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Sensitivity of medial-lateral load sharing to changes in adduction moments or angles in an asymptomatic knee joint model during gait

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ABSTRACT

Background: Osteoarthritis (OA) of the knee joint is a common disease accompanied by pain and impaired mobility. Despite some recent concerns on the lack of correlation between the medial load and the knee adduction moment (KAM), KAM is routinely considered as a surrogate measure of medial load and hence a marker where its reduction is the main focus of preventive and treatment interventions.

Research question: Determine the relative sensitivity of the tibiofemoral medial-lateral contact load partitioning to changes in the knee adduction angle (KAA) versus KAM.

Methods: Using a lower extremity hybrid musculoskeletal (MS) model driven by gait kinematics and kinetics, we compute here in asymptomatic subjects the sensitivity of the knee joint biomechanical response (muscle and ligament forces) in general and medial/lateral load partitioning in particular to the relative changes in the reported KAA versus changes in reported KAM (both by one standard deviation).

Results: As KAA increased (at constant KAM), so did the passive moment resistance of the knee joint which as a result and at all stance periods substantially reduced forces in lateral hamstrings while increasing those in medial hamstrings. At 25% and 75% stance as two highly loaded periods of gait, the drop in KAA (from + SD to –SD while at constant KAM) drastically reduced the medial contact force by 44% and 30% and the medial over lateral contact load and area ratios by 92% and 79% as well as 64% and 51%, respectively. In contrast, the equivalent alterations in KAM (by ± SD at constant KAA) had lower and less consistent effects (< 7%) showing much smaller sensitivity to changes in KAM alone. Ligament forces altered at various stance periods with inconsistent trends; peak values of 418 N in the anterior cruciate ligament (90% carried by the posterolateral bundle) and 1056 N in the patellar tendon were computed both at 25% stance and minimum KAA.

Significance: These findings indicate a poor correlation between KAM and tibiofemoral load distribution suggesting instead that KAA and knee alignment should be in focus as the primary marker of knee joint load partitioning and associated prevention and treatment interventions.

1. Introduction

Human knee joints experience loads and movements of substantial magnitudes during occupational, recreational and even regular daily living activities [1]. This demanding mechanical environment exposes them to a host of painful and debilitating deformities, injuries and degenerations involving both patellofemoral (PF) and tibiofemoral (TF) articulations. Osteoarthritis (OA) is one of the most prevalent MS disorders affecting approximately 27 million adults in the US alone [2] that is projected to further increase to 67 million by 2030 [3]. Incidence of knee OA, especially on the medial side that is often subject to a larger share of joint internal compression during gait [4], rises at a marked rate given ageing and obesity in general population [5].

Knee adduction moment (KAM) as the net external knee joint torque in the frontal plane is commonly considered as a surrogate measure of loading on the medial compartment [6] and hence a marker where its reduction is the main focus of interventions (e.g., shoe insole, gait modification, osteotomy, knee brace) to prevent the development and progression of medial OA [7]. However, some recent in vivo studies using instrumented implants have qualified the correlation between KAM and the medial compartment load as poor to average [8,9] or generally good but limited with large variabilities across activities and subjects [20]. Similarly, questions have been raised on the efficacy in reducing pain and symptoms of a reduction in KAM when wearing wedged insoles [10] and braces [7].

Varus malalignment has however been identified as a significant

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risk factor in medial knee OA [11]. Peak knee varus angle was found at 4.8 ± 6.1° in 44 patients with severe knee OA as compared to 2.9 ± 4.0° in 40 asymptomatic subjects [12]. Valgus high tibial osteotomy reduces the pain and progression of medial OA in patients [13]. In vivo measurements evaluate differences in the medial load of roughly one body weight (BW) between individuals with alignments of 4.5° abduction and 6.5° adduction [14] and a significant correlation between the frontal plane alignment and the medial loading during early stance [15]. Instrumented knee implant studies in gait estimate an increase in the medial load sharing by 5% for a 1° varus deviation from the neutral alignment [16]. MS model studies in gait have estimated an alteration of ˜51 N in peak medial force for each 1° change in the joint frontal alignment [17]. In a hybrid lower extremity model at mid-stance, a 1.5° drop in adduction angle was found much more effective in diminishing knee medial contact force and medial over lateral load ratio than a 50% reduction in KAM [18]. Similarly in another model study, the varus–valgus angle strongly influenced the lateral-medial load sharing [19].

Despite the foregoing sensitivity in the TF load partitioning to changes in the joint angle and alignment in the frontal plane, there are major concerns regarding the relative accuracy in skin-marker based measurements of the adduction-abduction angles [20,21]. Mean errors of up to 4.4° in the adduction angle are reported in gait when comparing skin markers versus intra-cortical pins [22]. The extent of such errors is used to justify the consideration of the knee joint as a 2D structure while overlooking the crucial out-of-sagittal plane rotations and moment equilibria [23].

