PROGRESSION OF ABNORMAL KINEMATICS AND EFFECTS OF A

ROTATIONAL EXERCISE ON KINEMATICS IN PATIENTS WITH KNEE

OSTEOARTHRITIS

G12201

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Chapter 3  “Reproducibility of Embedding Bony Coordinate Systems in the Distal Femur and Proximal Tibia” was originally included in my master’s thesis and is included in this dissertation again so that the entire project can be appropriately understood.

Chapter 6-2  “Effects of Knee Internal Rotation Exercises on Knee Adduction Moment and Function in Elderly Women with Knee Osteoarthritis: A Randomized Controlled Trial” was accepted by Rigakuryoho Kagaku

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<td>Anterior cruciate ligament</td>
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<td>ADL</td>
<td>Activities of daily living</td>
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<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>DOF</td>
<td>Degrees-of-freedom</td>
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<td>ISR</td>
<td>Inter-structural release</td>
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<td>KL</td>
<td>Kellgren and Lawrence</td>
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<td>KAM</td>
<td>Knee adduction moment</td>
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<td>KOOS</td>
<td>Knee injury and osteoarthritis outcome score</td>
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<td>MRI</td>
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<td>OA</td>
<td>Osteoarthritis / Osteoarthritic</td>
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<td>QOL</td>
<td>Quality of life</td>
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<td>RCT</td>
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RRR  Rotation restoration and realignment
SF-36  36-Item Short Form Health Survey
SD  Standard deviation
TKA  Total knee arthroplasty
US / U.S.  United States
USA  United States of America
WHO  World Health Organization
WHO-ILAR  WHO–International League of Associations for Rheumatology
WOMAC  Western Ontario and McMaster Universities
3D  Three-dimensional
3D-to-2D  Three-dimensional-to-two-dimensional
ABSTRACT

PROGRESSION OF ABNORMAL KINEMATICS AND EFFECTS OF ROTATIONAL EXERCISE ON KINEMATICS IN PATIENTS WITH KNEE OSTEOARTHRITIS

Knee OA is frequently seen in the elderly and causes considerable economic loss. Therefore, development of more effective treatment for knee OA is required. The first choice of treatment for knee OA is conservative therapy. Many studies have reported the effectiveness of exercises on the symptoms of knee OA, but this issue remains controversial because the mechanism to induce improvements has not yet been determined.

Firstly, we showed the validity of our new method of embedding joint coordinate systems for knee kinematic analyses. In our method, intra-researcher errors of translation for healthy knees was 0.19 mm (95% CI: 0.14, 0.25) and for OA knees 0.29 mm (0.19, 0.39), while inter-researcher error for healthy knees was 0.38
mm (0.28, 0.47) and for OA knee 0.62 mm (0.43, 0.82). Intra-researcher errors of rotation in healthy knees was 0.33° (95% CI: 0.24, 0.42) and in OA knees 0.51° (0.37, 0.65), while inter-researcher errors of rotation in healthy knees was 0.77° (95% CI: 0.62, 0.92) and in OA knees 1.15° (0.91, 1.39). Therefore, the results of this study will be referred to in subsequent kinematic studies to confirm the reproducibility of the local coordinate systems of the knee.

Secondly, we analyzed static knee alignment and dynamic knee kinematics. Static alignment was analyzed using MRI-derived three-dimensional bone models. The results of static alignment assessment were, 1) the tibia of grades 3, 4 translated posteriorly compared with those of grade 0-2, 2) the tibia of grade 4 translated laterally compared with those of grades 0-3, and 3) knee OA stage and tibial external rotation did not show any association. A 3D-to-2D registration technique was used for the analysis of knee kinematics. Kinematics during non-weight-bearing flexion and extension showed a tendency toward increased tibial posterior translation, knee adduction angle, and tibial external rotation in
position with progression of knee OA. The results of the kinematics during squatting and that during non-weight-bearing flexion and extension were similar. Since the progression of abnormal kinematics in knee OA have now been clearly shown, corrective exercises to treat knee OA should focus on the abnormal kinematics including tibial external rotation and posterior translation.

We utilized specific exercises to restore abnormal kinematics and examined the benefits and limitations of the exercise program. In a pilot study with an intervention period of 4 weeks, our exercise program to restore rotational alignment of the knee (RRR program) effectively decreased tibia external rotation during squatting. In addition, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was improved from 133.3 points to 15.7 points, and the 36-item Short Form Health Survey (SF-36) improved from 675 points to 755 points. In a randomized control trial with an intervention period of 4 weeks, the RRR program decreased knee adduction moment, though there was not a
significant difference from that in the control group. In a future study, we should examine the long-term effects of this exercise program.
CHAPTER 1

SPECIFIC AIM
Knee OA not only decreases QOL of patients and their families, but also aggravates social burdens on the country. An epidemiological survey in Japan estimated that 25 million people (8.6 million males and 16.7 million females) aged ≥40 years have radiographic knee OA. A more effective treatment for knee OA is needed.

Although there has been considerable debate on the prevention and treatment of knee OA, conclusions have not been reached. Exercise has been highly recommended in most global guidelines and guidelines from the Japanese Orthopedics Association contain similar recommendations. To date, studies have examined various exercises, but these conventional exercise programs should be reconsidered scientifically focusing on the risk factors for knee OA. The aim of this dissertation was to determine the mechanical risk factors for knee OA and then devise an effective exercise program.
The most important risk factor for knee OA is thought to be abnormal joint stress. The most commonly expressed reason for this is that OA most commonly occurs medially\textsuperscript{18} and in the knee joint\textsuperscript{19}. This is considered due to joint stress caused by abnormal knee joint motion\textsuperscript{20}. Precise analysis of angles demonstrated that the tibia in patients with end-stage knee OA demonstrated an external rotation position \textsuperscript{21} \textsuperscript{22}. However, there are no reports analyzing these angles in early knee OA.

We hypothesized that 1) the angle of tibial external rotation increases with the disease grade of knee OA, and 2) performing exercises designed to restore tibial external rotation would reduce pain and improve function in patients with knee OA.
CHAPTER 2

RESEARCH BACKGROUND
CHAPTER 2-1

Epidemiology

There have been a large number of epidemiological surveys published. In the Framingham study from the U.S. examining knee OA using MRI, 23.0% of the participants (mean age 69) were classified as Kellgren and Lawrence (KL) grade 2 or higher. The Dutch National Institute for PIVM (Public Health and the Environment) reported that 23.0% and 16.3% of right and left knee of the male participants (60-64 years old) had OA with KL grade 2 or higher, while those percentages reached 24.2% and 24.7% among female participants, respectively. The prevalence of knee OA in China was 2 to 3 times higher than that in the Framingham study. In the COPCORD (Community Oriented Program for Control of Rheumatic Disorders) study in Bangladesh, the prevalence of knee OA in the rural and urban areas was 7.5% and 11.5%, respectively. The WHO-ILAR (WHO–International League of Associations for Rheumatology) COPCORD study in a rural area of Iran showed that the prevalence of knee OA was 19.3%, while the
WHO-ILAR COPCORD study in Australian Aborigines showed the prevalence of knee OA was 3.1%\(^\text{20}\).

The prevalence of knee OA in Japan has been studied in several areas around the country. In an epidemiological study for radiological knee OA in females in Nagasaki prefecture, the prevalence were 35.8% in subjects aged 63-69 years old, 54.0% in 70-79-year-olds, and 63.3% in 80-89-year-olds\(^\text{30}\). These results were higher than that in Caucasians in the Framingham study (26.5% in 63-69 years old, 36.4% in 70-79 years old, and 52.3% in 80-89 years old). In Niigata, an epidemiological study demonstrated the prevalence of radiological knee OA in subjects aged 40-65 years old was 5.3% in males and 17.7% in females in 1979, and had increased to 12.0% in males and 26.1% in females in 1986\(^\text{31}\). In an epidemiological study conducted in mountain and fishing villages, 42.6% of males and 62.4% of females over 40 years old had radiological knee OA\(^\text{13,12}\). According to the Global Burden of Disease 2010 Study on knee OA in 21 regions of the world, the prevalence was 3.8% worldwide, 6.0% in the high-income population of the Asian Pacific region, 3.6-4.1%
in Europe, 4.1-4.2% in the U.S., and 4.1-4.2% in Africa. Therefore, the prevalence of knee OA in Japan is higher than that in the rest of the world.

Knee OA greatly affects not only the patient’s QOL but also the economy overall. In the U.S., the total medical cost including medications, physicians’ office visits, emergency room visits, other outpatient visits, total outpatient visits, hospitalizations per patient was reportedly US$12,905 per patient annually. In Canada, the annual cost per patient was reportedly CA$12,200. In Holland, the annual cost per knee OA patient was reported to be 10,452 Euros (productivity costs 83%, medical costs 17%)\(^{35}\). In Spain, the annual cost per patient with knee or pelvic OA was 1,502 Euros (total cost 86%, indirect cost 14%) and the national cost was 4,738 million Euros (0.5% of the gross national product)\(^{36}\). In Australia, the annual cost per patient of 65 years old or older with knee or hip OA was AU$0.1335 in males and AU$0.2049 Australian dollars in females\(^{37}\). Thus, knee OA is a worldwide problem involving high medical costs and establishing prevention and treatment strategies for knee OA is a great concern globally.
CHAPTER 2-2

Risk Factors of Knee Osteoarthritis

The first treatment option of knee OA is generally medication, activity control, and reasonable, easy and safe exercises. The latest Cochrane review indicated that exercise therapy is effective for pain relief and improvement of motor functions of knee OA patients\textsuperscript{38}. To date, several OA guidelines and systematic reviews of exercise effects on knee OA have been published (Table 2-1). Most of the guidelines concluded that exercise would be effective for knee OA.

However, the mechanisms underlying the effects induced by conventional exercises are often ambiguous and nonspecific. According to a review of the mechanisms of exercise effects, symptoms of knee OA may be improved by exercises due to combined effects on neuromuscular, peri-articular, intra-articular, psychosocial components as well as general fitness and health\textsuperscript{39}. 
**Neuromuscular**

Neuromuscular components include muscle, proprioception, balance and motor learning, energy absorbing capacity, and stability. In addition to muscle weakness, knee OA patients may experience reduced proprioceptive acuity, muscle activation deficiency, and functional knee instability. Neuromuscular components are considered to affect both sensorimotor function and functional stabilization.

**Peri-articular**

Peri-articular components include connective tissue and bone. Mechanical forces during exercise may modulate the morphology and structure of skeletal tissue, including ligaments and tendons.

**Intra-articular**

Intra-articular components include cartilage, inflammation and joint fluid. Intra-articular components may explain the beneficial effects of exercise on knee
OA. Since articular cartilage is considered mechano-sensitive tissue, it therefore perceives and responds to biomechanical signals. 39

*Psychosocial components*

Psychosocial components include increased well-being, increased self-efficacy, decreased depression, and placebo effects. There is also evidence that psychosocial interventions may decrease the experience of OA pain and disability. 44

*General fitness and health*

General fitness and health components include comorbidity, weight loss, and aerobic fitness. The efficacy of regular exercise has been confirmed not only for knee OA but also for other joints 45 as well as for the prevention of falls. 46

Accordingly, exercises have been applied empirically to date with the intention to influence the 5 components described above despite the absence of a clear understanding of the specific effects of exercises on knee OA symptoms. In
order to achieve maximum treatment effects, it would be preferable to design therapeutic exercise programs based on a greater understanding of the specific mechanisms. Risk factors that are most closely associated with the onset/progression of knee OA should be considered. Risk factors for knee OA can be classified into general factors and local factors that affect particular sites.

1) General risk factors

Age

The older the patients are, the higher the prevalence of OA in all joints including the knee. A review of the association between age and OA suggested that chondrocyte senescence contributes to cartilage degeneration by impairing the ability of these cells to maintain and repair the cartilage tissue. In this review, the authors described the “OA environment” as characterized by oxidative stress and production of cytokines potentially induced by mechanical stress.

Gene
Epidemiological studies of family histories and twins revealed associations between OA and genes. In their most recent study, the authors used the Human Genome Epidemiology Navigator to analyze 199 candidate genes that appeared to be associated with OA and identified 2 candidate genes (COL11A1 and VEGF (vascular endothelial growth factor)) that showed statistical correlations. However, the mechanism by which genes affect OA has not been entirely demonstrated: it is not technically or economically possible to provide genetic treatment in clinical settings at present.

**Gender**

The incidence of OA is higher in females than in males. This may be due to weight and hormone-related factors. There are correlations between patients’ gender and COL11A1 and VEGF, which are the genes detected in the genetic study described above. A correlation between OA and pregnancy or menopause has also been demonstrated. Various factors derived from gender and lifestyle also appear to be associated with the development of OA.
**Bone density**

High bone density is associated with onset of OA and low bone density (osteoporosis) is associated with progression of OA \(^6\) \(^2\) \(^6\) \(^3\) \(^6\) \(^4\) \(^5\) \(^6\) \(^6\). Cartilage located between highly dense subchondral bones is likely to be damaged by friction or compression stress. In osteoporosis, however, light elastic bones are considered to impose less stress on the cartilage \(^4\) \(^7\). In addition to the local stress, general factors such as nutrition and hormones have also been reported to be associated with knee OA and bone density \(^6\) \(^7\) \(^4\) \(^6\) \(^8\). These associations have not yet been entirely elucidated \(^6\) \(^4\).

**Nutrition**

It is desirable to obtain adequate nutrition in a well-balanced manner. Deficiencies of specific nutrients increase the incidence of OA onset \(^6\) \(^9\) \(^7\) \(^0\) \(^7\) \(^1\) \(^7\) \(^2\). Although it is easy to obtain necessary nutrients from meals and supplements these days, excessive intake of specific nutrients is more problematic. For example,
vitamins C and E effectively inhibit knee OA progression, but excessive intake of these vitamins increases the incidence of knee OA onset. Likewise, calcium is effective for improving osteoporosis, but excessive intake increases the incidence of myocardial infarction onset. Hence, it is necessary for patients to control their nutritional balance and take nutritional supplements only if there is a deficiency.

General risk factors are associated with knee OA, which is the most commonly reported OA, and the medial compartment is the most commonly affected region. A local disorder cannot be fully explained by general factors alone and the local biomechanical factors affecting specific joints are thought to be more important contributors.

2) Local risk factors

*Previous knee trauma*
According to the results of systematic reviews and meta-analyses on risk factors for knee OA onset, the highest correlation was detected between previous knee trauma and knee OA. ACL injury and meniscus injuries particularly result in a high incidence of OA knee onset despite conservative or surgical therapy. The mechanisms may include intraarticular bleeding and posttraumatic joint inflammation at the time of injury, degeneration of articular cartilage, meniscus, muscles and subchondral bones, change in neuromuscular coordination, and biological factors.

Repetitive stress on joints: Articular loads and knee OA

Repetitive stress on joints induces OA by damaging articular cartilage. Many epidemiological studies concluded that athletes and highly active people as well as those who more frequently bend their knees in their occupation and/or lifestyle have a higher incidence of knee OA compared to that in the general population.
Repetitive stress on joints: Effects of articular loads on healthy knees

Articular cartilage can be deformed by physiological loads. The thickness of the articular cartilage of the femur measured by MRI before and after running showed a reduction after running. Furthermore, the articular cartilage measured by MRI and ultrasound was thinner in the afternoon than in the morning. The thickness of the articular cartilage on the medial tibial side was significantly reduced in the high BMI group compared to that in the normal BMI group. A RCT demonstrated that the thickness of the articular cartilage was decreased in both the running and the cycling groups after 12 weeks, while that in the swimming, power-striding and control groups was not. Therefore, continuous and excessive loads can change the thickness of the articular cartilage.

Muscle

There is no agreement on the association between muscle weakness and knee OA. A review paper concluded that there was no relationship between muscle weakness and radiographic knee OA, although there was a relationship between
muscle weakness and symptoms of knee OA. A large study demonstrated that there was no relationship between the muscle weakness and knee OA. Females demonstrated a relationship between muscle weakness and knee OA, but males did not. A prospective longitudinal cohort study showed that the stronger the quadriceps muscle the higher the incidence of knee OA in knees with malalignment or laxity. This suggests that malalignment and instability of the knee are more strongly associated with knee OA than muscle weakness.

**Obesity**

There is evidence showing an association between obesity and knee OA. Although a biochemical association between obesity and knee OA has also been suggested, the mechanism is complicated and has not yet been entirely elucidated. Recently, a relationship between adipokine, which is associated with obesity, and knee OA has been attracting attention. Obesity can create both local and general risk factors affecting OA in a complex manner.
The local factors described above commonly increase the load on the knee and may be reiterated as “excessive and/or abnormal load” imposed on the knee. The joint stress or excessive and/or abnormal loading may accelerate cartilage damage and knee OA. Although homeostasis of joint cartilage is maintained by adequate mechanical stress (Figure 2-1), knee OA develops when the cartilage repair function collapses (Figure 2-2). Excessive mechanical stress changes the orientation of collagen fibers and causes structural deterioration as well as significantly increased chondrocytic cell death.

Chondrocytic cell death due to excessive mechanical stress has been confirmed in human cartilage cells. In addition, repeated mechanical stress also causes chondrocytic cell death. Abnormal mechanical stress also disrupts the balance of the repair function. Articular cartilage consists of collagen and proteoglycan primarily, in which type II collagen and aggrecan are the main components, respectively. However, these gene expression levels in the central region of the tibial plateau differ from those in the periphery of the tibial plateau.
under the same joint pressure (Figure 2-3). This means that abnormal contact kinematics of the femur and tibia may disrupt normal homeostasis of the cartilage. Therefore, improvement of the excessive and/or abnormal stress would be required in order to prevent and treat knee OA.

