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Association of Machine Learning–Based Predictions of Medial Knee Contact Force With Cartilage Loss Over 2.5 Years in Knee Osteoarthritis

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Objective. The relationship between in vivo knee load predictions and longitudinal cartilage changes has not been investigated. We undertook this study to develop an equation to predict the medial tibiofemoral contact force (MCF) peak during walking in persons with instrumented knee implants, and to apply this equation to determine the relationship between the predicted MCF peak and cartilage loss in patients with knee osteoarthritis (OA).

Methods. In adults with knee OA (39 women, 8 men; mean ± SD age 61.1 ± 6.8 years), baseline biomechanical gait analyses were performed, and annualized change in medial tibial cartilage volume (mm^3/year) over 2.5 years was determined using magnetic resonance imaging. In a separate sample of patients with force-measuring tibial prostheses (3 women, 6 men; mean ± SD age 70.3 ± 5.2 years), gait data plus in vivo knee loads were used to develop an equation to predict the MCF peak using machine learning. This equation was then applied to the knee OA group, and the relationship between the predicted MCF peak and annualized cartilage volume change was determined.

Results. The MCF peak was best predicted using gait speed, the knee adduction moment peak, and the vertical knee reaction force peak (root mean square error 132.88N; $R^2 = 0.81$, $P < 0.001$). In participants with knee OA, the predicted MCF peak was related to cartilage volume change ($R^2 = 0.35$, $\beta = -0.119$, $P < 0.001$).

Conclusion. Machine learning was used to develop a novel equation for predicting the MCF peak from external biomechanical parameters. The predicted MCF peak was positively related to medial tibial cartilage volume loss in patients with knee OA.

INTRODUCTION

Mechanical loading is implicated in the onset and progression of cartilage loss, a hallmark of knee osteoarthritis (OA) (1–7). Mechanical loads are theorized to be related to cartilage loss through their role in increasing compressive forces across joint surfaces (8). However, such a relationship has not yet been verified in patients with knee OA, since noninvasive, in vivo force measurement is not possible; direct measurement of knee contact forces is only possible using instrumented knee implants (9). Therefore, loads acting within native knees are estimated using musculoskeletal modeling from motion analysis data, or surrogate measures reflecting knee joint loading are calculated using inverse dynamics.

Key external biomechanical parameters used to describe loading across knee joint surfaces include the knee adduction moment (KAM), the knee flexion moment (KFM), the vertical knee reaction force (vKRF), gait speed, and measures of body size (height, body mass, and body mass index [BMI]). The KAM reflects

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the distribution of load between medial and lateral knee compartments (10). The KFM provides insight into net muscle contraction across the knee (11). During the stance phase, the quadriceps produce an internal knee extension moment to counterbalance the external KFM, increasing compressive forces within the joint (1). The vKRF represents an equal and opposite vertical force acting between the tibia and femur, without accounting for muscle forces (12). Finally, although gait speed and measures of body size do not directly reflect joint loading, these are main effectors of the vertical ground reaction force (13), a primary determinant of the KAM, KFM, and vKRF (12,14,15).

Due to the theoretical relationship between mechanical loads and cartilage degeneration, and due to the high prevalence of tibiofemoral OA in the medial compartment (16), measurement and prediction of medial knee contact forces (MCFs) are of particular interest. Direct measurements in patients with instrumented tibial prostheses and estimates from tibiofemoral contact force models confirm correlations between external biomechanical parameters and MCFs during gait (9,10,17–22). In patients with instrumented knee implants, the KAM (9,17–19), vKRF (10), and gait speed (17) were independently positively associated with the MCF. Interestingly, combining the KFM with the KAM enabled more useful predictions of the MCF than when either variable was analyzed separately (9,18), supporting the notion that these variables collectively describe the knee loading environment (1,3,18). Furthermore, higher body mass and BMI were each associated with greater peak knee compressive forces in persons with knee OA (20–22).