Using a lower extremity hybrid MS model [24] driven by gait kinematics-kinetics in asymptomatic subjects [25,26], we aim here to carry out a sensitivity analysis by computing, over the entire stance phase of gait, the effects of changes in the measured knee adduction angle (KAA) (by one standard deviation: ± SD) versus respective changes in reported estimated KAM (also by one SD) on the intact knee joint response in general and medial/lateral load partitioning in particular. In accordance with earlier results [18], we hypothesize that the internal TF load distribution in asymptomatic subjects is influenced primarily by changes in KAA as compared to KAM. Such notion has important consequences in measurements as well as prevention, treatment, rehabilitation and evaluation of associated joint disorders.

2. Methods

2.1. Hybrid musculoskeletal model

A validated 3D FE model of the entire knee joint (Fig. 1) consisting of bony structures (tibia, femur and patella) and their compliant articular TF and PF cartilage layers as well as menisci, major TF (ACL by 6 distinct elements and 2 bundles, PCL by 6 elements and 2 bundles, LCL by 3 elements, MCL by 5 elements) and PF (MPFL by 4 elements, LPFL by 3 elements) ligaments, patellar tendon (PT by 9 elements), quadriceps (four components), hamstrings (six components) and gastrocnemii (two components) is employed [4,27,28]. This detailed knee model has been introduced within a MS model of the lower extremity including hip and ankle joints and associated uni- and bi-articular muscles (Fig. 1) to simulate the stance phase of gait under in vivo kinematics/kinetics reported for asymptomatic subjects [25,26]. In brief and for the tibiofemoral joint, 3 reported [25] rotations at different stance periods are prescribed while 3 translations remain unconstrained. The patellofemoral joint is left completely free. As for the gait kinetics, the location of the resultant ground reaction force [26] at the foot is chosen to generate the 3 moments reported in gait [25]. These moments are resisted by both knee active musculature and passive ligamentous structures. Reported gait moments at the hip and ankle joints are however directly introduced in their respective moment equilibrium equations to be resisted only by their musculature as these joints are assumed frictionless. In this manner, our MS model is driven by both kinematics (measured rotations) and kinetics (estimated inverse dynamics moments) reported in the literature.

Bony structures are simulated as rigid bodies [29] while the articular cartilage layers and menisci are represented as non-homogeneous nonlinear depth-dependent composites of collagen fibril networks and isotropic hyperelastic matrices [30]. Ligaments are simulated by a number of nonlinear axial elements with initial prestrains, non-linear (tension-only) material properties, and initial cross-sectional areas of 42, 60, 18, 25, 99, 42.7, and 28.5 mm^2 respectively for ACL, PCL, LCL, MCL, PT, MPFL, and LPFL [28]. More description of the hybrid MS model can be found elsewhere [4].

2.2. Sensitivity analysis

The knee add-abd angles and moments in the reference case as the mean of recorded data [25] are varied; KAM or KAA is held constant each at a time (as the mean data) while varying the other one by one standard deviation (± SD). These changes cover most of available population datasets reported in the literature and the likely errors in measurements (Fig. 2). It is to be acknowledged that our aim is to perform a conventional sensitivity analysis (by vary one variable at a time) within the population-based data at large. In a subject-specific gait, however, alterations in KAM or KAA likely involve compensatory changes in remaining kinematics-kinetics of all lower extremity joints. Our data points considered while varying knee rotations and moments in the frontal plane represent gait of real subjects as they all fall well within the statistical scatter reported in the literature (Fig. 2). Moreover, contrary to the strong correlation reported elsewhere [31] between peak KAM and KAA, the large abd-add moment-angle dataset used in this study [25] yielded a coefficient of determination of $R^2 = 0.0017$ (Fig. 2) that attests to the lack of any correlation at all between these two knee variables. Finally, at each stance period, external KAM and changes therein (as well as other knee moments) [25,32] are represented through the action of reported ground reaction forces [26] applied at computed foot locations; changes in KAM are hence simulated by shifts in the location of the ground reaction forces that could simulate various interventions by foot wears.

2.3. Muscle force estimation

Muscle forces are evaluated iteratively and applied as additional external forces along with GRF, leg/foot weights and in vivo kinematics/kinetics recorded on asymptomatic subjects for reference (mean values) and altered conditions (± SD) [25,26,32] (Fig. 2) at each stance period of gait. It is to be emphasized that had we applied the final computed muscle forces along with the weights and GRF at each case (similar to the approach taken in forward dynamics [33]), exactly identical kinematics as those prescribed here in our MS model would have been computed. Static optimization along with a cost function of the sum of cubed stresses of all lower extremity muscles, subject to reaction moment equilibrium equations (3 at the hip taken as a frictionless spherical joint, 3 at the knee simulated in details with validated passive properties and 1 at the ankle), and inequality equations on muscle forces, are used to iteratively estimate muscle forces at each instance. Details of the muscle force estimation are provided elsewhere [4,27]. The nonlinear elastostatic analyses are carried out using ABAQUS (version 6.12, Simulia, Inc., Providence, RI, USA) finite element package program. Matlab (R2013a Optimization Toolbox, genetic algorithms and Fmincon) was used in the optimization algorithm.

