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ORIGINAL ARTICLE

# Three-Dimensional Biomechanical Gait Characteristics at Baseline Are Associated With Progression to Total Knee Arthroplasty

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*Objective.* To determine if baseline 3-dimensional (3-D) biomechanical gait patterns differed between those patients with moderate knee osteoarthritis (OA) who progressed to total knee arthroplasty (TKA) and those that did not, and whether these differences had predictive value.

*Methods.* Fifty-four patients with knee OA had ground reaction forces and segment motions collected during gait. 3-D hip, knee, and ankle angles and moments were calculated over the gait cycle. Amplitude and temporal waveform characteristics were determined using principal component analysis. At followup 5–8 years later, 26 patients reported undergoing TKA. Unpaired *t*-tests were performed on baseline demographic and waveform characteristics between TKA and no-TKA groups. Receiver operating curve analysis, stepwise discriminate analysis, and logistic regression analysis determined the combination of features that best classified TKA and no-TKA groups and their predictive ability.

*Results.* Baseline demographic, symptomatic, and radiographic variables were similar, but 7 gait variables differed (P < 0.05) between groups. A multivariate model including overall knee adduction moment magnitude, knee flexion/ extension moment difference, and stance-dorsiflexion moment had a 74% correct classification rate, with no overtraining based on cross-validation. A 1-unit increase in model score increased by 6-fold the odds of progression to TKA.

*Conclusion.* In addition to the link between higher overall knee adduction magnitude and future TKA, an outcome of clear clinical importance, novel findings include altered sagittal plane moment patterns indicative of reduced ability to unload the joint during midstance. This combination of dynamic biomechanical factors had a 6-fold increased odds of future TKA; adding baseline demographic and clinical factors did not improve the model.

#### **INTRODUCTION**

Knee osteoarthritis (OA) has no cure, with total knee arthroplasty (TKA) being the end-stage treatment for severe knee OA. TKA prevalence has increased exponentially worldwide, as has the number of younger TKA recipients (1,2). Increasing demands are exhausting orthopedic human resources, and dissatisfaction levels with TKA support the need to characterize modifiable factors that could alter progression to TKA. TKA surgical decision-making is based on both joint structural changes and patient complaints of pain and functional deficits (3). Biomechanical factors are thought to be catalysts for biochemical responses in the knee OA process, impacting both pain and structural changes (4,5). Different loading characteristics, including type, magnitude, direction, duration, and frequency, can produce different biologic responses on articular cartilage and other joint structures, and have differential effects on the production of inflammatory enzymes (6-8). Gait has been used as a model to study biomechanical factors in knee OA progression, with 4 longitudinal studies reporting higher knee adduction moment (KAM) magnitude features (9-12), higher lateral shear forces (12), and more recently

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## Significance & Innovations

- Frontal and sagittal plane baseline gait kinetics patterns were linked to future total knee arthroplasty (TKA).
- In addition to overall knee adduction moment magnitude, flexion moment patterns were predictive of progression to TKA.
- Conservative biomechanical interventions should consider biomechanical patterns in flexion and adduction, in addition to reducing adduction moment magnitudes.

higher knee flexion moment (KFM) peaks (10) at baseline associated with structural changes in the medial compartment at followup. Furthermore, a longitudinal study by Amin et al found 8–39% higher baseline KAM peaks for different tasks in older adults who developed pain at followup, with 13% higher KAM peaks during walking (13). Two additional longitudinal studies found that greater peak internal hip abduction moments and greater toe-out angles were associated with decreased risk of radiographic progression over 18 months (14,15).

Most mechanically based conservative interventions for those with medial compartment OA have aimed to reduce KAM magnitudes (14,16–18), a measure reflecting the ratio of medial to lateral joint load (19). Outcomes of these interventions have been consistent for improving symptoms (20), but efficacy has been equivocal with respect to KAM outcomes (18,21). Examining structural or symptomatic characteristics independently has been valuable in understanding OA progression, but these characteristics are not always well correlated (22). TKA offers a clinically important end point that has been used in biomarker studies to examine different rates of OA progression (23,24), but to our knowledge has not been used as an end point to examine the discriminatory value of gait metrics. Miyazaki et al (9) reported baseline peak KAM data on a small subset that progressed to TKA compared to those that did not undergo TKA, but no statistical analysis was conducted on these data.

This exploratory longitudinal study aimed to investigate the potential value of functional metrics in understanding progression of OA using TKA as a clinically relevant end point. The specific study objectives were 2-fold: 1) determine if 3-dimensional (3-D), dynamic lower-extremity kinematics and kinetics amplitude and temporal features during selfselected gait speeds differed between those with moderate medial compartment knee OA who progressed to TKA versus those that did not, and 2) determine if these features had predictive value for progression to TKA.

#### PATIENTS AND METHODS

**Patients.** Baseline gait analysis was conducted between 2003 and 2008 on 80 participants with moderate medial compartment knee OA, diagnosed using radiographic and clinical evidence (25), recruited from the clinical practice

of 1 high-volume orthopedic surgeon (WDS). Medial knee OA was based on radiographs (medial compartment joint space narrowing [JSN] grade equal to or greater than lateral compartment grade) (26). Moderate severity was based on clinical (i.e., not TKA candidate) and functional criteria (able to jog 5 meters, walk a city block, climb stairs reciprocally) (27). Institutional ethics approval was obtained.

