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MUSCULOSKELETAL LOADING IN THE SYMPTOMATIC AND ASYMPTOMATIC KNEES OF MIDDLE-AGED OSTEOARTHRITIS PATIENTS

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recruitment, experimental design and undertaking of gait experiments were performed by SER and TBB. The computational modelling pipeline was developed and implemented by PS with design input and technical guidance from YCL and MGP. Statistical analyses were designed and supervised by KMC and TBB, and undertaken by PS. All authors discussed and agreed on results and potential implications. The manuscript was initially prepared by PS, YCL and MGP, but all authors contributed substantially to its revision and final form.

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ABSTRACT

This study quantified the contributions by muscles, gravity and inertia to the tibiofemoral compartment forces in the symptomatic (SYM) and asymptomatic (ASYM) limbs of varus mal-aligned medial knee osteoarthritis (OA) patients, and compared the results with healthy controls (CON). Muscle forces and tibiofemoral compartment loads were calculated using gait data from 39 OA patients and 15 controls aged 49±7 years. Patients exhibited lower knee flexion angle, higher hip abduction and knee adduction angles, lower internal knee flexion torque but higher external knee adduction moment. Muscle forces were highest in CON except hamstrings, which was highest in SYM. ASYM muscle forces were lowest for biceps femoris short head and gastrocnemius but otherwise intermediate between SYM and CON. In all subjects vasti, hamstrings, gastrocnemius, soleus, gluteus medius, gluteus maximus and gravity were the largest contributors to medial compartment force (MCF). Inertial contributions were negligible. Highest MCF was found in SYM throughout stance. Small increases in contributions from hamstrings, gluteus maximus, gastrocnemius and gravity at the first peak; soleus and rectus femoris at the second peak; and soleus, gluteus maximus, gluteus medius and gravity during mid-stance summed to produce significantly higher total

MCF. Compared to CON, the ASYM limb exhibited similar peak MCF but higher mid-stance MCF. In patients, diminished non-knee-spanning muscle forces did not produce correspondingly diminished MCF contributions due to the influence of mal-alignment. Our findings emphasise consideration of muscle function, lower-limb alignment and mid-stance loads in developing interventions for OA, and inclusion of the asymptomatic limb in clinical assessments.

Keywords: knee adduction moment, medial compartment force, varus alignment, musculoskeletal model, muscle contributions

INTRODUCTION

Increased cyclic compressive loading in the medial compartment of the tibiofemoral-joint is associated with progression of medial knee osteoarthritis[1] (OA). Determining the root causes of elevated medial compartment force (MCF) is difficult, as a range of neuromuscular, morphological and structural changes associated with medial knee OA have been reported throughout the lower-limb. This includes varus mal-alignment and knee-joint laxity[2], strength deficits[3], elevated knee-spanning muscle co-activity[4], and hip abductor dysfunction[5].

As non-invasive measurement of joint forces is currently not feasible, the external knee adduction moment (EKAM) during gait has been proposed as a surrogate for load distribution[6], supported by studies using instrumented total knee replacements[7,8] (TKRs) and musculoskeletal modelling[9]. However, important limitations exist when relying on the EKAM to study joint loading as it only accounts for the ground reaction force[10] (GRF) and not the direct compressive effect of knee-spanning muscles[11], which can contribute up to one-half of the total MCF in healthy gait[12]. Yet surrogate models incorporating both EKAM and the internal knee extension torque, as a surrogate for knee-spanning muscle forces, have shown only limited improvements in MCF estimates[11]. Thus, a detailed examination of knee-

joint forces is necessary to understand and improve surrogate measures.

Muscles, gravity and inertia all contribute to the GRF by means of dynamic coupling[13] and hence also contribute to knee-joint forces and the EKAM[12]. Muscles contribute most to loading in healthy knees during weight-bearing activities[14], however, the relative contributions by lower-limb muscles to loading in osteoarthritic knees are not clearly established. A modelling study of healthy gait showed that non-knee-spanning muscles can account for up to one-half of the total MCF[12]. Notably, the gluteus medius provides most of the non-knee-spanning muscle contribution to MCF and almost all the EKAM in healthy gait[12]. Although OA-specific changes in muscle forces can impact the pattern of loading on the tibiofemoral compartments[15], no study to date has quantified the individual contributions by the lower-limb muscles, gravity and inertia to the pattern of forces in the osteoarthritic knee.