3. Results

Forces in hamstrings (Fig. 3) altered substantially as KAA varied by ± SD. Overall, larger KAA increased forces in medial hamstrings but reduced those in lateral hamstrings at all periods of stance. Variations were, however, more pronounced in lateral hamstrings than in

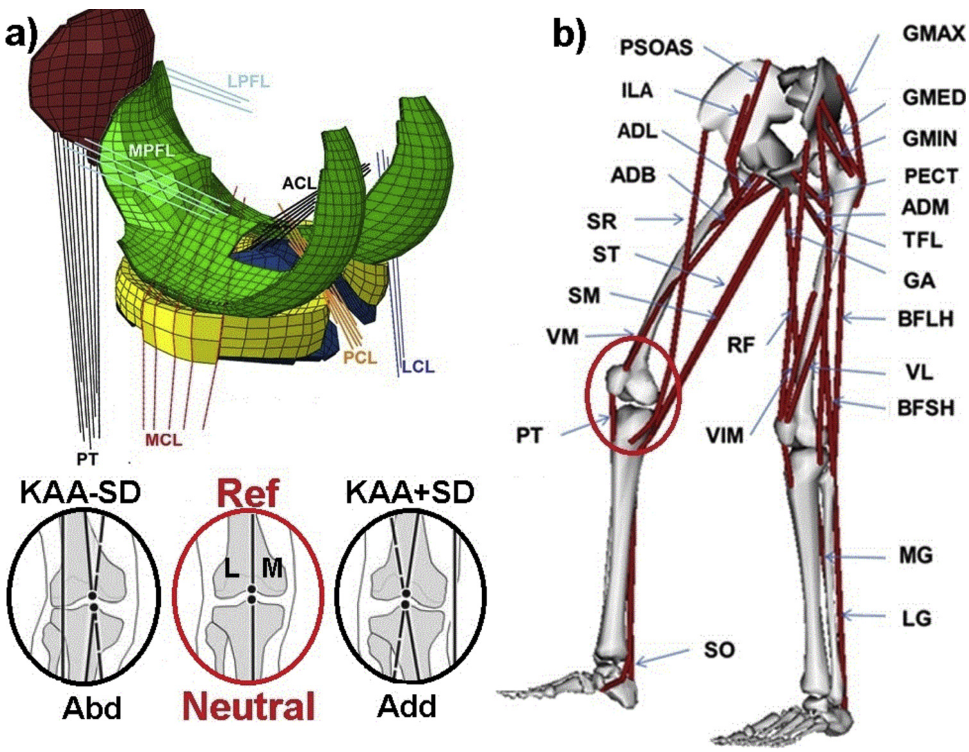

Fig. 1. (a) (Top left) Detailed knee FE model; tibiofemoral (TF) and patellofemoral (PF) cartilage layers, menisci, patellar Tendon (PT). Joint ligaments include lateral patellofemoral (LPFL), medial patellofemoral (MPFL), anterior cruciate (ACL), posterior cruciate (PCL), lateral collateral (LCL) and medial collateral (MCL). **(Bottom left)** schematic representation of changes in the mean knee adduction angle (KAA) by one standard deviation (± SD). **(b) (Right)** Schematic diagram showing the 34 muscles incorporated into the lower extremity model (Open Sim, Delp et al., [56]). Quadriceps components are vastus medialis obliquus (VMO), rectus femoris (RF), vastus intermidus medialis (VIM) and vastus lateralis (VL). Hamstrings components include biceps femoris long head (BFLH), biceps femoris short head (BFSH), semi membranous (SM) and TRIPOD made of sartorius (SR), gracilis (GA) and semitendinosus (ST). Gastrocnemius components are gastrocnemius medial (GM) and gastrocnemius lateral (GL). Soleus (SO) muscle is uni-articular ankle muscle. Hip joint muscles (not all shown) include adductor, long (ADL), mag (3 components ADM) and brev (ADB); gluteus max (3 components GMAX), med (3 components GMED) and min (3 components GMIN), iliacus (ILA), iliopsoas (PSOAS), quadriceps femoris; pectineus (PECT), tensor facia lata (TFL), periformis.

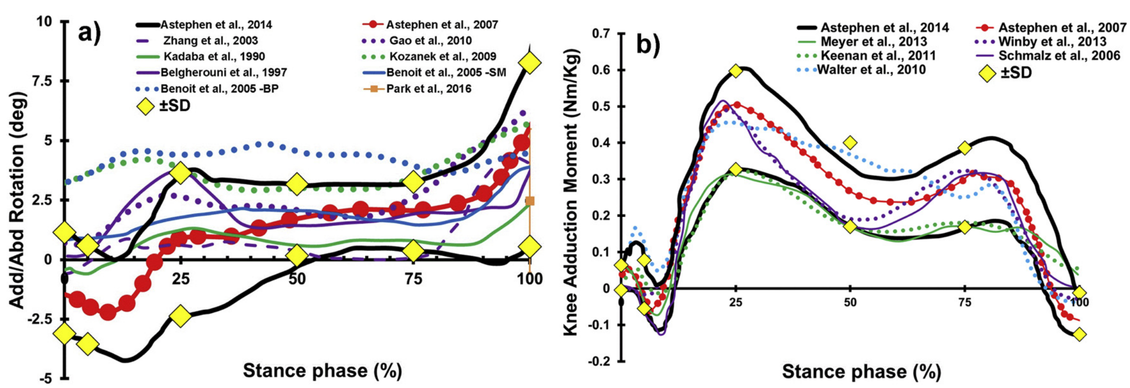

Fig. 2. Knee joint adduction angles (KAA) (a) and moments (KAM) (b) reported as mean values in asymptomatic subjects during the stance phase of gait. The values taken in our study at the stance phase are depicted by yellow diamonds based on reported mean ± SD measurements [32]. These changes cover most of major datasets reported in the literature and the likely errors in measurements [8,9,21,25,57–60,62–66]. Note that moments are reported normalized to BW (in our model = 61,9 kg). Positive rotations/moments denote adduction.