Ample evidence links external gait measures to medial cartilage loss in knee OA. For instance, a higher KAM peak (3,4) and KAM impulse (4,6) at baseline predicted greater loss of medial knee cartilage over 1–5 years. A greater KFM peak at baseline was associated with reduced medial knee cartilage over 5 years (3). Furthermore, a higher BMI at baseline predicted greater medial knee cartilage loss over 2 years (23). Interestingly, the impact of a higher KAM peak and KAM impulse at baseline on medial knee cartilage loss over 2.5 years was amplified with increasing BMI (7). Conversely, no known work has examined the relationship between vKRF or gait speed and morphologic cartilage changes in knee OA, though their relationship with cartilage loss seems logical as these parameters directly influence knee load magnitudes. Since instrumented knee prostheses lack cartilage, MCF measurements acquired with such technology cannot be used to directly predict cartilage loss. Instead, biomechanical and/or statistical predictions of MCF can be developed in persons with instrumented prostheses and then validated in the population of interest (i.e., patients with knee OA).

A primary research goal is to confirm whether knee contact forces are in fact related to cartilage loss. Thus far, studies have examined the relationship between external knee loading variables as surrogates of contact forces and medial knee cartilage loss. To our knowledge, the relationship between the MCF (what the surrogate measures are said to represent) and cartilage loss has not yet been modeled directly. The purpose of the present study was to confirm the relationship between the predicted MCF peak during walking and changes in medial tibial cartilage volume over a period of 2.5 years in participants with clinical and radiographic knee OA. To accomplish this, we developed an equation to predict the MCF peak from external knee loading parameters using data from patients with instrumented tibial prostheses, which was then used to predict the MCF peak for a separate sample of participants with knee OA. It was hypothesized that a higher predicted MCF peak at baseline would be associated with greater cartilage volume loss in patients with knee OA.

PATIENTS AND METHODS

This analysis was performed using 2 data sets: 1 from participants with knee OA and 1 from patients with instrumented tibial prostheses. First, gait biomechanics and knee cartilage volume change were documented in a subset of participants with knee OA enrolled in a longitudinal, observational study. This study was approved by the Hamilton Integrated Research Ethics Board (no. 10-475). Second, gait biomechanics data from a sample of patients who received instrumented knee implants were used to derive a statistical model predicting the MCF peak. This study was approved by the ethics board of the Charité Universitätsmedizin Berlin (no. EA4/069/06) and registered at the German Clinical Trials Register (no. DRKS00000606; www.orthoload.com). This research was completed in compliance with the Declaration of Helsinki. All participants provided written informed consent.

Participants with knee OA. The knee OA cohort comprised a convenience sample of 64 adults with clinical knee OA, ages 40–70 years, who were recruited from local rheumatology and orthopedic clinics. Clinical knee OA was diagnosed according to the American College of Rheumatology criteria (24). Potential participants were excluded if they had other types of arthritis, past lower extremity joint injury and/or surgery, ipsilateral hip or ankle conditions (including OA), regular need for an adaptive walking aid, or lower extremity trauma or intraarticular therapies within 3 months prior to commencing the study. If participants had bilateral OA, the more symptomatic knee was studied.

At baseline, Kellgren/Lawrence (K/L) scores (25) were determined by an experienced radiologist using anteroposterior weight-bearing knee radiographs acquired in a standardized fixed-flexion position (26). These measurements have demonstrated moderate-to–very good interobserver reliability with intraclass correlation coefficients (ICCs) ranging between 0.51 and 0.89 (27). In addition, descriptive statistics were recorded, including sex, age, height, body mass, BMI, and anatomic knee alignment (28). In the current analysis, only participants with radiographic knee OA (i.e., K/L score ≥2) at baseline and those who had baseline and follow-up cartilage measurements were included (n = 47). There were 39 women and 8 men included, with a mean ± SD age of 61.1 ± 6.8 years. Eighteen participants had a K/L score of 2, 18 participants had a K/L score of 3, and 11 participants had a K/L score of 4.

Cartilage morphology. At baseline and after ~2.5 years of follow-up, participants with knee OA underwent magnetic resonance imaging (MRI) of the study knee using the same 1T peripheral scanner (OrthOne; ONI Medical Systems). Participants underwent knee scans in the morning and were asked to minimize weight-bearing prior to MRI acquisition. For analysis of cartilage morphometry, MRI scans were acquired using a coronal, T1-weighted, fat-saturated, spoiled gradient-recalled acquisition in the steady-state sequence with an in-plane resolution of 0.3125 × 0.3125 mm and a slice thickness of 1.5 mm (60 msec repetition time, 12.4 msec echo time, 40° flip angle).