Non-pharmacologic interventions for knee OA which modify patient biomechanics are typically aimed at reducing the peaks of EKAM[16]. However, recent studies have found that elevated mid-stance EKAM is associated with greater disease severity[17] and future need for TKR[18]. Detailed knowledge of how elevated mid-stance knee-joint loads arise in patients may help guide the development of novel clinical interventions which more effectively reduce knee-joint loading throughout stance.

Furthermore, significant functional asymmetries exist between the symptomatic and asymptomatic limbs in unilateral knee OA[19] and the risk of progression to bilateral disease is high once unilateral disease is established[20]. Thus, understanding loading in the asymptomatic knee would help determine if and how the asymptomatic limb should also be considered in clinical interventions for unilateral knee OA.

This study aimed to quantify the contributions by muscles, gravity and inertia to the forces in the medial and lateral tibiofemoral compartments during walking in both the

symptomatic and asymptomatic limbs of varus mal-aligned medial knee OA patients, and to compare the results with healthy controls. As patients may walk with more knee-spanning muscle co-activation than healthy adults[4], we hypothesised that higher MCF in patients would arise from elevated contributions by the hamstrings, quadriceps and gastrocnemius. From findings of hip abductor force deficits in OA patients[5], we further hypothesised lower gluteus medius forces in patients, but based on the weak association between hip abductor function and EKAM[21], its contribution to MCF would not be significantly lower than controls.

METHODS

Design: Case-control study

Level of evidence: III

Participants and clinical assessment. Thirty-nine patients were recruited from a tertiary care centre specialising in orthopaedics, including rehabilitative and surgical (non-arthroplasty) interventions for knee OA. All patients were referred to the centre for potential limb-realignment surgery for one symptomatic knee with radiographic OA primarily affecting the medial compartment. Twenty-five controls matched for sex, age and body mass index (BMI) with no history of knee pain were recruited from the same community. Of these, 15 controls were matched to patients for walking speed after gait analysis. Methods for recruitment, inclusion and exclusion criteria, radiographic assessment, patient-reported measures and gait experiments are detailed in a previous publication[22]. Inclusion criteria for patients included varus mal-alignment of the lower-limb and diagnosis of medial knee OA based on the American College of Rheumatology criteria[23]. Symptoms were assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS)[24]. The extent of frontal-plane mal-alignment (mechanical axis angle) and OA severity (Kellgren-Lawrence grade) were measured from full-limb standing anteroposterior radiographs[25]. Frontal-plane alignment was

also measured in all participants using marker data from a static trial recorded during gait analysis. The study was approved by the Research Ethics Board for Health Sciences Research Involving Human Subjects of the University of Western Ontario (HSREB No. 09812E).

Gait experiments. All experiments were performed at the Wolf Orthopaedic Biomechanics Laboratory, Fowler Kennedy Sport Medicine Clinic, University of Western Ontario. Joint motion and GRF were recorded simultaneously as each participant walked at his or her preferred speed over level ground. Retro-reflective markers were attached to each subject using a 22-marker modified Helen Hayes protocol[26], with 4 additional markers used for static trials, placed on the medial knee-joint line and the medial malleolus for each leg. These additional markers were removed prior to gait testing. Three-dimensional marker positions were measured using an eight-camera motion capture system sampling at 60 Hz (Eagle EvaRT, Motion Analysis Corp., Santa Rosa, CA). A single strain-gauged force plate (Advanced Mechanical Technology Inc., Watertown, MA) sampling at 1200 Hz was used to measure all three components of the GRF and the centre of pressure during stance. For each subject, walking trials were repeated until five clean force plate strikes during stance were recorded per leg. Previous testing in this laboratory using these protocols found the kinematic and kinetic variables calculated from this task to be reliable ($ICC_{2,1}$: 0.73 to 0.96)[27]. Surface electromyographic (EMG) activity was recorded in a subset of five controls (right limb) and nine patients (symptomatic limb) for qualitative comparison with modelled muscle forces. Electrodes were placed over the bellies of the rectus femoris, lateral and medial vasti, lateral and medial hamstrings, lateral and medial gastrocnemius and tibialis anterior. Details of subject preparation, measurement and processing protocols for EMG, and participant characteristics of the EMG sub-cohort are provided as Supplementary Material.