Loads on the articular cartilage can be estimated using various biomechanical parameters. Knee adduction moment (KAM) is calculated as a function of the floor reaction force and the distance between the center of the knee and the floor reaction force line using a motion capture system. However, there are several problems with the validity of KAM. Markers attached to the skin in the motion capture system may move relative to the bones. Measurement errors would be larger in obese patients who are likely to have knee OA. A comparison between the kinematics obtained by the motion capture system using skin markers and radio-stereometric analysis (RSA) using tantalum markers implanted into the bones demonstrated that the maximum errors for knee extension, adduction, and internal rotation were 5 degrees, 2-4 degrees, and 11 degrees, respectively. The tibia
was internally rotated during knee flexion on radio-stereometric analysis, while it was externally rotated on the motion capture system. Hence, only primary movements such as knee extension can be reliably measured using skin markers\textsuperscript{124}. A joint coordinate system defined by bony landmarks differs from that obtained by actual joint movement, causing the kinematics to differ depending on the chosen coordinate system\textsuperscript{125}. KAM during gait measured using 5 different marker sets simultaneously showed minimum and maximum errors of 5.7 [Nm] and 6.8 [Nm], respectively. Thus, caution is required when discussing small changes or differences in KAM in biomechanical studies of knee OA, particularly when we estimate the amount of articular load using KAM.

Despite these problems, evaluations of KAM using the surface marker system have been widely carried out. KAM in patients with knee OA was larger than that in healthy people in a few studies\textsuperscript{126-128}, while there were no significant differences found in other studies\textsuperscript{129-131}. A systematic review and meta-analysis
concluded that KAM in patients with knee OA was similar to that in healthy persons. However, there was an association between KAM and pain due to knee OA, and these findings appear contradictory. Therefore, KAM has not been conclusively accepted as the main outcome measure to detect the progression of knee OA.
Table 2.1: Studies investigating effects of exercises on knee OA.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of review</th>
<th>Theme/Intervention</th>
<th>Treated joints</th>
<th>Conclusions on knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartels</td>
<td>Cochrane</td>
<td>Aquatic exercise</td>
<td>Hip and knee</td>
<td>There is moderate quality evidence that aquatic exercise may have small, short-term, and clinically relevant effects on patient-reported pain, disability, and QOL in people with knee and hip OA.</td>
</tr>
<tr>
<td>Zafar</td>
<td>SR &amp; MA</td>
<td>Whole-body vibration training</td>
<td>Knee</td>
<td>Whole-body vibration training reduces pain and improves function in individuals with knee OA.</td>
</tr>
<tr>
<td>Regnaux</td>
<td>Cochrane</td>
<td>High-intensity versus low-intensity physical activity or exercise</td>
<td>Hip and knee</td>
<td>There was insufficient evidence to determine the effect of different types of intensities of exercise programs.</td>
</tr>
<tr>
<td>Mat</td>
<td>SR</td>
<td>Physical therapies for improving balance and reducing falls risk</td>
<td>Knee</td>
<td>Strength training, Tai Chi and aerobics exercises improved balance and falls risk in older individuals with knee OA, while water-based exercises and light treatment did not significantly improve balance outcomes.</td>
</tr>
<tr>
<td>Lu</td>
<td>SR &amp; MA</td>
<td>Aquatic exercise</td>
<td>Knee</td>
<td>Aquatic exercise appears to have considerable short-term benefits compared with land-based exercise and no exercise in patients with knee OA.</td>
</tr>
<tr>
<td>Ferreira</td>
<td>SR</td>
<td>The effect of exercise therapy on knee adduction moment</td>
<td>Knee</td>
<td>Clinical benefits from exercise therapy were not associated with changes in the knee adduction moment.</td>
</tr>
<tr>
<td>Zacharias</td>
<td>SR &amp; MA</td>
<td>Muscle strength</td>
<td>Hip and knee</td>
<td>High-intensity resistance exercise demonstrated moderate quality of evidence for large and sustained improvements for knee muscle strength in knee OA patients, when compared to a control group.</td>
</tr>
<tr>
<td>Waller</td>
<td>SR &amp; MA</td>
<td>Aquatic exercise</td>
<td>Lower limb</td>
<td>The results indicate that aquatic exercise is effective in managing symptoms associated with lower limb OA.</td>
</tr>
<tr>
<td>McAlindon</td>
<td>OARSI guidelines</td>
<td>Guidelines for non-surgical management</td>
<td>Knee</td>
<td>Appropriate treatment modalities for all individuals with knee OA included biomechanical interventions, exercise (land-based and water-based), self-management and education, strength training, and weight management.</td>
</tr>
</tbody>
</table>

SR, Systematic review; MA, Meta-analysis; EULAR, European League Against Rheumatism; RM, Repetition maximum; OARSI, Osteoarthritis Research Society International
Table 2-1: Studies investigating the effects of exercises on knee OA (Cont.).

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of review</th>
<th>Theme/Intervention</th>
<th>Involved joints</th>
<th>Conclusion on knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juhl 143 2014</td>
<td>SR &amp; meta-regression analysis</td>
<td>Impact of exercise type and dose on pain and disability</td>
<td>Knee</td>
<td>Optimal exercise programs for knee OA should have one aim and focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance. For best results, the program should be supervised and carried out 3 times a week.</td>
</tr>
<tr>
<td></td>
<td>of RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uthman 144 2013</td>
<td>SR incorporating trial sequential analysis and network MA</td>
<td>Exercise</td>
<td>Lower limb</td>
<td>An approach combining exercises to increase strength, flexibility, and aerobic capacity is likely to be most effective in the management of lower limb OA.</td>
</tr>
<tr>
<td>Tanaka 144 2013</td>
<td>SR &amp; MA</td>
<td>Efficacy of strengthening or aerobic exercise on pain relief</td>
<td>Knee</td>
<td>Muscle strengthening exercises with or without weight-bearing and aerobic exercises are effective for pain relief in people with knee OA.</td>
</tr>
<tr>
<td>Fernandes 145</td>
<td>EULAR recommend</td>
<td>Non-pharmacological core management</td>
<td>Hip and knee</td>
<td>For knee OA, high-quality research evidence found that exercise reduces pain and improves physical function.</td>
</tr>
<tr>
<td>de Oliveira Melo 146</td>
<td>SR</td>
<td>Neuromuscular electrical stimulation for muscle strengthening</td>
<td>Knee</td>
<td>Best-evidence analysis showed moderate evidence in favor of neuromuscular electrical stimulation alone or combined with exercise for isometric quadriceps strengthening in elderly with OA.</td>
</tr>
<tr>
<td>Silva 149 2012</td>
<td>SR</td>
<td>Therapeutic exercise to improve balance in women</td>
<td>Knee</td>
<td>There is some evidence to indicate the effectiveness of proprioceptive exercises compared to general strengthening exercises in functional outcomes.</td>
</tr>
<tr>
<td>Loew 150 2012</td>
<td>Guideline</td>
<td>Aerobic walking program</td>
<td>Knee</td>
<td>Therapeutic exercises improved balance in women with knee OA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Facility, hospital, and home–based aerobic walking programs with other therapies are effective interventions in the shorter term for the management of patients with OA to improve stiffness, strength, mobility, and endurance.</td>
</tr>
</tbody>
</table>

SR, Systematic review; MA, Meta-analysis; EULAR, European League Against Rheumatism; RM, Repetition maximum; OARSI, Osteoarthritis Research Society International
Table 2.1: Studies investigating the effects of exercises on knee OA (Cont.).

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of review</th>
<th>Theme/Intervention</th>
<th>Involved joints</th>
<th>Conclusion of knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepley</td>
<td>SR</td>
<td>Electromyographic biofeedback on quadriceps strength</td>
<td>Knee</td>
<td>Effects were the strongest for Electromyographic biofeedback compared with that of placebo and exercise–only interventions.</td>
</tr>
<tr>
<td>Kristensen</td>
<td>SR</td>
<td>Resistance training</td>
<td>Various musculoskeletal conditions</td>
<td>Resistance training above 60% of 1RM may offer beneficial therapeutic effects in the treatment of knee OA.</td>
</tr>
<tr>
<td>Brantingham</td>
<td>SR</td>
<td>Manipulative therapy</td>
<td>Lower extremity disorders</td>
<td>There is a level of B (fair evidence from relevant studies) for short–term and C (limited evidence from studies/reviews) for long–term treatment of knee OA.</td>
</tr>
<tr>
<td>Wasielewski</td>
<td>SR</td>
<td>Electromyographic biofeedback for the quadriceps femoris</td>
<td>Various knee conditions</td>
<td>Chronic knee conditions, such as OA, did not benefit from electromyographic feedback.</td>
</tr>
<tr>
<td>Jansen</td>
<td>SR</td>
<td>Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilization</td>
<td>Knee</td>
<td>Exercise therapy plus manual mobilization showed a moderate effect on pain compared to small effects from either strength training or exercise therapy alone.</td>
</tr>
<tr>
<td>French</td>
<td>SR</td>
<td>Manual therapy</td>
<td>Hip and knee</td>
<td>This study could be considered inconclusive regarding the benefit of manual therapy on pain and function for knee OA.</td>
</tr>
<tr>
<td>Escalante</td>
<td>SR</td>
<td>Effects of exercise on functional aerobic capacity</td>
<td>Lower limb</td>
<td>Overall, exercise programs based on tai chi, aerobic, and mixed exercise seems to give better results than hydrotherapy programs, but the differences were not altogether clear.</td>
</tr>
<tr>
<td>Zhang</td>
<td>OARSI recommend</td>
<td>To update evidence for available therapies</td>
<td>Hip and knee</td>
<td>Strengthening and aerobic exercise are associated with relief of pain in knee OA. Water–based exercise resulted in relief of pain and improvement in function in knee OA.</td>
</tr>
<tr>
<td>Williams</td>
<td>SR</td>
<td>To develop an evidence–based booklet</td>
<td>Hip and knee</td>
<td>Both strengthening and cardiovascular exercise were effective for reducing pain and improving function in the short–term in knee OA.</td>
</tr>
<tr>
<td>Escalante</td>
<td>SR</td>
<td>Physical exercise</td>
<td>Lower limb</td>
<td>Exercise programs based on Tai Chi showed better results than mixed exercise programs, but without clear differences.</td>
</tr>
</tbody>
</table>

SR, Systematic review; MA, Meta-analysis; EULAR, European League Against Rheumatism; RM, Repetition maximum; OARSI, Osteoarthritis Research Society International
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of review</th>
<th>Theme/Intervention</th>
<th>Involved joints</th>
<th>Conclusion of knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fransen 159</td>
<td>SR &amp; MA</td>
<td>Land-based therapeutic exercise</td>
<td>Knee</td>
<td>Land-based therapeutic exercise has at least short-term benefit in terms of reduced knee pain and improved physical function for people with knee OA. Recommendations cover the use of 12 non-pharmacological modalities: education and self-management, regular telephone contact, referral to a physical therapist, aerobic, muscle strengthening and water-based exercises, weight reduction, walking aids, knee braces, footwear and insoles, thermal modalities, transcutaneous electrical nerve stimulation and acupuncture.</td>
</tr>
<tr>
<td>Zhang 160 2008</td>
<td>OARSI recommend</td>
<td>Management of OA</td>
<td>Hip and knee</td>
<td></td>
</tr>
<tr>
<td>Lee 161 2008</td>
<td>SR</td>
<td>Tai chi</td>
<td>Lower limb</td>
<td>Tai chi may be effective for pain control in patients with knee OA.</td>
</tr>
<tr>
<td>Lange 161</td>
<td>SR</td>
<td>Strength training</td>
<td>Knee</td>
<td>Resistance training improved muscle strength and self-reported measures of pain and physical function.</td>
</tr>
<tr>
<td>Fransen 162</td>
<td>Cochrane</td>
<td>Exercise</td>
<td>Knee</td>
<td>Land-based therapeutic exercise has at least short-term benefits in terms of reduced knee pain and improved physical function for people with knee OA.</td>
</tr>
<tr>
<td>Scott 163</td>
<td>SR</td>
<td>Exercise and physiotherapy reduce</td>
<td>Knee</td>
<td>Exercise and physiotherapy reduce pain.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pain and disability in people with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>knee OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pisters 164</td>
<td>SR</td>
<td>Exercise therapy</td>
<td>Hip and knee</td>
<td>Positive post treatment effects of exercise therapy on pain and physical function in patients with OA of knee were not sustained over the long term.</td>
</tr>
<tr>
<td>Bartels 165</td>
<td>Cochrane</td>
<td>Aquatic exercise</td>
<td>Hip and knee</td>
<td>Aquatic exercise appears to have some beneficial short-term effects for patients with knee OA while no long-term effects have been documented.</td>
</tr>
<tr>
<td>McCarthy 166</td>
<td>SR</td>
<td>Pulsed electromagnetic field therapy</td>
<td>Knee</td>
<td>Pulsed electromagnetic field therapy has little value in the management of knee OA.</td>
</tr>
<tr>
<td>Devos–Comby</td>
<td>MA</td>
<td>Exercise and self-management</td>
<td>Knee</td>
<td>Both patient education and exercise regimens had a modest, yet clinically important, influence on patients’ well-being.</td>
</tr>
<tr>
<td>Roddy 168 2005</td>
<td>SR</td>
<td>Aerobic walking or strengthening</td>
<td>Knee</td>
<td>Both aerobic walking and home-based quadriceps strengthening exercise reduce pain and disability from knee OA but there was no difference between the two on indirect comparison.</td>
</tr>
</tbody>
</table>
Table 2-1: Studies investigating the effects of exercises on knee OA (Cont.).

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of review</th>
<th>Theme/Intervention</th>
<th>Involved joints</th>
<th>Conclusion of knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fransen 169</td>
<td>SR</td>
<td>Land-based therapeutic exercise</td>
<td>Hip and knee</td>
<td>Land-based therapeutic exercise was shown to reduce pain and improve physical function in people with OA of the knee.</td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Baar 170</td>
<td>SR</td>
<td>Exercise therapy</td>
<td>Hip and knee</td>
<td>There is evidence of beneficial effects of exercise therapy in patients with OA of the knee.</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SR, Systematic review; MA, Meta-analysis; EULAR, European League Against Rheumatism; RM, Repetition maximum; OARSI, Osteoarthritis Research Society International
**Figure 2-1**: Mechanical signals and joint homeostasis. Overall joint homeostasis is dependent on the interaction of biomechanical signals across scales (inter-scale signaling) ranging from full body mechanics during ambulation to the local mechanical environment of the cell.\(^{113}\)
Figure 2-2: Mechanical force and cartilage property are constantly balanced in the healthy knee. On the other hand, this balance can be lost due to pathological mechanical force and/or compromised cartilage. 

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CHAPTER 2-3

Exercises for improving knee kinematics in knee osteoarthritis:

A systematic review

Introduction

Risk factors that are strongly associated with onset/progression of knee OA should be considered when designing an exercise program. Excessive loading associated with abnormal knee kinematics appears to be involved in knee OA. Since a systematic review of the effects of exercises on knee kinematics was not previously reported (Table 2-1), we performed a systematic review of the effects of exercises on knee kinematics in patients with knee OA to establish a foundation for future studies.

Methods

For this systematic review, we performed a broad search of PubMed using comprehensive combinations of key words including knee AND (osteoarthritis OR
osteoarthritic) AND (alignment OR kinematics) AND (strength OR training OR exercise OR “physical therapy” OR “physiotherapy”). Articles reviewed were published or available online between January 1, 2006 and August 13, 2016 and written in English. Inclusion was based on assessment by the first author (F.I.). Following this search, full-text manuscripts for the remaining studies were retrieved and read, and the final selection was made.

**Results**

The initial online search identified 574 potential studies (Figure 2-4). Finally, five studies met the specified inclusion criteria. In all studies, gait analyses were based on knee kinematics obtained with a motion capture system using skin markers (Table 2-2). The types of exercises included two studies on gait modification programs, one on a program using a biomechanical device, and two on muscle strength programs. The goal of the gait modification programs was to increase \(^{171}\) or decrease \(^{172}\) the foot progression angle. The former increase the foot external rotation and the latter decreases the foot internal rotation, and
interestingly both programs relieved pain. A biomechanical device was designed to modify the center of pressure of the foot and alter KAM. An exercise program using the biomechanical device decreased pain, but did not change the flexion angle of the knees and hips. Of the two muscle strength programs, one was a progressive resistance training program on the lower limbs, while the other was muscle strengthening exercises for hip abductors and adductors. The progressive resistance training did not change knee adduction angles over time or between groups. Improvements in shank adduction angle (it defined as inclination of the lower leg segment in the direction of knee joint adduction relative to neutral positions) were related to improvements in self-reported disability, but not to changes in muscle strength, gait velocity, or pain. Hip muscle strengthening did not change the foot external rotation angle during gait.

Discussion

The objective of this review was to determine the effects of exercises on knee kinematics in patients with knee OA and establish a foundation for future
studies. In five studies included in this review, gait analyses had been performed on knee kinematics using the motion capture system with skin markers before and after the exercise interventions. The kinematic parameters evaluated in this review were the foot progression angle, knee and hip flexion angles, and shank and knee adduction angles. The only parameter changed by the exercise was the foot progression angle.