Medial tibial cartilage volume was determined using automated, atlas-based segmentations of MRI scans (Qmetrics) (29). Test–retest precision error for medial tibial cartilage volume using the same 1T scanner was 3.6% (30). Baseline and follow-up cartilage values were used to calculate annualized cartilage volume change (mm^3/year) for each participant using the following equation:

$$\Delta\, Cartilage/year = \frac{Cartilage\ volume\ at\ follow\text{-}up - cartilage\ volume\ at\ baseline}{\text{No.}\ of\ years\ between\ time\ points}.$$

Biomechanical assessment. Within 1 week of the baseline MRI, participants with knee OA underwent gait analyses to calculate 3-dimensional (3-D) knee kinematics and kinetics during self-paced barefoot walking. Active infrared markers, mounted in triads on rigid plates, were fixated to the sacrum, and lateral aspects of the mid-thigh, mid-shank, and foot of the study leg. Standard bony anatomic landmarks were digitized to create participant-specific rigid link-segment models of the pelvis and leg, as described previously (31). Marker trajectories were collected at 100 Hz with a 9-camera motion capture system (Optotrak Certus; Northern Digital). Kinetics were recorded synchronously at 1,000 Hz with a floor-embedded force platform (OR6-7-1000; AMTI). Data from 5 self-paced barefoot gait trials, in which the foot of the study leg landed fully on the force platform, were collected.

Gait data were processed with commercial software (Visual 3D; C-Motion). Marker trajectory and force plate data were filtered with a second-order, low-pass (6 Hz cutoff), bidirectional Butterworth filter (32). External knee moments and reaction forces were resolved in a 3-D floating axis coordinate system (33) using inverse dynamics (12). The following external biomechanical parameters, representing theoretically relevant potential predictors of MCF (9,10,17–22), were computed and extracted for 5 gait cycles and then averaged: gait speed, external KAM peak, external KAM impulse, external KFM peak, and vKRF peak. Given the importance of the first KAM and KFM peaks to the progression of cartilage loss in knee OA (3,6), and to ensure analysis of temporally matched outcomes between participants, the peak values for the kinetic outcomes (i.e., KAM, KFM, vKRF) were extracted from the first 50% of the stance phase. The KAM impulse, which captures both the magnitude and duration of load (34), was computed for the entire stance phase using trapezoidal integration of only positive values.

In vivo knee loads in patients with instrumented knee implants. To allow for predictions of the in vivo MCF peak, gait data were also acquired in a separate sample of patients with force-measuring tibial prostheses as a result of total knee arthroplasty to treat advanced OA (n = 9; 3 women, 6 men; mean ± SD age 70.3 ± 5.2 years) (9,17,35). Details of the design, calibration, and accuracy of the instrumented tibial tray have been reported elsewhere (36,37). Gait data were collected over 8 years (1–3 time points per participant); the earliest time point was 11.2 months after implantation. Marker trajectories (100 Hz or 120 Hz; Vicon), ground reaction forces (1,000 Hz or 960 Hz; AMTI), and internal knee implant kinetics (~100 Hz; Innex; Zimmer) were collected synchronously during barefoot walking at self-determined slow, natural, and fast walking speeds. A range of walking speeds was included to capture greater variability in MCF peaks and to allow for broader generalizability of the model. Marker trajectory and force plate data were processed using the same rigid link-segment model and processing parameters (i.e., filter, joint coordinate system, inverse dynamics) as described for the knee OA group, and the same descriptive statistics and external biomechanical parameters were computed. To enable prediction of the MCF peak from external parameters and to ensure temporal consistency with the extracted kinetic outcomes (i.e., KAM peak, KFM peak, vKRF peak), the first peak of the MCF was extracted from the measured in vivo loads for each trial. In total, 218 gait trials were analyzed, representing an average of 24.2 trials per participant (minimum 7, maximum 40).

Predictions of the MCF peak. The best combination of predictors of the measured MCF peak was determined in patients with instrumented knee implants using the machine learning method Least Absolute Shrinkage and Selection Operator (LASSO) regression (38,39). LASSO is a regularized form of least squares regression that uses a tunable parameter (λ). When the lambda value is set to 0, LASSO is equivalent to least squares regression; as the lambda value increases, unimportant beta coefficients are reduced to 0. Model selection was therefore simplified to identify the lambda value between 0 and 100 with the smallest out-of-sample root mean square error (RMSE) using leave-one-out cross-validation (38,39). In other words, the RMSE was assessed for the samples of data left out during each cross-validation step and represents the prediction error for data not used to fit the model. To prevent data leakage, cross-validation was performed at the participant level instead of at the trial level.

