MOVEMENT ASYMMETRY AND CONTRALATERAL OSTEOARTHRITIS PROGRESSION AFTER UNILATERAL TOTAL KNEE ARTHROPLASTY: WHEN THE GOOD LEG GOES BAD

by

Moiyad Saleh Aljehani

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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by

Moiyad Saleh Aljehani

Approved: _____

Samuel C.K. Lee, Ph.D.
Director of the Interdisciplinary Graduate Program in Biomechanics and Movement Science

Approved: _____

Kathleen S. Matt, Ph.D.
Dean of the College of Health Sciences

Approved: _____

Louis F. Rossi, Ph.D.
Vice Provost for Graduate and Professional Education and
Dean of the Graduate College

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Dr. Joseph Zeni Jr, Ph.D.
Professor in charge of dissertation

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Dr. Lynn Snyder-Mackler, ScD
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Dr. Jeremy Crenshaw, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Dr. Allison Brown, Ph.D.
Member of dissertation committee

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ABSTRACT

Background: Total knee arthroplasty (TKA) is a successful surgical treatment for people with end-stage knee osteoarthritis (OA) [1,2]. More than 700,000 TKAs are performed annually in the United States [3], and that number is estimated to reach 3.5 million TKAs by 2030 [4]. Despite the success rate of this surgery, many individuals who get TKA develop a rapid onset (3.2 years [5]) of OA on the contralateral knee after the initial surgery [6]. Individuals after TKA are known to move asymmetrically [7,8] and have residual physical impairments in strength and range of motion [9,10], but it is not clear how these deficits contribute to contralateral OA progression. Abnormal joint biomechanics predict primary knee OA progression [11,12], but there is a lack of evidence about which biomechanical and clinical factors predict contralateral knee OA progression after unilateral TKA. Even though clinically meaningful information can be obtained through the use of motion analysis, the complexity of laboratory equipment and the associated costs are a major obstacle for clinicians when evaluating movement patterns for individuals with musculoskeletal disorders. There has been an increasing interest in using commercially available wireless shoe insoles for kinetic assessments in the clinical setting to measure the real-life performance [13].

Aims: Therefore, the overall goals of this project were to 1) quantify the influence of contralateral knee OA on movement patterns and movement symmetry and 2) identify biomechanical and clinical predictors of radiographic knee OA progression in the contralateral knee after unilateral TKA. We also developed methods to quantify force asymmetry in a clinical setting using vertical ground reaction force

acquired through commercially available shoe insoles. This will provide researchers and clinicians with more realistic estimates of asymmetry that may occur during actual activities of daily living.

Results: Results from our studies revealed that patients who have structural evidence of contralateral knee OA after TKA, even without contralateral symptoms, have altered walking patterns. Specifically, these individuals move more symmetrically, albeit more abnormally, in both limbs. In our predictive analyses, we found that the majority of individuals (62.5-78%) had radiographic progression of contralateral knee OA at multi-year follow-up. We did not identify any biomechanical predictors of contralateral OA progression, but contralateral quadriceps strength was significantly higher in the non-progressor group (25.4 ± 7.5 Nm/kg/m^2; p=0.033) and greater contralateral quadriceps strength was protective against OA progression (odds ratio=1.117; p=0.047; Table 3). For every one unit increase in quadriceps strength, the likelihood of being a non-progressor increased by 11.7%.

Conclusions: Participants with contralateral knee OA have more symmetrical gait, although they adopt a more abnormal and stiff-legged gait pattern bilaterally. Symmetrical movement patterns between limbs after surgery should not be the sole factor upon which movement recovery is based. Although abnormal biomechanics are known risk factors for primary knee OA, it is possible that the mechanisms that result in OA progression of the contralateral limb are different than primary knee OA progression. Quadriceps strength is a prognostic indicator for knee OA progression in the contralateral limb and should remain to be a primary focus of rehabilitation after unilateral TKA. These findings will help clinicians better educate patients and develop targeted strengthening interventions for improving contralateral joint health post-TKA.

Future work should evaluate other objective measures of OA progression and determine if cumulative measures of joint loading are related to OA worsening.

DEDICATION

To my mother, I dedicate this work to you.

Without whom I would have never made it through my academic journey.

Thank you for everything.

May Allah rest your soul in the highest rank of the Paradise.

Chapter 1

BACKGROUND, SIGNIFICANCE, AND INNOVATION

1.1 Background

Many individuals who get unilateral total knee arthroplasty (TKA) develop a rapid onset of osteoarthritis (OA) on the contralateral knee after the initial surgery [6]. Previous work from our lab found that this contralateral OA progression happens quickly, even in individuals who have no plans to have the contralateral knee replaced when undergoing the initial procedure. In addition, there is a wealth of evidence that shows biomechanical variables, such as greater adduction moments, are predictive of primary TKA and OA progression [11,12]. However, it is unknown if biomechanical and clinical variables predict contralateral OA progression after unilateral TKA. After TKA, there are many residual deficits, including weakness and movement impairments. Persistent unilateral lower limb weakness and learned movement asymmetries may be the underlying cause for why individuals continue to rely on the contralateral (non-operated) limb after unilateral TKA. It is possible that this reliance on the contralateral limb increases compressive and shear loads, and it is a factor in the high incidence and rapid rate contralateral OA progression.

Although previous literature has found that abnormal biomechanics, such as greater knee adduction moments [11,12], predict radiographic OA progression in individuals with primary knee OA, it is not clear if higher adduction moments after surgery will predict contralateral OA progression. One year after TKA, the adduction moment on the contralateral knee is 20% greater than the adduction moment on the

surgical knee [7]. Therefore, it is possible that this asymmetry in adduction moment in the contralateral knee may be a key factor in the high risk of contralateral knee OA progression. Other biomechanical changes, such as reduced joint excursion and increased knee stiffness, are known to occur in the presence of increasing OA severity [14], so it is possible that these variables after unilateral TKA could also drive structural changes in the contralateral knee. Our lab has done some preliminary work that showed reduced knee excursion after TKA on the operated and non-operated limbs are associated with future contralateral TKA [15]. Limited knee flexion and extension range of motion during repetitive gait cycles may cause the compressive knee load to be distributed over a smaller portion of the cartilage. This may expedite the wear and tear process.

Knee pain, muscle strength, and extension ROM are known as factors for predicting functional performance after unilateral TKA. Three years after TKA, the best predictor of functional performance is the status of the non-surgical knee including knee pain and muscle strength [16]. Previous work found that muscle weakness is negatively correlated with reduced functional levels in individuals with knee OA [17,18], suggesting that muscle weakness can be a risk factor for knee OA progression [19]. In addition, knee pain and quadriceps weakness in the operated limb after TKA may explain the observed asymmetrical movement patterns [20]. This asymmetry may lead to greater joint loads, and consequently greater contralateral OA progression.

Although our previous work has explored risk factors for contralateral OA progression, contralateral TKA was used as a surrogate for contralateral structural changes. The decision to undergo TKA is multifactorial and may not represent actual

changes to joint structure. It is possible that an individual who had a positive experience after the initial TKA may decide to undergo contralateral TKA, even if there was not a significant increase in pain or change in joint structure in that knee. Therefore, the studies in this dissertation will use objective measures of structural change within the knee to define contralateral OA progression. This may better elucidate biomechanical and clinical factors that drive structural change within the contralateral knee joint after unilateral TKA.

While identifying biomechanical asymmetries in the laboratory setting may be relevant, there is a need for kinetic assessments in the clinical setting. It is possible that data collected about movement patterns in a sterile motion analysis laboratory do not reflect actual movement strategies that occur when individuals perform challenging or longer duration activities. The rationale for this aim is identifying clinical impairments (e.g., pain and weakness) that are associated with greater asymmetry during prescribed functional tasks. Identification of the clinical impairments can help clinicians to develop/improve rehabilitation protocols in which clinicians can both evaluate and re-train movement patterns using real-time feedback.

1.2 Significance

1.2.1 Incidence and cost of total knee arthroplasty (TKA) are rising dramatically, with a high percentage of patients undergoing subsequent contralateral TKA after the initial (primary) surgery

The need for primary TKA has dramatically increased [4], and the population undergoing TKA has become younger [21]. *Primary TKA* refers to the initial TKA (ipsilateral) knee while the *secondary TKA* refers to surgery performed on the opposite

(contralateral) knee at a later date. After the initial TKA, many individuals rapidly develop osteoarthritis (OA) progressions in other lower limb joints and often require a secondary total joint replacement (49.5%) [6] with the contralateral TKA being the most likely procedure to be performed next [22]. Of those 49.5% of individuals who undergo a second joint replacement, 93% of these were for a contralateral TKA, as opposed to hip or ankle replacement [6]. Studies from our own lab have shown that 26.8% of patients require a contralateral TKA within only two years, while 3.2 years is the median time to contralateral TKA after the primary procedure [5]. This is concerning as the study from our laboratory only evaluated and followed-up with patients who were mostly unilaterally symptomatic at the time of the initial TKA and had no plans to replace the contralateral knee in the future.

There are more than 700,000 TKAs performed annually in the United States (US) [3] and that incidence is expected to reach 3.5 million by 2030 [4]. The hospitalization costs associated with each knee replacement are $15,673 US dollars [23]. If the number of TKAs reach 3.5 million as estimated, the total costs will reach $54.86 billion US dollars for TKAs in the US alone. Given that available evidence suggests that 26.8% of patients require a contralateral TKA within two years of the primary TKA, it is expected that the financial burden will continue increasing. Our project is significant because it will help to identify biomechanical and clinical factors that contribute to contralateral OA progression. This may lead to interventions that will reduce the overall number of people undergoing contralateral TKA and consequently improve patients' quality of life and reduce healthcare costs.

1.2.2 Current rehabilitation gap

Current rehabilitation strategies may not help patients avoid long-term functional impairments in the contralateral knee. Although there are improvements after TKA in self-reported function and pain, the overall walking ability and functional performance measures are still below the normative values for the older population after the procedure [24,25]. Compared to age-matched controls, individuals who are 1 year after TKA need 50% more time for stair climbing, are more likely to require handrail assistance on the stairs, and walk 20% slower over level ground [24,26]. Three years after TKA, progressive weakness and pain of the non-surgical limb [16] can contribute to a rapid decrease in both gait biomechanics [27] and function [28]. These functional impairments may be associated with greater reliance on the non-surgical limb, which causes movement asymmetries and overuse of the contralateral limb and potentially OA progression [29–31]. Also, movement asymmetries are not completely resolved with current rehabilitation approaches. Patients still rely more on the non-surgical side in tasks such as rising from a chair [30], walking [32], and climbing steps [33]. Therefore, *this dissertation will help in understanding modifiable and non-modifiable risk factors (such as age, sex, BMI, or other patient characteristics)* that should be considered when creating plans of care for individuals with OA.

1.2.3 Biomechanics, which is associated with OA progression, may be modifiable

Studies from tissue-level experiments have shown that excessive load placed on cartilage can cause structural deterioration [34]. Knee adduction moment is directly correlated with medial compartment loading of the knee joint [34]. Previous studies have shown that higher adduction moments at baseline predict radiographic OA progression [11,12]. The adduction moment was found to be a better predictor of OA progression than

pain or alignment, and for every 25% increase in the adduction moment, there was a 6-fold increase in the risk of OA progression [11,12]. Although this finding was substantiated for primary OA, it is not clear if greater contralateral knee adduction moments after surgery will predict contralateral OA progression.

Before TKA, patients with end-stage knee OA have knee pain and quadriceps weakness, which is correlated to asymmetrical movement patterns. This is a crucial topic to research because patients after TKA continue to rely on and overload the contralateral knee [20,33,35]. Even one year after TKA, the adduction moment on the contralateral knee is 20% greater than the adduction moment on the surgical knee [7]. Therefore, in addition to strengthening, the rehabilitation protocol should consider maintaining the integrity of the contralateral knee and normalizing movement patterns if they are found to be predictive of contralateral knee OA progression.

Several studies have shown that modifying kinematic movement patterns can reduce the adduction moment and joint loads in patients with knee OA [36,37,38,39,40,41,42]. Even after TKA, patients can modify their gait using biofeedback that promotes movement symmetry after TKA [20]. This is important as the preliminary work from our lab showed that reduced knee excursions on both operated and non-operated limbs after TKA were predictors of the contralateral TKA [15]. In that paper, we found that for every additional degree of the operated and contralateral knee flexion excursion at baseline, there was 10.2% and 9.1% risk reduction of future contralateral TKA, respectively. *The results from this project will provide insight into the biomechanical and clinical predictors that underlie the rapid non-surgical knee OA progression after the primary TKA*. This may inform specific movement retraining strategies that reduce

the risk for contralateral OA progression, and ultimately lead to better long-term outcomes after unilateral TKA.

1.2.4 Clinical predictors of OA progression

There are clinical factors related to primary knee OA progression, but these remain unknown for contralateral OA progression. It has been found that greater knee pain, muscle weakness, lower range of motion, and less functional outcomes are risk factors for primary knee OA progression. Being older and having lower performance (timed-up and go test, stair climbing test, Knee Outcome Survey - Activities of Daily Living Scale (KOS-ADLS), knee extension ROM and quadriceps strength) are predictors for TKA within two years [18]. Full knee ROM is a modifiable factor that can postpone the need for TKA in older adults [18]. Specifically, for every degree reduction in knee extension ROM, the odds of undergoing TKA increased 23% [18]. While these findings are important for primary TKA, it is not clear if they will be predictive of contralateral OA progression. After TKA, there is a shift in pain, range of motion, and function. The results from this study will be the first to explore clinical characteristics associated with contralateral OA progression.

1.2.5 The need for biomechanics testing in the clinical setting

Identification of the clinical impairments can help clinicians to develop/improve rehabilitation protocols in which clinicians can both evaluate and re-train movement patterns using wireless real-time feedback. Completion of Aim 3 will inform us of clinically relevant metrics that are related to asymmetrical loading during functional activities. It will also result in a new way of measuring the biomechanical outcomes outside the laboratory in a more clinical setting, which will save time and

help in improving functional outcomes and normalize biomechanics. It is known that individuals at baseline (before the TKA) who have asymmetrical quadriceps weaknesses move with asymmetrical gait patterns when measured in the biomechanics laboratory. In this project, we hypothesized that these gait asymmetries are going to get even worse when patients are challenged during a longer duration walking test for endurance (Six-Minute Walk Test).

1.2.6 Significance summary

To sum up, this project is significant because it can identify factors related to the preservation or deterioration of the contralateral limbs. This may lead to interventions that enhance the recovery process, maximize function, and improve patients' quality of life in the short and long term after TKA. Reducing contralateral TKAs may be exceptionally important as the population becomes younger and the surgery becomes more prevalent. The exploratory aim of this dissertation may also help bring relevant biomechanical measures that can be used for assessment or training, into the clinical setting.

1.3 Innovation

Although previous studies have evaluated the biomechanical and clinical predictors of primary knee OA progression, our project is innovative because it will combine biomechanical, clinical, and imaging data to evaluate individuals at risk of *contralateral* knee OA development or progression. Additionally, our project is innovative because it will include commercially available tools (foot insoles) to understand asymmetrical loading during functional activities which will have

implication for future planning of rehabilitation services for individuals with OA. The results from this project will provide insights into the biomechanical and clinical predictors that underlie the rapid non-surgical knee OA progression after the primary TKA. The results also will be useful for clinicians to help them evaluate their patient's gait mechanics in clinical settings. *This innovative approach will lead us to evaluate the functional performance and the long-term recovery of patients following TKA* and will *elucidate predictive factors that prevent/delay the contralateral OA progression and impact the contralateral TKA*. The results from this project are expected to provide researchers and clinicians with risk factors that inform rehabilitation plans to enhance the long-term integrity of both limbs, although the current focus is on the operated limb after TKA.

1.4 Specific aims

Total knee arthroplasty (TKA) is a successful surgical treatment for people with end-stage knee osteoarthritis (OA) [1,2]. More than 700,000 TKAs are performed annually in the United States [3], and that number is estimated to reach 3.5 million TKAs by 2030 [4]. Despite the success rate of this surgery, many individuals who get TKA develop a rapid onset of OA on the contralateral knee after the initial surgery [6]. The median time to contralateral TKA is 3.2 years after the primary procedure [5]. Even in patients with only one symptomatic side undergoing TKA, nearly 25% of them undergo contralateral TKA soon afterwards [5].

Individuals after TKA are known to move asymmetrically [7,8] and have residual physical impairments in strength and range of motion [9,10], but it is not clear how these deficits contribute to contralateral OA progression.

Work from our lab has shown that reduced knee flexion and extension excursions after unilateral TKA are predictors of contralateral TKA [15]. However, these studies have used TKA as an endpoint for OA progression. The decision to undergo TKA is multifactorial, and no studies have looked at radiographic progression on the contralateral knee. Although abnormal joint biomechanics has been shown to predict primary (surgical) knee OA progression [11,12], there is lack of evidence about which biomechanics as well as clinical factors that could predict contralateral (non-surgical) knee OA progression after unilateral TKA. Therefore, **the overall goal** of this project is to identify biomechanical and clinical predictors of radiographic knee OA progression in the contralateral knee after unilateral TKA. This goal will be accomplished by the following *specific aims:*

AIM 1: Compare the **sagittal plane biomechanics** in the contralateral limb between individuals with and without contralateral knee OA after unilateral TKA.

Hypothesis 1.1: individuals who underwent unilateral TKA with primarily unilateral symptoms, but who had concurrent contralateral knee OA as measured by radiographs would have less sagittal plane joint excursion and lower sagittal plane knee moments in the contralateral limb compared to individuals without contralateral knee OA.

Hypothesis 1.2: individuals after TKA with OA in the contralateral knee would have more symmetrical gait mechanics than individuals without contralateral knee OA.

AIM 2: Identify **biomechanical predictors** of radiographic OA progression in the contralateral (non-surgical) knee after *unilateral (primary) TKA*.

Hypothesis 2.1: individuals who demonstrate OA progression on their contralateral knee at long term follow-up after unilateral TKA will have higher knee adduction moments and lower knee flexion/extension excursions at baseline compared to those who do not demonstrate OA progression.

AIM 3: Identify **clinical predictors** of radiographic OA progression in the contralateral knee after *unilateral (primary) TKA.*

Hypothesis 3.1: individuals who demonstrate OA progression on their contralateral knee at long term follow-up after unilateral TKA will have worse performance in *clinical outcomes* at baseline, "e.g., quadriceps strength, six-minute walk test (6MWT), timed-up and go test, chair rise, and stair climbing test".

Hypothesis 3.2: individuals who demonstrate OA progression on contralateral knee at long term follow-up after unilateral TKA will have more knee pain and less knee extension range of motion on the contralateral side at baseline.

Table 1.1 Aim 2 and Aim 3 measurement sequence

	Additional Data for this Proposal	**Parent Study**		**Additional Data for this Proposal**
Study Component	**1**	**2**	**3**	**4**
	Baseline X-rays	Primary unilateral TKA	Biomechanical and clinical measurements	Follow up X-rays
	→			
Time Relative to TKA	1-2 months before TKA	Time of TKA	6-24 months after TKA	8-13 years after TKA

Although clinically meaningful information can be obtained through the use of motion analysis, the complexity of laboratory equipment and the associated costs are a major obstacle for clinicians when evaluating movement patterns for individuals with knee OA. The use of several trials may also not be representative of real-life performance when patients complete a variety of tasks or walk for longer durations.

There has been an increasing interest in using commercially available wireless shoe insoles for kinetic assessments in the clinical setting [13]. These shoe insoles may provide avenues for clinicians to understand biomechanical outcomes and consequently tailor rehabilitation program for patients with knee OA. Therefore, we are proposing an exploratory aim to use these insoles to quantify force asymmetry in a clinical setting.

AIM 4 (exploratory): Create procedures to measure bilateral vertical ground reaction force and kinetic symmetry in a clinical setting using commercially-available tools.

1.5 Summary and positive impact

Successful completion of previously mentioned aims will allow us to identify biomechanical and clinical risk factors for contralateral knee OA progression. This information will be foundational for our long-term research goal, which is to improve long-term functional performance and quality of life outcomes for individuals with OA after TKA through individualized evaluation and provision of rehabilitation programs that target both biomechanical and functional deficits.

Chapter 2

THE CONTRALATERAL KNEE MAY NOT BE A VALID CONTROL FOR BIOMECHANICAL OUTCOMES AFTER UNILATERAL TOTAL KNEE ARTHROPLASTY

NOTE: This is a published version of the following article: Aljehani M, Madara K, Snyder-Mackler L, Christiansen C, Zeni JA Jr. The contralateral knee may not be a valid control for biomechanical outcomes after unilateral total knee arthroplasty. Gait Posture. 2019 May;70:179-184. doi: 10.1016/j.gaitpost.2019.01.030. Epub 2019 Mar 8. PMID: 30878729.