In the five studies selected in this review, the skin marker system was the only method to measure kinematics and KAM during gait. Moreover, many studies utilized a skin marker system for gait analyses to evaluate knee kinematics and calculate KAM. Gait analyses using skin markers involve skin artifacts as well as errors in the local coordinate systems due to variability of the relative locations between the palpated skin marker placements and actual bony landmarks. Further studies will be necessary in the future to reveal knee kinematics using a more accurate measurement method.

The only kinematic parameter changed by the exercise was the foot progression angle. The foot progression angle is an angle of the entire lower limb
involving the foot, ankle, knee and hip joints, and the contribution of each joint varies across individuals \(^{177}\). The angles of joints other than knees varied greatly in patients with knee OA \(^{178}\). Hence, it is not known whether or not the correction of the foot progression angle would induce any effects on knees. Further studies are needed to investigate the effects of such exercise specifically on the knees and determine how it affects knee kinematics.

To conclude, the findings of this review are: 1) there has not been any review paper or experimental study that investigated the effects of exercises on the kinematics of knee OA. The measurement methods used to detect differences in knee kinematics before and after the exercise interventions were not sufficiently accurate. Hence, it remains unknown whether or not there were changes in knee kinematics due to the exercise programs. Thus, a future study is needed to design an exercise program that can restore knee kinematics and evaluated by a method that can detect small differences in knee kinematics as an effect of the exercise program.
Table 2-2: Studies investigating the effects of exercises to improve kinematics in patients with knee OA.

<table>
<thead>
<tr>
<th>Study</th>
<th>Male/female</th>
<th>OA classification</th>
<th>Age</th>
<th>BMI</th>
<th>Study design</th>
<th>Intervention protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt</td>
<td>7/9</td>
<td>KL 2: 4</td>
<td>64.8 ± 10.4</td>
<td>29.9 ± 6.8</td>
<td>Intervention study</td>
<td>Toe-out gait modification program (Real-time biofeedback of performance)</td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td>KL 3: 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KL 4: 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shull</td>
<td>6/4</td>
<td>KL 2: 3</td>
<td>60 ± 13</td>
<td>26.6 ± 4.7</td>
<td>Intervention study</td>
<td>Gait retraining program (Real-time sensing and feedback)</td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td>KL 3: 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KL 4: 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haim</td>
<td>0/25</td>
<td>KL 3 ± 0.9</td>
<td>62 ± 7</td>
<td>Not described</td>
<td>Intervention study</td>
<td>Customized program utilizing a foot-worn biomechanical device</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td>KL 2: 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KL 3: 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KL 4: 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foroughi</td>
<td>IG: 0/26</td>
<td>Outerbridge Classification</td>
<td>IG: Mild 6, Moderate 5, Severe 5, Very severe 10</td>
<td>IG: 64 ± 7, CG: 64 ± 8, CG: Mild 12, Moderate 3, Total: 64 ± 7, Total: 64 ± 7</td>
<td>RCT</td>
<td>Progressive resistance training (Unilateral knee extension, Standing hip abduction and adduction, Bilateral knee flexion, Leg press, and Plantar–flexion)</td>
</tr>
<tr>
<td>2011</td>
<td>CG: 0/28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IG: KL 2; 15, KL 3; 15, KL 4;</td>
<td>IG: 31.9 ± 5.2, CG: 33.2 ± 8.1</td>
<td>RCT</td>
<td>Hip abductor and adductor muscle strengthening exercises (Abduction in a lateral position, Abduction while standing, Standing wall isometric hip abduction, Adduction in a lateral position, Abduction while standing, and Towel squeezes)</td>
<td></td>
</tr>
<tr>
<td>Bennell</td>
<td>IG: 22/23</td>
<td>15</td>
<td>IG: 64.5 ± 9.1</td>
<td>IG: 27.5 ± 4.7</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>CG: 24/20</td>
<td>CG: KL 2; 15, KL 3; 14, KL 4;</td>
<td>CG: 64.6 ± 7.6, CG: 28.4 ± 4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IG, intervention group; CG, control group; KFM, Knee flexion moment
Table 2.2: Studies investigating the effects of exercises to improve kinematics in patients with knee OA (Cont.).

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Period of intervention</th>
<th>Outcome measurements</th>
<th>Kinematics measurement system</th>
<th>Kinematics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt 2014</td>
<td>None</td>
<td>10 weeks</td>
<td>Toe-out angle, KAM/KFM, WOMAC, Knee pain, Timed stair climb test</td>
<td>Motion capture system</td>
<td>Self-selected walking speed</td>
</tr>
<tr>
<td>Shull 2013</td>
<td>None</td>
<td>6 weeks</td>
<td>Foot progression angle, KAM, WOMAC, Knee pain</td>
<td>Motion capture system</td>
<td>Preferred treadmill walking speed</td>
</tr>
<tr>
<td>Haim 2012</td>
<td>None</td>
<td>9 months</td>
<td>Knee flexion angle, Hip flexion angle, WOMAC, SF-36, Knee alignment, KAM, Knee alignment</td>
<td>Motion capture system</td>
<td>Self-selected barefoot walking speed</td>
</tr>
<tr>
<td>Foroughi 2011</td>
<td>Sham-exercise program (Minimal load, non progressive exercise)</td>
<td>6 months</td>
<td>Shank adduction angle, Knee adduction angle, KAM, Muscle strength, Gait speed, OA symptoms</td>
<td>Motion capture system</td>
<td>Self-selected walking speed</td>
</tr>
<tr>
<td>Bennell 2010</td>
<td>No exercise treatment</td>
<td>12 weeks</td>
<td>contralateral pelvic drop, Maximum ipsilateral trunk lean, Muscle strength, Knee pain, WOMAC</td>
<td>Motion capture system</td>
<td>Self-selected walking speed</td>
</tr>
</tbody>
</table>

IG, intervention group; CG, control group; KFM, Knee flexion moment
**Table 2-2:** Studies investigating the effects of exercises to improve kinematics in patients with knee OA (Cont.).

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt 2014</td>
<td>Participants exhibited significant increases in self-selected toe-out angle and reported significant reductions in WOMAC pain, NRS pain, WOMAC total score, and late stance KAM following the intervention compared to baseline.</td>
</tr>
<tr>
<td>Shull 2013</td>
<td>Foot progression angle decreased (i.e., increased internal foot rotation) post-training compared to baseline. WOMAC pain and function scores were improved at post-training by 29% and 32%, respectively and visual-analog pain scale scores improved by two points.</td>
</tr>
<tr>
<td>Haim 2012</td>
<td>There was no significant difference in knee flexion angle or hip flexion angle between pre- and post-intervention. Patient self-reported WOMAC pain scores and function scores showed a significantly favorable outcome at the 9-month end-point. Significantly reduced KAM magnitude was noted during bare foot walking after three and nine months of treatment. There was no change in shank or knee adduction angles and KAM did not change over time or between groups.</td>
</tr>
<tr>
<td>Foroughi 2011</td>
<td>Muscle strength improved in both groups over time, but significantly more in the resistance training group. Pain, stiffness, disability and total WOMAC score improved in both groups over time, but the interaction effect was not significant. Improvements in shank adduction angle were related to improvements in self-reported disability, but not to changes in muscle strength, gait velocity, or pain.</td>
</tr>
<tr>
<td>Bennell 2010</td>
<td>There were no between-group differences in change of toe-out angle, peak external hip adduction moment, knee adduction impulse, or maximum ipsilateral trunk lean.</td>
</tr>
</tbody>
</table>

IG, intervention group; CG, control group; KFM, Knee flexion moment
Figure 2-3: Flow diagram showing screening process and search results.
CHAPTER 3

EMBEDDING BONY COORDINATE SYSTEMS
CHAPTER 3-1

Reproducibility of Embedding Bony Coordinate Systems in the Distal Femur and Proximal Tibia

Introduction

Modern biomechanics have established a variety of kinematic techniques using non-invasive methods, such as electrogoniometers, light-reflective markers, MRI, and 3D-to-2D registration technique. The accuracy of these methods has been improved with technology advancement, but random errors and systematic errors still exist. Kinematic data obtained in different laboratories may involve significant systematic errors due to a lack of standard joint and bony coordinate systems. Moreover, low reproducibility of defining the bony coordinate systems leads to random errors within a study. In reaction to the problem described above, method of automatically embedding joint coordinate system in the femur and tibia with a computer algorithm have been developed and
reported\textsuperscript{191}. The cylindrical axis is preferred to the transepicondylar axis because its accuracy is considerably higher\textsuperscript{192}.

The automated methods of embedding local coordinate systems are not suitable for OA knee. Osteophytes of the OA knee may cause major errors. For example, osteophytes of the medial tibial plateau translate the center of the medial-lateral axis to the medial plateau. Generally, this axis is defined first and serious errors subsequently occur in other axes. Furthermore, the femur and tibia of the OA knee develop torsion and curvature\textsuperscript{193, 194}. Therefore, rotation error may occur when the longitudinal axis of the joint coordinate system is automatically matched with femoral or tibial diaphysis. A manual method is good to resolve those problems because we can revise errors while confirming the joint coordinate system in real time. Therefore, we developed a custom program to establish standard bony coordinate systems of the tibiofemoral joint and to improve their reproducibility.

The aim of this study was to determine the reproducibility of a technique for embedding bony coordinate systems in the femur and tibia. We proposed two hypotheses: (1) the errors in embedding bony coordinate systems would be smaller
than those of conventional methods in healthy knees; and (2) the errors in embedding bony coordinate systems in OA knees would be acceptable on kinematic analyses, but larger than those in healthy knees. To confirm these hypotheses, we conducted a validation study and calculated intra- and inter-researcher reproducibility in both healthy and OA knees.

**Materials and Methods**

The study protocol was approved by the Nagasaki University Ethical Review Board. All participants signed the consent form prior to data collection. Participants were recruited at Nagasaki University Hospital.

Data on healthy knees without evidence of OA changes were obtained from the uninjured contralateral knee of patients with unilateral ACL deficiency. Knee OA was defined according to the American College of Rheumatology criteria by one orthopedist (T.M.) who had more than 20 year's experiences. Exclusion criteria for both healthy and OA knees were history of surgery or trauma. In addition, the
healthy knee group excluded women considering the possibility of future pregnancy, while the OA knee group included both women and men.

Ten OA knees (9 females and 1 male; 5 right and 5 left knees in 10 subjects) and 10 healthy knees (10 males; 5 right and 5 left knees in 10 subjects) were included in this study. Classifying the grade of knee OA according to the Kellgren-Lawrence system resulted in four patients in grade II, three grade III, and three grade IV.

All participants underwent CT scan (SIEMENS, SOMATOM Definition, Germany) of the knee. CT data were obtained with a slice pitch of 0.5mm spanning approximately 150 mm above and below the joint line of the knee. Exterior cortical bone edges were segmented using 3D-Doctor software (Able Software Corp., Lexington, MA), and these point clouds were converted into polygonal surface models by the first author. A length of 150 mm was necessary for the femur because the vertical axis is defined parallel to the distal 1/3 of the femoral shaft in the sagittal plane. A length of 150 mm was also necessary for the tibia to determine the
slope of the tibial plateau relative to the plane vertical to the tibial longitudinal axis.

The bony coordinate systems were embedded in the distal femur and proximal tibia using a custom GL-CordFitter (GLAB Corp, Higashi-Hiroshima). This is a JAVA-based software program compatible with Windows 7 and 8 and is now commercially available. A 3-dimensional bone model in STL format is prepared before using this program. This allows researchers to define bony coordinate systems using a sphere, cylinder, rectangle or oval to determine the primary axis based on the bony morphology as well as points or planes to determine the secondary axes.

The femoral coordinate system was defined around a virtual cylinder proposed by Eckhoff et al. The virtual cylinder is composed of medial and lateral cylinders sharing a co-axis with independently adjustable radii. First, the virtual cylinder was embedded in the distal femur by manipulating the cylinders in the virtual space and adjusting their radii to fit to the medial and lateral posterior condyles. Areas of the medial and lateral posterior condyles fitting the
circumference of the virtual cylinders were tibiofemoral contact areas at 15-115° flexion (Figure 3-1). The co-axis of the cylinder was defined as the Z-axis. After the position of the virtual cylinder relative to the femur was set, the length of the cylinder was adjusted to fit the top and bottom of the cylinder to the most prominent points of the medial and lateral condyles of the femur, and the midpoint of the co-axis was defined as the origin of the femoral coordinate system. The Y-axis was defined visually as the line parallel to the projection line of the femoral shaft onto the XY plane, which is perpendicular to the Z-axis through the origin. The X-axis was the cross product of the Y and Z-axes (Figure 3-2).

The tibial coordinate system was defined around a virtual rectangle fitted onto the contour of the tibial plateau at right angle to the tibial long axis. To avoid highly variable morphology and the high prevalence of osteophytes formation at the posterior contour of the OA tibial plateau, the rectangle was fitted at the level of the fibular apex parallel to the tibial plateau plane. The four lines of the rectangle were visually fitted onto the posterior co-tangent of the medial and lateral tibial condyles, the medial and lateral tangents of the medial and lateral tibial condyles,
respectively, and the anterior tangent of the medial tibial condyle. Then, the rectangle was translated superiorly so that it fit the bottoms of both tibial plateaus.

The center of the rectangle was defined as the tibial origin, through which the medial/lateral (Z) and anteroposterior (X) axes were defined as two axes of the tibial coordinate system. The vertical (Y) axis of the tibia was, by definition, a cross product of these two axes proximally (Figure 3-3).

The first author (F.I.), who was experienced with the above technique, embedded bony coordinate systems twice separated by an interval of three days, and the intra-researcher reproducibility was analyzed using Geomagic Studio's best-fit alignment algorithm (Geomagic Inc., NC). Another author (K.Y.) performed the same procedure once and the inter-researcher reproducibility was analyzed. The reproducibility value was expressed as an absolute A-value. Statistical analyses for reproducibility were performed using one-tailed t-test subsequent to F-test to compare the intra-researcher reproducibility. The level of significance was set at p<.05. Statistical analyses were performed using SPSS ver.13 (SPSS Inc., Chicago, US).
Results

The intra-researcher errors in the healthy femur, the means (95% confidence interval (95% CI)) of X, Y and Z-axes (translation/rotation) were 0.09 (0.02, 0.17) mm /0.15 (0.08, 0.22)°, 0.12 (0.04, 0.20) mm/0.28 (0.19, 0.36)°, and 0.36 (0.15, 0.57) mm/0.40 (0.00, 0.81)°, respectively. The intra-researcher errors of the healthy tibia, the means (95% CI) of X, Y and Z-axes (translation/rotation) were 0.30 (0.16, 0.43) mm/0.24 (0.06, 0.42)°, 0.14 (0.07, 0.21) mm/0.43 (0.23, 0.62)°, and 0.14 (0.07, 0.21) mm/0.44 (0.21, 0.67)°, respectively (Figure 3·4A, 4B).

The intra-researcher errors of the OA femur, the means (95% CI) of the X, Y and Z-axes (translation/rotation) 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. The intra-researcher errors of the OA tibia, the means (95% CI) of X, Y and Z-axes (translation/rotation) 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. There was no significant difference in the intra-researcher comparisons between the healthy and OA knees (Figure 3·4A, 4B).
The inter-researcher errors in the healthy femur, the means (95% CI) of the X, Y and Z-axes (translation/rotation) were 0.29 (0.12, 0.46) mm/0.20 (0.08, 0.32)°, 0.10 (0.05, 0.15) mm/0.92 (0.52, 1.32)°, and 0.47 (0.36, 0.58) mm/0.61 (0.44, 0.78)°, respectively. The intra-researcher errors of the healthy tibia, the means (95% CI) of the X, Y and Z-axes (translation/rotation) were 0.94 (0.59, 1.28) mm/0.97 (0.49, 1.46)°, 0.21 (0.12, 0.30) mm/0.97 (0.67, 1.27)°, and 0.25 (0.12, 0.38) mm/0.94 (0.49, 1.40)°, respectively. There were significant differences in the healthy knee comparisons between intra- and inter-researchers; these differences involved the tibial translation of the X-axis, the tibial rotations of the X- and Y-axis, and the femoral rotation of the Y-axis (Figure 3-4C, 4D).

The inter-researcher errors of the OA femur, the means (95% CI) of the X, Y and Z-axes (translation/rotation) were 0.49 (0.21, 0.78) mm/1.54 (0.92, 2.16)°, 0.12 (0.06, 0.17) mm/1.13 (0.51, 1.75)°, and 1.36 (0.75, 1.98) mm/0.73 (0.40, 1.05)°, respectively. The intra-researcher errors of the OA tibia, the means (95% CI) of the X, Y and Z-axes (translation/rotation) were 1.29 (0.70, 1.87) mm/1.39 (0.61, 2.16)°, 0.19 (0.10, 0.28) mm/1.18 (0.48, 1.88)°, and 0.28 (0.16, 0.40) mm/0.92 (0.59, 1.26)°,
respectively. There were significant differences between intra-researcher results in the healthy knee and inter-researcher results in the OA knee; these differences involved the femoral translations of the X- and Z-axes, the tibial translation of X-axis, the femoral rotations of X- and Y-axes, and the tibial rotations of the X- and Z-axes (Figure 3-4A, 4B).