Musculoskeletal modelling. A scaled-generic, three-dimensional, whole-body musculoskeletal model was used to calculate lower-limb muscle forces during the stance

phase of gait for each subject. The model was implemented in OpenSim[28] (version 3.2), an open-source musculoskeletal modelling package, and comprised of a 10-segment, 27-degree-of-freedom linkage actuated by 92 Hill-type muscle-tendon units. Ligaments and other soft tissues were not included. The head, arms and torso were lumped as a single rigid body, articulating with the pelvis via a ball-and-socket back-joint. Each hip was modelled as a ball-and-socket, and each ankle and subtalar-joint as a hinge. Each knee was modelled as a sliding ball-and-socket with the flexion-extension axis and prescribed fore-aft translation defined by Delp et al[29]. The model's segmental inertial properties, muscle-tendon attachment sites, and muscle-tendon paths were scaled based on segmental dimensions calculated from each subject's static trial.

For each trial, stance-phase joint angles were calculated using inverse kinematics, which found the model configuration at each time step that minimised the sum-of-squares of the distances between corresponding experimental markers and model markers[30]. The kinematics and GRF were input into the model and internal joint torques calculated using inverse dynamics. Individual muscle forces were calculated from the internal joint torques using static optimisation, which minimised the sum-of-squares of muscle activations subject to bounds imposed by each muscle's own force-length-velocity property[31]. The internal knee adduction and rotation torques were excluded from static optimisation. The modelled muscle activations were used to calculate the total quadriceps-hamstrings activation and co-contraction index as defined by Zeni et al.[32] The EKAM was calculated by multiplying the frontal-plane GRF by its moment arm about the knee-joint centre.

Contributions to GRF and tibiofemoral-joint forces. At each time step, the GRF was decomposed into contributions by individual muscles, gravity and inertia using a pseudoinverse-based approach[13]. Subsequently, the contribution by a single muscle to the tibiofemoral-joint force at each time step was calculated by placing the model in the

configuration defined by the joint angles, applying that muscle's force together with its contribution to the GRF, and solving the joint reaction equations[12]. This process was repeated to determine contributions by gravity, defined as the resistance of the skeletal linkage to the downward pull of the body's weight[33], and inertia, defined as all Coriolis and centrifugal forces combined. At each time step, the tibiofemoral-joint force was then separated into medial and lateral compartment forces acting at the medial and lateral contact points, respectively, by solving for equilibrium at the knee in three dimensions using a least-squares approach[12]. Estimates for the spatial locations of the medial and lateral contact points in three-dimensions were obtained at each time step by inputting the joint angles, GRF and muscle forces into a separate 18-degree-of-freedom model of the lower-limb incorporating a Hertzian contact-based 6-degree-of-freedom model of the knee[34], and solving for static equilibrium.

Statistical analyses. To compare participant characteristics and also to determine group differences amongst three limbs – the symptomatic (SYM) and asymptomatic (ASYM) limbs of patients, and also controls (CON) – at the peak values of joint angles, internal joint torques and muscle forces, a series of *t*-tests was performed while controlling the familywise error rate for the multiple comparisons. This procedure was also used to compare contributions to the compartment forces at the time instants corresponding to the peaks and the mid-stance minimum of the MCF. Specifically, for each quantity of interest, independent-samples *t*-tests were performed to compare the CON limb with the SYM limb, and also to compare the CON limb with the ASYM limb; while a paired *t*-test was performed to compare the SYM limb with the ASYM limb. Subsequently, the Holm-Bonferroni method, used to control the familywise error rate, was applied to the results of the three *t*-tests at a significance level $\alpha = 0.05$ to determine which pairs of limbs differed significantly.