2.1 Abstract

Background*:** Although unilateral symptoms and unilateral total knee arthroplasty (TKA) are common, many patients have bilateral radiographic osteoarthritis (OA). Because the contralateral (non-operated) limb is often used as a comparison for clinical and biomechanical outcomes, it is important to know if the presence of OA influences movement patterns in either limb. ***Research question: The purpose of this study was to compare bilateral sagittal plane biomechanics between subjects with and without contralateral knee OA after unilateral TKA. ***Methods*:** Fifty-three subjects who underwent unilateral TKA underwent three-dimensional gait analysis 6-24 months after surgery participated in this cross-sectional study. Kellgren-Lawrence (KL) OA severity in the contralateral limb was measured, and subjects were classified into either a non-OA (KL 0 or 1) or OA (KL 2-4) group. Mixed-model ANOVA tests with factors of group and limb were used to compare biomechanical measures. In the presence of a significant interaction effect, post-hoc comparisons were performed. ***Results*:** The OA group had more knee flexion at initial contact, less knee flexion and extension excursions, and less knee extension in the contralateral limb compared to the non-OA group. The non-OA group had significant differences between limbs, with more knee flexion at initial contact, less knee joint excursion, and less peak knee extension on the operated limb compared to the contralateral limb, whereas there were no limb differences for the OA group. Kinetic variables were not different in the ANOVA models. ***Significance and Interpretation*:** Subjects with contralateral knee OA have more symmetrical gait, although they adopt a more abnormal and stiff-legged gait pattern bilaterally. Researchers and clinicians should consider radiographic disease severity, not just symptoms, in the contralateral limb when identifying appropriate subject samples for unilateral biomechanical studies.

Symmetrical movement patterns between limbs after surgery should not be the sole factor upon which movement recovery is based.

2.2 Introduction

Total knee arthroplasty (TKA) is routinely used to reduce pain and improve function for patients with end-stage knee osteoarthritis (OA) [2]. Although most patients report substantial improvement in functional mobility, studies using three-dimensional motion analysis have revealed persistent abnormalities in gait kinetics and kinematics after surgery compared to age-matched controls [43]. A systematic review found that patients after TKA ambulate with residual deficits in the sagittal plane, exemplified by less knee joint excursion, less knee flexion during loading response, and lower joint moments in the operated limb [44]. These studies have led to clinical interventions designed to normalize movement patterns and improve sagittal plane biomechanics after surgery [45,46].

In biomechanical studies of patients after TKA, the contralateral (non-operated) limb, is often used as a control limb for comparative analysis [47,8]. While this may be appropriate for patients with unilateral OA, most individuals who report unilateral pain, actually have structural changes in both knees. In individuals who have primarily unilateral knee OA symptoms, 87.4% had radiographic evidence of bilateral OA [48]. It is likely that many of these patients will elect to undergo unilateral TKA because their symptoms are not severe enough to warrant simultaneous or staged TKA. For these individuals, it is important to determine if the contralateral OA influences movement patterns. If so, the contralateral limb may not serve as a true control comparator for clinical outcomes or biomechanical studies.

Patients with increasing severity of radiographic knee OA have progressively abnormal biomechanics [14]. Patients with more severe OA often have less knee flexion excursion and adopt a stiffer gait pattern in the lower extremity [14,49]. This gait pattern is similar to post-operative gait impairments in which patients after TKA walk with a characteristically stiff gait pattern on the operated side [50]. However, most previous work has evaluated the effect of progressive knee OA in a population of patients who have substantial joint symptoms. It is not known if patients who undergo TKA with unilateral symptoms, but who have bilateral radiographic OA, exhibit abnormal movement patterns on either limb. This is important for two reasons; 1) abnormal movement patterns in the presence of contralateral knee OA may lead to an under-reporting of gait abnormalities after TKA when that limb is used as a control comparator and 2) residual abnormal movement patterns, particularly reduced joint excursion, may result in larger forces over a smaller cartilage area [51]. This may perpetuate OA progression in the contralateral limb and, in part, explain the large prevalence of contralateral TKA after unilateral surgery [6,5].

The purpose of this study was to compare the sagittal plane biomechanics in the contralateral limb between subjects with and without contralateral knee OA after unilateral TKA. In this study, we specifically wanted to evaluate the effect of structural differences in the contralateral knee on movement patterns, as none of the patients had substantial symptoms on the contralateral side or were planning a contralateral TKA. We hypothesized that subjects who underwent unilateral TKA with primarily unilateral symptoms, but who had contralateral knee OA as measured by radiographs would have less sagittal plane joint excursion and lower sagittal plane knee moments in the contralateral limb compared to subjects without contralateral

knee OA. We also hypothesized that subjects after TKA with OA in the contralateral knee would have more symmetrical gait mechanics than those without contralateral knee OA. The findings from this study could have important implications for future research that uses the contralateral knee as a control comparator when measuring biomechanical outcomes.

2.3 Methods

2.3.1 Subjects

Subjects who underwent unilateral TKA for end-stage knee OA underwent three-dimensional gait analysis 6 to 24 months after surgery as part of a larger cross-sectional study [32]. In order to identify a symptomatically unilateral cohort of patients, subjects were excluded from this study if they reported maximal pain greater than or equal to 4 out of 10 in the contralateral knee at the time of the surgery, or were considering staged TKA for the contralateral knee. Hence, the subjects included as part of this study were intentionally largely asymptomatic on the contralateral at the time of the primary TKA. Subjects signed a written informed consent form approved by the Human Subjects Review Board at the University of Delaware before participating in the study.

2.3.2 Pain and KL grade

Age, BMI, sex, and knee pain were recorded at the time of biomechanical testing. Knee pain was assessed using a single pain question from the Knee Outcome Survey Activities of Daily Living Scale (KOS-ADLS) [52]. This pain was scored on a 0

to 5 scale, where is 0 indicates that the pain prevents all daily activities and 5 indicates no pain [52,53].

Pre-operative bilateral knee radiographs were obtained from patient records. Radiographic images were obtained using a posterior to anterior view with the knee flexed to 30 degrees. The Kellgren-Lawrence (KL) scale was used to quantify OA severity according to the following grades: no arthritis (0), doubtful (1), minimal (2), moderate (3), and severe (4) [54,55] in the contralateral knee. The radiographs were graded by a single examiner who underwent a structured training program and demonstrated intersession reliability in scoring. The examiner had excellent intersession reliability (ICC = 0.956) with a narrow confidence interval (95% CI = 0.921 – 0.975). The radiographic examiner was blinded to the biomechanical outcomes of subjects at the time of grading. Subjects were grouped according to their pre-operative KL grades in the contralateral knee. The "non-OA group" was defined as those with KL grade 0 or 1, while the "OA Group" had KL grades 2, 3, or 4 in the contralateral limb.

2.3.3 Biomechanical measurements

Subjects underwent a three-dimensional biomechanical analysis during shod gait at self-selected speed 6 to 24 months after TKA. Subjects were instructed to wear their regular athletic footwear (no sandals or high heel were allowed to use). Several biomechanics variables in the sagittal plane during the stance phase of gait were measured in both operative and non-operative limbs using an 8-camera motion analysis system (VICON, Oxford Metrics, London, England) and two embedded force plates (Bertec Corp., Worthington, OH, USA). Sagittal plane kinematic variables included 1) knee angle at initial contact, 2) knee flexion excursion, 3) knee extension

excursion, 4) peak knee flexion, and 5) peak knee extension. Kinetic variables included peak external knee flexion and extension moments. Variables were determined during the stance phase of the gait cycle (0 level on the figure means heel strike and 100% means toe off). Additionally, spatiotemporal parameters were computed.

Details of this testing have been published previously [32], but briefly, a total of 14 spherical retro-reflective anatomical markers (16 millimeters) were placed bilaterally on the head of the 5th metatarsal, two markers on the heel, lateral malleolus, lateral femoral condyle, greater trochanter, and iliac crest. Four rigid thermoplastic shells with four non-anatomical markers were applied on subjects' thigh and lower leg bilaterally. A rigid thermoplastic shell with 3 non-anatomical markers was used to track the pelvic motion. To minimize movement artifact, the rigid thermoplastic shells were secured with elastic wraps (Fabrifoam SuperWrap; Isokinetics Inc, De Queen, AR). Marker data were collected at 120 Hz sampling rate, while the force data were sampled at 1080 Hz.

Standing calibration was collected before walking trials to identify joint centers to create each segment's coordinate system. Then, subjects practiced walking while self-selected speeds were identified during a pre-session walking assessment. Five valid gait trials were recorded and used in the analysis. A valid trial was defined as a trial in which walking speed was between 95% and 105% of the average pre-determined self-selected speed, and the subject contacted each force platform without obvious targeting.

The marker trajectories were filtered with a 6 Hz low pass filter and force data were low-pass filtered at 40 Hz using a second order phase-corrected butterworth

filter. Knee joint kinematics were calculated using the Euler sequence (flexion/extension, abduction/adduction, rotation sequences). Kinetics were calculated based on three-dimensional inverse dynamics that were expressed as net external moments normalized body weight and height (kg × m). Data analysis and calculations were performed in Visual3D Software (C-Motion, Germantown, MD, USA).

2.3.4 Statistical analysis

Independent t-tests or Chi-Square tests were used to compare patient demographics. For the biomechanical comparisons, a 2x2 analysis of variance (ANOVA) was used to identify differences between groups (OA vs non-OA) and within groups (surgical vs contralateral limb). In the presence of a significant interaction effect, post-hoc Least Squares Difference (LSD) tests were used to compare the biomechanical variables within and between groups. The assumptions of the ANOVA and t-tests were examined and deemed to be appropriate for use. All statistical analyses were performed using SPSS 24. The alpha level was set at $p < 0.05$ for all analyses.

2.4 Results

Fifty-nine subjects had pre-operative X-rays available and were enrolled in the study. Of these, six subjects did not have valid biomechanical data and were excluded from the analysis. Eight of the remaining 53 subjects did not have pain data (non-OA group: 5, and OA group: 3), but were included for all biomechanical analyses. Therefore, 53 subjects were divided into OA (n=35; 66%) and non-OA (n=18; 34%) groups based on their KL grades of the contralateral knee at the time of surgery. There

were no significant differences between OA and non-OA groups in age, BMI, height, sex, walking speed, or pain (Table 2.1).

There were significant interaction effects for knee angle at initial contact, knee flexion excursion, knee extension excursion, and peak knee extension (Table 2.2). There were no significant interaction effects for peak knee flexion and peak knee flexion/extension moments. Post-hoc tests revealed significant differences in the contralateral knee between the OA and non-OA groups. The OA group had 4.5 more degrees of knee flexion at initial contact (p=0.008), 3 fewer degrees of knee flexion excursion (p=0.010), 3.8 less degrees of knee extension excursion (p=0.012), and 5.5 degrees less peak knee extension (p=0.009) compared to the non-OA group in the non-operated knee (Table 2.2). No significant differences were found between OA and non-OA groups for peak knee flexion or kinetic variables (Table 2.2; Figure 2.2). Visual inspection of the knee flexion curves supported findings from the discrete data points indicating less knee motion throughout the stance phase in the contralateral knee of the OA group (Figure 2.1).

Post-hoc comparisons between limbs revealed that the non-OA group had significant more knee flexion at initial contact (p=0.002), less knee flexion excursion (p=0.002), less knee flexion excursion (p=0.001), and less peak knee extension (p<0.001) on the operated limb compared to the contralateral limb (Figure 2.3). There were no differences between limbs for the OA group.

Table 2.1 Participant demographics (N= 53)

	Non-OA Group n= 18 (34%)	**OA Group n= 35 (66%)**	***p*-value**
Age (years)	66.0 (5.8)	68.4 (7.4)	0.253
BMI	30.7 (3.8)	31.6 (5.1)	0.501
Height (m)	1.7 (0.1)	1.7 (0.1)	0.215
Time Since Surgery (months)	12.9 (7.1)	16.3 (10.3)	0.142
Gender			
Female n (%)	10 (55%)	21 (60%)	0.756
Male n (%)	8 (45%)	14 (40%)	
Walking Speed (m/sec)	1.31 (0.2)	1.30 (0.1)	0.872
Contralateral Knee Pain	0.5 (1.0)	1.0 (1.0)	0.112
Operated Knee Pain	0.7 (0.8)	0.5 (0.7)	0.214

Data are presented as "Means (*Standard Deviations)"*
Knee pain was measured using a Likert scale, where is 0 indicates that the pain prevents all daily activities and 5 indicates no pain

Table 2.2 Kinematic variables for each group

	Non-OA Group	OA Group	*ANOVA p*-value
Knee Angle at Initial Contact **			
Contralateral	1.0˚ (5.5)	5.5˚ (5.7)	0.009 *
Operated	5.7˚ (5.4)	6.1˚ (4.7)	
Knee Flexion Excursion			
Contralateral	16.3˚ (3.3)	13.3˚ (4.0)	0.011 *
Operated	12.7˚ (2.7)	12.9˚ (4.1)	
Peak Knee Flexion			
Contralateral	17.2˚ (6.0)	18.8˚ (6.6)	0.567
Operated	18.4˚ (6.0)	19.0˚ (4.6)	
Knee Extension Excursion			
Contralateral	14.8˚ (5.1)	11.0˚ (5.1)	0.003 *
Operated	10.2˚ (4.9)	10.6˚ (4.8)	
Peak Knee Extension **			
Contralateral	2.5˚ (4.9)	8.0˚ (7.7)	0.009 *
Operated	8. 2˚ (5.4)	8.4˚ (5.1)	
Kinetics (peak external knee moments)			
Peak Knee Flexion Moment ***			
Contralateral	0.38˚ (0.15)	0.35˚ (0.16)	0.499
Operated	0.38˚ (0.13)	0.38˚ (0.15)	
Peak Knee Extension Moment ***			
Contralateral	-0.08˚ (0.10)	-0.05˚ (0.15)	0.099
Operated	-0.02˚ (0.11)	-0.06˚ (0.11)	

Data are presented as "Means (Standard Deviations)"
** Significant ($p < 0.05$)*
*** Positive values indicate knee flexion (lack of full extension)*
**** Negative values indicate external knee extension moment*

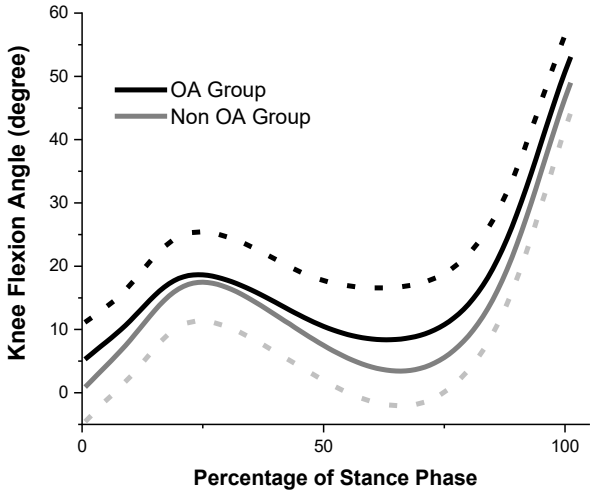

Figure 2.1 Knee flexion angles in the contralateral limb during stance phase of gait for the OA and non-OA groups

- The dashed lines represent standard deviations (SD).

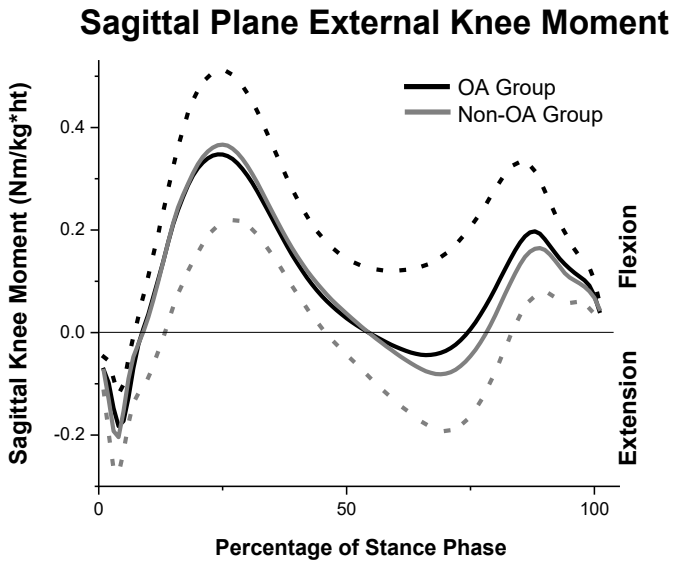

Figure 2.2 Sagittal plane knee moments in the contralateral limb during stance phase of gait for the OA and non-OA groups

- The dashed lines represent standard deviations (SD).

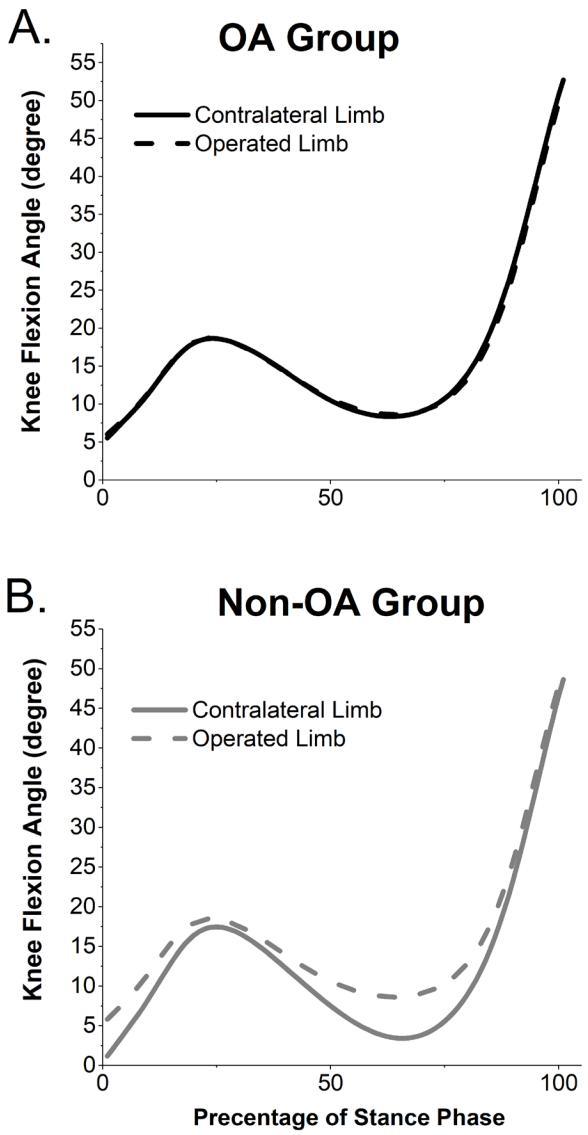

Figure 2.3 Curves demonstrating inter-limb symmetry for sagittal plane knee angles during stance phase of gait for the OA (A) and non-OA (B) groups

2.5 Discussion

The goal of this study was to compare the sagittal plane biomechanics in subjects with and without contralateral knee OA after unilateral TKA. We focused on sagittal plane biomechanics as these metrics have been the target of movement retraining programs after TKA [20] and represent common abnormalities that persist in the operated limb after TKA [44]. If clinicians and researchers are to use the contralateral limb as a control comparator, it is important to understand if structural changes in that knee, even without substantial joint pain, are related to abnormal movement patterns. We found that despite no difference in pain between groups, individuals who had structural OA in the contralateral limb moved more symmetrically, albeit more abnormal than individuals without contralateral knee OA.

Although all subjects in this study had no plans for contralateral TKA and all had pain less than 4 out of 10 in the contralateral limb, two-thirds (66%) of subjects had radiographic evidence of OA in the contralateral knee at the time of index surgery (primary TKA). This is concerning, as subjects with contralateral knee OA also had abnormal knee motion that was characterized by less knee flexion excursion and a sustained knee flexion throughout stance (Figure 2.1). These biomechanical differences existed between groups, even though there was no difference in contralateral knee pain (Table 2.1). This suggests that structural changes in the knee can affect knee biomechanics, even without substantial symptomatic changes. However, because we do not have preoperative biomechanical data, we cannot assume that the structural changes preceded changes in knee biomechanics. It is possible that the structural changes and/or the biomechanical abnormalities were present in the contralateral knee prior to the incidence or progression of contralateral knee OA.

Visual inspection of the ensemble curves (Figure 2.3) supported the findings of the discrete measures of difference (Table 2.2), showing that subjects in the OA group had more symmetrical movement patterns than the non-OA group throughout the stance phase. Movement symmetry has been suggested to be an optimal biomechanical outcome after TKA and rehabilitation treatment protocols have been designed to reduce inter-limb asymmetries [32,56,33,57,58]. This is a concept that is applied to many therapeutic areas, including patients with neurological conditions and other musculoskeletal pathologies, such as anterior cruciate ligament reconstruction [59]. While training biomechanical symmetry may be an ideal treatment approach for patients who have true unilateral pathology, our results suggest that biomechanical symmetry should not be the only factor upon which movement patterns are assessed after TKA. In our study, gait mechanics in the OA group could be considered bilaterally abnormal, even though they had surprisingly symmetrical movement patterns in the sagittal plane (Figure 2.3) and a lack of differences between limbs (Table 2.2). Normative values for knee excursion during weight acceptance in age-matched individuals is 15.5 degrees [60]. This value is higher than that found in the operated (12.9 degrees) and contralateral (13.3 degrees) knees of our OA group. To date, there is no clear evidence on how large a difference between limbs or between groups is clinically important. Differences in knee excursion between healthy older adults without OA and those with symptomatic knee OA was found to be 3.8 degrees [61]. Although our differences were smaller, the interaction effects from our ANOVA models suggest a significant difference in bilateral movement patterns in the OA and non-OA group. Future prospective and longitudinal studies that determine the effect of joint excursion on OA progression or functional decline are needed.

