DALHOUSIE UNIVERSITY

RELATIONSHIP BETWEEN KNEE ADDUCTION MOMENT PATTERNS EXTRACTED USING PRINCIPAL COMPONENT ANALYSIS AND DISCRETE MEASURES WITH DIFFERENT AMPLITUDE NORMALIZATIONS: IMPLICATIONS FOR KNEE OSTEOARTHRITIS PROGRESSION STUDIES

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Word count (abstract): 249
Word count (main text): 3654

Abstract

Background

Knee adduction moment features including peaks and impulses are commonly reported in knee osteoarthritis gait studies. **However, these discrete features do not necessarily capture loading patterns**. Principal component analysis extracts dynamic **patterns**, but can be difficult to interpret. **This methodological** study determined relationships between **external knee adduction moment** discrete measures and features extracted using **principal component analysis**, and examined **whether** amplitude-normalization methods **influenced differences in those with knee osteoarthritis who progressed to surgery versus those that did not.**

Methods

54 knee osteoarthritis patients had three-dimensional motion and ground reaction forces recorded during walking. K**nee adduction moments** were calculated using inverse dynamics and non-normalized and amplitude-normalized waveforms using two common methods were calculated. Patterns were extracted using **principal component analysis**. **Knee adduction moment** peak and impulse were calculated. Correlation coefficients were determined between two **knee adduction moment** patterns extracted and peak and impulse. T-tests evaluated between-group differences.

Findings

An overall magnitude pattern was correlated with peak ($r=0.88$-0.90, $p<0.05$) and impulse ($r=0.93$, $p<0.05$). **A** pattern capturing a difference between early and mid/late stance **knee adduction moment** significantly correlated with peak ($r=0.27$-0.40, $p<0.05$), but explained

minimal variance. **Between-group peak differences only were affected by amplitude-normalization** method.

Interpretation

Knee adduction moment overall magnitude pattern, peak, and impulse **were all correlated as they** capture a magnitude component. **The difference pattern** (ability to unload the joint during mid-stance) **captures a unique aspect of the knee adduction waveform from common discrete measures, as supported by the low correlations with knee adduction moment** impulse and peak.

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Key Words: Knee Osteoarthritis; Biomechanics; Gait; Knee Adduction Moment; Principal Component Analysis

1 Introduction

Evidence is emerging that implicates biomechanical factors in knee osteoarthritis (OA) progression[1-4], **a degenerative disease resulting in pain, stiffness, weakness, and joint instability.** The biomechanical literature has focused on the **external** knee adduction moment (KAM) because knee OA is more common in the medial compartment than the lateral compartment[5,6], the KAM provides an indication of the ratio of medial to lateral compartment loading[7], and both the KAM peak and impulse have been related to knee OA structural progression, including radiographic and cartilage volume changes[1,2,4]. Thus conservative interventions targeting the knee joint biomechanical environment have aimed to reduce **external** KAM peaks[8-17], and more recently the **external** KAM impulse[18] during walking.

Biomechanical intervention studies have been shown to consistently decrease symptoms[19], but are equivocal with respect to reducing KAM magnitude features[8,17,20-22] suggesting a disconnect between KAM peak/KAM impulse and altered symptoms. **In a** recent study **we** showed that **higher** overall KAM magnitude feature **plus** the inability to unload the knee during mid/late-stance based on principal component analysis **(PCA) of KAM and knee flexion moment waveforms** were associated with progression to total knee arthroplasty (TKA) surgery, a clinically important outcome of progression based on both symptoms and structural changes of knee OA[23]. The unloading features were captured as differences between the early and mid/late stance magnitudes **from the** PCA of the entire **external moment** waveform**s**, **indicating an altered pattern of loading which suggest a stiff knee gait[23]. A strength of** PCA **is that it** considers the entire waveform, extracting the main amplitude and temporal patterns in the data[24],

including magnitude, phase shifts, and difference operators between phases[25]. **PCA performs an eigen-decomposition of a covariance matrix of waveform data, so the patterns extracted are orthogonal and uncorrelated, thus capturing unique features in the waveform data**. PCA-derived features (PCs) of **external moment** waveforms, including overall magnitude and unloading features, have been related to OA presence[26,27], severity[26], progression to TKA[23] and treatment outcomes[28,29] **with post-TKA external moment patterns moving toward more asymptomatic patterns[30]**. However, since PCA can be difficult to interpret clinically, determining **if** discrete waveform features typically extracted from **external moment** waveforms (i.e. peak and impulse) **were related to PCA** features, or **whether** PCA provides additional information **that is important to understanding the OA processes not captured by discrete variables, would help clarify its role**. **This paper uses the KAM for illustration purposes, given its prevalence in knee OA gait studies and the finding that both discrete measures and PCs derived from the KAM have been shown to be highly reliable[31,32].**