medial hamstrings. Quadriceps forces also, though to a much smaller degree, decreased at greater KAA. Relatively smaller changes were computed in gastrocnemii (not shown). The effects were overall much less pronounced and in opposite directions when KAM was altered by ± SD.

Total force in ACL altered most at 25% stance reaching the peak of 418 N (90% carried by the posterolateral bundle) at minimum KAA (R-SD, Fig. 4a). It however increased with KAA at 75% stance. LCL force increased with KAA and reached its peak of ~318 N at TO (100% stance) under larger adduction angle. Relatively smaller changes were computed as KAM altered (Fig. 4b). Total force in PT closely followed activity levels in quadriceps muscles and peaked at 25% stance to 1056 N under smaller KAA (R-SD).

Alterations in KAA, unlike KAM, had substantial effects on TF compartmental loads (Figs. 5a, b) and medial/lateral load partitioning ratio (Fig. 5c); an increase in KAA drastically increased this ratio by substantially augmenting the load on the medial side while at the same time reducing that on the opposite lateral one (even to nil at 100%). Reverse trends were found when KAA decreased. Changes in KAM had however negligible effects (Fig. 5b, c). Contact areas on TF and PF joints followed nearly the same trends as their respective contact forces; lateral contact area substantially increased at lower KAA but dropped at higher KAA to the extent that it even totally disappeared at the toe off (i.e., separation with no contact). Medial contact area followed reverse trends at early and late stance (0, 5 and 100%) with little changes at and around mid-stance (25–75%). TF contact pressures followed similar trends as those in their respective contact forces (Fig. 5); peak contact pressures occurred on the medial side under larger KAA (e.g., at 25% stance from 8.4 MPa to 7.3 MPa in R-SD and 11.6 MPa in R + SD). The effect on contact stresses of changes in KAA was again much more pronounced when compared with changes in KAM.

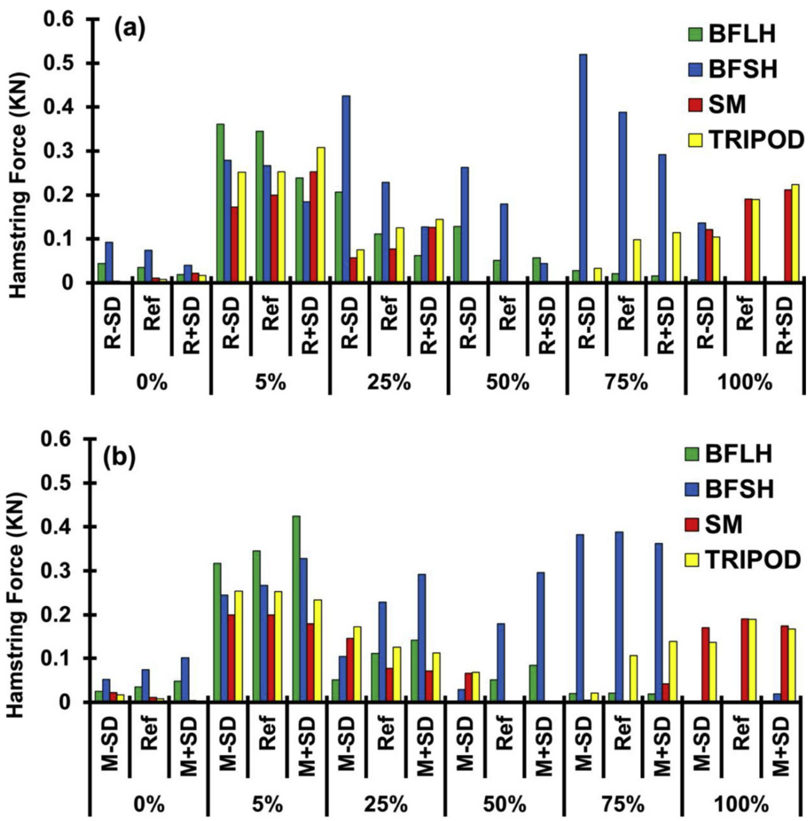

Fig. 3. Predicted hamstrings muscle forces (see Fig. 1 caption for muscle abbreviations) at various periods of stance under a) reference mean (Ref), mean + SD (R + SD) and mean-SD (R-SD) KAA conditions (at constant KAM), and b) reference mean (Ref), mean + SD (M + SD) and mean-SD (M-SD) KAM conditions (at constant KAA).