Table 1. Demographic, anthropometric, and gait data at baseline for the knee OA and instrumented knee implant groups*

	Knee OA (n = 47)	Knee implant (n = 9)	*P*
Female sex, no. (%)	39 (83)	3 (33)	0.001
Age, years	61.1 ± 6.8	70.3 ± 5.2	<0.001
Height, meters	1.63 ± 0.08	1.72 ± 0.04	0.002
Body mass, kg	76.1 ± 16.1	91.1 ± 12.5	0.010
BMI, kg/m^2	28.8 ± 5.8	30.8 ± 4.5	0.326
Coronal knee alignment, degrees	−2.3 ± 3.5†	2.4 ± 4.2‡	NA§
Gait speed, meters/second	1.17 ± 0.22	1.16 ± 0.11	0.350
KAM peak, Nm	25.03 ± 14.35	37.82 ± 13.53	0.017
KAM impulse, Nm × s	9.15 ± 6.58	15.72 ± 7.23	0.016
KFM peak, Nm	43.33 ± 18.09	30.78 ± 11.86	0.051
vKRF peak, N	749.64 ± 136.64	803.21 ± 113.79	0.275
Measured MCF peak, N	–	1,578.75 ± 264.21	–
Predicted MCF peak, N	1,355.25 ± 326.02	–	0.058¶

* Gait data are for overground barefoot walking trials performed at a self-selected, natural speed. Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; NA = not applicable; KAM = knee adduction moment; KFM = knee flexion moment; vKRF = vertical knee reaction force; MCF = medial knee contact force.

† Anatomic tibiofemoral angle determined from weight-bearing anteroposterior knee radiographs acquired in a fixed-flexion position (see ref. 28). A negative value indicates valgus alignment.

‡ Mechanical tibiofemoral angle (hip-knee-ankle angle) determined from standing anteroposterior full-leg radiographs (see ref. 28). A positive value indicates varus alignment.

§ Knee alignment measurements were not compared statistically, because anatomic (knee osteoarthritis [OA] sample) and mechanical (knee implant sample) alignments are inconsistent with one another (see ref. 28).

¶ Versus measured MCF peak in the knee implant group.

Potential predictors included height, body mass, BMI, gait speed, KAM peak, KAM impulse, KFM peak, and vKRF peak, as well as the squared versions of each term and all possible 2-way interactions. To create the final model, predictors with non-zero beta coefficients at the optimal lambda values were fitted to the data from all 218 trials using least squares regression. To account for non-independence of repeated measurements, a cluster-robust variance matrix was used (40).

Predicted MCF model fit parameters, including the fitted beta coefficients, R^2, and RMSE, as well as the out-of-sample cross-validation RMSE, were calculated. In addition, simple linear regressions were run for each of the identified predictors to determine how well they individually predicted the MCF peak.

Statistical analysis. Descriptive statistics were calculated as the mean ± SD for continuous data and the number (percentage) for categorical data. Demographic, anthropometric, and overground, self-paced gait data were compared between the 2 groups (knee OA and instrumented knee implant) using independent sample *t*-tests. If assumptions of normality or homogeneity of variance were not met, a 2-sample Mann-Whitney U test was used. To determine whether cartilage volume changed from baseline to follow-up in participants with knee OA, a 1-sample *t*-test was used.

To determine the relationship between the predicted MCF peak and the change in medial tibial cartilage volume, a 2-step approach was used. First, predictions of the MCF peak were calculated for all participants with knee OA using the aforementioned equation generated in patients with instrumented knee implants. Second, the relationship between the predicted MCF peak and the annualized cartilage volume change was fitted using ordinary least squares regression.

