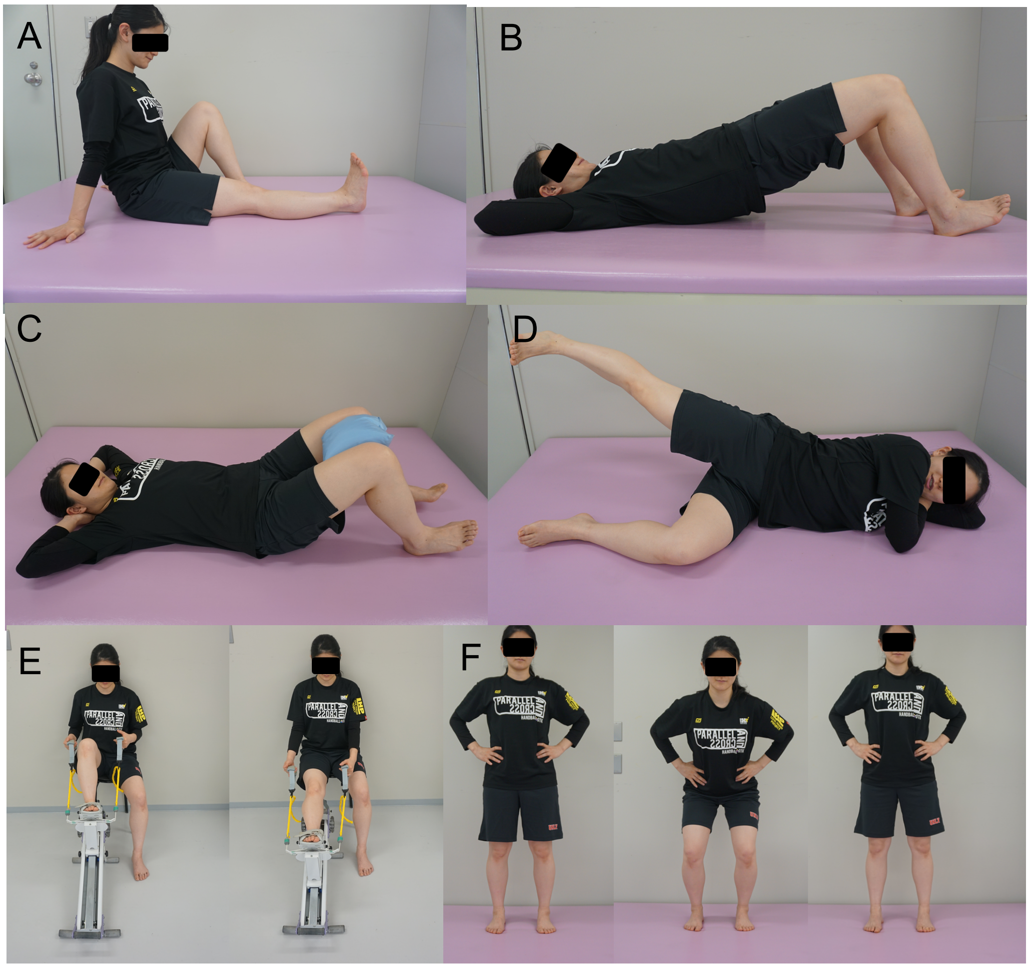

Figure 2. Six exercises performed by the control group.

A. Patella setting (the quadriceps activation). B. Bridge (the gluteus major and hamstrings activation). C. Isometric hip adduction (the hip adductors activation). D. Isometric hip abduction (the hip abductors activation). E. A leg press activity from 90° to 0° with the tibia in neutral internal/external rotation using ReaLine LegPress. F. A squat activity without tibial internal/external rotation from 0° to 60° flexion.

Compliance

A self-recording journal of home exercises was provided to the participants to evaluate adherence status. The recorded journal was shown to the therapist during the intervention sessions, so that the therapist modified the home exercise protocol to maximize the effectiveness.

Outcomes

Primary outcome variable was knee kinematics during the squat activity, namely knee adduction, external rotation, and lateral translation. Secondary outcome variable was MME volume and MME width in knee extension in the supine position.

Imaging

Squatting activity was chosen for knee kinematic analyses using sagittal fluoroscopy because of higher reproducibility compared with gait. A wide-based squatting activity was utilized to avoid overlapping of the contralateral knee using a single-planar fluoroscopic system with the imaging frequency of 15 Hz (SONIALVISION safire 17, Shimadzu Corporation, Kyoto, Japan). Participants started squatting from the fully extended position of the knee, flexed their knees to 90° in four seconds, and extended to the fully extended position in four seconds. The participants practiced the squatting activity in order to learn timing and speed in advance of imaging.

CT scanning were performed in order to create geometric femoral and tibial bone models. The participants underwent scanning with their knees fully extended in the supine position without loading using a CT scanner (Aquilion TSX-101A, Toshiba Medical Systems, Otawara, Japan). Axial slices were obtained with the settings of kilovoltage: 120 kVp, tube current: 70 mA, exposure time: 500 ms, exposure: 70 mAs, slice thickness: 0.50 mm, sampling 150 × 150 mm in-plane sampling, and imaging matrix: 512 × 512.

MRI scanning was conducted using a 1.5-tesla MRI scanner (MAGNETOM Aera, Siemens, Germany) and a knee coil (Tx/Rx 15-Channel Knee Coil, Siemens, Germany). The participants lay down on the scanner table with their knees fully extended without load in the supine position with the heels lifted by towel rolls to assure that the knee is fully extended under the gravity. Coronal slices of proton density sequences were used with the settings of slice thickness: 2.0 mm, intersection gap: 0 mm, slice resolution: 180 × 180 mm, imaging matrix: 384 × 384, acquisition time: 3m 58s, TE time: 11 ms, TR time: 3810 ms.

Models and Coordinate Systems

Geometric bone models of the femur and tibia were created from the CT images. Contour of cortical bone of the femur and tibia were manually segmented, and geometric bone models were created using a three-dimensional modelling software (3D-DOCTOR, Able Software Corporation, Lexington, MA). The bone models were smoothed using a reverse engineering software (Geomagic Studio 2013, Geomagic Inc., Research Triangle Park, NC).

Local coordinate systems were embedded onto the femur and tibia using a commercially available software (3D-Aligner, GLAB Corporation, Higashihiroshima, Japan). The femoral coordinate system was embedded in the distal femur using a virtual cylinder (Figure 3). The virtual cylinder consists of medial and lateral cylinders that share a co-axis and are size-adjustable independently. The cylindrical axis (medial/lateral axis), or Z-axis, was defined as a reference line of the femoral coordinate system. The femoral origin was defined as the midpoint between the medial and lateral ends of the cylindrical axis, which were defined as points on the cylindrical axis crossing the bony surface medially and laterally, respectively. A plane through the origin perpendicular to the Z-axis was defined as the sagittal plane on which the vertical axis (superior/inferior axis) or Y-axis, was located. The distal one-third of the femoral shaft was projected onto the sagittal plane and the central line of the projected femoral shaft was drawn. A line through the origin parallel to this central line in the sagittal plane was defined as the Y-axis. The anteroposterior axis, or X-axis, was defined as the cross product of the Z- and Y-axes.

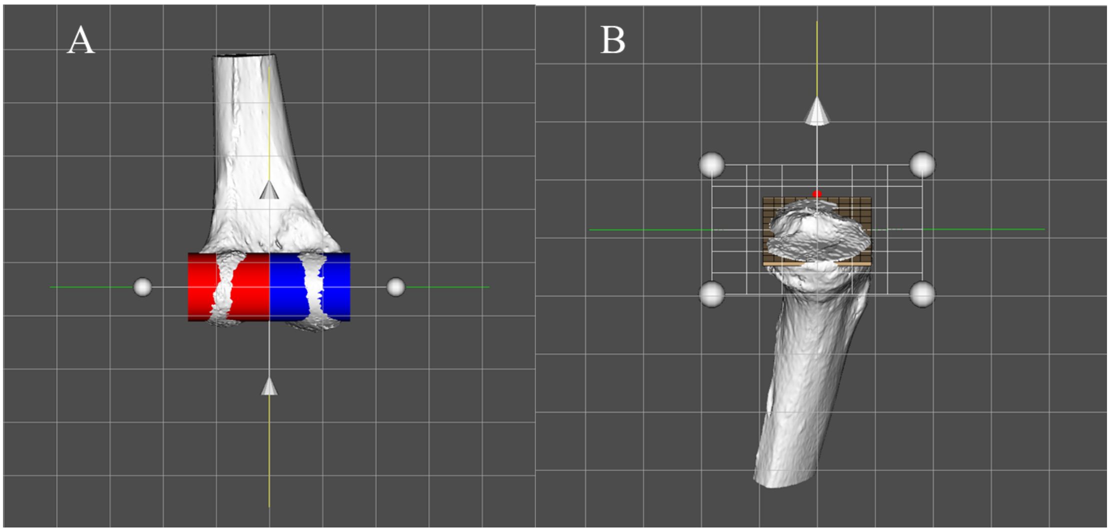

Figure 3. Method of embedding local coordinate systems of the femur and tibia.
A. The local coordinate system of the femur.
B. The local coordinate system of the tibia.

The tibial coordinate system was embedded in the proximal tibia using a virtual rectangle (Figure 3). A virtual rectangle was manipulated to be parallel to the tibial plateau plane, and fitted onto the contour of the tibial plateau at the top level of the fibular notch of the tibia. The top level of fibular notch was chosen because there is similarities in the contour and orientation of the mediolateral rotational axis to the tibial plateau, and there are no osteophytes even in the osteoarthritic knees. Four sides of the rectangle were fitted onto the tangent of the posterior contours of the medial and lateral tibial condyles, the medial and lateral tangents of the medial and lateral tibial condyles, and the anterior tangent of the medial tibial condyle. Then, the fitted rectangle was transferred superiorly along the vertical line perpendicular to the rectangle to the bottom of the medial tibial plateau. The origin of the tibial local coordinate system was defined as the center of the rectangle, and the medial/lateral (Z) and anteroposterior (X) axes were defined parallel to two sides of the rectangle. The superior/inferior (Y) axis was defined as a cross product of the X- and Y-axes.

