THE RELATIONSHIP BETWEEN MUSCLE STRENGTH AND MUSCLE ACTIVITY DURING WALKING WITH POST-JOINT REPLACEMENT FUNCTION FOR PATIENTS WITH END-STAGE KNEE OSTEOARTHRITIS

by

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Submitted in partial fulfillment of the requirements for the degree of Master of Science

At

Dalhousie University
Halifax, Nova Scotia
December 2024

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Abstract

Knee osteoarthritis is a prevalent and costly disease, that currently has no cure. The most common treatment to address end-stage knee osteoarthritis is total knee arthroplasty (TKA), but dissatisfaction rates up to 30% indicate a need to improve TKA rehabilitation. Previous studies have looked at changes in gait biomechanics before and after TKA, focusing on joint angles and moments, and have identified key features that change after TKA, including variability between sexes. Due to the role of muscles in controlling these factors, this study aimed to improve the understanding of the association between muscle function and post-TKA changes in walking speed as a measure of overall function.

Data collected one-week before and one-year post-TKA on 107 participants included walking speed, muscle strength, and EMG activity. Variables examined were knee flexor and extensor muscle strength, and muscle activity patterns representing prolonged activity and overall activity of knee flexor and extensor muscles during walking. This secondary analysis used linear models to determine how much variance pre-TKA values and pre-post TKA changes of the selected variables could explain in post-TKA changes in walking speed, and multivariate models to determine what combination of variables explained the most variance in post-TKA walking speed change. Due to differences between sexes found in previous work assessing pre- and post-TKA biomechanics, this study also conducted a sex-separated analysis using the same statistical methods, to explore differences between male and female TKA recipients.

Muscle activity patterns, particularly measures of prolonged activity of knee extensor muscles, explained significant variance in walking speed change for the Study Sample. The more notable findings came from the sex-separated analysis; no independent variables explained significant variance in post-TKA walking speed change for both male and female participant subsets, and multivariate models used none of the same variables between the two sexes.

This work supports that muscle activity patterns are an important target for TKA rehabilitation to improve walking speed as a measure of overall function. Findings indicate that features influencing post-TKA changes are sex-specific and support that future work should continue to conduct sex-separate analysis, including in the development of rehabilitation protocols. The targets identified in this work can be used in the development of TKA rehabilitation protocol to improve the outcomes of TKA surgery.

Acknowledgements

There are many people to whom I owe thanks because without their support, this thesis would not have been possible.

First and foremost, I owe a debt of gratitude to my supervisor, Dr. Cheryl Kozey. Your attention to detail and willingness to provide feedback has been crucial in the making of this thesis, and I am forever thankful that you decided to take me on as a student after already having planned your retirement. Thank you for your guidance over the last two years. I am honoured to be your final student.

To my committee members, Dr. Janie Astephen Wilson and Dr. Derek Rutherford, I owe a great deal of thanks to both of you for the valuable feedback you have provided and the patience you have afforded me over the last two years, I am incredibly grateful for your time and your help.

To Annemarie Laundanski and Stephanie Civiero for help with data management. I would not have been able to organize and sort through such a large data set without your MATLAB mastery.

To my parents, who have been my biggest supporters (both financially and emotionally) throughout my time in school. Thank you both for the many evenings spent watching recorded satellite TV over FaceTime and for taking my calls whenever I had a question that was, more often than not, related to the basics of being an adult. Mom, I am further grateful for the many containers of frozen soup and meals left behind after your visits that got me through the busiest weeks in school. Dad, I am grateful for your willingness to proofread my abstracts and posters, posing as a very valuable practice "ley

audience"- your lack of expertise in my particular subject area has proven incredibly valuable.

To my dog Zona (a.k.a. Zippy), for making sure that I got out of the house for my daily outdoors time, especially in the moments when I had myself glued to my computer for days on end. To you, I owe my newfound love of hiking, many of my most fond memories of exploring the natural beauty of Nova Scotia, and so many important life lessons. (If any dog knows how to read, it is Zona, so I wanted to cover my bases just in case.)

To the other half of the 2022-2024 MScRR cohort, Juliet Rowe, for our many study dates and last-minute adventures; my most productive days were ones we spent sat across from each other at the Oxford Taproom. Thank you for your constant encouragement and your willingness to go for a Hot Girl Walk at any moment. As an extension- thank you to the LBRF lab students for taking me in and allowing me to work alongside you in your lab, especially during the hot summer months when the LBRF lab was the only space with air-conditioning.

Finally, to my rowing teammates and community, both with Dal Rowing and North Star, for being my main social circle outside of the Forrest Building and for being a constant support over the last two years. Thank you for making daily 4:30am wake ups worth it.

I would also like to thank the Canadian Institutes of Health Research for the funding to complete this study.

Chapter 1: Introduction

1.1 Introduction

Osteoarthritis (OA) is a prevalent, debilitating, and costly condition that has been designated as a *serious disease* by the United States Food and Drug Administration (March et al., 2016). OA results in damage to joint tissues and structures surrounding the joint, including articular cartilage, bone, ligaments, menisci, muscles, nerves and joint capsule surfaces, resulting in pain and significant functional decline (Brandt et al., 2006; Lane et al., 2011; March et al., 2016). While OA has been characterized by the breakdown of cartilage and bone at the joint (Brandt et al., 2006; Eckstein et al., 2006), its diagnosis is complicated by the discordance between severity of symptoms and severity of structural tissue damage, based on radiographic evidence (Altman et al., 1986; Dieppe, 2004). About 4 million Canadians (Public Health Agency of Canada, 2020) and 10-12% of the global adult population have symptomatic OA (Hunter et al., 2014), with rates of diagnosis increasing every day (Arthritis Alliance of Canada, 2011; Wallace et al., 2017). OA causes significant individual burden, through symptoms such as severe pain, stiffness, and functional decline (Lane et al., 2011; March et al., 2016). This, in turn, causes a noticeable socioeconomic strain due to increased work absenteeism among those with OA (Badley et al., 2019; Hunter et al., 2014; March et al., 2016). It has been estimated that over 80% of the overall burden caused by OA is attributable to knee OA specifically (Vos et al., 2012). While there has been a focus on conservative management approaches, the numbers afflicted by OA nationally and globally are significant and growing (Arthritis Alliance of Canada, 2011; Badley et al., 2019; Hunter et al., 2014; Lane et al., 2011; Wallace et al., 2017). The focus of the proposed study, the knee, is one of the most common joints affected by OA (Cui et al., 2020; Hunter et al., 2014; March et al., 2016; Wallace et al., 2017). OA currently has no effective cure or treatments that clearly slow progression, since treatment approaches primarily address symptoms of the disease, not the structural changes. When all other treatments fail, severe knee OA is managed with knee surgery, including total knee arthroplasty (TKA). Since TKA is intended to reduce pain and improve function, and is not a cure, the current and predicted numbers of individuals with knee OA suggest the demand for TKA will continue to rise (Canadian Institute for Health Information, 2022; Kurtz et al., 2007, 2009; Singh et al., 2019).

In Canada, TKA has consistently been one of the top three most commonly performed inpatient procedures, with over 75,000 completed annually pre-pandemic (Canadian Institute for Health Information, 2022). Global demand for TKA is expected to increase each year and continue to increase exponentially for the foreseeable future (Kurtz et al., 2007; Singh et al., 2019). Despite the prevalence of TKA surgery, there is currently no standard of care for TKA rehabilitation in Canada (Canadian Institute for Health Information, 2020; Healthcare Excellence Canada, 2021). About 12% of patients in Canada who receive TKA report feeling neutral or dissatisfied with the outcome of their knee replacement after one year (Canadian Institute for Health Information, 2022) and worldwide, between 10 to 30% of patients have reported being unsatisfied with the outcomes of their surgery at 1-5 year follow-up, citing persistent pain and unmet functional expectations post-TKA (Alzahrani et al., 2011; Bierke et al., 2020; Bourne et al., 2010; Kane et al., 2005; Seil & Pape, 2011). Furthermore, rates of revision surgery within ten years following primary TKA are estimated around 6-12% (Labek et al., 2011;

Pabinger et al., 2013). The most common reasons for TKA revision surgeries are attributable to mechanical difficulties, such as instability and aseptic loosening (Canadian Institute for Health Information, 2022; Hamilton et al., 2015; Seil & Pape, 2011); these malfunctions can be associated with abnormal gait biomechanics and muscle activity patterns that either existed pre-surgery and were not addressed post-surgery or that were a result of the surgery itself (Astephen Wilson et al., 2010; Hilding et al., 1996; D. Wilson et al., 2012).

There is quantitative evidence to support improvements in overall function (walking speed), knee joint function (angles and moments) and muscle function (strength and activity patterns) following TKA (Hubley-Kozey & Astephen Wilson, 2017). Improvements in function are assessed using joint-level biomechanics, where deficits in knee joint moment patterns compared to asymptomatic joints remain post-TKA (Astephen Wilson et al., 2015; Hatfield et al., 2011; Hubley-Kozey & Astephen Wilson, 2017; Paterson et al., 2020; Yoshida et al., 2012), with differences illustrated between males and females (Astephen Wilson et al., 2015; Young-Shand et al., 2023). These differences in post-TKA improvements between males and females are partially attributable to pre-TKA biomechanics, as females with knee OA are found to walk with greater differences in gait features compared to asymptomatic females, than males with knee OA compared to asymptomatic males (Astephen Wilson et al., 2015; McKean et al., 2007; Young-Shand et al., 2023). This includes a more stiff-knee gait, represented by a lower knee flexion angle range and less dynamic knee moments during stance phase in females than males (Astephen Wilson et al., 2015). Recent findings show that although there are improvements in pre-TKA deficits in both frontal and sagittal plane angles and moments, the largest effect is found in the frontal plane (Outerleys et al., 2021). Given that reduced knee flexion angle range is a hallmark of increasing OA severity and knee flexion moments can contribute to implant migration (Astephen Wilson et al., 2010; Hilding et al., 1996) and pain (Smith et al., 2004) post-TKA, there is a need to improve sagittal plane features pre- and post- TKA.

Previous literature supports the importance of the muscles surrounding the knee in controlling joint motion and joint contact loads on the knee (Bennell et al., 2008, 2013; Schipplein & Andriacchi, 1991; Winby et al., 2009) and in stabilizing the knee joint during walking (Schipplein & Andriacchi, 1991; Winby et al., 2009). Recent work examining the associations between muscle activation patterns during gait and joint moments patterns that are linked to OA processes found the strongest correlations between prolonged knee extensor and flexor muscle activity patterns with sustained loading patterns in both frontal and sagittal planes, indicative of a stiff knee gait pattern (Hatfield et al., 2021b). In addition to less dynamic knee joint mechanics, individuals with knee OA have altered muscle activity, including higher and more prolonged activity during walking, that worsens across severity groups (Astephen Wilson et al., 2011; Hubley-Kozey et al., 2006, 2009, 2010, 2022; Rutherford et al., 2011, 2013). Those who are TKA surgical candidates are at the end stage of clinical OA progression and have significantly altered muscle activity prior to their surgery (Hubley-Kozey & Astephen Wilson, 2017). These pre-TKA alterations in muscle activity differ between males and females, with females showing worse overall patterns than males (Astephen Wilson et al., 2015).

Although maladaptive muscle activity patterns, such as higher overall activity, prolonged activity and co-activation often remain after TKA (Astephen Wilson et al., 2015; Benedetti et al., 2003; Hubley-Kozey et al., 2010; Hubley-Kozey & Astephen Wilson, 2017; Lundberg et al., 2016; Wilson et al., 1996), it has been shown that some muscle activity patterns during gait do change significantly following TKA, including decreased mid-stance activity of KF and KE muscles and improved temporal coordination between agonist and antagonist and medial and lateral muscle sites (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2010). These improvements towards asymptomatic muscle activity patterns demonstrate the ability of lower leg muscles to adapt to structural changes and changes in pain by modifying activation patterns. However, the improved muscle activity for patients post-TKA have been found to remain outside of the established variance of asymptomatic patterns (Hubley-Kozey et al., 2010; Lundberg et al., 2016), and the changes that occur pre-post TKA have shown to be sex specific, as females have been found to retain more severe muscle activity patterns post-TKA (Astephen Wilson et al., 2015). The retention of more severe muscle activity patterns post-TKA, such as more knee flexor and extensor prolonged activity, can pose a risk for poor joint functional outcomes, including a stiff knee gait (Hatfield et al., 2021b). Furthermore, specific preoperative muscle activation patterns, including more prolonged knee extensor and plantar flexor activity during gait, was associated with greater implant motion at two-year post -TKA follow-up, a predictor of implant migration over time (D. Wilson et al., 2012). While knee extensor (KE) muscle strengthening has been a primary focus of post TKA rehabilitation (Alrawashdeh et al., 2021; Konnyu et al., 2023), these above findings support that a rehabilitation focus on appropriate muscle activation patterns during gait could alter the abnormal loading features that are associated with poor TKA outcomes, and suggest further investigation on the differences between the influences of these patterns based on the sex of patients.