At followup, 64 participants were able to be reached by telephone to inquire if 1) they had received TKA since baseline gait analysis, and 2) if they had not had TKA, whether they were willing to have a followup radiograph. Twenty-six participants reported they had TKA since baseline testing (mean ± SD time from baseline to TKA was  $4 \pm 3$  years). Twenty-eight participants reported they had not had TKA (no-TKA group), and agreed to a followup radiograph (mean  $\pm$  SD time from baseline to followup radiograph was  $8 \pm 2$  years). Nine participants did not have TKA, but declined to participate (5 too busy, 3 moved, and 1 had other health issues), and 1 received a high tibial osteotomy since baseline (Figure 1). Therefore, the telephone screening resulted in a sample size of 54 participants. The orthopedic surgeon was not aware of baseline gait data when surgical decisions were made.

**Procedure.** At baseline, demographic data, frontal plane alignment (from standing calibration trial), and self-reports of physical activity, pain, and function were recorded. Standard, weight-bearing anteroposterior and lateral radiographs were taken at baseline and followup (no-TKA group) or at baseline and pre-TKA (TKA group) to determine baseline structural severity and proportions of participants progressing structurally (increase in medial JSN grade) (9). All radiographs were graded by an orthopedic surgeon (WDS) using the Kellgren/Lawrence (K/L) (28) scale to grade overall severity, and the Scott Feature (26) scale to grade medial and lateral JSN. Baseline radiographs were graded twice with between-grading agreement 95%, 98%, and 93% for K/L, medial, and lateral JSN grades, with weighted kappa coefficients of 0.91, 0.99, and 0.91, respectively. Followup radiographs were graded once (after the followup radiograph or pre-TKA).

Frontal plane alignment was calculated using motioncapture data from a standing calibration trial as the angle formed between 1) the line connecting the anterior superior iliac spine (ASIS) and the knee joint center (midpoint between medial and lateral epicondyles) and 2) the line connecting the knee and ankle joint centers (midpoint between medial and lateral malleoli). In a subset of 35 participants, this alignment measure correlated well with alignment derived from standing full-leg radiographs (r = 0.75). Larger ASIS knee-ankle angles (i.e., closer to 180°) indicated more varus. An ASIS knee-ankle angle of approximately 175° corresponded to neutral.

Physical activity was assessed via self-report that asked participants how many times they engaged in physical activity "sufficiently prolonged and intense to cause sweating and a rapid heart rate." They were classified as active if they answered  $\geq$ 3 days/week. This self-report questionnaire was validated on 25 participants for capturing minutes spent in moderate physical activity based on



Figure 1. Baseline ensemble average knee adduction (A) and flexion (B) moments for the total knee arthroplasty (TKA; red line) and no-TKA (blue line) groups, with the mean waveforms from a previously published (30,35) age- and sex-matched asymptomatic (ASY) control group (black line; n = 54, 16 females, mean  $\pm$  SD age 57.2  $\pm$  8.7 years) shown for comparison purposes only. Positive values denote adduction and flexion moments. Mean waveforms for participants in the 5th (grey broken line) and 95th percentile (black broken line) of principal component (PC) 2 scores are also shown to illustrate that this feature captures the difference between phases of the gait cycle (more bimodal shape with higher first peak for knee adduction moment [KAM] [A] and a distinct biphasic pattern for knee flexion moment [KFM] [B]). The TKA group had a significantly higher overall KAM magnitude, less of a difference between the early and midstance KAM magnitudes (closer to the 5th percentile for KAMPC2 score), and decreased late-stance extension compared to early KFMs (closer to the 5th percentile for KFMPC2 score) at baseline compared to the no-TKA group (P < 0.05). HS = heel strike on study leg.

accelerometer data. Self-reported pain and function at baseline (and at followup in the no-TKA group) were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (29).

Biomechanical gait analysis. 3-D motion and ground reaction force data were collected at baseline using 2 Optotrak 3020 (Northern Digital) cameras and an AMTI force platform (Advanced Medical Technology), sampling at 100 Hz and 1,000 Hz, respectively. To monitor segment motion, 16 infrared-emitting diodes were placed over anatomic landmarks (triads on pelvis, thigh, shank, and foot segments, and individual markers on shoulder, greater trochanter, lateral epicondyle, and lateral malleolus) using a standardized protocol (30). Eight virtual points (right and left ASIS, medial epicondyle, fibular head, tibial tuberosity, medial malleolus, second metatarsal, and heel) were digitized during quiet standing. Participants wearing comfortable shoes performed at least 5 self-selected pace gait trials across a 5-meter walkway. Waveform characteristics extracted from knee biomechanical gait data using this protocol have been found to be reliable, particularly sagittal angles and moments and frontal plane moments (intraclass correlation coefficients 0.70–0.94) (31).

**Data analysis.** Motion and force data were digitally filtered (recursive fourth-order Butterworth) at 8 Hz and 60 Hz, respectively, and then used to calculate 3-D hip, knee, and ankle angles (32), and external moments using inverse dynamics (33,34); both were expressed in the joint coordinate system (32). Angles and moments were timenormalized to percent of gait cycle (heel-strike to heel-strike) using linear interpolation techniques (30,35). Moments of force were amplitude-normalized to body mass (30,35). For each variable an ensemble average profile was created for each participant by averaging the trial waveforms.