The reliability of embedding the coordinate systems onto the tibia and femur with osteoarthritic changes were examined in a previous dissertation from our laboratory[11]. The intra-researcher errors of embedding the femoral coordinate system onto the OA femur for the X- and Y- and Z- axes were 0.20 [0.01, 0.40] mm/0.10 [0.05, 0.15]°, 0.09 [0.03, 0.15] mm/0.54 [0.24, 0.84]°, and 0.49 [0.16, 0.82] mm/0.43 [0.25, 0.61]°, respectively[11]. The intra-researcher errors of the OA tibia for the X- and Y- and Z- axes were 0.56 [0.22, 0.91] mm/0.86 [0.32, 1.40]°, 0.15 [0.08, 0.23] mm/0.39 [0.28, 0.50]°, and 0.21 [0.03, 0.40] mm/0.78 [0.28, 1.28]°, respectively[11].

3D-to-2D registration

In vivo three-dimensional (3D) positions and orientations of the femur and the tibia were determined using a 3D-to-2D registration technique[25]. The femoral and tibial bone models were projected onto the fluoroscopic images, and its six degree-of-freedom (6DOF) positions and orientations were iteratively adjusted to match with the bony outer edge on the fluoroscopic images using a custom image registration program (JointTrack, University of Florida, FL) (Figure 4). The estimated accuracy of the registration method was 0.53 mm for in-plane translation, 1.6 mm for out-of-plane translation, and 0.54° for rotations[26]. Out-of-plane translation was excluded from the analysis because of the lower accuracy due to lateral fluoroscopy. 6DOF joint kinematics were computed using a commercial software (3D-JointManager, GLAB Corporation, Higashihiroshima, Japan). The joint coordinate system utilized in this software was based on the projection angles of the fixed tibial coordinate system. Kinematic data for tibial anterior translation, adduction and external rotation as a function of knee flexion angles with an increment of 10° were analyzed.

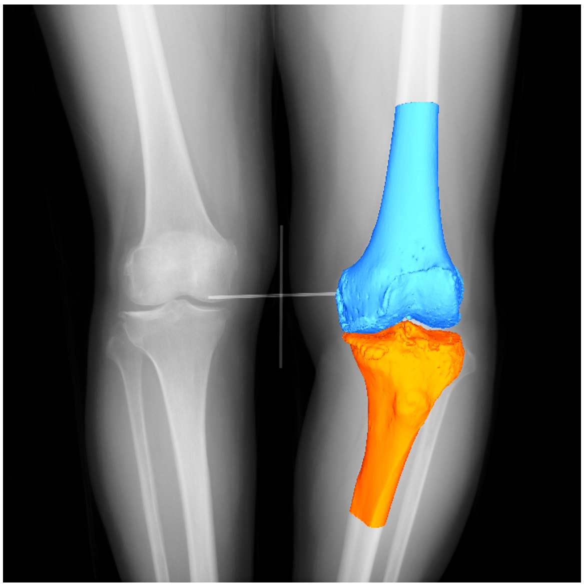

Figure 4. Matching of the femur and tibia bone during stepping activity using 3D-to-2D registration technique.

Medial Meniscus Extrusion (MME)

Medial meniscus models to analyze the MME width and volume were created from MRI. Contour of cortical bone of the femur and tibia and that of the medial meniscus were manually segmented, and geometric bone and meniscal models were created using 3D-DOCTOR. The bone and meniscus models were smoothed using Geomagic Studio 2013. The local coordinate systems of the MRI-derived tibia and femur were defined using the coordinate systems on the CT-derived models. A best-fit algorism in the Geomagic Studio 2013 was used obtain the combined CT-derived and MRI-derived models, and the coordinate system of the CT-derived models were shared by the MRI-derived models.

A model of the medial tibial plateau was created by cutting the MRI-derived tibial bone model at the level at 10.0 mm inferior from the origin parallel to the XY plane. Then, the contour of the cross-sectional model was thickened superiorly for 30.0 mm to create a thickened cross-sectional model (thickened model). MME volume was defined as the volume of the MM model outside the thickened model. MME width was the distance between the contour of the thickened model and the most medial contour of the MM on the Z-axis (Figure 5).

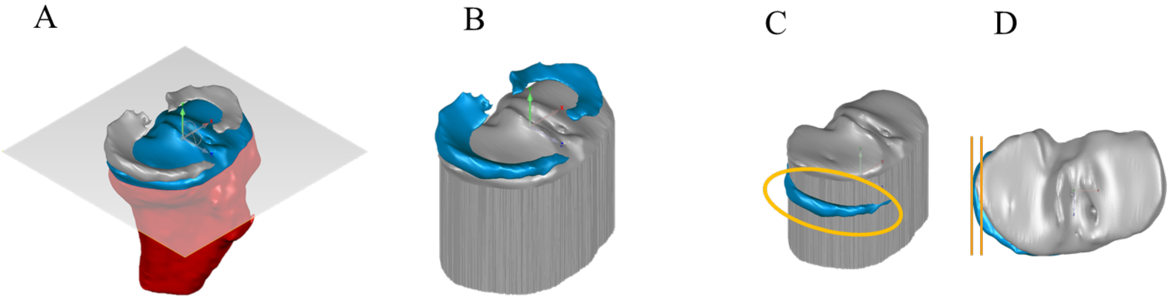

Figure 5. Creating the medial meniscal extrusion model using a coronal MRI.

A. The medial plateau model (blue) and the meniscus model (gray) are shown. The tibial plateau model is created by cutting the original tibial bone model at the level of 10.0 mm inferior to the tibial plateau (the ZX plane).

B. The meniscus model (blue) and the thickened cross-sectional model (gray) are shown.

C. The medial meniscus is shown in blue color. The MME volume is defined as the volume of the medial meniscus model outside the thickened cross-sectional model.

D. The MME model (blue) and the tibial plateau are shown from the axial view. The MME width is the distance from the outer edge of the thickened model to the outer edge of the medial meniscus model through the Z-axis.

Statistical analysis

Sample size was calculated based on the primary outcome (knee kinematics during stepping activity) using a power analysis program (G*Power version 3.1.9.2, Franz Faul, Germany). A sample size of 17 patients was needed to provide moderate effect size (f = 0.25), alpha level of 0.05, power of 0.8, numerator difference = 6, number of groups = 14 with statistical design of F test of two-way ANOVA (fixed effects, special, main effects and interactions). Assuming a 15% dropout to follow-up, 20 patients were enrolled for each group.

The statistical analyses were performed on an intension-to-treat basis. All data were normally distributed using the Shapiro-Wilk test. The primary and secondary outcome analyses were conducted using two-way repeated-measure ANOVA with Sidak post hoc test. Statistical analyses were performed using a statistical software and post hoc analyses were performed using SPSS Statistics version 23 (IBM Corporation, Armonk, NY). Effect sizes were obtained using G*Power version 3.1.9.2 (Franz Faul, Germany). A significance level was set at $\alpha = 0.05$.

Results

Demographics

327 patients who visited the center to see the surgeon who was in charge of recruitment was assessed for eligibility criteria (Figure 6). At baseline, 39 participants who met all the criteria was randomly allocated into the RRR group and the control group with the sample sizes of 19 and 20 participants, respectively. Screening was started on January 15, 2016 and continued to December 5, 2018 on that day targeted number of participants was satisfied. 19 participants of the RRR group

completed the intervention, and 1 participant dropped out because of deciding to receive unilateral knee arthroplasty. 18 participants of the control group completed the intervention, and 2 participants dropped out because of another joint disease and internal medical disease. The RRR group and the control group had baseline age (median [interquartile range]) 71 (69–75) and 71 (66–74), height (mean [95% coefficient interval]) 155.9 [152.1, 159.7] cm and 155.7 [152.3, 159.0] cm, body mass 58.2 [54.5, 61.9] kg and 60.7 [55.6, 65.7] kg, and body mass index (BMI) 24.0 [22.6, 25.3] kg/m^2 and 25.0 [23.0, 27.1] kg/m^2, respectively, with no significant differences (Table 1).