A second issue related to the OA gait literature making between study comparisons difficult is that two main amplitude-normalization procedures have been used in these studies. The first method amplitude-normalizes the **external** KAM to body weight times height to control for differences in body size between participants[1,2]. The rationale for this normalization is that taller, heavier people have heavier, longer, and wider body segments, resulting in greater segment moments of inertia and moment arm lengths[33], **but sometimes units reported are not consistent between studies[2,34]**. Other studies[26,27,29,30] have normalized waveforms to body mass to provide an indication of the KAM magnitude **relative to body mass alone.** The rationale for amplitude-normalizing to mass only is that there is less variability in height than in mass[35].

Normalization reduces the variability among participants, allowing for comparisons of deviations from a standard, however if the overall goal is to quantify the absolute load the knee is experiencing, amplitude-normalizing removes some of that signal and non-normalized moments have also been reported[36].

The overall goal of this **methodological s**tudy was to investigate the influence of two factors that **potentially** impact interpretation of results in the study of frontal plane knee joint moments and knee OA progression. The two factors were the type of variable extracted from **external** KAM waveforms (i.e. discrete or patterns) and **the** amplitude-normalization approach. Three **study** aims were: i) to determine associations between **external** KAM discrete measures and **external** KAM patterns extracted using PCA, ii) to examine the effects of different methods of KAM amplitude-normalization on the **correlation** results and iii) to determine whether the variables used or normalization technique altered findings related to baseline **between-group** differences for those with moderate medial knee OA who progressed to TKA and those that did not. **For aim 3, results for PCA features normalized to body mass have been published[23], so the new between-group findings are for the discrete variable results and the different normalization approaches.**

2 Methods

2.1 Participants

Data for this study were collected as part of a longitudinal study on OA progression on 54 participants with moderate medial compartment knee OA that underwent baseline gait analysis in the Dynamics of Human Motion laboratory at Dalhousie University between 2003-2008[23]. At baseline, participants were diagnosed (WDS) using radiographic and clinical evidence, as defined by the American College of Rheumatology[37]. All patients were not candidates for TKA at baseline testing and met the **moderate classification** functional criteria of being able to jog 5 metres, walk a city block, and climb stairs reciprocally[38]. During follow-up telephone interviews **at least five years** after baseline gait analysis, 26 participants reported receiving TKA since baseline (TKA group, mean time from baseline to TKA was 4 (±3) years). Twenty-eight participants reported they had not had TKA (no-TKA group). Institutional ethics approval was obtained for this study.

Three-dimensional lower limb biomechanics analysed using PCA **and normalized to body mass** have previously been presented for the TKA and no-TKA groups[23], **but the new results are** related to the methodological issues associated with the **external** KAM waveforms to address the specific study objectives.

2.2 Procedure

Demographic data (age, sex, mass, height) and self-reports of pain and function (Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC[39]) were collected, and standard, weight-bearing anterior-posterior and lateral radiographs were taken to determine structural severity at baseline. One high-volume orthopaedic surgeon **(WDS)** graded the

radiographs using the Kellgren and Lawrence (KL) grading scale[40] **to determine overall severity and the Scott Feature scale[41] to grade medial and lateral joint space narrowing.**

2.3 Gait Analysis

A standard procedure previously reported[27] was used to monitor segment motion during gait, using 16 infrared-emitting diodes placed on specific anatomical landmarks (including triads placed on pelvis, thigh, shank, and foot segments) and eight virtual points. Three-dimensional marker motion during self-selected speed gait was collected using a two-camera Optotrak™ 3020 motion capture system (Northern Digital Inc, Waterloo ON) sampling at 100 Hz. Three-dimensional ground reaction forces were recorded at 1000 Hz using an AMTI™ force platform (Advanced Medical Technology Inc, Watertown MA). Participants performed at least five successful gait trials across a five-metre walkway wearing comfortable shoes. **External** KAM variables obtained using this standardized protocol, including discrete and waveform features have been shown to be reliable, with intra-class correlation coefficients ranging from 0.91 to 0.94[31].