Previous studies have found that gait patterns become more symmetrical two and three years after TKA [43]. By several years after TKA, it is also known that many patients experience a predictable decline and strength and function of the contralateral knee [16]. It is conceivable that the improved symmetry several years after TKA is the result of the persistent decline in the status of the contralateral limb, not an improvement in the operated side [57]. This hypothesis is supported by the findings of this study. Structural changes associated with greater OA severity in the contralateral knee seem to be the primary driver of limb symmetry. Subjects who did not have OA in the contralateral knee presented in the typical post-operative fashion of asymmetrical movement in which only the operated limb deviated from normal values.

Even though sagittal plane knee excursions were different between groups, there was no difference in peak knee flexion. Clinically, there has been an emphasis on restoring normal peak knee flexion so that the quadriceps can act to absorb the force of the body with each step. Our findings suggest that therapists attempting to normalize knee biomechanics after TKA should attempt to increase knee extension at initial contact and increase knee extension at midstance (Figure 2.1). Most subjects walked with a stiff and flexed knee joint throughout the majority of the stance phase and failed to come to full extension at midstance in the operated limb. Future work should determine whether these differences in knee extension during gait are related to loss of active knee extension range of motion, or due to residual abnormalities in limb coordination strategies. Although slower walking speeds are related to less joint excursion during gait [14,62], this does not appear to be a factor in our sample since both groups had similar walking speeds.

Although this study identified distinct differences in movement patterns between those with and without contralateral knee OA, there are some limitations to our methods. Future research should determine whether other measures of OA severity, including joint space width or magnetic resonance imaging features, are more beneficial in determining how early OA may influence biomechanics. Due to the nature of testing, subjects with substantial health comorbidities were excluded from this analysis. The results from this study may not be generalizable to all patients after the TKA. We also did not evaluate the association between many clinical measures and movement patterns. Although we found that the OA group did not have significantly greater pain, it is possible that other factors such as weakness, poor proprioception, or feelings of instability were related to reduced joint excursions. Future studies should consider including other clinical measures when determining the underlying cause for abnormal movement patterns in both limbs after TKA.

There were also limitations related to sample size and statistical approach in this analysis. Given that this was a preliminary research into the effect of the presence of contralateral knee OA and movement patterns, we intended to identify all variables that may be included for future longitudinal studies. It is also possible that given our smaller sample size, we did not have enough power to detect a statistical difference, should a true difference exist, for all of the outcomes. Therefore, we cannot assume that a true difference does not exist for all of the biomechanical metrics. Future work should seek to replicate our study using a larger sample size powered for biomechanical variables that may be inherently more variable. To address some of these limitations, we reported the effect size and provided confidence intervals (Tables 2.2) to better quantify the magnitude of differences between groups.

2.6 Conclusions

The majority of subjects with primarily unilateral symptoms have bilateral radiographic OA at the time of primary TKA even though they were considered as unilateral TKA patients at the time of surgery. Subjects with contralateral knee OA do not have more contralateral knee pain, but do have gait that is more symmetrical, albeit more abnormal, than those without contralateral knee OA. Symmetrical movement patterns should not be the sole factor upon which movement recovery is based. The contralateral knee cannot be used as a valid control limb after unilateral TKA in the presence of radiographic knee OA. Researchers and clinicians should consider radiographic disease severity in the contralateral limb when developing research protocols, screening patients, or creating treatment plans.

2.7 Funding and acknowledgments

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Chapter 3

KNEE BIOMECHANICS AND CONTRALATERAL KNEE OSTEOARTHRITIS PROGRESSION AFTER TOTAL KNEE ARTHROPLASTY

NOTE: This is a published version of the following article: Aljehani MS, Christensen JC, Snyder-Mackler L, Crenshaw J, Brown A, Zeni JA Jr. Knee biomechanics and contralateral knee osteoarthritis progression after total knee arthroplasty. Gait Posture. 2022 Jan;91:266-275. doi: 10.1016/j.gaitpost.2021.10.020. Epub 2021 Oct 30. PMID: 34775230.

3.1 Abstract

***Background*:** Despite the success rate of Total Knee Arthroplasty (TKA), many patients undergo contralateral TKA. It is possible that altered gait mechanics after unilateral TKA play a role in the progression of contralateral OA progression. ***Research question*:** The purpose of this study was to identify biomechanical predictors of radiographic OA progression in the contralateral (non-surgical) knee after unilateral (primary/initial) TKA. In addition, this study quantified for patients who had contralateral OA progression. ***Methods*:** Biomechanical outcomes were collected 6-24 months after unilateral primary TKA and were used to predict changes in contralateral OA severity at follow-up. Participants were divided into "Progressor" and "Non-Progressor" groups based on changes in Kellgren-Lawrence (KL) OA grade and Joint Space Width (JSW) between baseline and follow-up testing sessions. Biomechanical factors during walking were peak knee adduction moment, knee flexion/extension excursions, knee angle at initial foot contact, and peak knee flexion/extension. Multiple independent t-tests were used to examine the magnitude of differences in biomechanical variables between the groups. Logistic regression was used to examine the association between the biomechanical predictors and change in KL scores and JSW. ***Results*:** The mean time between surgery and follow-up x-rays was 8.8 (2.4) years. Of 40 participants, 62.5-78% had contralateral radiographic knee OA progression by follow-up. There were no significant differences in the biomechanical variables between groups. For the regression analysis, none of the biomechanical variables were found to be predictors for contralateral OA progression. ***Significance*:** Although abnormal biomechanics are known risk factors for primary knee OA, it is possible that the mechanisms that result in OA progression of the contralateral limb are different than primary knee OA progression. Future work should

evaluate other objective measures of OA progression and determine if cumulative measures of joint loading are related to OA worsening.

3.2 Introduction

Total knee arthroplasty (TKA) is a common surgical treatment for people with end-stage knee osteoarthritis (OA)[1,2]. More than 700,000 TKAs are performed annually in the United States (US)[3], and that number is expected to increase 4-fold by 2040[63]. Despite the benefits of TKA, many individuals who undergo unilateral TKA experience a progression of OA on the contralateral knee after the initial surgery[6]. This progression can happen quickly, and for those who require a contralateral TKA, the time to second surgery is only 3.2 years[5]. Even in patients who are unilaterally symptomatic at the time of the primary procedure, nearly 25% of these patients undergo contralateral TKA within several years[5].

It is possible that altered gait mechanics after unilateral TKA play a role in the progression of contralateral OA progression[15]. Specifically, greater joint loading, as measured by higher knee adduction moments, is a known risk factor for primary OA progression[11,12] and reduced knee flexion excursion is a risk for undergoing TKA in the future[15,64]. Individuals after unilateral TKA tend to favor the contralateral limb during functional and weight-bearing tasks like walking[32] and rising from a chair[30]. Specifically, these individuals place greater force on the contralateral limb and have higher adduction moments in the contralateral knee[32]. It is possible that reliance on the contralateral knee after index TKA is an underlying cause of radiographic contralateral OA progression, but this has not been fully explored.

Previous work from our lab revealed that altered movement patterns after TKA, specifically reduced sagittal plane motion (i.e. stiff-legged gait patterns), are associated with future contralateral TKA use[15]. While this study explored the relationship between biomechanics and contralateral OA progression, it used time to contralateral TKA as an end-point and did not examine the association between biomechanics and radiographic changes in the contralateral knee. Undergoing TKA is usually indicative of OA progression, but the decision to undergo TKA is multifactorial and may be driven by factors other than structural and symptomatic changes in the knee joint. Identification of risk factors is an essential first step to developing interventions that preserve the long-term joint integrity of operative and non-operative.

Therefore, the primary purpose of this study was to identify biomechanical predictors of radiographic OA progression in the contralateral (non-surgical) knee after unilateral (primary/initial) TKA. We hypothesized that individuals who demonstrate OA progression on their contralateral knee will have higher knee adduction moments and lower knee flexion/extension excursions at baseline compared to those who do not demonstrate OA progression.

3.3 Methods

3.3.1 Study design

This was a longitudinal prognostic study that utilized a participant pool from a previous observational cross-sectional study, which will be referred to as the "parent study". As part of the parent study, biomechanical[32] outcomes were collected 6-24

months after unilateral primary TKA (Table 3.1; Study Component 3). For the current analysis, we collected pre-operative x-rays from the medical record (Study Component 1) and had participants undergo follow-up x-rays (Study Component 4) to quantify OA severity. Biomechanical measurements collected at baseline (6-24 months after TKA) were used to predict changes in contralateral OA severity at follow-up.

Table 3.1 Measurement sequence

	Additional Data for this Study	**Parent Study**		**Additional Data for this Study**
Study Component	**1**	**2**	**3**	**4**
	Baseline X-rays	Primary unilateral TKA	Biomechanical measurements	Follow up X-rays
	→	→	→	→
Time Relative to TKA	1-2 months before TKA	Time of TKA	6-24 months after TKA	5.5-13 years after TKA

3.3.2 Participants

Participants in this study were individuals who participated in the parent study and agreed to return for the follow-up radiographic assessment. In the parent study, participants were recruited through a local group of orthopedic surgeons who perform tricompartmental cemented TKA with a medial parapatellar approach using either a posterior cruciate-retaining or posterior stabilized prosthesis. In the parent study, participants were enrolled if they had end-stage unilateral knee OA and underwent primary unilateral TKA. In order to obtain a primarily unilaterally symptomatic sample, participants were excluded from the parent study if they: 1) were scheduled for or planned a contralateral TKA, 2) reported pain greater than 4 out of 10 in the contralateral knee, 3) had any other lower extremity surgeries, or 4) had limited physical function due to musculoskeletal involvement in the spine or lower extremities. Participants who underwent revision surgery were excluded from this study.

For the current analysis, all participants who participated in the parent study (N=229) were attempted to be contacted and informed about the follow-up study. Letters were sent to all participants informing them of the additional study procedures. Interested participants (n=60) contacted the research coordinator for screening and scheduling. Forty-two participants had biomechanics and x-ray data. Subjects were excluded from this analysis if they had KL Grade 4 in either the medial or lateral compartment. Prior participating in the study, participants signed a written informed consent form approved by the Human Subjects Review Board at the University of Delaware. Previous work on knee kinematics found that the minimal clinically important differences (MCID) between limbs was 3 degrees[65] for knee flexion excursion. Because knee flexion excursion has been previously linked to contralateral

OA progression[64], we used this as the basis for our sample size. We found that a sample size of 34 individuals was sufficient to identify difference between groups, should one exist.

3.3.3 Biomechanical measurements

Biomechanical Measurements were acquired during over-ground walking at a self-selected speed. Detailed information on the biomechanical setup has been previously reported[10,29,30]. Briefly, lower limb joint kinematics were captured using retro-reflective markers tracked via an 8-camera high-speed motion analysis system (VICON, Oxford Metrics, London, England) at 120-Hz. Kinetic (peak ground reaction force and joint moments) and kinematic (peak angles and excursions) variables were calculated with 3-dimensional instrumented motion analysis. Two force platforms (Bertec Corp., Worthington, OH, USA) (1080-Hz) synchronized with the cameras recorded the ground reaction force data to measure the lower extremity joint kinetics. Anatomical markers were bilaterally placed at acromioclavicular joints, iliac crests, greater trochanters, medial and lateral femoral epicondyles, medial and lateral malleoli, and first and fifth metatarsal heads. Non-anatomical markers (tracking markers) included 1) two markers placed on the back of the shoes, 2) one shell with fixed three markers placed on the pelvis at the sacrum, and 3) five shells with four fixed markers each placed on the posterior thoracic area, the lateral thighs, and the lateral shanks.

After placing markers bilaterally and obtaining a standing calibration, participants walked until they achieved at least 5 successful walking trials at a consistent velocity[66]. To control for walking velocity, the average speed of the

measured successful walking trials was maintained within +/- 5% of the individual's average walking speed that was obtained prior to the start of the data collection. A successful walking trial was described as a trial in which the participants contacted each forceplate with different leg, and without intentionally targeting the force plates. Joint angles and moments during walking using a standard inverse dynamics approach integrating kinematic and kinetic data (Visual 3D, C-Motion, Germantown, MD)[66]. Euler X-Y-Z sequence were used to calculate the knee joint angles (flexion/extension, abduction/adduction then rotation sequences). Force platforms data were filtered at (40-Hz) while marker trajectories were low pass filtered at (6-Hz) using a second order phase-corrected butterworth filter.

Given the previous work linking biomechanics to OA progression[15,11,12,64], the biomechanical variables of interest for study (Figure 3.1) were overall peak external knee adduction moment (normalized to body mass and height), and knee flexion/extension excursions during stance. Since work from our lab has revealed that full knee ROM is a modifiable factor that can postpone the TKA need (population aged between 46-78)[18], we also measured other biomechanical factors, such as knee angle at initial contact and peak knee flexion/extension during stance (Figure 3.1). Biomechanical changes on the operated and non-operated limbs are associated with contralateral TKA use; therefore, both limbs were evaluated in the current analysis.

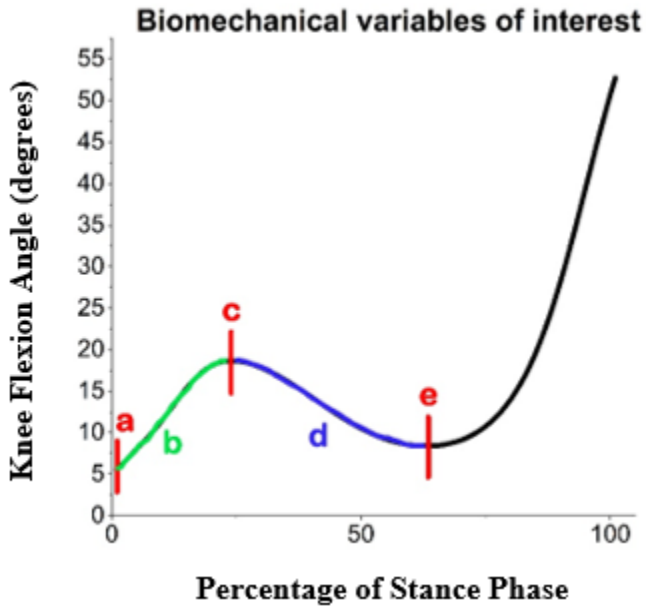


Figure 3.1 Biomechanical variables of interest

a. Knee Angle at Initial Contact
b. Knee Flexion Excursion calculated as the difference between Initial Contact and Peak Knee Flexion
c. Knee Angle at Peak Knee Flexion
d. Knee Extension Excursion calculated as the difference between Peak Knee Flexion and Peak Knee Extension
e. Knee Angle at Peak Knee Extension

3.3.4 Radiographic reading and digital x-ray assessment

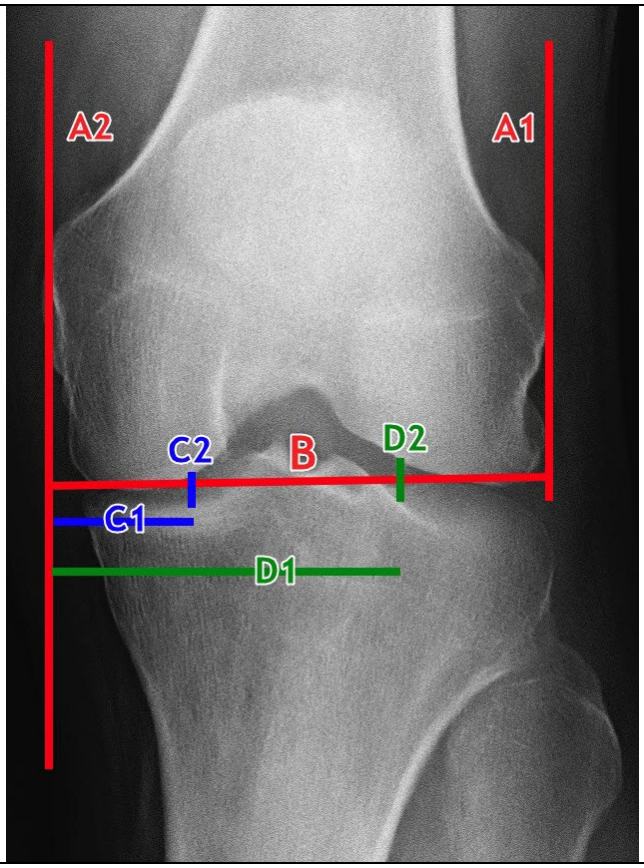
Radiographic images were obtained at two time points (pre-operative and follow-up; Table 3.1). If the participant agreed to participate in this follow-up analysis, bilateral posterior to anterior (PA) bent-knee (20-degree) radiographs were obtained. The time between TKA and follow-up x-ray varied depending on the participant's original testing date. In the event the individual underwent a contralateral TKA at the time they were re-contacted for this study, pre-operative x-rays of the contralateral knee from the medical records were obtained. In addition to these follow-up x-rays, bilateral weight-bearing PA bent-knee radiographs taken prior (1-2 months) to the primary TKA were retrieved from patients' records. Osteoarthritis Research Society International (OARSI) has recommended that a semi-flexed knee view is a valid method to evaluate structural severity in knee OA clinical trials[67].

Because the follow-up radiographs were digital, SigmaView software (Agfa HealthCare Corporation, Greenville, SC, USA) were used to measure Kellgren-Lawrence (KL) grades. The KL scale[54] has five grades of increasing OA severity: none (0), doubtful (1), minimal (2), moderate (3), and severe (4)[54]. Grade-0 indicates no presence of pathological changes. Grade-1 indicates doubtful joint space narrowing and the possible formation of osteophytes, while grade-2 shows definite osteophytes and possible joint space narrowing. Grade-3 indicates definite joint space narrowing, moderate multiple osteophytes, possible bony ends deformity, and some sclerosis may present. Grade-4 indicates large osteophytes, severe sclerosis, definite deformity in bone ends, and obvious narrowing of joint space. KL grading was performed separately for the medial and lateral compartments. Previous work found that KL grade is a significant predictor for contralateral OA progression to TKA[68]. Although there is some subjectivity inherent in the KL scoring, it evaluates joint alignment,

bony (osteophyte) formation, cartilage width changes, and articular cartilage deformation[69], all of which are relevant for classifying OA severity. The evaluator (MSA) in this study underwent a standardized KL training program and graded all of the X-rays. The grader had excellent intersession reliability (ICC = 0.956) with a narrow confidence interval (95% CI = 0.921 – 0.975). This grader was blinded to participants' biomechanical data at the time of grading.

In addition to KL scoring, the X-rays were also evaluated for joint space width (JSW) in the medial and lateral compartments. To quantify JSW (mm), the distal femoral width was measured first by drawing segment that is tangent to both medial and lateral femoral condyles. Then, drawing a 90-degree angle with a horizontal arm that is tangent to the most prominent point on femoral epicondyle for each compartment. Based on the recommendation from the Osteoarthritis Initiative (OAI)[70], locations at 25% and 70% of the distal femoral width, starting from the medial compartment, will be identified. In the OAI dataset, this method was compared to Magnetic Resonance Imaging (MRI) measures of cartilage loss[70]. OAI suggested these locations because they found that these locations can monitor the progression based on the knee alignment. Using JSW at 25% is optimal for Varus knees, while 70% is a preferred location for Valgus knees. These location measurements made with the medial side of the joint as the reference point (0%). JSW was calculated as the distance of the vertical line between the femur and the tibia at the 25% (medial compartment) and 70% (lateral compartment) locations. An example of a measured X-ray is in Figure 3.2.

Figure 3.2 Radiographic grading



A1: Tangent line to the lateral femoral epicondyle
A2: Tangent line to the medial femoral epicondyle
B: Distal femoral width
C1: Location recommended by osteoarthritis Initiative (OAI) at 25% of the distal femoral width (medial compartment)
C2: Joint Space Width (JSW) at the medial compartment
D1: Location recommended by OAI at 70% of the distal femoral width (lateral compartment)
D2: JSW at the lateral compartment

All measurements are in millimeter (mm).

3.3.5 Defining the OA progression

Osteoarthritis Research Society International (OARSI) suggests that OA progression should be presented in a dichotomous form; hence, to categorize individuals as "progressors or non-progressors"[71]. We defined OA progression using change in KL grade and joint space width (JSW). Our decision to use two different methods is because KL scores and JSW capture different anatomical structures and have a different level of subjectivity. Although KL score is less objective, it can evaluate joint alignment, bony (osteophyte) formation, cartilage width changes, and articular cartilage deformation[69,72]. The JSW is less subjective and evaluates the cartilage thinning and width changes in objective terms (millimeters "mm") on a continuous scale[70].

For the KL method, participants were divided into two groups based on the maximum changes in the KL score in either the medial or lateral compartments of the contralateral knee between the initial pre-operative radiographs and the follow-up period. Individuals who demonstrated worsening KL grades (at least 1-point change in either compartment) were defined as "progressor group". Individuals without a change in KL grade in either the medial or lateral compartment were classified as "non-progressor group". Given that individuals with KL grade 4 cannot demonstrate progression, individuals with grade 4 contralateral knee OA at baseline were excluded from the current analysis.

For the JSW method, there is a heterogeneity of reported cut-off points for JSW that define progressors in the literature. The suggested values for progressor range from (0.12 to 0.84 mm)[71] and (0.50 to 0.80 mm)[73] as a change in JSW from baseline to follow up[73]. Cooper and colleagues[74] suggested using 0.5 mm as a cut-off in minimum joint space narrowing which reflects a clinical relevant progression in

individuals with knee OA. Bruyere and colleagues[73] found that individuals who had joint space narrowing >0.50 mm within 3 years follow-up were more likely to have total joint replacement over the next 5 years than individuals without similar radiographic progression. Given that 0.50 mm appears to be a common mid-point across studies, participants were divided into two groups based on a decrease of 0.5 mm or more in the medial or lateral compartments of the contralateral knee.