**Principal component analysis (PCA).** Biomechanical features were extracted using PCA, a technique that reduces large volumes of data into a smaller number of features (principal components [PCs]) capturing amplitude, difference

| Table 1. Participant demographics, spatiotemporal gait characteristics and self-reported symptoms forthe no-TKA and TKA groups at baseline* |                |                 |                     |              |      |  |  |  |  |
|---|----------------|-----------------|---------------------|--------------|------|--|--|--|--|
|   | No-TKA         | ТКА             | Mean<br>difference† | 95% CI       | Р    |  |  |  |  |
| Sex (female/male), no.  | 9/19           | 7/19            |                     |              |      |  |  |  |  |
| Age, years  | $57.9 \pm 7.3$ | $60.2\pm9.3$    | -2.4                | (-7.0, 2.2)  | 0.30 |  |  |  |  |
| Mass, kg  | $95.4\pm20.1$  | $92.9 \pm 13.7$ | 2.6                 | (-6.8, 11.9) | 0.59 |  |  |  |  |
| BMI, kg/m <sup>2</sup>  | $31.5\pm6.2$   | $30.9\pm4.7$    | 0.6                 | (-2.4, 3.6)  | 0.67 |  |  |  |  |
| K/L grade‡  | 3              | 3               |                     |              | 0.13 |  |  |  |  |
| Medial joint space‡   | 2              | 2               |                     |              | 0.05 |  |  |  |  |
| Alignment (ASIS-knee-ankle)   | $176.2\pm3.0$  | $174.8\pm3.3$   | 1.4                 | (-0.3, 3.2)  | 0.10 |  |  |  |  |
| Physical activity, active/sedentary, no.§   | 9/11           | 12/10           |                     |              |      |  |  |  |  |
| Spatiotemporal gait characteristics   |                |                 |                     |              |      |  |  |  |  |
| Velocity, meters/second   | $1.3\pm0.2$    | $1.2\pm0.2$     | 0.1                 | (-0.1, 0.2)  | 0.29 |  |  |  |  |
| % stance  | $63.7\pm1.8$   | $64.7\pm2.1$    | -1.0                | (-2.1, 0.1)  | 0.07 |  |  |  |  |
| % swing   | $36.3\pm1.8$   | $35.3\pm2.1$    | 1.0                 | (-0.1, 2.1)  | 0.07 |  |  |  |  |
| Stance time, seconds  | $0.7\pm0.1$    | $0.7\pm0.1$     | 0.0                 | (-0.1, 0.01) | 0.14 |  |  |  |  |
| WOMAC scores  |                |                 |                     |              |      |  |  |  |  |
| Pain (range 0–20)   | $6.3\pm4.6$    | $7.4\pm3.6$     | -1.1                | (-3.3, 1.2)  | 0.35 |  |  |  |  |
| Stiffness (range 0–8)   | $3.2\pm1.7$    | $4.0 \pm 1.4$   | -0.7                | (-1.6, 0.1)  | 0.09 |  |  |  |  |
| Function (range 0–68)   | $20.4\pm14.5$  | $24.4\pm11.0$   | -4.0                | (-11.1, 3.2) | 0.27 |  |  |  |  |
| Total (range 0–96)  | $30.0\pm20.3$  | $35.7\pm15.0$   | -5.8                | (-15.7, 4.2) | 0.25 |  |  |  |  |

Values are the mean  $\pm$  SD unless indicated otherwise. TKA = total knee arthroplasty; 95% CI = 95% confidence interval; BMI = body mass index; K/L = Kellgren/Lawrence; ASIS = anterior superior iliac spine; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

+ Mean differences are differences between the no-TKA and TKA groups.

<sup>‡</sup> Median values presented for ordinal radiographic data. *P* values based on Mann-Whitney U tests.

§ Baseline physical activity questionnaires were not completed for 13 participants.

operators, and phase shifts from the waveforms (36,37). PCA is advantageous when discrete variables are difficult to pick out, such as in OA populations (31), and has shown between-day reliability in the knee OA population (31). To minimize the potential for extracting erroneous features and "overfitting" (38), and to produce stable PCs reflective of key features in the waveform data, a data set was formed (n = 149) for each gait variable, consisting of ensemble average profiles for asymptomatic (n = 64) and moderate knee OA participants (n = 85). Using a standard procedure, a  $149 \times 101$  matrix (X) was formed for each angle and moment waveform separately, consisting of the ensemble average profile for each participant (36). Next, a covariance matrix (C) was calculated (30,36), and an eigenvector-eigenvalue decomposition of C resulted in a transform matrix (101  $\times$  101) of the PCs (eigenvectors). PCs accounting for a sum of at least 90% of the total variance of the large data set (with individual PCs not contributing <1% of variance to the total) were retained for statistical hypothesis testing (36). PC scores were calculated for each participant's original waveform. Waveforms for each participant for each variable were reconstructed, and reconstructed waveforms were visually compared to measured waveforms to ensure salient features were retained. Gait data processing and PCA were performed using custom Matlab (Mathworks) programs.

Statistical analysis. Assumptions of normality and equal variances were examined using Kolmogorov-Smirnov and Levene's tests for all continuous variables (alpha equals 0.05). Unpaired Student's *t*-tests determined between-group differences in demographics, alignment, walking speed, self-reported pain and function, and PC scores for each gait

variable (alpha equals 0.05). Mann-Whitney U tests were conducted on ordinal radiographic data (K/L and JSN scores). To quantify which combination of gait variables best discriminated between groups, variables that significantly differed between groups were entered into a stepwise, multivariate linear discriminate analysis. Group separation was quantified with correct classification rate for all original cases. Model overtraining was estimated with crossvalidation (iterations of all cases except 1) classification rates (39). Using the multivariate linear discriminant model, discriminant model scores were calculated for all participants. Scores were used as input for a receiver operating characteristic (ROC) curve analysis to determine the optimal model cut point that discriminated between the 2 groups (i.e., maximizing sensitivity and specificity). Discriminant model scores were entered into a logistic regression analysis to determine the predictive ability of the model. An adjusted model, including gait variables and baseline demographic and clinical characteristics (alignment, K/L score, JSN score, WOMAC total score, WOMAC pain score, age, sex, and mass), was also evaluated. Statistical analyses were completed using Minitab (version 16), except for the discriminate analysis, which was completed using SPSS Statistics (version 20.0.0; IBM), and the ROC curve analysis, which was performed using MedCalc software (version 12.5.0).