The focus on KE muscle strengthening has, in part, been based on literature showing those with severe OA have reduced KE strength compared to asymptomatic and moderate OA individuals, particularly in females (Bennell et al., 2008, 2013; McKean et al., 2007), and that KE strength decreases in the month following TKA (Mizner et al., 2005a, 2011; Stevens et al., 2003; Yoshida et al., 2008). Improvements in KE muscle strength have typically been found by 12-months post-TKA (Astephen Wilson et al., 2015; Benedetti et al., 2003; Hubley-Kozey et al., 2010; Mizner et al., 2011; Yoshida et al., 2008), approaching but not fully achieving asymptomatic strength levels at long-term follow-up (Walsh et al., 1998; Yoshida et al., 2008, 2013), with greater KE strength associated with improved function measures post-TKA. Less well studied are the knee flexor (KF) muscles, despite lower KF strength reported in severe versus moderate knee OA (Bennell et al., 2008, 2013) and that pre-post TKA increases in KF strength have been found (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2010), but again do not reach asymptomatic levels at long term follow-up (Walsh et al., 1998). Also, more KF strength was positively correlated with both frontal and sagittal plane dynamic loading patterns during walking for those with OA, whereas KE strength was significantly correlated with the sagittal plane dynamic loading pattern only (Hatfield et al., 2021b). These studies support a focus on the role of both KF and KE strength in post-TKA rehabilitation.

Pre-TKA KE strength (Mizner et al., 2005b) and pre-post TKA increases in KE strength (Mizner et al., 2005a, 2011; Yoshida et al., 2008) have been associated with improved function pre-post TKA based on clinical tests at one, three, and 12-months post-operatively. No studies were found that examined the relationship between KF muscle strength and functional or patient reported outcomes pre-post TKA. Together the research supports that a gap exists in the literature and that there is a need to better understand the potential role of pre- and post- TKA changes in KE and KF muscle function in outcomes following TKA, and that investigation may shed further light on the role of muscle strengthening in pre- and post- TKA rehabilitation.

Together, the literature supports that sufficient knee joint muscle strength and appropriate muscle activity patterns, both timing and magnitude, during functional activities are required for muscles to function effectively to produce joint motion, joint stabilization, and influence joint loading (Bennell et al., 2008, 2013; Hatfield et al., 2021b; Manal et al., 2015; Schipplein & Andriacchi, 1991) and that they improve post-TKA but deficits remain (Astephen Wilson et al., 2015; Benedetti et al., 2003; Hubley-Kozey et al., 2010; S. Wilson et al., 1996). There is a gap in the literature with respect to linking these muscle activity patterns and KF strength to post-TKA outcomes. Furthermore, there has been very little work looking at differences between sexes, especially pre-post TKA. Implementing rehabilitation protocols that address modifiable targets, like muscle strength and specific muscle activity patterns that are predictive of poor outcomes, has the potential to improve both long- and short-term TKA outcomes.

Walking speed provides an objective marker of an individual’s functional and overall health status. It has been referred to as the “sixth vital sign”, because self-selected walking speed reflects various underlying physiological processes, and has the potential to predict future health status (Fritz & Lusardi, 2009; Middleton et al., 2015). Further, since hip and knee OA have been identified as strong contributors to walking difficulties (King et al., 2018) and amount of walking has found to be associated with risk of functional limitation in those with or at-risk of having knee OA (White et al., 2014), it is a particularly valuable outcome to assess in the knee OA and pre-TKA population. Those with severe knee OA walk at slower self-selected speeds than healthy asymptomatic and moderate OA individuals (Hubley-Kozey et al., 2009; Kaufman et al., 2001; Zeni et al., 2010; Zeni & Higginson, 2009), indicative of progressively worse overall function with severity; generally, a greater proportion of those who have the most deficits in walking speed are females (Young-Shand et al., 2023). Walking speed has shown to improve following TKA (Astephen Wilson et al., 2015; Bączkowicz et al., 2018; Hatfield et al., 2011; Hubley-Kozey et al., 2010; McClelland et al., 2007; Outerleys et al., 2021; Vahtrik et al., 2014), thus self-selected walking speed can provide important information about the functional status of patients following surgery. The association between pre-TKA and pre-post TKA changes in muscle function features with pre-post TKA changes in walking speed as an objective marker of an individual's functional status, have not yet been examined, and could help provide stronger evidence to support a more comprehensive pre- and post- TKA rehabilitation program that focuses more broadly on muscle function.

In summary, research to date has not yet addressed the association between the magnitude of the change in pre-post TKA measures of muscle function, including KE and KF strength and activity patterns during walking, with the magnitude of change in an objective measure of overall function (walking speed). The overall goal of this study was to address this gap through a comprehensive examination of pre-TKA values and pre-post TKA changes in both KE and KF muscle function features, including activity patterns linked to poor outcomes in knee OA and muscle strength, and their association with pre-post TKA changes in overall function, using self-selected walking speed. Understanding these relationships aimed to help identify targets for improving functional outcomes of TKA surgery. Conducting sex-specific analyses of these relationships aimed to shed further light on the differences between male and female muscle activity patterns to help develop more patient-specific protocols. The overall goal was addressed through the study specific aim and three specific objectives below.

1.2 Study Aim

To determine whether pre-TKA and/or pre-post TKA changes in knee joint muscle function are associated with changes in overall function after TKA surgery in patients with severe knee osteoarthritis.

1.3 Specific Objectives

Objective 1: To determine the strength of the associations between pre-TKA and/or pre-post TKA change scores in knee extensor and flexor muscle strength and muscle activation features during walking that have been linked to poor outcomes in knee OA with pre-post TKA changes in overall function using self-selected walking speed, in individuals who undergo TKA surgery.

Objective 2: To determine what combination of pre and/or pre-post TKA changes in knee extensor and flexor activity patterns and muscle strength explain the most variance in post-TKA functional improvements, using self-selected walking speed, in individuals who undergo TKA surgery.

The overarching hypothesis was that both pre-TKA and pre-post TKA changes in strength and overall magnitude and prolonged activity of knee extensor and flexor muscles during walking would explain significant variance in pre-post TKA changes in self-selected walking speed, and that a combination of pre-TKA and pre-post TKA change scores of muscle strength and activity patterns would explain the largest variance in pre-post TKA changes in self-selected walking speed, indicating that both pre-TKA status and the changes in muscle function pre-to post-TKA are factors associated with improvements in function following TKA surgery.

Objective 3: To determine if there are differences between males and females who undergo TKA surgery in which muscle function features explain the largest variance in pre-post TKA changes in self-selected walking speed and in the combination of muscle function features that explain more variance in pre-post TKA changes in self-selected walking speed.

Based on the differences between sexes in muscle function described above for those with knee OA, the exploratory hypothesis was that there would be differences in the muscle function features that explained the most variance in pre-post TKA change in self-selected walking speed following surgery between males and females, and secondly, that a different combinations of muscle function features would be selected to explain more variance in pre-post TKA changes in self-selected walking speed for males and females.

The hope is that the results from this study will advance understanding of the association of pre-TKA and pre-post TKA changes in muscle strength and/or activity patterns with changes in overall function following TKA. This thesis includes a brief review of the relevant literature in Chapter 2, followed by a description of the proposed methodology to address the specific study objectives in Chapter 3. Results for the Total Study Sample and sex specific analyses are in Chapters 4 and 5 respectively, a discussion of the results, summary and conclusions in Chapter 6.

Chapter 2: Background

2.1 Knee Osteoarthritis

Osteoarthritis (OA) is a degenerative condition that results from damage to the tissues and structures surrounding a joint. OA is typically diagnosed based on clinical signs and symptoms as well as imaging evidence of structural degradation (Altman et al., 1986) and has been characterized as having both a *disease* and as an *illness* component (Lane et al., 2011). As a disease, OA involves the progressive breakdown of joint tissues and structures surrounding the joint, including articular cartilage, bone, ligaments, menisci, muscles, nerves and joint capsule surfaces (Lane et al., 2011). As an illness, OA causes joint pain, swelling and stiffness (Lane et al., 2011), that often are the main cause of disruptions and limitations in performing daily activities (Dieppe, 2004; March et al., 2016). Due to the heterogenous nature of OA, there is often a discordance between the severity of symptoms and the severity of structural damage in many individuals with OA (Altman et al., 1986; Dieppe, 2004; Wallace et al., 2017), which can complicate diagnosis and identifying targets for treatment. Osteoarthritis is one of the most common musculoskeletal conditions affecting adults, with 10-12% of the adult population having symptomatic OA (Hunter et al., 2014; Wallace et al., 2017).) In 2011, a report estimated that at least 1 in 8 Canadians are afflicted with OA (Arthritis Alliance of Canada, 2011), and in 2016, it was estimated that over 240 million globally people live with hip and/or knee OA (March et al., 2016). Current prevalence data for knee OA estimates that worldwide, about 23% of individuals aged 40 and older have knee OA (Cui et al., 2020).

OA is one of the fastest growing major health conditions in Years Lost to Disability (March et al., 2016). The impact that OA can have on an individual is substantial; the pain, disability and reduced quality of life caused by OA leads to increased physician visits, poor sleep quality, lower self-rated mental health, significant activity limitations, and work absenteeism (Badley et al., 2019; Hunter et al., 2014). About 80% of individuals with OA have functional limitations and about 25% are unable to perform common activities of daily living (Hunter et al., 2014; March et al., 2016). These burdens carry over to the workforce, where people with OA are two to three times more likely to be out of the labour force than those with no chronic health conditions (Badley et al., 2019; Hunter et al., 2014), thus creating socioeconomic strain on the individual and on society.

The knee, being a weight-bearing joint that endures large amounts of dynamic loading in daily activities, is one of the most common joints affected by OA (Cui et al., 2020; Hunter et al., 2014; March et al., 2016; Wallace et al., 2017). Knee OA has been considered a "wear and tear" disease, being associated with overuse of the joint, and is thought of by many to be a normal by-product of aging. However, OA is not a normal aging process and is not a disease exclusive to older adults (Arthritis Alliance of Canada, 2011; Carbone & Rodeo, 2017; March et al., 2016), demonstrated by recent findings of OA rates increasing most rapidly among people 45-55 years old (Kozey et al., 2023). Prevalence of knee OA increases with age, however the strength of age as a risk factor is likely a consequence of cumulative exposure to other risk factors over time as well as the biological changes that occur in aging that make joint tissues less responsive to changes in loading environment (Wallace et al., 2017; Zhang & Jordan, 2010). Knee OA is responsible for over 80 percent of the total estimated overall burden caused by OA (Vos et al., 2012).

Both biomechanical and biochemical processes influence the initiation and progression of knee OA, resulting in the characteristic breakdown of cartilage and bone at the joint (Andriacchi et al., 2009; Eckstein et al., 2006; Guilak, 2011; Wallace et al., 2017). For healthy articular cartilage, cyclic loading under normal physiological conditions is necessary to maintain cellular homeostasis and general health of the tissue (Guilak, 2011). Healthy cartilage adapts to progressive increases in magnitude and repetition of these cyclic loads by increasing thickness in the regions that accept the most force (Andriacchi et al., 2004, 2006). Progressive degradation, such as that which is associated with OA, indicates that the normal balance of metabolic activities of the chondrocytes has been disrupted (Andriacchi et al., 2004, 2006, 2009; Guilak, 2011). There is no known cure for OA, or strategy to slow structural progression of OA; treatments have only been effective at reducing symptoms of OA, in particular, pain (March et al., 2016). When a patient has severe structural damage to the joint and treatments are no longer able to reduce symptoms they experience, the patient is considered to have *end-stage* knee OA. Because there are no disease-modifying approaches to reverse structural degradation for end-stage knee OA, the only treatment is total joint replacement surgery.