RESULTS

Patients demonstrated symptoms of knee OA based on KOOS (Table 1), greater varus mal-alignment and radiographic disease severity (Table 2). Due to the large number of statistical analyses, *P*-values for joint angles, internal joint torques, muscle forces and contributions to knee-joint forces are provided as Supplementary Material, with only significant results described below.

Peak knee flexion and ankle plantarflexion angles were lower in OA patients (Figure 1A, top), but peak hip abduction and knee adduction angles were higher (Figures 1A and 1B, top). Patients showed lower magnitudes of peak hip adduction, knee flexion and ankle plantarflexion torques, with lowest torques seen for SYM (Figure 1A, bottom). EKAM was highest in patients, specifically SYM (Figure 1B, bottom). Peak knee-spanning muscle forces were lower in SYM than CON, except hamstrings (Figure 2). Hip- and ankle-spanning muscle forces for SYM were lower than CON, with the greatest differences seen for gluteus medius and soleus (Figure 2). Muscle forces for ASYM were intermediate between SYM and CON, except biceps femoris short head and gastrocnemius, where ASYM was lowest.

Peak total quadriceps-hamstrings activation and co-contraction index were higher in SYM than CON (Figure 3A), but showed large standard deviation. The pattern of muscle forces in both patient and control EMG sub-cohorts were in good agreement with EMG although some differences were evident, particularly prolonged vasti EMG activity in mid-stance for controls, and a burst of gastrocnemius EMG activity during early-stance for patients (Figure 3B).

Peak MCFs (Figure 4, top) in SYM were higher than ASYM (first peak: 6% higher; second peak: 8% higher) and CON (first peak: 6% higher; second peak: 9% higher). The largest difference between SYM and CON occurred at the mid-stance minimum, approximately 38% of stance (0.39 BW or 26% higher in SYM). In all limbs, knee-spanning muscles contributed approximately one-third of the first peak of the MCF, but more than one-

half of the second peak. Gravity's contribution to MCF was compressive and consistently highest for SYM. For CON, the lateral compartment was compressed throughout stance, while SYM and ASYM experienced short periods of lateral compartment unloading (Figure 4, bottom). Knee-spanning muscles always compressed the lateral compartment while non-knee-spanning muscles unloaded it. Inertial contributions were negligible (<0.03 BW) and not considered further. Individual contributions to net tibiofemoral-joint forces are provided as Supplementary Material.

For each contributor to the peaks and mid-stance minimum of MCF, mean differences amongst the three limbs were small (Figure 5, top). In all limbs, vasti was the largest knee-spanning contributor at the first peak of MCF. Gastrocnemius was the largest knee-spanning contributor at the mid-stance minimum and second peak. Gluteus medius was the largest non-knee-spanning muscle contributor at both peaks and the mid-stance minimum. Vasti contributions were lowest in SYM. Gravity, hamstrings, gastrocnemius, and gluteus maximus contributions to MCF were all highest in SYM at the first peak and mid-stance minimum of MCF. Soleus and rectus femoris contributions were highest in SYM at the second peak.

The largest knee-spanning contributors to the lateral compartment force were vasti and hamstrings at the first peak, and gastrocnemius and biceps femoris short head at the second peak (Figure 5, bottom). Gluteus medius, which unloaded the lateral compartment, was the largest non-knee-spanning contributor.

DISCUSSION

This study aimed to quantify and compare the contributions by muscles, gravity and inertia to the tibiofemoral compartment forces during healthy and osteoarthritic gait. We hypothesised that higher MCFs in OA patients would be due to elevated contributions from the hamstrings, quadriceps and gastrocnemius, and that the gluteus medius contribution would not be significantly reduced. While patients exhibited higher peak MCFs, only hamstrings showed

higher contributions in patients; vasti and gastrocnemius contributions were lower at the first and second peak respectively. Patients' gluteus medius contributions to MCF were not significantly lower than controls at the peaks, and were in fact higher through mid-stance. Thus, our first hypothesis was only partially supported and our second confirmed.