Discussion

The aim of this study was to determine the reproducibility of our technique of embedding bony coordinate systems in the femur and tibia. On intra-researcher comparisons, there were no significant differences in translations and rotations of the femur and tibia between healthy and OA knees. In healthy knees, there was a significantly larger inter-researcher error compared to the intra-researcher error: translation of the X-axis of the tibia (means 0.94mm (95% CI: 0.59, 1.28)), rotation of the X-axis of the tibia (0.97° (0.49, 1.46)), and rotation of the Y-axis of the femur (0.92° (0.52, 1.32)) and tibia (0.97° (0.67, 1.27)). In OA knees, the significantly larger inter-researcher error compared to the intra-researcher error involved
translations of the X-axis of the femur (means 0.49mm (95% CI: 0.21, 0.78)) and
tibia (1.29mm (0.70, 1.87)), translation of the Z-axis of the femur (1.36mm (0.75, 1.98)),
rotations of the X-axes of the femur (means 1.54° (0.92, 2.16)) and tibia (1.39° (0.61, 2.16)),
rotation of the Y-axis of the tibia (1.13° (0.51, 1.75)), and rotation of the Z-axis of the tibia (0.92° (0.59, 1.26)).

The inter-researcher error in healthy knees showed that tibial translation of the X-axis (antero-posterior translation),
tibial rotation of the X-axis (adduction-abduction), and femoral and tibial rotations of the Y-axis
(internal/external rotation) were more susceptible to error. For the rotatory definition of the Z-axis (flexion-extension),
the long femoral or tibial shaft became the index. On the other hand, errors occurred more easily in the Y-axis
(internal/external rotation) because of the short distance between the pivot point and bony edge on the cross-sectional plane.
The tibial antero-posterior width of the XY plane was changed when an error occurred in the rotation of the tibial Y-axis,
because the tibial cross section had an elliptical shape. This might increase the tibial antero-posterior (X-axis in the XY plane) translation. Error in the tibial
rotation of X-axis (adduction-abduction) could be produced by a difference in the respective heights of the medial and lateral tibial plateau.

The inter-researcher errors in OA knees showed that the femoral and tibial translations of the X-axis (anterior-posterior translation), femoral translation of the Z-axis (medial-lateral translation), femoral and tibial rotations of the X-axis (adduction-abduction), femoral rotation of the Y-axis (internal-external rotation), and tibial rotation of the Z-axis (flexion-extension) were susceptible to error. The significant difference in the axial value was greater in OA knees than in healthy knees. This may have been due to morphological changes \(^{196, 197, 79}\) and osteophytes \(^{198, 199}\) in the OA knee. For example, it was difficult to embed a cylinder on femoral posterior condyles due to the morphological changes. This causes an error in the X-axis (antero-posterior) translation and Y-axis (internal-external rotation) of the femur. Osteophytes of the femur occurring on the femoro-tibial joint surface might reduce the precision of X-axis rotation (adduction-abduction). These reproducibility values will become criteria in future studies.
None of the previous studies have evaluated the embedding of a joint coordinate system in the OA knee. Miranda et al.\textsuperscript{191} presented an automated method to define anatomical coordinate systems for 3D bone models of the femur and tibia. They reported that differences in the location and orientation of the anatomical coordinate systems between specimens were 1.5 mm for translations and 2.5° for rotations, respectively. Using our manual method, intra-researcher errors of translation were 0.19 mm (95% CI: 0.14, 0.25) in healthy knees and 0.29 mm (0.19, 0.39) in OA knees, while inter-researcher errors were 0.38 mm (0.28, 0.47) in healthy knees and 0.62 mm (0.43, 0.82) in OA knee. Intra-researcher errors of rotation were 0.33° (95% CI: 0.24, 0.42) in healthy knees and 0.51° (0.37, 0.65) in OA knees, while inter-researcher errors were 0.77° (95% CI: 0.62, 0.92) in healthy knee and 1.15° (0.91, 1.39) in OA knees. Errors of our method for healthy OA knees were smaller than those of the automated method.

There are some limitations in this study. OA knees from grade II to grade IV were considered together. Reproducibility must be calculated according to classification in the future. How two bone models are fitted and calculation of their
error were limitations. Geomagic Studio’s best-fit alignment algorithm allows two bone models with a rotary order of XYZ axes, which may itself become a source of error.

Conclusions

Intra-researcher reproducibility in embedding bony coordinate systems using this method was better than that using conventional methods in the healthy knee, and there was no significant difference in the OA knee. Inter-researcher reproducibility was inferior to intra-researcher reproducibility.

Conflict of Interests

None of the authors has any financial or personal relationships related to this study that could be deemed a conflict of interest.
**Figure 3-1:** Areas of the medial and lateral posterior condyles fitting the circumference of the virtual cylinders were tibiofemoral contact areas at 15°-115° flexion
Figure 3-2: A virtual cylinder was fitted onto the medial and lateral posterior condyles of the femur. The co-axis of the cylinder was defined as the flexion-extension axis of the femur.
Figure 3-3: A virtual rectangle was fitted onto the tibial plateau at the level of fibular apex.
Figure 3-4A: Translation difference of intra-researcher errors. Error bars represent 95% CI.
**Figure 3-4B:** Rotation difference of intra-researcher errors. Error bars represent 95% CI. There was no significant difference in the intra-researcher comparisons between healthy and OA knees.
**Figure 3-4C**: Translation difference of inter-researcher errors. Error bars represent 95% CI. ※: p < 0.05, †: p < 0.01 compared to the intra-researcher error in healthy knees, tested with one-tailed t-test.
Figure 3-4D: Rotation difference of inter-researcher errors. Error bars represent 95% CI. ※: p < 0.05, †: p < 0.01 compared to the intra-researcher error in healthy knees, tested with one-tailed t-test.
CHAPTER 4

STATIC ALIGNMENT IN MEDIAL KNEE OSTEOARTHRITIS
CHAPTER 4-1

Association between the Stage of Medial Knee Osteoarthritis and Static Knee Alignment

Introduction

In OA, both bones and cartilage degenerate as the disease progresses, causing pain and dysfunction. The knee joint shows the highest incidence of OA and knee OA is associated with both social and economic problems. The global morbidity of radiographic knee OA has been estimated to be 3.8%\(^7\)\(^{32}\). An epidemiological survey in Japan showed that the prevalence of radiographic knee OA was 42.6% in men and 62.4% in women over the age of 40\(^{13}\), suggesting that 25,300,000 people (8,600,000 men and 16,700,000 women) aged \(\geq 40\) years are affected by radiographic knee OA. In a large-scale review of patients with OA and varying degrees of disability, the total annual costs of OA were estimated to range from $1,750 to $2,800\(^{200}\). Total per diem cost was $10,042 \pm $1,305 and total
hospital cost was $17,894 ± $4,270 for Total Knee Arthroplasty. Thus, the prevention of knee OA is a critical issue.

Knee alignment is an index of disease stage and joint stress. Knee alignment and pain worsen with disease stage. Distressing features of knee OA are the pain itself (particularly intense and unpredictable pain) and the impact of pain on mobility, mood and sleep. Dynamic alignment of the OA knee was analyzed three-dimensionally during various activities, such as walking, stair climbing, and squatting. Static knee alignment such as that during sleep has also been reported. Nagao et al. reported the internal rotation alignment of OA knees using echo. However, Matsui et al. reported that OA knees showed external rotation alignment on CT images. The former study was performed in an abdominal position, while the latter was performed with the lower limbs fixed. Both studies evaluated the limbs in two dimensions. Precise evaluations of static non-weight bearing 3D alignment of the healthy and OA knee have not yet been reported. Therefore, the aim of this study was to determine the differences in static non-weightbearing 3D alignment of OA knees at various disease stages.
Although there has not been an in vivo study that evaluated static 3D alignment, some studies have analyzed bone motion in detail. With regard to tibial anteroposterior/mediolateral translation, it has been reported that OA knees showed posterior/lateral translation compared to that in healthy knees\textsuperscript{21,207}. As for tibial rotation, various results have been reported. During squat, OA knees showed external rotation\textsuperscript{21,22}, but internal rotation was demonstrated at initial contact during gait, which is a more dynamic activity than squat\textsuperscript{208}. Dynamic 3D alignment of severe knee OA has been reported to show posterior/lateral translation and abnormal rotation of the tibia.

We hypothesized that static non-weightbearing 3D alignment of the OA knee would show 1) posterior translation of the tibia, and 2) lateral translation of the tibia; and 3) external rotation of the tibia.

**Methods**

In compliance with the Declaration of Helsinki, we carefully considered each patient’s human rights as well as the physical and mental risks, and protected
all personal information. The study protocol was approved by the ethics committees of Nagasaki University Hospital, where the data were collected, and Hiroshima International University. Subjects were recruited from patients consulting Nagasaki University Hospital.

All patients enrolled in this study showed evidence of medial knee OA on X-ray. The contralateral healthy knees in patients diagnosed with unilateral ACL or/and meniscus injury were examined as controls. Exclusion criteria included: (i) a history of surgery in the lower limbs; (ii) disease of the central nervous system; (iii) women of childbearing potential; (iv) communication disorder; and (v) lack of informed consent.

1) **CT imaging of the knee joint**

Subjects stood in a relaxed posture with straight knees. CT (SIEMENS, SOMATOM Definition, Germany) data were obtained with a slice pitch of 0.5mm spanning approximately 150mm above and below the joint line of the knee.

2) **Creation of 3D bone models**
Exterior cortical bone edges were segmented using 3D-Doctor software (Able Software Corp., Lexington, MA), and 3D models of the femur, tibia, and knee (a set of the femur and tibia) model were created.

3) Embedding the coordinate system in the 3D models

Bony coordinate systems were embedded in the distal femur and proximal tibia using a custom program VHkneefitter (University of Colorado Health Sciences Center, Aurora, Co). The femoral coordinate system was defined around a virtual cylinder proposed by Eckhoff et al. The tibial coordinate system was defined around a virtual rectangle fitted onto the contour of the tibial plateau at a right angle to the tibial long axis.

4) Measuring alignment of 3D models

The femur model and the tibia model were fitted to form the knee model using Geomagic Studio's best-fit alignment algorithm (Raindrop Geomagic, Inc.). Knee alignment in a comfortable posture imaged on CT was calculated with six degrees-of-freedom. The outcomes were the knee alignment comprised of the
anterior/superior/lateral position of the tibia in relation to the femur and the angle of flexion/adduction/external tibial rotation.

The grade of knee OA was classified according to Kellgren and Lawrence grade. For multiple group comparisons of age, height, weight, BMI, and alignment, homogeneity of variance was assessed by the Levene test according to KL grade. Parametric comparisons used one-way ANOVA. One-way ANOVAs were followed by Tukey's honestly significant difference adjustment for multiple comparisons. If Levene tests were significant, significances of individual differences was evaluated using Kruskal-Wallis test. Post hoc tests were Mann-Whitney U test and Bonferroni correction for multiple comparisons was applied. Chi-square test used gender as a categorical variable and Bonferroni correction for multiple comparisons was applied. Statistical analyses were performed using SPSS ver.13 (SPSS Inc., Chicago, US) and the level of significance was set at α<.05.

Results
Total number of knees was 106 (51 men and 55 women). 34 knees (33 men/1 woman) were classified as grade 0, 17 (8/9) grade 1, 26 (5/21) grade 2, 19 (4/15) grade 3, and 10 (1/9) grade 4. Analysis of gender distribution showed significantly differences between Grade 0 and Grades 1-4 (Table 4-1).

Age(years)/height(m)/weight(kg)/BMI of subjects were as follows: grade 0 was 28.2 (95% Confidence Interval (95% CI): 25.7, 30.7)/1.71(1.68, 1.73)/73.6(67.7, 79.6)/25.2(23.4, 27.0), grade 1 was 55.4(51.3, 59.5)/1.60(1.56, 1.65)/62.9(56.2, 69.7)/24.2(22.7, 25.7), grade 2 was 61.3(57.1, 65.4)/1.58(1.55, 1.62)/65.8(61.8, 69.9)/26.2(24.8, 27.6), grade 3 was 69.3(64.9, 73.7)/1.52(1.50, 1.55)/63.1(59.2, 66.9)/27.2(25.4, 29.1), and grade 4 was 71.9(66.2, 77.6)/1.51(1.47, 1.54)/61.6(56.7, 66.5)/27.2(25.0, 29.4). There were significant differences in age (grade 0 vs. 1-4, grade 1 vs. 3, 4, and grade 2 vs.3, 4) and height (grade 0 vs. 1-4 and grade 1 vs. 4), but there was no significant difference in BMI (Table 4-1).

1) Translation of tibia in relation to the femur (Table 4-2).

Tibial anterior translation was 6.5 mm (95% CI: 4.9, 8.1), 6.7 mm (5.1, 8.4), 6.3 mm (4.5, 8.1), 0.7 mm (-1.8, 3.1), and 1.3 mm (-2.4, 5.1) from grade 0 to 4 in order
There were significant differences between grade 0 and 3/4 (p=0.000/0.028), between grades 1 and 3/4 (p=0.002/0.045), and between grade 2 and 3/4 (p=0.001/0.045). Tibial lateral translation was 4.4 mm (95% CI: 3.8, 5.1), 3.9 mm (3.1, 4.7), 4.0 mm (3.3, 4.7), 3.9 mm (2.9, 5.0), and 6.6 mm (4.9, 8.4) (Figure 4-2).

There were significant differences between grades 0 and 1/2/3/4 (p=0.025/0.009/0.005/0.008). Tibial superior translation was -29.0 mm (95% CI: -29.7, -28.3), -26.2 mm (-27.2, -25.2), -24.8 mm (-28.2, -21.4), -24.8 mm (-25.9, -23.7), and -26.7 mm (-28.1, -25.4) (Figure 4-3). There were significant differences between grades 0 and 2/3 (p=0.009/0.022).

2) Alignment of tibial rotation (Table 4-2).

Tibial external rotation was 2.8° (95% CI: 1.2, 4.5), 3.6° (1.3, 5.9), 1.9° (-1.1, 4.8), 0.6° (-1.7, 2.9), and 1.4° (-0.1, 3.0) from grade 0 to 4 in order (Figure 4-4). There were no significant differences among these groups. Knee adduction alignment was -0.3° (95% CI: -0.8, 0.3), -0.1° (-1.2, 1.0), -0.4° (-1.2, 0.3), 1.9° (0.9, 2.9), and 3.0° (1.0, 5.1) (Figure 4-5). There were significant differences between grades 4 and 0/2 (p=0.000/0.001). Knee flexion alignment was -6.1° (95% CI: -7.8, -4.5), -3.8° (-5.8,
-1.8), -4.3° (-6.2, -2.4), 0.7° (-2.4, 3.8), and 0.4° (-0.9, 1.6) (Figure 6). There were significant differences between grades 0 and 3/4 (p=0.000/0.005) and between grades 2 and 3 (p=0.01).

Discussion

The results of this study showed that: 1) the tibia in grades 3, 4 translated posteriorly compared to those in grades 0-2; 2) the tibia in grade 4 translated laterally compared to those in grades 0-3; and 3) there was no association between knee OA stage and tibial external rotation. Findings 1) and 2) supported our hypothesis, but 3) was contrary to our hypothesis.

The tibia with severe OA translated posteriorly and laterally in this study. Knee extension/flexion consists of a rolling and sliding motion, causing the tibia to translate anteriorly during knee extension. Severe OA caused limitation of knee extension in this study. Thus, it is considered that the tibia in the severe OA knee did not shift anteriorly. The tibia in the severe OA knee shifted laterally, which is in accord with previous findings. The medial joint space in knee OA narrows
with disease progress. It was reported that knee OA is related to extrusion of the medial meniscus. Lateral translation in the severe OA knee may be related to joint space narrowing and meniscus extrusion. However, none of the previous studies examined these points in detail. Further investigation is needed to completely elucidate these topics. For the reasons outlined above, it is considered that the tibia of the later-stage OA knee translates posteriorly and laterally.

Regarding tibial external rotation, there were no significant differences among the groups. Measurement conditions in this study differed from those of previous studies. Our hypothesis was created with reference to previous studies that analyzed knee kinematics during squatting. A systematic review and meta-analysis reported that individuals with knee OA exhibited increased co-contraction of the lateral knee muscles. In dynamic and weight-bearing condition, tibial external rotation would increase. Accordingly, it is considered that knee OA stage and tibial external rotation were not associated in a static and non-weight bearing position.
This study has several strengths and limitations. Joint coordinate systems were embedded to minimize the influence of bony deformation. The virtual cylinder were embedded to correspond to the arc traced by the tibia articulating with the femur as the knee was flexed 15° to 115°. Using this method, the femoral coordinate system was less affected by deformation of the femur body or osteophytes. The virtual rectangle was fitted at the level of the fibular apex parallel to the tibial plateau plane in order to avoid the highly variable morphology and high prevalence of osteophytes formation at the posterior contour of the OA tibial plateau. We checked that the inter-researcher RMS (root mean square) of the translations/rotations was less than 0.5 mm/1.1 degrees for the femur and less than 1.1 mm/1.3 degrees for the tibia in healthy knees, and the translations/rotations were less than 1.7 mm/1.9 degrees for the femur and less than 1.6 mm/1.9 degrees for the tibia in OA knees. This method can analyze alignment with high reproducibility. On the other hand, grade 0 was the contralateral knee of patients with unilateral ACL injury and/or meniscus injury and included a high percentage of young men. The anatomical features of the ACL-injured knee differed from that
of healthy knees\textsuperscript{214}\textsuperscript{215} and there were gender differences in the anatomical features\textsuperscript{214}. However, these limitations were considered necessary to avoid radiation exposures for potentially pregnant women and thus inevitable. Consequently, we considered that these study results have high validity.