#### RESULTS

No significant (P > 0.05) baseline between-group differences were found for demographic variables, radiographic variables, alignment, activity levels, spatiotemporal gait characteristics, or WOMAC scores (Table 1). Ten participants in

| Table 2. Three-dimensional knee angle and moment PC scores for the no-TKA and TKA groups* |    |                              |   |                  |                 |                     |              |       |
|---|----|------------------------------|---|------------------|-----------------|---------------------|--------------|-------|
| Gait<br>variable  | PC | Explained<br>variance,<br>%† | Interpretation  | No-TKA           | ТКА             | Mean<br>difference‡ | 95% CI       | Р     |
| Flexion angle   | 1  | 62.8                         | Overall magnitude   | $204.9\pm41.9$   | $183.0\pm56.1$  | 21.8                | -5.4, 49.1   | 0.11  |
| 0   | 2  | 14.7                         | Phase shift   | $44.4\pm26.5$    | $51.7\pm28.1$   | -7.34               | -22.3, 7.6   | 0.33  |
|   | 3  | 10.4                         | Late stance, swing difference                                     | $160.5\pm22.3$   | $159.6\pm26.4$  | 0.9                 | -12.5, 14.3  | 0.89  |
|   | 4  | 6.5                          | Early stance, late stance<br>difference                           | $-10.8 \pm 18.8$ | $-19.7\pm18.4$  | 8.9                 | 1.2, 19.1    | 0.08  |
| Adduction angle   | 1  | 73.5                         | Overall magnitude   | $17.9\pm30.8$    | $4.1\pm29.7$    | 13.8                | -2.8, 30.3   | 0.10  |
|   | 2  | 9.9                          | Early, midstance, and late swing angle                            | $-1.5 \pm 11.7$  | $-1.9\pm10.7$   | 0.4                 | -5.7, 6.6    | 0.89  |
|   | 3  | 6.7                          | Mid, late stance angle  | $-6.8\pm9.3$     | $-11.0\pm10.0$  | 4.2                 | -1.1, 9.5    | 0.12  |
| Rotation angle  | 1  | 54.5                         | Overall magnitude   | $28.5\pm47.0$    | $6.8\pm49.2$    | 21.7                | -4.6, 48.0   | 0.10  |
|   | 2  | 22.2                         | Early stance/late swing,<br>late stance/early swing<br>difference | $2.3\pm32.5$     | $-3.2 \pm 31.0$ | 5.5                 | -11.9, 22.9  | 0.53  |
|   | 3  | 8.1                          | Late stance angle   | $8.0\pm17.3$     | $9.1\pm28.1$    | -1.1                | -14.1, 11.9  | 0.86  |
|   | 4  | 3.7                          | Stance, swing difference  | $26.3\pm15.6$    | $19.2\pm14.4$   | 7.1                 | -1.1, 15.3   | 0.09  |
| Flexion moment  | 1  | 44.1                         | Overall magnitude   | $0.36\pm0.91$    | $0.18 \pm 1.29$ | 0.18                | -0.43, 0.80  | 0.55  |
|   | 2  | 37.9                         | Flexion/extension moment<br>difference§                           | $1.74\pm1.01$    | $1.18\pm0.86$   | 0.56                | 0.04, 1.07   | 0.03  |
|   | 3  | 7.1                          | Phase shift   | $-0.43\pm0.29$   | $-0.39\pm0.30$  | -0.04               | -0.20, 0.12  | 0.65  |
|   | 4  | 2.4                          | Heel strike extension moment                                      | $0.39\pm0.25$    | $0.32\pm0.19$   | 0.07                | -0.05, 0.19  | 0.27  |
| Adduction moment  | 1  | 63.7                         | Overall magnitude§  | $2.38\pm0.70$    | $3.21\pm1.00$   | -0.83               | -1.31, -0.36 | 0.001 |
|   | 2  | 15.9                         | Early, midstance difference§                                      | $0.44\pm0.45$    | $0.14\pm0.45$   | 0.30                | 0.05,  0.54  | 0.03  |
|   | 3  | 7.0                          | Mid, late stance difference                                       | $-0.34\pm0.26$   | $-0.36\pm0.27$  | 0.03                | -0.12, 0.17  | 0.73  |
|   | 4  | 3.7                          | Swing magnitude   | $-0.10\pm0.26$   | $-0.10\pm0.25$  | -0.01               | -0.14, 0.13  | 0.94  |
| Rotation moment   | 1  | 52.4                         | External, internal rotation<br>moment difference                  | $0.62\pm0.38$    | $0.59\pm0.27$   | -0.03               | -0.09, 0.02  | 0.73  |
|   | 2  | 34.2                         | Midstance moment  | $0.43\pm0.32$    | $0.51\pm0.41$   | 0.03                | -0.15, 0.21  | 0.42  |
|   | 3  | 5.5                          | Internal rotation moment phase shift                              | 0.07±0.10        | 0.10±0.10       | -0.08               | -0.28, 0.12  | 0.26  |

\* Values are the mean  $\pm$  SD unless indicated otherwise. PC = principal component; TKA = total knee arthroplasty; 95% CI = 95% confidence interval.

+ Explained variance refers to how much variability in the larger data set (n = 149) was accounted for by a particular PC.

<sup>‡</sup> Mean differences are differences between the no-TKA and TKA groups.