4. Discussion

Using a hybrid lower extremity MS model including a detailed complex 3D FE model of the entire intact knee joint [23,24] driven by *in vivo* joint kinematics-kinetics recorded in gait of normal subjects [25,26], we aimed here to perform sensitivity analyses by quantifying the effects of changes in measured KAA (by one standard deviation) (Fig. 2a) versus changes in measured KAM (also by ± SD) [32]

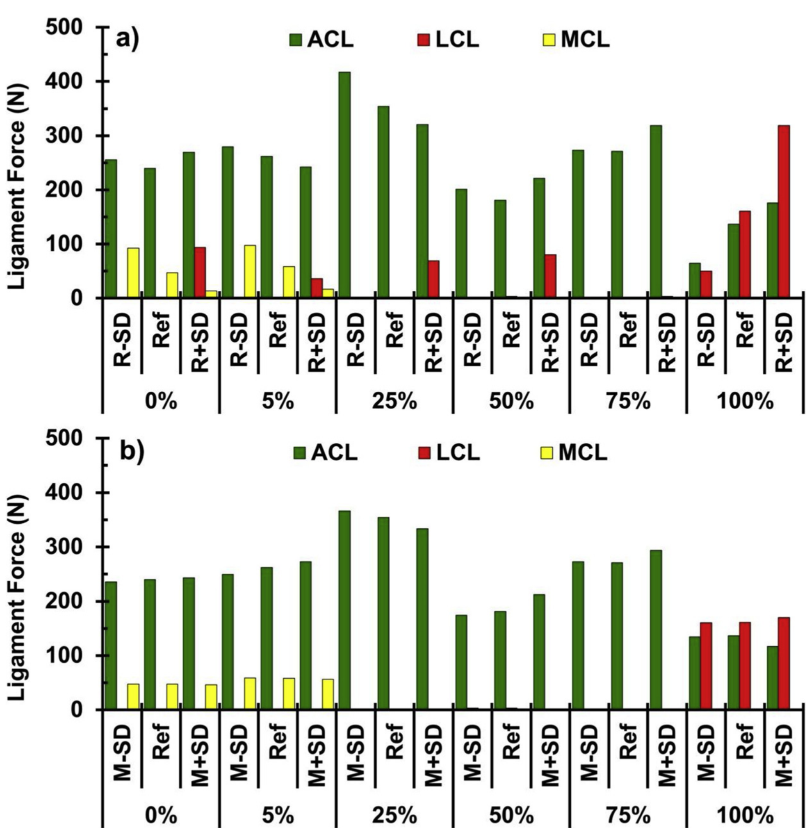

Fig. 4. Predicted variation of total (by vector summation of forces in respective sub-elements) ACL, LCL and MCL forces during the stance phase of gait under mean (Ref) and mean ± SD add/abd (a) rotations (R ± SD at constant KAM) and (b) moments (M ± SD at constant KAA). Forces in PCL, MPFL and LPFL remained negligible and those in PT followed forces in quadriceps.