To conclude, in static non-weightbearing 3D alignment, the tibia with severe OA translates posteriorly and laterally, while external rotation of the tibia is unrelated to OA stage.
Table 4-1: Mean values (95% CI) of biological characteristics of the subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>33/1*</td>
<td>8/9</td>
<td>5/21</td>
<td>4/15</td>
<td>1/9</td>
</tr>
<tr>
<td>Age [year]</td>
<td>28.2*</td>
<td>55.4†</td>
<td>61.3‡</td>
<td>69.3</td>
<td>71.9</td>
</tr>
<tr>
<td></td>
<td>(25.7, 30.7)</td>
<td>(51.3, 59.5)</td>
<td>(57.1, 65.4)</td>
<td>(64.9, 73.7)</td>
<td>(66.2, 77.6)</td>
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<td>(1.47, 1.54)</td>
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<td>(22.7, 25.7)</td>
<td>(24.8, 27.6)</td>
<td>(25.4, 29.1)</td>
<td>(25.0, 29.4)</td>
</tr>
</tbody>
</table>

*: Grade 0 vs. 1, 2, 3, 4; †: Grade 1 vs. 3, 4; ‡: Grade 2 vs. 3, 4; §: Grade 1 vs. 4

(p<0.05). There were significant differences in sex, age, and height. BMI was not significantly different among the groups.
**Table 4-2**: Results of the knee alignment. Mean values (95% CI).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tibial translation [mm]</th>
<th>Tibial rotation [degree]</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Anterior</td>
<td>Superior</td>
</tr>
<tr>
<td>Grade 0</td>
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<td></td>
</tr>
<tr>
<td>(N=34)</td>
<td>6.5*</td>
<td>-29.0$^§$</td>
</tr>
<tr>
<td>Grade 1</td>
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</tr>
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<td>(N=17)</td>
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<td>(-27.2, -25.2)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6.3$^†$</td>
<td>-24.8</td>
</tr>
<tr>
<td>(N=26)</td>
<td>(4.5, 8.1)</td>
<td>(-28.2, -21.4)</td>
</tr>
<tr>
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</tr>
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<td>(N=19)</td>
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<td>(-25.9, -23.7)</td>
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<td>Grade 4</td>
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<tr>
<td>(N=10)</td>
<td>(-2.4, 5.1)</td>
<td>(-28.1, -25.4)</td>
</tr>
</tbody>
</table>

*: vs. Grade 3 (p=0.000), vs. Grade 4 (p=0.028). †: vs. Grade 3 (p=0.002), vs. Grade 4 (p=0.045). ‡: vs. Grade 3 (p=0.001), vs. Grade 4 (p=0.045). §: vs. Grade 2 (p=0.009), vs. Grade 3 (p=0.022). ‖: vs. Grade 4 (p=0.025). ¶: vs. Grade 4 (p=0.009). **: vs. Grade 4 (p=0.005). ††: vs. Grade 4 (p=0.008). ‡‡: vs. Grade 3 (p=0.000). §§: vs. Grade 3 (p=0.001). ‖‖: vs. Grade 3 (p=0.000), vs. Grade 4 (p=0.005). ¶¶: vs. Grade 3 (p=0.01).
Figure 4-1: Tibial anterior translation.

Mean values and 95% CI are shown. ★ vs. Grade 3 (p=0.000), † vs. Grade 4 (p=0.028), ‡ vs. Grade 3 (p=0.002), § vs. Grade 4 (p=0.045), ∥ vs. Grade 3 (p=0.001), ¶ vs. Grade 4 (p=0.045).
Figure 4-2: Tibial lateral translation.

Mean values and 95% CI are shown. *: vs. Grade 4 (p=0.025), †: vs. Grade 4 (p=0.009), ‡: vs. Grade 4 (p=0.005), §: vs. Grade 4 (p=0.008).
Figure 4-3: Tibial superior(+) / inferior(-) translation.

Mean values and 95% CI are shown. *: vs. Grade 2 (p=0.009), †: vs. Grade 3 (p=0.022).
Figure 4-4: External tibial rotation.

Mean values and 95% CI are shown. There were no significant differences among the groups.
Figure 4-5: Knee adduction alignment.

Mean values and 95% CI are shown. *: vs. Grade 4 (p=0.000), †: vs. Grade 4 (p=0.001).
Figure 4-6: Knee flexion alignment.

Mean values and 95% CI are shown. *: vs. Grade 3 (p=0.000), †: vs. Grade 4 (p=0.005), ‡: vs. Grade 3 (p=0.01).
CHAPTER 5

DYNAMIC ALIGNMENT IN MEDIAL KNEE OSTEOARTHRITIS
CHAPTER 5-1

Progression of Abnormal Knee Kinematics during Knee Extension in Primary Knee Osteoarthritis: A 3D-to-2D registration technique

Introduction

Knee OA is a progressive musculoskeletal disorder and the mechanism of disease progression is poorly understood. The global prevalence of knee OA is 3.8%\(^{32}\). The prevalence of knee OA classified as KL grade II or greater was reported to be 61.9% in subjects aged ≥ 60 years (ROAD study)\(^{12}\) and 44% in subjects aged ≥ 80 years (Framingham study)\(^{73}\). Knee OA is also becoming a major economic burden\(^{200}\). Understanding the mechanism of knee OA is important for its prevention and treatment.

A detailed understanding of disease progression in knee OA is essential for its prevention and treatment. The kinematics of the knee joint changes as the OA disease stage progresses. Changes in knee kinematics increase joint stress and cause progression of knee OA. A study that used a three-dimensional motion...
analysis system including a 6 DOF electrogoniometer reported that reverse screw-home motion during terminal knee extension occurred as progression of the knee OA disease stage increased\(^{179}\). However, the knee kinematics throughout the range of flexion and extension movements in OA knees is not yet understood. Accordingly, the purpose of the present study was to analyze the kinematics of the knee during non-weight-bearing exercises in each knee OA disease stage in order to gain a better understanding of the progression process.

Detailed *in vivo* studies have reported abnormal kinematics in OA knees during weight bearing exercises. Reports regarding the amount of anterior-posterior translation of the tibia have indicated that the tibia shifts posteriorly in OA knees, compared to that in healthy knees\(^{21}\)\(^{207}\). Varied results have been reported in regard to tibial rotational alignment. The OA knee is externally rotated during squatting motions\(^{21}\)\(^{185}\)\(^{22}\). Compared to squatting, initial contact when walking causes greater loading and at that time point, the OA knee is internally rotated\(^{208}\). In terms of knee OA kinematics, posterior translation of the tibia as well as rotational abnormalities have been reported.
Our hypothesis is that as the disease stage of knee OA advances: 1) the degree of tibial posterior translation increases; and 2) the angle of tibial external rotation increases during knee flexion movements performed in non-weight-bearing flexion and extension.

Methods

This study is a laboratory-based, cross-sectional study. In compliance with the Declaration of Helsinki, we carefully considered each patient's human rights as well as the physical and mental risks, and protected all personal information. The study protocol was approved by the ethics committees of Nagasaki University Hospital, where the data were collected, and Hiroshima International University. Subjects were recruited from patients consulting Nagasaki University Hospital.

Healthy knees and OA knees were included in this study. Medial knee OA was diagnosed based on the American College of Rheumatology criteria. Radiographic levels of OA were classified using the KL System. Healthy contralateral knees of patients diagnosed with unilateral ACL and/or meniscus
injury were examined as controls. Exclusion criteria were: (i) a history of surgery in the lower limbs; (ii) disease of the central nervous system; (iii) women of childbearing potential; (iv) communication disorder; (v) lack of informed consent.

Knee extension-flexion in an upright sitting position was chosen for knee kinematic analysis. One knee extension-flexion cycle was defined as movement from maximal extension to maximal flexion and return to maximal extension. Subjects practiced the activity until the motion became smooth and they felt comfortable before testing began.

The fluoroscopy unit (Shimazu, Cvision Safire, Kyoto, Japan) used in this study was equipped with a square, 17-inch flat-panel. The imaging frame rate was at 5 Hz and the image size was 1024 × 1024 pixels. Fluoroscopic surveillance was performed for only one cycle of knee extension-flexion in order to minimize radiation exposure.

All knees underwent CT (SIEMENS, SOMATOM Definition, Germany) scanning with a 0.5 mm slice pitch spanning approximately 150 mm above and below the knee joint line. Geometric bone models of the femur and tibia were
created from the CT images. Exterior cortical bone edges were segmented using 3D-Doctor software (Able Software Corp., Lexington, MA) and were converted into polygonal surface models using Geomagic Studio software (Geomagic, Research Triangle Park, NC, USA). Local coordinate systems were embedded in each bone using the custom VH KneeFitter program (University of Colorado Health Sciences Center, Aurora, Co) that allows all the procedures detailed below to be performed in a virtual space with high reproducibility. We have shown that our techniques for embedding the femoral and tibial coordinate systems are highly reproducible. Intra-researcher RMS of the translations/rotations was less than 0.5 mm/0.75 degrees for the femur and less than 0.4 mm/0.6 degrees for the tibia. Inter-researcher RMS of the translations/rotations was less than 0.5 mm/1.1 degrees for the femur and less than 1.1 mm/1.3 degrees for the tibia.

**Femoral coordinate system**

The cylindrical axis was utilized as a reference line of the femoral coordinate system\textsuperscript{195}. The femoral origin was defined as the midpoint of the medial and lateral ends of the cylindrical axis, which were points on the cylindrical axis
crossing the bony surface medially and laterally, respectively. A plane through the origin perpendicular to the cylindrical axis was defined as the sagittal plane on which the vertical axis and anteroposterior axis would be 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 on the sagittal plane was defined as the vertical axis. The anteroposterior axis was obtained as the cross product of the cylindrical axis and vertical axis.

*Tibial coordinate system:*

The tibial coordinate system was defined around a virtual rectangle fitted onto the contour of the tibial plateau. The rectangle was fitted at the fibular apex level parallel to the tibial plateau plane in order to avoid fitting onto highly variable morphology at the posterior contour of the tibial plateau. The four lines of the rectangle were fitted onto: 1) the co-tangent of the posterior contours of the medial and lateral tibial condyles; 2) the medial tangent of the medial tibial condyle; 3) the lateral tangent of the lateral tibial condyle; and 4) the anterior tangent of the
medial tibial condyle. Then, the rectangle was translated superiorly so that it fit the bottoms of both tibial plateaus. The center of the rectangle was defined as the tibial origin, through which the medial/lateral and anteroposterior axes were defined as two axes of the tibial coordinate system. The vertical axis of the tibia was, by definition, the cross product of these two axes proximally.

In vivo three-dimensional positions and orientations of the femur and the tibia were determined using the 3D-to-2D registration technique. Using the custom JointTrack program (sourceforge.net/projects/jointtrack), the bone model was projected onto the fluoroscopic image, and its three-dimensional pose was iteratively adjusted to match its silhouette with the silhouette of the bones on the fluoroscopic images (Figure 5-1). Manual matching was first performed, then an automated matching procedure was performed using the nonlinear least-squares (modified Levenberg–Marquardt) technique. Six DOF position and orientation of femoral and tibial bone models in the virtual space were obtained and knee kinematics were computed in Cardan angles. The estimated accuracy of this matching method was 0.53 mm for in-plane translation, 1.6 mm for out-of-plane
translation, and $0.54^\circ$ for rotations $^{216}$. We excluded out-of-plane translation from the study analysis.

Once the registration procedures were complete for a sequence of the activity, 6 DOF joint kinematics were computed using a commercial software 3D-JointManager (GLAB Inc., Higashi-Hiroshima, Japan) (Figure 5-2). The joint coordinate system utilized in this software was based on the projection angles of the fixed tibial coordinate system $^{124}$. Kinematics was analyzed for tibial anterior translation, adduction and external rotation as function of knee flexion with an increment of $5^\circ$.

**Statistical analysis**

*Characteristics of subjects*

We performed the Bartlett test on age, body height, body weight and body mass index (BMI) in order to determine homoscedasticity. If homogeneity of variance was observed, then we performed a one-way ANOVA and performed the Tukey HSD (honest significant difference) test as the post hoc test. If homogeneity
of variance was not observed, then we performed the Kruskal-Wallis H test and used Scheffe’s method to perform the post hoc test. For gender, we performed chi-square test and used Harberman’s residual analysis as the post hoc test.

Knee kinematics

We performed a two-way ANOVA of the “knee flexion angle” and “grade” to analyze knee kinematics. If there were significant differences in the main effect, defined as “grade”, then we performed Tukey’s HSD test as the post hoc test. If there were significant differences between the main effect and the “interaction effect”, then we performed a simple main effect test and a Bonferroni test as the post hoc test. Statistical analysis during the present study was performed on the data obtained from the knee flexion angles that were measured during this study, which differed in certain groups of individuals.

The level of significance was set at p<.05. Statistical analyses were performed using SPSS ver.13 (SPSS Inc., Chicago, US).

Results
A total of 112 knees were enrolled, including 27 males and 1 female for grade 0, 8 males and 10 females for grade I, 2 males and 25 females for grade II, 6 males and 22 females for grade III, and 3 males and 8 females for grade IV, respectively. Grade 0 in males and Grades II and III in females were relatively more prevalent and the difference was significant. The range of knee flexion angle commonly observed in all five groups was between 15 and 70° during knee flexion and extension (Table 5-1).

**Tibial external rotation** (Figure 5-3)

The external rotation angle of tibia tended to increases with progression of knee OA. In all grades, the tibia rotated internally in the knee flexion phase and rotated externally in the knee extension phase. During knee extension from 70 to 15°, the amounts of variation of tibial external rotation were 4.8 (95%CI: 3.0, 6.7), 3.7 (1.3, 6.2), 4.6 (2.5, 6.7), 2.6 (1.0, 4.1), and 0.8° (-1.6, 3.2) in order from grade 0 to IV. There were significant differences between grade 0 and grade III from 70 to 15°, between grade 0 and grade IV from 70 to 25°, between grade I and grade III from 60 to 15°, and between Grade I and Grade IV from 70 to 35°. During knee flexion from
15 to 70°, the ranges of motion of tibial external rotation were -3.4 (95% CI: -5.1, -1.6), -5.4 (-8.9, -1.9), -3.9 (-5.6, -2.2), -3.9 (-5.3, -2.4), and -2.9° (-5.2, -0.7) in order from grade 0 to IV. There were significant differences between Grade I and Grade III from 15 to 70° and between Grade I and Grade IV from 20 to 70°.

**Knee adduction** (Figure 5-4)

During knee extension from 70 to 15°, the largest angles of knee adduction were 2.3 (95% CI: 1.5, 3.2), 3.0 (1.7, 4.2), 2.3 (1.4, 3.1), 3.3 (2.4, 4.2), and 4.6° (2.7, 6.6) in order from grade 0 to IV. There were significant differences between grade 0 and IV and between grade II and IV at 15°. During knee flexion from 15 to 70°, the largest angles of knee adduction were 2.1 (95% CI: 1.3, 2.9), 3.2 (1.9, 4.4), 2.3 (1.3, 3.2), 3.6 (2.9, 4.5), and 6.1° (4.5, 7.7) in order from grade 0 to IV. There were significant differences between grade 0 and grade IV from 15 to 70°, between grade II and grade IV from 15 to 70°, between grade I and grade IV at 15 and from 50 to 70°, between grade 0 and III at 65 and 70°, and between Grade III and Grade IV from 60 to 70°.

**Tibial posterior translation** (Figure 5-5)
The tibia in grades III and IV translated more posteriorly than those in grades 0 to II. During knee extension from 70 to 15°, maximal posterior translations were \(-4.2\) (95%CI: \(-5.0, -3.5\)), \(-4.3\) (\(-5.4, -3.3\)), \(-4.1\) (\(-5.0, -3.2\)), \(-2.0\) (\(-2.9, -1.0\)), and \(-2.2\)mm (\(-4.1, -0.4\)) in order from grade 0 to IV. There were significant differences between grade 0 and grade III from 70 to 15°, between grade I and grade III from 70 to 15°, between grade 0 and grade IV from 70 to 50°, and between grade II and III from 55 to 15°. During knee flexion from 15 to 70°, maximal posterior translations were \(-4.0\) (95%CI: \(-4.8, -3.2\)), \(-5.3\) (\(-6.3, -4.3\)), \(-4.4\) (\(-5.4, -3.3\)), \(-2.3\) (\(-3.2, -1.3\)), and \(-2.5\)mm (\(-4.2, -0.7\)) in order from grade 0 to IV. There were significant differences between grade I and grade III from 15 to 70°, between grade II and grade III from 15 to 55°, between grade I and grade IV from 35 to 60°, and between grade 0 and III from 45 to 70°.

**Discussion**

The purpose of the present study was to analyze the kinematics of the knee during non-weight-bearing flexion and extension in each OA disease stage in order
to gain a better understanding of the progression process. With progression of knee OA, there was a trend toward increased tibial posterior translation, knee adduction angle, and tibial external rotation during knee extension and flexion.