2.4 Data Analysis

Motion and force data were digitally filtered (recursive fourth order Butterworth) at 8 Hz and 60 Hz respectively, and used to identify heel strike and toe-off to define one gait cycle (heel strike to heel strike on the same foot). Three-dimensional knee external moments were calculated using inverse dynamics[42,43] and expressed in the joint coordinate system[44]. For PCA analysis and

calculation of peak **external** KAM, KAM waveforms were time-normalized to percentage of gait cycle (i.e. 101 data points) using a linear interpolation technique[26,27,45]. Waveforms were not time-normalized for calculation of KAM impulse, as **this variable captures magnitude and duration of** the KAM. KAM waveforms were kept in original units (Nm), and then two amplitude-normalization methods were applied i) amplitude-normalized to body mass (Nm/kg), and ii) amplitude-normalized to body weight **in N** times height (**Nm/N*m**).

Peak **external** KAM was calculated as the peak occurring in the first 40% of the gait cycle[31]. **External** KAM impulse was calculated according to Equation 1, where KAM(t) = external KAM at time (t); a = time (t) at heel strike; and b = time (t) at toe off[46].

$$\text{Impulse} = \int_{a}^{b} KAM\ (t)dt \qquad \text{Equation 1}$$

Discrete variables were calculated for each trial for each participant, and then mean KAM peak and impulse were calculated for each participant. For PCA analysis, time-normalized **external** KAM waveforms for each trial were averaged to create ensemble average profiles for each participant and PCs were calculated from these ensemble averages.

2.5 Principal Component Analysis

For PCA analysis, **a** data matrix was constructed from a larger dataset of 149 **external** KAM waveforms (**X**=149x101) for asymptomatic (n=64) and moderate knee OA (n=85) participants **that had participated in previous gait studies in our laboratory, including the 54 study**

participants. The larger number of waveforms aimed to improve the robustness and generalizability of patterns extracted[47]. PCA was applied using a standard procedure[27,45,48] **where a covariance matrix, [C], of the original data was calculated, and an eigenvector decomposition ($C=U\Lambda U^T$) was** used to derive the transform matrix, **[U],** of PCs **and associated eigenvalues [Λ]. For the current study,** PC scores **(Z)** were calculated for **external** KAM waveforms for the 54 **longitudinal** study participants **only using $Z = (X - \bar{X})U$. PC scores quantify how closely a participant's original waveform matches the shape of a PC. Eigenvalues were used to calculate the percent trace and determine how much of the total variance each PC (eigenvector) explained. To interpret the PCs, a percent variation explained was calculated throughout the gait cycle, representing how much variation in the original waveform was explained by a specific PC[49]. To aid in interpretation, the means of the five highest and lowest scoring original waveforms were plotted and the waveforms were visually compared.**

For this study, KAMPC1 (capturing overall shape and magnitude, **and explaining 63.7% of the variance of the larger dataset**) and KAMPC2 (capturing the relative difference between early and mid/late-stance amplitude, **and explaining 15.9% of the variance of the larger dataset**) scores were retained for statistical hypothesis testing, **given that these features have demonstrated ability to differentiate** between asymptomatic control participants and those with moderate knee OA[26,27], and **predictive potential** for progression to TKA[23]. **KAM waveforms for each participant were reconstructed based on a linear combination of the eigenvector (PC) times the weighting coefficient (PC score), and a root mean squared error was calculated (0.08 (0.02) Nm/kg)) between measured and reconstructed waveforms, and the**

two waveforms were visually compared as a quality control check to ensure that salient features were retained. Custom (Matlab, Mathworks Inc, Natick MA) programs were used to process gait data and perform PCA.

