



The effects of knee pain on knee contact force and external knee adduction moment in patients with knee osteoarthritis

Yamagata, Momoko
Taniguchi, Masashi
Tateuchi, Hiroshige
Kobayashi, Masashi
Ichihashi, Noriaki

(Citation)

Journal of Biomechanics, 123:110538

(Issue Date)

2021-06-23

(Resource Type)

journal article

(Version)

Accepted Manuscript

(Rights)

© 2021 Elsevier Ltd.

This manuscript version is made available under the CC-BY-NC-ND 4.0 license
<http://creativecommons.org/licenses/by-nc-nd/4.0/>

(URL)

<https://hdl.handle.net/20.500.14094/90008442>



The effects of knee pain on knee contact force and external knee adduction moment in patients with knee osteoarthritis

Momoko Yamagata^{1,2,3}, Masashi Taniguchi², Hiroshige Tateuchi⁴, Masashi Kobayashi⁵, Noriaki Ichihashi²

¹ Graduate School of Human Development and Environment, Kobe university, 3-11 Tsurukabuto, Nada-ku, Kobe, Hyogo 657-0011, Japan

² Department of Physical Therapy, Human Health Science, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo, Kyoto 606-8507, Japan

³ Research Fellow of the Japan Society for the Promotion of Science, 5-3-1 Kojimachi, Chiyodaku, Tokyo 102-0083, Japan

⁴ Department of Preventive Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan

⁵ Kobayashi Orthopaedic Clinic, 50-35 Kuzetakada-cho, Minami-ku, Kyoto, 601-8211, Japan

Corresponding Author:

Momoko Yamagata

Graduate School of Human Development and Environment, Kobe university, 3-11 Tsurukabuto, Nada-ku, Kobe, Hyogo 657-0011, Japan

Tel: +81-78-803-7811. E-mail address: myamagata@people.kobe-u.ac.jp

Keywords: knee osteoarthritis; musculoskeletal model; gait; knee contact force; knee adduction moment

Word Count: 3353 words

Abstract

Knee osteoarthritis (OA) is a major cause of knee pain, leading to physical dysfunction. External knee adduction moment (KAM), a surrogate measure of knee contact force (KCF) in the medial compartment, is related to knee pain, but the association between KCF and pain severity remains unclear. This study aimed to reveal the differences in KCF due to pain severity. Twenty-eight patients with knee OA were evaluated knee symptoms including pain severity via the Knee Society Score. Based on the median symptom score, 17 points in this study, subjects were classified as having Mild symptomatic OA ($n = 15$) and Severe symptomatic OA ($n = 13$). Subjects walked three times at a comfortable speed along a six-meter walkway, and we calculated KAM during the stance phase. KCF magnitude and distribution were also computed using the subject-specific musculoskeletal model, considering physical characteristics such as the femorotibial angle measured by X-ray. No differences in physical characteristics such as femorotibial angle and gait speed were found by symptom severity, whereas KAM and medial KCF at minimum and second peak in Severe symptomatic OA patients were significantly greater than those in Mild symptomatic OA. A significant medial shift of KCF in Severe symptomatic OA was also seen at first peak and minimum. Severe symptomatic OA had a greater medial KCF and medial shift of KCF. Detailed evaluations of KCF magnitude and distribution in addition to KAM would provide crucial information on

knee contact force in relation to symptom severity.

The effects of knee pain on knee contact force and external knee adduction moment in patients with knee osteoarthritis

1. Introduction

Knee osteoarthritis (OA) is a major cause of knee pain which can lead to physical dysfunction. While evaluating structural changes using X-ray is one way of representing the characteristics of knee OA, a previous study revealed that physical function in symptomatic knee OA is determined more by knee pain evaluated through a questionnaire than by structural change on X-ray (Creamer et al., 2000). Similar findings were also observed in several studies (Hochberg et al., 1989; McAlindon et al., 1993), and it is clear that knee pain severity is a better predictor of physical dysfunction, such as walking disabilities, than radiographic severity. Given that gait biomechanics are different between asymptomatic and symptomatic patients with knee OA (Aststephen Wilson et al., 2017; Sritharan et al., 2017), verifying biomechanical alterations with the severity of knee pain is a reasonable approach to providing a crucial information to prevent progression of knee OA and physical dysfunction.

The external knee adduction moment (KAM) during gait is related to knee OA

progression and knee pain severity (Miyazaki et al., 2002). Three indices in the KAM during the stance phase are typically evaluated: the first and second peaks in KAM occurring in the 0–50% and 50–100% stance phases and the minimum peak in KAM occurring during the mid-stance phase (Astegh Wilson et al., 2017; Mündermann et al., 2005). Since KAM can be easily calculated using motion capture systems, it is widely used as a surrogate measure of medial knee contact force (KCF_{Medial}) (Birmingham et al., 2007). On the other hand, a previous study measuring KCF_{Medial} using instrumented knee implants has shown that there is a large variation in the correlation between KAM and KCF_{Medial} due to high inter-individual variability ($R^2 = 0.09 - 0.97$) (Kutzner et al., 2013). Those findings, however, might be affected by several factors related to the surgery, such as alterations of muscle strength and joint structure. Clarifying the extent to which KAM reflects KCF_{Medial} for the non-operated knee is essential in accurately using and interpreting KAM.