2.2 Total Knee Arthroplasty

Total knee arthroplasty (TKA) is a surgical procedure that involves the removal of damaged bone and cartilage, and the placement of implants made of metal and/or plastic with the goal to restore alignment and function of the knee and reduce pain caused by knee OA (American Academy of Orthopaedic Surgeons, 2020). TKA is performed almost exclusively on patients with end-stage knee OA, with 99.3% of patients in Canada receiving TKA due to OA (Canadian Institute for Health Information, 2022). TKA has been one of the most frequently performed orthopedic procedures (Kane et al., 2005); global rates of TKA average around 175 procedures/100,000 people (Kurtz et al., 2011). In Canada, TKA has consistently been one of the top three most commonly performed inpatient procedures, with over 75,000 completed annually pre-pandemic (Canadian Institute for Health Information, 2022). In 2011, the country with the highest rate of TKA globally was the United States (Kurtz et al., 2011), and more recently, over one million procedures have been completed annually (Singh et al., 2019). Global demand for TKA is expected to increase each year and continue to increase exponentially for the foreseeable future (Kurtz et al., 2007; Singh et al., 2019).

Globally and in Canada, females make up a larger percentage of TKA patients than males (Canadian Institute for Health Information, 2022; Kurtz et al., 2011), which is consistent with the higher risk for females in developing OA (Badley et al., 2019; Cui et al., 2020; Zhang & Jordan, 2010). The most common age range to receive TKA in Canada is 65-74 years old, with just over 40% of patients receiving surgery within that age range (Canadian Institute for Health Information, 2022). An increase in the demand for total joint replacement surgeries among younger patients is predicted within the next decade; it is estimated that by 2030 over 50% of TKA procedures will be performed on patients less than 65 years old (Kurtz et al., 2009; Schreurs & Hannink, 2017). Current Canadian numbers are approaching these estimates; about 35% of patients who receive knee primary replacement surgery are less than 65 years old (Canadian Institute for Health Information, 2022).

Increasing prevalence of OA and demand for TKA is related to lifestyle changes; physical inactivity and obesity are found to be risk factors for the progression of primary OA (March et al., 2016), both of which are more common among the modern adult population compared to previous generations (Wallace et al., 2017). Further, post-traumatic OA currently accounts for approximately 12% of all OA cases (Brown et al., 2006; Maia et al., 2023). Among younger demographics, there is a higher incidence of post traumatic OA, specifically related to sports injuries. In particular, anterior cruciate ligament tears are a common precursor to knee OA and are commonly caused by incident during sport (Andriacchi et al., 2006; Carbone & Rodeo, 2017; Hall et al., 2012; Lohmander et al., 2007). These data show that the problem is prevalent, and that demand will continue to increase, with younger populations being of particular concern in recent years.

Because TKA is only a treatment and not a cure for OA, the demand for TKA among increasingly younger patients presents an additional burden to healthcare systems. The younger a patient is at the time of their primary surgery, the higher likelihood there is that the same individual will need revision surgery within their lifetime (Schreurs & Hannink, 2017), as the integrity of joint implants diminish over time, including the regression of the implant into the bone, progressive wear on implant surfaces, or the loosening of the implant components. A 2011 systematic review demonstrated the need for more follow-up studies that include younger patients who receive TKA, as there is limited data to compare the success of the procedure in the younger population to the success of the procedure in the overall population (Keeney et al., 2011). However, registries reporting on revision surgeries have been able to show some important comparisons between younger and older patients. For example, lower ten-year implant survival rates have been reported among younger patients when using cut-off ages of 55 (Rand et al., 2003; W-Dahl et al., 2010), 60 (Himanen et al., 2005), and up to 70 years old (Bayliss et al., 2017) to define a 'young' TKA patient. Further, ten-year revision rates of TKA have been found to be three times higher among patients who received surgery before 55 years of age compared to those who were over 55 years of age at the time of the surgery (W-Dahl et al., 2010). These findings emphasize the need to reduce the rates of primary TKA among younger populations to reduce the burden on healthcare systems.

A possible explanation for lower long term implant success rates in younger populations is that implant longevity is more greatly preserved by lower levels of stress on the joint, which is consistent with older patients having higher implant survival rates, as older adults place less strenuous demands on their joints (Himanen et al., 2005; Rand et al., 2003; W-Dahl et al., 2010). The majority of TKA revision surgeries in the overall patient population are performed for reasons attributable to mechanical abnormalities, such as instability and loosening (Canadian Institute for Health Information, 2022; Hamilton et al., 2015; Seil & Pape, 2011), which can arise as a result of residual alterations in gait mechanics following many years of pain and instability due to knee OA. Higher amounts of activity, as well as more strenuous activity in the years following surgery, mean that younger people put their implants a higher risk for malfunction, and will therefore need revision surgery sooner than an older adult with the same implant (Kurtz et al., 2009; Schreurs & Hannink, 2017). Further, younger people tend to have higher expectations of joint function following surgery and therefore are more likely to be disappointed by the outcome of the surgery (Parvizi et al., 2014), further increasing the likelihood of revision surgery among this population.

Despite a high prevalence, there is currently no standard of care for TKA rehabilitation (Canadian Institute for Health Information, 2020; Healthcare Excellence Canada, 2021), leading to diverse outcomes for patients following surgery. A 2005 systematic review found that TKA is associated with significant functional improvement (Kane et al., 2005); however, functional improvement does not predict patient satisfaction following the procedure. Satisfaction rates for TKA vary worldwide, with studies reporting that between 10 to 30% of patients were unsatisfied with their surgery (Alzahrani et al., 2011; Bierke et al., 2020; Bourne et al., 2010; Kane et al., 2005; Seil & Pape, 2011). In Canada, satisfaction rates for TKA are high, however 12% of patients who receive TKA report feeling neutral or dissatisfied with the outcome of their knee replacement after one year (Canadian Institute for Health Information, 2022). Reported rates of revision surgery were between 6-12% within ten years following primary TKA surgery (Labek et al., 2011; Pabinger et al., 2013). A recent systematic review has shown that TKA often significantly improves patients' self-reported quality of life (QOL), but that many factors can influence the success of the procedure, such as pre-surgical pain, mental health scores, obesity, and time spent on the surgical waiting list (Da Silva et al., 2014).

In summary, TKA is a common procedure with high rates of overall success. However, projected increases in demand for TKA over the next decade would place an elevated burden on healthcare systems that is not sustainable. To address this, research should focus on improving potential rehabilitation protocol, in order to increase long-term success of the procedure.

2.3 TKA Rehabilitation Programs

A recent systematic review concluded that rehabilitation delivered in acute (0-2 weeks) and post-acute (2 weeks- 6 months) phases results in similar improvements in muscle strength, QOL, and satisfaction (Konnyu et al., 2023). Other recent studies show that extending the hospital stay for patients post-TKA to allow for more supervised rehabilitation time by medical professionals immediately after surgery does not reliably increase long-term knee function of those receiving knee replacements (Dávila Castrodad et al., 2019; Rak et al., 2022), and that for many patients, receiving TKA as an outpatient surgery can provide similar patient outcomes with decreased costs to the healthcare system (Bodrogi et al., 2020; Dávila Castrodad et al., 2019; Vendittoli et al., 2021).

Current systematic reviews have shown that prescribed outpatient rehabilitation programs can improve measured functional and patient reported outcomes following TKA (Alrawashdeh et al., 2021; Konnyu et al., 2023), but researchers and clinicians have not yet identified what rehabilitation program characteristics can improve different outcomes most effectively for different individuals (Alrawashdeh et al., 2021; Kane et al., 2005; Konnyu et al., 2023; Losina et al., 2016). Since numerous different factors can alter outcomes from the surgery, a single, common rehabilitation program is unlikely to create significant improvements for most individuals. Research has shown that patients who undergo standard rehabilitation programs still have significant impairments and functional limitations 3 to 6-months after TKA (Bade et al., 2010; Brenneman & Maly, 2018), which suggests that more intensive interventions may be required to improve function to the level of healthy adults. This emphasizes that a one-size-fits-all approach to TKA rehabilitation does not provide improvements for most individuals and indicates that more personalized approach could create more significant overall improvements. The key to developing patient-specific TKA rehabilitation is determining what factors are related to poor outcomes from TKA; some of the factors that can have the most influence on TKA outcomes are gait features.

2.4 Knee Osteoarthritis and Gait Biomechanics

Gait features have been shown to be altered with OA severity. The structural damage and pain associated with OA result in functional decline; for those with knee OA, difficulty with walking is commonly reported (Hunter et al., 2014; March et al., 2016). Furthermore, since OA has a mechanical etiology, gait has been used as an in-vivo model to understand the mechanics associated with joint loading and OA processes, to assess changes at the local joint mechanical environment, and to assess overall patient function (Andriacchi et al., 2004, 2009; Griffin & Guilak, 2005; Guilak, 2011; Guilak et al., 1994, 2004). Due to the burden that is placed on individuals and on society due to losses of mobility often experienced with increasing OA severity (Badley et al., 2019; Hunter et al., 2014; March et al., 2016), it is important to understand which features are most greatly affected by OA and which features play a role in the progression of OA, in order to better understand current interventions and to develop future interventions with the goal reduce or prevent losses in mobility for those with OA, thus relieving some of the burden caused by the condition.

Several biomechanical features measured during walking have been shown to be altered in individuals with knee OA compared to those without knee OA, among those with varying OA severity levels, following interventions, and as predictors of long-term progression outcomes. These gait metrics include stride characteristics, walking speed, three-dimensional knee joint kinematics, kinetics, and lower limb muscle activation. Self-selected walking speed, sometimes regarded as the “sixth vital sign” provides a marker of an individual’s functional and overall health status, having the potential to predict future health status and reflect various underlying physiological processes (Fritz & Lusardi, 2009; Middleton et al., 2015). Joint angles during walking provide an indication of the motion of the knee joint and hence an assessment of knee joint function. The most common joint angle of interest has been the knee flexion angle (KFA), and, in medial compartment knee OA, the knee adduction angle (KAA). The features most often assessed in knee OA gait studies are the external knee joint moments, which serve as surrogate measures of joint loading and can give an estimate of the magnitude and direction of forces through the knee. External joint moments are calculated using inverse dynamics, which allow researchers to estimate knee joint function. Inverse dynamics uses ground reaction forces measured by in-ground force plates and linear and angular kinematics collected using motion capture technology, combined with anthropometric measurements (Begg et al., 1989; Chambers & Sutherland, 2002; Minns, 2005; Ren et al., 2008).

Knee joint moments in each plane provide different information about the loading environment of the knee. In the sagittal plane, the external knee flexion moment (KFM) and knee extension moment (KEM) provide information on the magnitude and pattern of load through the knee joint at various points in the gait cycle (Creaby, 2015; Manal et al., 2015). In the frontal plane, the knee adduction moment (KAM) has been the most common feature assessed in medial tibiofemoral knee OA, providing information on the ratio of medial to lateral loading on the knee joint surface (Hurwitz et al., 1998; Kutzner et al., 2013; Schipplein & Andriacchi, 1991). A less frequently studied moment is the knee rotation moment (KRM) in the transverse plane of the leg. The KRM can provide informational on rotational forces on the joint surfaces where increased shearing forces can cause cartilage thinning in the knee (Andriacchi et al., 2006). Fewer studies on muscle activation patterns exist in the knee OA gait literature, however muscle activation during walking plays an important role in controlling knee joint moments (Bennell et al., 2008, 2013; Manal et al., 2015; Schipplein & Andriacchi, 1991), and has been found to vary among those with increasing OA severity (Astephen Wilson et al., 2017; Hubley-Kozey et al., 2008, 2009; Rutherford et al., 2011, 2013; Zeni et al., 2010). Gait studies have been utilized in OA research to assess changes in structural or clinical status across knee OA severity through cross-sectional studies, to predict structural or clinical progression outcomes using longitudinal follow up studies, and to assess the effects of interventions using a pre-post treatment design.