 $\$  Indicates a significant between-group difference (P < 0.05).

the TKA group and 14 in the no-TKA group, representing 65% and 56% of those not at the JSN ceiling score of 3, respectively, progressed radiographically from baseline. Twenty of 28 participants (71%) in the no-TKA group at followup (approximately 8 years) self-reported improvement or no change in WOMAC score (mean  $\pm$  SD total WOMAC score 18.2  $\pm$  16.4 at followup).

Interpretations for extracted knee angle and moment PCs and statistical results are in Table 2. Significant betweengroup differences (P < 0.05) showed the TKA group had higher KAM overall shape and magnitude (KAMPC1), smaller differences between early and midstance KAM magnitudes (KAMPC2), and smaller late-stance knee extension compared to early stance knee flexion moments (KFMPC2) than the no-TKA group at baseline. These differences corresponded to percent differences of 32–68% for PC scores. Mean KAM and KFM waveforms are in Figure 1, as are mean waveforms for the 5th and 95th percentile PC2 scores. For comparison purposes only, previously published mean waveforms from an age- and sex-matched asymptomatic control group (30,35) are shown. The TKA group's mean waveforms were closer in shape to the 5th percentile waveforms, whereas the no-TKA group was closer to the 95th percentile waveforms for both KAM and KFMPC2.

Interpretations for extracted hip and ankle angle and moment PCs and statistical results are in Tables 3 (hip) and 4 (ankle). Significant between-group differences (P < 0.05) in hip and ankle biomechanical measures (Figure 2) showed the TKA group had smaller 1) differences between stance and swing hip adduction angles (PC2), 2) differences between stance and swing ankle flexion angles (PC3), 3) early to midstance ankle dorsiflexion moments (AFMPC4), and 4) differences between early and late-stance ankle rotation moments (PC2) than the no-TKA group at baseline. As with the knee, the TKA group was more similar to the 5th percentile waveforms.

Since only gait variables significantly differed between groups, these were entered into the stepwise multivariate linear discrimination analysis. KAMPC1 emerged as the dominant variable in the model, with a coefficient of 0.85, followed by KFMPC2 (coefficient of -0.53) and AFMPC4 (coefficient of -0.48). Correct classification rate was 74.1% (7 participants in the TKA group and 7 participants in the no-TKA group misclassified), with a cross-validated rate of

| Table 3. Three-dimensional hip angle and moment PC scores for the no-TKA and TKA groups* |    |                              |   |                  |                  |                     |               |      |
|--|----|------------------------------|---|------------------|------------------|---------------------|---------------|------|
| Gait<br>variable   | РС | Explained<br>variance,<br>%† | Interpretation  | No-TKA           | ТКА              | Mean<br>difference‡ | 95% CI        | Р    |
| Flexion angle  | 1  | 70.3                         | Overall magnitude   | $131.1\pm68.7$   | $155.8\pm47.0$   | -24.7               | -56.7, 7.3    | 0.13 |
| 0  | 2  | 15.0                         | Late stance extension   | $78.3\pm31.9$    | $72.7 \pm 24.6$  | 5.6                 | -9.9, 21.1    | 0.47 |
|  | 3  | 7.4                          | Phase shift   | $7.1 \pm 15.2$   | $8.5 \pm 17.2$   | -1.3                | -10.3, 7.6    | 0.76 |
| Adduction angle  | 1  | 77.7                         | Overall magnitude   | $23.5\pm29.6$    | $21.9 \pm 24.0$  | 1.6                 | -13.1, 16.2   | 0.83 |
| 0  | 2  | 10.3                         | Mid stance to swing<br>difference§                                    | $38.3 \pm 12.4$  | $30.7 \pm 14.0$  | 7.5                 | 0.3, 14.8     | 0.04 |
|  | 3  | 6.2                          | Early stance to swing<br>difference                                   | $9.9\pm9.0$      | $7.8\pm10.8$     | 2.1                 | -3.4, 7.5     | 0.44 |
| Rotation angle   | 1  | 62.4                         | Late stance to early<br>stance/late swing<br>difference               | $-11.3 \pm 58.7$ | $-43.0 \pm 55.4$ | 31.6                | 0.5, 62.8     | 0.05 |
|  | 2  | 18.2                         | Late stance/early swing<br>magnitude                                  | $44.8\pm26.9$    | $42.1\pm30.8$    | 2.8                 | -13.1, 18.6   | 0.73 |
|  | 3  | 6.0                          | Mid stance to midswing difference                                     | $1.9\pm15.2$     | $4.7\pm21.1$     | -2.8                | -13.0, 7.4    | 0.58 |
|  | 4  | 4.4                          | Early to late swing<br>difference                                     | $-1.7\pm13.6$    | $4.5\pm19.1$     | -6.2                | -15.4, 2.9    | 0.18 |
| Flexion moment   | 1  | 60.3                         | Overall magnitude   | $1.79 \pm 1.13$  | $1.91 \pm 1.91$  | -0.12               | -0.99, 0.75   | 0.78 |
|  | 2  | 12.0                         | Early stance flexion<br>moment  | $-1.63\pm0.67$   | $-1.65\pm0.49$   | 0.02                | -0.30, 0.34   | 0.90 |
|  | 3  | 7.7                          | Late stance to late swing difference                                  | $-0.34\pm0.58$   | $-0.01\pm0.58$   | -0.32               | -0.64, -0.01  | 0.05 |
|  | 4  | 5.3                          | Swing magnitude   | $1.22\pm0.46$    | $1.26\pm0.41$    | -0.04               | -0.28, 0.19   | 0.71 |
| Adduction<br>moment  | 1  | 57.5                         | Overall magnitude   | $5.45\pm1.77$    | $4.76\pm1.62$    | 0.69                | -0.24, 1.62   | 0.14 |
|  | 2  | 22.2                         | Phase shift   | $1.36 \pm 1.05$  | $0.94\pm0.77$    | 0.43                | -0.08, 0.93   | 0.10 |
|  | 3  | 5.4                          | Midstance magnitude<br>relative to early and late<br>stance magnitude | $0.61\pm0.46$    | $0.86 \pm 0.56$  | -0.25               | -0.53, 0.03   | 0.08 |
|  | 4  | 3.6                          | Early swing magnitude   | $-0.59\pm0.47$   | $-0.65\pm0.32$   | 0.06                | -0.16, 0.28   | 0.59 |
| Rotation moment  | 1  | 57.9                         | Overall magnitude   | $-0.40\pm0.54$   | $-0.47\pm0.80$   | 0.07                | -0.31, 0.45   | 0.71 |
|  | 2  | 21.2                         | Midstance to late stance difference                                   | $0.65\pm0.35$    | $0.46\pm0.38$    | 0.19                | -0.01, 0.39   | 0.06 |
|  | 3  | 5.6                          | Phase shift   | $0.11\pm0.19$    | $0.12\pm0.21$    | -0.01               | -0.12, 0.10   | 0.88 |
|  | 4  | 4.0                          | Early swing magnitude   | $-0.33\pm0.16$   | $-0.24\pm0.15$   | -0.09               | -0.17, -0.001 | 0.05 |