Several studies compare KAM with estimated KCF using musculoskeletal modeling systems, including the AnyBody Modeling System (AnyBody, Aalborg, Denmark). A previous study on healthy older adults has concluded that KAM is relatively useful in reflecting KCF_{Medial} during gait; it found moderate to strong correlations of KAM at the first and second peaks with KCF_{Medial} (Ogaya et al., 2014).

Conversely, another study on knee OA patients revealed that KAM at the first peak is a strong predictor of KCF_{Medial} , but such a strong correlation was not seen in KAM at the second peak (Richards et al., 2018). The low correlation between second-peak KAM and KCF_{Medial} might result from the lower limb alignment. Since inter-individual differences in varus alignment would be greater in knee OA patients compared to healthy older adults (Matsumoto et al., 2015), a subject-specific model which considers the femorotibial angle (FTA) should be utilized, especially in knee OA patients. No studies, however, have explored the correlation between KAM and estimated KCF_{Medial} using a musculoskeletal model considering subject-specific FTA.

In addition to KCF_{Medial} , medial-lateral KCF distribution is also used as an index for characterizing gait pattern. An earlier study showed that there were greater KCF_{Medial} and lower KCF in the lateral compartment (KCF_{Lateral}) in knee OA patients, resulting in a KCF shift from the lateral to the medial compartment as compared to healthy adults (Mannisi et al., 2019). Furthermore, gait modifications used by knee OA patients such as toe-in gait and wide-steps gait have been shown to not change the KCF_{Medial} , but to change the KCF distribution (KCF_{Ratio} ; the ratio of KCF_{Medial} relative to total knee contact force, KCF_{Total}) (Richards et al., 2018). There is a possibility that KCF_{Ratio} corrections reflect the comprehensive changes in KCF_{Medial} and KCF_{Lateral} , which would

make it a key factor in determining the relationship between gait pattern and knee pain.

However, the difference in the estimated KCF-relevant variables including KCF_{Ratio} due to symptom severity is still unclear.

The purposes of this study were to reveal: 1) the correlation between KAM and KCF_{Medial} considering subject-specific FTA, and 2) the differences of KCF-relevant variables due to symptom severity. We proposed the following hypotheses: 1) KAM has a strong correlation with estimated KCF_{Medial} considering subject-specific FTA throughout the stance phase, and 2) KAM and estimated KCF-relevant variables in severe symptomatic OA patients would be greater than those in mild symptomatic OA patients.

2. Methods

2.1. Subjects

Twenty-eight female patients with symptomatic medial knee OA were recruited from one community orthopedic clinic. The sample size required for an unpaired t-test [effect size = 1.24 (large), α error = 0.05, power = 0.80] was calculated using the G*power software (version 3.1.; Heinrich Heine University, Düsseldorf, Germany), and the ideal sample size was 24. Using standing anteroposterior radiographs of the bilateral knees, an orthopedic surgeon determined the severity of knee OA based on the Kellgren/Lawrence (K/L) grade and measured the FTA as the lateral angle between the femoral and tibial anatomical axes (Hashimoto et al., 2019). The intraclass correlation coefficients (ICC) of FTA, medial joint space, and lateral joint space were strongly reliable [ICC(1,1) range, 0.947–0.998; ICC(1,1), 0.958–0.998; ICC(1,1), 0.888–0.995]. The inclusion criteria were as follows: radiographic medial OA (i.e. K/L grade ≥ 1) in one or both knees, no surgery to both limbs, no neurological or balance disorders requiring assistive devices, and could walk without an assistive device in daily life. We also included patients with K/L grade 1 for early knee OA (Mahmoudian et al., 2017). Prior to the experiments, all subjects were informed about the purpose and procedures of this

study and gave written informed consent. Ethical approval was granted by the Research Ethics Committee of Kyoto University.

The symptom section (Symptom Score), which was derived from the Knee Society's Knee Scoring System (KSS) 2011 Japanese edition (Taniguchi et al., 2015), was completed, with total scores ranging from 0 to 25 points. Higher scores indicated less severe symptoms. Based on the median symptom score, 17 points in this study, subjects were classified into two groups: 15 subjects with mild symptoms (Mild symptomatic OA; Symptom Score \geq 17 points) and 13 subjects with severe symptoms (Severe symptomatic OA; Symptom Score $<$ 17 points). This symptom score was almost equivalent to the median score in a previous study (Taniguchi et al., 2021). We also evaluated the functional part (Function Score) of the KSS which covers the patient's ability to "walk and stand", "Standard Activity", and "Advanced Activities." The maximum Function Score is 100 points, with higher scores indicating less severe functional disability. The physical characteristics are shown in Table 1.

2.2. Gait analysis

After a static trial for calibration of the gait model, subjects walked along a six-meter walkway at a comfortable speed. Kinematics data during walking were collected

using eight infrared cameras with motion capture systems (Vicon, Oxford, UK) sampling at 100Hz, and low-pass filtered at 6Hz with 4th order, zero-lag Butterworth filter. Reflective markers were placed based on the Vicon Plug-in-Gait full-body model marker placement protocol to define body segments. Ground reaction forces were measured using two force plates embedded in the walking path, sampling at 1000Hz (Kistler, Winterthur, Switzerland), and low-pass filtered at 20Hz with 4th order, zero-lag Butterworth filter (Tateuchi et al., 2017, 2014).

