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A statistically-augmented computational platform for evaluating meniscal function

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Abstract

Meniscal implants have been developed in an attempt to provide pain relief and prevent pathological degeneration of articular cartilage. However, as yet there has been no systematic and comprehensive analysis of the effects of the meniscal design variables on meniscal function across a wide patient population, and there are no clear design criteria to ensure the functional performance of candidate meniscal implants. Our aim was to develop a statistically-augmented, experimentally-validated, computational platform to assess the effect of meniscal properties and patient variables on knee joint contact mechanics during the activity of walking. Our analysis used Finite Element Models (FEMs) that represented the geometry, kinematics as based on simulated gait and contact mechanics of three laboratory tested human cadaveric knees. The FEMs were subsequently programmed to represent prescribed meniscal variables (circumferential and radial/axial moduli - E_{cm} , E_{rm} , stiffness of the meniscal attachments - S_{lpma} , S_{lamp}) and patient variables (varus/valgus alignment - VVA, and articular cartilage modulus - E_c). The contact mechanics data generated from the FEM runs were used as training data to a statistical interpolator which estimated joint contact data for untested configurations of input variables. Our data suggested that while E_{cm} and E_{rm} of a meniscus are critical in determining knee joint mechanics in early and late stance (peak 1 and peak 3 of the gait cycle), for some knees that have greater laxity in the mid-

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Conflict of Interest

None

stance phase of gait, the stiffness of the articular cartilage, E_c , can influence force distribution across the tibial plateau. We found that the medial meniscus plays a dominant load-carrying role in the early stance phase and less so in late stance, while the lateral meniscus distributes load throughout gait. Joint contact mechanics in the medial compartment are more sensitive to E_{cm} than those in the lateral compartment. Finally, throughout stance, varus-valgus alignment can overwhelm these relationships while the stiffness of meniscal attachments in the range studied have minimal effects on the knee joint mechanics. In summary, our statistically-augmented, computational platform allowed us to study how meniscal implant design variables (which can be controlled at the time of manufacture or implantation) interact with patient variables (which can be set in FEMs but cannot controlled in patient studies) to affect joint contact mechanics during the activity of simulated walking.

Keywords

Meniscal Replacement; Finite Element Analysis; Statistical Analysis; Knee; Sensitivity

1. Introduction

Menisci of the knee are wedge-shaped fibrocartilage discs that stabilize the joint (Makris et al., 2011) and distribute load across the articulating surfaces (Ahmed and Burke, 1983; Fukubayashi and Kurosawa, 1980; Gilbert et al., 2014; Guo et al., 2013). Due to high mechanical demands and a poorly developed vascular network, once injured, menisci have limited healing potential (Makris et al., 2011). Surgical treatment of the damaged meniscus is the most commonly performed orthopedic procedure (Rodkey, 2000), yet meniscal allograft transplantation is the only option currently available in the United States to replace the removed tissue (Hutchinson et al., 2014; Rodeo, 2001). The use of allografts is limited by graft availability, the difficulty of size matching, and risk of disease transmission (Rodeo, 2001). Meniscal implants have been developed in an attempt to provide pain relief and prevent pathological degeneration of articular cartilage (Vrancken et al., 2013). While their clinical use in Europe has yielded mixed results (Hutchinson et al., 2014), the potential to provide an off-the-shelf, reliable solution to meniscal deficiency is appealing (Elsner et al., 2010). But to achieve this goal requires that the functional characteristics of candidate implant designs be evaluated prior to clinical use.

Animal models have been used for preclinical assessment of substitute menisci (Chiari et al., 2006; Maher et al., 2010; Tienen et al., 2006), however, because of differences in knee geometry and loading environment to those of the human knee, animal models do not predict with sufficient certainty the response of the human knee to the presence of the implant. Physical cadaveric models allow for the function of native and substitute menisci to be assessed under static load (Elsner et al., 2010; Seitz et al., 2012; Wünschel et al., 2011), or under more complex multidirectional dynamic loads (Bedi et al., 2012; Bedi et al., 2010; Gilbert et al., 2014; Wang et al., 2014c). However, all physical models are limited by the difficulties of testing large numbers of specimens, and the variability in geometry and kinematics across cadaveric specimens which can confound any conclusions made. Computational models of the human knee joint allow for knee geometry or tissue material