To assess the fidelity of the MCF peak predictions in the knee OA group, and their relationship with cartilage change, additional analyses were performed. Reliability of the MCF peak predictions was determined using data from a subsample of knee OA patients (n = 40) for whom gait data were available from a second occasion ~6 months following the baseline assessment. Relative and absolute test–retest reliabilities were estimated using a Shrout and Fleiss type 2,1 ICC and the SEM, respectively. Furthermore, the predictive model of cartilage change was assessed for assumptions of linear regression, including linearity, normality of residuals, and homoscedasticity. Finally, a multivariate linear regression model between the identified predictors of the MCF peak and cartilage volume change was created. The goodness of fit of this multivariate model was compared to that of the MCF peak model using the likelihood ratio test. All data and statistical analyses were performed with StatsModels for Python 3.7 (41).

RESULTS

At baseline, the knee OA group had a higher proportion of women (*P* = 0.001), and patients with knee OA were on average younger (*P* < 0.001) than those in the instrumented knee implant group. Participants with knee OA also tended to be shorter (*P* = 0.002) and weigh less (*P* = 0.010) (likely attributable to the sex discrepancy between groups); however, the groups did not differ in BMI (*P* = 0.326). Demographic and anthropometric data as well as all tested biomechanical parameters for the knee OA group and the instrumented knee implant group are described in Table 1. The KAM peak (Δ = −12.79 Nm; *P* = 0.017) and KAM impulse (Δ = −6.57 Nm × s; *P* = 0.016) were lower in the knee OA group compared to the instrumented knee implant group. No between-group

Table 2. Final linear regression model to predict the measured MCF peak from external biomechanical gait outcomes in the patients with instrumented knee implants*

	β	SE	*P*
Intercept	−446.21	303.75	0.142
Gait speed, meters/second	398.06	67.90	<0.001
KAM peak, Nm	15.27	3.35	<0.001
vKRF peak, N	1.27	0.32	<0.001

* Final linear regression model included fit parameters of R^2 = 0.81 (P < 0.001), root mean square error (RMSE) = 132.88N, and cross-validation RMSE = 196.58N. MCF = medial knee contact force; KAM = knee adduction moment; vKRF = vertical knee reaction force.

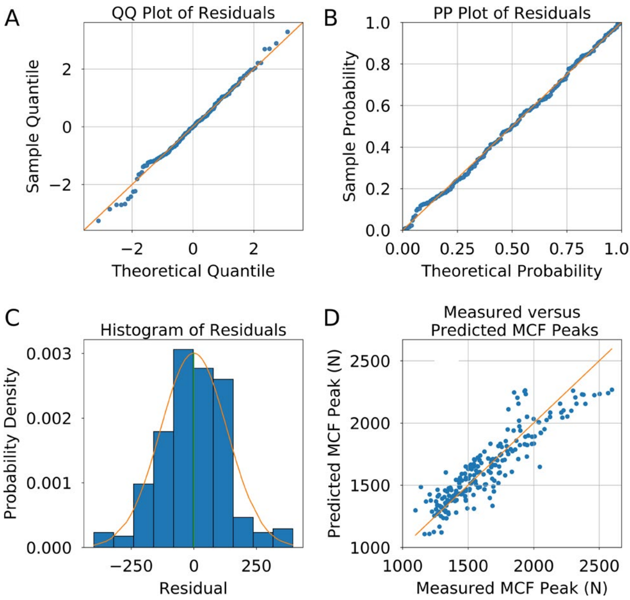

Figure 1. Visual assessment of model fit for the medial knee contact force (MCF) peak as predicted from external biomechanical gait outcomes. A Q–Q plot of residuals (**A**), a P–P plot of residuals (**B**), a histogram of residuals (**C**), and a scatterplot of measured versus predicted MCF peaks (**D**) are shown. For the Q–Q plot, P–P plot, and histogram, the solid orange line represents a theoretical normal distribution. For the Q–Q plot and P–P plot, limited deviation of the blue scatter points from the orange line indicates that the residuals follow a normal distribution. In the scatterplot of measured versus predicted MCF peaks, the orange line represents a 1:1 relationship between measured and predicted values; tighter fit of the scatter points indicates smaller error in the predicted MCF peak.

differences were observed for gait speed, KFM peak, vKRF peak, or measured/predicted MCF peak ($P > 0.05$).