The angle of tibial external rotation was greater in grades III and IV than in grades 0 and I. This result supported our hypothesis. The medial and lateral compartments in knee OA become more rigid than those in healthy knees. Furthermore, knee OA patients have rigid iliotibial bands. Excessive tension applied to the iliotibial band causes external rotation of the leg. The knee joint has a greater range of rotational motion when it is in a flexed position than in an extended position and the lateral compartment moves more than the medial compartment. Accordingly, we consider that in knee OA, there is a reduced anterior translation of the lateral compartment during knee extension and the knee is externally rotated. As a result, the tibia is externally rotated in end-stage knee OA and there may be a reduced range of tibial rotational motion.

The angle of internal rotation was greater in grade IV than other grades. This result supported our hypothesis. However, there were no significant
differences between grades 0 and III. The cylinder axis used in the present study was fitted to and incorporated in the medial and lateral femoral condyles. For this reason, it was difficult for the angle of adduction to change during the knee flexion movements performed in non-weight-bearing exercises. Accordingly, we consider that the angle of adduction was greater in grade IV cases than other grades.

There was a greater degree of posterior translation of grade III and IV tibia than grade 0 to II tibia. This result supported our hypothesis. The normal joint needs arthrokinematic movements of roll and slide, but in knee OA, the tibia locates posteriorly because of quadriceps femoris muscle weakness and knee stiffness along with knee instability. In addition, tibial external rotation may disturb tibial anterior translation. Accordingly, there is greater posterior translation of the tibia in knee OA when knee flexion movements occur during non-weight-bearing exercises.

Exercise is a recommended treatment for knee OA. Knee joint range of motion exercises and flexion exercises are easy and can be widely performed
because pain does not readily appear during non-weight-bearing exercises. In the present study, we clarified that there is a relationship between the disease stage of the knee OA and the angle of external rotation of the tibia, the knee adduction angle and the degree of posterior translation of the tibia. The knee adduction angle varies along the frontal plane in association with cartilage wear, while tibial external rotation and posterior translation are abnormal femoral motions that occur at the tibial plate. It is difficult to restore the former, but it is possible to restore the latter by means of exercise and physical therapy. Accordingly, we consider that exercises to improve tibial external rotation and posterior translation are needed to treat knee OA.

There are several limitations and strengths in this study. The subjects with the healthy knee were younger than the patients with knee OA and were recruited from patients with unilateral ACL deficiency or meniscus injury. The ACL-injured knee may have had anatomical risk factors. In addition, most of the healthy knee group were men and there may be anatomical differences between men and women. To our knowledge, differences in rotational kinematics between
the genders have not been reported and we considered that the effect of the difference in gender distribution on rotational kinematics was minimal. We excluded data regarding mediolateral translation from the results because it was assumed that the accuracy of these data was reduced. There may be a difference in mediolateral translation between the OA grades, and future research will be required to confirm this point. One of strengths of this study was high internal validity. As stated above, we have shown that our techniques for embedding the femoral and tibial coordinate systems are highly reproducible. The 3D-to-2D registration technique using single-plane lateral fluoroscopy, which was used in this analysis, is a well-established technique to measure dynamic weightbearing knee kinematics in vivo. All of the output of the 3D-to-2D registration technique used in the present study were analyzed by a single researcher (F.I.). This may have decreased the external validity. However, the 3D-to-2D registration technique requires considerable experience. There are no previous reports in which a single researcher analyzed ≥100 knees and we can state with some pride that the matching precision was high.
Conclusion

This study showed that during knee extension and flexion, tibial posterior translation, knee adduction angle, and tibial external rotation in position tended to increase with progression of knee OA. We consider that exercises to improve tibial external rotation and posterior translation are needed to treat knee OA.
**Table 5-1**: Demographic characteristics of the subjects.

Means (95%CI). ∗1 : Grade 0 vs. 1-4; †2 : Grade 0 vs. 2-4; ‡3 : Grade 0 vs. 3; §4 : Grade 1 vs. 3, 4; ∥5 : Male > Female; ¶6 : Male < Female.

<table>
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<th>Grade 3</th>
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<td>(25.9, 28.5)</td>
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Figure 5.1: 3D-to-2D registration technique was used to determine the kinematics of knees.
**Figure 5-2**: The joint coordinate system utilized in a commercial software

3D-JointManager (GLAB Inc., Higashi-Hiroshima, Japan) is based on the projection angles on the fixed tibial coordinate system.
Figure 5-3: Tibial external rotation during knee extension and flexion. Statistical analysis was performed across the entire range of 70-15° for knee flexion in the flexion phase and 15-70° in the extension phase (the range marked in white on the graph).
Figure 5-4: Knee adduction angle during knee extension and flexion.
Figure 5-5: Tibial posterior translation during knee extension and flexion.
CHAPTER 5-2

Progression of abnormal knee kinematics during squat in primary knee osteoarthritis: A 3D-to-2D registration technique

Introduction

Knee OA is a serious condition that impairs ADL and QOL. The global prevalence of knee OA is 3.8%, with a prevalence of 6.0% in the high-income Asia Pacific region. The high prevalence of knee OA in Asia is considered related to lifestyle habits that involve frequent squatting motions. Accordingly, we need to clarify the details of squatting motions during knee OA.

The kinematics of the OA knee during squatting motions has not been closely analyzed in each OA disease stage. Saari et al. used dynamic radiostereometry to compare a group of 10 healthy knees and a group of 14 OA knees (according to the Ahlback classification, four knees were classified as grade I, five knees as grade II, two knees as grade III, two knees as grade IV and one knee as grade V). Moro-oka et al. and Hamai et al. used a 3D-to-2D model
registration technique to compare a group of 6 healthy knees to a group of 12 OA knees (according to the KL classification, one knee was classified as grade III and 11 knees were classified as grade IV). Yue et al. used the same method to compare a group of 22 healthy knees to a group of 11 OA knees (according to the KL classification, four knees were classified as grade III and seven knees were classified as grade IV). However, these were comparisons made between healthy and OA knees. The progression process of abnormal knee kinematics during squatting remains unknown. Accordingly, the purpose of the present study was to analyze the kinematics of the knee during squatting motions in each OA disease stage in order to gain a better understanding of the progression process.

The kinematics in knees affected by OA differs from those in healthy knees. Reports regarding the amount of anterior-posterior translation of the tibia have stated that the tibia shifts posteriorly in OA knees compared to that in healthy knees. Although there were no significant differences between healthy and OA knees in terms of the angle of knee adduction, the healthy knees were in a neutral position while the OA knees were in a varus position. The angle of tibial external
rotation was larger in OA knees than in healthy knees. Accordingly, we consider that posterior translation of the tibia and tibial external rotation are observed as knee OA progresses.

The hypothesis of this study is that as the disease stage of knee OA progresses: 1) posterior translation of the tibia increases; 2) the angle of knee abduction increases; and 3) the angle of external rotation of the tibia increases during squatting.

**Methods**

The subjects, methods and statistics were the same as in the previous study.

Wide-based squatting was chosen for knee kinematic analyses. First, the subjects stood on pre-set foot prints, so that everyone maintained the same stance width, allowing their feet to be oriented at 90° to each other and positioned 1.5 times shoulder-width apart. Then, the subjects performed squat with their hips at 45° of external rotation, during which the knee over the toe position was maintained.
Subjects were instructed that the maximal flexion angle during squat should be “as deep as possible”. They kept their back straight and nearly upright (within 20° of forward tilt) throughout the activity. Subjects were requested not to allow their knee to move beyond the toes so that the knee would remain within the fluoroscopic screen. Subjects were also instructed to maintain equal weight-bearing on both legs. One squat cycle was defined as movement from maximal extension to maximal flexion and then returning to maximal extension. Subjects practiced the activity until the motion became smooth and they felt comfortable before testing began.

Results

A total of 112 knees were enrolled, including 27 males and 1 female for grade 0, 8 males and 10 females for grade I, 2 males and 25 females for grade II, 6 males and 22 females for grade III, and 3 males and 8 females for grade IV, respectively. There were significantly more males in Grade 0 and significantly more females in Grades II and III. The range of knee flexion angle commonly
observed in all five groups was between 20 and 65° during knee flexion and extension.

**Tibial external rotation** (Figure 5-6)

The external rotation angle of the tibia tended to increase with progression of knee OA. In all grades, the tibia rotated internally in the knee flexion phase and rotated externally in the knee extension phase. During knee flexion from 20 to 65°, the amounts of variation in the tibial external rotation were -5.5 (95%CI: -7.1, -3.9), -7.1 (-9.1, -5.2), -7.4 (-9.2, -5.7), -8.1 (-9.3, -6.9), and -8.2° (-12.6, -3.9) in order from grade 0 to IV. There were significant differences between grade I and grade III from 25 to 45° and between grade I and grade IV from 20 to 50°. During knee extension from 65 to 20°, the ranges of motion for tibial external rotation were 5.9 (95%CI: 4.6, 7.1), 8.6 (6.5, 10.6), 8.9 (7.4, 10.4), 8.9 (7.6, 10.2), and 8.0° (4.6, 11.5) in order from grade 0 to IV. There were significant differences between grade 0 and grade II from 25 to 20°, between grade 0 and grade III from 40 to 20°, between grade 0 and grade IV from 45 to 20°, and between Grade 1 and Grade 4 from 50 to 40°.

**Knee adduction** (Figure 5-7)
During knee flexion from 20 to 65°, the largest angles of knee adduction were 2.2 (95%CI: 1.5, 3.0), 2.6 (1.6, 3.6), 2.6 (1.5, 3.7), 4.1 (3.3, 4.9), and 6.1° (4.3, 7.8) in order from grade 0 to IV. There were significant differences between grade 0 and grade IV from 20 to 60°, between grade II and grade IV from 20 to 60°, between grade 0 and grade III from 20 to 40°, and between grade I and grade IV at 20 and from 30 to 55°. During knee flexion from 65 to 20°, the largest angles of knee adduction were 1.9 (95%CI: 1.2, 2.7), 2.7 (1.6, 3.7), 2.2 (1.2, 3.2), 3.4 (2.5, 4.4), and 5.6° (3.7, 7.6) in order from grade 0 to IV. There were significant differences between grade 0 and grade IV from 65 to 20°, between grade II and grade IV from 65 to 20°, and between grade I and grade IV from 65 to 30°.

*Tibial posterior translation* (Figure 5-8)

The tibia of grades III and IV were translated more posteriorly than those in grades 0 to II. There were significant differences between grade 0 and grade III from 20 to 65°, between grade I and grade III from 20 to 65°, between grade II and grade III from 20 to 65°, between grade I and grade IV from 35 to 60°, between grade II and grade IV from 35 to 60°, and between grade 0 and grade IV from 40 to
65°. There were significant differences between grade 0 and grade III from 65 to 20°, between grade I and grade III from 65 to 20°, between grade II and grade III from 65 to 20°, between grade 0 and grade IV from 65 to 25°, and between grade I and grade IV from 50 to 35°.

Discussion

The purpose of the present study was to analyze the kinematics of the knee during squatting at each OA disease stage in order to gain a better understanding of the progression process. With progression of knee OA, tibial posterior translation, knee adduction angle, and tibial external rotation in position tended to increase during squat.

The angle of tibial external rotation increased as the disease stage of knee OA advanced. This result supported our hypothesis. OA knees were more externally rotated than healthy knees in a study that was performed using the same analytical methods. A dynamic radiostereometric study showed that the femoral lateral flexion facet center was more anterior in OA knees than in healthy knees. These
studies compared healthy knees with knees affected by end-stage OA, but the results were the same as those found in the present study. There is greater biceps femoris muscle activity in knee OA patients during stair ascent and descent than in healthy individuals of the same age \({228}\). The biceps femoris acts to rotate the tibia externally. Accordingly, we consider that posterior translation of the lateral tibia and tibial external rotation are observed as knee OA progresses.

The angle of knee adduction was greater in grade III and IV cases than grade 0 to II cases. This result supported our hypothesis. Generally, grade II is defined as a “possible narrowing of the joint space”, while definite joint space narrowing is observed in grade III \({229}\). A study that measured the varus and valgus laxity of the knee during non-weight-bearing exercises reported that the angles were 12.0 ± 3.8°, 11.5 ± 5.4°, 11.9 ± 4.3°, 15.1 ± 5.1° and 15.9 ± 5.4° for grades 0 through to IV, respectively \({230}\). Changes were observed between grades II and III although there were no statistically significant differences. The reason a more prominent difference in the angle of adduction was found in our study may be because we performed our measurements during weight-bearing exercises.
Accordingly, during weight bearing, the angle of knee adduction during knee flexion movements showed the greatest difference between grades II and III.

The grade III and IV tibia exhibited more posterior translation than the grade 0 to II tibia. This result supported our hypothesis. A dynamic radiostereometric study also showed that there was a greater posterior translation of the tibia in OA knees than in healthy knees. It is thought that the tibia of knee OA translated posteriorly because of the higher ratios of hamstrings to quadriceps and knee stiffness along with knee instability. In addition, tibial external rotation may disturb tibial anterior translation. Accordingly, posterior translation of the tibia during squatting movements increases from grade III onward.

Squatting is a movement that is performed frequently during daily life, but this movement is difficult for patients with knee OA to perform. Squatting motions that are performed in the presence of abnormal knee kinematics increase knee joint stress and may cause progression of knee OA. In the present study, we clarified the relationship between the disease stage of knee OA and the angle of external rotation of the tibia, the knee adduction angle and the degree of posterior translation of the
tibia. The knee adduction angle varies along the frontal plane in association with cartilage wear. Meanwhile, tibial external rotation and posterior translation are abnormal femoral motions that occur at the tibial plate. It is difficult to restore the former, but it is possible to restore the latter by means of exercise and physical therapy. Accordingly, we consider that improving tibial external rotation and posterior translation during squatting motions not only reduces pain during daily life but is also associated with preventing the progression of knee OA.

There are several limitations and strengths in this study. Subjects with healthy knees were younger than the patients with knee OA and were recruited from patients with unilateral ACL deficiency. The ACL-injured knee may have had kinematic risk factors. In addition, only males were recruited for the healthy knee group and there may be anatomical or biomechanical differences between men and women. To our knowledge, differences in rotational kinematics between the genders have not been reported. Therefore, we consider that the difference in gender distribution had minimal effect on rotational kinematics. We excluded data in mediolateral translation from the results because it was assumed that the
accuracy of these data was reduced. There may be a difference in mediolateral translation between the OA grades, which requires future research. A wide-based squat was selected to avoid overlap of the contralateral knee during fluoroscopic surveillance. Even though this movement is not commonly performed during activities of daily living, it allowed improved reproducibility of the movement and we consider that this variation in movement would be minimal effects on the results.

One of the strengths of this study was high internal validity. As indicated above, we have shown that our techniques for embedding the femoral and tibial coordinate systems are highly repeatable. The 3D-to-2D registration technique using single-plane lateral fluoroscopy, which was used in this analysis, is a well-established technique to measure dynamic weightbearing knee kinematics in vivo. All of the output of the 3D-to-2D registration technique used in the present study were analyzed by a single researcher (F.I.). This may have decreased external validity. However, the 3D-to-2D registration technique requires considerable experience. There are no previous reports in which a single researcher analyzed ≥100 knees and we can state with some pride that the matching precision was high.
Conclusion

With progression of knee OA, there was a tendency toward increasing tibial posterior translation, knee adduction angle, and tibial external rotation in position during squat. We consider that improving tibial external rotation and posterior translation during squatting motions not only reduces pain during daily life but is also associated with preventing the progression of knee OA.
Figure 5-6: Tibial external rotation during squatting.
**Figure 5-7**: Knee adduction angle during squatting.
Figure 5-8: Tibial posterior translation during squatting.
CHAPTER 6

EFFECTS OF THE KNEE ROTATIONAL EXERCISE PROGRAM
CHAPTER 6-1

The Effect of Tibial Internal Rotation Exercises on the Symptoms and Kinematics in People with Medial Knee Osteoarthritis: a Pilot Study

Introduction

Knee OA is a degenerative disease that impairs activities of daily living. According to large-scale studies using radiographic evaluations, 33% of patients over the age of 60 were diagnosed with knee OA. An epidemiological survey in Japan reported that the prevalence of radiographic knee OA was 42.6% in men and 62.4% in women over the age of 40, suggesting that 25,300,000 people (8,600,000 men and 16,700,000 women) aged ≥ 40 years are affected by radiographic knee OA. The cost for TKA is approximately $20,700 and the lifetime cost to knee OA patients ranges from $37,100 (no TKA) to $57,900 after TKA. This indicates the importance of knee OA prevention and treatment.

Identification of the cause of knee OA is important to reduce symptoms and slow disease progression. The knee joint has the highest prevalence of OA, and most
cases demonstrate medial knee OA. This prevalence is thought to be caused by localized mechanical stress. Mechanical stress may be increased by abnormal knee kinematics. Modification of abnormal knee kinematics is required to effectively treat knee OA. Many guidelines with respect to knee OA recommend promoting muscle strength and weight loss. The abnormal kinematics are generally not considered and none of the exercise programs in previous studies have focused on improving the abnormal knee kinematics. Therefore, the aim of this pilot study was to determine where an exercise program could modify abnormal kinematics in the knee with medial OA, and to formulate a future research hypothesis.