This study is not without limitations. Firstly, we potentially underestimated the magnitudes of quadriceps forces in both patients and controls because the internal knee adduction torque was not included in our static optimisation solution, and because we did not explicitly input the elevated quadriceps-hamstrings co-activation typically reported for varus-maligned patients[35]. Hypothetically, if vasti forces in patients exceeded controls, then so too would vasti contributions to the first peak of MCF. Our control EMG sub-cohort also demonstrated uncharacteristic elevated vasti activity between 35-50% stance (Figure 3B), possibly required for frontal-plane knee stability as our controls demonstrated non-trivial levels of static and dynamic knee varus (Table 2 and Figure 1). Thus mid-stance vasti forces for controls were potentially also underestimated (Figures 2 and 3B). Nevertheless the impact of frontal-plane stability and co-activation on muscle forces is not well established. Up to 16% of frontal-plane stability may be contributed by muscles in varus mal-aligned individuals[36], but this is highly variable, with some individuals demonstrating almost no muscular contribution[37]. By applying OA-type activation patterns, Brandon et al.[15] found higher quadriceps forces, yet Adouni et al.[38], who included frontal-plane internal torques in a geometry-based contact model with ligaments, did not. In contrast, our patients demonstrated lower quadriceps forces and higher hamstrings forces (Figure 2), but nevertheless showed higher co-contraction indices and total quadriceps-hamstrings activity (Figure 3A). Notably, modelling studies which took into account OA-type co-activity[9,15] reported differences in first peak MCF between patients and controls which were not markedly greater than those found in our present study. Importantly, Adouni et al.[38] found that lower-limb alignment, which was

accounted for in our present study, was more important in determining compartment loads than pure frontal-plane moments applied to the knee.

Secondly, we did not explicitly model pain and OA-related functional and morphological changes, such as atrophy[3], strength deficits[39] and activation failure[3] of the quadriceps. As these changes compete with the demand for greater co-activations[40] and frontal-plane stability[10], the net effect on muscle and joint forces is difficult to predict. To some extent, we may have indirectly included these factors by virtue of the differing kinetics and kinematics between our patient and control groups (Figure 1).

Finally, our use of scaled-generic models for high-BMI individuals may have affected the accuracy of our alignment measures. Despite all care taken in marker placement on subjects and in ensuring model scaling errors were minimised, a 4^o bias between marker-based and radiographic static alignment measures occurred (Table 2). In our high-BMI subjects this result was likely due to disparities in hip-joint centre location, an important factor for accurately determining alignment[41]. Bias in marker-based dynamic alignment measures can be variable[42]. Assuming 4^o represents a worst-case, for representative trials of one control and one patient, we subtracted 4^o from the frontal-plane joint angles and recalculated muscle forces. MCF was reduced by only about 7% in both subjects, a small difference which presumably affected all subjects. Thus our findings should not be materially impacted by this observed bias.

Notwithstanding these limitations, our results are consistent with experimental and model-predicted data available in the literature. Increasing dynamic varus mal-alignment from CON to SYM, as evidenced by increasing hip and knee adduction angles, was accompanied by greater EKAM[43]. The magnitudes of the MCF for CON were within the range of reported model predictions[12,14,15], but slightly higher than those measured using instrumented TKRs[44]. The MCF also showed a higher second peak compared to the first peak

as reported in a TKR study by Kutzner et al.[44]. Elevated MCF in patients occurred throughout mid-stance not just at peaks (Figure 4), in agreement with recent modelling studies[9,15]. Brief periods of unloading occurred on the lateral compartment during mid-stance in patients, and also on the medial compartment near toe-off in many subjects, implying that joint-opening would need to be resisted by knee ligaments[10]. Recent modelling studies also found similar periods of joint-opening during gait[9,12,15].

The muscles that contributed most to MCF in controls also contributed most in patients walking at the same speed, and were the prime movers in gait[45]: (1) knee-spanning: vasti, hamstrings and gastrocnemius; and (2) non-knee-spanning: gluteus maximus, gluteus medius and soleus. Small alterations to the magnitudes of these contributions had considerable impact on knee-joint loading. Contributions to MCF by gluteus maximus, hamstrings, soleus and gastrocnemius – as well as gravity – were slightly greater in patients (Figure 5, top). These small but significant increases in the magnitudes of muscle and gravity contributions summed to produce the higher total MCF.