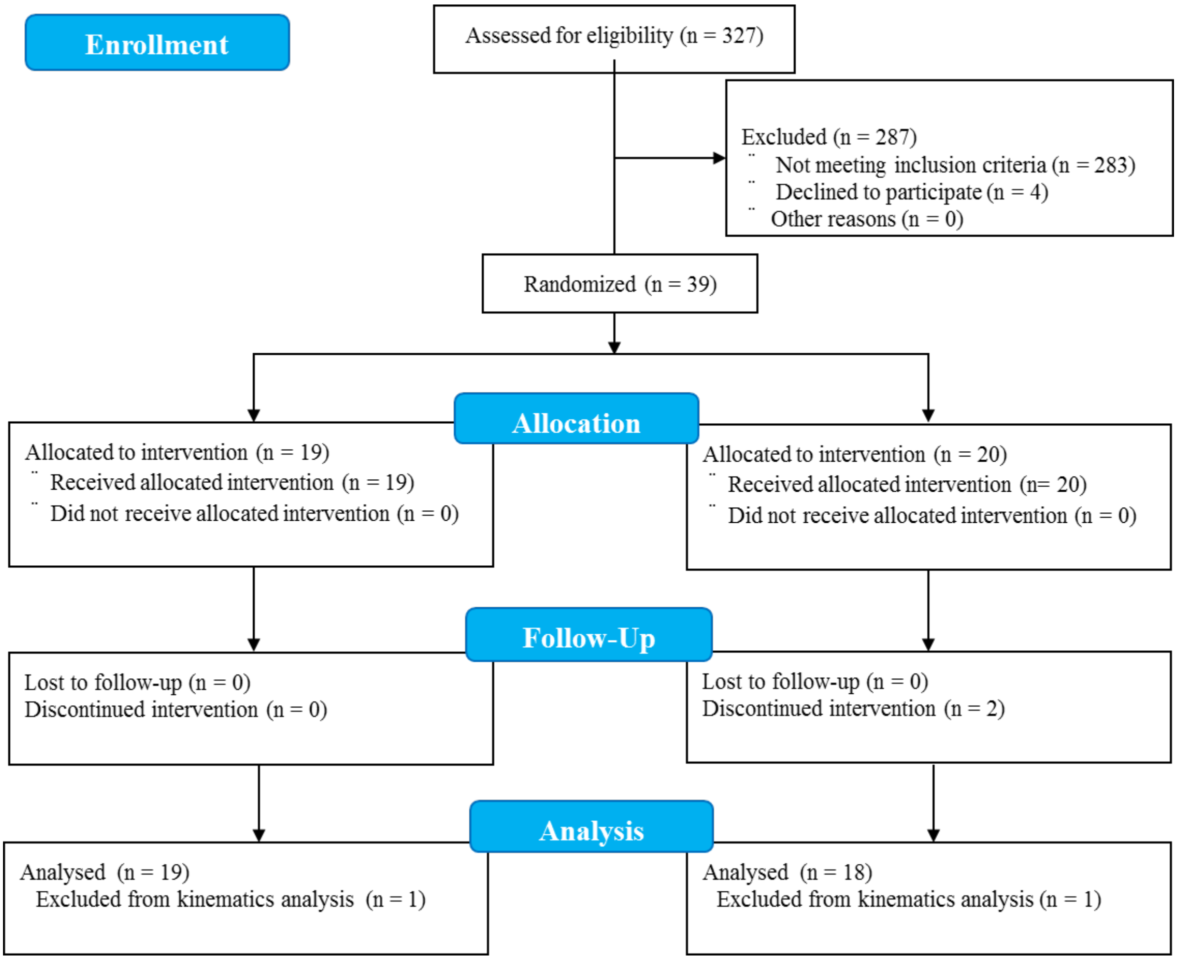

Figure 6. Flow diagram of the progress through the phases of this randomized controlled trial.

Table 1. Demographic data of the RRR and control group at pre- and post-intervention

Variables	RRR group (n = 19)		Control group (n = 20)		P-value
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	
Sex	13 females 6 males		14 femaies 6males		
Age (years)	71 (69–75)		71 (66–74)		0.771
Height (cm)	156.2 [152.3, 160.2]		155.7 [152.3, 159.0]		0.819
Body mass (kg)	58.3 [54.4, 62.3]		60.7 [55.6, 65.7]		0.449
BMI（kg/m^2）	23.9 [22.5, 25.3]		25.0 [23.0, 27.1]		0.340
Radiographic severity					
KL grade 1	6 (6)		6 (4)		
KL grade 2	4 (1)		5 (2)		
KL grade 3	9 (6)		9 (8)		

Age was shown as median [interquartile range], and height, body mass, and BMI are shown as means [95% coefficient interval]. KL grade is presented as number (number of females). P-values are shown for between group comparisons from Man-Whitney U test for age and t-test for height, body mass and BMI. RRR = rotation restoration and realignment; BMI = body mass index; KL = Kellgren-Lawrence.

Kinematics

There were no interactions of the intervention and knee flexion angle on tibial lateral translation (p = 1.000), adduction (p = 0.999) and internal rotation (p = 1.000) in the RRR group. In addition, there were no interactions on tibial lateral translation (p = 0.998), adduction (p = 0.512) and internal rotation (p = 0.971) in the control group.

Both the RRR and control groups demonstrated no differences in tibial lateral translation in each knee flexion angle between pre- and post-intervention. Greater tibial lateral translation with knee extension at post-intervention in the RRR group (between 15° and 25°, 15° and 30°, and 20° and 30°, p = 0.017, 0.001, 0.024, respectively) (Table 2, Figure 7). Both the RRR and control groups demonstrated no differences in knee adduction in each knee flexion angle between pre- and post-intervention and greater knee adduction as knee flexion angle increased at both pre-intervention (between 15° and 20°, 15° and 25°, 15° and 30°, and 20° and 30°, p = 0.035, 0.002, < 0.001, and < 0.001, respectively) and post-intervention (between 15° and 25°, 15° and 30°, and 20° and 30°, p = 0.002, < 0.001, and < 0.001, respectively) (Table 2, Figure 8). Both the RRR and control groups demonstrated no differences in tibial internal rotation in each knee flexion angle between pre- and post-intervention and there were no significant difference in tibial internal rotation as knee flexion angle increased at both pre- and post-intervention (Table 2, Figure 9).

Table 2. Tibial kinematics during stepping activity of the RRR and control group at pre- and post-intervention.

	Knee flexion angle	RRR group				Control group			
		Pre-intervention	Post-intervention	P-value	Effece size	Pre-intervention	Post-intervention	P-value	Effect size
Lateral translation (mm)	15°	5.4	5.3 † ‡	1.000	0.03	4.7	4.2	1.000	0.16
		[4.1, 6.7]	[4.0, 6.6]			[3.4, 6.0]	[2.9, 5.5]		
	20°	5.0	4.9 ||	1.000	0.03	4.3	4.1	1.000	0.10
		[3.7, 6.3]	[3.6, 6.2]			[3.0, 5.7]	[2.7, 5.4]		
	25°	4.8	4.5	1.000	0.11	4.3	3.8	0.992	0.20
		[3.5, 6.1]	[3.2, 5.8]			[3.0, 5.7]	[2.4, 5.1]		
	30°	4.9	4.2	0.983	0.24	4.1	3.6	0.999	0.14
		[3.5, 6.2]	[2.8, 5.6]			[2.7, 5.5]	[2.2, 5.0]		
Adduction (°)	15°	2.6*†‡	2.3† ‡	1.000	0.10	3.4† ‡	2.0† ‡	0.519	0.59
		[1.3, 3.4]	[1.2, 3.5]			[2.2, 4.6]	[0.9, 3.2]		
	20°	3.1 § ||	2.7 § ||	0.998	0.14	3.9 §	2.5||	0.499	0.63
		[1.5, 3.7]	[1.6, 3.9]			[2.7, 5.1]	[1.3, 3.7]		
	25°	3.6¶	3.3¶	1.000	0.08	4.6	2.9	0.288	0.84
		[2.0, 4.2]	[2.2, 4.5]			[3.3, 5.8]	[1.6, 4.1]		
	30°	4.0	3.8	1.000	0.06	4.4	3.3	0.715	0.57
		[2.9, 5.1]	[2.7, 5.0]			[3.2, 5.7]	[2.1, 4.5]		
Internal rotation (°)	15°	2.5	2.7	1.000	0.03	4.5	2.2	0.926	0.33
		[-0.6, 5.7]	[-0.5, 6.0]			[1.0, 7.9]	[-1.1, 5.5]		
	20°	2.6	2.2	1.000	0.10	4.9	3.2	0.982	0.26
		[-0.6, 5.8]	[-1.1, 5.4]			[1.4, 8.3]	[-0.2, 6.5]		
	25°	2.8	1.9	0.999	0.11	4.8	3.4	0.994	0.21
		[-0.4, 6.0]	[-1.4, 5.2]			[1.3, 8.3]	[0.1, 6.8]		
	30°	2.8	1.6	0.994	0.18	4.9	3.7	0.997	0.19
		[-0.2, 5.9]	[-1.5, 4.7]			[1.6, 8.1]	[0.5, 6.9]		

Values are shown as mean [95% coefficient interval]. RRR = rotation restoration and realignment.

* significant between 15° and 20°, † significant between 15° and 25°, ‡ siginificant between 15° and 30°, § sigfinicant between 20° and 25°, || significant between 20° and 30°, ¶ siginificant between 25° and 30°.

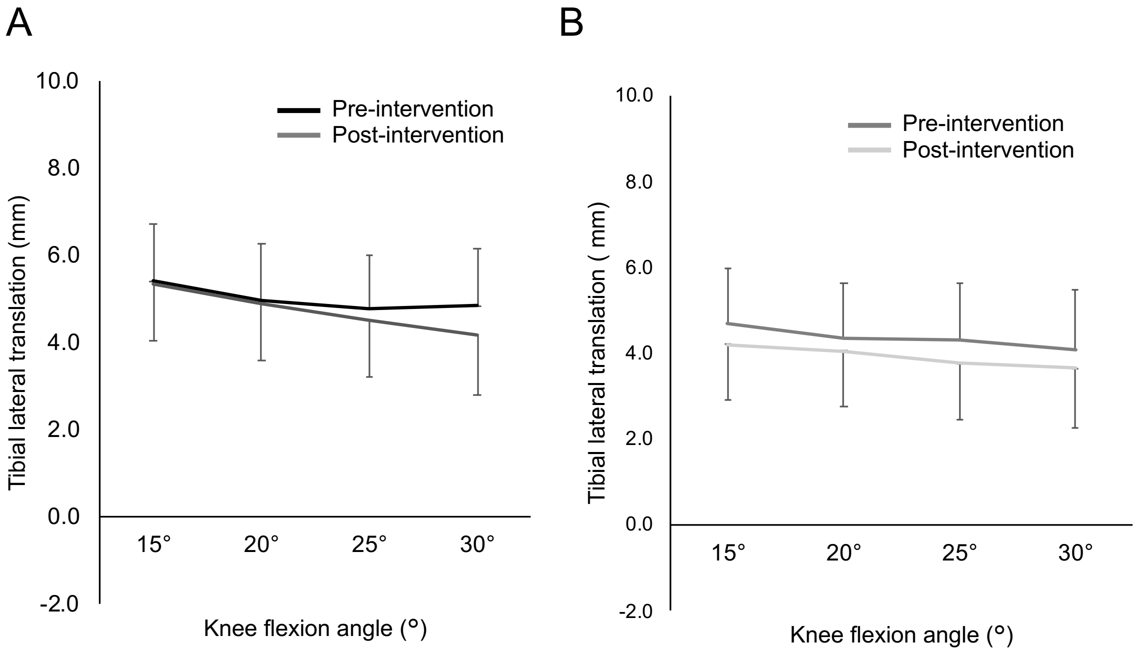

Figure 7. Tibial lateral translation of the RRR and control groups at pre- and post-intervention.