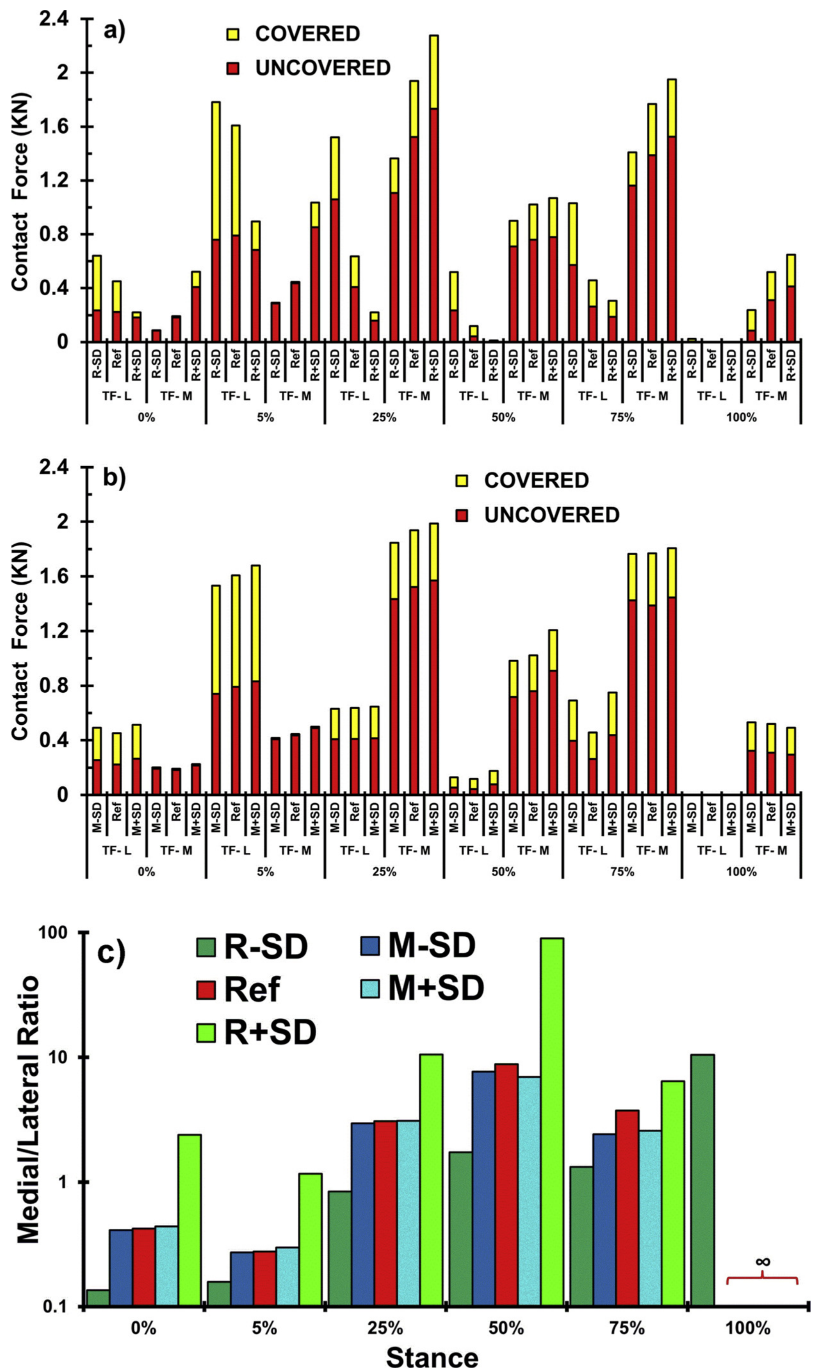

Fig. 5. Total contact forces on tibiofemoral lateral (L) and medial (M) plateaus at covered (transferred via menisci) and uncovered (transferred at cartilage-cartilage interface) areas at various periods of stance under mean (Ref) and mean ± SD add/abd (a) angles (R ± SD at constant KAM) and (b) moments (M ± SD at constant KAA). At the bottom; (c) the logarithmic variation of medial over lateral contact force ratio at various periods of stance under mean (Ref) and mean ± SD add/abd angle (R ± SD) and moment (M ± SD) conditions. At TO, lateral plateau is completely unloaded except for the R-SD condition.

(Fig. 2b) on the knee joint response in general and medial-lateral load partitioning in particular. This work expands on an earlier one [18] carried out only at the mid-stance under alterations of ± 1.5° in KAA or ± 50% in KAM. Computed results clearly support our hypothesis that, despite equivalent variations in prescribed adduction-abduction angles (KAA) and moments (KAM) by one SD, the internal load distribution in the knee joint is influenced primarily by changes in KAA (or in the knee alignment in the frontal plane) with little sensitivity to changes in KAM when KAA is kept constant.

At identical net external KAM, changes in KAA substantially altered forces in medial and lateral hamstrings (Fig. 3); with peak increases of 145 N in BFLH and 300 N in BFSH when KAA dropped from 3.63° varus (R + SD) to 2.38° valgus (R-SD) at 25% stance period. At the same time, forces in medial hamstrings followed opposite trends though at smaller magnitudes. These trends are expected to continue under greater alterations in KAA. Foregoing concurrent opposite changes in hamstrings activation levels and hence in the portion of the adduction moment resisted by muscles despite a constant external KAM are due to the substantial variation in the knee joint passive resistant moment in the frontal plane. In other words, under identical applied KAM but at larger knee adduction angles (i.e., R + SD), a greater portion of the net applied KAM (specially at critical 25, 50 and 75% stance periods, Fig. 2b) are transferred from the knee lateral hamstrings (BFLH and BFSH) muscles to the passive knee tissues. This relegation of the knee moment resistance in the frontal plane from the active musculature to the passive knee joint occurs due to changes in KAA. The knee passive structures play an important role in the joint equilibrium in the frontal plane [34] especially at greater joint compression forces expected in gait [35]. At full extension position, Marouane et al. [35] reported an increase of 20 Nm in the knee passive adduction resistant moment when the adduction angle rose by only ˜1.2° under 1800 N axial compression force. In contrast and at constant KAA, reverse changes but at smaller magnitudes were overall noted when KAM increased.

As KAA increased within one standard deviation (from –SD to + SD) at constant KAM (Fig. 5a), the medial contact forces substantially increased whereas the lateral ones diminished. This occurred consistently at all stance periods to the extent that the medial load in contrast to the reference condition exceeded the lateral one even at early stance periods (0% and 5%) and that the lateral plateau was completely unloaded at TO (100%). The medial over lateral contact force ratio substantially increased at greater KAA and reached its extremes (minimum-maximum) values of 0.1–2.4, 0.2–1.2, 0.8–10.6, 1.7–90, 1.3–6.4 and 10-∞ (infinity) under min-max KAA values along the stance from HS to TO (Fig. 5c). Alterations in measured KAA by one SD could hence change the estimated medial force by over 50% BW.

On the other hand and in clear contrast, as KAM increased at constant KAA, much smaller and less consistent variations were noted. These results clearly highlight the importance of changes in KAA in dictating the load partitioning among the medial and lateral compartments of the TF joint. To reduce contact loads on the medial side, one should hence control the knee alignment through adduction-abduction angles. Results indicate that a more uniform (i.e., balanced) contact load distribution between TF plateaus (ratios of ˜1 in Fig. 5c) can only be achieved, when compared to our reference angles, at larger adduction angles in early stance (0% and 5%) whereas at smaller adduction angles thereafter in stance (25–100%). The effect of changes in KAM is far less pronounced in this respect.