In patients with instrumented knee implants, the identified parameters that best predicted the MCF peak using LASSO regression were gait speed, KAM peak, and vKRF peak. The optimal lambda value of the LASSO regression was 10.5. The linear model fit using the predictors identified from the LASSO analysis and all data from the 218 trials showed $R^2 = 0.81$ ($P < 0.001$) and RMSE = 132.88N (Table 2). Leave-one-out cross-validation showed that the model had an out-of-sample RMSE of 196.58N. Figure 1 shows a visual assessment of model fit for the predicted MCF peak model, including a Q–Q plot, a P–P plot, a histogram of residuals, and a plot of measured versus predicted MCF peaks. Simple linear regression of the identified predictors showed that they were each related to the MCF peak (gait speed $R^2 = 0.19$ [$P = 0.018$]; KAM peak $R^2 = 0.55$ [$P = 0.006$]; vKRF peak $R^2 = 0.49$ [$P = 0.025$]) (Table 3).

For the knee OA group, the mean ± SD follow-up time was 2.57 ± 0.53 years. Between baseline and follow-up assessments, medial tibial cartilage volume was reduced by a mean ± SD of 47.95 ± 65.72 mm^3/year ($P < 0.001$), which is equivalent to a mean ± SD of 2.63 ± 3.88% per year. The mean ± SD total change in cartilage volume over the duration of the study was 6.39 ± 9.41%, which was greater than the measurement error of 3.6%. No evidence of a ceiling effect on cartilage change was observed in participants with K/L grade–4 knees, as this subgroup experienced significant cartilage loss over the duration of the study ($P = 0.005$). Test–retest reliability estimates for the predicted MCF peak were as follows: ICC = 0.908 (95% confidence interval 0.833–0.950) and SEM = 102.48N, which is equivalent to 7.6% of the group mean. The predicted MCF peak was a significant predictor of annualized change in medial tibial cartilage volume over a period of 2.5 years (RMSE 52.60 mm^3/year; $R^2 = 0.35$, $\beta = -0.119$ [$P < 0.001$]) (Figure 2). An R^2 of 0.35 renders a Cohen's f^2 of 0.54, signifying a large effect of the MCF peak on cartilage loss (42). The multivariate model of cartilage volume change containing the 3 predictors of the MCF peak (gait speed, KAM peak, vKRF peak) produced an R^2 of 0.41 ($P < 0.001$); however, the goodness of fit was not different between the multivariate model and the single predictor (MCF peak) model ($P = 0.094$).

DISCUSSION

This study is the first to provide direct evidence that the MCF is positively related to loss of medial tibial cartilage volume in people with knee OA, supporting the notion that mechanical loading is a key contributor to structural disease progression. While direct measurement of knee contact forces in patients with instrumented tibial prostheses represents the gold standard for determining internal joint loads, such measurements are not possible in native knees. Accurate and reliable predictions of the MCF peak can be statistically modeled based on specific external biomechanical gait parameters obtained with motion analysis and inverse dynamics. The implication of a higher gait speed, KAM peak, and vKRF peak when increasing the compressive forces across the joint surfaces and ultimately contributing to cartilage

Table 3. Univariate linear regression models between each predictor of the MCF peak identified by LASSO regression (gait speed, KAM peak, vKRF peak) and the measured MCF peak in patients with instrumented knee implants*

	β	SE	*P*
Gait speed model†			
Intercept	894.57	174.58	<0.001
Gait speed, meters/second	643.98	216.17	0.003
KAM peak model‡			
Intercept	743.19	200.67	<0.001
KAM peak, Nm	22.43	6.13	<0.001
vKRF peak model§			
Intercept	74.82	548.80	0.892
vKRF, N	1.95	216.17	0.006

* LASSO = Least Absolute Shrinkage and Selection Operator (see Table 2 for other definitions).
† Gait speed model included fit parameters of $R^2 = 0.19$ ($P = 0.018$), RMSE = 275.86N, cross-validation RMSE = 330.97N.
‡ KAM peak model included fit parameters of $R^2 = 0.55$ ($P = 0.006$), RMSE = 206.60N, cross-validation RMSE = 268.33N.
§ vKRF peak model included fit parameters of $R^2 = 0.49$ ($P = 0.025$), RMSE = 218.29N, cross-validation RMSE = 311.14N.