properties to be varied *in silico*. Finite element models (FEMs) have been used to understand the effect of meniscal design variables, which can be controlled at time of manufacture or implantation, (for example, meniscus size and shape, meniscus modulus, and stiffness of the meniscal attachment), and patient variables, which can be set in FEMs but cannot be controlled in patient studies, (for example, bone modulus, cartilage modulus, and limb alignment) on knee joint contact mechanics (Adouni and Shirazi-Adl, 2014; Elsner et al., 2010; Haut Donahue et al., 2003; Haut Donahue et al., 2004; Leatherman et al., 2014; Papaioannou et al., 2008; Pena et al., 2005; Shirazi and Shirazi-Adl, 2009; Vaziri et al., 2008; Yao et al., 2006). However, these variables have been studied without consideration of knee-to-knee variability in geometry and are usually tested under simplified loading conditions that do not mimic activities of daily living. Most importantly, even when activities of daily living are mimicked (Adouni et al., 2012; Mononen et al., 2013), outputs from computational models are rarely compared to those from physical models, thus confidence in the results are lacking. As yet there has been no systematic and comprehensive analysis of the effects of the meniscal design variables on meniscal function across a wide patient population, and there are no clear design criteria to ensure the functional performance of candidate meniscal implants.

The aim of the current study was to develop a statistically-augmented, experimentally-validated, computational platform to assess the effect of meniscal properties (radial/axial and circumferential moduli, and stiffness of the meniscal attachments), and patient variables (varus-valgus alignment and articular cartilage modulus) on knee joint contact mechanics during the activity of walking.

2. Methods

Our approach consists of two stages (Fig. 1): (1) Development of experimentally validated FEMs of three human knees in which the activity of walking is simulated. Using three knees for this step allows us to be confident that our FEM results are physically meaningful for three different anatomies and kinematic profiles. (2) Application of a statistical interpolator to the FEM results allows the study the effect of patient variables and meniscal design variables on joint contact mechanics. The interpolator allows for the effect of meniscal and articular cartilage material properties and joint alignment across the geometries and anatomies of the three knees to be characterized.

Comparison between the physical cadaveric models and the computational FEMs

Three human cadaveric knees with no history of surgery or trauma (Supplementary material, Table 1) were scanned on a clinical 3T MRI scanner (GE Healthcare, Waukesha, WI) using an 8-channel phased array knee coil (Invivo, Gainesville, FL). A 3D CUBE and a 3D SPGR with frequency selective fat suppression image series (Gold et al., 2007; Koff et al., 2013) were acquired (Wang et al., 2014a). MRIs were manually segmented using custom software and used as input for the creation of the knee-specific FEMs. When necessary, segmentation discrepancies were resolved by consensus by three individuals: a research assistant with 5 years' experience, a research scientist with 10 years' experience and a board certified musculoskeletal radiologist with 8 years' experience. The segmentation rules were defined

prospectively: image slices which displayed the anatomy of interest were segmented, except in cases of partial volume averaging (Schneider et al., 2012).

Knee kinematics (6 degree of freedom of movement of the femur relative to the tibia) were computed during simulated walking, in which each knee was simultaneously subjected to dynamic flexion/extension angles, axial forces, anterior/posterior forces and internal/external torques (Bedi et al., 2013; Gilbert et al., 2014; Wang et al., 2014a; Wang et al., 2014b). Varus-valgus angles (VVA) and medial-lateral translations were not controlled, but the tibia was free to move in these directions. Contact stresses were measured using a thin electronic sensor with a matrix of 23×34 sensing elements (sensels) (4010N, Tekscan Inc, MA), which was placed on the tibial plateau underneath the menisci. The physical experiment was repeated three times for each cadaveric knee to assess repeatability.

The relative position of the extracted geometries from the MRI scans were positioned to match that of its respective physical model using a 3D digitizer (Wang et al., 2014a). MRI models were then meshed with hexahedral elements and imported into COMSOL Multiphysics (Burlington, MA). The bottom surface of the meniscus matched the contact surface of the tibial cartilage in the unloaded state, and subsequent conformity between the meniscus and tibial cartilage was guided by the contact algorithm of COMSOL Multiphysics, without any pre-assumption of the contact between the soft tissues. Each finite element model in the current study was driven by knee-specific kinematics from the physical measurements. Specifically, anterior-posterior translation, medial-lateral translation, varus-valgus angle, internal-external angle, flexion-extension angle, and axial force were applied to the mid-point of the femoral epicondylar axis. The kinematics of each knee as measured from the physical models are directly influenced by the presence of the ligaments, therefore, using these kinematics to drive the finite element model made it less critical to include the ligaments in the finite element models. Since the alignment of the MRI models was matched to the physical models, kinematics of each knee were zeroed with their initial values to form the kinematics inputs of FEMs. Articular cartilage and menisci were modeled as elastic materials with geometric nonlinearity to take account of possible large deformation. The menisci were assumed to be transversely isotropic. Meniscal attachments were modeled as linear springs with lengths of 11 mm (Hauch et al., 2010). Contact was modeled between the femoral cartilage and meniscus, the meniscus and tibial cartilage, and the femoral cartilage and tibial cartilage for both the lateral and medial compartments, resulting in six contact pairs, all of which were assumed to be frictionless. Material properties were set as the mid-values of previously reported measurements (Table 1).