\* Values are the mean  $\pm$  SD unless indicated otherwise. PC = principal component; TKA = total knee arthroplasty; 95% CI = 95% confidence interval.

+ Explained variance refers to how much variability in the larger data set (n = 149) was accounted for by a particular PC.

+ Mean differences are differences between the no-TKA and TKA groups.

 $\$  Indicates a significant between-group difference (P < 0.05).

74.1%  $\pm$  0.8%. Based on ROC curve analysis, a criterion value of -0.24 for this model discriminated between groups with a sensitivity of 84.6% and specificity of 71.4%. Logistic regression analysis showed that a 1-unit increase in discriminant model score increased the odds of being in the TKA group by 5.7 times. The gait model was adjusted by including alignment, K/L score, JSN score, WOMAC total score, WOMAC pain score, age, sex, and mass. The same 3 gait variables (and no other demographic or clinical variables) emerged as significant discriminators.

### DISCUSSION

No clinical, demographic, or functional variables differed at baseline; only biomechanical gait patterns differed between those who progressed to TKA versus those who did not.

Dynamic gait variables had predictive value, but other risk factors (static alignment, structural severity, pain, function, and demographic factors), did not change the multivariate prediction model. This finding is consistent with previous adjusted univariate gait models for structural progression (9-11,14). Miyazaki et al did not perform statistical comparisons on a small subset of participants who went on to TKA within 6 years, but their TKA group tended to have higher KAM peaks, and were also older, had more varus alignment, more JSN, and more pain than their no-TKA group at baseline (9). Higher structural disease and pain severity values at baseline potentially explain their TKA outcome. In contrast, severity differences in clinical variables at baseline do not explain the present findings. Two factors that influence need for TKA, structural and symptom severity (3), were similar at baseline for both groups. Radiographic (K/L and JSN) scores were similar between the 2 groups, and self-report of pain