The rationale for defining OA progression using maximum KL grade and minimal JSW (as opposed to separating the medial and lateral compartment for KL, or using the 25% and 70% locations for JSW) is based on clinical observations and previous evidence[70]. Patients are typically concerned with symptoms (pain) and loss of function more so than the location of the impairment (medial vs. lateral compartment) and individuals undergo TKA for both medial and lateral compartment symptoms. However, it should be noted that knee adduction moment is only predictive of medial compartment progression. Therefore, we performed a sub-analysis of OA progression in the medial compartment of KL grade and 25% JSW location of the distal femoral width, which is a standard location for identifying the change in the medial compartment.

3.3.6 Statistical analysis

Participants were divided into two dichotomous groups defined as the "progressor group" or "non-progressor group" based on changes in the KL score (the maximum change in either the medial or lateral compartments) in the contralateral knee between the initial pre-operative radiographs and the follow-up radiographs. Separately, we also defined "progressors" and "non-progressors" based on the change in the JSW. The statistical analyses were performed in two steps. First, multiple

independent t-tests were used to examine the magnitude of differences in biomechanical variables between the two groups. Second, hierarchical logistic regressions were used to examine the association between the biomechanical predictors and the dependent variables (progressor and non-progressor). The predictors were entered in the regression model as follows: Block 1) demographics (age, BMI, sex); Block 2) biomechanical variables. This analysis was performed separately based on progression defined from KL scores and from JSW scores.

Since our primary definition of progressor was based on changes in either the medial or lateral tibiofemoral compartment, a sub-analysis was performed to identify predictors of medial compartment progression. The adduction moment is a surrogate measure of medial compartment joint loading[19], so higher adduction moments are unlikely to contribute to lateral compartment disease. Therefore, an additional analysis was performed to determine if peak adduction moment was predictive of changes in the medial tibiofemoral compartment. In this sub-analysis we divided the KL group based on the medial compartment only, not the maximum KL score. The alpha level was set at 0.05 for all regression analyses. While all odds ratios are presented as a one unit change in the variable, we also calculated the odds of 1 SD change for the adduction moment, given that a 1-unit change in the adduction moment is not physiologically likely. Results for the one-unit change are shown in the table, and 1 SD change are shown in the manuscript text.

3.4 Results

3.4.1 Participants:

Sixty participants were able to be re-contacted and participated in the follow-up study. Of these participants, pre-operative x-rays were able to be obtained from 42 participants. Two of these participants were excluded because they had a KL grade of 4 at baseline x-ray in the contralateral knee in either the medial (n=1) or lateral (n=1) compartment. Forty participants were included in the KL analysis while 38 participants were included in the JSW analysis due to magnification issues of 2 baseline x-rays that precluded accurate distance measurements, but still allowed for KL scoring. No multicollinearity was found in our sample; variance inflation factor (VIF) values were less than 2 and tolerance values exceeded 0.6[75].

3.4.2 KL Score Results:

At the time of baseline testing, participants had mean age of 66.5 (6.8) years and BMI of 32.0 (4.7) kg/m^2. The mean time between surgery and follow-up x-rays was 7.8 (2.5) years. There were 19 males and 21 females. No significant differences were found in sex, age, BMI, and height between progressor and non-progressor groups. At the baseline, the majority of the progressors had KL grade 1 or 2 (n=22) in the contralateral knee (Table 3.2).

Of 40 participants included in the KL analyses, 25 participants (62.5%) had contralateral radiographic knee OA progression by follow-up and 15 (37.5%), had no change. Of those 25 participants that changed KL scores, 12 changed one grade level, 10 changed two grade levels and 3 changed three grade levels.

There were no significant differences in the biomechanical variables between groups. There was also no significant difference in adduction moment in the medial

compartment subset analysis (Table 3.3). For the regression analysis, none of the biomechanical variables were predictors for contralateral OA progression (Table 3.4).

As shown in Table 3.4, the odds ratio was large for the adduction moment (21.22 [95% CI: 0.14 – 3299.89]) because the 1-unit change in adduction moment is not physiologically likely. Therefore, in addition to calculating the 1-unit change in odds ratio, we also calculated the odds ratios based on 1-standard deviation (SD) change. A one-standard deviation change was 0.145 Nm/kg for the non-operated side. For every 1 SD change, the risk of KL progression was 3.005 (p=0.235).

3.4.3 JSW Results:

At the time of baseline testing, participants had mean age of 65.1 (5.6) years and BMI of 31.5 (3.9) kg/m^2. The mean time between surgery and follow-up x-rays was 8.8 (2.2) years, p=0.000 (Table 3.2). There were 18 males and 19 females. No significant differences were found in sex, age, BMI, and height between progressor and non-progressor groups (Table 3.2).

Of 38 participants included in the JSW analyses, 29 participants (78%) had contralateral radiographic knee OA progression by follow-up. There were no significant differences in the biomechanical variables between groups (Table 3.3). For the regression analysis, none of the biomechanical variables were predictors for contralateral OA progression (Table 3.4).

As with the risk of KL progression, we also calculated the odds of JSW progression for a 1 SD change in adduction moment because a 1-unit change in the adduction moment is not physiologically likely. A one-standard deviation change was 0.147 Nm/kg for the non-operated side and the for every 1 SD change, the risk of JSW progression was -0.054 (p= 0.983).

Table 3.2 Participant demographics

	Based on KL scores (N = 40)			Based on JSW (N = 37)		
	Progressor Group n = 25 (62.5%)	**Non-Progressor Group n = 15 (37.5%)**	**p -value**	**Progressor Group n = 29 (78%)**	**Non-Progressor Group n = 8 (22%)**	**p -value**
Sex Male n (%) Female n (%)	 10 (40%) 15 (60%)	 9 (60%) 6 (40%)	0.220	 14 (48%) 15 (52%)	 4 (50%) 4 (50%)	0.931
Age (years)	67.2 (5.9)	65.7 (7.6)	0.481	67.2 (6.6)	63.0 (4.7)	0.098
BMI (kg/m2)	31.5 (4.4)	32.6 (5.0)	0.476	32.2 (5.1)	30.8 (2.7)	0.443
Height (meter)	1.7 (0.1)	1.7 (0.1)	0.839	1.7 (0.1)	1.7 (0.1)	0.860
Gait Speed (meter/second)	1.33 (0.17)	1.34 (0.15)	0.932	1.33 (0.16)	1.36 (0.18)	0.833
Time between Surgery and Follow-up X-ray (years)	7.64 (1.96)	8.00 (3.07)	0.652	7.3 (1.8)	10.4 (2.6)	0.000 *
Baseline KL score (Grade: n)	1: 11 2: 11 3: 3	1: 7 2: 4 3: 4	-	-	-	-

Data are presented as “Means (Standard Deviations)”
BMI = Body Mass Index

Table 3.3 Progressor vs non-progressor (maximum KL of the medial and lateral compartments)

Biomechanical Variables	Side	Based on KL scores					Based on JSW				
		Progressor (n=25; 62.5%) Mean (SD)	Non-progressor (n=15; 37.5%) Mean (SD)	Mean Difference (95% CI)	Cohen's *d*	p-value	Progressor (n = 29; 78%) Mean (SD)	Non-progressor (n = 8; 22%) Mean (SD)	Mean Difference (95% CI)	Cohen's *d*	p-value
Knee Flexion Excursion (degrees)	Operated	12.9 (3.1)	14.7 (3.2)	1.78 (-0.29 – 3.86)	-0.59	0.089	13.8 (3.4)	12.7 (3.0)	1.17 (-1.51 – 3.84)	0.34	0.382
	Contralateral	15.4 (3.4)	15.1 (4.3)	-0.27 (-2.277 – 2.22)	0.08	0.825	15.1 (3.1)	16.1 (6.0)	-0.95 (-4.06 – 2.17)	-0.27	0.542
Knee Extension Excursion (degrees)	Operated	10.7 (4.4)	11.9 (4.9)	1.26 (-1.80 – 4.32)	-0.27	0.411	11.8 (4.3)	9.4 (5.9)	2.36 (-1.40 – 6.12)	0.53	0.211
	Contralateral	13.7 (5.3)	12.6 (6.0)	-1.13 (-4.80 – 2.54)	0.20	0.537	14.1 (4.7)	12.7 (7.6)	1.38 (-3.00 – 5.76)	0.27	0.525
Knee Angle at Initial Contact (degree)	Operated	5.3 (4.2)	6.0 (6.4)	-0.69 (-4.08 – 2.70)	-0.14	0.684	5.5 (5.2)	5.6 (5.5)	0.14 (-4.13 – 4.42)	-0.02	0.946
	Contralateral	3.3 (5.5)	4.3 (7.2)	-1.04 (-5.14 – 3.05)	-0.17	0.609	3.7 (4.9)	2.5 (6.9)	-1.23 (-5.61 – 3.15)	0.26	0.573
Peak Knee Flexion (degree)	Operated	18.2 (4.3)	20.7 (6.6)	-2.47 (-5.95 – 1.01)	-0.49	0.159	19.3 (5.6)	18.3 (4.5)	-1.02 (-5.43 – 3.38)	0.19	0.640
	Contralateral	18.7 (5.8)	19.4 (8.4)	-0.77 (-5.34 – 3.80)	-0.10	0.735	18.9 (5.8)	18.6 (6.2)	-0.28 (-5.08 – 4.51)	0.05	0.906
Peak Knee Extension - Mid stance knee angle (degree) **	Operated	-7.5 (4.8)	-8.8 (5.3)	-1.22 (-4.54 – 2.11)	0.27	0.463	7.5 (5.1)	8.8 (5.8)	1.34 (-2.86 – 5.53)	-0.25	0.522
	Contralateral	-4.9 (6.1)	-6.8 (10.1)	-1.90 (-7.07 – 3.28)	0.25	0.462	4.8 (4.0)	5.9 (10.9)	1.10 (-8.02 – 10.22)	-0.19	0.786

Progressor vs non-progressor (maximum KL of the medial knee compartment)											
	Based on KL scores						Based on JSW				
	Side	Progressor (n=23; 57.5%) Mean (SD)	Non-progressor (n=17; 42.5%) Mean (SD)	Mean Difference (95% CI)	Cohen's *d*	p-value	Progressor (n = 26; 70%) Mean (SD)	Non-progressor (n = 11; 30%) Mean (SD)	Mean Difference (95% CI)	Cohen's *d*	p-value
Peak Knee Adduction Moment (Nm/kg)	Operated	0.308 (0.106)	0.274 (0.099)	0.0336 (0.03 – 0.10)	0.34	0.315	0.287 (0.101)	0.293 (0.119)	-0.0062 (-0.07 – 0.08)	-0.06	0.871
	Contralateral	0.386 (0.156)	0.433 (0.127)	-0.0465 (-0.14 – 0.05)	-0.33	0.321	0.402 (0139)	0.407 (0.170)	0.0049 (-0.10 – 0.11)	0.00	0.927

Data are shown in degrees and presented as “Means (Standard Deviations)”

** Negative value means lack of knee extension

Table 3.4 Logistic regression analysis

	Based on KL scores			Based on JSW		
Predictors	**Nagelkerke R Square**	**Odds ratio (95% CI)**	**p-value**	**Nagelkerke R Square**	**Odds ratio (95% CI)**	**p-value**
Contralateral Peak Knee Adduction Moment (Nm/kg)	0.231	21.22 (0.14 – 3299.89)	0.235	0.054	0.948 (0.01 – 136.66)	0.983
Contralateral Knee Flexion Excursion (degrees)	0.002	1.02 (0.86 - 1.21)	0.820	0.018	1.077 (0.855 - 1.356)	0.531
Contralateral Knee Extension Excursion (degrees)	0.014	1.04 (0.92 - 1.17)	0.527	0.017	0.953 (0.825 - 1.102)	0.515
Contralateral Knee Angle at Initial Contact "Heel Strike" (degrees)	0.009	1.03 (0.93 - 1.15)	0.599	0.014	1.045 (0.901 - 1.213)	0.562
Contralateral Peak Knee Flexion (degrees)	0.004	1.02 (0.93 - 1.12)	0.728	0.001	1.009 (0.880 - 1.156)	0.902
Contralateral Peak Knee Extension (degrees)	0.019	1.03 (0.95 - 1.12)	0.459	0.646	0.970 (0.855 - 1.101)	0.641

Data are presented as "Odds ratio (95% confidence interval (CI))"
Each model was adjusted for Age, BMI, Sex
Odds ratios represent the change in risk of OA progression associated with a 1-unit increase in the metric of interest (Exp(B)).

3.5 Discussion

In this study, we found that the incidence of radiographic knee OA progression in the contralateral knee was 62.5% based on KL score and 78% based on joint space narrowing by an average of 8.3 years follow-up from initial TKA. This is a relatively large incidence of OA progression within an 8-year window. A previous study that evaluated primary OA progression over an average of 6.6 years, found that 22.7% of the participants demonstrated radiographic progression[76]. However, that was in a primary OA cohort, and the incidence of progression in the contralateral knee may differ as biomechanics are known to be altered after TKA. One previous study found that contralateral TKA use in a general sample of patients was 46% within 3 years of the index surgery[6]. However, these studies relied on contralateral TKA use and did not evaluate objective measures of OA progression. Clinicians should be aware that even in patients who are largely asymptomatic in the contralateral knee at baseline, OA progression is common. Despite this, we did not find any association between OA progression and movement patterns.

In this study, OA severity was assessed using both KL scores and the JSW. While they are often interpreted similarly from a clinical perspective, each outcome provides different information about anatomical structure. KL grades consider joint alignment, osteophyte (bony) formation, and articular cartilage deformation when quantifying severity[69], while JSW is a more objective measure that considers solely the thickness of the cartilage on a continuous scale[70]. Because both approaches revealed contralateral knee OA progression, it can be assumed that the contralateral knee OA progression is due to not only cartilage thinning, but also the development of osteophytes and changes in gross joint structure. However, there was a slightly larger

incidence when using the JSW method (78%) when compared to the KL scores (62.5%). This may suggest that joint space narrowing occurs even if the patient does not develop osteophytes or bony deformation. The difference in incidence may also be related to the subject's baseline joint structure. Eleven of 25 participants (56%) in the progressor group had KL scores of 2 or 3 at baseline, suggesting they already had osteophytes and bony changes. Therefore, it is likely that subsequent changes in joint quality may be solely limited to cartilage thinning and not the development of larger or additional osteophytes. However, the difference in incidence using the two methods (KL vs JSW) was relatively small, and the majority of patients had OA progression regardless of the method used to quantify it.

Studies from tissue-level experiments have shown that excessive load placed on cartilage can cause structural deterioration[34]. Although previous literature has found that greater knee adduction moments at baseline predict radiographic OA progression in individuals with primary knee OA[11,12], we did not find a similar relationship in the contralateral knee after. Even though patients are more likely to rely on the contralateral leg after surgery, and experience larger adduction moments on the contralateral side[20], this did not appear to be a risk for contralateral OA progression. Given that the one-unit change in adduction moment represents a large increase in this metric, it is unlikely that a patient would experience a one-unit change with OA progression or with an intervention. This is why the values for the odds ratio in Table 3.4 are exceptionally large, albeit not significant. The more clinically relevant risk values are discussed in the text for a 1 SD change in adduction moment. These risks were consistent with what was found for the 1-unit change in that an increase in

adduction moment did not significantly predict an increase in the risk of OA progression.

However, the lack of associated between biomechanics and KL progression should be interpreted with caution for several reasons. First, although knee adduction moment is correlated with medial compartment loading[34], it is only a partial contributor to overall joint load. Other factors, including the knee flexion moment[77] and muscle activity[78] need to also be considered when discussing compressive forces in the local joint environment.

Second, knee adduction moments are related to OA severity[79] and individuals with higher KL grades have higher adduction moments. In this study, participants with higher KL grades at baseline had higher average adduction moments (mean [SD]): KL 1 = 0.182 (0.105), KL 2 = 0.199 (0.120), KL 3 = 0.243 (0.137); p=0.0012. The time-series curve (Figure 3.3) also shed insight to the progressively larger adduction moments with an increase in OA severity. It is possible that individuals with lower KL grades at baseline are more likely to progress to higher grades at follow-up. This is inherent in the way the KL grading system is designed. The change from a 1 to a 2 requires on the development of a single osteophyte. To change from a 3 to a 4, a patient must develop large osteophytes, severe sclerosis, bony deformity, and large and obvious narrowing of joint space. In this study, there were 19 participants with KL grade 1 at baseline and 11 of these participants (58%) progressed at the follow-up. There were 6 participants with KL grade 3 at baseline and only 2 (33%) progressed by follow-up. Although this is not significant (chi-square 2.44, p=0.12), it may be attributed to the low sample size.

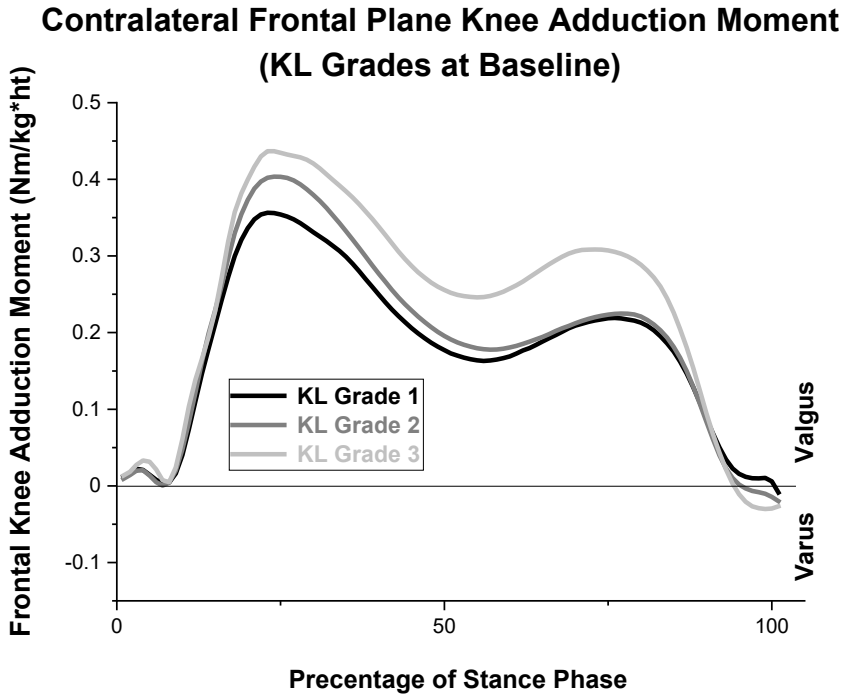
In both the progressor and non-progressor groups, individuals walked with characteristic gait of those with knee OA and TKA. Specifically, both groups landed with knee in a flexed position at initial contact and did not come to full knee extension at midstance, which has shown to be common in this population [15,64]. This supports previous work that found that gait patterns after TKA do not return to normal; often patients continue to walk with flexed knee gait patterns with attenuated sagittal plane motion on the operated side[80]. While this may contribute to residual functional deficits, alterations in the joint loading environment[81], as well as risk of contralateral TKA, it did not appear to be a risk for radiographic changes based on KL scores (Table 3.3). It is worth noting that although the difference between progressors and non-progressors for knee flexion excursion was small, it did approach significant levels and had a moderate effect size, with the non-progressors having more knee flexion excursion in the operated limb (Table 3.3). Given the fact that previous work has shown normal joint excursions are related to functional performance and reduce the risk of contralateral TKA, clinicians should still ensure that patients move with normal knee flexion during the stance phase of gait because limited knee flexion can contribute to residual pain after TKA[82]. While differences in sagittal plane motion between groups may be below the minimal detectable difference (MDD) for knee flexion angles[83], the MDD for knee flexion excursion has not been reported.

Biomechanical changes alone, may not be the driving cause behind OA initiation and progression. Previous work has found that greater joint loads, combined with a greater BMI, was associated with larger loss of cartilage volume in the medial compartment[84]. Similarly, abnormal knee alignment (excessive varus) in the presence of higher body mass, also increases the risk of OA[85]. We also only evaluated these

subjects during gait in a controlled environment. It is possible that physical activity and cumulative loading in the real-world may also influence the rate and incidence of OA progression. Future work should determine if the risk of OA in the presence of biomechanical abnormalities increases in certain subsets of the patient population. Although we accounted for differences in BMI, abnormal biomechanics may predispose those who have systemic metabolic conditions such as diabetes, abnormal knee alignment, or greater physical activity and higher cumulative load to OA progression.

There are several limitations in this study that may also contribute to our negative findings. Our sample was limited to individuals who were enrolled in a previous study and were interested in participating in this follow-up analysis. Due to the smaller sample size, we might have been underpowered to detect statistical differences for all of the outcomes. In light of this, we have added the effect size and confidence interval for our primary outcomes (Table 3.3). Another limitation is that we did not record or have any data for other risk factors, such as physical activity, that may have influenced the total load experienced by the joint during the follow-up period. Gait biomechanics capture a small snapshot of an individual's movement profile in a constrained environment. Capturing movement patterns in a variety of functional tasks, as well as a measure of cumulative loading, may provide additional insight into how movement patterns influence structural progression.