To characterize the walking pattern, we calculated gait speed, cadence, and stride length. Using a standard inverse dynamics approach, the following variables on the more affected side based on symptoms were also evaluated with Vicon Nexus2.7.1 (Vicon, Oxford, UK): the first peak of KAM (KAM_p1), the second peak of KAM (KAM_p2), minimum KAM (KAM_min), and KAM impulse (integral of KAM during the stance phase). Note that KAM indices were not normalized by body weight in order to evaluate the absolute loading to the knee joint. Five practice trials were conducted, and the starting point was adjusted to allow the subjects to naturally step on the force plate. For further analysis, the variables were averaged across the three successful trials.

2.3. Musculoskeletal model

To estimate the contact forces of the medial and lateral compartments in the knee joint, we used the Twente Lower Extremity Model version 2 (TLEM2) included in the Mocap Lower Body Model in the Anybody Modeling System v.7.1 (De Pieri et al., 2018). The model contains the following 11 segments: pelvis, both sides of femurs, patellas, shanks, talus, and feet. Eight joints providing 16 degrees of freedoms (DOFs) are included; hip and knee joints are modeled as spherical (3 DOFs), and talocrural and subtalar joints are modeled as hinges (1 DOF). The model of each lower limb contains 55 muscles, and is divided into 169 elements. The muscle elements were modeled using a full-blown Hill model that consisted of contractile and viscoelastic elements. Since there was a possibility that the ligament structures in knee OA patients with a varus malalignment would differ from people with normal alignment, in the inverse dynamics, we did not include reaction moments in the mediolateral and transverse directions to account for resistance provided by the ligamentous structures of the knee joint.

Initially, we created a scaled musculoskeletal model for each subject based on anthropometric data (Lund et al., 2015). FTA was measured in each subject and was applied to create a subject-specific model. Markers' data during gait were used to optimize the lengths and widths of segments. Secondly, the scaled model and motion capture data, such as the markers' trajectories and ground reaction forces, provided input data for

inverse dynamics analysis. For muscle forces, the numerical optimization procedure using a 3rd order polynomial muscle recruitment criterion was utilized to minimize the sum of muscle activation cubed. Muscle activity is defined as force delivered by the muscle (N) divided by maximum muscle strength (N) for the scaled physiological cross-sectional area.

As one method to divide the total internal contact force of the knee joint into forces on the medial and lateral compartments, we added 12 nodes equally on the scaled medial and lateral condyles of the tibia to acquire joint reaction force, in addition to the center of the knee in the original model (Fig. 1). We defined medial and lateral internal contact forces as the sum of reaction forces acquired in the 12 nodes, and reported these as KCF_{Medial} and KCF_{Lateral} . For further statistical comparisons, the values at three peaks for KCF_{Medial} ($KCF_{\text{Medial_p1}}$, $KCF_{\text{Medial_p2}}$, and $KCF_{\text{Medial_min}}$) and KCF_{Lateral} ($KCF_{\text{Lateral_p1}}$, $KCF_{\text{Lateral_p2}}$, and $KCF_{\text{Lateral_min}}$) were extracted. KCF_{Ratio} was also computed at the three peaks of KCF_{Medial} ($KCF_{\text{Ratio_p1}}$, $KCF_{\text{Ratio_p2}}$, and $KCF_{\text{Ratio_min}}$). The KCF_{Ratio} was calculated as the ratio of KCF_{Medial} to total knee contact force, and a value of 0.5 meant that there was an equal distribution of the load on the medial and lateral compartments, whereas a value greater than 0.5 indicated that there was a greater load on the medial compartment compared to the load on the lateral compartment.

2.4 Statistical analysis

Pearson's correlation analyses were performed to test the correlation between KAM and KCF_{Medial} at p1, p2, and min.

To test the differences in general gait parameters, KAM, and KCF-relevant variables (i.e., KCF_{Medial}, KCF_{Lateral}, and KCF_{Ratio}) due to the symptom severity, unpaired t-tests were performed to compare between the Mild symptomatic OA and Severe symptomatic OA groups. To further understand the relationship between symptom severity and variables for knee loadings, two additional analyses were conducted: Spearman's correlations of KAM and KCF-related variables with symptom score, and paired t-tests for comparisons between more and less affected limbs. All analyses were performed using SPSS (Version 18, PASW Statistics, Chicago) and the significance level was set at $p = 0.05$.

3. Results

There were significant differences in the Function Score as well as the Symptom Score between groups (Table 1). No significant differences were found with regard to other physical characteristics. There were also no differences observed between the two groups in terms of gait speed, stride length, and cadence (Table 2).

At the first peak, there was a moderate statistical association between KAM and KCF_{Medial} ($r = 0.68$, $p < 0.001$). Stronger associations between KAM and KCF_{Medial} were seen at the second peak ($r = 0.75$, $p < 0.001$) and at the minimum ($r = 0.77$, $p < 0.001$).