| Table 4.      Three-dimensional ankle angle and moment PC scores for the no-TKA and TKA groups* |    |                              |   |                 |                 |                     |             |      |
|---|----|------------------------------|---|-----------------|-----------------|---------------------|-------------|------|
| Gait<br>variable  | РС | Explained<br>variance,<br>%† | Interpretation                                | No-TKA          | ТКА             | Mean<br>difference‡ | 95% CI      | Р    |
| Flexion angle   | 1  | 55.5                         | Overall magnitude                             | $15.7\pm36.2$   | $27.5\pm50.8$   | -11.8               | -36.2, 12.6 | 0.33 |
|   | 2  | 23.3                         | Phase shift                                   | $0.0\pm22.1$    | $-9.7\pm17.8$   | 9.7                 | -1.2, 20.6  | 0.08 |
|   | 3  | 7.7                          | Stance to swing difference§                   | $43.9 \pm 13.0$ | $35.1 \pm 14.4$ | 8.9                 | 1.4, 16.4   | 0.02 |
|   | 4  | 5.4                          | Early swing magnitude                         | $-23.6\pm13.6$  | $-29.5\pm14.3$  | 6.0                 | -1.7, 13.6  | 0.12 |
| Adduction angle   | 1  | 58.2                         | Overall magnitude                             | $-15.7\pm32.5$  | $-26.8\pm36.1$  | 11.0                | -7.8, 29.8  | 0.25 |
|   | 2  | 17.4                         | Midstance to early and late stance difference | $9.3\pm16.8$    | $13.6\pm13.2$   | -4.3                | -12.6, 3.9  | 0.30 |
|   | 3  | 7.3                          | Mid stance magnitude                          | $17.1 \pm 7.2$  | $21.0\pm11.7$   | -3.9                | -9.3, 1.5   | 0.15 |
|   | 4  | 4.4                          | Late swing magnitude                          | $-8.0\pm7.3$    | $-2.7\pm12.6$   | -5.2                | -11.0, 0.5  | 0.07 |
| Rotation angle  | 1  | 66.6                         | Stance to swing difference                    | $16.5\pm28.1$   | $17.1\pm29.1$   | -0.6                | -16.2, 15.1 | 0.94 |
|   | 2  | 12.5                         | Mid stance magnitude                          | $15.7\pm17.1$   | $20.3\pm11.8$   | -4.6                | -12.6, 3.4  | 0.25 |
|   | 3  | 8.5                          | Early to late stance difference               | $26.8\pm9.2$    | $27.7 \pm 14.2$ | -1.0                | -7.6, 5.6   | 0.76 |
|   | 4  | 4.5                          | Late swing/early stance magnitude             | $15.1\pm6.9$    | $13.9\pm7.9$    | 1.2                 | -2.9, 5.2   | 0.57 |
| Flexion moment  | 1  | 48.2                         | Dorsiflexion magnitude                        | $3.44\pm0.89$   | $3.24\pm0.72$   | 0.20                | -0.24, 0.64 | 0.36 |
|   | 2  | 24.1                         | Phase shift                                   | $-3.05\pm0.53$  | $-2.99\pm0.45$  | -0.06               | -0.33, 0.21 | 0.64 |
|   | 3  | 16.7                         | Mid to late stance difference                 | $2.02\pm0.42$   | $2.01\pm0.52$   | -0.08               | -0.34, 0.18 | 0.55 |
|   | 4  | 5.8                          | Early-mid stance dorsiflexion<br>magnitude§   | $-0.75\pm0.28$  | $-0.93\pm0.19$  | 0.17                | 0.04, 0.30  | 0.01 |
| Adduction<br>moment   | 1  | 93.9                         | Overall magnitude                             | $1.21\pm0.58$   | $1.20\pm0.67$   | 0.01                | -0.33, 0.35 | 0.95 |
| Rotation<br>moment  | 1  | 75.3                         | Mid-late stance external rotation magnitude   | $0.10\pm0.39$   | $0.03\pm0.41$   | 0.10                | 0.01, 0.20  | 0.58 |
|   | 2  | 14.5                         | Early to late stance difference§              | $0.23\pm0.17$   | $0.13\pm0.18$   | 0.10                | 0.01, 0.20  | 0.03 |
|   | 3  | 4.6                          | Early stance external rotation magnitude      | $0.05\pm0.10$   | $0.04\pm0.08$   | 0.02                | -0.03, 0.06 | 0.50 |

\* Values are the mean  $\pm$  SD unless indicated otherwise. PC = principal component; TKA = total knee arthroplasty; 95% CI = 95% confidence interval.

+ Explained variance refers to how much variability in the larger data set (n = 149) was accounted for by a particular PC.

*‡* Mean differences are differences between the no-TKA and TKA groups.

§ Indicates a significant between-group difference (P < 0.05).

and function differences between groups were less than the minimum clinically important difference (40). For those without a grade 3 JSN ceiling value at baseline, comparable percentages in both groups progressed structurally; however, an interesting finding was that no one in the no-TKA group was on a waiting list for TKA at followup. Although no conclusions can be drawn with respect to symptom or functional changes in severity influencing TKA decision-making given the lack of pre-TKA WOMAC scores, the majority of the no-TKA group self-reported that symptoms did not worsen over the 8-year followup. Therefore, evidence supports that clinical decision-making was not based solely on structural severity.

Physical activity is thought to influence joint structures and pain in knee OA related to an increased frequency of loading (41,42), but self-reports of physical activity were similar between groups. Only 2 longitudinal studies assessing structural progression included physical activity. One did not complete an analysis on findings (43). The other did not find that self-reported physical activity changed the prediction model (14). The latter is consistent with our findings; however, future work, including quantitative physical activity counts or physical activity categories (sedentary to vigorous), is needed to draw stronger conclusions regarding the effect of loading frequency on progression.

Seven biomechanical gait features differed between groups at baseline, suggesting that functional metrics have potential value in predicting TKA outcome. Higher overall KAM magnitude (KAMPC1) in the TKA group supports increased ratio of medial loading relative to body mass throughout the gait cycle, as illustrated in Figure 1A. This is consistent with previous studies linking higher KAM impulse and average stance magnitude (11,12) and in part peak KAM (9,10) to structural progression. More interesting were KAM and KFM dynamic pattern differences (PC2 scores) between groups, capturing waveform shape differences. These include a smaller difference between early and midstance KAM magnitudes (KAMPC2) and smaller knee flexion/extension moment range (KFMPC2) found in the TKA group. These patterns have been previously associated with knee OA severity (35), but not progression. The KAMPC2 finding indicates less ability to unload or shift load between medial and lateral compartments during midstance in the TKA group at baseline. The inability to shift the load during midstance is indicative of more sustained loading pattern in the TKA group, as illustrated by the shape of the 5th percentile waveform (Figure 1A). Similarly, our finding that the knee flexion/extension moment range (KFMPC2) was lower in the TKA group is consistent with a "stiff knee" gait. This feature captures



Figure 2. Baseline ensemble average hip adduction angles (A), ankle rotation moments (B), ankle flexion angles (C), and ankle flexion moments (D) for the total knee arthroplasty (TKA) (red line) and no-TKA (blue line) groups, with the mean waveforms from a previously published (30,35) asymptomatic (ASY) control group as shown for comparison purposes only (black line). Positive values denote adduction, internal rotation, and plantarflexion. Mean waveforms for participants in the 5th (grey broken line) and 95th percentile (black broken line) of principal component (PC) scores are also shown. The TKA group had less of a difference between the stance and swing hip adduction angles, less of a difference between the early stance ankle internal rotation and late-stance external rotation moment, less dorsiflexion during stance, and decreased dorsiflexion moments during early stance at baseline than the no-TKA group (P < 0.05), as indicated by their waveform shapes being closer to the 5th percentile waveforms for each variable. HS = heel strike on study leg. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.22564/ abstract.