2.6 Statistical Analysis

Assumptions of normality and equal variances were examined using the Kolmogorov-Smirnov and Levene's tests, respectively. Pearson product moment correlation coefficients were calculated to determine relationships among variables (KAMPC1 and KAMPC2 scores, **external** KAM peak and **external** KAM impulse), with R^2 values calculated to determine the amount of variance explained by the relationships. Unpaired Student's t-tests were used to detect significant differences in KAM peaks, KAM impulses, KAMPC1 scores, and KAMPC2 scores between the TKA and no-TKA groups. To address the effect of amplitude-normalization, the above analyses were performed for non-amplitude-normalized KAM waveforms, KAM waveforms amplitude-normalized to body mass, and KAM waveforms amplitude-normalized to body weight times height. For all tests, the significance level (α) was 0.05. All analyses were completed using Minitab™ (Minitab Inc, State College PA).

3 Results

Participant demographics for the TKA and no-TKA groups have previously been published[23] but are presented in Table 1. No significant between-group differences were found for all variables at baseline, with similar radiographic disease distribution between the two groups. Correlation coefficients between KAMPC1 and KAMPC2 scores and KAM peak and impulse for the three

methods of amplitude-normalization are in Table 2. KAMPC1 (Figure 1a), **captured t**he overall shape and magnitude of the **external** KAM, **based on the variance explained by the PC throughout the gait cycle and visually examining the waveforms of the highest and lowest scoring original waveforms (Figure 1c). KAMPC1** was significantly correlated with both the peak KAM and KAM impulse, regardless of amplitude-normalization method. Variance explained ranged from 77% to 86%. KAMPC2 (Figure 1b) captured the difference between the early and mid/late-stance KAM magnitudes, **based on higher variance explained by the PC at those phases of the gait cycle and examining the waveforms of the highest and lowest scoring original waveforms (Figure 1d). KAMPC2** was not significantly correlated with the KAM impulse, regardless of amplitude-normalization method. KAMPC2 was correlated with the **external** KAM peak, for all methods of amplitude-normalization, but this relationship only accounted for only 8-16% of the variance. As expected, **since PCA is an eigen-decomposition of waveform data which results in orthogonal patterns extracted**, KAMPC1 and KAMPC2 were not correlated. The KAM peak and impulse were significantly correlated, with variance explained ranging from 58% to 59%. **Normalization did not affect general correlation findings, but the biggest differences in correlation coefficients depending on method of amplitude-normalization were for KAMPC2.**

Table 1.

Participant demographics, spatiotemporal gait characteristics, and self-reported symptoms for the no-TKA and TKA groups. Data are presented as mean (standard deviation) unless otherwise noted.

	TKA	**No-TKA**	**p-value**
Sex	7 female	9 female	
	19 male	19 male	
Age (years)	60.2 (9.3)	57.9 (7.3)	0.30
Mass (kg)	92.9 (13.7)	95.4 (20.1)	0.59

	TKA	No-TKA	p-value
BMI (kg/m2)	30.9 (4.7)	31.5 (6.2)	0.67
KL gradea	3	3	0.13
Velocity (m/s)	1.2 (0.2)	1.3 (0.2)	0.29
Stance time (s)	0.74 (0.07)	0.71 (0.08)	0.14
WOMAC (/96)	35.7 (15.0)	30.0 (20.3)	0.25

A Median values presented for ordinal radiographic data. P-values based on Mann–Whitney *U* tests

Table 2.

Correlation coefficients (r) between knee adduction moment (KAM) PC1 and PC2 scores and the KAM peak and impulse. Data non-amplitude-normalized (Non), normalized to mass (Mass) and normalized to weight times height (Size).

	Peak KAM			KAM impulse			KAMPC1		
Normalization	**Non**	**Mass**	**Size**	**Non**	**Mass**	**Size**	**Non**	**Mass**	**Size**
Peak KAM				0.77*	0.76*	0.77*	0.90*	0.88*	0.88*
KAM impulse	0.77*	0.76*	0.77*				0.93*	0.93*	0.93*
KAMPC1	0.90*	0.88*	0.88*	0.93*	0.93*	0.93*			
KAMPC2	0.27*	0.39*	0.40*	−0.23	−0.15	−0.13	−0.12	−0.04	−0.03

*Indicates a significant correlation ($p < 0.05$).