Increased duration of muscle contributions to MCF was also important in producing higher MCF in patients. Gastrocnemius at the first peak, and rectus femoris at the second peak, provided small but influential contributions to MCF at time instants not related to their peak muscle forces (Figure 5, top), a result of prolonged and slightly elevated muscle forces at these specific instants in OA patients (Figure 2). Our finding is commensurate with the elevated early-stance gastrocnemius EMG activity in our patient sub-cohort (Figure 3B, bottom), and with EMG studies of osteoarthritic gait that also reported prolonged and elevated gastrocnemius and rectus femoris activity in early and late stance respectively[4,17]. Our patient EMG sub-cohort experienced a burst of gastrocnemius activity around 20-25% of stance (Figure 3B, bottom), similar to Rutherford et al.[4], which was not reflected in the pattern of calculated muscle forces (Figure 2 and Figure 3B, bottom). Thus although our

gastrocnemius forces indeed showed increased early-stance activity, the magnitude of the gastrocnemius contribution to the first-peak of MCF in patients may actually be higher than our present results would suggest.

Large deficits in non-knee-spanning muscle forces in OA patients did not produce correspondingly diminished contributions by those muscles to the MCF. In patients, peak gluteus medius forces were lower than controls (Figure 2), in agreement with evaluations of hip abductor performance in knee OA[5]. However the corresponding reductions in the contributions to MCF were not significant at either peak (Figure 5, top). In fact gluteus medius contributions were higher in patients throughout mid-stance (Figure 5). Interestingly, gluteus maximus and soleus muscles forces were also lower in patients, but their contributions to MCFs were higher than controls (Figure 5, top). Non-knee-spanning muscles can only load the knee-joint indirectly by means of dynamic coupling via the GRF[12]. Thus, the insensitivity of MCF contributions to changes in non-knee-spanning muscle forces suggests that factors related to the kinematic chain, such as lower-limb mal-alignment, also strongly influence how non-knee-spanning muscles load the knee via the GRF. In particular, the relative influences of frontal-plane alignment and non-knee-spanning muscle forces on EKAM may determine the distribution of non-knee-spanning muscle contributions between the tibiofemoral compartments. For example, gluteus medius compressed the medial compartment but unloaded the lateral compartment (Figure 5) because it is the principal contributor to EKAM[12] due to its large medially-directed GRF contribution vector during gait[45]. Greater varus mal-alignment would presumably amplify this EKAM contribution[43] by increasing its moment arm about the knee. Hence large deficits in gluteus medius forces in our patients may have been offset by greater mal-alignment, producing a limited net change in EKAM, and hence also MCF contributions. This mechanism may explain the minimal association between hip abductor function and EKAM[21], and why hip-abductor training did

not reduce EKAM in varus mal-aligned OA patients[46].

Differences in knee-spanning muscle contributions to MCF between OA patients and controls were more concomitant with differences in the respective muscle forces. In particular, higher hamstrings and lower vasti muscle forces (Figure 2) were associated with higher and lower contributions to MCF, respectively (Figure 5, top). This occurred because direct compression of the knee by knee-spanning muscles dominated loading via the GRF[12].

Contributions by gravity, which arise from the resistance of the skeletal linkage to the body's weight[33], played an essential role in producing the higher first peak of MCF in patients. The magnitude of gravity's contribution was always small because the weight of the body is mostly borne by muscles[33]. But with progression from CON to SYM, increasing severity of mal-alignment (Figure 1) directed more of gravity's contribution through the medial compartment (Figure 4). Thus, presumably, correcting mal-alignment in patients would directly reduce MCF by more equally distributing gravity's contribution between the two compartments.