A. Tibial lateral translation of the RRR group.

B. Tibial lateral translation of the control group.

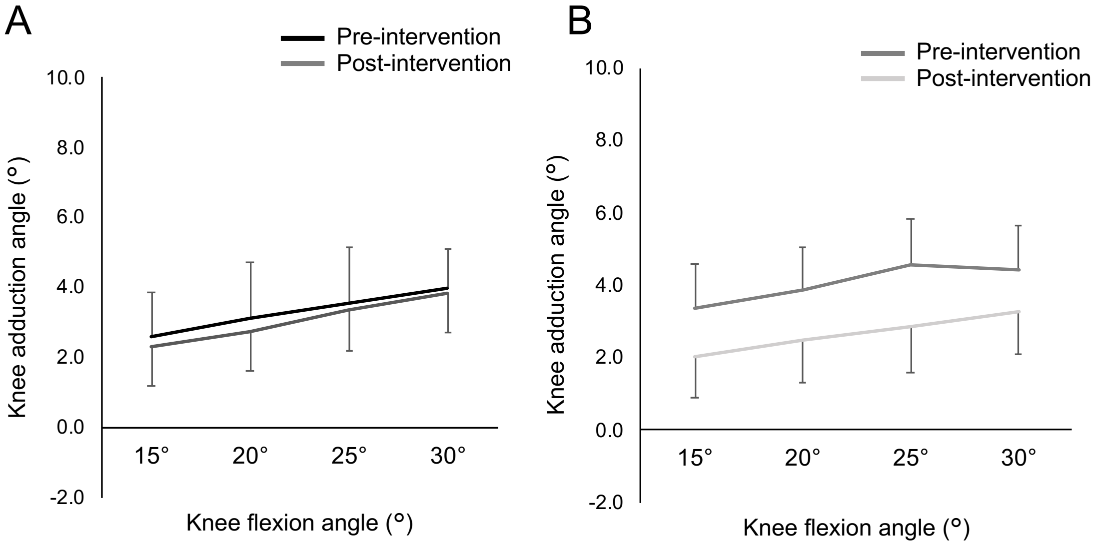

Figure 8. Knee adduction angle of the RRR and control groups at pre- and post-intervention.

A. Knee adduction angle of the RRR group.

B. Knee adduction angle of the control group.

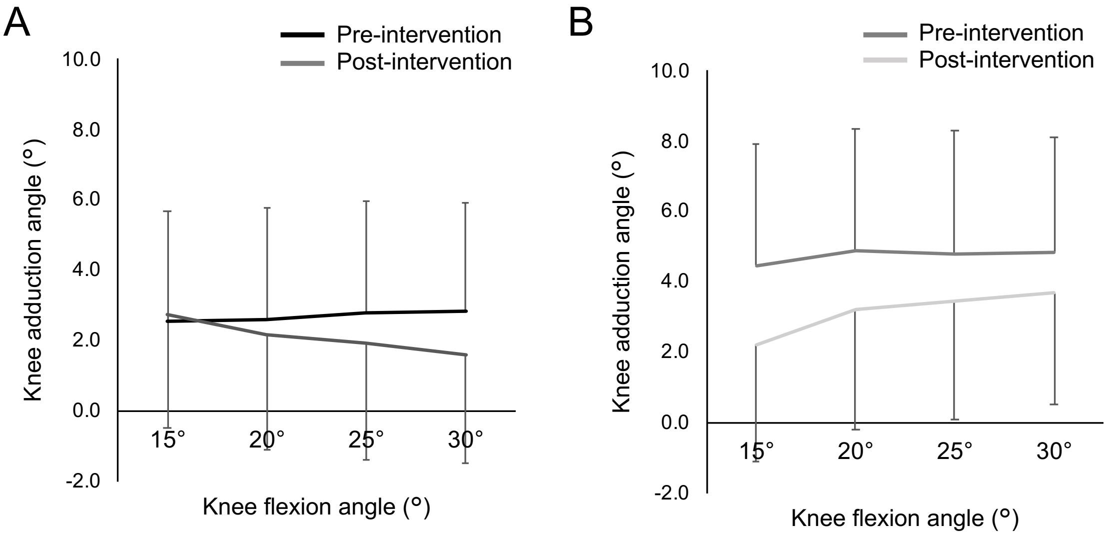

Figure 9. Tibial internal rotation angle of the RRR and control groups at pre- and post-intervention.
A. Tibial internal rotation angle of the RRR group.
B. Tibial internal rotation angle of the control group.

MME volume and MME width

MME volume and MME width in both the RRR group and the control group did not change significantly. MME volume at pre- and post-intervention were 1142 mm^3 and 1147 mm^3 in the RRR group, and 1154 mm^3 and 1171 mm^3 in the control group, respectively (Table 3). MME width at pre- and post-intervention were 5.1 mm and 5.2 mm in the RRR group, and 5.1 mm and 5.3 mm in the control group, respectively. Knee adduction with knee extended without loading at pre- and post-intervention were -0.3 [-1.4, 0.9]° and -0.4 [-1.6, 0.8]° in the RRR group, and -0.9° and -1.0° in the control group, respectively. Tibial internal rotation at pre- and post-intervention were 0.8 [-2.2, 3.8] mm and 0.9 [-2.4, 4.3] mm in the RRR group, and 0.5 [-1.8, 2.8] mm and 0.2 [-2.7, 3.0] mm in the control group, respectively. Knee flexion at pre- and post-intervention were

-3.2 [-6.2, -0.2]° and -4.3 [-7.0, -1.9] ° in the RRR group, and -4.7 [-6.9, -2.6] ° and -4.8 [-7.6, -2.0] ° in the control group, respectively. Tibial anterior translation at pre- and post-intervention were 4.6 [3.1, 6.1] mm and 4.4 [2.7, 6.1] mm in the RRR group, and 3.2 [1.7, 4.8] mm and 3.2 [1.7, 4.7] mm in the control group, respectively. Tibial lateral translation at pre- and post-intervention were 5.0 [4.1, 5.9] mm and 5.0 [4.1, 5.9] mm in the RRR group, and 4.0 [2.8, 5.1] mm and 4.0 [2.8, 5.3] mm in the control group, respectively.

Table 3. Volume and width of medial meniscal extrusion (MME) and knee alignment at pre- and post-intervention

	RRR Group			Control Group			P-value
	Pre-intervention	Post-intervention	P-value	Pre-intervention	Post-intervention	P-value	
MME volume (mm^3)	1142	1147	0.323	1154	1171	0.233	0.848
	[865, 1418]	[876, 1418]		[850, 1458]	[838, 1503]		
MME width (mm)	5.1	5.2	0.890	5.1	5.3	0.685	0.842
	[3.7, 6.4]	[3.9, 6.5]		[3.7, 6.6]	[3.8, 6.8]		
Knee alignment							
Adduction (°)	-0.3	-0.4	0.111	-0.9	-1.0	0.620	0.440
	[-1.4, 0.9]	[-1.6, 0.8]		[-2.1, 0.0]	[-2.3, 0.1]		
Internal rotation (°)	0.8	0.5	0.682	0.9	0.2	0.184	0.499
	[-2.2, 3.8]	[-1.8, 2.8]		[-2.4, 4.3]	[-2.7, 3.0]		
Flexion (°)	-3.2	-4.3	0.115	-4.7	-4.8	0.769	0.366
	[-6.2, -0.2]	[-7.0, -1.9]		[-6.9, -2.6]	[-7.6, -2.0]		
Anterior translation (mm)	4.6	4.4	0.296	3.2	3.2	0.920	0.509
	[3.1, 6.1]	[2.7, 6.1]		[1.7, 4.8]	[1.7, 4.7]		
Lateral translation (mm)	5.0	5.0	0.991	4.0	4.0	0.528	0.656
	[4.1, 5.9]	[4.1, 5.9]		[2.8, 5.1]	[2.8, 5.3]		

Values are shown as mean [95% coefficient interval]. P-values within group and p-value between groups are shown. RRR = rotation restoration and realignment; MME = medial meniscal extrusion.

Discussion

This study aimed to reveal the potential effects of an exercise program designed to induce tibial medial translation on knee kinematics and the MME in individuals with KOA. The findings of this study were that there was no significant difference in tibial lateral translation, adduction and internal rotation during stepping activity between pre- and post-intervention, and that there was no significant difference in the MME volume, MME width, and knee alignment without loading between pre- and post-intervention.

Kinematics in patients with medial KOA showed tibial external rotation, adduction, and posterior translation [5, 27]. Hamai et al.[12] reported that KOA patients immediately before total knee arthroplasty showed knee adduction of 3.7°, external rotation, and lateral translation of 7.4 mm during stepping activity. Amount of tibial lateral translation in this study was smaller than that in the previous study. This may be caused by difference of KL grades. Ikuta et al.[27] reported that increase of knee adduction was observed as knee flexion angle increased from 10° to 30° during a squatting activity. The same trend of knee adduction was observed in this study. In the same study by Ikuta et al. [27], increase of tibial external rotation was observed as knee flexion angle decreased from 30° to 10° during the squatting activity. In the RRR group, the similar kinematics was observed at pre-intervention. However, decrease of tibial internal rotation as the knee flexed was observed at post- intervention. The RRR program was designed to induce tibial internal rotation by activating the medial hamstrings repeatedly. Actual kinematics during the RRR program should be investigated in the future studies.

The MME volume, MME width, and knee alignment without loading did not show significant difference between pre- and post-intervention in the both RRR and control groups. The MME may be appeared by being pushed by the medial femoral condyle on the tibial plateau. However, the RRR program and conventional exercise program also did not change knee kinematics at pre- and post-interventions. Effective exercise program on the MME has been unclear.