Figure 3.3 Contralateral Knee Adduction Moment – Sagittal Plane



KL Grades at Baseline

First Peak (KL1=0.356), (KL2=0.404), (KL3=0.437)
Second Peak (KL1=0.219), (KL2=0.225), (KL3=0.308)

3.6 Conclusions

We anticipated that the knee adduction moment and knee joint excursions would be associated with contralateral knee OA progression, but our findings did not support this hypothesis. It is possible that the mechanisms that result in OA progression of the contralateral limb are different than primary knee OA progression. Future work should determine if cumulative measures of joint loading are related to OA worsening.

3.7 Funding and acknowledgments

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Chapter 4

QUADRICEPS STRENGTH PROTECTS AGAINST CONTRALATERAL KNEE OSTEOARTHRITIS PROGRESSION FOLLOWING TOTAL KNEE ARTHROPLASTY

Moiyad Saleh Aljehani, PT, MPT, DPT[1, 2]; Jesse C. Christensen, PT, DPT, PhD[3]; Lynn Snyder-Mackler, PT, ScD, FAPTA[1]; Jeremy Crenshaw, MS, PhD[1]; Allison Brown, PT, PhD[4]; Joseph A. Zeni Jr., PT, PhD[4]

[1] University of Delaware, Department of Physical Therapy, Newark, DE, USA

[2] Umm Al-Qura University, Department of Physical Therapy, Makkah, Saudi Arabia

[3] University of Utah, Department of Physical Therapy & Athletic Training, Salt Lake City, UT, USA

[4] Rutgers, The State University of New Jersey, School of Health Professions, Department of Rehabilitation and Movement Sciences, Physical Therapy Program North, Newark, NJ, USA

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4.1 Abstract

Background: As younger and more active individuals undergo total knee arthroplasty (TKA), preserving the integrity of the operated and non-operated joints is essential for successful long-term outcomes. This is particularly important as almost 50% of individuals who undergo unilateral TKA receive a contralateral TKA within 10 years.

Objective: To identify clinical predictors of knee osteoarthritis (KOA) progression in the contralateral knee after unilateral TKA.

Methods: 42 individuals who underwent unilateral TKA participated in this longitudinal observational study. Participants were defined as either "non-progressors" or "progressors" based on radiographic changes in the contralateral knee from baseline (6-24-months post-TKA) to minimum of 6-year follow-up. Radiographic progression was measured with Kellgren-Lawrence (KL) scores and knee joint space width. Predictors included age, sex, BMI, knee pain, range of motion, knee girth, quadriceps strength and functional performance. Differences between progressors and non-progressors were analyzed using t-tests and clinical predictors for progression were identified with logistic regression models.

Results: 25 (62.5%) and 29 participants (78%) demonstrated KOA progression based on KL and knee joint width measures, respectively. Contralateral quadriceps strength was significantly higher in the non-progressor group (25.4+7.5 $Nm/kg/m^2$; p=0.033) and quadriceps weakness was a predictor of KOA progression (odds ratio=1.117; p=0.047) post-TKA. No other clinical predictor was related to contralateral KOA post-TKA.

Conclusions: Quadriceps strength is a prognostic indicator for KOA progression in the contralateral limb. These findings will help clinicians better educate

patients and develop targeted strengthening interventions for improving contralateral joint health post-TKA.

4.2 Introduction

In the United States, more than 700,000 total knee arthroplasty (TKA) procedures are performed each year [3]. Total knee arthroplasty is one of the most common and effective elective procedures to manage chronic joint pain and disability associated with end-stage knee osteoarthritis (KOA) [2]. As the age-range of appropriate candidates widens and the incidence of KOA increases, the number of TKAs performed each year is expected to increase six-fold to 3.48 million procedures by 2030 [4].

After undergoing a primary TKA, many individuals rapidly develop KOA progression in other lower limb joints. Forty to 50% of patients who undergo a primary unilateral joint replacement require an additional joint replacement on another lower limb joint within 5 years (49.5% of those with TKA; 40.2% of those with THA) [6]. Of those who require an additional joint replacement, the contralateral knee is most likely to be replaced [22]. Previous work from our lab has shown that the time from primary TKA to contralateral TKA is short with a mean of 3.5 years and more than one-quarter undergoing contralateral TKA within two years [15,5]. This rapid progression to contralateral TKA occurs in individuals who were asymptomatic in the contralateral knee at baseline and did not have plans to replace any other joints.

Clinical predictors such as knee pain, muscle weakness, limited range of motion, and low functional performance are risk factors for primary KOA progression [18], however, it is unclear if these same relationships exist in contralateral KOA progression post-TKA. Although patient-reported outcomes are commonly improved post-TKA, individuals still demonstrate residual knee pain, quadriceps weakness, reduced joint mobility and poorer functional performance measures compared to health-matched peers [9]. Much of these residual impairments are associated with

compensatory strategies that distribute loading away from the operative limb thereby resulting in greater reliance and greater forces on the contralateral limb [29]. This is important because these impairments do not often resolve and are observed even years after unilateral TKA [33,35]. It is possible that these impairments, and the subsequent reliance on the contralateral limb, is an underlying cause of contralateral KOA progression.

Therefore, the purpose of this study was to identify clinical predictors of radiographic KOA progression in the contralateral knee after primary unilateral TKA. We hypothesized that individuals who demonstrate KOA progression on the contralateral knee after unilateral TKA will have 1) worse clinical metrics (six-minute walk test, timed-up and go test, timed chair rise, and timed stair climbing test), and 2) more knee pain, less knee extension range of motion, and lower quadriceps strength on the contralateral limb at baseline. Successful identification of clinical predictors for contralateral KOA progression may lead to individualized evaluation and provision of rehabilitation programs that target functional deficits and improve long-term outcomes.

4.3 Methods

4.3.1 Study Design

This longitudinal observational study is a follow-up analysis from an original cross-sectional study. In the parent study, clinical outcomes [56] were collected 6-24 months after unilateral primary TKA (Figure 1; Study Component 3). For this follow-up analysis, radiographic images were collected from the medical record to quantify

KOA severity at baseline (prior to TKA). In addition, follow-up radiographs were collected 5.5-13 years after initial TKA and change in KOA severity was evaluated.

Figure 4.1 Measurement sequence

Study component			
1	**2**	**3**	**4**
Baseline x-rays (1-2 months before TKA)	Primary unilateral TKA (Time of TKA)	Clinical measurements (6-24 months after TKA)	Follow up x-rays (5.5-13 years after TKA)

4.3.2 Participants

Participants from the parent study [56] who agreed to return for follow-up radiographic assessment were included in this analysis. All participants met the following inclusion criteria: non-operative knee pain was less than or equal to 4 out of 10 on a visual analog scale; no prior joint replacement procedure to either limb and no plans of undergoing a joint replacement on the contralateral limb within 12 months after the primary procedure and no revision surgeries. All participants were recruited through a local group of orthopedic surgeons who utilize the same pre- and post-operative TKA care pathway.

For the current analysis, letters were sent to all participants from the parent study (N=229) informing them of procedures of this additional follow-up study. Participants who were interested in this follow-up study contacted the research coordinator for screening and scheduling (n=60). In the event the individual did not have a contralateral TKA at the time of re-contact, the participants radiographic images were performed. If the individual reported he or she had a contralateral TKA since baseline testing, we obtained the pre-operative radiographic images of the contralateral knee from the medical records. We were able to obtain pre-operative x-rays from 42 participants. Two of them were excluded due to having Kellgren-Lawrence (KL) grade of 4 at baseline x-ray in either the medial (n=1) or lateral (n=1) compartment of the contralateral knee.

The 6-minute walk test (6MWT) and timed up and go (TUG) are clinical measures linked to symptomatic KOA progression [18]. Previous work on 6MWT found minimal clinically important differences of 79 [86] and 84 [87] meters between individuals with asymptomatic KOA and those without KOA. Further study showed a 36.7% change in the TUG score as a minimal clinically important differences for individuals

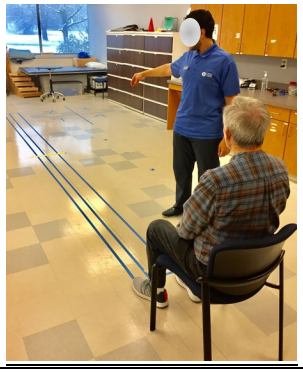
with KOA [86]. Therefore, we used this as the basis for our sample size. We found that a sample size of 20 individuals was sufficient to identify difference between groups. All participants signed a written informed consent form approved by the Human Subjects Review Board at [redacted].

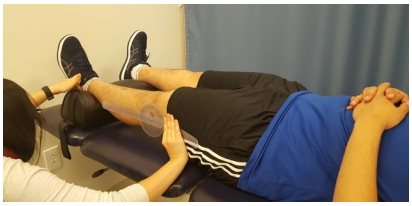
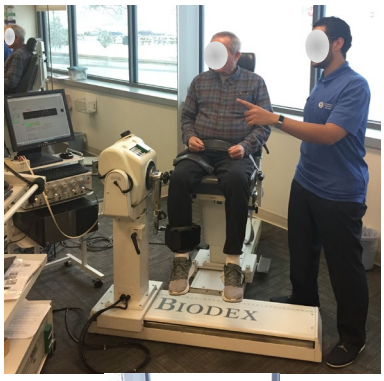
4.3.3 Clinical Measurements

A battery of clinical tests was performed at the baseline session (6-24 months after TKA). Participants rated their current knee pain on a 0-10 scale (where 0 indicated no pain and 10 indicated the worse imaginable pain). Clinical measures including active knee flexion and extension range of motion (ROM) and knee girth measurements were performed with the participants in the supine position. The ROM measures were performed using standard goniometry [88] with knee girth being measured at the mid-patellar level using a tape measure. For functional testing, the 6MWT, TUG, and Stair-Climbing Test (SCT) were evaluated. For all performance tests, the participants were asked to complete the tests "as quickly as possible, while still being safe." Isometric quadriceps strength was measured on an electromechanical dynamometer (KINCOM, Chattecx Corp, Harrison, TN) in which the participants were seated with the knee flexed to 75 degrees. For the self-reported functional performance, participants also completed the Knee Outcome Survey - Activities of Daily Living Scale (KOS-ADLS) [56]. The KOS-ADLS is a self-reported, fourteen-item questionnaire which evaluates the ability to perform the activity of daily living (ADL) and how activity performance is affected by knee symptoms and conditions [89]. Scores were presented as a percentage, in which 100% indicates no functional limitations. All

clinical measurements were performed by testers who were familiar with the measurements and completed standardized training.

Figure 4.2 Clinical testing

1. Six-Minute Walk test (6MWT): Participants were asked to cover as much distance as they can while walking on level ground for six minutes. This test is commonly used in geriatric populations to quantify functional endurance of the lower extremities. A physical therapist was following behind the participant for the duration of the test to offer assistance if needed.	
2. Timed Up and Go test (TUG): This test measures the time it takes a person to rise from a standard height chair (seat height 46 cm), walk 3 meters, and return to a seated position in the same chair. One practice test is performed followed by two recorded trials.	
3. Stair-Climbing Test (SCT): Participants are timed as they ascend and descend 12 standard steps. A handrail is available for the participants during testing. One practice test is performed followed by two recorded trials. The SCT measures a higher level of function than the TUG; therefore, reduces the possibility of a ceiling effect.	

4. Active Range of Motion (ROM): Joint ROM of both knees were measured using a long-arm goniometer. The landmarks to measure the range of motion were knee joint center (axis), greater trochanter, and lateral malleolus. Participants were asked to straighten (extend) or bend (flex) their knees as much as possible several times. The maximal amount of extension and flexion were recorded.	 
5. Quadriceps Strength Testing: Participants were seated on an isokinetic dynamometer and a measuring arm will be secured to the ankle. The knee was positioned at 75 degrees of flexion and will not move during testing. The participants performed three practical trials at 50%, 75%, and 100% of their maximum strength as a warm-up. Then, three recorded trials were collected at 100% of their maximum strength. This was performed for the surgical and non-surgical limbs.	

4.3.4 Radiographic Assessment

Radiographic images were obtained at two time points (pre-operative and follow-up; Figure 1). First, pre-operative bilateral weight-bearing posterior to anterior bent-knee (20 degrees of flexion) radiographs were retrieved from patients' records. These images are routinely acquired in clinical settings prior to TKA (1-2 months before the primary TKA). Second, follow-up bilateral posterior to anterior bent-knee radiographs were obtained using the same radiographic protocol as pre-operative procedures. The time to follow-up varied depending on the subject's original testing date. A semi-flexed knee view is a recommended valid method from the Osteoarthritis Research Society International to evaluate structural severity in KOA clinical trials [67].

The evaluator in this study (MSA) underwent a standardized training program for the KL scoring system and knee JSW. Following the training program, the evaluator demonstrated excellent intersession reliability (ICC = 0.956) and a narrow confidence interval (95% CI = 0.921 – 0.975). To eliminate the inter-rater error and avoid testing bias in grading radiography and joint space width, the same evaluator graded the imagines. This evaluator was blinded to participants' clinical data at the time of grading.

4.3.5 Defining the Knee Osteoarthritis Progression

KOA progression was defined using changes in Kellgren-Lawrence (KL) grade and narrowing of the knee joint space width (JSW) based on international recommendations [71]. The KL scale [54] ranks severity on a 0-4 scale where (0) indicates no pathological changes, (1) indicates doubtful joint space narrowing and the possible formation of osteophytes, (2) indicates definite osteophytes and possible joint space

narrowing, (3) indicates definite joint space narrowing, moderate multiple osteophytes, possible bony ends deformity, and some sclerosis, and (4) indicates large osteophytes, severe sclerosis, definite deformity in bone ends, and obvious narrowing of joint space [54]. Using the KL grade methodology, participants were dichotomized into two groups (progressors or non-progressors) based on the maximum structural changes in either the medial or lateral joint compartments of the contralateral knee between the pre- and post-operative follow-up. Individuals were included in the progressors group if they demonstrated worsening KL grades (at least 1-point change) from baseline. The non-progressors group were individuals without a KL grade change. Individuals with KL grade 4 in the contralateral knee at baseline were excluded from the current analysis as no further KOA progression could be determined at follow-up.

For the knee JSW method, the narrowest point at either the medial or the lateral knee compartment was measured to define the KOA progression. Suggested values for the progressor group ranged from a 0.12 to 0.84 mm [71] and 0.50 to 0.80 mm [73] narrowing in knee JSW from pre- to post-operative follow-up [73]. It has been shown that a 0.5 mm cut-off in joint space narrowing will reflect a clinically relevant progression in KOA [74]. Therefore, participants were dichotomized into two groups (progressors or non-progressors) based on the amount of medial or lateral joint compartment collapse of the contralateral knee between the pre- and post-operative follow-up. The progressors group were individuals with a reduction of 0.5 mm or more in the medial or lateral compartments of the contralateral knee. The non-progressors group were individuals with less than 0.5 mm change in contralateral knee joint space width.

4.3.6 Statistical Analysis

Statistical analyses were performed in two steps. First, differences in clinical variables were compared between groups (progressors and non-progressors) using multiple independent t-tests. Second, the associations between the clinical predictors and the group assignment (progressors and non-progressors) were assessed using separate hierarchical logistic regressions. The clinical predictors were entered in the regression model as: Block 1) demographics (age, body mass index, sex); Block 2) clinical measures (isometric quadriceps strength, 6-Minute Walk Test, Timed Up and Go Test, timed chair rise test and Stair-Climbing Test) or self-reported function (KOS-ADLS). Regression models were created to predict membership in the non-progressors group. Higher odds ratios indicate greater likelihood of being a non-progressors. Independent analyses were done for both KL grade and JSW methods. Given the potential influence of sex on predictive factors, exploratory analyses were performed. 2*2 ANOVAs were performed for each clinical variable with sex and progressor status as fixed factors. Significant interaction effects were reported. Approximately 10% of the clinical predictors (knee pain, ROM, KOS-ADLS) were missing at random, and imputation was performed using the median score of the non-missing values [90]. Alpha level for statistical significance was set at $p \leq 0.05$. Effect sizes for the independent t-tests were calculated using Cohen's d statistic. Cohen's d values $\leq$ 0.20 represent a small effect, ≥ 0.50 represent a medium effect and ≥ 0.80 represent a large effect [91]. Analyses were performed using IBM SPSS (Version 26) statistical software package (Armonk, NY, USA).

4.4 Results

4.4.1 Participants

Sixty participants agreed to participate in the study and underwent follow-up radiographic and clinical evaluation. Of this cohort, 42 participants had complete pre- and post-operative radiographic and clinical evaluation variables for the analysis. Two participants were excluded based on KL grade of 4 in baseline radiographs in the contralateral knee. Therefore, 40 participants between the ages of 58 and 74 (mean age 66.6±6.5 years, 48% male, body mass index 31.9±4.6 kg/m^2) were included in the KL imaging analysis (Table 1). There were magnification errors for 3 of the baseline radiographs and JSW measurements could not be performed on these individuals, therefore only 37 participants were included for this analysis.

4.4.2 Kellgren-Lawrence (KL) Score Analysis

The average time between pre- and post-operative follow-up was 7.8±2.5 years. Twenty-five participants (62.5%) were classified into the KL progressor group. No significant differences in sex, age, body mass index, gait speed or time to follow-up were found were found between groups (Table 1). No significant differences were found between groups for any of the clinical variables (Table 2). For the regression analysis, none of the clinical outcomes were found to be related to contralateral KOA progression (Table 3). In the sex-stratified analyses, operated knee extension ROM at follow-up demonstrated the only significant interaction (p=0.024) when sex and progression status were included as fixed factors in the exploratory ANOVA. In the operated knee, males who were non-progressors had more knee extension ROM (-0.2 degrees) than males who progressed (1.1 degrees; i.e. lacking full knee extension). The opposite was found in the females. In the operated knee, females who were non-

progressors had less knee extension ROM (0.2 degrees) than did the females who progressed (-2.3 degrees, i.e. hyperextension).

4.4.3 Knee Joint Space Width (JSW) Analysis

The average time between pre- and post-operative follow-up was 8.8±2.2 years for the 37 subjects evaluated using JSW. Twenty-nine participants (78%) were classified into the progressors group, defined as a narrowing in JSW greater than 0.5 mm. There were no significant differences in sex, age, body mass index, or gait speed, but individuals in the progressor group did have a significantly shorter time between baseline and follow-up (Table 1). For the clinical variables, contralateral quadriceps strength was significantly higher in the non-progressors group (25.4±7.5 Nm/kg/m^2) compared to the progressors group (18.9±7.3 Nm/kg/m^2); p=0.033; Table 2. Greater contralateral quadriceps strength was also a predictor of being a non-progressor (odds ratio=1.117; p=0.047; Table 3). For every one unit increase in quadriceps strength, the likelihood of being a non-progressor increased by 11.7%. While in a sub-analysis we found that for every one unit increase in the quadriceps strength, the likelihood of being a progressor decrease by 10%.