the biphasic flexion/extension pattern as illustrated by the 95th percentile waveform (Figure 1B) typical of asymptomatic gait (35). The TKA group's mean and 5th percentile waveforms illustrate a reduction in the biphasic pattern (Figure 1B) typical of those with more severe OA (35). A recent study showed that higher peak KFM was associated with structural progression in those with OA (10), and these results highlight a potential difference between structural progression and the TKA end point. Of note is that the no-TKA group did have 14 individuals who progressed structurally, which could explain their higher overall peak KFM. Furthermore, the TKA KFMPC1 scores in Table 2 have large variability, which can impact the overall magnitude, as evident in the 5th percentile KFM waveform where the peak was similar to the mean no-TKA group waveform. Therefore, the feature related to progression to TKA was a smaller difference between peak KFM and knee extension moment, suggesting sustained loading but can include high or low KFM peaks. Low early KFM peaks can reflect decreased quadriceps strength, sometimes referred to as quadriceps avoidance gait (44); however, when agonist and antagonist co-activation is present, as is the case with knee OA during walking (27), a direct relationship with quadriceps strength from inverse dynamics should be made cautiously. Furthermore, the 5th percentile waveform indicates that a flexion moment is maintained throughout stance in some participants and likely would not relate to low quadriceps strength. A relatively large study of OA patients (n = 265) showed no association between quadriceps strength and tibiofemoral joint cartilage loss, although quadriceps strength deficits were associated with increased pain (45). The literature and the present findings suggest a more complicated relationship between muscle strength and gait variables, and the role that quadriceps muscle strength plays in progression to TKA requires further exploration.

In contrast to structural progression (14), the only hip gait variable that differed between groups was the smaller difference in frontal plane angle between stance and swing for the TKA group. This kinematic variable did not emerge as a significant discriminator in the multivariate discriminate analysis, and how it would impact knee joint loading was not evident. However, the lower stance dorsiflexion angle and moment provides additional evidence of "stiff gait" in the TKA group, with the latter emerging as a significant discriminator in the multivariate model. While it is recognized that the entire lower extremity kinetic chain can impact knee joint loading, the 2 main characteristics in the prediction model were related to knee joint moments, i.e., KAM overall magnitude and a decreased ability to unload the joint. This combination of features supports a higher and potentially more sustained joint loading pattern as a mechanism for progression to TKA, which is consistent with the diverse biologic responses of cartilage and other joint structures to different loading characteristics (6-8).

Thus far, biomechanically based conservative intervention studies have targeted frontal plane mechanics, particularly the peak KAM. The present study provides support for overall KAM magnitude, as well as evidence that other kinetic patterns might provide additional targets for slowing progression to TKA. This combination of variables (KAMPC1, KFMPC2, AFMPC4) showed a 6-times higher odds ratio of progression to TKA and a 74% correct classification rate that was robust based on cross validation. A limitation is the small sample, which could overestimate the correct classification and prediction model. To address this limitation, we tested whether the prediction model was overtrained using statistical cross validation. However, a rigorous validation is needed on an independent test set to assess the predictive value of this 3-factor biomechanical model. While the potential exists for a type I error given the multiple *t*-tests, the multivariate discriminant analysis supports a combined effect of higher overall KAM magnitude plus an altered KFM pattern consistent with an inability to unload the joint.

Study limitations could also explain the 26% error in correct classification. Considerable clinical decision-making is involved when selecting TKA candidates. Although this may be more homogeneous in government-funded versus private-funded health care systems, there is still potential for bias. The baseline surgeon performed 17 of 26 surgeries (65%) with 5 of the 7 (71%) in the TKA group incorrectly classified as operated on by the baseline surgeon. While no systematic effect of surgeon on incorrect classifications is apparent, these numbers are small and surgeon variability in clinical decision-making could impact findings. Another factor in TKA decision-making is patient willingness (46), which was not measured. Presumably, some participants in the no-TKA group were unwilling to have surgery. This could underestimate the biomechanical differences contributing to the 26% misclassification error. Finally, results must be interpreted within the limitations of inverse dynamics. Muscle forces are significant contributors to joint contact loading (47), and muscle force modeling could potentially provide better estimates of joint loads since muscle activation patterns are altered for those with knee OA (27). Muscle models, however, are also based on assumptions, with few including patient-specific data; therefore, results from these models, as well as from inverse dynamics, need to be interpreted within their limitations.

Despite these limitations, a 74% classification rate provides a solid foundation for the predictive potential of this 3-factor biomechanical model for TKA progression. A point worth noting is that knee kinetic differences in the TKA group were consistent with increased symptomatic and structural severity data reported from cross-sectional studies (35). Therefore, it could be interpreted that knee biomechanics are a more sensitive metric to assess OA severity, potentially detecting progressive changes before they appear symptomatically or radiographically. The ultimate goal is to objectively assess risk and identify objective metrics that aid in the development and evaluation of conservative interventions aimed at reducing progression to TKA.

In conclusion, lower extremity dynamic joint biomechanical features during gait differed at baseline between individuals with moderate knee OA who progressed to TKA versus those that did not, despite similar demographic, physical activity, radiographic, and symptomatic factors. In addition to the link between greater overall KAM magnitude and future TKA, an outcome of clear clinical importance, novel findings included a KFM and dorsiflexion moment pattern indicative of stiff gait. Collectively these features illustrated that gait metrics capturing higher and more sustained loading have potential value in predicting progression to TKA.

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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 submitted for publication. Dr. Hubley-Kozey 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.

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