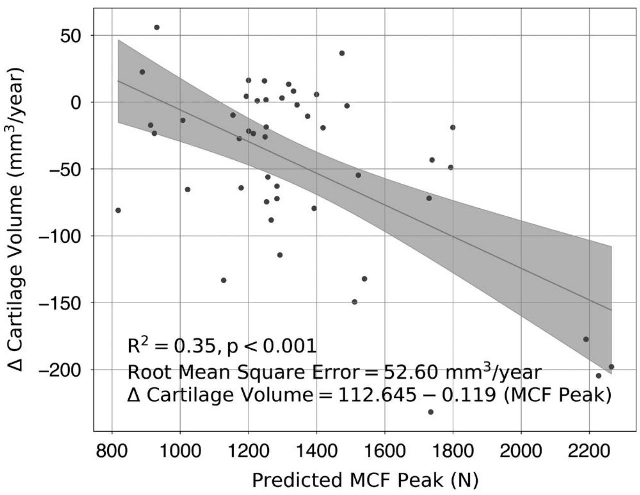

Figure 2. Predicted medial knee contact force (MCF) peak versus annualized change in medial tibial cartilage volume over 2.5 years in participants with knee osteoarthritis. The fitted model (diagonal line) and its 95% confidence band (shaded area) are overlaid on a scatterplot of individual observations (n = 47 subjects).

breakdown make these biomechanical parameters ideal targets for intervention. Strategies to reduce the magnitude of the MCF peak may curb the deleterious effects of knee biomechanics on the progression of cartilage loss in knee OA.

The predicted MCF peak explained 35% ($P < 0.001$) of the variance in 2.5-year changes in medial tibial cartilage volume. Prior studies have modeled the relationship between biomechanical outcomes (e.g., KAM) and medial tibial cartilage volume change; however, direct comparisons with the current model are not possible, because either the R^2 was not reported (6) or the model included multiple covariates (7). Instead, our multivariate analysis may provide insight into this. The multiple linear regression model of cartilage change that included the 3 predictors of the MCF peak (gait speed, KAM peak, vKRF peak) as individual variables yielded an R^2 of 0.41 ($P < 0.001$). It was expected that this multivariate model would yield a higher R^2 than that of the single predictor MCF peak model, because it is based on the same core predictors but has more degrees of freedom (3 versus 1). The greater degrees of freedom with the same inputs necessarily improve model flexibility and fit, thereby decreasing the RMSE and increasing the R^2. Nonetheless, the goodness of fit between the 2 models was not different. Therefore, the MCF peak model predicted cartilage loss in a way that was comparable to that of the best possible linear combination of the same core predictors, demonstrating good generalizability of the MCF peak prediction equation in the OA group. Ultimately, the fact that the measurement of interest (MCF peak) had the ability to predict the future outcome (cartilage loss) to which it is theorized to be related (8) provides predictive validity (43), a form of criterion validity, for the MCF peak equation.

In the current analysis, the MCF prediction model showed a positive relationship between all predictors and the MCF peak, explaining 81% of the variance. These findings, and those from the univariate regression analyses, corroborate findings from prior works in patients with instrumented knee implants. For instance, single-subject analyses that included different gait patterns (e.g., normal, medial thrust, walking poles) showed that the first KAM peak was independently associated with the first MCF peak ($R^2 = 0.57$) (18); the current study showed nearly the same strength of association ($R^2 = 0.55$). In a different analysis, the first vKRF peak predicted the first MCF peak ($R^2 = 0.38$) (10); a stronger association ($R^2 = 0.49$) between these variables was observed in the present study, which may be attributed to its larger sample size (n = 9 versus n = 1). The only known study examining the link between gait speed and the MCF was performed on baseline data from the same patients with instrumented knee implants included in the current analysis. In that study, gait speed explained 49% of the variance in the MCF peak during the early stance phase (17). The current study noted a weaker univariate association ($R^2 = 0.19$), likely because the MCF was analyzed as a discrete peak rather than continuous data (17). Ultimately, it seems intuitive that the MCF is best predicted by a combination of measures that reflect axial loading (vKRF), mediolateral force distribution (KAM), and a general mediator of knee loads (gait speed).