The results of between-group comparisons of knee joint moments and estimated KCF are shown in Figure 2. KAM_{min} , KAM_{p2} , $KCF_{\text{Medial_min}}$, and $KCF_{\text{Medial_p2}}$ in Severe symptomatic OA patients were significantly greater than those in Mild symptomatic OA patients ($p < 0.05$). $KCF_{\text{Lateral_p1}}$ in Severe symptomatic OA patients was significantly lower than that in Mild symptomatic OA patients ($p < 0.05$). Severe symptomatic OA patients had significantly greater KAM and KCF_{Medial} impulses than Mild symptomatic OA patients (Table 3). KCF_{Ratio} in Severe symptomatic OA patients was also significantly higher than those in Mild symptomatic OA patients at the

first and minimum peaks ($p < 0.05$; Table 4). Similar results were observed from correlation analyses; KAM_min, KAM_p2, KCF_{Medial_min}, and KCF_{Medial_p2} were increased with low symptom scores (KAM_min: $\rho = -0.57$, KAM_p2: $\rho = -0.46$, KCF_{Medial_min}: $\rho = -0.57$, and KCF_{Medial_p2}: $\rho = -0.42$), and KCF_{Lateral_p1} was decreased with low symptom scores ($\rho = 0.40$).

The results of the comparisons between the more and less affected lower limbs are shown in Table 5. KCF_{Medial_min}, and KCF_{Medial_p2} in the more affected limb were significantly greater than those in the less affected limb ($p < 0.05$). No significant differences were found for the other variables.

4. Discussion

The main purpose of this study was to explore the correlation between KAM and KCF_{Medial} in knee OA patients during gait, and the differences in KAM and KCF-relevant indices by symptom severity. A moderate to strong correlation between KAM and KCF_{Medial} was found throughout the stance phase, supporting our hypothesis that KAM was associated with KCF_{Medial}. KAM and KCF_{Medial} at the minimum and second peaks, and KCF_{Ratio} at the minimum and first peaks were significantly greater in Severe

symptomatic OA patients compared to Mild symptomatic OA patients. Severe symptomatic OA patients also displayed greater KAM and KCF_{Medial} impulses compared to those with Mild symptomatic OA patients. These findings partly supported our hypothesis that KAM and KCF-relevant variables in severe symptomatic OA patients would be greater than those in mild symptomatic OA patients. This is the first study to verify that, upon consideration of the subject-specific alignment of the lower limb, the estimated KCF differs in relation to symptom severity in knee OA patients.

Knee OA patients with severe symptoms had greater KAM_{p2}, KAM_{min}, and KAM impulse than patients with mild symptoms, and the correlation analysis revealed that KAM in mid- and late-stance phases increased with an increase in knee pain. KCF_{Medial} also had a significant correlation with KAM. The lack of knee unloading and increased knee impulse with symptom severity was consistent with previous findings (Asthephen Wilson et al., 2017). Since alterations by symptom severity have been observed even when comparing knee loading between individuals with the same radiographic severity (Thorp et al., 2007), high KAM during gait would be related more to severe pain than to a severe K/L grade. The relationship between the symptom severity and the knee loading during gait observed by inter-individual comparisons might not simply be applicable to the intra-individual comparisons given the results of the

comparisons between more- and less-affected lower limbs. However, we determined that KAM through the stance phase can be a reasonable substitute for KCF_{Medial} estimated by a musculoskeletal model that considers patient-specific FTA. While causal relationships cannot be established, our results show that KAM is relatively useful in reflecting KCF_{Medial} during the stance phase, and they implied that the lack of knee unloading and repetitive loading in the medial compartment might lead to severe pain.

An earlier study has shown an associations of greater cartilage loss with a decrease in the co-activation of lateral knee muscles (vastus lateralis and biceps femoris) that reflect low KCF_{Lateral} (Hodges et al., 2016). Severe symptomatic OA in this study had low KCF_{Lateral} in addition to a tendency of having high KCF_{Medial} during the earlier stance phase, resulting in an increase in the KCF_{Ratio} . In other words, OA patients with severe symptoms could not place their load in the lateral compartment, leading to the load shifting to the medial compartment. KCF distribution is affected by the distribution of muscle forces and ligament tension in addition to the frontal knee alignment (Adouni and Shirazi-Adl, 2014; Saliba et al., 2017), and the tension in lateral knee muscles and soft tissues play an important role in the avoidance of placing extreme loads on the medial compartment (Schipplein and Andriacchi, 1991). High activity of lateral knee muscles might also be helpful in increasing knee joint stability without increasing the

KCF_{Medial} (Brandon et al., 2014). Given that there were no between-group differences in FTA in this study, the distribution of muscle forces controlling KCF distribution might be greatly related to symptom severity, implying that a re-distribution of muscle forces might be necessary to reduce knee pain.

While a significant correlation between KAM and KCF_{Medial} was found in this study, different elements such as muscle forces may account for differences in KCF_{Medial}, unlike KAM. Indeed, previous studies have revealed that KAM reduction brought on by gait modification did not always correspond to KCF reduction (Kinney et al., 2013; Walter et al., 2010). Moreover, other studies have shown that pain mitigation brought on by different interventions did not affect KAM (Al-Khlaifat et al., 2016; Bennell et al., 2010) and the gait modification for KAM reduction led to high co-activation of medial and lateral knee muscles that would increase KCF (Booij et al., 2020). The interventions focused on changing the distribution of muscle forces leading to a change in KCF_{Medial}, as compared to an intervention focused on KAM reduction, might be an effective method of pain mitigation.