This study employed stratified sampling with sex. As a result, number of females and males were nearly the same. On the other hand, number of participants with KL grade was not equal. Knee kinematics in patients with medial KOA was different between the KL grades[27]. Specific exercise program might be needed in the process of KOA progression. Characteristics of the participants in both groups were appropriate to the representative of primary and medial KOA. A single researcher embedded the local coordinate systems of the tibia and femur, which reduced potential errors. This study had dropout of two participants in the control group. Reasons for the dropout were discovering another joint disease or cancer, and no adverse event from the intervention. Home exercise in the both groups were carried out without causing any problems on the knee. The results of this study can be applied to primary medial KOA patients with mild and moderate osteoarthritic change.

This study had a few limitations. Firstly, this study employed the stepping activity to analyze knee kinematics. Daily symptoms appear during activities such as walking, stairs, and squatting activities in patients with medial KOA. The result of study cannot directly apply to these activities. Secondly, this study had no participants with KL grade 0. In recent years, understanding pathology of early-stage KOA attracts researchers' attention. Development of exercise therapy for earlier-stage KOA would be needed in order to prevent onset and progression of KOA. Further studies would be conducted that includes patients with early-stage KOA or so-called healthy subjects.

In conclusion, the RRR program with tibial internal rotation exercise did not improved knee kinematics, the MME volume or MME width in patients with mild and moderate medial KOA. Development of an exercise program to improve knee kinematics would have social and clinical value to improve patients' activities of daily living and QOL and contribute to prevent KOA progression.

Conclusions

Conclusion of this study was that the RRR program with tibial internal rotation exercise and the conventional exercise program did not improve knee kinematics during stepping activity in patients with mild and moderate medial KOA.

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CHAPTER 5

Effects of an exercise program with tibial internal rotation on symptoms, physical function, and external knee adduction moment during gait in patients with knee osteoarthritis: A randomized controlled trial

Introduction

Knee osteoarthritis (KOA) is a common musculoskeletal disease with difficulties in the daily activities. 3.8 (95% uncertainty interval: [3.6, 4.1])% of the population in the world had symptomatic radiographic KOA[1]. It accounts for 267 million patients with KOA using the number of the world population in 2010. Representative symptoms of KOA are knee pain, swelling, and stiffness. Symptoms of KOA were reportedly associated with decline in activities of daily living, limitation of participation and anxiety or depression, and consequently led to decline in quality of life (QOL)[2]. In addition, one or more coexistent diseases were accompanied with patients with KOA or hip osteoarthritis[3]. Caporali et al.[4] concluded that comorbidities decreased the QOL and worsen the joint function in patients with OA of the hand, knee, or hip. Prevalence rate of symptomatic radiographic KOA would rise with aging[1, 5, 6]. The number of aged people was reportedly 0.6 billion in 2015, and would increase to 1.3 billion in 2040[7]. Patients with KOA will increase in the future. Therefore, development of treatment for KOA would be an urgent necessity.

Exercise therapy on KOA reduced knee pain, and improved physical function[8, 9]. The quadriceps muscle strengthening reduced knee pain in patients with varus or neutral knee alignment[10]. However, a systematic review on exercise therapy concluded that exercise program did not decrease external knee adduction moment (KAM)[11]. Quadriceps muscle strengthening did not decrease peak KAM during gait neither in patients with varus knee alignment from baseline 4.28 ± 0.63 to post-intervention 4.40 ± 0.76 Nm/BW/HT, where BW stands for body weight (kg) and HT stands for height (m), or in patients with neutral knee alignment from baseline 3.58 ± 0.94 to post-intervention 3.63 ± 1.11 Nm/BW/HT [10].

The hip adductor muscle strengthening reduced knee pain, but did not decrease peak KAM in patients with KOA from baseline 2.97 [2.70, 3.24] to post-intervention 2.96 [2.68, 3.24] Nm/kg, and in the control participants from 2.47 [2.28, 2.66] to 2.52 [2.31, 2.73] Nm/kg[12]. On the other hand, there are a few positive studies. An exercise program including strengthening of the quadriceps, hamstrings, and hip abductors decreased about 9% of peak KAM during gait[13]. In addition, eight-week combination of lower leg muscles strengthening and neuromuscular control did not decrease peak KAM during gait, but significantly decreased peak KAM during one-leg rising activity[14]. Therefore, effects of exercise therapies on the knee kinetics in KOA patients are controversial. The objective of this study was to determine if an exercise therapy would improve symptoms and knee kinetics in patients with KOA.

KAM during gait was greater in patients with medial KOA[12, 15]. Some gait training programs reportedly decreased KAM. KAM after gait modification interventions with visual feedback of KAM for six months was lower than KAM after walking exercise[16]. KOA comparing to knees without OA had significantly higher peak KAM (2.96 ± 0.93 vs. 3.65 ± 1.23 Nm/BW/HT, respectively) and peak lever arm (2.46 ± 0.82 vs. 3.25 ± 1.03 cm, respectively) [17]. In addition, foot plantar pressure pattern of KOA patients demonstrated significantly smaller center of pressure (COP) index (-5.87 ± 5.6) than healthy controls (-0.45 ± 3.05), indicating KOA patients loaded on more lateral aspect of the foot during stance phase of gait[18]. Accordingly, biomechanical approach may be an important component of exercise program in order to reduce KAM. A leg press activity with tibial internal rotation (Rotation Restoration and Realignment (RRR) program) would be a possibility of achieving the kinetic change. The RRR program instantly decreased visual distance between the medial condyles of the femur during standing from 5.1 ± 2.8 to 4.5 ± 2.8 cm[19]. The RRR program demonstrated medial shift of the COP during gait[20]. It is speculated that higher recruitment of the medial hamstrings caused by internal tibial rotation might induce medialization of the tibia. From the above, the RRR program may reduce KAM in KOA by shortening lever arm and/or shifting the COP medially.

The hypotheses of this study were that the leg press activity with tibial internal rotation would 1) reduce knee pain and improve physical function, and 2) reduce KAM. To test the hypotheses, a small randomized controlled trial utilizing a three-dimensional motion analysis system and questionnaire were used, and results were compared between the RRR program and conventional exercise program. Significance of this study was to determine effects of exercise therapies on KAM, knee pain, joint stiffness and physical function, and to contribute to development of treatment methods for KOA and delay of KOA progression.

Materials and Methods

Study design

This study was a single-blinded, randomized controlled trial (RCT). Protocol of this study involved a baseline data acquisition, intervention for three months, and data acquisition after intervention. This RCT was approved by the institutional review boards (IRB) of Hiroshima Prefectural Rehabilitation Center and Hiroshima International University (approval number: 19–029). Participants of this study was recruited from the outpatients with KOA visiting Department of Orthopaedics at Hiroshima Prefectural Rehabilitation Center in Higashihiroshima City.

Higashihiroshima is a medium-sized city with the population of about 185,000 in 2017. Hiroshima Prefectural Rehabilitation Center has 160 hospital beds and is fulfilling a central role in providing artificial joint surgeries in the local area. Single experienced orthopaedic surgeon was in charge of recruitment. Recruitment was continued until the needed sample size of participants was enrolled. Written informed consent, approved by the IRB, was obtained from all the individual participants included in this study.

Eligibility criteria

Inclusion criteria of this study were Japanese, aged from fifty to eighty, primary medial KOA, and Kellgren-Lawrence (KL) grade 1 to 3. Exclusion criteria were valgus deformity, secondary KOA, history of knee injury or knee surgery, undertaking physical therapy or having a plan to undertake physical therapy at another medical institution, inflammatory diseases (for example rheumatoid arthritis and gout), difficulty in visiting Hiroshima Prefectural Rehabilitation Center regularly, difficulty in undertaking exercise therapy for some reasons, having risks of internal medicine, impaired cognitive function, mental illness, or communication disorders. Discontinuance criteria were withdrawal request from participants, difficulty in continuing intervention due to worsening of KOA symptoms and/or coexisting illness, apparent lack of compliance, and surgeon's judgement to abandon the intervention for some reasons.

Allocation and blinding

Participants was randomly allocated to one of the two groups: the RRR group performing tibial internal rotation exercises and control group performing general muscle strengthening exercises. Random allocation stratified by sex using a computer-generated random table was performed in the sequential order of consenting participation. Participants, the surgeon and a researcher who performed biomechanical testing were blinded from allocation until the outcome assessments were finished. The analysis was performed by a single investigator who was blinded until the outcome assessments were finished.

Interventions and compliance

Intervention was performed by two physical therapists on a one-to-one basis in a room invisible from outside and the participants were not allowed to communicate with each other. Concealing the allocation information for therapists was impossible because the same physical therapists performed the interventions for both groups. The intervention manuals for both groups were provided to the therapists to assure that the same intervention was provided to all participants in each group.

Intervention were performed at the single medical institution. A forty minutes intervention session was given weekly for three months accompanied by home exercises which were given personally and modified at each intervention session considering participants' knee condition and familiarization of exercises to provide gradual load. Both groups used a commercial leg press device (ReaLine LegPress, GLAB Corporation, Higashihiroshima, Japan), which allows assistive or resistive tibial internal/external rotation, as well as a leg press activity with or without tibial rotation. There are a set of rubber bands on both sides of the foot plate, which allows assistive or resistive tibial internal rotation, as well as resistive leg press exercise with or without tibial rotation.

The RRR group performed three exercises (Figure 1); (1) tibial internal-external rotation exercises with the knee at 90°, (2) a leg press activity with tibial maximal internal rotation from 90° to 0° using ReaLine LegPress, and (3) a squat activity with tibial internal rotation (knee-out squat) from 0° to 60° flexion. The knee-out squat was instructed to stand with the feet at shoulder width apart, flex the knee to 60° in neutral position, perform knee-out motion by external rotation of the hip while the feet were maintained in the parallel position, then extend the knees to 0° while maintaining hip external rotation. Manual soft tissue release (inter-structural release: ISR) was given, if necessary, to increase the tibial internal rotation, which was targeted to the subcutaneous tissue of the popliteal region, the iliotibial tract, the biceps femoris, gastrocnemius, fibular longus, pes anserinus, patellar tendon, and the infrapatellar fat pad. Home exercises for the RRR group consisted of four exercises with the tibial internal rotation: sitting tibial internal rotation exercise with knee flexed, active knee extension exercise with the tibial maximal internal rotation, active knee flexion exercise with the tibial internal rotation, and the knee-out squat with hip in external rotation relative to the tibia, causing tibial internal rotation in the knee.