Most gait studies have determined knee OA severity using metrics of structural progression from medical imaging modalities (e.g., radiographs, magnetic resonance imaging) to grade severity based on observable characteristics, such as the extent of joint space narrowing, the formation of osteophytes, or altered shape of bone ends involved in the joint. The few studies that use a clinical definition of severity and progression consider both the disease and illness components of OA. The clinical definition used in research for determining OA severity and progression is consistent with OA diagnosis followed by a physician (Altman et al., 1986) and with an Osteoarthritis Research Society

International sponsored position paper that sought to define OA (Lane et al., 2011). Clinical assessments of OA severity and progression have included structural severity assessments, functional assessment, scores on patient-reported outcome measures (PROMs), and assessment of clinical management. An example of a clinical definition for patients with moderate knee OA includes those with a Kellgren-Lawrence structural severity grade of 1-3, who were able to perform functional tasks including walking a city block, jogging five meters and climbing stairs in a reciprocal manner, and were not surgical candidates (Hubley-Kozey et al., 2006), with severe OA defined as those with a Kellgren-Lawrence structural severity grade of 3 or 4 and were diagnosed with severe OA by an orthopedic surgeon who recommended TKA as treatment (Hubley-Kozey et al., 2008). Given that symptoms and structural damage are not well correlated (Altman et al., 1986; Dieppe, 2004; Wallace et al., 2017), clearly reporting the definition of OA severity and progression can help explain differences among studies and more easily allow for comparison among the current literature. Since the proposed study is assessing changes before and after TKA, it is key to understand how gait features change as people approach pre-TKA levels of OA severity.

2.4.1 Assessing Changes in Gait Biomechanics with Knee OA

Cross-sectional studies have identified features during walking that differ between individuals with and without knee OA. Patients with OA have been found to walk slower than asymptomatic individuals (Kaufman et al., 2001); some factors that contribute to this are more time spent in stance phase of gait (Landry et al., 2007), and significantly shorter stride length (Baliunas et al., 2002) for individuals with moderate OA compared to asymptomatic controls. Patients with moderate OA have also been found to make initial contact with the ground in a more extended knee position when walking at self-selected walking speeds (Baliunas et al., 2002; Mündermann et al., 2005) and have overall smaller knee range of motion compared to asymptomatic controls (Baliunas et al., 2002).

Studies have also identified differences in joint moment features in individuals with OA when compared to an asymptomatic population (Hubley-Kozey & Astephen Wilson, 2017). In general, those with OA have been found to have greater KAM features than asymptomatic controls, including greater overall adduction moment through stance (Landry et al., 2007; McKean et al., 2007), and greater peak values (Baliunas et al., 2002; Hurwitz et al., 2002; Kaufman et al., 2001; Lewek et al., 2004). In addition, patients with OA tend to have different KFM-KEM features compared to asymptomatic controls, including smaller overall KFM magnitudes (Landry et al., 2007) and reduced peak (Kaufman et al., 2001) and terminal stance KEM magnitudes (Baliunas et al., 2002). Although these results are from studies on patients with mild-moderate knee OA, it is clear that patients with OA develop gait features characteristic of the condition that differ from those without OA. Cross-sectional progression studies have been conducted to pinpoint what features develop and progress as OA severity increases.

Cross-sectional studies have been conducted to look at how gait features vary at different levels of knee OA severity using different metrics and definitions of severity. Studies looking at OA progression have found walking speed to be associated with OA severity, where patients with more severe OA walk at slower speeds, due to increases in stance percentage, stride time, and stance time and decreases in stride length (Astephen et al., 2007; Hubley-Kozey et al., 2009; Kaufman et al., 2001; Landry et al., 2007; Thorp et al., 2007; Zeni et al., 2010; Zeni & Higginson, 2009). This association between walking speed and OA severity is primarily found in studies using clinical severity, as there is a strong relationship between reports of pain and gait speed measured in the lab (Astephen Wilson et al., 2011).

A narrative review summarized that as OA severity increases, individuals tend to walk with increased KAM values (Hubley-Kozey & Astephen Wilson, 2017), including greater first peak KAM magnitudes (Mündermann et al., 2005; Thorp et al., 2006), greater overall magnitude of KAM during stance (Astephen Wilson et al., 2011), and greater KAM impulse (Thorp et al., 2006) with increasing structural severity. One proposed reason for higher KAM values among those with higher structural severity is that they have more medial joint laxity; evidence has shown that increased medial joint laxity present in patients with OA can be a contributor to increased KAM in early stance (Lewek et al., 2004). This is consistent with increases in structural severity, as medial joint space narrowing is a common criterion in the assessment of structural severity (Kellgren & Lawrence, 1957) and contributes to medial joint laxity. Clinical severity studies have identified higher mid-stance KAM magnitudes to be a feature discriminating all participants with OA from asymptomatic controls, but not between severity levels (Astephen et al., 2007); other studies have not found this feature to contribute significantly to gait differences among OA severity levels (Astephen et al., 2008).

A narrative review summarizes the evidence of progressive changes in sagittal plane gait characteristics with increasing OA severity (Hubley-Kozey & Astephen Wilson, 2017). This review highlighted that among the various discrete measures of KFA throughout gait, KFA during stance is consistently found to be lower among patients with higher levels of severity (Hubley-Kozey & Astephen Wilson, 2017). Studies have found that decreased peak mid-stance KEM is reduced only in those with more severe OA, but not in those with more moderate OA severity (Astephen et al., 2008), as evidenced by studies on moderate OA groups finding no significant difference in mid-stance KEM-KFM features compared to asymptomatic individuals (Baliunas et al., 2002; Landry et al., 2007). Decreases in KFM magnitudes have been found among those increasing in structural severity (Zeni & Higginson, 2009) and decreases in early stance KEM have been found to progress with increasing severity (Astephen et al., 2007). Decreasing KEM and KFM magnitudes throughout gait among people with increasing OA severity results in an overall lower KFM-KEM range (Astephen et al., 2007, 2008; Zeni & Higginson, 2009), which is consistent with a “stiff-knee” gait pattern that can be indicative of reduced willingness to load the joint due to pain or perceived instability in patients with more severe OA (Astephen Wilson et al., 2017; Childs et al., 2004; Creaby, 2015; Zeni et al., 2019).

To investigate the relationship between symptoms and structural progression, studies have looked at the differences in key joint moments between patients with similar levels of radiographic progression but different symptoms. In some of these studies, individuals with symptomatic OA have been found to walk with higher KAM values, including peak KAM and KAM impulse (Thorp et al., 2007), as well as higher KAM magnitude and less mid-stance unloading (Astephen Wilson et al., 2017) than asymptomatic individuals with the same radiographic severity. In contrast, a study looking at the relationship between pain and biomechanical features found no relationship between peak KAM and pain (Maly et al., 2008), which could simply mean that pain is not the primary symptom playing a role in clinical progression of OA. This same study found knee flexion-extension range during walking to explain a significant portion of the variance in pain intensity among participants (Maly et al., 2008). Minimal evidence has been provided connecting KFM features to symptoms. A comparison study between symptomatic and asymptomatic individuals of the same radiographic severity found the symptomatic group to have lower peak KFM than the asymptomatic group (Astephen Wilson et al., 2017). A study comparing gait features of patients with moderate OA with and without joint effusion found those with effusion to walk with a more flexed knee during stance, associated with a lower KEM in mid to late stance (Rutherford et al., 2012). These findings help demonstrate a connection between knee flexion and the manifestation of symptoms in knee OA progression.

There are also key gait characteristic changes that are present in asymptomatic individuals with radiographic evidence of OA. Individuals with cartilage damage but no symptoms have been found to have less extension of the leg as well as decreased KEM in late stance when compared to those with no cartilage damage or symptoms (Edd et al., 2015). In a longitudinal study, higher early stance KEM peak at baseline for asymptomatic individuals was associated with cartilage thickness decreases at 7–9-year follow-up (Erhart-Hledik et al., 2021). This longitudinal study also found first peak KAM to be negatively associated with cartilage change in the femoral regions but positively associated with cartilage change in the anterior medial tibia region and suggest that more investigation is required to fully understand this effect (Erhart-Hledik et al., 2021). Overall, these findings suggest that some changes in gait characteristics precede the development of OA symptoms and are risk factors for the onset and progression of OA (Edd et al., 2015; Erhart-Hledik et al., 2021).

The cross-sectional studies characterizing gait feature changes at different levels of OA severity allow the monitoring of gait characteristic changes in individuals with OA; the findings from these studies provide information about how the OA process affects gait features of patients with OA. The information provided by these studies is important to the proposed study as it identifies the gait metric differences among those who are candidates for TKA compared to those with moderate OA and those without OA. Those who are candidates for TKA typically have a KL grade of 3 or 4, high pain, and poor reported function. These patients typically walk slower, with lower KFA and KEM-KFM range, and have greater KAM magnitude features; these features provide important targets for the restoration of asymptomatic gait patterns among those who undergo TKA surgery.

2.4.2 Gait Biomechanics in Predicting Progression of Knee OA

Longitudinal studies have examined whether gait features are a risk factor for OA progression, and findings allow for the prediction of which individuals are likely to progress in OA severity. A recent systematic review has found that greater KAM features at baseline are commonly associated with increased risk of OA progression within varying follow-up times (D’Souza et al., 2022). Studies assessing structural progression have found higher mid-stance minimum KAM (Costello et al., 2020), higher KAM impulse (Bennell et al., 2011; Chang et al., 2015), higher KAM peaks (Chang et al., 2015; Chehab et al., 2014; Davis et al., 2019; Miyazaki, 2002), and greater early to mid-stance differences in KAM (Davis et al., 2019) to be associated with increased structural progression; these studies used either radiographic or MRI imaging to assess structural progression and had follow up periods between 1 to 7+ years. Early work found a strong relationship between peak KAM and structural progression by means of joint space narrowing (Miyazaki, 2002); however, more recent work has found no relationship between peak KAM and measures of structural progression, with no differences in cartilage loss found at 12-month follow up (Bennell et al., 2011) or in medial joint space narrowing found at an average of 7-years follow-up (Costello et al., 2020). Studies that used a clinical definition for progression have found higher first peak, overall KAM amplitude and KAM impulse, and a smaller first peak to mid-stance difference to increase odds of progression to TKA by 5–8-year follow-up (Hatfield et al., 2015b, 2015a). Smaller first peak to mid-stance KAM differences found in those that progress clinically differs from the finding of greater early to mid-stance KAM differences in those that progress structurally (Davis et al., 2019) and could indicate the emphasized role of smaller KAM difference in the progression of OA symptoms. However, Costello (2020), when separating those who progressed clinically with no structural progression, found no differences in any discrete metrics or patterns of knee moments, including KAM features, between those that did and those that did not progress clinically within their follow-up time.

Although changes in sagittal plane features are key changes that have been identified among increasing levels of OA severity, most longitudinal studies have found minimal or no evidence of differences in KFM features between groups that do and do not progress structurally (Chang et al., 2015; Chehab et al., 2014; Costello et al., 2020; Davis et al., 2019). In contrast, a study using a clinical definition did find significantly smaller KFM-KEM range present at baseline in a group of patients with moderate OA that progressed to TKA within 5-8 years (Hatfield et al., 2015b). A smaller KFM-KEM range present in clinically progressing individuals, but not structurally progressing individuals highlights this feature as playing a role in the development of symptoms rather than structural degradation. Although structural progression studies have not found significant predictive value of flexion moments, both a smaller KFA at heel strike and a larger KFA at mid-stance have been found to be associated with greater losses in medial tibial cartilage thickness (Favre et al., 2016). The KRM is not commonly assessed by gait studies, but some studies have found an increase in mid-stance internal KRM (Costello et al., 2020) as well as higher rotation moment range (Davis et al., 2019) to be associated with structural progression of OA.