In this study, knee OA patients with grades ranging from K/L grade 1 to 4 and FTA from 176 to 186 degrees were included. The advantage of this study was to use a patient-specific musculoskeletal model that considered the different varus alignments

across subjects. However, we did not consider the effect of ligaments. A previous study added certain reaction moments which account for joint resistance brought on by tension in the ligaments (Richards et al., 2018); however, we did not add this moment to our model since the ligamentous structures and tension in the knee may be altered in patients with large alignment deformations (Schulze-Tanzil, 2019). The differences in the methods may be one of the reasons why the magnitudes and time profiles of KCF in this study slightly differed from those in previous studies. A modified model which takes into consideration elastic ligament bundles would be necessary for future studies.

There were some limitations to this study. First, we focused on only female patients in this study because females typically present with a higher prevalence (Neogi and Zhang, 2013; Prieto-Alhambra et al., 2014) and feel greater knee pain than males (Glass et al., 2014). However, considering that KAM during gait in female patients was lower than that in male patients (Kumar et al., 2015), it is possible that the same findings observed in this study might not be seen in male patients. Future studies considering sex-related differences in the relationship between OA symptoms and knee loading during gait are therefore warranted. Second, the causal relationships between knee pain and KCF during gait are still unclear, thus a longitudinal study is needed. Finally, we could not identify why the results regarding the relationship between symptom severity and knee

loading was slightly different between inter- and intra-individual comparisons. One interpretation was that feeling knee pain itself might change the compensatory strategies resulting in such differences, although future studies are needed for a proper interpretation.

5. Conclusions

Knee OA patients with severe symptoms had greater KCF_{Medial} , KCF_{Ratio} , and KAM during gait as compared to patients with mild symptoms, indicating that patients with severe symptomatic OA displayed a high magnitude of medial KCF and a medial shift of KCF. Detailed evaluations of KCF magnitude and distribution resulting from muscle force distribution in addition to KAM would be valuable in providing crucial information to develop a deeper understanding of the association between gait pattern and knee symptoms in knee OA patients.

Compliance with ethical standards

Conflict of interest:

The authors declare that they have no conflict of interest.

Acknowledgment

296 We thank Mr. Toshihiko Kikuchi at TERRABYTE Co., Ltd for his advice on the
297 musculoskeletal model. This work was supported by a Grant-in-Aid for Young Scientists
298 (Start-up) (19K24284).

299

Reference

- Adouni, M., Shirazi-Adl, A., 2014. Partitioning of knee joint internal forces in gait is dictated by the knee adduction angle and not by the knee adduction moment. *J. Biomech.* 47, 1696–1703. <https://doi.org/10.1016/j.jbiomech.2014.02.028>
- Al-Khlaifat, L., Herrington, L.C., Hammond, A., Tyson, S.F., Jones, R.K., 2016. The effectiveness of an exercise programme on knee loading, muscle co-contraction, and pain in patients with medial knee osteoarthritis: A pilot study. *Knee* 23, 63–69. <https://doi.org/10.1016/j.knee.2015.03.014>
- Astephen Wilson, J.L., Stanish, W.D., Hubley-Kozey, C.L., 2017. Asymptomatic and symptomatic individuals with the same radiographic evidence of knee osteoarthritis walk with different knee moments and muscle activity. *J. Orthop. Res.* 35, 1661–1670. <https://doi.org/10.1002/jor.23465>
- Bennell, K.L., Hunt, M.A., Wrigley, T. V., Hunter, D.J., McManus, F.J., Hodges, P.W., Li, L., Hinman, R.S., 2010. Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: A randomised controlled trial. *Osteoarthr. Cartil.* 18, 621–628. <https://doi.org/10.1016/j.joca.2010.01.010>

318 Birmingham, T.B., Hunt, M.A., Jones, I.C., Jenkyn, T.R., Giffin, J.R., 2007. Test-retest
 319 reliability of the peak knee adduction moment during walking in patients with
 320 medial compartment knee osteoarthritis. *Arthritis Care Res.* 57, 1012–1017.
 321 <https://doi.org/10.1002/art.22899>

322 Booi, M.J., Richards, R., Harlaar, J., van den Noort, J.C., 2020. Effect of walking with
 323 a modified gait on activation patterns of the knee spanning muscles in people with
 324 medial knee osteoarthritis. *Knee* 27, 198–206.
 325 <https://doi.org/10.1016/j.knee.2019.10.006>

326 Brandon, S.C.E., Miller, R.H., Thelen, D.G., Deluzio, K.J., 2014. Selective lateral
 327 muscle activation in moderate medial knee osteoarthritis subjects does not unload
 328 medial knee condyle. *J. Biomech.* 47, 1409–1415.
 329 <https://doi.org/10.1016/j.jbiomech.2014.01.038>

330 Creamer, P., Lethbridge-Cejku, M., Hochberg, M.C., 2000. Factors associated with
 331 functional impairment in symptomatic knee osteoarthritis. *Rheumatology* 39, 490–
 332 496. <https://doi.org/10.1093/rheumatology/39.5.490>

333 De Pieri, E., Lund, M.E., Gopalakrishnan, A., Rasmussen, K.P., Lunn, D.E., Ferguson,
 334 S.J., 2018. Refining muscle geometry and wrapping in the TLEM 2 model for
 335 improved hip contact force prediction. *PLoS One* 13, 1–19.