Outcomes

Contact mechanics parameters were calculated at three points in the gait cycle where the applied axial force magnitude peaked – at 4%, 14% and 45% of the gait cycle, hereafter referred to as peaks 1, 2 and 3 (Supplementary material, Fig. 1). Since VVA was not controlled in the physical model, it was used as a tuning parameter for each knee-specific FEM: at peaks 1, 2 and 3 of the gait cycle, VVA was varied until medial-lateral compartment load sharing matched that measured in the corresponding physical cadaveric model. The resulting VVA from each FEM was then compared to its physical counterpart

(Fig. 2B). For both the FEM and the physical model, the position of the weighted center of contact (WCoC) (Gilbert et al., 2014) was calculated for peaks 1, 2 and 3 of the gait cycle. WCoC takes into account both the locations and magnitudes of the contact stresses (Wang et al., 2014c). Comparisons between FEMs and physical measurements were made using a custom MATLAB program (MATLAB R2012b, MathWorks, Natick, MA), which superimposed a grid of sensels across the FEM tibial plateau contact stress maps to represent the sensels in the physical experiment. Quantitative comparisons between the contact stress maps generated from the FEM and the physical model for each peak of the gait cycle were also made using normalized cross correlation function of MATLAB. The algorithm normalized the contact stress maps from each of the FEM and the physical model with the sum of the contact stress in each map, respectively, (Lewis, 1995), and then compared the resulting maps. Subsequent to this comparison, VVA was included as one of the variable inputs for the statistical analysis of the combined effect of patient variables on joint contact mechanics.

Statistical analysis of the effects of patient and meniscal design variables on knee joint mechanics

The effect of the following variables on joint contact mechanics in the FEM were studied: patient variables (VVA and modulus of the articular cartilage E_c) and meniscal variables (circumferential modulus of the meniscus E_{cm} , radial/axial modulus of the meniscus E_{rm} , stiffness of the lateral-posterior and medial-anterior meniscal attachments S_{lpma} , and stiffness of the lateral-anterior and medial-posterior meniscal attachments S_{lamp}), shown in Table 1. To avoid complexities associated with modeling large variations in VVA without modeling the associated effect on joint kinematics, the VVA variation was limited to $\pm 0.2^\circ$ within the tuned value at peaks 1, 2 and 3 of the gait cycle (Table 2). Finally the knee geometry and kinematics also potentially affected the computed outputs and these were captured in the three knee-specific FEMs. A set of 26 FEM runs for each knee was implemented in which the magnitude of the variable inputs were prescribed using a space-filling algorithm (Dragulji et al., 2012). An additional 135 runs were then selected for each knee using a grid pattern approach (Supplementary Materials, Fig. 3) to ensure adequate coverage of the design space. Using a custom MATLAB program (Svenson et al., 2014), contact mechanics outputs were predicted at additional input combinations based on a Gaussian Process interpolator (Santner et al., 2003). Global sensitivity indices (SIs) for the 6 variables on the load sharing between the medial and lateral (M/L) compartments, on the load sharing between the cartilage-cartilage (C-C) and cartilage-meniscus (C-M) zones in the medial and lateral compartments, and on contact forces in each individual zone were computed using univariate analyses. When common input effects were exhibited across knees, multivariate analysis was used to construct overall sensitivity indices using the software Gaussian Process Models for Simulation Analysis (GPM/SA) (Higdon et al., 2008).

3. Results

Comparison between the physical cadaveric models and the computational FEMs

Physical experiments showed high repeatability of joint kinematics and M/L load sharing for each individual knee (Fig. 2). The tuned VVA for each FEM was within the physical measurement ranges (Fig. 2b). The regions of contact stress in the FEM and physical model were qualitatively and quantitatively similar, with normalized cross correlation values within 69–85% (Fig. 3 and Supplementary material, Table 2). Locations of the WCoCs from both models were within 1 mm in both medial-lateral and anterior-posterior directions (Fig. 3 and supplementary material, Table 3).

Statistical Analysis of the effects of patient and design variables on knee joint mechanics

Multivariate analyses were performed for cases where the results of the univariate analyses for all three knees followed similar trends, which was the case for all outcome measures at peaks 1 and 3 of the gait cycle. At peak 2, the responses of joint contact to the variables studied were different across knees thus only univariate analyses were performed.

Load sharing between the medial and lateral compartments

Multivariate analyses that combined data from the three knees showed that for peaks 1 and 3 in the gait cycle, 93% and 85% of the variation, respectively, was due to VVA, with increasing varus rotation resulting in increased load through the medial compartment (Fig. 4). The effects of all other variables were small (Table 3). The univariate analyses of the peak 2 data provided that for knee 1, 55% of the variation was due to VVA, 18% to E_c , and 15% to E_{cm} . This was in stark contrast to knees 2 and 3, in which over 82% of the variation was due to VVA, and the contributions of other variables were less than 10%.