Figure 1. Three exercises of the RRR group.

A. Tibial internal-external rotation exercises with the knee at 90°. B. A leg press activity with tibial maximal internal rotation from 90 ° to 0° using ReaLine LegPress. C. A squat activity with tibial internal rotation (knee-out squat) from 0° to 60° flexion.

The control group performed six exercises (Figure 2); (1) patella setting (the quadriceps activation), (2) bridge (the gluteus major and hamstrings activation), (3) isometric hip adduction (the hip adductors activation), (4) isometric hip abduction (the hip adductors activation), (5) a leg press activity from 90° to 0° with the tibia in neutral internal/external rotation using ReaLine LegPress, and (6) a squat activity without tibial internal/external rotation from 0° to 60° flexion. Home exercises for the control group consisted of four exercises: patella setting, bridge, isometric hip adduction, and squat.

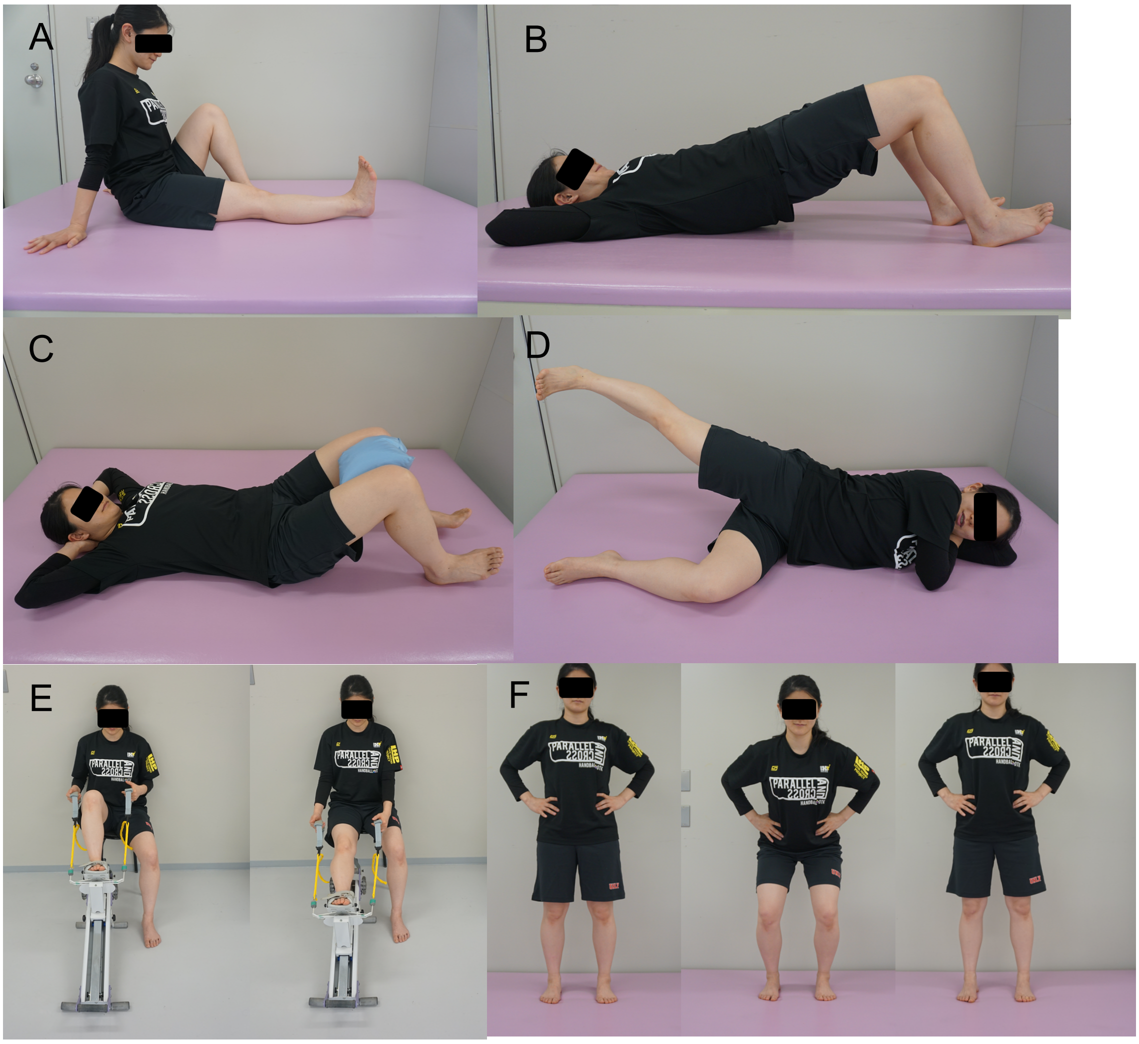

Figure 2. Six exercises performed by the control group.

A. Patella setting (the quadriceps activation). B. Bridge (the gluteus major and hamstrings activation). C. Isometric hip adduction (the hip adductors activation). D. Isometric hip abduction (the hip abductors activation). E. A leg press activity from 90° to 0° with the tibia in neutral internal/external rotation using ReaLine LegPress. F. A squat activity without tibial internal/external rotation from 0° to 60° flexion.

A self-recording journal of home exercises was provided to the participants to evaluate adherence status. The recorded journal was shown to the therapist during the intervention sessions, so that the therapist modified the home exercise protocol to maximize the effectiveness.

Data acquisition and analyses

Outcomes

Primary outcome variable was change of a pain component of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) involving self-reported knee pain, joint stiffness, and physical function. Secondary outcome variables were self-reported total score, stiffness, physical function, 1st and 2nd peak KAM.

Sequence of data acquisition was three-dimensional motion capture to analyze kinematics and kinetics, and the WOMAC questionnaire. Two researchers who were blinded from allocation collected data for kinematics and kinetics of gait analyses.

Three-dimensional motion capture

Kinetic data were collected using a 12-camera three-dimensional motion capture system (120 Hz, SMART-DX400, BTS Bioengineering Corp., Quincy, MA). Twenty-two (10 mm-diameter) retroreflective markers were attached by the single researcher in accordance with the Davis Heel protocol [21]. Participants practiced walking prior to data acquisition in order to be familiar with walking at a split-belt treadmill system (1000 Hz, ITR-5018-BL400, Bertec Corp., Columbus, OH).

Prior to a testing session, a static standing calibration was performed. Participants were instructed to look at an object on the wall in front of the participants at the same height with the participant's eyes during testing trials. Participants walked barefoot at their self-selected usual/comfortable and maximal speed, and data was acquired for ten seconds after their walking became stable. Gait speed was increased stepwisely by 0.5 km/h for safety, and adequate rest was applied between trials to avoid fatiguing. Outcome variables were normalized 1st and 2nd peak KAM by body weight (Nm/kg).

Self-reported knee pain, joint stiffness and physical function

Self-reported knee pain, joint stiffness, and physical function was assessed using the WOMAC[22]. A 100-mm scale was used to assess each subscale of the WOMAC questionnaire and indicated that higher scores meant worse pain, stiffness or physical function. The WOMAC reportedly had high reproducibility and validity in Japanese[23].

Statistical analyses

Sample size was calculated based on the primary outcome (the WOMAC pain scale) using a power analysis program (G*Power version 3.1.9.2, Franz Faul, Germany). A sample size of 16 patients was needed by calculating with statistical design of two dependent means, alpha level of 0.05, power of 0.8, and assumption of mean improvement of the WOMAC pain scale in the control group as 12.0 ± 19.2[24] and mean improvement in RRR group as 20.0 ± 12.0 Assuming a 20% dropout to follow-up, 20 patients were enrolled for each group.

The statistical analyses were performed on an intension-to-treat basis. Normal distribution of the demographic data was assessed using the Shapiro-Wilk test, and difference of the demographic data was assessed using two-sample t-test and Mann-Whitney U test. The primary outcome analysis was conducted using two-sample t-test. Interaction of times and intervention on secondary outcome variables were assessed using split-plot design analysis of variance (ANOVA) with post hoc test with Sidak correction. Statistical analyses were performed using a statistical software (SPSS Statistics version 23, IBM Corporation, Armonk, NY). Effect sizes were obtained using G*Power. A significance level was set at α = 0.05.

Results

Demographics

327 patients visited the center and saw the surgeon in charge of recruitment to be assessed for the eligibility criteria. At baseline, 39 participants met all the criteria and was randomly allocated to the RRR (n = 19) and the control (n = 20) groups (Figure 3). Screening was started on January 15, 2016 and continued until December 5, 2018, when the targeted number of participants was collected.