Our present study emphasises the complex interactions amongst muscles, gravity and the kinematic chain in influencing knee-joint loading which may have implications for clinical intervention. In particular, our findings suggest that small improvements in the functional performance of knee-spanning muscles during gait, such as minimising aberrations and/or prolonged activity in vasti, hamstrings, rectus femoris and gastrocnemius may provide considerable benefit by reducing the duration and magnitude of direct compressive knee loads contributed by these muscles throughout stance. However, reductions in contributions from non-knee-spanning muscles and gravity, which indirectly exert forces on the knee via the GRF[12], may be better garnered from improvements to the kinematic chain, in particular the correction of mal-alignment. This may be especially beneficial for reducing mid-stance MCF, which was higher in patients due mainly to elevated contributions by non-knee-

spanning muscles and gravity (Figure 4). While improved lower-limb alignment has been associated with reduced mid-stance EKAM[22,47], our study extends this finding to further suggest that it may decrease the actual mid-stance MCF by reducing the magnitudes of non-knee-spanning muscle and gravity contributions (Figure 5). Overall, a combined intervention strategy targeting restoration of muscle function and lower-limb alignment would potentially produce the best clinical outcome for varus mal-aligned patients. Thus, our results provide a biomechanical rationale supporting the use of realignment procedures with concurrent functional rehabilitation.

Despite the ASYM limb experiencing a larger knee adduction angle and greater EKAM than CON, only the mid-stance MCF was significantly different; peak MCFs were not (Figure 4). Most of the ASYM limbs in the present sample had pre-existing OA-type structural changes in the tibiofemoral-joint evident on radiographs (Table 2) and also demonstrated walking kinematics and kinetics resembling SYM but to a lesser degree (Figure 1). This type of asymptomatic radiographic OA is common[48] but its biomechanics are not well-studied. Our results suggest that elevated mid-stance MCF (Figure 4) is a factor in the pathomechanics of knee OA that may be influential throughout all stages of disease, and may be more sensitive than peaks in detecting differences between more and less symptomatic limbs. In fact our finding of elevated mid-stance MCF in patients points towards increasing medial compartment impulse with progression from CON to SYM. These findings are consistent with the association of both mid-stance EKAM[49] and EKAM impulse[50] with structural disease severity. Hence, our present results support consideration of mid-stance loads in the ASYM limb in clinical assessments and interventions to mitigate the risk of progression to symptomatic bilateral disease.

In conclusion, we found that greater magnitude and longer duration of contributions by the prime movers and gravity were responsible for higher MCF in patients throughout

stance. Knee-spanning muscles, non-knee-spanning muscles and gravity contributed to MCF loading by different mechanisms, with the influence of lower-limb alignment more important in the latter two. Hence, both muscle forces and varus mal-alignment were factors contributing to higher MCF in patients. Altered kinematics, muscle forces and elevated mid-stance MCF were found in the ASYM limb. Our findings emphasise the need to consider muscle function, alignment and mid-stance loads in the development of interventions for OA, and support the inclusion of the ASYM limb in clinical assessments.

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FIGURE CAPTIONS

Figure 1. (A) Joint angles (top row) and internal torques (bottom row) for hip flexion, hip adduction, knee flexion and ankle plantarflexion for healthy controls (CON), and the symptomatic (SYM) and asymptomatic limbs (ASYM) of OA patients during stance. (B) Mean knee adduction angle (top row) and external knee adduction moment (bottom row) for

these three limbs. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs of limbs (*). Statistical significance calculated at the peak values for joint angles and torques.

Figure 2. Calculated lower-limb muscle forces for healthy controls (CON), and the symptomatic (SYM) and asymptomatic (ASYM) limbs of OA patients during stance. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs of limbs (*). Statistical significance calculated at the peak values for muscle forces.

Figure 3. (A) Total activation of the quadriceps and hamstrings (top row) and co-contraction index for the quadriceps and hamstrings (bottom row) for all CON and SYM limbs calculated using the static optimisation results for all patients and controls. (B) Comparison of measured EMG (thin line) and calculated major knee-spanning muscle forces (thick line) for the control sub-cohort in the right limb (5 subjects, top row) and the OA patient sub-cohort in the symptomatic limb (9 subjects, bottom row). The muscle forces and EMG signals presented are the ensemble averaged time histories for each sub-cohort. Participant characteristics for the EMG sub-cohorts are presented as Supplementary Material.

Figure 4. Contributions by all knee-spanning muscles, all non-knee-spanning muscles and gravity to the medial (top row) and lateral (bottom row) compartment forces for healthy controls (CON), and the symptomatic (SYM) and asymptomatic (ASYM) limbs of OA patients during stance. The contributions by inertia are very small (<0.03 BW) and are not shown. Positive values are compressive. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs

of limbs (*). Statistical analyses were performed at the time instances corresponding to the peaks and mid-stance minimum of the medial compartment force. Mid-stance minimum occurred at approximately 38% of stance.