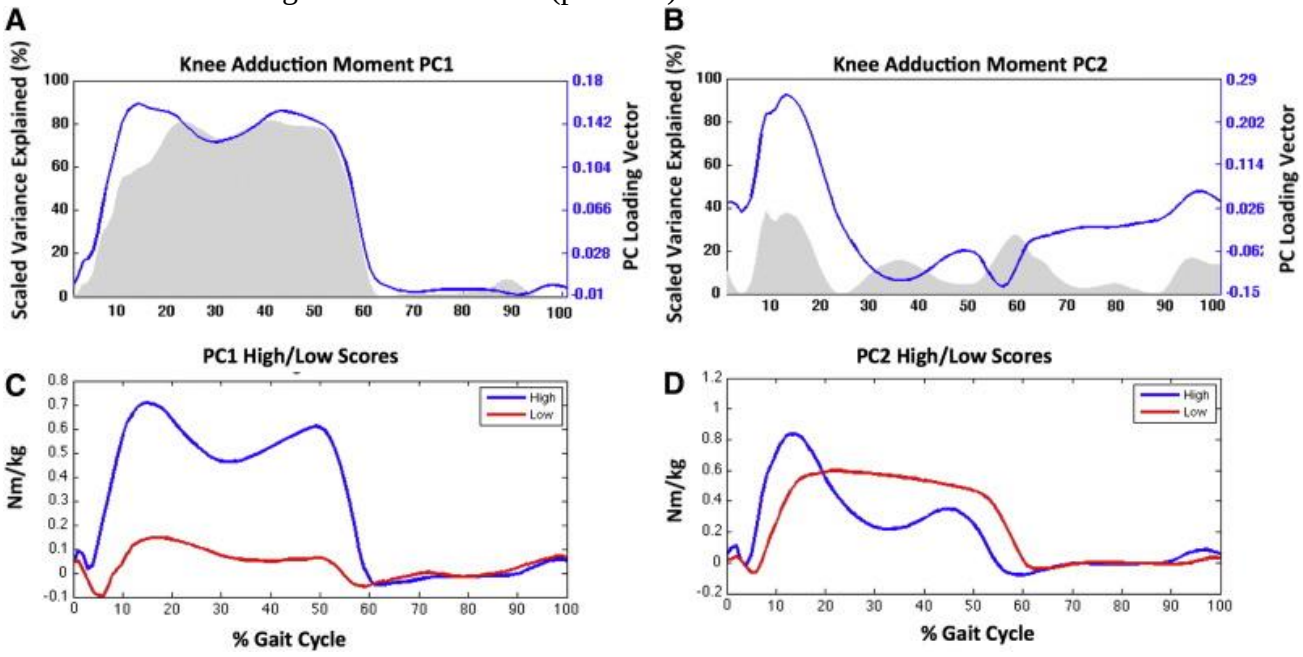

Fig. 1.

Knee adduction moment (KAM) principal component (PC) 1 (A) and 2 (B) loading vectors. Percent variation explained throughout the gait cycle of the principal components is plotted on the left y-axis and is indicated by the grey shaded area. The mean original waveforms for a subset of participants with high (n = 5) and low (n = 5) KAMPC1 (C) and KAMPC2 (D) scores indicated that KAMPC1 captured the overall shape and magnitude of the knee adduction moment during the stance phase of the gait cycle, whereas KAMPC2 captured the relative difference between the early and mid/late-stance knee adduction moment magnitudes.

Mean values for KAM peak, KAM impulse, KAMPC1 score, and KAMPC2 score for the two groups, for each method of amplitude normalization, are in Table 3. Significant between-group baseline differences were found for peak KAM normalized to body weight times height only, whereas KAM impulse, KAMPC1 scores, and KAMPC2 scores for all normalization methods were different ($p<0.05$). KAM peak, impulse, and KAMPC1 score were significantly higher in the TKA group than the no-TKA group. KAMPC2 score was lower in the TKA group. Percent differences ranged from 14-17% for the peak KAM, 32-36% for the KAM impulse, 26-30% for KAMPC1 score, and 100-175% for KAMPC2 scores **found in Table 3.**

Table 3.

Knee adduction moment (KAM) outcome measures for the TKA and no-TKA groups for the three methods of amplitude-normalization. Moments were non-amplitude-normalized (Nm), normalized to mass (Nm/kg), and normalized to body weight times height (Nm/N*m). Data presented as mean (standard deviation).