There is a difference in knee kinematics between the normal knee and OA knee. Although many studies have analyzed OA knee kinematics, few studies have analyzed bone motion in detail. A recent in vivo study obtaining highly accurate measurements found that the tibia rotates externally throughout the range of knee motion in patients with knee OA. We also confirmed that the tibia in OA knees rotate externally relative to those in healthy knees. Tibial mediolateral
translation in OA knees was more lateral than that in healthy knees \(^{21,207}\). Based on these findings, the tibia of the OA knee rotates externally and translates laterally.

Our research hypothesis was that exercises designed to restore tibial external rotation would improve knee rotational kinematics in the knee with medial OA.

**Methods**

*Institutional Review Board and recruitment*

This study was designed as a pilot study comparing patients before and after intervention without a control group. In compliance with the Declaration of Helsinki, appropriate consideration was given each patient's human rights, the physical and mental risks, and the protection of personal information. The study protocol was approved by the ethics committees of Kanagawa Prefectural Shiomidai Hospital, where the data were collected, and Hiroshima International University.

*Objective and methods*
Inclusion criteria were women aged between 50 and 70 years diagnosed with medial knee OA; those with a history of major trauma in the lower limbs or a disease of the central nervous system were excluded. Three patients (5 knees) who gave their informed consent to participate were enrolled in this study (Table 6.1).

Prior to the exercise intervention, patients underwent knee kinematics analysis and answered questionnaires. Patients visited the hospital once a week and performed the exercises while a physical therapist verified the way exercises were performed. On all other days patients performed the exercise twice a day at home. After 4 weeks, patients underwent the same assessment as prior to the intervention. The results of all assessments conducted before the interventions were compared with those conducted after the intervention.

**Outcomes**

The outcomes were knee kinematics and questionnaires. Knee kinematics was analyzed with a 3D-to-2D registration technique that matches three-dimensional bone models to fluoroscopic images taken (Dyna Direct, Toshiba Medical Systems Corp, Tochigi, Japan). Bone models of the femur and tibia were
created by extracting the contour of the bone cortex on CT (Zomatom plus-4 VZ, Siemens, Munich, Germany) using commercial software (3D-Doctor, Able Software, Lexington, MA). Local coordinate systems were embedded in each bone using the custom VH Knee Fitter program (University of Colorado Health Sciences Center, Aurora, Co). Wide-based squat and step were chosen for knee kinematic analyses. The squats were performed several times from a position with the knees extended to a position of maximum knee flexion, after which one image was taken from the medial side of knee using a flat panel detector. Stepping was performed in place and images were obtained from the front. For analysis of steps, a single image showing complete loading on the measurement side was selected. The captured images were then matched to the bone models using JointTrack software \(^{184}\). Knee kinematics were determined from the 6 DOF positions and orientations of each bone model using Cardan angles \(^{124}\) and the 3D-JointManager commercial software (GLAB Inc., Higashi-Hiroshima, Japan). The questionnaires used the Western Ontario and McMaster Universities Arthritis Index (WOMAC) in a 100-mm Visual Analog Scale format combined with the SF-36 \(^{234} 235\).
Interventions

The RRR (rotation restoration and realignment) program designed to restore tibial external rotation were composed of self-release and tibial internal rotation exercises.

Self-release

The purpose of self-release was to detach the skin from the muscles and joint capsules to achieve better muscle and joint flexibility. Self-release was performed on the lateral and posterior thigh, the popliteal region, and the area around the knee. For example, in self-release of the lateral thigh, the knee was flexed and extended 10 times while pinching any part of the lateral thigh with the fingers (Figure 6-1). The fingers were then shifted to pinch a slightly different site and the knee was once again flexed and extended while the thigh was pinched. By repeating this, self-release of the lateral thigh was performed evenly. The same process was repeated for the posterior thigh, the popliteal region, and the area around the knee for a total of 10 minutes at each site. Self-release was performed every day before tibial internal rotation exercises.
**Tibial internal rotation exercises**

The purpose of the tibial internal rotation exercises was to restore the internal rotation alignment of the tibia. At hospital, patients used the ReaLine LegPress (GLAB Inc., Higashi-Hiroshima, Japan) to perform tibial internal rotation exercises once a week. At the hospital, patients performed 3 sets of tibial internal rotation exercises 10 times per set, after which they performed 5 sets of knee flexion and extension exercises with the tibia in the internal rotation position 10 times per set (Figure 6-2). At home, patients performed tibial internal rotation exercises, knee flexion and extension exercises with the tibia in the internal rotation position (Figure 6-3A), and knee-out squats (Figure 6-3B) 20 times each twice a day.

**Statistical analysis**

There was no statistical analysis of knee kinematics or responses to the questionnaires.

**Results**

**Kinematics**
Wide-based squat imaged from inside

The common squat range of motion of the 5 knees was 10–70° of flexion and 70–10° of extension before the intervention, and 0–60° of flexion and 60-0° of extension after the intervention. The tibial external rotation during flexion pre- and post-intervention were 0.6° (95% Confidence intervals (95% CI): -7.4, 8.5) and -2.9° (-8.9, 3.1) at 10°, -6.4° (-14.5, 1.8) and -9.5° (-16.8, -2.2) at 35°, and -13.7° (-19.8, -7.5) and -13.1° (-20.2, -6.0) at 60°, respectively (Figure 6-4). Averages of these values were -6.4° (-12.3, -0.5) pre-intervention and -8.9° (-14.0, 3.8) post-intervention. Tibial external rotation during extension pre- and post-intervention were -12.5° (-18.5, -6.6) and -13.8° (-20.3, 7.3) at 60°, -7.2° (-12.7, -1.6) and -9.5° (-15.8, -3.2) at 35°, and -0.4° (-5.1, 4.2) and -2.9° (-9.0, 3.3) at 10°, respectively (Figure 6-4). Averages of these values were -6.9° (-11.2, -2.6) pre-intervention and -9.0° (-13.8, -4.2) post-intervention. The knee adduction during flexion pre- and post-intervention were 1.5° (-0.5, 3.5) and 2.2° (0.4, 4.1) at 10°, 3.4° (1.3, 5.6) and 3.4° (2.4, 4.3) at 35°, and 2.8° (0.6, 5.0) and 2.6° (0.3, 4.9) at 60°, respectively (Figure 6-5). Averages of these values were 2.8° (1.3, 4.3) pre-intervention and 3.2° (2.1, 4.3)
post-intervention. The knee adduction during extension pre- and post-intervention were 2.3° (0.8, 3.8) and 2.7° (0.6, 4.7) at 60°, 2.7° (1.8, 3.6) and 3.4° (2.0, 4.8) at 35°, and 0.4° (-1.1, 2.0) and 2.3° (0.8, 3.9) at 10°, respectively (Figure 6-5). Averages of these values were 2.1° (1.1, 3.2) pre-intervention and 3.0° (1.9, 4.1) post-intervention. The tibial anterior translation during flexion pre- and post-intervention were 9.1mm (7.6, 10.7) and 9.8mm (8.7, 11.0) at 10°, 8.2mm (7.4, 9.0) and 8.5mm (7.0, 10.0) at 35°, and 8.8mm (7.4, 10.2) and 9.1mm (6.9, 11.4) at 60°, respectively (Figure 6-6). Averages of these values were 8.5mm (7.7, 9.3) pre-intervention and 8.9mm (7.8, 10.0) post-intervention. The tibial anterior translation during extension pre- and post-intervention were 9.3mm (8.1, 10.5) and 9.6mm (7.2, 12.0) at 60°, 9.7mm (9.1, 10.3) and 9.8mm (8.4, 11.1) at 35°, and 10.7mm (7.8, 13.7) and 10.0mm (8.5, 11.4) at 10°, respectively (Figure 6-6). Averages of these values were 9.8mm (8.7, 10.9) pre-intervention and 9.8mm (8.7, 10.9) post-intervention.

_Stepping in place imaged from the front_
Maximum tibial lateral shift relative to the femur was 5.3mm (95% CI: 3.2, 7.4) pre-intervention and 4.7mm (2.4, 7.0) post-intervention. Maximum knee adduction angle was 1.5° (0.0, 3.1) pre-intervention and 1.9° (0.2, 3.7) post-intervention.

*Questionnaires*

The mean score of the three patients for the WOMAC was 133.3 points before intervention and 15.7 points after intervention (Pain: 34.3 before/4.0 after, Stiffness: 9.0/3.3, Physical Function: 90.0/8.3). The mean score of the three patients for the SF-36 was 675 points before intervention and 755 points after intervention.

*Discussion*

The aim of this pilot study was to determine whether the RRR program would modify rotational kinematics of the knee with medial OA, and to formulate a future research hypothesis. This program tended to reduce tibial external rotation
and lateral translation, but increase knee adduction. It also tended to improve knee pain and function.

None of the previous studies have restored abnormal kinematics of OA knee by exercise. However, improvement of abnormal knee kinematics is necessary to reduce excessive joint stress. During squat, the tibia in medial knee OA rotates externally relative to that in the healthy knee and tibial mediolateral translation in OA knees is more lateral than that in healthy knees. The RRR program improved both tibial external rotation and lateral translation. The medial hamstrings rotated the tibia internally in cadaveric knee study, while the iliotibial band caused the tibia to rotate externally and translate laterally. Therefore, we considered that the RRR program improved dysfunction of the medial hamstrings and stiffness of the lateral thigh. On the other hand, adduction angles increased after the RRR program. In cadaveric knee study, knee adduction increased with the iliotibial band under unloaded or low-loaded conditions. Knee-out squat might increase knee adduction. Intervention to avoid increasing the adduction angle will need to be developed in the future. Based on the findings
outlined above, the RRR program ought to be able to restore tibial external rotation and lateral translation of the OA knee.

The RRR program improved knee functions (WOMAC) and health-related quality of life (SF-36). Although a systematic review and meta-analysis of randomized controlled trials previously reported that exercise improved WOMAC and SF-36 in knee OA, two recent systematic reviews reported that valgus bracings to achieve realignment did not improve WOMAC. The RRR program was designed to restore tibial external rotation in patients with medial knee OA. Clarifying the mechanism underlying the effect of the RRR program will be a subject for future analysis.

This study has several strengths and limitations. For example, the 3D-to-2D registration technique offers highly accurate analysis and was of a sufficient level for the hypothesis test. Another strength of this study was ensuring that all patients performed the exercises twice a day by having each patient keep a journal of their exercises. By contrast, the small sample size was a limitation of this study. The 5 knees had a common knee flexion angle of 10–60° with a mean range of
motion for external rotation of -6.64° (SD 4.26°) before intervention and -8.96° (SD 3.40°) after intervention. To obtain an alpha error of 0.05 and power of 0.8, the total number of samples should have been 24. In addition, the lack of a control group for comparison is also a limitation.

**Conclusion**

The RRR program reduces the tibial external rotation angle in knee OA patients, which may improve knee pain and function. We can conclude that this is a valid hypothesis for future randomized controlled studies.

**Conflicts of interest**

The ReaLine LegPress and the 3D-JointManager commercial software used in this study are products of the co-author’s (KG) company.
Table 6-1: Background Data for the 3 subjects.

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Figure 6.1: Self-release of the lateral thigh.

The lateral thigh was pinched with finger (left), and the knee is flexed and extended 10 times (right). After that the fingers are shifted to pinch a slightly different site and the knee is once again flexed and extended while the thigh is pinched.
Patients rotated the lower leg internally (left and middle), after which they extended knee with the lower leg in an internal rotation position (right) using the ReaLine LegPress (GLAB, Hiroshima, Japan).
Figure 6-3: Tibial internal rotation exercises and knee-out squats.

(Top) Patients performed lower leg internal rotation exercises (leftmost and second from the left), knee extension (third from left) and flexion (rightmost) exercises with the lower leg in the internal rotation position.

(Bottom) Patients stood with feet shoulder width apart (leftmost), bent the knee (second from the left), opened the knees (the third from left), and lengthened the knee in that position (rightmost). Knee-out squat induced internal rotation of the tibia relative to the femur.
Tibial external rotation during squatting

Figure 6-4: Mean values and 95% CI are shown. The common squat range of motion is shown by a line or dotted-line. Digits within the figure indicate the number of knees.
Knee adduction angle during squatting

**Figure 6-5:** Mean values and 95%CI are shown. The common squat range of motion is shown by a line or dotted line. Digits in the figure indicate the number of knees.
The tibial anterior translation during squatting

Figure 6-6: Mean values and 95%CI are shown. The common squat range of motion is shown by a line or dotted-line. Digits in the figure indicate the number of knees.
CHAPTER 6-2

Effects of Knee Internal Rotation Exercises on Knee Adduction Moment and Function of Elderly Women with Knee Osteoarthritis: A Randomized Controlled Trial

Introduction

Knee OA is an irreversible, degenerative disease and causes a decrease in ADL. According to large-scale studies, X-ray assessment demonstrated that 33% of individuals aged ≥ 60 years have knee OA. Thus, it is estimated that 25,300,000 individuals in Japan have latent knee OA. There are conservative and invasive forms of treatment for knee OA. Generally, conservative therapy is indicated for early to moderate knee OA, while invasive treatment is indicated for end-stage knee OA. Invasive treatment is a major physical, psychological and economic burden for patients. Causal treatment, which considers the disease mechanism, is a desirable form of conservative therapy to treat knee OA. It is therefore imperative
for us to gain a better understanding of the mechanisms of OA onset and progression.

OA most commonly occurs medially 18 in the knee joint 19. Therefore, we cannot ignore the effects of localized mechanical stress on the medial knee as a risk factor for progression. Since external KAM is considered a risk factor for knee OA 240, interventional studies have aimed to reduce KAM 175 242 243 244 245. Khalaj et al. 246 performed a review regarding the effects of exercise on KAM in knee OA patients. There is only one paper by Thorp et al. 247 showing that exercise reduced KAM. In all other studies, exercise did not reduce KAM. However, Thorp et al. implemented an exercise program centered on muscle strength exercises and stretching, but they did not indicate whether or not they considered the mechanism of knee OA progression.

Taking into consideration the abnormal external rotation kinematics of the lower leg that is characteristic of OA knees 21 22, we devised a rotation restoration and RRR program with the intention of normalizing rotational kinematics. The RRR program improves varus alignment 248 and has been confirmed to result in medial deviation of the center of foot pressure 249, which is laterally deviated in knee
OA patients. However, we do not know how the RRR program affects the KAM values. For this reason, the purpose of this study was to gain a better understanding of the effects of the RRR program, which improves characteristic external rotational alignment of the leg in medial knee OA, on knee function and KAM during walking.

The hypothesis of this study is that the RRR program, which focused on restoring external rotation of the leg, will be able to reduce KAM in elderly individuals with knee OA.

Methods

Subjects

This study was based on the principles outlined in the Declaration of Helsinki and conducted with consideration of the physical and psychological suffering of the subjects as well as protection of personal information. The study protocol was approved by the Shimokitazawa Hospital Ethics Review Committee. Subjects were recruited by approaching neighborhood associations in the areas
surrounding Shimokitazawa Hospital. The inclusion criteria for subjects were: (1) experiencing knee joint pain during daily life; (2) varus alignment with no contact between the two femoral medial epicondyles when standing in a stationary upright position; and (3) Japanese women aged 60 to 85 years old. The exclusion criteria were: (1) individuals unable to walk independently; (2) individuals currently receiving treatment at a medical institution for orthopedic disorders of the lower limbs; (3) individuals with a history of surgery on the lower limbs; (4) patients with rheumatoid arthritis or gout; (5) individuals at high risk due to internal medical conditions; (6) patients with dementia; (7) patients with psychiatric disorders; (8) individuals with impaired communication; and (9) lack of informed consent. A single researcher explained the details of the study to the applicants and those who gave their consent were enrolled as subjects. Subjects were randomly allocated to two groups in advance using a table of random numbers.

Methods

This study was a randomized controlled study comparing an RRR program group to a conventional exercise group (who performed quadriceps exercises).
Baseline measurements of subjects involved gait analysis and the completion of a questionnaire survey. Thereafter, the subjects received a booklet with commentary and photographs demonstrating the exercise and an exercise journal. The subjects were allocated to either the RRR program group or the conventional exercise group using a table of random numbers. The researcher then provided explanations and practiced with each subject until the subject was able to independently perform the tasks. Subjects were required to perform exercises once a day for four weeks. In order to improve compliance, we asked subjects to document their exercises in a journal and we periodically confirmed the exercise methods and performance status via an interview or telephone call. The same gait analysis and questionnaire survey were administered at the baseline and repeated after four weeks of intervention. During the present study, subjects who completed more than 16 days of home exercises (four-sevenths of 28 days) were included in the outcome analysis. Gait analysis and the questionnaire survey were administered blindly by the same researcher before and after intervention.
The RRR program group performed interstructural release (ISR) and internal rotational exercises intended to restore external rotation of the leg (Figure 6-7). We theorized that abnormal external rotation kinematics of the leg are caused by adhesions between the skin or subcutaneous tissue and the muscles or joint capsule and habitual performance of knee joint movements with the leg in external rotation. The purpose of the ISR was for the subjects to easily resolve abnormal interstructural collateral force transmission by themselves. Fundamentally, subjects were required to pinch the skin anywhere on the posterior surface of the knee joint, the lateral side of the thigh, or the lateral side of the knee joint and then flex the knee joint ten times. Thereafter, they were required to pinch a slightly different site and repeat the flexion of the knee joint ten times. ISR was performed at all of the sites described above approximately ten minutes before exercising.