Load sharing between the C-C and C-M zones in the medial compartment

Multivariate analyses from the three knees estimated that for peaks 1 and 3 in the gait cycle (Table 4), 47% and 68% of the variation was due to E_{cm} , 27% and 10% was due to VVA, 17% and 12% was due to E_{rm} . The effects of all other variables were close to 0. At peak 1, most of the load was distributed to the C-M zone, while it was shifted to C-C zone at peak 3 (Supplementary Materials, Fig. 4A). The univariate analyses of the peak 2 data estimated that 20% of the variation in load sharing between C-C and C-M zones of knee 1 was due to E_c , yet E_c contributed less than 6% in the other two knees; approximately 23% of the variation in C-M loading sharing for knee 1 and 2 was due to VVA, yet VVA contributed to 8% of the variation found in the knee 3. Greater load was distributed to the C-M zone than the C-C zone for knees 1 and 3, while the opposite was true for knee 2 (Fig. 5A).

Load sharing between the C-C and C-M zones in the lateral compartment

Multivariate analyses found that for peaks 1 and 3 in the gait cycle, 35% and 45% of the variation was due to E_{cm} , 46% and 30% was due to VVA, and approximately 14% was due to E_{rm} . For peaks 1 and 3, most of the load was distributed to the C-M zone (Supplementary Materials, Fig. 4B). The univariate analyses of the peak 2 data estimated that 47% of the variation in load sharing for knee 1 was due to E_c , yet E_c contributed less than 6% in the

other two knees; over 16% of the variation in knees 2 and 3 was due to VVA and E_{rm} , yet VVA and E_{rm} contributed less than 7% in knee 1. For peaks 1 and 3, more load was distributed to the C-M zone than the C-C zone for knees 2 and 3, while for knee 1 the opposite was the case (Fig. 5B). For all knees at all three peaks, the contributions of the S_{lamp} and S_{lpma} were close to 0; increasing varus rotation increased the proportion of load through the meniscus in the medial compartment, while decreasing that in the lateral compartment (Fig. 5); increases in E_{cm} or E_{rm} increased the proportion of the load transmitted through the meniscus on both medial and lateral compartments.

Total forces in the C-C and C-M zones of the medial compartment

Multivariate analyses found that for peaks 1 and 3 of the gait cycle (Table 5), 39% and 47% of the variation of forces in the medial C-C zone was due to VVA, but only 10% and 12% of that in the medial C-M zone was due to VVA; E_{cm} had greater effect on the magnitude of force through the medial C-M zone (53% and 67% at peaks 1 and 3, respectively) than that in the medial C-C zone (26% and 33%); E_{rm} contributed 9–16% to C-C and C-M forces, while the effects of all other variables were less than 6%. The univariate analyses of the peak 2 data estimated that, for knee 1, VVA contributed 29% for the variation of forces in the medial C-C zone, yet VVA contributed less than 10% of the variation of force in the medial C-C zone of knees 2 and 3 and medial C-M zone of all three knees.

Total forces in the C-C and C-M zones of the lateral compartment

Multivariate analyses found that for peaks 1 and 3, approximately 72% of the variation of forces in the lateral C-C zone was due to VVA, but only 32% and 13% of that in the lateral C-M zone was due to VVA; E_{cm} contributed to approximately 15% of the variation of forces in the lateral C-C zone, and 32% and 52% of that in the lateral C-M zone at peaks 1 and 3, respectively. E_{rm} contributed to approximately 7% of the variation of forces in the lateral C-C zone, and approximately 32% of that in the lateral C-M zone, while all other variables had minimal effects. The univariate analyses of the peak 2 data showed that 37% and 41% of the variation of knee 1 in the lateral C-C and C-M zones was due to E_c , while E_c contributed less than 5% for knees 2 and 3.

4. Discussion

We successfully developed a statistically-augmented, experimentally-validated, computational platform which was used to study the effects of patient and meniscal design variables on knee joint contact mechanics. Our analysis used individual FEMs to represent the geometry, kinematics as based on simulated gait and contact mechanics of three laboratory tested human cadaveric knees. The FEMs were subsequently programmed to represent prescribed meniscal variables (circumferential and radial/axial moduli - E_{cm} , E_{rm} , and stiffness of the meniscal attachments- S_{lpma} , S_{lamp}) and patient variables (varus/valgus alignment – VVA, and articular cartilage modulus - E_c). The contact mechanics data generated from the FEM runs were input to a statistical interpolator which were used to predict the joint contact data for untested configurations of variable inputs. Thus our approach allowed us to study how meniscal implant design variables (which can be controlled at the time of manufacture or implantation) interact with patient variables (which

can be set in FEM runs but cannot be controlled in patient studies) to affect joint contact mechanics during the activity of simulated walking. We found that a complex interplay between meniscal properties, E_{cm} and E_{rm} , and the patient variable VVA influenced joint contact mechanics in the early and late stance phase of gait, while for a certain sub-population of knees, E_c significantly affected contact force distributions in the mid-phase of stance.