		TKA	**No TKA**	**Percent Difference**	**P-Value**
Non-amplitude-normalized	KAM peak	57.1 (17.7) Nm	49.7 (16.1) Nm	14%	0.12
	KAM impulse*	23.7 (8.2) Nm*s	17.1 (6.9) Nm*s	32%	0.002
	KAMPC1 score*	296.0 (93.6)	227.9 (77.9)	26%	0.006
	KAMPC2 score*	2.2 (42.6)	32.9 (39.8)	175%	0.009

		TKA	No TKA	Percent Difference	P-Value
Amplitude-normalized to body mass	KAM peak	0.63 (0.19) Nm/kg	0.53 (0.15) Nm/kg	17%	0.05
	KAM impulse*	0.26 (0.08) Nm*s/kg	0.18 (0.06) Nm*s/kg	36%	<0.001
	KAMPC1 score*	3.21 (1.00)	2.38 (0.70)	30%	0.001
	KAMPC2 score*	0.14 (0.45)	0.44 (0.45)	103%	0.020
Amplitude-normalized to body weight times height	KAM peak*	3.67 (1.11) Nm/Nm	3.10 (0.87) Nm/Nm	17%	0.04
	KAM impulse*	1.51 (0.48) Nm*s/Nm	1.06 (0.36) Nm*s/Nm	35%	<0.001
	KAMPC1 score*	0.19 (0.06)	0.14 (0.04)	30%	0.001
	KAMPC2 score*	0.01 (0.03)	0.03 (0.03)	100%	0.028

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

In summary, amplitude-normalization **method** had **minimal** effect on the correlations between variables, as seen in Table 2, with little effect on the between-group differences as seen in Table 3, except for peak KAM.

4 Discussion

The results of this study addressed the first aim, **showing that** the three magnitude variables were correlated; specifically suggesting that **external** KAM impulse and KAMPC1 could be used interchangeably, especially if there are minimal differences in stance duration. Higher correlations between KAMPC1 and the KAM impulse, compared to the peak, likely reflect that both KAMPC1 and KAM impulse consider the entire stance phase, whereas the peak does not. While **peak and impulse were significantly correlated, over 40% of the variance was not**

explained by a linear association. Perhaps the large unexplained variance can in part be explained by the change in loading pattern as the disease reaches the severe state; the early stance magnitude decreases and the mid-stance magnitude increases, making the first peak lower and more difficult to pick out[31,50]. **Hence using the two discrete variables interchangeably needs to be done with caution.**

While KAMPC2 and peak KAM had a significant correlation, regardless of normalization, only 8-16% of the variance was explained by this relationship. Thus, the majority (over 84%) of the variance between the early and mid/late-stance values (KAMPC2) was not explained by the initial peak. KAMPC2 was not related to the impulse, clearly indicating that the impulse does not capture this ability to unload the knee from early to mid/late-stance. A high KAMPC2 score **can** only be achieved with a specific KAM waveform shape: high early stance magnitude and low mid/late-stance magnitude. In contrast, a high KAM impulse could occur with a variety of KAM waveform shapes as illustrated by the example in Figure 2. **Both** original KAM waveforms have similar KAM impulses, but different KAMPC2 scores. As expected based on the orthogonality of the eigenvector decomposition, KAMPC2 was not related to KAMPC1. Hence, KAMPC2 captures a unique feature of the KAM that is not **overall** amplitude-dependent, indicating that analysis of KAM waveforms using PCA provides different information than that obtained by examining commonly used discrete features. This unloading feature has been associated with knee OA presence[26,27], severity[26], treatment outcomes[30] and progression to TKA[23].

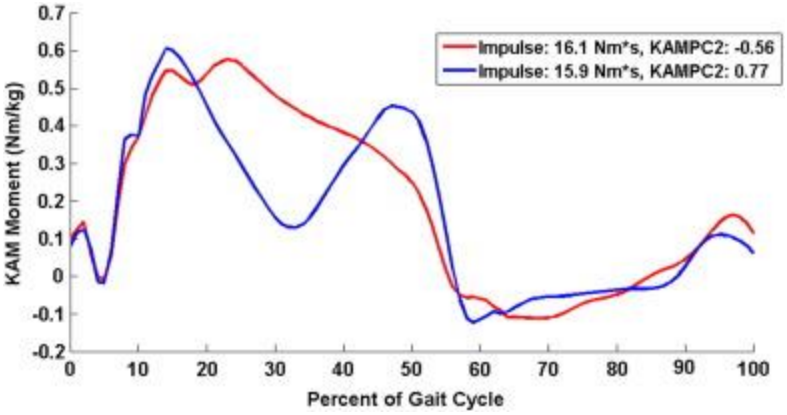

Fig. 2.