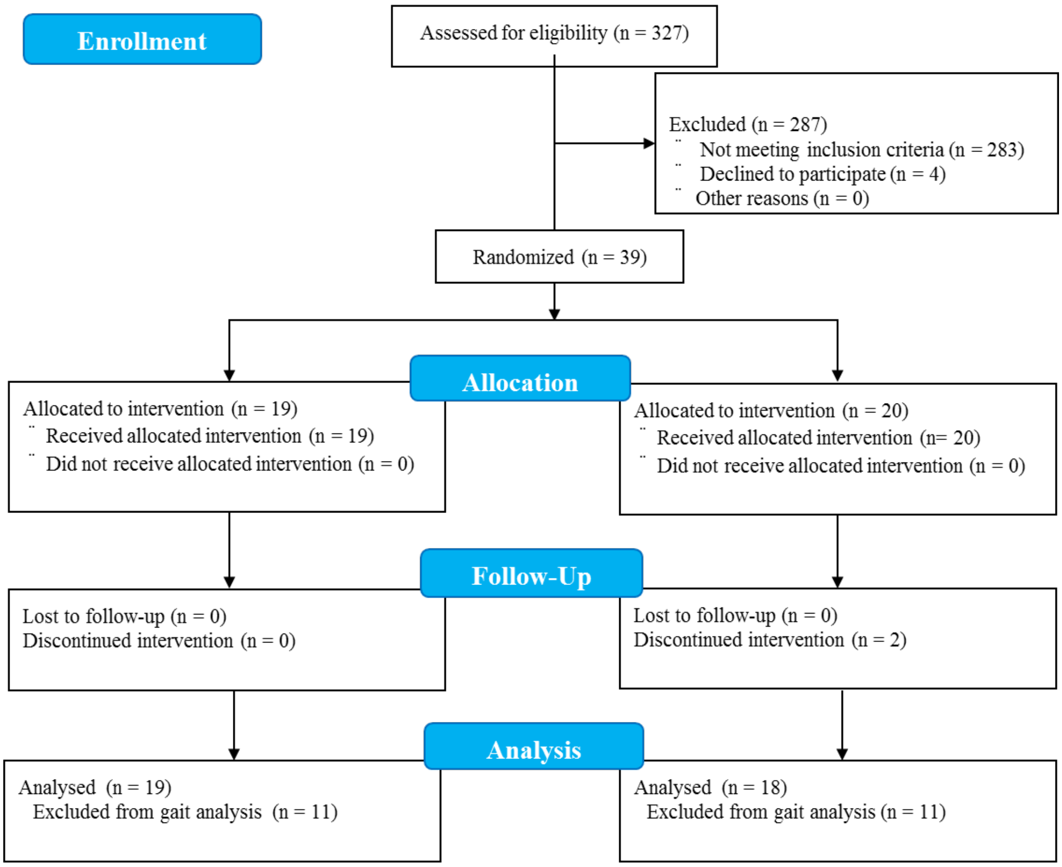

Figure 3. Flow diagram of the progress through the phases of this randomized controlled trial.

19 participants of the RRR group completed the intervention. 18 participants of the control group completed the intervention, and 2 participants dropped out because of discovering another joint disease or cancer. Clinical outcomes for 19 and 18 participants in each group were analyzed. 21 participants at baseline were excluded from the gait analyses because of imperfect data caused by calibration failure. Therefore, gait analyses were performed for 8 participants in the RRR group and 7 participants in the control group. The RRR group and the control group had baseline age (median [interquartile range]) 71 (69–75) and 71 (66–74) ($p = 0.771$), height (mean [95% coefficient interval]) 156.2 [152.3, 160.2] cm and 155.7 [152.3, 159.0] cm ($p = 0.819$), body mass 58.3 [54.4, 62.3] kg and 60.7 [55.6, 65.7] kg ($p = 0.449$), and body mass index (BMI) 23.9 [22.5, 25.3] kg/m^2 and 25.0 [23.0,

27.1] kg/m^2 ($p = 0.340$), respectively, with no significant difference (Table 1).

Table 1. Demographic data of the RRR and control group at pre- and post-intervention

Variables	RRR group (n = 19)		Control group (n = 20)		P-value
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	
Sex	13 females 6 males		14 femaies 6males		
Age (years)	71 (69–75)		71 (66–74)		0.771
Height (cm)	156.2 [152.3, 160.2]		155.7 [152.3, 159.0]		0.819
Body mass (kg)	58.3 [54.4, 62.3]		60.7 [55.6, 65.7]		0.449
BMI（kg/m^2）	23.9 [22.5, 25.3]		25.0 [23.0, 27.1]		0.340
Radiographic severity					
KL grade 1	6 (6)		6 (4)		
KL grade 2	4 (1)		5 (2)		
KL grade 3	9 (6)		9 (8)		

Age was shown as median [interquartile range], and height, body mass, and BMI are shown as means [95% coefficient interval]. KL grade is presented as number (number of females). P-values are shown for between group comparisons from Man-Whitney U test for age and t-test for height, body mass and BMI. RRR = rotation restoration and realignment; BMI = body mass index; KL = Kellgren-Lawrence.

WOMAC

In inter-group comparisons, the amount of change in WOMAC pain scale for the RRR and the control groups were 58.8 [29.0, 88.7] and 48.5 [4.6, 92.4], respectively, with no significant difference ($p = 0.681$, $d = 0.14$). In addition, there was no significant interaction on total score, stiffness, and function scales of the WOMAC ($p = 0.771$, 0.723, and 0.938, respectively) (Table 2).

Table 2. Self-reported pain, stiffness, function of the RRR and control group at pre- and post-intervention

	RRR group				Control group				P-value for interaction
	Pre-intervention	Post-intervention	P-value	Effece size	Pre-intervention	Post-intervention	P-value	Effect size	
WOMAC									
Total score	408.2	119.3	0.004	0.94	651.0	324.2	0.001	0.93	0.771
	[228.4, 588.0]	[30.2, 208.4]			[454.7, 847.3]	[89.4, 559.0]			
Pain	83.9	25.1	0.002	0.83	121.6	73.1	0.010	0.79	0.681
	[46.3, 121.6]	[9.2, 41.0]			[78.5, 164.7]	[27.5, 81.2]			
Stiffness	45.3	11.8	0.003	0.76	54.3	26.3	0.013	0.64	0.723
	[22.5, 68.1]	[2.6, 21.1]			[27.5, 81.2]	[7.3, 45.2]			
Function	278.9	82.3	0.005	0.92	450.1	260.8	0.008	0.72	0.938
	[140.5, 417.4]	[10.9, 153.8]			[298.9, 601.2]	[69.9, 451.8]			

Values are shown as mean [95% coefficient interval]. P-values within group and p-value between groups are shown. RRR = rotation restoration and realignment; WOMAC = the Western Ontario MacMaster University Osteoarthritis Index.

In intra-group comparisons, the total score of the WOMAC in the RRR group at baseline and follow-up were 408.2 [228.4, 588.0] and 119.3 [30.2, 208.4], respectively, with significant difference (p = 0.004, d = 0.94) , and those in the control group were 651.0 [454.7, 847.3] and 324.2 [89.4, 559.0], respectively, with significant difference (p = 0.001, d = 0.93) (Table 2). Pain scale in the RRR group at baseline and follow-up were 83.9 [46.3, 121.6] and 25.1 [9.2, 41.0], respectively, with significant difference (p = 0.002, d = 0.83), and those in the control group were 121.6 [78.5, 164.7] and 73.1 [27.5, 81.2], respectively, with significant difference (p = 0.010, d = 0.79) (Table 2). Stiffness scale in the RRR group at baseline and follow-up were 45.3 [22.5, 68.1] and 11.8 [2.6, 21.1], respectively, with significant difference (p = 0.003, d = 0.76), and those in the control group were 54.3 [27.5, 81.2] and 26.3 [7.3, 45.2], respectively, with significant difference (p = 0.013, d = 0.64) (Table 2). Function scale in the RRR group at baseline and follow-up were 278.9 [140.5, 417.4] and 82.3 [10.9, 153.8], respectively, with significant difference (p = 0.005, d = 0.92), and those in the control group were 450.1 [298.9, 601.2] and 260.8 [69.9, 451.8], respectively, with significant difference (p = 0.008, d = 0.72) (Table 2).

Gait analysis

There was no significant interaction on 1st peak KAM and 2nd peak KAM (p = 0.998 and 0.152, respectively) (Table 3). In the RRR group, 1st peak KAM at baseline and follow-up were 0.92 [0.78, 1.1] and 0.97 [0.80, 1.14] Nm/kg with no significant difference (p = 0.501, d = 0.40) (Table 3). In the control group, those at baseline and follow-up were 0.91 [0.77, 1.06] and 0.96 [0.78, 1.14] Nm/kg with no significant difference (p = 0.530, d = 0.18) (Table 3). On the other hand, 2nd peak KAM at baseline and follow-up in the RRR group were 0.53 [0.38, 0.67] and 0.46 [0.31, 0.61] Nm/kg, respectively, with no significant difference (p = 0.129, d = 0.76, power = 0.43)(Table 3). 2nd peak KAM in the control group were 0.60 [0.44, 0.76] and 0.62 [0.46, 0.79] Nm/kg, respectively, with no significant difference (p = 0.577, d = 0.21, power = 0.07) (Table 3).

Table 3. 1st and 2nd peak KAM of the RRR and control group at pre- and post-intervention.

		Pre-intervention	Post-intervention	P-value	Effect size	P-value for amount of change	P-value for interaction
1st peak KAM	RRR group	0.92 [0.78, 1.06]	0.97 [0.80, 1.13]	0.501	0.40	0.998	0.771
	Control group	0.91 [0.76, 1.06]	0.96 [0.78, 1.14]	0.530	0.18	0.152	0.681
2nd peak KAM	RRR group	0.53 [0.38, 0.67]	0.46 [0.31, 0.61]	0.129	0.43	0.998	0.771
	Control group	0.60 [0.44, 0.76]	0.62 [0.46, 0.79]	0.577	0.21	0.152	0.681

Values are shown as mean [95% coefficient interval]. P-values within group and p-value between groups are shown. RRR = rotation restoration and realignment; KAM = external knee adduction moment.

Discussion

This 3-month RCT aimed to determine an effect of exercise program on symptoms and kinetics in patients with KOA. The main findings of this study were that the RRR program and the conventional exercise program improved self-reported knee pain, stiffness, and physical function in the WOMAC. However, there were no significant differences between the groups. Next, both exercise program did not reduce 1st and 2nd peak KAM, in which there were no significant differences in the intra-group comparisons.

Effects of exercise therapies are reportedly effective to decrease knee pain and improve physical function[8]. Bennell et al.[25] reported that both neuromuscular exercise and quadriceps strengthening exercise for 12 weeks improved knee pain and physical function, with no significant between-group difference. Foroughi et al.[26] reported that progressive resistance training to lower extremity muscles with high intensity for six months improved knee pain, joint stiffness, and physical function. On the other hand, Sled et al.[12] reported that hip adduction muscle strengthening improved knee pain, but did not improve joint stiffness. Real-time biofeedback with emphasis on the foot progression with external rotation decreased pain scale by mean 28.4% and total score by 28.5% of the WOMAC[27]. Gait retraining program designed to reduce KAM for six weeks decreased pain scale by mean 49% and total score by 42% of the WOMAC[16]. Both the RRR program and conventional exercise program in this study improved self-reported outcomes including joint stiffness. The RRR program was reportedly an effective exercise program with tibial internal rotation with intension to restore normal rotational kinematics. Hanada et al.[28] showed that time of 10-m walking, timed-up and go test, knee pain during gait improved at post-intervention of the exercise program with tibial internal rotation exercise. In addition, the RRR group had no dropout of participants in this study. Therefore, the RRR program is considered a safe exercise program to improve knee pain, stiffness, and physical function in patients with medial KOA.