A benefit to our study design lies in the ability to combine the results from all three knees, across all variables studied, in the form of a multivariate analysis. Thereby, we can make general comments about the effect of variables across a wide population of knees represented by the geometries and kinematics of the three knees that were modeled. The three knees modeled had different joint laxity, radiographic assessment of cartilage and meniscal integrity, and joint size. The differences in the response of the knees to the simulated walking cycle can be seen by examining the variation in the location of force distributed across the tibial plateau throughout gait (whether in the C-C zone, or the C-M zone, Fig. 5) and in the degree of translation and rotation of the femur relative to the tibia (Fig. 6 and Supplementary Material Fig. 2).

Despite this variability, remarkable consistencies were found in the responses of knees to changes in VVA. VVA for each knee had a dominant effect on load sharing between the medial and lateral compartments (Fig. 4 and Table 3) at all three peaks of the gait cycle. More varus angles had increased load transmission through the medial compartment, which is consistent with previous studies (Adouni and Shirazi-Adl, 2014; Andriacchi, 2013; Felson et al., 2013; Sharma et al., 2001; Yao et al., 2008), with forces becoming more concentrated in the medial C-C zone with increasing varus angle (Fig. 5). We also found that across knees, changes in VVA caused more variation of the force in the C-C zone than in the C-M zone for both medial and lateral compartments (Table 5). This finding can be explained by the fact that articular cartilage in the C-M zone is protected by the wedge-shaped meniscus (Andriacchi et al., 2009), which serves as a buffer to absorb changes in force incurred in that zone, while the C-C has no such buffer and is therefore more sensitive to joint alignment changes. This finding may also be explained by the protrusion of the meniscus, however further studies are needed to investigate this relationship. It should be noted that while, all other variables were chosen to span the range of the normal population, VVA was restricted to $\pm 0.2^\circ$ about the tuned VVA of each knee, at each phase of gait that was studied. Such a restriction was necessary because larger changes in VVA would lead to changes in kinematics that could not be realistically modelled in our knees, which relied on the kinematics from experimental models as inputs. Thus, the results from this analysis cannot necessarily be expanded to the goal of understanding the effect of VVA angle across the wider population on joint mechanics.

Remarkable consistencies were also found in the effect of the variables that were studied on knee joint contact mechanics in the early and late stance phase of gait (at peak 1 and peak 3 of the gait cycle). Multivariate analysis indicated that E_{cm} contributed more than E_{rm} to the magnitude and the ratio of the total force experienced in the C-C and C-M zones (Table 4 and 5). Thus, the importance of the circumferential fiber network to overall meniscal function is emphasized. While several meniscal replacements have been reinforced with

circumferential fibers in an attempt to recapitulate this function (Chiari et al., 2006; Elsner et al., 2010; Fisher et al., 2013; Kelly et al., 2007; Tienen et al., 2006), no implant thus far has matched the E_{cm} to that of the native meniscus. Furthermore, we found that at peaks 1 and 3 of the gait cycle, E_{cm} had greater effects on load sharing between C-C and C-M zones in the medial compartment than in the lateral compartment (47% and 68% vs 35% and 45%, Table 4). This finding suggests that joint contact mechanics in the medial compartment are more sensitive to E_{cm} than that in the lateral compartment in the early and late stance phase of gait, further implying that E_{cm} of the medial meniscal replacement needs particular attention. For the medial compartment, at peak 1, most of the load was distributed to the C-M zone, while at peak 3, it was shifted to the C-C zone. For the lateral compartment, most of the load was distributed to the C-M zone throughout the 3 peaks of the gait cycle. These findings are consistent with a previous cadaveric study by Gilbert et al. (2014) and suggest that the medial meniscus plays a dominant load carrying role in the early stance and less so in late stance, while the lateral meniscus functions to distribute load throughout gait.

The effect of variable inputs on joint contact mechanics was less consistent in the mid-stance phase of the gait cycle (peak 2). The differences observed across all three knees at peak 2 of the gait cycle were dominated by the results generated from the sub-population of knees exemplified by the anatomy and kinematics of knee 1. Knee 1 had greater medial and posterior translations than knees 2 and 3 (Fig. 6), which indicate a less stable knee joint (Williams et al., 2001). As such, increased forces were experienced in the C-C zone when compared to all other knees (Fig. 5). This finding is consistent with a previous study by Yao et al. (2008) which found that medial-lateral and anterior-posterior translations led to pronounced variations in joint contact mechanics. With higher forces through the C-C zone, it is to be expected that as the stiffness of the articular cartilage in that zone increases, higher forces will be transmitted, and visa versa. This finding has important clinical consequences as it indicates that osteoarthritic cartilage, which has a lower modulus than healthy cartilage (Mow et al., 2005), will have lower forces through the C-C zone, and higher forces through the meniscus. Our study therefore suggests that in the sub-population of higher laxity knees, with evidence of early osteoarthritis, meniscal replacements should be designed so that they can withstand higher forces, specifically in the mid-stance phase of gait, than in an otherwise stable and healthy knee joint.