Two original KAM waveforms for participants with similar KAM impulses, but different KAMPC2 scores. The blue waveform had a KAM impulse of 15.9 Nm*s and a KAMPC2 score of 0.77. The red waveform had a KAM impulse of 16.1 Nm*s and a KAMPC2 score of − 0.56. KAMPC1 scores for the blue and red waveforms were 2.4 and 3.9, respectively. Note: for visualization purposes, the KAM waveforms were time-normalized to percentage of gait cycle, but KAM impulses were calculated from non-time-normalized waveforms.

The new between-group findings are related to the **external** KAM peak and impulse, two discrete variables previously associated with knee OA structural progression[1,2,4]. The **external** KAM peak was higher in the group that progressed to TKA than in the no-TKA group when it was amplitude-normalized to body weight times height only, **although body mass normalization differences were close to significant (p=0.05). These differential results likely reflect the reduction in the between group variance associated with normalizations compared to non-normalized values along with relatively small** between-group percent differences for peak **external** KAM **(range14-17%).** Inconsistent findings among studies have been reported for peak KAM related to structural progression[1,2,4]. In contrast, KAM impulse was higher in the TKA group than no-TKA group for non-normalized values and both methods of amplitude-normalization, consistent with the results for structural progression studies[2,51]. The stability and size of the between subject variability across normalizations compared to the

percent differences between groups (32-36%) suggest that the impulse is a sensitive measure for detecting differences between groups. **This KAM impulse finding is consistent with between-group differences in KAMPC1 (overall shape and magnitude) normalized to body mass previously reported[23], as well as the two new KAMPC1 results (non-normalized and normalized to body size). Thus, between-group differences exist regardless of normalization for these two measures capturing overall magnitude.**

The higher percent differences for KAM impulse compared to KAM peak, and the finding that significant between-group differences persisted despite the method of amplitude-normalization, suggests that KAM impulse is a more discriminative metric for a TKA outcome than the peak, consistent with the finding that KAM impulse, but not peak, was able to predict medial tibial cartilage volume loss (i.e. structural progression) over one year[2]. KAM impulse captures overall magnitude and exposure to load, rather than loading at only one point in the gait cycle, and therefore reflects loading of different regions of cartilage. It also captures the duration of loading throughout the gait cycle**, since it is calculated from non-time-normalized waveforms**. **I**n this study, the TKA group spent 0.03 seconds longer in stance each gait cycle: a difference of 4% (not statistically significant) whereas the between-group differences in KAM impulse were over 30%. Hence higher KAM magnitude was the greater contributor to the difference in KAM impulse.

The between-group differences for KAMPC2 (difference between early and mid/late-stance magnitude) **were also** not dependent on amplitude-normalization. **Findings were consistent with those previously reported for the body mass normalized values[23],** indicating less difference between the early and mid/late-stance **external** KAM magnitudes (KAMPC2) for the

TKA group, **or an inability to unload to medial compartment**, rather than the typical pattern seen in asymptomatic individuals[26,27]. **This suggests a "stiff" knee gait, as mentioned, and the low correlations with other variables supports its uniqueness (Table 2).**

While clinical decision-making in TKA surgery[23] is a potential limitation for looking at the between-group differences, the main goal was to compare differences in outcomes derived from discrete and PCA analyses across normalization procedures. **An additional limitation is the small proportion of women in the study relative to men, given the higher percentage of women with knee OA in the general population, potentially limiting the generalizability of the between-group findings as well as the generalizability of the patterns extracted, since sex differences have been noted in osteoarthritic gait[52]. However, there was approximately the same proportion of women in the TKA and no-TKA groups (30%), so it is unlikely that sex differences would have affected the significant between-group findings.**