336 <https://doi.org/10.1371/journal.pone.0204109>
 337 Glass, N., Segal, N.A., Sluka, K.A., Torner, J.C., Nevitt, M.C., Felson, D.T., Bradley,
 338 L.A., Neogi, T., Lewis, C.E., Frey-Law, L.A., 2014. Examining sex differences in
 339 knee pain: The multicenter osteoarthritis study. *Osteoarthr. Cartil.* 22, 1100–1106.
 340 <https://doi.org/10.1016/j.joca.2014.06.030>
 341 Hashimoto, S., Terauchi, M., Hatayama, K., Saito, K., Chikuda, H., 2019. Younger
 342 patients with high varus malalignment of the contralateral knee may be candidates
 343 for simultaneous bilateral total knee arthroplasty. *Knee Surgery, Sport. Traumatol.*
 344 *Arthrosc.* 27, 2173–2180. <https://doi.org/10.1007/s00167-019-05472-9>
 345 Hochberg, M.C., Lawrence, R.C., Everett, D.F., Cornoni-Huntley, J., 1989.
 346 Epidemiologic associations of pain in osteoarthritis of the knee: Data from the
 347 national health and nutrition examination survey and the national health and
 348 nutrition examination-i epidemiologic follow-up survey. *Semin. Arthritis Rheum.*
 349 18, 4–9. [https://doi.org/10.1016/0049-0172\(89\)90008-5](https://doi.org/10.1016/0049-0172(89)90008-5)
 350 Hodges, P.W., van den Hoorn, W., Wrigley, T. V., Hinman, R.S., Bowles, K.-A.A.,
 351 Cicuttini, F., Wang, Y., Bennell, K., 2016. Increased duration of co-contraction of
 352 medial knee muscles is associated with greater progression of knee osteoarthritis.
 353 *Man. Ther.* 21, 151–158. <https://doi.org/10.1016/j.math.2015.07.004>

354 Kinney, A.L., Besier, T.F., Silder, A., Delp, S.L., D'Lima, D.D., Fregly, B.J., 2013.
 355 Changes in in vivo knee contact forces through gait modification. *J. Orthop. Res.*
 356 31, 434–440. <https://doi.org/10.1002/jor.22240>
 357 Kumar, D., Souza, R.B., Subburaj, K., MacLeod, T.D., Singh, J., Calixto, N.E., Nardo,
 358 L., Link, T.M., Li, X., Lane, N.E., Majumdar, S., 2015. Are There Sex Differences
 359 in Knee Cartilage Composition and Walking Mechanics in Healthy and
 360 Osteoarthritis Populations? *Clin. Orthop. Relat. Res.* 473, 2548–2558.
 361 <https://doi.org/10.1007/s11999-015-4212-2>
 362 Kutzner, I., Trepczynski, A., Heller, M.O., Bergmann, G., 2013. Knee Adduction
 363 Moment and Medial Contact Force-Facts about Their Correlation during Gait.
 364 *PLoS One* 8, 8–15. <https://doi.org/10.1371/journal.pone.0081036>
 365 Lund, M.E., Andersen, M.S., de Zee, M., Rasmussen, J., 2015. Scaling of
 366 musculoskeletal models from static and dynamic trials. *Int. Biomech.* 2, 1–11.
 367 <https://doi.org/10.1080/23335432.2014.993706>
 368 Mahmoudian, A., van Dieën, J.H., Baert, I.A.C., Bruijn, S.M., Faber, G.S., Luyten, F.P.,
 369 Verschueren, S.M.P., 2017. Changes in gait characteristics of women with early
 370 and established medial knee osteoarthritis: Results from a 2-years longitudinal
 371 study. *Clin. Biomech.* 50, 32–39.

372 <https://doi.org/10.1016/j.clinbiomech.2017.10.004>

373 Mannisi, M., Dell’Isola, A., Andersen, M.S., Woodburn, J., 2019. Effect of lateral
 374 wedged insoles on the knee internal contact forces in medial knee osteoarthritis.
 375 Gait Posture 68, 443–448. <https://doi.org/10.1016/j.gaitpost.2018.12.030>

376 Matsumoto, T., Hashimura, M., Takayama, K., Ishida, K., Kawakami, Y., Matsuzaki,
 377 T., Nakano, N., Matsushita, T., Kuroda, R., Kurosaka, M., 2015. A radiographic
 378 analysis of alignment of the lower extremities - initiation and progression of varus-
 379 type knee osteoarthritis. Osteoarthr. Cartil. 23, 217–223.
 380 <https://doi.org/10.1016/j.joca.2014.11.015>

381 McAlindon, T.E., Cooper, C., Kirwan, J.R., Dieppe, P.A., 1993. Determinants of
 382 disability in osteoarthritis of the knee. Ann. Rheum. Dis. 52, 258–262.
 383 <https://doi.org/10.1136/ard.52.4.258>

384 Miyazaki, T., Wada, M., Kawahara, H., Sato, M., Baba, H., Shimada, S., 2002.
 385 Dynamic load at baseline can predict radiographic disease progression in medial
 386 compartment knee osteoarthritis. Ann. Rheum. Dis. 61, 617–622.
 387 <https://doi.org/10.1136/ard.61.7.617>

388 Mündermann, A., Dyrby, C.O., Andriacchi, T.P., 2005. Secondary gait changes in
 389 patients with medial compartment knee osteoarthritis: Increased load at the ankle,

390 knee, and hip during walking. *Arthritis Rheum.* 52, 2835–2844.