While the stiffness of the attachment of a meniscal implant to the host tissue cannot be controlled at the time of manufacture, it is a feature that can be controlled at the time of implantation. The stiffness of the meniscal-bone attachments, within the ranges studied, was found to have a minimal effect on joint contact mechanics (Fig. 4–5 and Table 3–5), which is inconsistent with the findings of Haut Donahue et al. 2003. The range of fixation stiffness values used in our study (120–270 N/mm) is based on recent experimental measurements as reported by Hauch et al. (2010), which is an order of magnitude lower than that used by Haut Donahue et al. (500–30000 N/mm). Furthermore, our computational model quantified joint contact mechanics under multidirectional forces, while the study of Haut Donahue et al. simulated only axial forces. A recent cadaveric study reported that different methods of graft fixation had a significant effect on joint contact mechanics (Wang et al., 2014c), which at face value might seem to contradict the results presented herein. However, it should be noted that when a graft is used to replace the meniscus, fixation extends through a tunnel in

the tibial bone; thus the effective length of the attachment is greater than that used in the current computational model where linear springs insert directly into a bone of infinite stiffness. As such, the data generated in this study, cannot be directly applied to grafts.

Our study has several limitations. The statistically-augmented approach is based on a cadaveric model in which the activity of walking is simulated (Bedi et al., 2013; Gilbert et al., 2014; Wang et al., 2014a; Wang et al., 2014b; Wang et al., 2014c). This approach was necessary to enable a full comparison of the FEM data to that of the physical model. The use of a kinematically driven model was critical during this validation phase of our studies. However, before investigating certain clinical conditions, such as meniscectomy or ligament deficiencies, it may be necessary to also include force-driven models that would capture the influence on kinematics and knee stability. In the FEM, articular cartilage was modeled as a homogeneous linear elastic material, thus ignoring its inhomogeneous, anisotropic, and biphasic features (Guo et al., 2014; Mow et al., 2005). Since we are studying gait at a loading rate of 0.5 Hz, the elastic material model is a reasonable starting point for modeling the force distribution across the tibial plateau (Ateshian et al., 2007). However, this simplification complicated our efforts to fully validate the FEM outputs with the physical model outputs in the sense of Higdon et al. (2008). We chose to program the FEM with mid-value properties of that reported in literature, as opposed to actual properties measured from the three specimens tested in the physical cadaveric models. As a consequence, when comparing the contact mechanics of both models, the WCoCs values (which quantify a weighted assessment of contact location, rather than absolute contact stress value) provided the most robust comparison metric. Locations of WCoCs from the FEMs and physical measurements were within 1 mm from each other, which provided strong confidence in the FEMs. Furthermore, in the current study, strains in most region of the meniscus were less than 30%, which is within the linear range (Mow et al. 2005), but small regions at the inner edge of the meniscus, where the tissue is thin, had strains of up to 37%. In future studies, the regional variation, nonlinearity, and inhomogeneity of the articular cartilage and meniscus could be included in the FEM (Gu and Li, 2011; Mononen et al., 2012; Shirazi et al., 2008) so that their contributions to the variation of joint contact mechanics can be analyzed in detail. Finally, while our model provides a comprehensive analysis of the contact stresses acting perpendicular to the articular cartilage surface, an analysis of the stresses through the tissue, and the frictional characteristics of the surface were outside the scope of the study.

In summary, we have combined a physical model with a statistically-augmented computational model to assess the effect of meniscal properties and patient variables on knee joint contact mechanics. Our data suggest that while E_{cm} and E_{tm} of a meniscus are critical in determining knee joint mechanics in early and late stance (peak 1 and peak 3 of the gait cycle), for some individual knees in the mid-stance phase of gait, the stiffness of the cartilage E_c can influence force distribution across the tibial plateau. Joint contact mechanics in the medial compartment are more sensitive to E_{cm} than those in the lateral compartment. The medial meniscus plays a dominant load carrying role in the early stance phase and less so in late stance, while the lateral meniscus carries load throughout gait. Finally, throughout stance, VVA of the patients' knee can overwhelm these relationships while the stiffness of meniscal attachments in the range studied have minimal effects on the knee joint mechanics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

The computational platform combines the physical model, the finite element model (FEM), and the statistical analysis so that the effect of patient variables and meniscal design variables on joint contact mechanics can be studied. Knee-specific geometry for 3 knees, obtained using MRI, was used to construct a knee specific FEM. Each knee was physically subjected to forces intended to mimic gait (ISO14243-1), while kinematics and contact mechanics were recorded. Knee specific joint kinematics were input to the FEM, and a comparison between the contact mechanics of the FEM to that measured from the physical model was made. Two patient variables and four meniscal design variables were then varied in 6-dimensional space simulating scenarios for a wide patient population. Global sensitivity analysis was used to estimate variables' effects on load sharing between the medial and lateral compartments (M/L), on load sharing between the cartilage-cartilage and cartilage-meniscus zones (C/M) in the medial and lateral compartments, and on forces in each individual zone.