At 25/75% stance as two highly loaded periods of gait, the drop in KAA (from + SD to –SD) reduced the medial contact force by 44/30% and the medial over lateral load and contact area ratios by 92/79% and 64/51%, respectively. In contrast, the equivalent decrease in KAM reduced those same measures at much smaller relative values of 7/-2%, 5/6% and -1/1%, respectively (negative signs denote increases). Our results agree with previous findings; Tetsworth and Paley [36] reported a 20% increase in the medial compartment load with a 5° increase in varus alignment. Wong et al. [37] reported that 3 to 5° increases in tibial varus alignment result in a 50% increase in the force transmitted across the medial compartment. Instrumented knee implant measurements in five patients evaluated a 5% increase in medial load during gait following a 1° varus from a neutral alignment [16]. Lerner et al. [17], using radiography and a MS model of an individual with an instrumented knee implant, estimated during gait a change of 51 N in the peak medial contact force for each 1° deviation in TF varus alignment. Our results, however, show more drastic changes with averaged increases of ˜168 N (or 9%) and 201 N (or 11%) for each 1° increase in varus at the first (25%) and second (75%) peaks, respectively. The differences are due partly to (1) the assumed fixed contact point algorithm used in these studies since contact forces are very sensitive to the location of contact points in the frontal plane [23] and (2) the collection of data in patients with implanted knees.

In accordance with the popular trend, numerous studies have focused on KAM and changes therein as a primary measure of loading on the knee medial plateau. External KAM has routinely been considered as a surrogate measure to estimate and control TF joint internal load distribution [7,38] and as a marker for the medial OA [39]. Some findings however indicate otherwise [9,40,41]. In corroboration with our current predictions, Meyer et al. [9] and Walter et al. [8], using instrumented implants, have questioned an association between KAM and medial-lateral load partitioning. Despite the expected drop in KAM when using lateral wedged footwear [10,42], reduction in pain and medial share of contact forces have remained less consistent [40,43]. Systematic reviews of the biomechanical effects of valgus knee braces have shown either moderate-to-high effects on knee loading in patients with OA [44] or no long-term effects in ACL-deficient or reconstructed subjects [45]. According to our results, an important confounding parameter is the short- and long-term alterations in KAA as compared to KAM.

Our study estimates for the first time the effect of reported changes during gait in KAM and KAA (by ± SD) on the joint medial-lateral load distribution during the entire stance phase of gait. The interpretations should, however, be made in the light of some limitations. We used a single knee geometry reconstructed from a female cadaveric specimen. Though the input structural and material properties in the knee joint are generic (taken from the literature) and could vary with age, sex and body weight, we have extensively validated this model with available in vitro and in vivo data [4,30,35,46]. The lower extremity musculature as well as joint kinematics-kinetics were taken from the data on asymptomatic subjects in the literature. Very good agreement is found when validating estimated muscle forces with recorded average EMG of the same subjects whose mean gait kinematics-kinetics drive the model [25] (Fig. 6). Predicted activation levels in quadriceps and gastrocnemii muscles are also in satisfactory agreement with others reported in the literature [47–51]. Due to the focus of the current study on the relative effects of changes in KAA and KAM in intact knees, alterations in the geometries, material properties, and remaining prescribed gait kinematics-kinetics could affect only the extent of changes while the conclusions are expected to remain valid. In view of the considerable time and effort needed for a comprehensive statistical analysis [52–55], we used the limited “vary one variable at a time” approach in which either KAA or KAM was altered based on a large population dataset while the remaining prescribed moments and angles at all joints were left unchanged. With a coefficient of determination $R^2 = 0.0017$, no correlation existed between the input variables (KAA and KAM) [25] during the stance phase that supports their consideration as independent variables. Moreover, to compare the sensitivity of results to changes in abd-add angles and moments, we altered each, one at a time, by one standard deviation of the same dataset. This appears to be a reasonable approach as it covered most of available datasets in the literature (Fig. 2) and allowed for direct comparisons when altering two dis-similar quantities (i.e., angle and moment). It is to be noted that as KAA, for example, is varied or remains unchanged, alterations in the magnitude of KAM is caused by inter- and intra-subject variations in the location of foot-ground contact pressure center due to gait itself or various interventions (e.g., wedged soles and footwears). Antagonistic co-activity was not considered. Due to computed small relative changes in the length of muscles during stance periods (< 2% strain to their initial length), estimated muscle forces denote active components (Figs. 3 and 6) [61]. The incompressible elastic response of soft tissues considered here is appropriate for short-term loading present during gait. Finally, the current findings apply to asymptomatic subjects; an extension to OA or ACL-deficient subjects requires modifications in input gait kinematics-kinetics [25] and joint material/structural properties [4].