Joint contact forces have been predicted using 2 primary modeling methods: statistical and musculoskeletal. Statistical models predict measured contact forces from extracted biomechanical measurements, such as from patients with instrumented knee implants (9,10,17–19). For single-subject analyses of different gait patterns, the lowest reported RMSEs were 15% (10) and 32% body weight (18) for the first MCF peak. Alternatively, musculoskeletal models estimate the muscle forces necessary to generate the measured joint mechanics, resolving for physiologic joint loads (44–47). For example, using the common approach of minimizing the sum of muscle activations squared, an error of 40% body weight was obtained for the predicted first peak of the compressive joint reaction force (cJRF: compressive tibiofemoral load along the long axis of the tibia) during gait (47). By tuning muscle parameters of the same general model to match the peak cJRF*, lower errors were achieved (e.g., RMSE of 28% body weight over the entire gait cycle waveform) (44). More complex approaches have incorporated subject-specific musculoskeletal geometry, joint kinematics determined from fluoroscopy, and different electromyography-informed optimization methods to resolve muscle forces (45). These approaches, depending on the model and optimization used, yielded RMSEs from ~22% to 105% body weight (~150N to >700N) when predicting the MCF for the stance phase waveform. The current analysis yielded a cross-validation RMSE of 196.58N (22.0% body weight) and an RMSE of 132.88N (14.9% body weight) when tested on all participants used to fit the model. These errors are comparable to

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*The authors tuned a set of muscle synergies which penalized individual muscles or groups of muscles using weighting constants. All possible weighting constants were tested, and the combination that produced the smallest compressive force with an error less than 20% was selected.

those from the aforementioned “best” statistical models (10,17) and the most complex musculoskeletal models (45).

However, when comparing the ability of models to predict their respective outcomes, factors other than reported errors must be considered. First, predictions from most statistical models and all musculoskeletal models referenced above were fitted and then tested on data from a single participant, likely resulting in overfit models. Given the rarity of the data and complexity involved in modeling, the analysis of a single participant is not surprising and represents unique, important data to advance the field. Second, while muscle parameter tuning can reduce model errors, this approach is only possible with data from instrumented prostheses (44,45). Without muscle tuning, RMSEs were relatively high at ~100% body weight for predictions of the entire MCF stance phase waveform (45). Third, the resources and competencies required for scaling musculoskeletal models, as well as collecting and analyzing medical imaging, fluoroscopy, and electromyography data are immense. Finally, no known comparable studies have performed any form of model validation. The comparable errors obtained in the present analysis using only motion capture data, model validation using both cross-validation and predictions of cartilage loss in persons with knee OA, the excellent reliability of the MCF predictions in the knee OA group, and the considerably lower barrier to implementation make using such a statistical equation to predict the MCF appealing.

This study had limitations. Most patients with knee implants were men, whereas most knee OA patients were women. Furthermore, the equation to predict the MCF peak was derived using gait data from 9 patients with total knee replacements. Yet, the observed relationship between the predicted MCF peak and cartilage volume loss in persons with knee OA provides criterion validity of the generated equation. In addition, the MCF prediction equation was based on barefoot gait data only, thereby limiting its generalizability to shod conditions. Finally, the knee OA sample comprised mostly older, overweight women with radiographic disease. Thus, the extent to which the association between the predicted MCF peak and cartilage loss can be extended to other populations is uncertain.

In conclusion, results from this study provide robust evidence supporting the role of higher MCFs in cartilage volume loss in persons with clinical and radiographic knee OA. Using gold standard measurements from patients with instrumented tibial prostheses, reliable, accurate, and generalizable predictions of the MCF peak were statistically modeled based on key external biomechanical gait parameters obtained with motion analysis and inverse dynamics. This work acts as a stepping stone toward confirming the theoretical relationship between the MCF and cartilage loss; with technological and analytical advancements, future studies can improve upon our predictions. Nonetheless, these findings underscore the notion that accurate knee load predictions can be obtained without the need for far more resource-intensive approaches. Strategies to reduce the MCF magnitude may aid in curbing structural disease progression associated with mechanical loading in knee OA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Brisson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Brisson, Gatti, Maly.
Acquisition of data. Brisson, Damm, Maly.
Analysis and interpretation of data. Brisson, Gatti, Duda, Maly.

ADDITIONAL DISCLOSURES

Author Gatti is the Founder of NeuralSeg Ltd., a provider of medical image analyses that support research conducted within academic and industry settings. NeuralSeg was not involved in the analysis of magnetic resonance imaging data in the current study.

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