The findings from longitudinal studies can be used to provide information on the gait features that may play a role in the progression of OA and can serve as a marker of who is at risk for OA progression. These studies have identified features that have shown to be maladaptive, which can serve as targets for intervention to slow the progression of OA and can allow healthcare professionals to identify patients that may need additional interventions to prevent adverse effects of OA. This approach has the potential slow or reduce the number of patients reaching end-stage OA and thus requiring TKA and can lessen the load on the healthcare system.

2.4.3 Total Knee Arthroplasty and Gait Biomechanics

There are several studies that report changes in biomechanical features during walking following TKA surgery. A systematic review in 2007 showed that although post-TKA patients do not tend to walk as fast as asymptomatic controls, they do improve their walking speed to similar pace across the patient population (McClelland et al., 2007). More recent work supports this, with gait studies showing that over time, TKA generally leads to improvements in the altered gait features of individuals with severe knee OA, but that residual alterations in functional outcomes can remain compared to asymptomatic controls without knee pathologies (Bączkowicz et al., 2018; Benedetti et al., 2003; Vahtrik et al., 2014; Walsh et al., 1998). Most studies have found increases in walking speed and stride length following surgery, which are improvements towards more asymptomatic gait characteristics (Astephen Wilson et al., 2015; Bączkowicz et al., 2018; Hatfield et al., 2011; Hubley-Kozey et al., 2010; Outerleys et al., 2021; Vahtrik et al., 2014). This increase in gait speed is associated with an improvement in function, which in turn has many health benefits, including decreased risk of disability, falls or hospitalization, and increased independence (Fritz & Lusardi, 2009; Middleton et al., 2015).

Walking speed is a particularly important outcome from TKA surgery, since hip and knee OA have been identified as strong contributors to walking difficulties (King et al., 2018) and greater amounts of daily walking have been associated with less risk of functional limitation in those with or at risk of knee OA (White et al., 2014). Together, this means that individuals with OA are at greater risk of overall functional decline due to increased risk of walking difficulties. Further, since those with severe OA, who are the candidates for TKA, walk with significantly slower walking speeds compared to moderate OA and asymptomatic populations (Hubley-Kozey et al., 2009; Zeni et al., 2010; Zeni & Higginson, 2009), they are at particularly elevated risk of functional decline. Thus, walking speed is an important feature to assess in pre-post TKA research.

One of the primary goals of TKA is to restore neutral joint alignment, which for patients with medial compartment knee OA, involves correcting a varus deformity.

Therefore, for most patients, the most reported improvement in local joint mechanics are in the frontal plane, including decreases in KAM magnitude features and adduction angles (Outerleys et al., 2021). Studies have found a reduction in overall KAM and decrease in midstance KAM values (Hatfield et al., 2011) and decreases in both first and second maximum adduction moments along with an increased maximum abduction moment (Benedetti et al., 2003). Other improvements in KAM features include more mid-stance unloading one-year after surgery (Astephen Wilson et al., 2015). These findings indicate a decrease in medial joint loading post-surgery, which is to be expected due to the nature of the surgery; what is given less attention for TKA procedures is how to improve the deficits in sagittal plane features that are present in those with clinically severe knee OA. Patients who receive TKA also make improvements in sagittal plane characteristics. Increased early stance KFM peaks and increased late stance KEM peaks, coupled with an increase in KFA magnitude (Astephen Wilson et al., 2015; Hatfield et al., 2011; Outerleys et al., 2021), show that OA patients tend to make some reductions in the characteristic stiff-knee gait following TKA. However, a study using principal component analysis with the goal of quantifying achievable levels of improvement in gait biomechanics following TKA found that only about half of people with severe OA who receive TKA significantly improve their gait patterns toward asymptomatic (Outerleys et al., 2021) and suggests developing strategies aimed to make simultaneous improvements to both sagittal and frontal plane characteristics.

In 2007, a systematic review found that people with knee OA who had TKA walked with less total range of knee motion than asymptomatic controls without musculoskeletal conditions or any surgical procedures affecting their knees (McClelland et al., 2007); this has been corroborated in more recent studies. A smaller range of motion in the sagittal plane during both swing and stance phases of gait for the affected leg was common among patients who had received TKA compared to asymptomatic controls (Benedetti et al., 2003; Hatfield et al., 2011; McClelland et al., 2007; Zeni et al., 2019). Furthermore, post-TKA patients do not tend to demonstrate the biphasic sagittal moment pattern that is present in asymptomatic individuals (Benedetti et al., 2003; Hatfield et al., 2011; McClelland et al., 2007; Zeni et al., 2019). Along with reduced range of motion in the sagittal plane, significant deficits in improvement toward asymptomatic for both first and second KEM peaks have been found to remain 24-months post-surgery, despite patients participating in a standard rehabilitation program (Benedetti et al., 2003).

Overall, knee joint moment patterns can help predict risk of joint structural damage and clinical progression, and there are further studies that have looked at whether preoperative joint moments can influence the success of the procedure, including looking at outcomes of joint implant integrity and patient reported outcomes. In the frontal plane, a higher overall magnitude of KAM was correlated to TKA tibial implant migration, a relationship not highlighted by other TKA outcome studies (Astephen Wilson et al., 2010). Higher peak KFM during gait preoperatively has found to be associated with TKA tibial component aseptic loosening at 6-month and 2-year follow-up (Hilding et al., 1996) and with patients who develop post-surgical anterior knee pain than those that do not develop post-surgical anterior knee pain at 12-18 month follow-up (Smith et al., 2004), demonstrating that higher peak KFM during gait before surgery can be predictive of negative overall outcomes post-surgery. More recent work found that a lower constant magnitude external KFM (i.e., constant KEM) preoperatively, characteristic of the “stiff-knee" gait pattern, was related to higher levels of post-surgical tibial implant migration at 6-month follow-up (Astephen Wilson et al., 2010), likely due to less impact attenuation during weight acceptance that would typically be present in a more dynamic KFM-KEM waveform. The stiff-knee gait pattern that commonly remains in patients after TKA can put individuals at risk for a progression towards TKA in the contralateral limb (Zeni et al., 2019), as these asymmetrical gait patterns overload the joints on the opposing limb. These outcomes highlight the importance of proper pre-surgical pre-habilitation and post-surgical rehabilitation to reduce the severity and impact of these altered gait patterns on TKA outcomes. However, there are limitations to using inverse dynamics to estimate loading at the joint and to understand potential targets for functional improvements.

Since many studies use discrete features of joint moments throughout gait, it is important to consider how discrete moment features capture limited information about the entire waveform of moments in each plane, so they do not provide an entire picture of what is occurring at the joint throughout the gait cycle. The moments measured using inverse dynamics are the net resultant external joint moments and therefore do not account for antagonistic activity (Buchanan et al., 2005). This means that in the presence of coactivity, the magnitude and direction of all the individual forces on the joint surfaces or muscle forces cannot be determined. Given the knowledge that there are several possible ways to approach the normalization of joint moments, as discussed in a recent narrative review (Hubley-Kozey & Astephen Wilson, 2017), it is important to note that in some cases, results can be affected by normalization techniques, which poses another barrier to the comparison of these features (Hatfield et al., 2015a). External joint moments do not measure contact loads on the joint, so they do not provide precise information about the loading environment of the joint. It is possible to address some of these gaps in information by using a hybrid approach that uses muscle activity information as well as inverse dynamics to help with the modelling of joint reaction forces (Buchanan et al., 2005; Holder et al., 2020). Furthermore, some discrete metrics have been found to be correlated with waveform features extracted using Principal Component Analysis (Hatfield et al., 2015a), which means that it can also be possible to infer more general waveform patterns from discrete values.

In summary, knowing what gait features change as OA progresses provides biomarkers for assessing improvements following interventions. Specifically, looking at how gait features change after a major joint surgery such as TKA can provide important information about the success of the procedure, and how it might be improved. Looking at muscle function can provide additional information that can help with the interpretation of joint moments, with the goal to address the causes of some of the changes in biomechanical features that occur throughout progression of OA.

2.5 Knee Osteoarthritis and Muscle Function

Muscles play an important role in movement and knee joint loading during gait, as dynamic muscle forces are critical to producing limb motion, stabilizing the knee joint during walking, and impact attenuation (Bennell et al., 2008, 2013; Manal et al., 2015; Schipplein & Andriacchi, 1991); thus, muscle function, including knee extensor and flexor muscle strength and activity patterns, are important to knee joint function. Recent evidence has demonstrated that muscle activation patterns and strength differences are able to explain significant variance in moment difference features during gait for those with moderate medial compartment knee OA (Hatfield et al., 2021b), emphasizing the roles of both muscle strength and of muscle activity patterns during gait in changes that occur with OA.

Muscle strength, specifically of KE muscles, has been found to play an important role in measures of knee function (Mizner et al., 2005b; Yoshida et al., 2008). Two narrative reviews summarize previous muscle strength and knee OA studies, indicating that significantly lower knee joint muscle strength is found in those with OA compared to asymptomatic controls, with the most consistent findings being of strength deficits in KE muscles (Bennell et al., 2008, 2013). These narrative reviews further highlight that there are many possible explanations for the decreases in muscle strength found in those with OA, including pain, anxiety, motivation, effusion, muscle atrophy, or poor joint mechanics (Bennell et al., 2008, 2013); other studies have been working on assessing the effect of these. For example, increases in maximal voluntary contractions and activation of KE muscles were found with pain reduction via injection of a local anaesthetic, suggesting that pain plays at least in part, a role in muscle strength and activation (Hassan, 2002). Swelling at the knee has also been found to have a statistically significant relationship with KE strength, with greater post-operative knee swelling being related to greater decreases in KE strength in post-TKA patients, which suggests that swelling may have an inhibitive effect on muscle strength or muscle activity (Holm et al., 2010).

Changes in muscle activity for those with OA can be assessed using electromyography. Electromyography (EMG) uses electrodes to detect and record the electrical activity of muscle tissues (Konrad, 2005; Kumar & Mital, 1996). An electromyogram is the spatial and temporal summation of all motor unit action potentials within the pickup region of the electrode; the motor unit action potential is the summated electrical activity of all muscle fibers activated within a motor unit. Therefore, the EMG signal is the composite electrical sum of all activity within the pickup region. The electrical activity detected by EMG is causally related to muscle contraction by means of *excitation-contraction coupling*. The resulting EMG signal does not directly assess the muscle force produced but measures the motor unit action potentials that trigger muscle contraction. EMG signals therefore provide information about the activity of muscles in terms of timing, amplitude, and duration of activity of specific muscles and muscle groups (Konrad, 2005; Kumar & Mital, 1996). For people with knee OA, EMG can serve as a useful tool for observing and analysing changes in muscle activity patterns during gait, since muscles can alter joint loading due to forces produced across the joint and forces to produce joint motion, and therefore can be impacted by OA-related symptoms and joint tissue degradation (Bennell et al., 2008, 2013)

Since there are clear differences in kinetics and kinematics during gait for those with knee OA, which are more distinct with severe knee OA, and since lower limb muscles have an important influence on knee joint movement and loading, it is important to look at muscle activity changes throughout gait, known as muscle activation patterns. Cross-sectional studies have found abnormalities in muscle activation patterns during walking for patients with OA (Childs et al., 2004; Hubley-Kozey et al., 2006; Lewek et al., 2004), and across OA severity levels (Astephen Wilson et al., 2017; Hubley-Kozey et al., 2008, 2009; Rutherford et al., 2011b, 2013; Zeni et al., 2010) and are discussed below. These changes in neuromuscular features and activity during gait influence the abnormal moments that are produced and demonstrate the direct effect of muscles in mechanical changes while walking for people with OA, as discussed in narrative review (Bennell et al., 2008, 2013).