Exercise program to improve knee kinetics in patients with KOA has not been determined so far. A systematic review on the effect of exercise therapy on KAM in patients with KOA concluded that exercise therapy improved knee pain and physical function, but did not reduce KAM[11]. On the other hand, there were a few studies that reported that interventions reduced KAM. Thorp et al.[13] reported that exercise program with strengthening of hip abductors, hamstrings, and quadriceps for 4 weeks reduced about 9% of peak KAM during gait. This study had a limitation of small number of participants. In addition, Thorstensson et al.[14] reported that exercise program to improve muscle strengthening and neuromuscular control of the lower extremity for 8 weeks reduced peak KAM during one-leg raise, but did not reduce KAM during gait. This study also had limitation of small number of participants and difference in activity from walking. A real-time visual feedback program decreased 1st peak KAM of 6.98%[29]. Real-time biofeedback with emphasis of external foot progression decreased 2nd peak KAM by mean 10.5%[27]. The RRR program in this study did not reduce 1st or 2nd peak KAM with statistical significance. However, mean 13.2% of 2nd KAM reduction was observed, which may be clinically significant in some patients. With the small power of 0.43 for the 2nd peak KAM reduction, the required number of patients was 16 patients to exceed the power of 0.80. Therefore, the conclusion would be that we cannot rule out that the RRR program can reduce 2nd

KAM.

The foot orientation during gait may affect peak KAM. In a study on the effect of foot external rotation angle on peak KAM, Fukaya et al.[30] showed that peak KAM had negative correlation with foot external rotation angle at foot strike in patients with KL grade > 3. On the other hand, in a study on the effect of visual real-time feedback on KAM, Wheeler et al.[31] showed that most of participants (14/16 healthy subjects) answered that gait modification of toe-in (or foot in internal rotation) was effective. These previous studies suggested that tibial external or internal rotation kinematics had possible influence with kinetics. Specific kinematics in patients with medial KOA was tibial external rotation, posterior translation, adduction[32], and lateral translation[33]. These kinematic changes may lengthen the lever-arm of knee adduction. The RRR program in this study was an exercise program with repeated tibial internal rotation which may induce activation of the internal rotators including sartorius, gracilis, semitendinosus, semimembranosus, and popliteus[34]. Though the RRR program was intended to restore tibial rotational kinematics or reduce lateral translation, its effects on foot orientation or peak KAM is inconclusive.

This study employed stratified sampling with sex. As a result, number of females and males were nearly the same. On the other hand, number of participants with KL grade was not equal. Characteristics of the participants in both groups were appropriate to the representative of primary and medial KOA. A single researcher attached retroreflective markers to the participants in the process of data acquisition of gait analysis, which reduced potential measurement bias. In addition, gait speed for data analysis was equal in both before and after the intervention. During gait, all participants completed a session. This study had dropout of two participants in the control group. Reasons for the dropout were discovering another joint disease or cancer, and no adverse event from the intervention. Home exercise in the both groups were carried out without causing any problems on the knee. The results of this study can be applied to primary medial KOA patients with mild and moderate osteoarthritic change.

This study had a few limitations. Firstly, there was a lack of sample size. 2nd KAM in the RRR group did not have a significant improvement by the intervention. Required sample size to reach significant difference was 19. Secondly, this study had no participants with KL grade 0. In recent years, understanding pathology of early-stage KOA attracts researchers' attention. Development of exercise therapy for earlier-stage KOA would be needed in order to prevent onset and progression of KOA. Further studies would be conducted that includes patients with early-stage KOA or so-called healthy subjects. Thirdly, this study had no participants with KL grade 4. Standard treatment for patients with end-stage KOA would be total knee arthroplasty. Further studies should be investigated that intend to develop exercise program for prevention of end-stage KOA.

In conclusion, the RRR program with tibial internal rotation exercise improved knee pain, joint stiffness, and disabilities in patients with mild and moderate medial KOA. Development of exercise program to reduce KAM as a biomechanical marker of load to the knee would have social and clinical value to improve patients' activities of daily living and QOL and contribute to prevent KOA progression.

Conclusions

Conclusion of this study was that the RRR program with tibial internal rotation exercise improved knee pain, joint stiffness, and disabilities in patients with mild and moderate medial KOA. Clinical significance of this study would be that the RRR program would be safe and effective on the symptoms of KOA. The biomechanical effects of the RRR program on the knee remains unanswered. Considering 13.2% reduction of 2nd peak KAM, more studies on the effects of RRR program on the peak KAM are needed.

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CHAPTER 6

Discussion and Conclusions

This study aimed to identify an exercise therapy to improve 6 degrees-of-freedom knee alignment, to reduce medial meniscal extrusion (MME), and/or to reduce external knee adduction moment (KAM). A validation study of measurement method of the MME was conducted to determine if measurement of the MME using the MRI-derived tibial models would be comparable to measurement of the MME using the CT-derived tibial models. Next, a randomized controlled trial (RCT) was conducted to determine effects of an exercise program designed to induce tibial medial translation (Rotation Restoration and Realignment [RRR] program) on knee kinematics and the MME in individuals with knee osteoarthritis (KOA). Lastly, an RCT was conducted to determine if an exercise program would improve symptoms and knee kinetics in patients with KOA.

The validation study of the measurement method of the MME showed that the medial tibial plateau does not present significant morphological difference between the CT- and MRI-derived models, and that both models can be used as a reference to measure the MME in patients with mild and moderate medial KOA. This study had a few limitations. First, the MRI sequences of this study were not specialized for analyzing bone morphology. This study employed a clinical sequence for analyzing medial meniscal disorder. Surface differences were similar to the findings of previous studies. Secondly, this study employed coronal slices in the MRI and the slice pitch was 2.0 mm. This might affect the morphology at the anterior or posterior margin of the medial meniscus, which can cause some errors in volume and lesser extent in distance. Therefore, caution is necessary when comparing data from different studies due to errors caused by the segmentation method on MRI and when comparing two-dimensional and three-dimensional (3D) measurements of the MME. Thirdly, manual segmentation of the medial meniscus was done by single researcher. The segmentation process performed by one observer had an advantage in reducing inter-observer errors, which may be more appropriate in a small study with 10 samples. However, it has a limited generalizability. Fourthly, this study applied the level of 10.0 mm as the reference cut point of the tibial plateau model. All the tibia in this study had no identifiable osteophytes at the level 10 mm below the tibial plateau plane. However, careful attention would be needed when analyzing the MME with greater osteophyte in the tibial plateau. Consequently, the MME measurement method using the MRI-derived 3D tibial models by avoiding measuring the osteophytes near the tibial plateau is highly valid.

An RCT showed that both the RRR program and conventional exercise program did not show significant difference in knee kinematics during stepping activity and the MME volume and MME width. This study had a few limitations. Firstly, this study employed the stationary stepping activity to analyze knee kinematics. Daily symptoms appear during activities such as walking, stairs, and squatting activities in patients with medial KOA. The result of study cannot directly apply to these activities, although the stepping activity is very similar to walking. Secondly, this study had no participants with KL grade 0. In recent years, understanding pathology of early-stage KOA attracts researchers’ attention. Development of exercise therapy for earlier-stage KOA would be needed in order to prevent onset and progression of KOA. Further studies would be conducted that includes patients with early-stage KOA or so-called healthy subjects. Consequently, effects of the RRR program with tibial internal rotation exercise on knee kinematics, the MME volume or MME are not clear in patients with mild and moderate medial KOA.

The RCT showed that both the RRR and conventional exercise programs improved knee pain, joint stiffness, and physical function in patients with mild and moderate medial KOA. 2nd KAM reduction by 13.2% in the RRR program was observed, which may be clinically significant in some patients. This study had a few limitations. Firstly, there was a lack of sample size. 2nd KAM in the RRR group did not have a significant improvement by the intervention. Required sample size to reach significant difference was 19. Secondly, this study had no participants with KL grade 0. Development of exercise therapy for earlier-stage KOA would be needed in order to prevent onset and progression of KOA by modifying biomechanical component which may accelerate OA progression. Further studies would be conducted that includes patients with early-stage KOA or so-called healthy subjects. Thirdly, this study had no participants with KL grade 4. Standard treatment for patients with end-stage KOA would be total knee arthroplasty. Further studies should investigate to develop an exercise program for prevention of TKA procedures in patients with end-stage KOA. Consequently, the RRR program with tibial internal rotation exercise improves knee pain, joint stiffness, and disabilities in patients with mild and moderate medial KOA.

Again, this study aimed to identify an exercise therapy to improve 6 degrees-of-freedom knee alignment, to reduce MME, and/or to reduce KAM. In conclusion. the exercise program with tibial internal rotational exercise is effective on improvement of knee pain, joint stiffness, physical function in patients with mild and moderate medial KOA. Clinical significance of this study would be that the RRR program involving tibial internal rotation during a leg press activity is safe and effective on the symptoms of KOA. However, the biomechanical effects of the RRR program on the knee remains unanswered. Development of more effective exercise program to reduce KAM as a biomechanical marker of load to the knee and improve knee kinematics would have social and clinical value to contribute to prevent KOA progression. Further studies on effects of the RRR program on knee kinematics and kinetics should be conducted.

BIOGRAPHICAL SKETCH

Goro Watanabe received his bachelor's degree from Osaka University of Foreign Studies (Department of Foreign Affairs), Minoh, Japan, in 2005.Thereafter, he entered Hiroshima International University Graduate School of Medical Technology and Health Welfare Sciences, and received his Master of Science (Medical Engineering and Technology) in 2016. His major area of interest is the knee.