Table 4.1 Participant demographics

	Based on KL scores (N = 40)			Based on JSW (N = 37)		
	Progressor Group n = 25 (62.5%)	**Non-Progressor Group n = 15 (37.5%)**	**p -value**	**Progressor Group n = 29 (78%)**	**Non-Progressor Group n = 8 (22%)**	**p -value**
Sex Male n (%) Female n (%)	 10 (40%) 15 (60%)	 9 (60%) 6 (40%)	0.220	 14 (48%) 15 (52%)	 4 (50%) 4 (50%)	0.931
Age (years)	67.2 (5.9)	65.7 (7.6)	0.481	67.2 (6.6)	63.0 (4.7)	0.098
BMI (kg/m2)	31.5 (4.4)	32.6 (5.0)	0.476	32.2 (5.1)	30.8 (2.7)	0.443
Height (meter)	1.7 (0.1)	1.7 (0.1)	0.839	1.7 (0.1)	1.7 (0.1)	0.860
Gait Speed (meter/second)	1.33 (0.17)	1.34 (0.15)	0.932	1.33 (0.16)	1.36 (0.18)	0.833
Time between Surgery and Follow-up X-ray (years)	7.64 (1.96)	8.00 (3.07)	0.652	7.3 (1.8)	10.4 (2.6)	0.000 *
Baseline KL score (Grade: n)	1: 11 2: 11 3: 3	1: 7 2: 4 3: 4	-	-	-	-

Data are presented as “Means (Standard Deviations)”
BMI = Body Mass Index

Table 4.2 Progressor vs non-progressor

Clinical Variables	Side	Based on KL scores					Based on JSW				
		Progressor (n=25; 62.5%) Mean (SD)	Non-progressor (n=15; 37.5%) Mean (SD)	Mean Difference (95% CI)	Cohen's *d*	p-value	Progressor (n = 29; 78%) Mean (SD)	Non-progressor (n = 8; 22%) Mean (SD)	Mean Difference (95% CI)	Cohen's *d*	p-value
6MWT (meter)	N/A	529.05 (78.50)	567.40 (78.48)	38.35 (-13.55 – 90.24)	-0.50	0.143	545.40 (80.93)	550.39 (86.19)	-4.99 (-71.48 – 61.50)	-0.06	0.880
TUG (second)	N/A	8.56 (1.68)	7.60 (1.90)	-0.95 (-2.12 – 0.21)	0.56	0.106	8.13 (1.67)	8.13 (1.98)	0.00 (-1.41 – 1.41)	0.00	0.995
SCT (second)	N/A	13.59 (3.75)	11.97 (2.96)	-1.62 (-3.92 – 0.68)	0.48	0.163	13.00 (3.75)	12.46 (2.80)	0.54 (-2.36 – 3.44)	0.16	0.706
Quadriceps Strength (N.m/kg/m^2)	Operated	17.80 (6.85)	17.77 (6.24)	-0.03 (-4.41 – 4.35)	0.00	0.989	17.39 (6.85)	19.43 (5.58)	-2.03 (-7.40 – 3.33)	-0.32	0.446
	Contralateral	18.82 (6.96)	22.18 (8.43)	3.36 (-1.62 – 8.33)	-0.46	0.180	18.92 (7.28)	25.44 (7.50)	-6.51 (-12.45 – -.057)	-0.92	**0.033 ***
Knee Pain (1 to 5)	Operated	0.48 (0.71)	0.53 (0.74)	0.05 (-0.43 – 0.53)	-0.07	0.823	0.45 (0.74)	0.88 (0.64)	-0.43 (-1.01 – 1.55)	-0.61	0.146
	Contralateral	0.50 (0.86)	0.77 (1.01)	0.27 (-0.38 – 0.92)	-0.30	0.408	0.52 (0.82)	0.71 (0.95)	-0.19 (-0.94 – 0.55)	-0.23	0.597
Hip Pain (1 to 5)	Operated	0.27 (0.63)	0.08 (0.28)	-0.20 (-0.57 – 0.18)	0.37	0.216	0.24 (0.60)	0.14 (0.39)	0.10 (-0.39 – 0.57)	0.18	0.688
	Contralateral	0.41 (0.85)	0.23 (0.83)	-0.18 (-0.78 – 0.42)	0.22	0.551	0.24 (0.60)	0.86 (1.46)	-0.62 (-1.97 – 0.74)	-0.75	0.314
Active Knee Flexion ROM (Degree)	Operated	120 (10)	118 (7)	-2.36 (-8.16 – 3.44)	0.23	0.415	122 (8)	116 (8)	5.47 (-1.27 – 12.22)	0.77	0.108
	Contralateral	131 (11)	132 (7)	1.53 (-5.21 – 8.27)	-0.11	0.647	131 (10)	132 (9)	-1.07 (-9.64 – 7.49)	-0.10	0.800

Active Knee Extension ROM (Degree)	Operated	- 1.0 (3)	0.0 (2)	0.77 (-1.21 – 2.75)	-0.38	0.434	- 0.8 (3)	0.3 (2)	-0.51 (-2.99 – 1.97)	-0.40	0.679
	Contralateral	- 1.5 (3)	- 2.0 (3)	-0.27 (-2.42 – 1.88)	0.17	0.801	- 1.3 (3)	- 1.7 (4)	0.39 (-2.31 – 3.10)	0.13	0.768
KOS-ADLS (0 to 100)	Operated	88.11 (8.06)	86.74 (9.11)	-1.37 (-6.97 – 4.22)	0.17	0.623	87.52 (9.25)	86.79 (6.47)	0.74 (-6.37 – 7.84)	0.09	0.835
	Contralateral	93.29 (10.21)	88.15 (9.70)	-5.13 (-12.34 – 2.07)	0.53	0.156	93.00 (9.86)	88.37 (11.60)	4.61 (-4.39 – 13.62)	0.47	0.303

Data are shown in degrees and presented as "Means (Standard Deviations)"

*** Negative value means lack of knee extension*

[§]*Effect size categories (0.20=small, 0.50=medium, 0.80=large).*

Table 4.3 Logistic regression analysis

Predictors	Based on KL scores			Based on JSW		
	Nagelkerke R Square	Odds ratio (95% CI)	p-value	Nagelkerke R Square	Odds ratio (95% CI)	p-value
6MWT (meter)	0.075	0.994 (0.985 – 1.002)	0.146	0.001	1.001 (0.991 – 1.011)	0.876
TUG (second)	0.093	1.394 (0.924 – 2.103)	0.114	0.000	0.995 (0.629 – 1.586)	0.995
SCT (second)	0.072	1.164 (0.939 – 1.442)	0.166	0.007	0.954 (0.752 – 1.210)	0.697
Contralateral Quadriceps Strength	0.062	0.942 (0.863 – 1.028)	0.181	0.174	1.117 (1.001 – 1.245)	**0.047 ***
Contralateral Knee Pain (1 to 5)	0.028	0.723 (0.341 – 1.535)	0.399	0.014	1.304 (0.502 – 3.390)	0.586
Contralateral Hip Pain (1 to 5)	0.016	1.335 (0.525 – 3.394)	0.544	0.111	1.989 (0.832 – 4.753)	0.122
Contralateral Active Knee Flexion ROM (Degree)	0.009	0.982 (0.910 – 1.059)	0.636	0.003	1.012 (0.925 – 1.107)	0.792
Contralateral Active Knee Extension ROM (Degree)	0.003	1.032 (0.817 – 1.303)	0.794	0.005	0.957 (0.724 – 1.265)	0.759
Contralateral KOS-ADLS (1 to 100)	0.081	1.053 (0.979 – 1.053)	0.165	0.050	0.961 (0.890 – 1.037)	0.303

Data are presented as “Odds ratio (95% confidence interval (CI))”
Each model was adjusted for Age, BMI, Sex

4.5 Discussion

The large incidence of radiographic KOA progression in the contralateral knee (78% using JSW; 62.5% using KL scores) underscores the need to identify clinical predictors of contralateral KOA progression after unilateral TKA. In this study, we found that contralateral knee strength at baseline was a predictor of future radiographic KOA progression when using JSW measures. Lower extremity strength is an important component of normal function, particularly in individuals with KOA [18] and those after TKA [16]. Observational studies have also found quadriceps strength to be a predictor for primary KOA progression [19], although there is conflicting evidence on this topic [92]. Some studies have found that the association between muscle properties and KOA progression is modified by sex [93], and the relationship may be more pronounced in women. However, in our exploratory sex-stratified analyses, we did not see an influence of sex on the strength and KOA progression. However, we did find an interaction effect for knee extension ROM. Specifically, male KL progressors were more likely to lack knee extension in the operated knee at baseline. The opposite was true for females, as female KL progressors were more likely to demonstrate baseline knee hyperextension ROM in the operated knee. Although this was only an exploratory aspect of the study, it is possible that deviations from full knee extension have differential consequences for men and women. Our preliminary findings indicate that operated knee hyperextension ROM may be a risk factor for women, whereas an operated knee flexion contracture may be a risk factor in men for progressive KOA in the contralateral limb. This should be explored in future prognostic studies powered to compare differences between sexes.

Prior investigators have found muscle weakness to be associated with symptomatic KOA progression, but not structural progression [94]. However, all previous studies have focused on primary OA progression and have not evaluated the association between quadriceps strength and OA progression post-TKA. Our results indicate that there is an association between quadriceps strength and contralateral OA risk. Clinicians should be aware that the status of the non-operated limb at baseline may be predictive of OA progression in the future. KL scores and JSW were both used to evaluate OA severity in this study. Although they are frequently interpreted the same way from a clinical perspective, each outcome measure evaluates different structural markers of OA progression. When quantifying severity, KL scores take into consideration joint alignment, articular cartilage deformation, and osteophyte (bony) formation, while JSW is a more objective measure that solely relies on the thickness of the cartilage to quantify OA progression [70]. In this study, a larger incidence of contralateral knee OA progression was found in JSW method (78%) when compared to the KL scores (62.5%), which may be due to how these measures quantify severity and change in severity. It is possible that there was loss of cartilage (or joint space narrowing) without associated changes in osteophytes or alignment. This is particularly true given that 11 of 25 participants (56%) had KL scores of 2 or 3 at baseline. This would assume that these individuals had bony changes and osteophytes at baseline as well. It may be more likely to see changes in cartilage thickness, rather than see further enlargement of osteophytes or degradation of subchondral bone and joint alignment.

The mechanism by which quadriceps weakness may lead to OA progression is not clear. Quadriceps weakness is a nearly universal finding in individuals with knee

OA [95] and quadriceps weakness tends to increase as the severity of OA increases [96]. Interventional studies have found that strengthening programs may be beneficial by preventing structural damage [97] and improving functional ability [98] for individuals with knee OA. It is possible that normal strength allows patients to move in a more normal fashion [99], reduce abnormal joint loading, or reduce joint laxity and instability [100] during weight-bearing activities. Given the fact that abnormal movement patterns are linked to OA progression, greater muscle strength may be one protective mechanism against abnormal movement patterns and subsequent structural decline.

It is also possible that quadriceps strength acts as a protective factor by means that are not biomechanical in nature. Higher physical activity (steps per day) has been shown to be protective against symptomatic decline in patients with knee OA [101]. Quadriceps strength is also associated with greater physical activity [102]. It is possible that strength is a mediating factor in physical activity, or vice versa, which may offer some protection against structural changes within the joint. Future prospective and mechanistic studies should explore the potential mechanisms by which quadriceps strength offers protection against structural changes in primary and contralateral knee OA. We found that for every one unit increase in quadriceps strength, the likelihood of being a non-progressor increased by 11.7%. This is particularly important as we only found quadriceps strength to be protective against JSW narrowing, and not KL changes. This difference may be related to the greater incidence of JSW progression, or it may be due to an inherent way in which the quadriceps protect cartilage health, but do not protect against other changes in the joint, such as alignment or osteophyte development.

Previous work found that 22.7% of participants had contralateral radiographic knee OA progression an average of 6.6 years after the index TKA [76], while other studies have found up to 46% of patients undergo contralateral TKA with 3 years after the primary TKA [6]. Knowing that participants in our study were identified as having unilateral symptomatic knee OA at baseline, a radiographic progression rate of 62.5-78% in the contralateral knee is high. Although this study was not powered to quantify incidence, this high percentage is surprising. Given the association between contralateral knee strength and structural progression, clinicians should consider including bilateral strengthening into post-operative rehabilitation protocols. While future prospective studies are warranted to determine the potential effectiveness of a strengthening intervention, the association and high incidence suggest that bilateral strengthening after surgery may be beneficial.

There are several limitations in this study that may contribute to the lack of additional predictor variables. Previous work has found that higher baseline KL scores were associated with better clinical outcomes after TKA [103]. It is possible that baseline KL scores in both the operated and non-operated limb were confounding factors in predicting outcomes. We also did not record other potentially more potent risk factors, such as physical activity, that may have influenced the total load experienced by the joint during the follow-up period. A more robust set of predictor variables is warranted in future prospective observational studies.

4.6 Conclusions

Most individuals demonstrated contralateral knee OA progression after primary TKA. This high incidence is concerning, particularly since subjects included

in this study had primarily unilateral symptoms at baseline. Contralateral quadriceps strength is a predictor associated with joint space narrowing at follow-up. While future interventional studies are needed, the inclusion of bilateral strengthening into post-operative rehabilitation may be beneficial for patients who undergo unilateral TKA.

4.7 Funding and acknowledgments

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Chapter 5

USING FOOT INSOLES (LOADSOL) TO MEASURE ASYMMETRY DURING WALKING AND FUNCTIONAL ACTIVITIES

5.1 Abstract

Although clinically meaningful information can be obtained through the use of motion analysis, the complexity of laboratory equipment and the associated costs are a major obstacle for clinicians when evaluating movement patterns for individuals with musculoskeletal disorders. The use of several trials may also not be representative of real-life performance when patients complete a variety of tasks or walk for longer durations. There has been an increasing interest in using commercially available wireless shoe insoles for kinetic assessments in the clinical setting [13]. These shoe insoles may provide avenues for clinicians to understand biomechanical outcomes and consequently tailor rehabilitation program for patients with knee OA. Therefore, this exploratory aim used these insoles to help in quantifying force asymmetry in a clinical setting. The aim of this technical note was to create procedures to measure bilateral vertical ground reaction force and kinetic symmetry in a clinical setting using commercially-available tools. This will provide researchers and clinicians with more realistic estimates of asymmetry that may occur during actual activities of daily living.

5.2 Introduction

While identifying biomechanical asymmetries in the laboratory setting may be relevant, there is a need for kinetic assessments in the clinical setting. It is possible that data collected about movement patterns in a sterile motion analysis laboratory do not reflect actual movement strategies that occur when individuals perform challenging or longer duration activities. The rationale for this technical note is to create procedures to measure bilateral vertical ground reaction force that would be beneficial in patient's populations where asymmetry is a concern. These procedures

will allow for the measurement of force asymmetry in the clinical setting using commercially available tools. These procedures can be integrated into research studies to evaluate movement asymmetry or can be used as interventions to re-train movement patterns using real-time feedback. Treatment for many orthopaedic and neurological conditions include movement and symmetry training and methods to reliably test, monitor, and train force symmetry between limbs will be helpful to clinicians who treat a variety of conditions.

The purpose of this technical note was to create procedures to measure bilateral vertical ground reaction force that would be beneficial in patients' population where asymmetry is a concern. Biomechanical data in this study were collected in a functional context during extended walking, where fatigue or pain may influence and change the magnitude or types of asymmetry. This may better reflect real-world patient behavior and provide more accurate and relevant biomechanical information for treating patient-specific movement deficits.

5.3 Methods

5.3.1 Research design

This is a technical note describing the methods that can be employed in clinical settings. These methods proposed in this technical note were tested in a single participant who completed clinical and biomechanical testing.

5.3.2 Participant

A 32-year-old healthy male participant was recruited to complete the following prescribed procedures (Appendix E).

5.3.3 Clinical Data Collection

Clinical measures included the six-minute walk test (6MWT), chair rise test, active knee range of motion, and quadriceps strength testing (Figure 5.1). The participant also was asked several questions about his pain. Specifically, he was asked about his "average pain over the past week" for each knee and hip, as well as the neck and back. He was asked to rate the pain from 0 to 10, where 0 is no pain, and 10 is the worst imaginable pain. The participant was asked about knee pain on a scale from 0-10 before starting the Six-Minute Walk test (6MWT), after minute 1 of the test, and at the end of the test. Fatigue was also evaluated on a scale from 0-10 after minute 1 of the 6MWT and at the end of the test.

1. Six-Minute Walk test (6MWT): The participant was asked to cover as much distance as he can while walking on level ground for six minutes. This test is commonly used in geriatric populations to quantify functional endurance of the lower extremities. A physical therapist was following behind the participant for the duration of the test to offer assistance if needed.	
2. Chair Rise Test: This test measures how many sit-to-stand counts the participant can perform in 30 seconds. The participant was allowed to use the arms of the chair if required when rising from and returning to the chair during the chair rise test.	

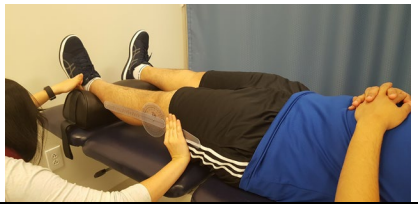
3. Active Range of Motion (ROM): Joint ROM of both knees were measured using a long-arm goniometer. The landmarks to measure the range of motion were knee joint center (axis), greater trochanter, and lateral malleolus. Participants were asked to straighten (extend) or bend (flex) their knees as much as possible several times. The maximal amount of extension and flexion were recorded.	
4. Quadriceps Strength Testing: The participant was seated on an isokinetic dynamometer and a measuring arm was secured to the ankle. The knee was positioned at 75 degrees of flexion and was not moved during the testing. The participant performed three practical trials at 50%, 75%, and 100% of his maximum strength as a warm-up. Then, three recorded trials were collected at 100% of their maximum strength. This was performed for both limbs.	

Figure 5.1 Clinical testing for aim 4

5.3.4 Biomechanical Data Collection (Insoles Description)

We used commercially available wireless shoe insoles (Loadsol, Novel Electronics, St. Paul, MN, USA) (200Hz) to measure force symmetry between limbs when the participant was walking outside gait laboratory and performing movement tests, such as the six-minute walk test (6MWT). The device has a flat cable that attached to a small sensor box. Data were transmitted to an iPod touch in real-time (Figure 5.2a). To prevent interference with the patient's movement and comfort, the small sensor box was attached to the shoelaces. The Loadsol comes in different layouts based on each lab/therapist needs (Figure 5.2b). Our layout is divided up into three regions, which allows forces from forefoot, midfoot, and rearfoot to be differentiated. That allowed us to evaluate each region individually and also evaluate the summed forces.

Figure 5.2a The insoles get attached to the shoes and it comes with different sizes. Easy to apply and use.

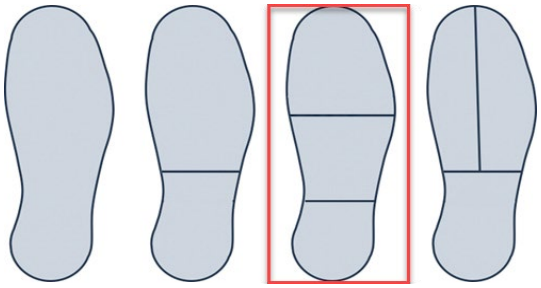


Figure 5.2b Different layouts for different needs. The red square indicates the layout was used in this study, which can differentiate rearfoot, midfoot, and forefoot forces.

Pictures adapted from the novel.de website (http://www.novel.de/novelcontent/loadsol)

Figure 5.2 Samples of the insoles and layouts

5.3.5 Insoles Validity and Reliability

Validation studies of the wireless in-shoe system (Novel Loadsol/Pedoped) for ground reaction force measurement were used to assess the validity and reliability of the system. These studies have shown moderate to excellent intraclass correlation coefficient (ICC) with various activities/conditions [13,104,105,106]. A recent study showed the ICCs during walking for the peak force (0.84-0.99), loading rate (0.80-0.96), and the impulse (0.90-0.97) [104]. The same study demonstrated excellent between-day reliability (>0.76) during walking and running. Another recent research showed that the ICC was (0.77-0.99) during single-hops and stop-jumps for peak impact force, loading rate, and impulse [13]. The data collected in this technical note is a number of steps, average contact time [mescs], average peak force [N], average loading rate [N/s], average cadence, and foot contact (% of trial).

5.3.6 Biomechanical Data Collected During Functional Testing

During the six-minute walk, two wireless shoe insoles were placed in the participants' shoes to record the foot forces. These insoles were placed into the soles of the participant's own footwear and were only worn during the duration of the six-minute walk. The insoles recorded the whole six-minute walk data, and these data was stored on the tablet then was exported as Excel files for further analysis and processing. The reasons of collecting the biomechanical data during the 6MWT are to measure if the participant get fatigued or became asymmetrical at the end of the test. Forces and symmetry were averaged over the whole first, third, and sixth minute to produce three separate symmetry scores.

5.3.7 Insoles Data Collection

5.3.7.1 Software and Insoles Setup

The Loadsol App can be downloaded on an iOS/Android tablet. We downloaded the App on an iOS tablet "iPod touch" (Apple Inc., Cupertino, CA, USA). We then placed the insoles in the participants' shoes and attached the electronic boxes to the laces of the shoes as shown in Figure 5.2a The software was linked to the insoles through the Bluetooth.

5.3.7.2 Insoles Calibration

The insoles need to be calibrated before they can collect data to obtain precise measurement results, which takes less than 10 minutes. The sensors are calibrated from the manufacturer; although, the level of precision might be affected by temperature and humidity. The exact body weight of the participants was measured and entered in the system before starting the calibration. We performed the calibration using the participant's weight standing in the shoes with the insoles inside (foot-shoe interface), which can be valid until the insoles get reset. A deviation within -/+ 5% of body weight was acceptable. After inserting the insoles inside the patient's shoes as shown in (Figure 5.2a), we entered the exact weight that measured at the time of calibration on the screen (Figure 5.3). We then zeroed the force when the foot left off the ground in order to obtain accurate information. This is an important step during which time the participant is required to stand on a single leg while not moving. The participant could use a finger on a vertical surface (e.g., wall) to maintain a stability. Finally, the resolution display of forces was set to 5 N (e.g., 580, 585, 590, … etc.).

Figure 5.3 Calibration interface

5.3.7.3 Real-time Measurements from the insoles

After the calibration, the insoles were zeroed (tared) when the foot was unweighted so only the plantar forces generated by the participant's standing or moving were recorded during the trials and compression between the shoe, foot and insole were ignored. To start recording the trial, we tapped the start button and asked the participant to walk (Figure 5.4). The Loadsol App has two different modes: 1) horizontal (landscape) and vertical (portrait). The horizontal mode shows the real-time curves while the vertical mode is designed to show the biofeedback in a patient-friendly manner. For the purpose of this technical note, we only used the horizontal mode since we did not provide patients with biofeedback during the walking trials. The biofeedback mode can be used to achieve movement retraining in future research.

Figure 5.4 Real-time measurements interface

5.3.8 Insoles Data Processing

5.3.8.1 Insoles Data Storage

All biomechanical data collected from the insoles were electronically stored in the associated iOS tablet, and data were de-identified. We extracted the first minute, minute 3, and the last minute of the 6MWT in three separated files within the tablet. The software was automatically calculated the biomechanical variables of interest (Table 5.1 below) for Minute 1, Minute 3, and Minute 6 separately. Then, we recorded the values of the biomechanical variables of interest in a hard copy de-identified data collection form, which was entered in an excel file and was compiled with the participant all data. The raw data from the insoles was exported in an excel spreadsheet to be used for future analyses.