Exercise involved internal rotation movements of the leg in an upright sitting position. After the internal rotation movements, the knee joint was maintained in an internally rotated position and subjects performed three sets of ten repetitions of extension movements, flexion movements and knee-out squats (Figure 6-8).
In the conventional exercise group, based on the methods used by Thorp et al.\textsuperscript{247} to reduce KAM, subjects performed (1) three types of exercises to strengthen the muscle groups surrounding the knee joint (quadriceps femoris muscle setting, knee joint flexion exercises in a prone position, knee joint extension exercises in an upright sitting position); (2) two types of exercises to strengthen the hips joint abductor muscle group (hip joint abduction exercises in a standing position, hip joint abduction exercises in a lateral recumbent position); (3) two types of exercises to strengthen the lower leg muscle groups (squatting, exercises involving ascent and descent), giving a total of seven types of exercises. In addition, subjects also performed: (4) two types of stretches for the hip joint abductor muscle group (in a standing position, the leg on the side being stretched is moved anteriorly, without stretching the trunk on the contralateral side; then the leg on the side being stretched is moved posteriorly and the hip joint abductor muscle group is similarly stretched). Subjects who felt that the exercise load was light were provided with additional resistance in the form of an exercise tube.
Outcomes included walking speed, the first and second peak KAM values for the knee joint during walking, the knee injury and KOOS questionnaire results and the SF-36 score. In subjects with pain in both knee joints, the side with more severe pain was the target of investigation. The test motion during gait analysis was to walk freely at optimum speed and the target for analysis was the fourth step. We used eight infrared cameras with the Locus 3D MA-3000 three-dimensional motion analysis system (Anima Corporation, Japan) to perform gait analysis, and used the MG-200, a portable, three-dimensional force plate (Anima Corporation, Japan), to perform KAM measurements. Infrared reflective markers were attached to the subject on the left and right over the acromion, anterior superior iliac spine, greater trochanter, lateral femoral epicondyle, the lateral malleolus and the head of the fifth metatarsal.

The Mann-Whitney test was used for statistical analysis and the two groups were compared before and after intervention. We also compared the amount of change in the conventional exercise and RRR exercise groups. We used SPSS ver.
13 (SPSS Inc., USA) and a free statistical software R ver. 3.1.1 as statistical analysis software and a p value of <0.05 was considered significant.

Results

There were 34 subjects who gave their consent to participate in the present study. A total of seven were excluded: six did not meet the inclusion criteria or met the exclusion criteria, while one was unable to participate due to scheduling conflicts. This left a total of 27 subjects who were randomly allocated to the two groups (13 subjects in the conventional exercise group and 14 subjects in the RRR program group). Of these, one subject from the conventional exercise group was excluded because the subject did not participate in the outcome measurements. Five subjects from the RRR program group were also excluded because two subjects did not participate in the outcome measurements, one subject developed lower back pain during the intervention period and two did not have time to do the exercises). The final number of subjects was therefore 12 subjects in the conventional exercise group (seven right knees, five left knees) and nine subjects in the RRR program
group (six right knees, three left knees) (Figure 6-9). There were no significant differences between these two groups in terms of age, body height, body weight or BMI, but the number of days on which exercise was performed was significantly lower in the RRR program group at 19.9 days (95%CI: 18.4, 21.4) than in the conventional exercise group at 24.4 days (22.5, 26.4 days) (p = 0.01) (Table 6-2).

We observed a significant difference between the two groups in terms of the amount of change in the SF-36 role physical scores (RRR program group: +7.4 [95% CI: 0.4, 14.4], conventional exercise group: -8.3 [-18.3, 1.7], p = 0.036) and the total SF-36 score (RRR program group: +49.0 [15.4, 82.7], conventional exercise group: -17.9 [-59.1, 23.3], p = 0.033). There were no significant differences in terms of the KOOS, walking speed, first KAM (amount of change in the conventional exercise group: 0.016 (95%CI: -0.027, 0.060) [N*m/(Ht*BW)], amount of change in the RRR program group 0.046 (-0.087, -0.006) [N*m/(Ht*BW)], p = 0.065), or the second KAM (values presented as previous: -0.020 (-0.054, 0.015) [N*m/(Ht*BW)], and -0.025 (-0.063, 0.013) [N*m/(Ht*BW)], p = 1.00) (Table 6-3).
Discussion

The purpose of the present study was to gain a better understanding of the effects of the RRR program on KAM of knee pain in elderly patients and the effects on knee joint function. There were no significant differences between the first and second KAM values in the RRR program group. Furthermore, there were no significant differences when the amount of change was compared to that in the conventional exercise group. There was a significantly greater amount of change in terms of the SF-36 role physical scores and total scores in the RRR program group than in the conventional exercise group. There were no significant differences in the KOOS scores.

The absence of significant changes in KAM values in the RRR program group was thought to be due to re-alignment of the knee joint along the horizontal plane following the intervention. However, there was no treatment for other joints that contribute to walking movement. A mechanical shock absorption mechanism is required for the talocrural joint and talocalcaneal joint in addition to the knee joint, during the loading response when the first KAM increases. During the terminal
stance when the second KAM increases, the dynamic stability of the talocrural joint, due to powerful eccentric contraction during plantar flexion, and stabilization due to the reduction of valgus in the talocalcaneal joint are both important. The RRR program used in the present study involved knee joint exercises in the sitting and standing positions. Going forward, we need to verify knee kinematics during walking and the effectiveness of the interventions that improve the function of the hip and ankle joints.

There was a significantly greater amount of change in terms of the SF-36 role physical scores and total scores in the RRR program group than in the conventional exercise group. However, there was no significant increase on comparison of values before and after intervention. Therefore, the significant increase in the RRR program group was thought to be caused by an interaction between the increased score in the RRR program group and the decreased score in the conventional exercise group. The role physical score contains items that evaluate the effects of psychological factors on work and normal activities. We find it hard to believe that differences in movement intervention greatly affected
the psychological responses of the subjects. This may have been affected by some kind of psychological changes in the subjects during the intervention period.

There were a number of strengths and limitations in this study. One of the strengths was the fact that all researchers were blinded, except for the researcher who gave guidance regarding exercise. Other strengths include the fact that three-dimensional motion analysis infrared reflective markers used during the present study had a spatial coordinate detection error rate of ±0.1% (within 1 mm for each 1 m of space) and that the errors originating from the machine were small. Limitations included the fact that not all subjects underwent X-ray examinations and that it was not possible to determine the severity of knee OA in those subjects. Previous studies also showed the clinical effectiveness of the RRR program, but the sample size was small in all groups and we were not able to obtain strong evidence. Another limitation in the present study was the inadequate sample size. The absence of significant differences between the groups may have been due to incorporation of a β error. The partial η² obtained during the present study was
0.171. To obtain a statistical power of 0.8 using the same study design, then a total of 41 subjects would be required.

Acknowledgment

We would like to extend our deepest gratitude to the Anima Corporation for their guidance regarding three-dimensional motion analysis during this study.
Table 6-2: Characteristics of subjects and the number of exercise days

<table>
<thead>
<tr>
<th></th>
<th>Conventional exercise (N=12)</th>
<th>RRR program (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>71.4 (68.7, 74.2)</td>
<td>72.6 (66.9, 78.2)</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>155.7 (153.4, 158.0)</td>
<td>152.9 (149.0, 156.8)</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>51.8 (48.3, 55.3)</td>
<td>53.3 (49.2, 57.5)</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>21.3 (20.3, 22.2)</td>
<td>22.8 (21.2, 24.4)</td>
</tr>
<tr>
<td>Days of exercise [days]</td>
<td>24.4 (22.5, 26.4) ※</td>
<td>19.9 (18.4, 21.4) ※</td>
</tr>
</tbody>
</table>

Means (95% CI). ※; indicates a significant difference (p=0.01).
Table 6-3: SF-36, KOOS, and Gait.
Means (95% CI). ※ indicates a significant difference (p<0.05).

<table>
<thead>
<tr>
<th></th>
<th>Conventional exercise group (N=12)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Outcome</td>
<td>Amount of change</td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>79.2 (74.4, 83.9)</td>
<td>79.6 (73.9, 85.3)</td>
<td>0.4 (-5.7, 6.6)</td>
<td></td>
</tr>
<tr>
<td>Role physical</td>
<td>90.6 (86.2, 95.1)</td>
<td>86.5 (74.3, 98.6)</td>
<td>-4.2 (-14.8, 6.5)</td>
<td></td>
</tr>
<tr>
<td>Body pain</td>
<td>60.0 (47.3, 72.7)</td>
<td>65.4 (53.8, 77.0)</td>
<td>5.4 (-1.6, 12.4)</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>59.4 (51.6, 67.2)</td>
<td>58.6 (49.7, 67.4)</td>
<td>-0.8 (-7.7, 6.1)</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>61.5 (50.8, 72.1)</td>
<td>60.4 (49.2, 71.6)</td>
<td>-1.0 (-8.7, 6.6)</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>94.8 (90.3, 99.3)</td>
<td>89.6 (78.8, 100.3)</td>
<td>-5.2 (-15.8, 5.4)</td>
<td></td>
</tr>
<tr>
<td>Role emotional</td>
<td>93.8 (89.0, 98.5)</td>
<td>85.4 (72.5, 98.3)</td>
<td>-8.3 (-18.3, 1.7)</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>75.4 (67.1, 83.8)</td>
<td>71.3 (62.9, 79.6)</td>
<td>-4.2 (-9.4, 1.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>614.6 (578.8, 650.4)</td>
<td>596.7 (530.0, 663.4)</td>
<td>-17.9 (-59.1, 23.3)</td>
<td></td>
</tr>
</tbody>
</table>

| KOOS               |                                    |       |                 |
|--------------------|                                    |       |                 |
| Symptoms           | 78.9 (71.9, 85.8)                  | 77.4 (71.5, 83.2) | -1.5 (-5.4, 2.4) |
| Pain               | 76.9 (68.1, 85.6)                  | 76.9 (67.1, 86.6) | 0.0 (-9.1, 91.4)  |
| Function, daily living | 89.0 (84.6, 93.4)                  | 88.5 (81.9, 95.0) | -0.5 (-7.1, 6.1)  |
| Function, sports and recreational activities | 69.6 (57.7, 81.5) | 67.1 (56.1, 78.1) | -2.5 (-12.9, 7.9) |
| QOL                | 67.2 (55.9, 78.5)                  | 67.7 (57.6, 77.8) | 0.5 (-9.6, 10.7)  |
| **Total**          | 381.5 (344.0, 418.9)               | 377.5 (339.9, 415.1) | -4.0 (-35.2, 27.3) |

| Gait               |                                    |       |                 |
|--------------------|                                    |       |                 |
| Gait speed [km/h]  | 4.16 (3.93, 4.39)                  | 4.09 (3.84, 4.33) | -0.07 (-0.27, 0.13) |
| 1st KAM [N*m/(Ht*BW)] | 0.315 (0.242, 0.388)               | 0.331 (0.261, 0.401) | 0.016 (-0.027, 0.060) |
| 2nd KAM [N*m/(Ht*BW)] | 0.328 (0.258, 0.398)               | 0.308 (0.241, 0.376) | -0.020 (-0.054, 0.015) |

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Table 6-3: SF-36, KOOS, and Gait (Cont.).
Means (95% CI). ※ indicates a significant difference (p<0.05).

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Baseline</th>
<th>Outcome</th>
<th>Amount of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>80.6 (72.9, 88.2)</td>
<td>87.2 (80.9, 93.6)</td>
<td>6.7 (0.7, 12.6)</td>
</tr>
<tr>
<td>Role physical</td>
<td>85.4 (74.4, 96.5)</td>
<td>91.0 (82.6, 99.4)</td>
<td>5.6 (−3.8, 14.9)</td>
</tr>
<tr>
<td>Body pain</td>
<td>76.0 (64.6, 87.4)</td>
<td>78.7 (68.5, 88.8)</td>
<td>2.7 (−1.4, 6.8)</td>
</tr>
<tr>
<td>General health</td>
<td>65.7 (56.9, 74.5)</td>
<td>70.3 (62.6, 78.0)</td>
<td>4.7 (−1.7, 11.0)</td>
</tr>
<tr>
<td>Vitality</td>
<td>71.5 (64.8, 78.2)</td>
<td>73.6 (65.1, 82.2)</td>
<td>2.1 (−5.4, 9.5)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>83.3 (62.6, 104.1)</td>
<td>97.2 (93.8, 100.6)</td>
<td>13.9 (−4.8, 32.5)</td>
</tr>
<tr>
<td>Role emotional</td>
<td>87.0 (79.3, 94.8)</td>
<td>94.4 (87.7, 101.2)</td>
<td>7.4 (0.4, 14.4) ※</td>
</tr>
<tr>
<td>Mental health</td>
<td>81.7 (74.4, 88.9)</td>
<td>87.8 (82.4, 93.1)</td>
<td>6.1 (−2.7, 14.9)</td>
</tr>
<tr>
<td>Total</td>
<td>631.2 (586.0, 676.4)</td>
<td>680.3 (651.9, 708.6)</td>
<td>49.0 (15.4, 82.7) ※</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KOOS</th>
<th>Baseline</th>
<th>Outcome</th>
<th>Amount of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>84.5 (79.5, 89.6)</td>
<td>85.7 (80.6, 90.9)</td>
<td>1.2 (−2.9, 5.3)</td>
</tr>
<tr>
<td>Pain</td>
<td>84.9 (80.5, 89.2)</td>
<td>84.9 (79.3, 90.5)</td>
<td>0.0 (−6.0, 6.0)</td>
</tr>
<tr>
<td>Function, daily living</td>
<td>90.5 (86.4, 94.6)</td>
<td>94.6 (91.1, 98.1)</td>
<td>4.1 (0.8, 7.3)</td>
</tr>
<tr>
<td>Function, sports and</td>
<td>75.6 (69.1, 82.0)</td>
<td>82.2 (75.1, 89.3)</td>
<td>6.7 (−0.2, 13.6)</td>
</tr>
<tr>
<td>recreational activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL</td>
<td>75.7 (66.0, 85.4)</td>
<td>79.2 (70.6, 87.8)</td>
<td>3.5 (−1.3, 8.2)</td>
</tr>
<tr>
<td>Total</td>
<td>411.2 (389.9, 432.5)</td>
<td>426.6 (406.6, 446.6)</td>
<td>15.4 (4.5, 26.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gait</th>
<th>Baseline</th>
<th>Outcome</th>
<th>Amount of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait speed [km/h]</td>
<td>3.86 (3.56, 4.17)</td>
<td>3.78 (3.28, 4.29)</td>
<td>−0.08 (−0.39, 0.23)</td>
</tr>
<tr>
<td>1st KAM [N<em>m/(Ht</em>BW)]</td>
<td>0.370 (0.287, 0.453)</td>
<td>0.323 (0.241, 0.406)</td>
<td>−0.046 (−0.087, −0.006)</td>
</tr>
<tr>
<td>2nd KAM [N<em>m/(Ht</em>BW)]</td>
<td>0.372 (0.270, 0.474)</td>
<td>0.347 (0.245, 0.449)</td>
<td>−0.025 (−0.063, 0.013)</td>
</tr>
</tbody>
</table>

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Figure 6-7: Knee internal rotation exercises

Leg internal rotation exercise ((1) and (2)), knee extension with the leg internally rotated (from (1) to (3)), knee flexion with the leg internally rotated ((1), (2) and (4)). The subject used their own hand to confirm medial contraction of the hamstrings and performed the movements while grasping the thigh in order to avoid compensatory movement of the hip joint.
**Figure 6-8**: Knee-out squat

A rolled up towel was placed beneath the cuboid bone and the legs were positioned shoulder width apart (1), then the knee joint was flexed (2). The knee joint is placed in an internally rotated position during the knee-out squat (3), then extension of the knee joint is performed in this position (4). Finally, the subject consciously contracts the gluteus maximus muscle and adopts a completely extended position (1).
Figure 6-9: Flowchart of the protocol of this study.
CHAPTER 7

DISCUSSION AND CONCLUSION
Knee OA frequently develops in elderly persons and not only decreases QOL for patients and their families but also aggravates social burdens on the country. Therefore, more effective treatment of knee OA is required. The first choice of treatment for knee OA is conservative therapy. Although many studies have reported the effects of exercise on knee OA, this issue remains controversial. These exercise programs have not clearly focused on the underlying cause of OA. Progression of the abnormal kinematics in OA knee places excessive stress on the cartilages.

We assessed changes in the knee kinematics with progression of OA and analyzed these data to improve understanding of abnormal kinematics in the OA knee. Firstly, we confirmed the validity of the joint coordinate system embedding to improve knee kinematics analyses. Secondly, we analyzed static knee alignment and dynamic knee kinematics during knee extension-flexion and squatting. These studies demonstrated that the tibia in OA knee were displaced posteriorly, and showed increased adduction and external rotation. We considered that it is possible
to restore tibial external rotation and posterior translation using an exercise program.

Therefore, we devised a series of exercises to restore abnormal kinematics and evaluated the effects and limitations. The pilot study showed that this exercise program restored abnormal kinematics and improved pain and function in OA knee. An RCT compared this exercise program to conventional exercise for 4 weeks. There was no significant difference in KAM, knee pain, or function between the two exercise groups. In the future, we should examine the long-term effects of this exercise protocol.


251. **蒲田和芳**: リアライン・トレーニング＜体幹・股関節編＞. 2014.
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