While an advantage of PCA is that features are derived from the data itself, removing the subjectivity of deciding which discrete features are relevant to extract from waveform data, a disadvantage is that extracted patterns only explain variation in the participant group examined. This can limit the generalizability of the patterns. For this reason, large datasets are recommended to generate robust patterns[47], **and we applied PCA** to a dataset of 149 waveforms from asymptomatic participants and participants with moderate knee OA to increase the robustness and generalizability of the patterns. Higher order principal components can be difficult to interpret, however the first few patterns usually capture the overall shape and magnitude, difference operators, and phase shifts in waveforms, which are more easily

interpreted[25], and typically no more than three PCs are needed to capture the majority of variance in the waveforms[23]. **For** those with knee OA, the first two PCs from the **external** KAM have been associated with progression to TKA[23]**, and in this case the first two PCs captured about 80% of the variance (KAMPC1 explained 63.7% of the variance, KAMPC2 explained 15.9% of the variance) and hence are the main features. This is not to say that other higher order features might not be highly correlated with the two discrete measures examined, but we chose to examine correlations between features associated with knee OA progression. This study is a proof in principle of the value of examining the entire waveform using the KAM, however three-dimensional forces and muscle activation patterns provide a more comprehensive view of the loading environment, so future work could look at the effects of analysis type and normalization method on other biomechanical waveforms.**

In conclusion, relationships were found between PC amplitude features and discrete measures **and support that** the two features capturing overall magnitude (KAM impulse and KAMPC1) could perhaps be used interchangeably. KAMPC2 captured a unique waveform feature of the relative inability to unload the joint from early to mid/late-stance that was not captured by any other feature examined. Hence PCA provides additional information not captured by common discrete measures. Normalization approaches had minimal effects on the relationships among features, but the peak KAM between-group differences were affected by normalization type. Higher KAM impulses and KAMPC1 magnitude, along with decreased ability to unload the joint (KAMPC2), were present at baseline in those who progressed to TKA compared to those who did not, regardless of normalization, and the more than two-fold higher percent difference between groups for these features indicate that they are a more discriminatory metric for

progression to TKA than the peak. This paper provides a baseline for comparison of features derived from **external** KAM waveforms and normalization approaches used in the study of knee joint biomechanics in knee OA gait studies, **shedding light on the potential value of more complete analysis of the entire waveform.**

Acknowledgements

The authors would like to thank all of the study participants for their major contribution to this work, and acknowledge the students and staff of the Dynamics of Human Motion laboratory for their assistance in data collection and processing.

Author Contributions

GH made substantial contributions to the study conception and design, data analysis and interpretation, drafting and editing the manuscript, and preparing for submission.
WDS made substantial contributions to the clinical interpretation, diagnosing and recruiting participants, scoring and interpreting clinical data, and editing the manuscript.
CLK made substantial contributions to the study conception and design, data analysis and interpretation, editing the manuscript, and preparing for submission, and also provided funding.

Role of the Funding Source

The authors would like to thank the Canadian Institutes of Health Research (Grant number 115057-CHK) for operating funding and the Nova Scotia Health Research Foundation, Killam Trust, Natural Sciences and Engineering Research Council of Canada, for fellowship funding (GH). The authors acknowledge that the funding sources had no involvement in study design,

data collection, analysis, and interpretation, writing of the manuscript, and in the decision to submit the manuscript for publication.

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Figure Legends

Figure 1: Knee adduction moment (KAM) principal component (PC) 1 (A) and 2 (B) loading vectors. **Percent variation explained throughout the gait cycle of the principal components is plotted on the left y-axis, and is indicated by the grey shaded area**. The mean original waveforms for a subset of participants with high (n=5) and low (n=5) KAMPC1 (C) and KAMPC2 (D) scores indicated that KAMPC1 captured the overall shape and magnitude of the knee adduction moment during the stance phase of the gait cycle, whereas KAMPC2 captured the relative difference between the early and mid/late stance knee adduction moment magnitudes.

Figure 2: Two original KAM waveforms for participants with similar KAM impulses, but different KAMPC2 scores. The blue waveform had a KAM impulse of 15.9 Nm*s and a KAMPC2 score of 0.77. The red waveform had a KAM impulse of 16.1 Nm*s and a KAMPC2 score of -0.56. **KAMPC1 scores for the blue and red waveforms were 2.4 and 3.9, respectively.** Note: for visualization purposes, the KAM waveforms were time-normalized to percentage of gait cycle, but KAM impulses were calculated from non-time-normalized waveforms.