391 <https://doi.org/10.1002/art.21262>

392 Neogi, T., Zhang, Y., 2013. Epidemiology of Osteoarthritis. *Rheum. Dis. Clin. North*

393 *Am.* 39, 1–19. <https://doi.org/10.1016/j.rdc.2012.10.004>

394 Ogaya, S., Naito, H., Iwata, A., Higuchi, Y., Fuchioka, S., Tanaka, M., 2014. Knee

395 adduction moment and medial knee contact force during gait in older people. *Gait*

396 *Posture* 40, 341–345. <https://doi.org/10.1016/j.gaitpost.2014.04.205>

397 Prieto-Alhambra, D., Judge, A., Javaid, M.K., Cooper, C., Diez-Perez, A., Arden, N.K.,

398 2014. Incidence and risk factors for clinically diagnosed knee, hip and hand

399 osteoarthritis: Influences of age, gender and osteoarthritis affecting other joints.

400 *Ann. Rheum. Dis.* 73, 1659–1664. <https://doi.org/10.1136/annrheumdis-2013->

401 203355

402 Richards, R.E., Andersen, M.S., Harlaar, J., van den Noort, J.C., 2018. Relationship

403 between knee joint contact forces and external knee joint moments in patients with

404 medial knee osteoarthritis: effects of gait modifications. *Osteoarthr. Cartil.* 26,

405 1203–1214. <https://doi.org/10.1016/j.joca.2018.04.011>

406 Saliba, C.M., Brandon, S.C.E., Deluzio, K.J., 2017. Sensitivity of medial and lateral

407 knee contact force predictions to frontal plane alignment and contact locations. *J.*

408 Biomech. 57, 125–130. <https://doi.org/10.1016/j.jbiomech.2017.03.005>

409 Schipplein, O.D., Andriacchi, T.P., 1991. Interaction between active and passive knee
 410 stabilizers during level walking. J. Orthop. Res. 9, 113–119.
 411 <https://doi.org/10.1002/jor.1100090114>

412 Schulze-Tanzil, G., 2019. Intraarticular Ligament Degeneration Is Interrelated with
 413 Cartilage and Bone Destruction in Osteoarthritis. Cells 8.
 414 <https://doi.org/10.3390/cells8090990>

415 Sritharan, P., Lin, Y.C., Richardson, S.E., Crossley, K.M., Birmingham, T.B., Pandy,
 416 M.G., 2017. Musculoskeletal loading in the symptomatic and asymptomatic knees
 417 of middle-aged osteoarthritis patients. J. Orthop. Res. 35, 321–330.
 418 <https://doi.org/10.1002/jor.23264>

419 Taniguchi, M., Ikezoe, T., Kamitani, T., Tsuboyama, T., Ito, H., Matsuda, S., Tabara,
 420 Y., Matsuda, F., Ichihashi, N., 2021. Extracellular-to-intracellular water ratios are
 421 associated with functional disability levels in patients with knee osteoarthritis:
 422 results from the Nagahama Study. Clin. Rheumatol.
 423 <https://doi.org/10.1007/s10067-021-05591-0>

424 Taniguchi, N., Matsuda, S., Kawaguchi, T., Tabara, Y., Ikezoe, T., Tsuboyama, T.,
 425 Ichihashi, N., Nakayama, T., Matsuda, F., Ito, H., 2015. The KSS 2011 Reflects

426 Symptoms, Physical Activities, and Radiographic Grades in a Japanese Population.
 427 Clin. Orthop. Relat. Res. 473, 70–75. <https://doi.org/10.1007/s11999-014-3650-6>
 428 Tateuchi, H., Koyama, Y., Akiyama, H., Goto, K., So, K., Kuroda, Y., Ichihashi, N.,
 429 2017. Daily cumulative hip moment is associated with radiographic progression of
 430 secondary hip osteoarthritis. Osteoarthr. Cartil. 25, 1291–1298.
 431 <https://doi.org/10.1016/j.joca.2017.02.796>
 432 Tateuchi, H., Taniguchi, M., Takagi, Y., Goto, Y., Otsuka, N., Koyama, Y., Kobayashi,
 433 M., Ichihashi, N., 2014. Immediate effect of Masai Barefoot Technology shoes on
 434 knee joint moments in women with knee osteoarthritis. Gait Posture 40, 204–208.
 435 <https://doi.org/10.1016/j.gaitpost.2014.03.190>
 436 Thorp, L.E., Sumner, D.R., Wimmer, M.A., Block, J.A., 2007. Relationship between
 437 pain and medial knee joint loading in mild radiographic knee osteoarthritis.
 438 Arthritis Rheum. 57, 1254–60. <https://doi.org/10.1002/art.22991>
 439 Walter, J.P., D’Lima, D.D., Colwell, C.W., Fregly, B.J., 2010. Decreased knee
 440 adduction moment does not guarantee decreased medial contact force during gait.
 441 J. Orthop. Res. 28, 1348–1354. <https://doi.org/10.1002/jor.21142>
 442

Table 1. Physical characteristics (n = 28)