Because OA is a chronic condition, patients become accustomed to the symptoms, such as pain and instability, that they experience while walking and the gait changes that they make to minimize the effect of those symptoms (Leporace et al., 2021; Rutherford et al., 2012). Simulated effusion at the knee joint has been shown to inhibit quadriceps muscle activity during strength testing and dynamic tasks, including walking and single leg-drops, by using injections of saline on asymptomatic participants (Palmieri-Smith et al., 2007; Torry et al., 2000). These studies showed decreased quadriceps activity following acute effusion (Torry et al., 2000) and more decreases in quadriceps activity with more simulated acute effusion (Palmieri-Smith et al., 2007) in asymptomatic participants. However, more recent work provides evidence that arthrogenic muscle inhibition and acute effusion models don’t accurately reflect what is happening in the presence of inflammation, pain and pathology (Rice et al., 2014; Rice & McNair, 2010), such as in knee OA. A study assessing knee mechanics and muscle activity differences between OA patients with and without knee effusion during walking found greater overall quadriceps activity and more prolonged hamstring activity in those with knee OA who had effusion (Rutherford et al., 2012), supporting previous evidence. Thus, the difference between the findings in these studies can be explained by the effusion condition of the patients; the study that found quadriceps activity to decrease tested acute effusion, while the study that found quadriceps activity higher in those with effusion had tested those with chronic joint effusion of the knee. This suggests that acute effusion is more likely to inhibit a muscle signal, whereas chronic effusion, that which is present in patients with OA, does not influence muscle signals to the same degree (Rutherford et al., 2012).

Over time, neuromuscular patterns adapt to produce muscle forces in ways that provide stability, reduce pain, and allow for confidence while walking (Bennell et al., 2008, 2013; Hubley-Kozey et al., 2009; Rutherford et al., 2011b, 2012, 2013). Evidence has shown that rehabilitation programs focused on muscles are able to improve gait outcomes for individuals with OA, including overall functional performance measures as well as muscular function (Fisher et al., 1997; LaStayo et al., 2009), which shows that muscles provide effective targets for gait rehabilitation. These principles can be applied to post-TKA rehabilitation to improve surgical outcomes; however, since different individuals develop their own unique gait patterns (Leporace et al., 2021), more research is required to address the ways in which rehabilitation programs can be personalized to individual goals, thus providing patient-specific care to improve the overall success of the procedure.

2.5.1 Assessing Changes in Muscle Function with Knee OA

Cross-sectional studies have examined changes in muscle activity during gait between those with and without knee OA (Childs et al., 2004; Hubley-Kozey et al., 2006; Lewek et al., 2004) and across knee OA severity levels (Astephen Wilson et al., 2017; Hubley-Kozey et al., 2008, 2009; Rutherford et al., 2011b, 2013; Zeni et al., 2010). Studies have consistently found greater overall amplitudes and more prolonged activation of both quadriceps and hamstrings in patients with more structural severity (Rutherford et al., 2013; Zeni et al., 2010). Consistent with the studies assessing structural severity, those assessing clinical severity have also found higher overall amplitude and duration of activation for quadriceps and hamstrings muscles with increasing progression (Astephen Wilson et al., 2017; Hubley-Kozey et al., 2009; Rutherford et al., 2011b); specifically, studies have also found that higher muscle activity are more pronounced in the lateral compared to the medial hamstrings (Astephen Wilson et al., 2017; Hubley-Kozey et al., 2009; Rutherford et al., 2011b).

Increases in overall amplitude and duration of activation can lead to increased co-contraction. Studies investigating the co-contraction of the major muscles surrounding the knee have found high degrees of agonist-antagonist coactivity around the knee joint for patients with more clinically severe OA (Hubley-Kozey et al., 2008, 2009), particularly on the lateral side; lateral hamstrings and vastus lateralis co-contraction was found to increase along with knee OA severity (Hubley-Kozey et al., 2009). This is consistent with attempts to selectively lessen medial compartment joint loading, as OA is a medial compartment-dominated disease (Hubley-Kozey et al., 2006). In contrast, a study on moderate severity medial compartment OA found no difference in vastus lateralis-lateral hamstrings co-contraction for those with OA compared to controls, using the same method of calculating co-contraction index; in fact, this study only found a difference in vastus medialis-medial gastrocnemius co-contraction (Lewek et al., 2004). This increase in vastus medialis-medial gastrocnemius co-contraction among those with moderate OA is generally thought to explain an attempt to reduce medial joint laxity across the joint (Lewek et al., 2004).

The findings from these cross-sectional studies give researchers more information about how the OA process affects muscle activity during walking. Overall, findings from gait studies show that people with OA tend to develop higher antagonistic muscle activity, resulting in more co-contraction. A certain amount of co-contraction is necessary to maintain dynamic joint stability during walking (Schipplein & Andriacchi, 1991), but patients with OA have higher amounts of co-contraction than asymptomatic patients. Since there were consistent findings between studies looking at clinical and structural severity alike, this could indicate that symptoms such as pain and instability could explain the increased co-activity with progression of OA, as people with more severe symptoms may feel the need to increase joint stiffness to prevent pain or giving way while walking (Astephen Wilson et al., 2017; Rutherford et al., 2013). These muscle activation changes can serve as a measure of functional ability throughout the disease process as they provide unique information that addresses both symptomatic and structural progression (Rutherford et al., 2011b).

2.5.2 Muscle Function in Predicting Progression of Knee OA

There are few longitudinal studies that have looked at whether muscle function features, including muscle strength and activity patterns during gait, can predict progression of knee OA severity. When comparing strength measures between groups that do and do not progress in OA severity, studies have found no difference in quadriceps or hamstrings strength at baseline between groups that progress structurally (Costello et al., 2020; Davis et al., 2019) or clinically (Costello et al., 2020; Hatfield et al., 2021a) by 3-8+ year follow-up.

Using structural progression outcomes, two studies examined medial compartment knee OA, and progression outcomes from radiographic (Davis et al., 2019) and MRI (Hodges et al., 2016) images, resulting in varying conclusions based on different methodological approaches. Hodges et al. (2016) defined medial and lateral muscle co-contraction based on a percent of the gait cycle that both medial or lateral (vasti and hamstrings) sites respectively were activated above a threshold activation. They found that higher medial co-contraction and lower lateral co-contraction was significantly associated with greater medial cartilage loss from MRI imaging, explaining 25% variance at one-year follow up. This study also found that a greater medial to lateral co-contraction ratio was positively associated with greater cartilage loss, explaining 19% variance in medial cartilage loss (Hodges et al., 2016). A study that examined co-contraction using activation amplitudes found higher overall and more prolonged lateral hamstring activity at baseline in moderate knee OA participants who had an increase in medial joint space narrowing at 3-year follow-up using radiographic imaging versus those that did not (Davis et al., 2019). In neither study were knee OA symptom progression considered, although Davis et al. provided baseline measures whereas Hodges et al. did not. It is not possible to compare between these two studies as the threshold for onset and offset of co-contraction duration was not clearly identified.

Using clinical criteria, prolonged mid-stance activity of all quadriceps and hamstrings muscles at baseline were greater in those with moderate medial compartment knee OA who progressed clinically to TKA (Costello et al., 2020; Hatfield et al., 2021a). Specifically, higher magnitude of hamstrings activity is associated with progression to TKA at varying long-term follow-up times, more notably in the lateral hamstrings (Costello et al., 2020; Hatfield et al., 2021a). To support the findings on increased lateral hamstring activity, greater lateral co-contraction at baseline has been found to be associated with progression to TKA (Hatfield et al., 2021a).

Separating those who progressed structurally with no clinical progression found no significant muscle activity differences at baseline between progression and non-progression groups using structural criteria (Costello et al., 2020). This result supports findings from cross sectional studies that found no relationship between radiographic severity and neuromuscular measures but a significant correlation with pain, suggesting that neuromuscular factors have a more significant relationship with pain and other factors not assessed by radiographic severity (Astephen Wilson et al., 2011). Given that the features predictive of progression were found to have more consistent ties to clinical progression than structural progression, they likely relate to symptomatic changes more strongly than to structural changes. This demonstrates the role of symptoms in the muscle activity changes that occur with OA progression.

Findings from longitudinal studies provide information about what muscle activation features during walking contribute to the progression of OA severity. Most studies found a relationship between prolonged muscle activation, characterized by increased mid-stance activity, and progression of OA. This connection likely exists as prolonged muscle activation results in sustained joint loading, which creates an unhealthy environment for cartilage synthesis (Andriacchi et al., 2004, 2009). Co-contraction, which is also found to be associated with increasing OA severity, can lead to more rapid muscle fatigue due to increased metabolic cost with increased muscle activity (Silder et al., 2012).

Overall, the findings among gait studies indicate that different treatment approaches may be needed to slow the rates of TKA compared with those designed to slow structural changes, such as those targeted to reduce KAM magnitude. Muscle activity research can allow for a better perspective of OA as a whole-joint condition, by giving more information about what occurs in the structures surrounding the joint. Muscle activity changes can be used to monitor how people change over time by serving as a biomarker for structural and/or clinical severity and can provide information for who is at risk for more rapid OA progression. In this way, muscle activity features can be looked at as risk factors that can serve as targets for treatments and can be used to help assess the effectiveness of treatments that aim to improve function or slow OA progression. Because passive tissue responds structural changes, such as joint space narrowing, this can lead to muscles compensating for symptoms such as looseness and instability (Rutherford et al., 2013). There is evidence that functional deficits due to OA can be addressed by targeting muscles (Fisher et al., 1997), thus, muscles serve as a modifiable target that can address other biomechanical changes associated with OA progression; if patients can adjust their muscular responses to these changes, it is possible that they can reduce the impact that OA has on the function of their joint.

2.6 Total Knee Arthroplasty and Muscle Function

Assessing muscle function before and after TKA has found differences in features of muscle function post-surgery that that could serve as targets for pre- or post-TKA rehabilitation protocols, features that can be used to track improvement after surgery, and pre-surgical features that can pose a risk for surgical outcomes.

Muscle strength increases are common following TKA; studies have found significant increases in KF (Hubley-Kozey et al., 2010) and KE (Hubley-Kozey et al., 2010; Mizner et al., 2005a, 2011; Yoshida et al., 2008) muscle strength for patients one year after receiving TKA, although they remain lower than asymptomatic strength levels

(Walsh et al., 1998). Initial KE strength decreases within the month following TKA are commonly found (Mizner et al., 2005a, 2011; Yoshida et al., 2008) and are primarily attributable to lack of voluntary muscle activation immediately following the surgery (Mizner et al., 2003, 2005c; Stevens et al., 2003). Consistent across the literature is evidence that increases in KE strength are correlated with improved function based on clinical tests and patient self-reports (Mizner et al., 2005a, 2011; Yoshida et al., 2008). Therefore, rehabilitation protocols aimed specifically toward furthering increases in KE strength can increase short and long-term functional recovery beyond what has been achieved by conventional rehabilitation programs (Petterson et al., 2009).

A narrative review summarizes that studies looking at muscle activity before and one-year after TKA have found general improvements in muscle activation levels and patterns of muscle activity during gait toward those more consistent with moderate OA and asymptomatic gait characteristics (Hubley-Kozey & Astephen Wilson, 2017). These improvements include a reduction in overall amplitude and reduced prolonged activity during mid-stance of all three quadriceps muscles and the lateral hamstrings (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2010), increased lateral and medial gastrocnemius amplitude in late stance, a shift of medial gastrocnemius activation to earlier in stance phase of gait, and improvements in coordination of muscle activation timing between medial and lateral gastrocnemius sites (Hubley-Kozey et al., 2010; Hubley-Kozey & Astephen Wilson, 2017). Increased gastrocnemius activation in late stance is indicative of more force generated before toe-off, which is consistent with faster walking speed (Hubley-Kozey et al., 2010). Amplitude decreases in quadriceps and hamstrings muscles during stance are partially due to a reduction in the need for active muscle stiffness during single leg stance, and a reduction in overall and mid-stance specific activity for lateral hamstrings leads to a more balanced activation between lateral and medial sites after surgery, which are likely made possible because of improvements in joint stability and alignment following surgery (Hubley-Kozey et al., 2010).