In summary, results of the present study clearly demonstrate that, under gait identical kinematics-kinetics, the relative inter-compartmental partitioning of contact loads is substantially influenced by changes in KAA but remains much less sensitive to alterations in KAM. This is due to the much greater passive knee joint resistant moment at larger varus angles that diminishes the activity in lateral hamstrings under varus external moments. These findings explain the poor correlation between KAM and TF compartment loading during gait suggesting that, in contrast to the popular notion, the internal load partitioning is instead dictated by changes in KAA. As a consequence and for effective assessments of various prevention and treatment

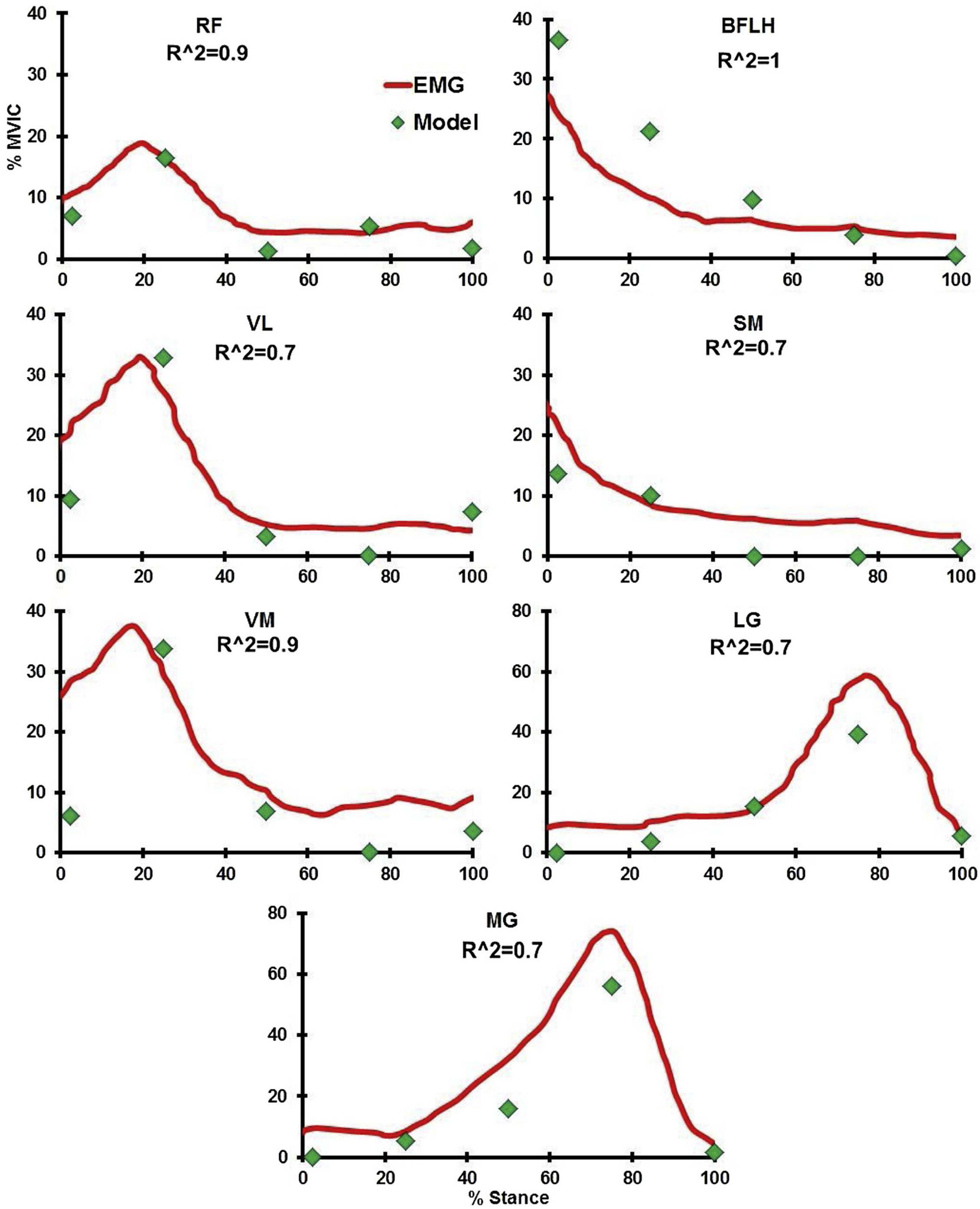

Fig. 6. Ensemble averaged measured (solid lines) EMG (normalized to their peak at maximum voluntary contraction) [25] and estimated muscle forces (in the Model driven by gait data from the same subjects) normalized to their isometric maximum (taken as 0.6 MPa times muscle physiological cross-sectional area in mm^2) during the stance phase for various knee muscles (RF: rectus femoris, VL: vastus lateralis, VM: vastus medialis, BFLH: long-head bicep femoris, SM: semi membraneous, LG: lateral gastrocnemius, MG: medial gastreocnemius). Coefficients of determination R^2 are listed. For the HS (heel strike), estimations at 0% and 5% are averaged for this comparison.

managements, the present findings emphasize the importance of recording KAA and TF alignment and changes therein in various interventions that aim to control the knee joint load distribution.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions statement

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content.

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