Fig. 2.

The varus-valgus angle (VVA) of each knee was tuned so that load sharing between the medial and lateral compartments (M/L) matched that of the corresponding physical model at peaks 1, 2 and 3 of the gait cycle. (a) M/L load sharing as measured from the physical cadaveric models during three repeated tests on each knee. The shaded area represents the standard deviation. (b) Physical measurements of varus-valgus rotation. Closed circles are the VVAs from the FEM that resulted in M/L load sharing that matched the corresponding physical model. The VVAs from the FEM and the physical model were in close agreement.

Fig. 3.

Comparison between contact stress maps on the tibial cartilage surface at peak 2 from the physical model (A), the corresponding knee-specific FEMs with superimposed sensel-grid to mimic the physical sensels (B), and without the superimposed grid (C). White stars represent the location of the weighted centers of contact (WCoCs) on the tibial compartments. The location of peak contact stresses and the patterns of contact are similar, while differences in the magnitude of peak contact stress were found between the FEMs (B, C) and the physical model (A).

Fig. 4.

Main effect plots of load sharing between the medial and lateral compartments (M/L) at 3 peaks in the gait cycle. The x-axis represents scaled inputs, where 0 is the minimum value of each input (E_c , VVA, E_{cm} , E_{rm} , S_{lpma} , S_{lamp}) and 1 is the maximum value of each input. Lines with a positive slope indicate that as the variable being considered increases, increased load is transmitted through the medial compartment. A multivariate analysis was conducted for peaks 1 and 3 of the gait cycle, while due to distinct behavior of the knees at peak 2 (also see Table 3 for main effect sensitivity indices), only univariate analyses were performed, and so the data for each individual knee are presented.

Fig. 5.

Main effect plots from univariate analyses of load sharing between the cartilage-cartilage (C-C) and cartilage-meniscus (C-M) contact zones (C/M) at peak 2 of the gait cycle. A y-axis value of less than 1, indicated that more load is transmitted to the C-M zone than the C-C zone. (A): In the medial compartment, most of the load was transmitted through the meniscus for knees 1 and 3 regardless of the variables studied, while knee 2 had more load transmitted to the C-C zone. (B): In the lateral compartment, load was predominantly in the C-M zone for knees 2 and 3, while for knee 1, more load was transmitted to the C-C zone.

Fig. 6. Medial-lateral (A) and anterior-posterior (B) translations (movement of the femur relative to the tibia) in mm measured from the physical experiments, which were used as part of the knee-specific kinematics input for FEMs. At peak 2 of the axial force in the gait cycle, knee 1 had greater medial and posterior translations than the other two knees (indicated by the arrows).

Table 1

The notation, units, and ranges of variable inputs for FEMs. The first input is patient variable that can be set in FEM studies but cannot be controlled in physical studies, and the other four inputs are meniscal design variables, which can be controlled at the time of manufacture or implantation.

Variable Inputs for FEMs	Lower Bound	Upper Bound
Elastic modulus of the articular cartilage, E_c (MPa) (Li et al., 2003; Mow et al., 2005; Shepherd and Seedhom, 1999)	11.5	35
Circumferential modulus of the meniscus, E_{cm} (MPa) (Fithian et al., 1990; Tissakht and Ahmed, 1995)	80	220
Radial/axial modulus of the meniscus, E_{rm} (MPa) (Mow et al., 2005; Tissakht and Ahmed, 1995)	11.5	35
Stiffness of the lateral-anterior and medial-posterior meniscal attachments, S_{lamp} (N/mm) (Hauch et al., 2010)	150	270
Stiffness of the lateral-posterior and medial-anterior meniscal attachments, S_{lpma} (N/mm) (Hauch et al., 2010)	120	180

Table 2

The ranges of varus-valgus angle for FEMs. Varus-valgus angle is patient variable that can be set in FEM studies but cannot be controlled in physical studies. VVA variation was limited to $\pm 0.2^\circ$ within the tuned value at peaks 1, 2 and 3 of the gait cycle.