While there is evidence of improvement; residual alterations in muscle activity patterns during gait remain post-TKA, and TKA patients generally do not reach asymptomatic muscle activity patterns by 24 to 46+ month follow-up (Benedetti et al., 2003; S. Wilson et al., 1996). Studies have found prolonged activation of vastus lateralis, vastus medialis, and lateral hamstrings to remain after TKA (Benedetti et al., 2003; Hubley-Kozey & Astephen Wilson, 2017; Lundberg et al., 2016; S. Wilson et al., 1996). This prolonged activation is likely aimed at controlling load acceptance during single leg support of stance phase during walking and is residual from pre-surgical stiff-knee gait (Benedetti et al., 2003). Investigation comparing TKA patients to a control group found increased co-contraction times for vastus lateralis-lateral hamstring pairing during walking for TKA subjects compared to asymptomatic controls (Lundberg et al., 2016), which is consistent with pre-surgical co-contraction patterns. Research has found a negative relationship between quadriceps-hamstrings co-contraction at 3-months post-TKA and the KE strength of the operated limb 1-year post-TKA (Yoshida et al., 2013), meaning that patients who maintain co-contraction in the short-term are more likely to have deficits in KE strength in the long-term. This study further found a strong relationship between hamstring muscle recruitment and KE strength at both 3-month and 1-year post-TKA, showing that more hamstring engagement was associated with decreased KE strength (Yoshida et al., 2013). There are several possible explanations for the connection between these two findings, but this study makes it clear that muscles can provide important information for improving post-TKA rehabilitation by highlighting deficits in improvements among TKA recipients.

Research has begun to look at the relationship between preoperative muscular activation during gait and outcomes of TKA surgery and have found that there are preoperative muscle activity features that are associated with damaged implant integrity over time. Prolonged activation of gastrocnemius and vastus medialis muscles during stance, specifically, a combination of elevated gastrocnemius activity during early to mid-stance and prolonged activation of vastus medialis in mid to late stance during gait have been found to be significantly positively correlated with greater implant motion at two-year post -TKA follow-up, a predictor of implant migration over time (D. Wilson et al., 2012). Further, preoperative quadriceps strength can explain significant variance in performance-based functional assessments at one-year post TKA (Mizner et al., 2005b). These features serve as clear areas of focus for TKA rehabilitation moving forward as they have shown to have strong associations with negative surgical outcomes. These features have not been found to be related to patient-reported outcomes (Mizner et al., 2005b), meaning there is less information about how these features influence a patients' subjective experience following TKA.

Since these characteristics of joint moment and muscle activation patterns that are associated with progression in knee OA (Hatfield et al., 2015b, 2015a, 2021a) are altered following TKA (Astephen Wilson et al., 2015; Hatfield et al., 2011; Hubley-Kozey et al., 2010) and predictive of post-TKA implant migration (Astephen Wilson et al., 2010; Hilding et al., 1996; D. Wilson et al., 2012) and pain (Smith et al., 2004), they serve as important metrics to assess as potential targets for TKA rehabilitation. Further, given the relationship between specific muscle activation features and joint moment features (Hatfield 2021b), there are characteristics of muscle activation patterns during gait that can be used to target knee moment features that have been previously examined in studies assessing post-TKA outcomes, such as overall muscle activation amplitude and prolonged muscle activation (Astephen Wilson et al., 2017; Hatfield et al., 2021b, 2021a). Overall, previous research provides evidence that supports muscle function as a potential avenue for targeting the improvement of joint function features pre-post TKA, with the potential to improve overall outcomes of TKA surgery.

2.7 Sex Differences in Knee Osteoarthritis Gait and TKA Outcomes

Features that could serve as targets for intervention will vary between individuals, notably, between sexes. Differences between sexes have been found in the changes that occur in gait biomechanics and muscle activity with the progression of OA, and in changes following TKA. Studies looking at sex effects of OA-related gait feature changes have found that females with OA exhibit greater differences compared to asymptomatic than males do, which suggests that there are differences in how the disease affects each of the sexes (Astephen Wilson et al., 2015; Kaufman et al., 2001; McKean et al., 2007; Young-Shand et al., 2023).

Further, evidence has shown that TKA can elicit different results depending on sex of the patient. While there are general improvements in KFA range among patients post-surgery, women maintain less range of motion from late stance to mid-swing and more constant KFM and KRM during stance compared to men one-year after TKA, which are both characteristic of more severe OA gait patterns (Astephen Wilson et al., 2015). Both preoperatively and post-operatively, men maintain higher overall KAM compared to women, but both sexes see improvements in mid-stance unloading following TKA (Astephen Wilson et al., 2015). The above findings indicate that there is room for improvement in TKA protocol for individuals with severe knee OA to improve post-operative joint biomechanics, and that one possible method for addressing these deficits in improvement is to implement patient-specific rehabilitation.

Recent work has begun to identify sex differences in muscle strength and activity patterns across OA severity. Females typically have more severe gait patterns associated with OA than males, some of which can be explained by differences in muscle strength and muscle activation patterns between the sexes (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2022; Kaufman et al., 2001; McKean et al., 2007). In addition to having lower mass-normalized strength values for three lower leg muscle groups, knee extensors, knee flexors, and plantarflexors (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2022), females with OA have greater decreases in strength for knee extensors and plantar flexors across increasing severity levels and lower knee flexor strength for severe OA patients compared to both moderate OA and asymptomatic patients, whereas males have significantly lower strength in all three muscle groups for severe OA patients, and no decreases in strength across increasing severity for any muscle group (Hubley-Kozey et al., 2022). A recent study found that overall, there is a more generalized co-activation pattern during gait in females with severe OA, compared to males with more severe OA, who tend to have more specific muscle activity patterns (Hubley-Kozey et al., 2022). Further, sex-specific differences in changes in muscle activity have been found for patients post-TKA. In particular, women were found to retain more prolonged quadriceps and gastrocnemius activity throughout stance post-TKA compared to men (Astephen Wilson et al., 2015). These sex-specific findings emphasize the need for individualized OA interventions, as males and females experience different deficits through OA progression, and different changes following TKA.

In summary, OA is a common condition with increasing prevalence, and thus the demand for TKA is also increasing. Evidence has indicated that the development of more patient-specific rehabilitation programs has the potential to improve the success of TKA and therefore reduce the demand for secondary TKA, lessening the load on healthcare systems. Gait studies have shown significant relationships between gait features and measures of OA progression, including the influence of these features in post-TKA rehabilitation. However, there remains a gap in the current literature looking at the relationship between gait features and post-TKA outcomes, including functional outcomes. Self-selected walking speed provides an effective measurement of functional outcomes following TKA and can serve as an estimate of overall function, which in part, reflects the success of the procedure. Thus, changes in walking speed following TKA have been shown to provide important information about the overall success and implications of the procedure. Since gait features are strongly influenced by muscle function, there are important connections between muscle function and OA progression and TKA recovery. Muscle function, including muscle strength and muscle activity patterns during walking, have been shown to play important roles in TKA outcomes, but studies have not yet looked at the relationship and predictive value of these muscle function features in pre-post TKA changes in walking speed. Knowing more about this relationship can help identify targets for future interventions which can improve the success of TKA. Thus, the current study investigated this relationship using pre- and post-TKA data from patients with end-stage OA, including measures of muscle strength, muscle activity patterns during walking, and walking speed. In addition, this study conducted sex-specific analyses of these relationships, to better shed light on differences in outcomes between male and female patients and be able to provide more patient-specific rehabilitation targets.

Chapter 3: Methods

3.1 Participants

This study included a secondary analysis of data collected in the Dynamics of Human Motion (DOHM) Laboratory between 2003 and 2017 as part two research projects addressing common elements related to pre-post TKA gait features. The complete data set (CDS) of 150 participants with end-stage knee OA included participants who received primary TKA, had a Kellgren-Lawrence grade of at least 1, and were able to walk at least six meters without assistance. Any volunteers with uncontrolled cardiovascular conditions, rheumatoid arthritis, or any previous major lower extremity surgery were excluded. The proposed study sample included participants with radiographic evidence of tibiofemoral OA who had pre-TKA and post-TKA measures of the following data: EMG recordings of knee extensor (KE) and knee flexor (KF) activity during gait, scores on PROMs questionnaires, KE and KF strength measures, leg segment motion and ground reaction forces to calculate walking speed and foot contact timing to identify each gait cycle. The Study Sample (n=107) included all participants in the CDS who had available pre- and post-TKA walking speed and pre- and post-TKA KE and KF muscle activation and strength measures (Figure 4.1). For all surgeries, orthopaedic surgeons followed typical standard-of-care at the time of surgery, which included different implant types.

3.2 Data Collected

Within one-year prior to surgery, patients underwent x-ray imaging that was graded by one of two orthopedic surgeons that demonstrated high repeatability (Hatfield et al., 2015b; McKean et al., 2007), for knee OA severity using a standard Kellgren-

Lawrence global grading scale (Kellgren & Lawrence, 1957) and the Scott feature-based scoring system (Scott et al., 1993), to assess joint-space narrowing. Participants were tested in the DOHM laboratory within three-weeks prior to (pre-) and approximately one-year after (post-) TKA surgery, completing walking trials, muscle strength testing, and PROMs questionnaires at both time points. The study was approved by research ethics board CDHA-RA/2015-081. Upon arrival at the laboratory, participants signed an informed consent form and completed their PROMs questionnaires, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), used in this study (Angst et al., 2005; Bellamy et al., 1988; Collins et al., 2011; Impellizzeri et al., 2011; *WOMAC Osteoarthritis Index*, 2021). Sex and age in years were recorded for each participant. Then, height in centimeters and mass in kilograms were recorded using a stadiometer and balance scale respectively.

3.2.1 Outcome Variable- Self-Selected Walking Speed

Using standard methods found to have good to high day-to-day reliability for the knee OA patient population (Hubley-Kozey et al., 2013; Robbins et al., 2013), three-dimensional (3D) motion, 3D ground reaction forces, and EMG were collected simultaneously for the surgical limb during overground walking trials at self-selected walking speed. These methods have been described in the above studies, are described in detail below and are consistent with published guidelines (Hermens et al., 2000; Merletti, 1999; *SENIAM*, n.d.; Wu et al., 2002, 2005),

Calibration of the recording volume was performed to ensure all motion capture cameras were capturing the movement volume. Force plates were zeroed to make sure that without pressure, they read zero across all channels. The standard protocol included placing infrared light emitting diodes on anatomic joint landmarks, and rigid diode triads were placed on the sacrum, thigh, shank, and foot of the surgical limb, as illustrated in *Figure 3.1.* Participants were asked to stand in the middle of the recording volume to allow digitization of virtual points. Participants performed 5-10 practice trials along the collection walkway to warm up and to establish their self-selected walking speed. Practice trials allowed the researcher to ensure that at least one footfall per gait cycle would occur on a force plate. Following practice trials, participants completed 5-7 walking trials along a 6-meter-long walkway. Self-selected walking speed was monitored using infrared light timing gates, spaced 3.12 meters apart; and participants were required during the test trials to walk within 10% of their self-selected speed established in practice trials. *Figure 3.2* is an illustration of the walkway used for overground walk trials in the lab.

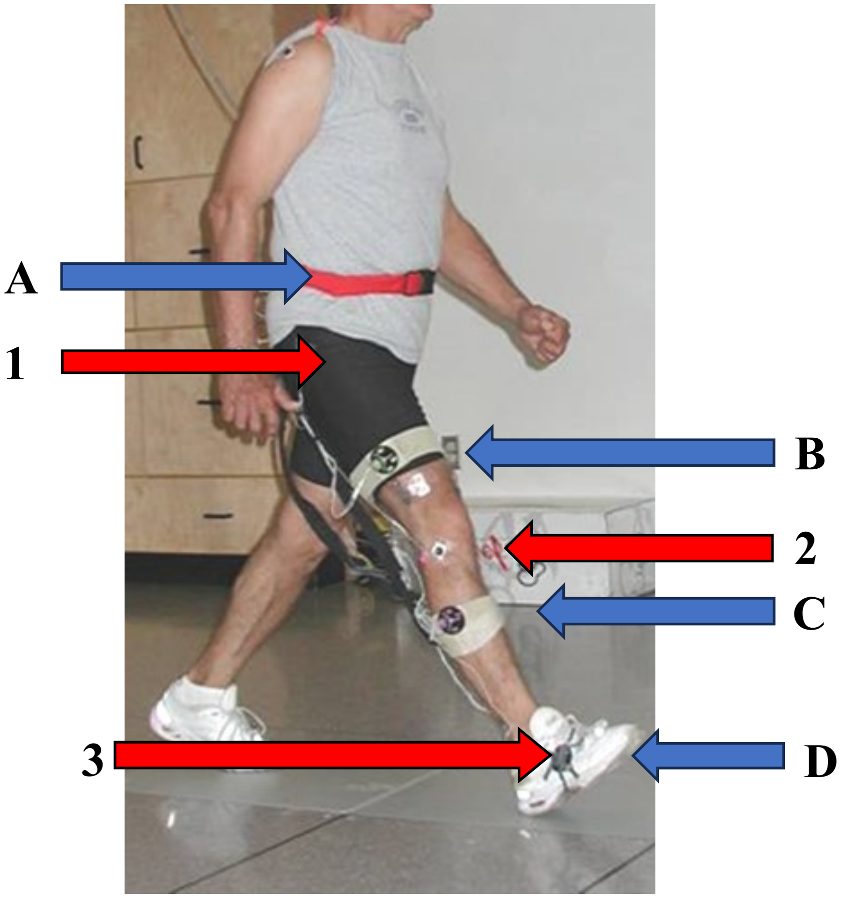

Figure 3. 1: Participant performing overground walk trial. Image shows participant instrumented with infrared diodes placed for motion-capture. Blue arrows point to rigid diode triads: A- Sacrum, B- Thigh, C- Shank, and D- Foot. Red arrows point to individual diodes on participant: 1- Greater Trochanter, 2- Lateral Epicondyle, 3- Lateral Malleolus.