Figure 5. Contributions by individual knee-spanning muscles, non-knee-spanning muscles and gravity to the medial (top row) and lateral (bottom row) compartment forces at the time steps corresponding to the first peak (left column) and the second peak (right column) and mid-stance minimum (centre column) of the medial compartment force. Positive values are compressive. Mid-stance minimum occurred at approximately 38% of stance. Abbreviations: GAS, gastrocnemius; VAS, vasti; HAMS, hamstrings; GMAX, gluteus maximus; GMED, gluteus medius; BFSH, biceps femoris short head; RF, rectus femoris; SOL, soleus; and GRAV, gravity. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs of limbs (*).

Table 1. Participant characteristics of the knee OA patient and healthy control groups.

	Control ***n* = 15**	**OA Patient** ***n* = 39**	***P***
Age, yrs	49 (7)	49 (7)	0.869
BMI, kg/m^2	26.5 (4.8)	28.2 (3.6)	0.177
Mass, kg	77 (15)	89 (17)	***0.015***
Height, m	1.70 (0.10)	1.78 (0.09)	***0.006***

Females, no. (% of total)	4 (27%)	8 (21%)	0.634
Walking speed, m/s	1.21 (0.07)	1.20 (0.10)	0.575
KOOS subscale scores, 0–100			
Pain	-	55 (18)	-
Symptoms	-	54 (18)	-
Activities of daily living	-	65 (20)	-
Sport and recreation	-	31 (23)	-
Knee-related quality of life	-	29 (19)	-

Values are presented as mean (standard deviation) unless otherwise indicated. *P*-values were calculated using Student's *t*-tests. Significance level was defined as $\alpha = 0.05$. Statistically significant differences are shown in ***bold italic***. KOOS: Knee Injury and Osteoarthritis Outcome Score (0 = maximum symptoms, 100 = no symptoms).

Table 2. Characteristics of the symptomatic (SYM) and asymptomatic (ASYM) limbs of the knee OA patients, and healthy controls (CON).

	CON ***n* = 15**	**SYM** ***n* = 39**	**ASYM** ***n* = 39**	***P***
Stance time, sec	0.71 (0.05)	0.75 (0.06)	0.75 (0.05)	***CS:* < *0.001***; ***CA:* < *0.001***; SA: 0.719
Gait events, % of stance				
Contralateral toe-off	23 (3.6)	25 (5.2)	24 (4.8)	***CS:* < *0.001***; ***CA: 0.047***; ***SA: 0.006***
Contralateral heel-strike	75 (2.1)	74 (2.0)	75 (2.6)	***CS: 0.017***; CA: 0.279; ***SA:* < *0.001***
Static knee adduction angle, deg	6 (6)	13 (5)	8 (6)	***CS:* < *0.001***; ***CA: 0.002***; ***SA:* < *0.001***
Mechanical axis angle, deg	-	9 (3)	4 (3)	***<* *0.001***
KL grade 0/1/2/3/4, patients	-	0/1/10/15/13	4/14/11/10/0	-

Values are presented as mean (standard deviation) unless otherwise indicated. *P*-values were calculated using Student's *t*-tests. A Holm-Bonferroni correction was used to identify statistically significant differences. Significance level was defined as $\alpha = 0.05$. Statistically

significant differences are shown in ***bold italic***. Static knee adduction angle was calculated using inverse kinematics from static trial marker data (positive values represent varus). Mechanical axis angle was measured from full-limb standing anteroposterior radiographs (positive values represent varus). Comparison pairs: CON and SYM (CS); CON and ASYM (CA), SYM and ASYM (SA). KL grade: Kellgren and Lawrence grade (0 = no OA, 4 = severe OA).

Fig1-IK-ID-EKAM-FINAL .

Fig2-MuscleForces-FINAL .

Fig3-CCI-QHA-EMG-FINAL .

Fig4-KneeForce-TimeHistory-FINAL .

Fig5-KneeForce-PeakContribs-FINAL .