5.3.8.2 Biomechanical Variables of Interest

We collected the following ***biomechanical variables***: the symmetry of average peak ground reaction force (GRF) of both limbs, loading rate, and impulse (Table 5.1). The loading rate is defined as the rate at which the force increases during an individual's foot strike during walking [104]. We calculated the loading rates from the time the force reached 20% of the first peak, to the time the force reached 80% of the first peak force. In the event there was an impact transient (AKA heel impact peak), we used the peak of the impact transient to define our linear loading range. We selected this area of the curve because it is the most linear area during initial limb loading [107,108,109]. Average loading rate was calculated over the same period as the total change in force divided by the total change in time [107]. Impulse was defined as the area under the force curve constrained by the time axis. In the Loadsol software, the impulse is known as Force Time Integral (FTI). The larger the load and the longer it is applied generates a greater impulse. In order to define the stance phase for each gait cycle, we calculated the average contact time of steps (ms), which is the amount of time in a step in which the total force is equal or higher than the defined threshold of 20 N. This threshold was used to identify initial contact and toe off. Data were processed and analyzed using the native Loadsol software (Table 5.1; Figure 5.5). The variables noted in Table 5.1 as (A through C) are depicted in Figure 5.5. For all force calculations, we used the summed forces from all three measured regions in the foot (forefoot, midfoot, and rearfoot) for our calculations.

Table 5.1 The calculations and definitions of the biomechanical variables of interest.

	Variable	Calculation/Definition	Unit
A	**Average Peak Force**	The maximum force values of the right and left steps in taking (e.g., clinicians can use operated and non-operated sides). Then, average peaks for minute 1 and minute 6 can be calculated. The peak of each step can be defined, then calculating their averages. That can be done for minute 1 and separately for minute 6 to be able to compare the differences between these two-time points (minute 1 vs minute 6).	**N**
B	**Average Loading Rate**	The loading rate (LR) for each step is calculated from the time the force reaches 20% of the first peak, to the time the force reaches 80% of the first peak force: $$LR_{HI} = \frac{F_{80} - F_{20}}{t_{80} - t_{20}}$$ Then, averaged for all left and right steps is calculated.	**N/s**
C	**Impulse = Force Time Integral (FTI)**	It shows on the interface screen the whole impulse through the entire selected region. $$FTI = \int_0^t f(F)dt$$ FTI: Force time integral [Ns]. F: Force [F]. t: Time [s].	**Ns**

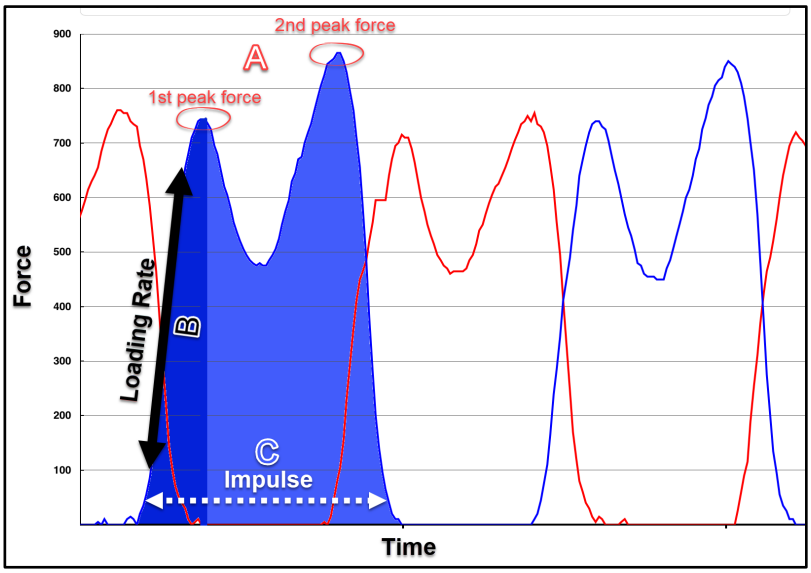


Figure 5.5 The Loadsol interface showing the data display

- The variables (A to C) depicted are described in details in Table 5.1

5.3.8.3 Calculation of the Change in Gait Symmetry

In order to evaluate change or improvement in function over time, repeated measures should be assessed on the same participant at multiple timepoints [110]. In this technical note, we measured the interlimb symmetry (right vs. left) using the symmetry index (SI). Previous literature reported the use of absolute values in calculating the gait symmetry [111]; however, absolute values was not used in this technical note as it eliminates the direction of the symmetry. The interlimb symmetry was calculated for the biomechanical variables using the following formula [112,113,114,115,116].

$$Symmetry\ Index\ (SI) = 2\ \frac{nonaff - aff}{nonaff + aff}\ x\ 100\%$$

Where "*Nonaff*" is the gait variable for the non-affected limb and "*Aff*" is the gait variable for the affected limb. An SI value of zero indicates a perfect symmetry

between the two limbs (no differences between the Nonaff and the Aff limbs). Values greater than zero (positive) indicates that the "*Nonaff*" is larger than the "*Aff*", *(+%)*. While the values less than zero (negative) indicates that the "*Nonaff*" is smaller than the "*Aff*", *(-%)*.

5.4 Results

After collecting the data, the region of interest can be selected on the iPod screen (minutes 1, 3, and 6) and the biomechanical variables will be displayed (Figure 5.6). Data from Figure 5.6 can be written in the collection form as shown in Table 5.2.

Figure 5.7 shows the symmetry graphs of three different times during the 6MWT (minute 1, minute 3, and minute 5). In our case, the forces were higher in minute 1 than minute 3 and 6, (Table 5.2; Figure 5.7).

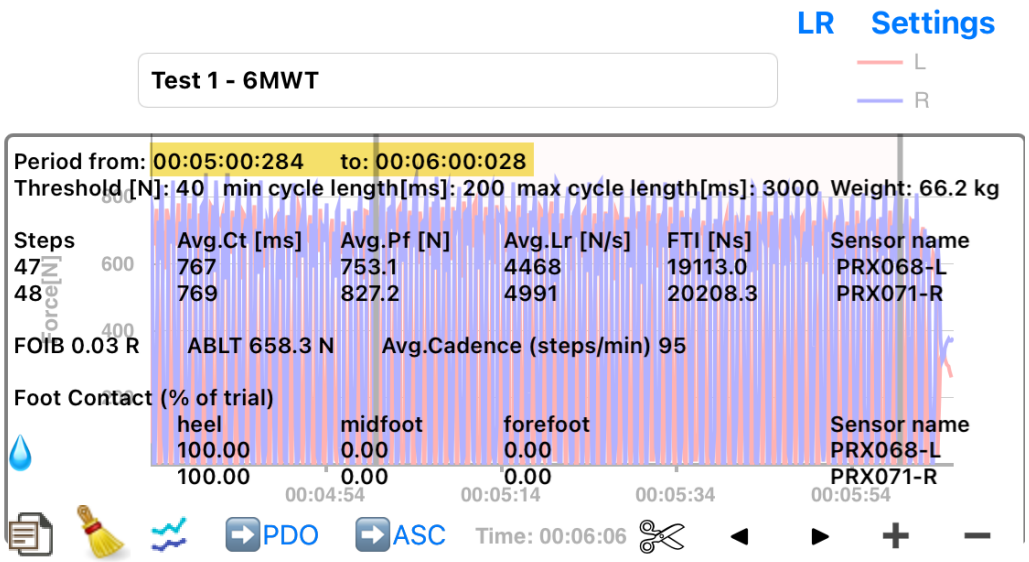


Figure 5.6 An example of the time window of minute 6

Table 5.2 An example of the data collection section of the biomechanics variable in the Six Minute Walk Test

	Minute 0-1		Minute 2-3		Minute 5-6		All 6 Mins	
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Number of Steps	47	47	48	48	47	48	294	293
Average Contact Time [mescs]	763	758	757	757	767	769	766	763
Average Peak Force [N]	784	869	761	856	753	827	759	845
Average Loading Rate [N/s] W	4823	5235	4624	5264	4468	4991	4635	5156
Average Cadence (steps/min)	97		97		95		97	
FOIB (Factor of ImBalance)	0.01 R		0.03 R		0.03 R		0.03 R	
ABLT (Averaged Body Load over Time)	666.8 N		664.2 N		658.3 N		661.9 N	

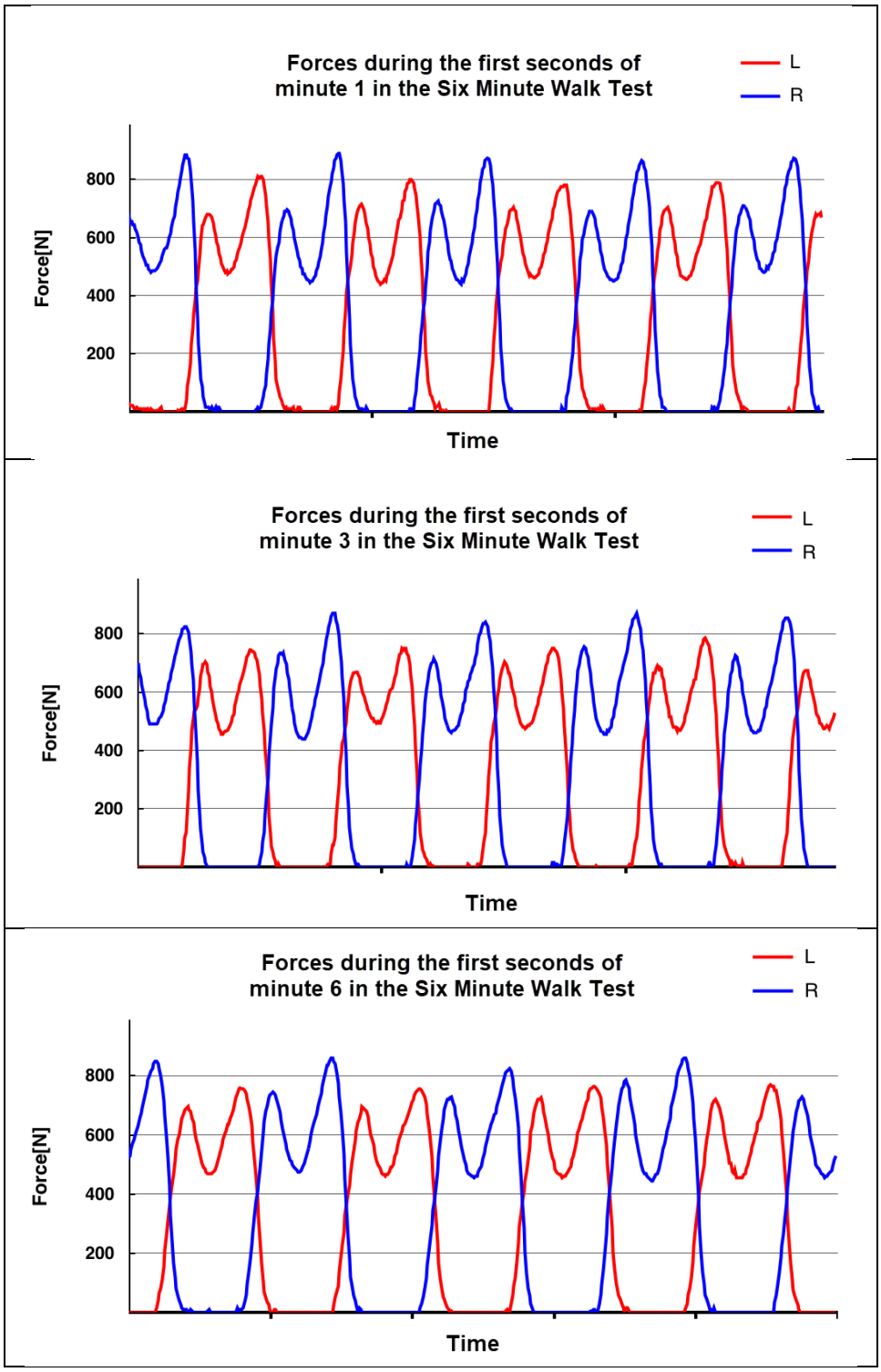

Forces during the first seconds of minute 1 in the Six Minute Walk Test
L
R
Force[N]
800
600
400
200
Time
Forces during the first seconds of minute 3 in the Six Minute Walk Test
L
R
Force[N]
800
600
400
200
Time
Forces during the first seconds of minute 6 in the Six Minute Walk Test
L
R
Force[N]
800
600
400
200
Time

Figure 5.6 Forces during the 6MWT (minute 1, 3, 6). We calculated the average of each minute individually.

5.5 Discussion

During the walking test, we expect to find walking asymmetry at Minute 1 and Minute 6 for most individuals after TKA. Even if there is asymmetry during Minute 1, we expect to see worsening symmetry at Minute 6. We think that these changes in symmetry will be associated with quadriceps weakness on the operated limb. Identifying the clinical factors related to worsening asymmetry is important because it will provide therapists with targeted impairments to address during treatment sessions. Reducing the reliance on the contralateral limb is difficult if the underlying impairments are not addressed. Findings from such study will also provide clinicians with realistic estimates of asymmetry that occur during actual activities of daily living. The information from this kind of research would help in developing improved *rehabilitation protocols* in which clinicians can both ***evaluate and re-train movement patterns*** using real-time force sensors.

5.5.1 Potential Problems/Limitations and Alternative Approaches

There are two potential problems clinicians might face during the data collection using the insoles. First, it is anticipated that it would be challenging to hold the iPod touch and follow the participant during the 6MWT or other functional outcomes. The strategy to overcome this challenge would be attaching an iPod touch to the participants' arm using a Velcro strap or asking the participant to put it in his/her pocket. By using this strategy, the signal disconnection between the insoles' sensor and the tablet will be minimized and consequently minimizing data loss. Second, clinicians expected to encounter issues with device calibration. There are two strategies to overcome the calibration issues: 1- manually calculate the body weight

and compare that with the force seeing on the iPod touch before the data collection, and 2- perform the calibration on a hard surface to standardize the setting surface (calibration) and the actual walking track.

Although we assume that participants might walk more asymmetrically at the end of the walking test for specific population, some participants may become more symmetrical. Being more symmetrical at the end of the walking test may happen due to worsening of the contralateral limb, given our calculation of symmetry (5.3.8.3). For example, a participant may *start* the test walking asymmetrically (normal contralateral mechanics and poor affected limb mechanics) and *end* the test with being symmetrical (poor contralateral mechanics and poor affected limb mechanics). Our proposed analysis using symmetry will not be able to identify the difference in good or bad changes in symmetry. Therefore, as an alternative approach, researchers may compare raw force data at Minute 1 vs Minute 6, in addition to symmetry values. This will allow to better understand the types of changes that are occurring related to symmetry.

5.6 Conclusion

Procedures to measure bilateral vertical ground reaction force in a clinical setting can be beneficial in patients' populations where asymmetry is a concern. The procedures described in this technical note provide methods by which movement symmetry and individual limb forces can be measured during real-world activities, particularly those for which endurance and fatigue may influence movement patterns.

5.7 Funding and acknowledgments

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Appendix A

PROCEDURE MANUAL FOR GRADING RADIOGRAPHS

I. Alignment (use PA bent radiograph) (Kraus 2005 Arthritis Rheum)-example image located at end of protocol

A. Draw a segment across the base of the tibial spines with the endpoint at the tip of each spine
B. Draw a segment 100 mm in length from the midpoint of the segment in previous step inferiorly along axis of the tibia.
C. Draw a segment perpendicular to segment in previous step across width of tibia. Delete segment along tibia from previous step.
D. Draw a segment 100 mm in length from the middle of the femoral notch superiorly along the axis of the femur
E. Draw a segment perpendicular to segment in previous step across the width of the femur. Delete segment along the femur from previous step.
F. Draw an angle with the vertex bisecting the segment at the tibial spines and each arm bisecting the segments along the width of the femur and tibia, respectively
G. Record the medial angle as the alignment (***Note: SigmaView will output the acute angle. If patient has valgus alignment, the output angle will need to be subtracted from 360° to obtain the medial angle.)
H. Calculate offsets according to the following: Felson. 2009. *Osteoarthritis* Cartilage. Can anatomic alignment be measured from a knee radiograph substitute for mechanical alignment from full limb films

II. Joint Space Width (JSW) (use PA bent radiograph) example image and guide for filling out grading sheet located at end of protocol

A. All measurements written without parentheses; all locations (x) written within parentheses
B. All location measurements are made beginning from the medial side of the joint
C. Determine Distal Femoral Width
    1. Draw segment that is tangent to both femoral condyles
    2. Draw a 90° angle with horizontal arm parallel/overlapping segment previously drawn and vertical arm tangent to most prominent point on femoral epicondyle for each compartment
    3. Adjust segment previously drawn in #1 so each end-point is located at the 90° angle
    4. Record this value at each LE as the distal femoral width (c, d)
D. Determine 0.250 and 0.700 locations (x)
    1. For each LE, calculate 0.250 and 0.700 based off of the distal femoral width measurement
    2. Record each of these 4 locations within parentheses in the "JSW (0.250; 0.700)" section (l, n, t, v)
E. Measure mJSW:
    1. Beginning at involved LE, measure and record medial and lateral compartment mJSW (g, i)
        a. Record mJSW location (f, i) within parentheses by using a parallel segment to segment drawn in #A1/A3 drawn beginning at the vertical arm of the medial compartment 90° angle to the location of the mJSW location
        b. Record this location from 0-100% relative to the distal femoral width (e, h)

c. Using relative location calculated in previous step for each compartment, calculate (x) location for uninvolved LE using its distal femoral width and record (o, q)

2. Calculate mJSW of both uninvolved compartments using locations calculated in previous step (o, q)and record (p, r)
3. If overall mJSW of uninvolved compartments is less than in previous step at a different location, also make this measurement
   a) Record this measurement (w, y) and location (x, z) for each uninvolved compartment at the bottom line of comments section

F. Measure JSW at 0.250 and 0.700 (greatest responsiveness to change in OAI cohort – Duryea 2010 Arthritis Care Res)
   1. Measure for each of the 4 compartments using the locations (l, n, t, v) calculated in step D and record (k, m, s, u)

III. KL Grades (use PA bend radiograph)

A. Kellgren, Lawrence. 1957. Radiological assessment of osteo-arthrosis.

IV. SigmaView User Tips

A. Right click and drag will always adjust contrast
   1. Click on contrast button to return to original contrast
B. Right click to move or remove a segment or angle
C. Segments and angles can be adjusted by left clicking and dragging the ends when respective tool is chosen
D. Measurements on the image can be moved if in the way by left-clicking over them and dragging
E. All angle measurements will give you the acute angle (<90°)

Radiographic Grading

Subject ID: _____

Date: _____

Grader: ___ Michael Axe, MD ___ Lynn Snyder-Mackler, PT, ScD, SCS, FAPTA

___ Joseph Zeni Jr, PT, PhD ___ Moiyad Aljehani, PT, MPT, DPT

PA Bent:

	Left: **INVOLVED**			Right:
Alignment (degrees):	____a_____		____b_____	
Distal Femoral Width:	____c_____		____d_____	
	Lateral	Medial	Medial	Lateral
Lateral mJSW (x)	___e (f)____			
___-- (o)____				
JSW (mm):	___g____			
___p____				
Medial mJSW (x)		___h (i)____	__-- (q)_____	
JSW (mm):		___j____	__r_____	
JSW (0.250; 0.700)	___k (l)____	___m (n)____	__s (t)_____	
___u (v)____				
KL Grade:	0	0	0	0
	1	1	1	1
	2	2	2	2
	3	3	3	3
	4	4	4	4

Comments:

_____

_____

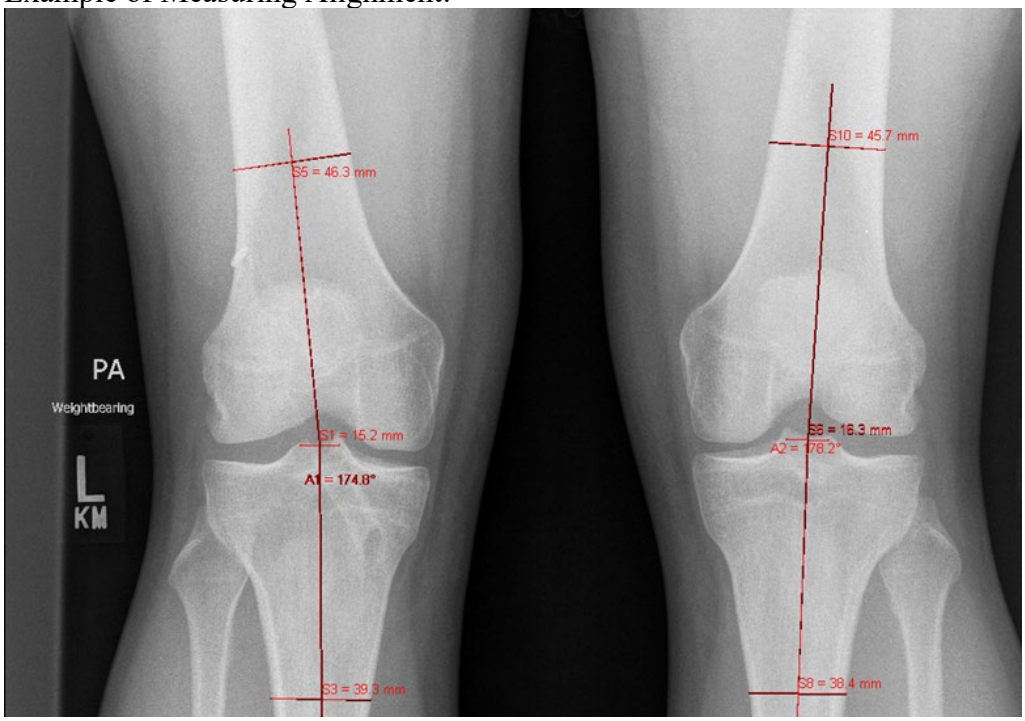
_____

_Overall Right mJSW: Medial: w (x) Lateral: y (z)_____

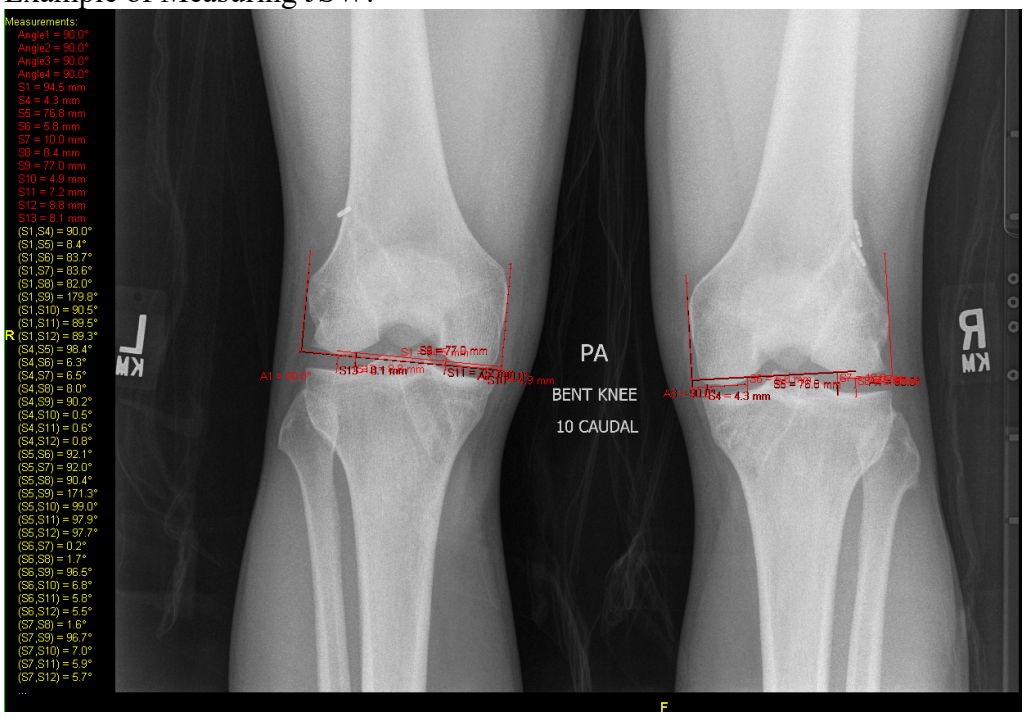
*Minimal Joint Space Width (mJSW)

*Kellgren-Lawrence Grade (KL Grade)

Example of Measuring Alignment:



Example of Measuring JSW:



Appendix B

KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE FOR JOINT REPLACEMENT (KOOS-JR), ENGLISH VERSION 1.0

KOOS, JR. KNEE SURVEY

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Stiffness The following question concerns the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.				
1. How severe is your knee stiffness after first wakening in the morning?				
None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐
2. Twisting/pivoting on your knee				
None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐
3. Straightening knee fully				
None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐
4. Going up or downstairs				
None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐
5. Standing upright				
None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐
Function, daily living The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following				

activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.				
6. Rising from sitting				
None	Mild	Moderate	Severe	Extreme
□	□	□	□	□
7. Bending to floor/pick up an object				
None	Mild	Moderate	Severe	Extreme
□	□	□	□	□

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Appendix C

KNEE OUTCOME SURVEY ACTIVITIES OF DAILY LIVING SCALE (KOS-ADLS), AND GLOBAL RATING SCALE (GRS)

Knee Outcome Survey
Activities of Daily Living Scale

Patient code: _____
Today's Date: _____

Instructions:
The following questionnaire is designed to determine the symptoms and limitations that you experience because of your knee while you perform your usual daily activities. Please answer each question by **checking the one statement that best describes you over the last 1 to 2 days**. For a given question, more than one of the statements may describe you, but please mark only the statement which best describes you during your usual daily activities.

Symptoms
To what degree does each of the following symptoms affect your level of daily activity? (check one answer on each line)

	I Do Not Have the Symptom	I Have the Symptom But It Does Not Affect My Activity	The Symptom Affects My Activity Slightly	The Symptom Affects My Activity Moderately	The Symptom Affects My Activity Severely	The Symptom Prevents Me From All Daily Activities
Pain	☐	☐	☐	☐	☐	☐
Stiffness	☐	☐	☐	☐	☐	☐
Swelling	☐	☐	☐	☐	☐	☐

Giving Way, Buckling or Shifting of Knee	□	□	□	□	□	□
Weakness	□	□	□	□	□	□
Limping	□	□	□	□	□	□

Functional Limitations with Activities of Daily Living

How does your knee affect your ability to… (check one answer on each line)

	Activity Is Not Difficult	**Activity is Minimally Difficult**	**Activity is Somewhat Difficult**	**Activity is Fairly Difficult**	**Activity is Very Difficult**	**I am Unable to Do the Activity**
Walk?	□	□	□	□	□	□
Go up stairs?	□	□	□	□	□	□
Go down stairs?	□	□	□	□	□	□
Stand?	□	□	□	□	□	□
Kneel on the front of your knee?	□	□	□	□	□	□
Squat?	□	□	□	□	□	□
Sit with your knee bent?	□	□	□	□	□	□
Rise from a chair?	□	□	□	□	□	□

How would you rate the <u>overall function</u> of your knee during your <u>usual daily activities</u>? (please check the <u>one</u> response that best describes you)

□ normal
□ nearly normal
□ abnormal
□ severely abnormal

As a result of your knee injury, how would you rate your current level of daily activity? (please check the one response that best describes you)

- ☐ normal
- ☐ nearly normal
- ☐ abnormal
- ☐ severely abnormal

Global Rating Scale (GRS):
How would you rate the current function of your knee on a scale from 0 to 100 with 0 being the inability to perform any activity and 100 being your level of knee function prior to your injury, including sport?

_____

Appendix D

PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS-10)

Global Health-PROMIS Global Health (10) SF

	Please respond to each item by marking one box per row	**Excellent**	**Very good**	**Good**	**Fair**	**Poor**
Global 01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Global 09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A Little**	**Not at All**
Global 06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
Global 10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very Severe**
Global 08	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 07	How would you rate your pain on average?	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 No Pain — Worst Imaginable Pain				

Appendix E

FOOT INSOLES DATA COLLECTION FORM

Using Insoles to Measure Foot Force after Total Knee Arthroplasty

Time Point (Months since surgery): _____ **ID:** _____ **Age:** _____
Date: _____ **Sex**: M / F **Height:** _____ **Weight:** _____

Surgical Knee: LEFT RIGHT
Tester: _____ **Surgery Date:** _____ **Surgeon:** _____

Have you had any falls since surgery? Y / N
If Yes, How many? Injuries? _____
Complications since surgery (infection, manipulation, femoral fractures, heart problems, etc.) _____
Re-hospitalization? YES / NO Reason? _____

Surgery other than total knee replacement (when, procedure)
_____
Injection (when, how many)
_____

Are you planning to replace one of the following joints?
Opposite side: (KNEE / HIP) When? _____
Same Side: (HIP) When? _____

Blood Pressure (mmHg)**:**
Systolic: _____
Diastolic: _____
Time: _____

PAIN SCORES

("Rate your pain from 0 to 10 where 0 is no pain and 10 is the worst imaginable pain")

Average past week

Left Knee _____ Left Hip _____ Low Back _____

Right Knee _____ Right Hip _____ Neck Pain _____

ROM (Active)	**Girth (cm)**
LEFT Knee Flexion: _____	
RIGHT Knee Flexion: _____	RIGHT - Knee Girth: _____
LEFT Knee Extension: _____	LEFT - Knee Girth: _____
RIGHT Knee Extension: _____	

30s Chair Stand Test:

Number in 30 seconds: _____ Using Arm Rest: Yes / No

Did they finish exercises in a standing or sitting position? _____

Six Minute Walk (6MW): Distance: _____ Manual Step Count: _____

Assistive Device: _____

Did participant complete the Six Minute Walk: _____

Did participant stop walking to rest at any point during the Six Minute Walk: ____

If so, how many rests did the participant take during the Six Minute Walk: _____

If they terminated early, for how long (duration) did they walk: _____

How often do you take *pain* medicine (Circle One)?

A- More than once per day (5) B- Once per day (4)
C- Few times per week (3) D- Once a week (2)
E- Less than once a week (1) F- Never (0)

What type of pain medicine? _____

Is the Medicine for the TKA? Yes / No

How do you perceive your operated knee?

A) Like a native or natural joint D) Like an artificial joint with major restriction
B) Like an artificial joint with no restriction E) Like a non-functional joint
C) Like an artificial joint with minimal restriction

On a scale from 0 (complete dissatisfaction) to 100 (complete satisfaction), how with the outcome of your knee replacement? _____/100

Questionnaire Scores:

KOOS-JR: _____
KOS-ADLS: _____
PROMIS GLOBAL 10: _____
GLOBAL RATING SCALE (GRS): _____

Other comments or details of complications and re-hospitalization:

Insoles data (6MW): Circle the peak force of the whole test

	Minute 0-1		**Minute 2-3**		**Minute 5-6**	
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Number of Steps						
Average Contact Time [mescs]						
Average Peak Force [N]						
Average Loading Rate [N/s] W						
Lower Limit [N/s]						
Upper Limit [N/s]						
Average Cadence						
Foot Contact (% of trial):	----------					
Heel						
Midfoot						
Forefoot						
FOIB (Factor of ImBalance)						
ABLT (Averaged Body Load over Time)						

Note: Averages are over last step

Insoles data (30s Chair Stand Test): Circle the peak force of the whole test

	Second 0-5		**Second 15-20**		**Second 25-30**	
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Number of Rises						
Average Contact Time [mescs]						
Average Peak Force [N]						
Average Loading Rate [N/s] W						
Lower Limit [N/s]						
Upper Limit [N/s]						
Foot Contact (% of trial):	----------					
Heel						
Midfoot						
Forefoot						
FOIB (Factor of ImBalance)						
ABLT (Averaged Body Load over Time)						

Appendix F

IRB/HUMAN SUBJECTS APPROVAL

1- Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	October 5, 2016
TO:	Lynn Snyder-Mackler
FROM:	University of Delaware IRB
STUDY TITLE:	[143664-14] Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	October 5, 2016
EXPIRATION DATE:	February 24, 2017
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review per 45 CFR 46. 110 (b)(2)

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB (HUMANS) has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: February 20, 2017

TO: Lynn Snyder-Mackler
FROM: University of Delaware IRB (HUMANS)

STUDY TITLE: [143664-15] Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: ***APPROVED - Data Analysis Only***
APPROVAL DATE: February 20, 2017
EXPIRATION DATE: February 24, 2018
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category #9

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB (HUMANS) has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: February 28, 2018

TO: Lynn Snyder-Mackler
FROM: University of Delaware IRB

STUDY TITLE: [143664-16] Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: Approved for Data Analysis Only
APPROVAL DATE: February 28, 2018
EXPIRATION DATE: February 24, 2019
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(9)*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB (HUMANS) has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	April 19, 2019
TO:	Lynn Snyder-Mackler
FROM:	University of Delaware IRB
STUDY TITLE:	[143664-17] Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED for DATA ANALYSIS ONLY
APPROVAL DATE:	April 19, 2019
EXPIRATION DATE:	February 24, 2020
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(8)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research FOR DATA ANALYSIS ONLY and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on February 24, 2020. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	February 4, 2020
TO:	Lynn Snyder-Mackler
FROM:	University of Delaware IRB
STUDY TITLE:	[143664-18] Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED FOR DATA ANALYSIS ONLY
APPROVAL DATE:	February 4, 2020
EXPIRATION DATE:	February 24, 2021
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(8)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on February 24, 2021. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	March 5, 2021
TO:	Lynn Snyder-Mackler
FROM:	University of Delaware IRB
STUDY TITLE:	[143664-19] Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	Approved for Data Analysis Only
APPROVAL DATE:	March 5, 2021
EXPIRATION DATE:	February 24, 2022
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(8)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on February 24, 2022. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	February 24, 2022
TO:	Lynn Snyder-Mackler
FROM:	University of Delaware IRB
STUDY TITLE:	[143664-20] Impairments and Altered Movement Patterns 6 months, 1 year and 2 years following Total Knee Arthroplasty
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	February 24, 2022
EXPIRATION DATE:	February 24, 2023
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(8)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on February 24, 2023. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

2- Using Insoles to Measure Foot Force after Total Knee Arthroplasty

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	October 23, 2019
TO:	Moiyad Aljehani, PT, MPT, DPT
FROM:	University of Delaware IRB
STUDY TITLE:	[1389249-2] Using Insoles to Measure Foot Force after Total Knee Arthroplasty
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
EFFECTIVE DATE:	October 23, 2019
NEXT REPORT DUE:	April 10, 2020
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your Amendment/Modification submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for, and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

The UD IRB REQUIRES the submission of a PROGRESS REPORT DUE ON April 10, 2020. A continuing review/progress report form must be submitted to the UD IRB at least 45 days prior to the due date to allow for the review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	April 29, 2020
TO:	Moiyad Aljehani, PT, MPT, DPT
FROM:	University of Delaware IRB
STUDY TITLE:	[1389249-4] Using Insoles to Measure Foot Force after Total Knee Arthroplasty
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
EFFECTIVE DATE:	April 29, 2020
NEXT REPORT DUE:	April 10, 2021
REVIEW TYPE:	Administrative Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Administrative Review in compliance with the pertinent federal regulations.

In-person research interaction with subjects cannot begin until the UD moratorium in response to the declaration of national emergency related to the COVID-19 pandemic is lifted. Please continue to reference https://research.udel.edu/coronavirus for the most up-to-date recommendations.

As the Principal Investigator for this study, you are responsible for, and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

The UD IRB REQUIRES the submission of a PROGRESS REPORT DUE ON April 10, 2021. A continuing review/progress report form must be submitted to the UD IRB at least 45 days prior to the due date to allow for the review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	July 6, 2021
TO:	Moiyad Aljehani, PT, MPT, DPT
FROM:	University of Delaware IRB
STUDY TITLE:	[1389249-6] Using Insoles to Measure Foot Force after Total Knee Arthroplasty
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
EFFECTIVE DATE:	July 6, 2021
NEXT REPORT DUE:	April 10, 2022
REVIEW TYPE:	Administrative Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

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The UD IRB REQUIRES the submission of a PROGRESS REPORT DUE ON April 10, 2022. A continuing review/progress report form must be submitted to the UD IRB at least 45 days prior to the due date to allow for the review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	March 15, 2022
TO:	Moiyad Aljehani, PT, MPT, DPT
FROM:	University of Delaware IRB
STUDY TITLE:	[1389249-7] Using Insoles to Measure Foot Force after Total Knee Arthroplasty
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
EFFECTIVE DATE:	March 15, 2022
NEXT REPORT DUE:	April 10, 2023
REVIEW TYPE:	Administrative Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Administrative Review in compliance with the pertinent federal regulations.

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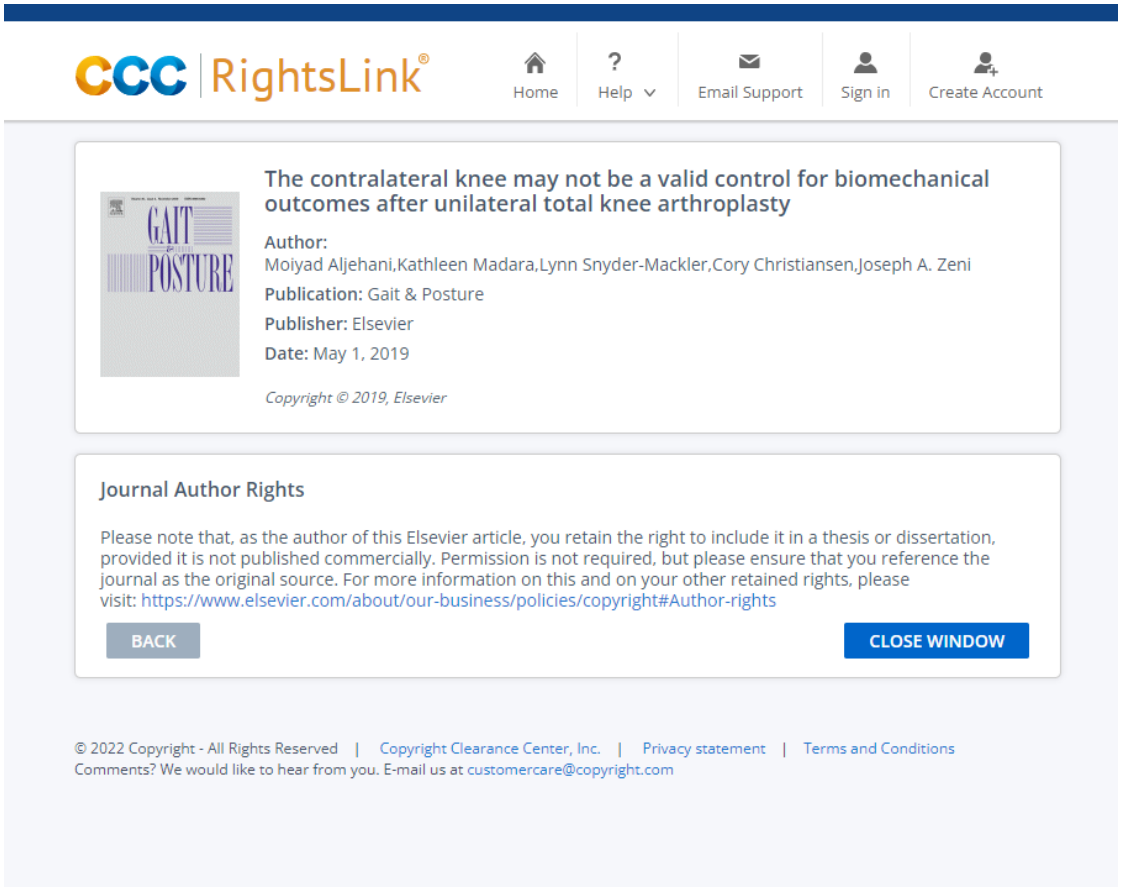
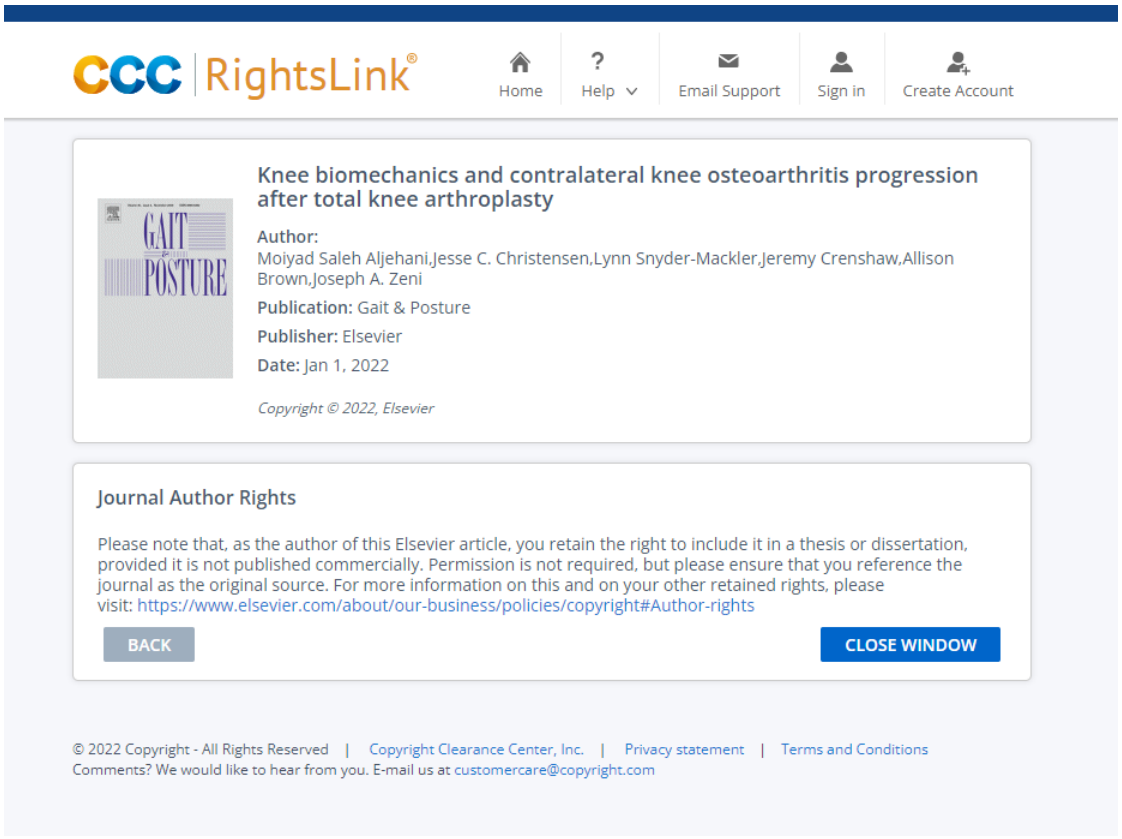
Appendix G

PERMISSIONS

Chapter 2: Aim 1



Chapter 3: Aim 2