Varus-valgus Angle (VVA)		Lower Bound	Upper Bound
Peak 1	Knee 1	-0.51	-0.11
	Knee 2	-0.03	0.37
	Knee 3	0.00	0.40
Peak 2	Knee 1	-1.01	-0.61
	Knee 2	-0.45	-0.05
	Knee 3	0.31	0.71
Peak 2	Knee 1	-0.65	-0.25
	Knee 2	0.15	0.55
	Knee 3	-1.25	-0.85

Main effect Sensitivity Indices (SIs) of variable inputs for load sharing between medial and lateral (M/L) compartments. Due to the distinct behavior of knee 1 at peak 2 compared with that of the other two knees, multivariate analysis was not performed for peak 2. SIs over 0.15 are highlighted with bold font.

Table 3

Variables		Patient Variables		Meniscal Design Variables			
		E _c	VVA	E _{cm}	E _{rm}	S _{lamp}	S _{lpma}
Peak 1	Knee 1	0.01	0.97	0.00	0.00	0.00	0.00
	Knee 2	0.02	0.76	0.07	0.12	0.00	0.00
	Knee 3	0.00	0.81	0.07	0.09	0.00	0.01
Multivariate Analysis		0.01	0.93	0.02	0.02	0.00	0.00
Peak 2	Knee 1	0.18	0.55	0.15	0.10	0.00	0.01
	Knee 2	0.01	0.82	0.08	0.07	0.00	0.01
	Knee 3	0.00	0.88	0.03	0.07	0.01	0.00
Peak 3	Knee 1	0.02	0.90	0.02	0.02	0.02	0.00
	Knee 2	0.00	0.80	0.08	0.08	0.00	0.01
	Knee 3	0.00	0.88	0.03	0.06	0.00	0.00
Multivariate Analysis		0.01	0.85	0.03	0.05	0.02	0.00

Main effect SIs of variable inputs for load sharing between C-C and C-M zones (C/M). Results of multivariate analyses are shown for peaks 1 and 3. Multivariate analysis was not performed for peak 2. SIs over 0.15 are highlighted with bold font.

Table 4

Variables	Patient Variables		Meniscal Design Variables			
	E _c	VVA	E _{cm}	E _{rm}	S _{lamp}	S _{lpma}
Medial Compartment						
Peak 1	0.01	0.27	0.47	0.17	0.00	0.01
Peak 3	0.01	0.10	0.68	0.12	0.01	0.02
Peak 2	Knee 1	0.20	0.38	0.15	0.01	0.00
	Knee 2	0.00	0.24	0.50	0.22	0.01
	Knee 3	0.06	0.08	0.52	0.30	0.01
Lateral Compartment						
Peak 1	0.00	0.46	0.35	0.14	0.00	0.00
Peak 3	0.07	0.30	0.45	0.13	0.00	0.01
Peak 2	Knee 1	0.47	0.40	0.07	0.01	0.00
	Knee 2	0.02	0.31	0.38	0.24	0.01
	Knee 3	0.06	0.16	0.40	0.33	0.01

Table 5

Main effect SIs of variable inputs for force in different contact zones. Results of multivariate analyses are shown for peaks 1 and 3. Multivariate analysis was not performed for peak 2. SIs over 0.15 are highlighted with bold font.

Variables		Patient Variables		Meniscal Design Variables			
		E _c	VVA	E _{cm}	E _{rm}	S _{lamp}	S _{lpma}
Medial Compartment							
Peak 1	C-C	0.02	0.39	0.26	0.09	0.01	0.02
	C-M	0.01	0.10	0.53	0.09	0.02	0.02
Peak 3	C-C	0.00	0.47	0.33	0.16	0.01	0.00
	C-M	0.06	0.12	0.67	0.13	0.00	0.01
Peak 2	C-C 1	0.29	0.40	0.22	0.07	0.00	0.00
	C-C 2	0.00	0.58	0.25	0.15	0.00	0.01
	C-C 3	0.05	0.28	0.38	0.26	0.01	0.00
	C-M 1	0.01	0.09	0.55	0.32	0.00	0.01
	C-M 2	0.04	0.20	0.56	0.17	0.01	0.00
	C-M 3	0.10	0.15	0.52	0.21	0.00	0.01
Lateral Compartment							
Peak 1	C-C	0.00	0.72	0.15	0.08	0.00	0.00
	C-M	0.01	0.32	0.32	0.32	0.00	0.01
Peak 3	C-C	0.06	0.71	0.14	0.06	0.00	0.00
	C-M	0.00	0.13	0.52	0.31	0.01	0.01
Peak 2	C-C 1	0.37	0.25	0.25	0.11	0.00	0.00
	C-C 2	0.00	0.70	0.17	0.11	0.00	0.00
	C-C 3	0.05	0.50	0.25	0.18	0.00	0.00
	C-M 1	0.41	0.12	0.43	0.02	0.02	0.00
	C-M 2	0.01	0.07	0.51	0.36	0.00	0.02
	C-M 3	0.03	0.21	0.37	0.35	0.02	0.00