	Mild symptomatic OA (n = 15)	Severe symptomatic OA (n = 13)	<i>p</i> -value	95% CI
Age (yr)	67.4 (6.4)	71.1 (4.1)	.091	-7.93 – 0.58
Height (m)	1.54 (0.05)	1.55 (0.06)	.651	-7.82 – 3.64
Weight (kg)	53.4 (8.7)	58.7(6.7)	.087	-11.38 – 0.82
Kellgren and Lawrence Grade (of the more affected knee)	I: 3, II: 6, III: 4, IV: 2	I: 1, II: 3, III: 6, IV: 3	–	–
Femoro-tibial angle (of the more affected knee)	178.0 (2.8)	179.3 (5.4)	.421	-4.56 –1.97
Symptom Score	19.4 (1.9)	12.3 (3.0)	.001 *	5.08 – 8.95
Function Score	76.8 (13.6)	63.2 (12.2)	.009 *	3.56 – 23.74

The values are mean (SD). The 95% confidence intervals (CI) for the differences between Mild and Severe symptomatic OA are shown. * < 0.05.

Table 2. Gait variables

	Mild symptomatic OA	Severe symptomatic OA	<i>p</i> -value	95% CI
Gait Speed (m/s)	1.2 (0.2)	1.1 (0.2)	.109	-0.03 – 0.27
Stride length (m)	1.1 (0.2)	1.0 (0.1)	.416	-0.07 – 0.16
Cadence (steps/min)	126.7 (7.9)	119.4 (11.3)	.074	-0.45 – 14.50

The values are mean (SD). The 95% confidence intervals (CI) for the differences between Mild and Severe symptomatic OA are shown.

Table 3. Impulses of knee joint moments and internal knee contact forces ($\times 10^2$)

	Mild symptomatic OA	Severe symptomatic OA	<i>p</i> -value	95% CI
KAM (Nm.s)	20.9 (7.5)	32.3 (9.6)	.002 *	-18.06 – -0.48
KCF _{Lateral} (N.s)	218.8 (132.9)	188.3 (82.8)	.481	-57.16 – 118.15
KCF _{Medial} (N.s)	556.6 (132.6)	707.9 (119.1)	.004 *	-249.86 – -52.73

The values are mean (SD). The 95% confidence intervals (CI) for the differences between Mild and Severe symptomatic OA are shown. * < 0.05.

Table 4. Loading distribution

	Mild symptomatic OA	Severe symptomatic OA	<i>p</i> -value	95% CI
KCF _{Ratio_p1} (norm)	0.7 (0.1)	0.8 (0.05)	.034 *	-0.14 – -0.01
KCF _{Ratio_min} (norm)	0.7 (0.08)	0.8 (0.05)	.044 *	-0.11 – -0.002
KCF _{Ratio_p2} (norm)	0.8 (0.1)	0.8 (0.07)	.319	-0.10 – 0.03

The values are mean (SD). The 95% confidence intervals (CI) for the differences between Mild and Severe symptomatic OA are shown. * < 0.05.

Table 5. Results of the comparison between more and less affected limbs

	More affected limb	Less affected limb	<i>p</i> -value	95% CI
KAM_p1 (Nm)	35.9 (11.2)	35.1 (10.7)	.632	-2.51 – 4.05
KAM_min (Nm)	21.5 (9.0)	19.9 (7.4)	.148	-0.58 – 3.66
KAM_p2 (Nm)	28.6 (9.7)	26.9 (8.9)	.153	-0.70 – 4.20
KCF _{Medial} _p1 (N*10 ²)	15.8 (3.8)	14.8 (4.2)	.127	-0.32 – 2.38
KCF _{Medial} _min (N*10 ²)	9.0 (2.3)	8.4 (2.5)	.044 *	0.01 – 1.24
KCF _{Medial} _p2 (N*10 ²)	12.1 (2.5)	11.2 (3.2)	.037 *	0.01 – 1.86
KCF _{Lateral} _p1 (N*10 ²)	6.6 (4.0)	6.0 (3.3)	.158	-0.27 – 1.56
KCF _{Ratio} _p1 (norm)	0.8 (0.09)	0.8 (0.08)	.982	-0.03 – 0.03
KCF _{Ratio} _min (norm)	0.8 (0.08)	0.8 (0.08)	.558	-0.04 – 0.02
KCF _{Ratio} _p2 (norm)	0.8 (0.08)	0.8 (0.09)	.605	-0.03 – 0.16

The values are mean (SD). The 95% confidence intervals (CI) for the differences between the more and less affected limbs are shown. * < 0.05.

Figure captions

Fig 1. Schematic illustrations of muscles and reaction forces on medial and lateral compartments. For medial and lateral internal contact force, twenty nodes were equally added on the medial and lateral condyles of the tibia, separately. The blue dot represents the center of reaction force on each condyle.

Fig 2. Time profiles of knee loading indices: Averaged across subject data are shown with standard deviation shades from initial contact (0%) to toe off (100%) of the more affected side. Data in mild and severe symptom patients are shown in black solid line and red dotted line, respectively. Top panel: External knee adduction moment (KAM), Middle panel: Knee contact force on the medial compartment (KCF_{Medial}), Bottom panel: Knee contact force on lateral compartment (KCF_{Lateral}). * Significant differences ($p < 0.05$) between groups.