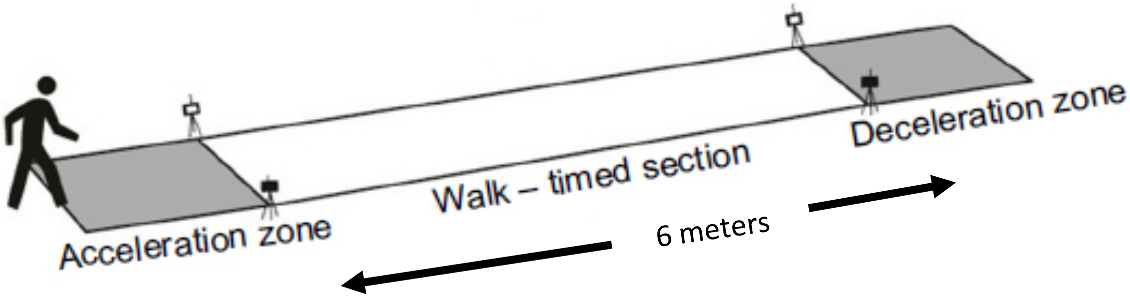

Figure 3. 2: Walkway for overground walk trials. The walkway includes a 6-meter-long collection walkway in between two sets of timing gates placed 3.12 meters wide. The collection walkway is within the capture volume of the motion-capture cameras. The walkway includes acceleration and deceleration zones on either side of the collection walkway to allow participants to walk at self-selected speed for the entirety of the recorded part of their walking trials. The force plates are embedded in the floor at approximately the mid-point between the two sets of timing gates.

3.2.2 Independent Variables

Muscle Activation

Silver/silver chloride surface EMG electrodes (0.79mm^2 contact area, Bortec Inc., Calgary, Alberta) were placed on the surgical limb in bipolar configuration at 7 different muscle sites on the surgical leg: vastus medialis (VM), vastus lateralis (VL), rectus femoris, medial and lateral hamstrings (MH, LH), and medial and lateral gastrocnemius. This study focused on knee flexors and extensors and included data from the vasti muscles (VL, VM) and the hamstrings muscles (LH, MH), to assess differences between medial and lateral compartments of knee flexor and extensor muscles. Placement of EMG electrodes followed the standard protocol (Hubley-Kozey et al., 2006, 2013) including skin preparation, electrode placement and validation. Skin preparation involved shaving and wiping the skin where the electrodes were applied with an alcohol/water solution to reduce skin impedance.

The standard electrode placements previously published (Hubley-Kozey et al., 2006; Rutherford et al., 2011a) are illustrated in Figure 3.3. For the two vasti (KE) muscles the anterior superior iliac spine (ASIS) was the proximal landmark for electrode placement, and placement was measured with the knee in 45-degree flexion. Electrodes for the VM were placed at 80% of the distance along the line from the ASIS to the medial joint line; VL electrodes were placed at 75% of the distance along the line from the ASIS to the lateral joint line. Electrode placement for hamstrings muscles used the ischial tuberosity as the proximal landmark for electrode placement, and placement was measured with the knee at 45-degree flexion. Electrodes for the MH and LH were placed at 50% of the distance along a line between the ischial tuberosity and the medial and lateral joint lines, respectively. Electrodes at each muscle site were spaced 20mm center-to-center, in line with the muscle fibres. A reference electrode was placed over the tibial shaft. Palpation of muscles and assessment of EMG recording quality during resisted movements were used to validate electrode placement. A second set of isolated movements was performed for the adjustment of gains to ensure the collection of a good quality signal and to assess crosstalk.

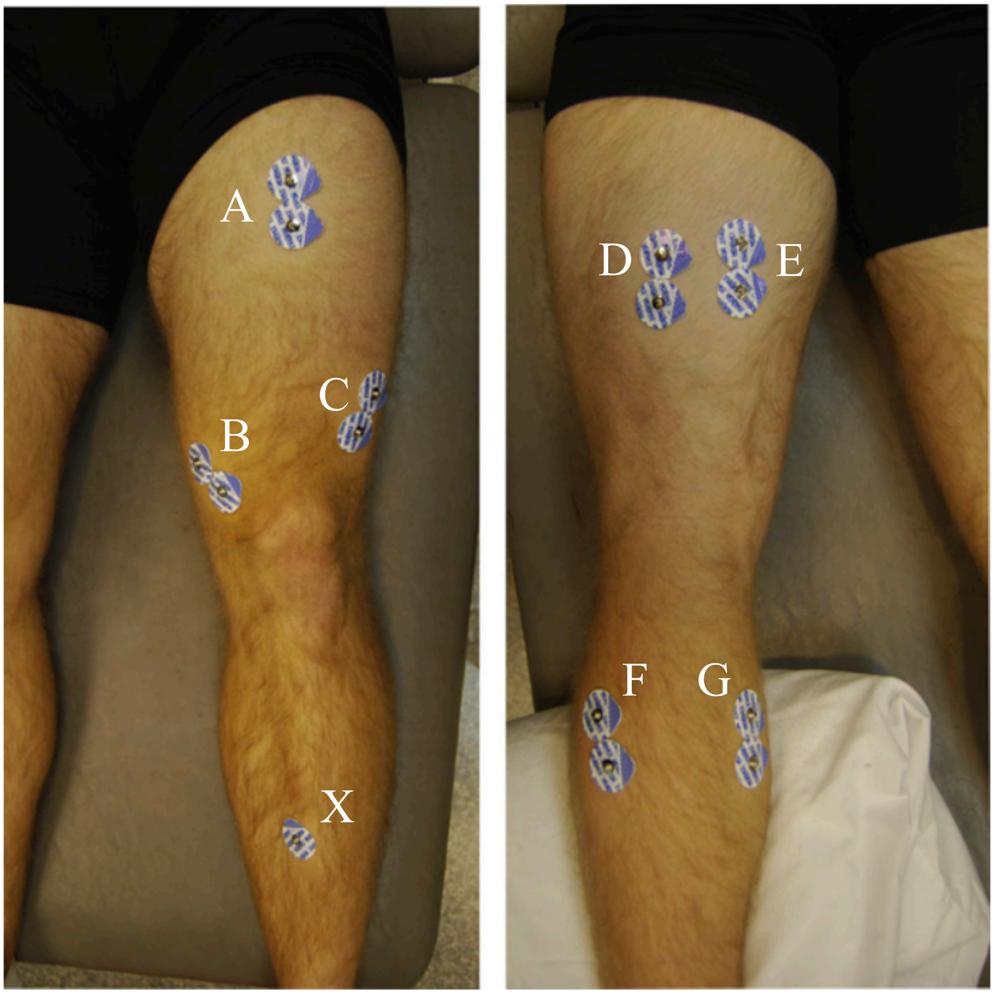

Figure 3. 3: EMG electrode placement. Image on the left shows an anterior view of the legs, with one reference electrode placed on the tibial shaft (X) and electrodes placed in bipolar configurations on the following muscles: A- Rectus Femoris, B- Vastus Medialis, C- Vastus Lateralis. Image on the right shows a posterior view of the legs, with electrodes placed in a bipolar configuration on the following muscles: D- Lateral Hamstrings, E- Medial Hamstrings, F- Lateral Gastrocnemius, G- Medial Gastrocnemius.

Muscle activity was pre-amplified 500x, then further amplified (bandpass filtered at 10-1000 Hz, common-mode rejection ratio 115 dB at 60 Hz, input impedance ~ 10 Gohm) using two eight-channel surface EMG systems (AMT-8 EMG, Bortec Inc., Calgary, Alberta, Canada). Three-dimensional infrared motion sensors were sampled at

100Hz using an optoelectric motion capture system with two Optotrak cameras (Optotrak 3020, Northern Digital Inc., Waterloo, Ontario, Canada). Three-dimensional ground reaction forces were recorded from one force platform (Advanced Medical Technology Inc., Watertown, Massachusetts, USA) embedded in the walkway. EMG and force plate signals were both analog to digitally converted at 1000 or 2000Hz using the analogue data capture feature of the Optotrak System (16 bit +/- 2V) (Northern Digital Inc., Waterloo, Ontario, Canada) to be synchronized together and stored for later processing.

Muscle Strength and EMG Normalization

Following overground walking trials, the muscle activity for each participant was recorded while the participant lay relaxed in a supine position to collect participant bias, which provides the baseline resting muscle activity that each participant has while muscles relaxed. Participants then performed seven maximal effort isometric contraction exercises aimed to elicit maximal activation from each muscle for amplitude normalization, and to provide a measure of muscle strength for the knee flexor and knee extensor muscle groups, using methods shown to have between-day reliability in knee OA participants (Hubley-Kozey et al., 2006, 2013). Isometric contractions were performed against an isokinetic dynamometer (Cybex^{TM}, Lumex, New York, USA; ©Biodex, Shirley, New York, USA). Dynamometer arm lengths were adjusted for each participant at each exercise position to ensure the axis of rotation of the dynamometer was matching the axis of rotation of their knee. When securing participants into the dynamometer, researchers ensured straps were not placed directly on top of EMG electrodes, to prevent production of additional noise.

Strength testing exercises (Hubley-Kozey et al., 2006, 2010; Rutherford et al., 2011a) performed against the dynamometer using a standard procedure included: *i)* knee extension sitting in supine with knee at 45° of flexion, *ii)* knee flexion lying in supine with knee at 15° of flexion, *iii)* knee extension lying in supine with knee at 15° of flexion, *iv)* knee flexion sitting in supine with knee at 55° of flexion, *v)* knee flexion in prone position with knee at 55° of flexion, vi) plantar flexion in supine with knee close to full extension, and vii) single leg heel rise against resistance. Exercises i and ii, knee extension at 45° flexion and knee flexion at 15° flexion, were selected as the strength tests as they were collected for the greatest number of participants Study Sample participants. *Exercise i* was chosen since knee extension at 45° elicited the greatest moment of force from KE muscles (Hubley-Kozey et al., 2006), had the highest muscle activation of both the VL and VM (Rutherford et al., 2011a) and has been reported for participants across OA severity and pre-post TKA (Hubley-Kozey et al., 2009, 2010; McKean et al., 2007; Rutherford et al., 2013), providing a body of literature for comparison of results from the present study. *Exercise ii* was selected as most participants in in the Study Sample had data for knee flexion at 15° flexion, 15° flexion is the strength test within the most functional range that is transferrable to walking and it elicited higher activation for both hamstring muscles compared to knee flexion at 55° in supine (Rutherford et al., 2011a).

Torque and EMG data were collected simultaneously during each exercise effort. Each exercise was performed twice, with at least 60 seconds of rest in between each effort. Participants received standardized verbal encouragement during each exercise to elicit maximal effort. Participants were given a practice trial and were given feedback on their performance for torque production. Between practice trials and recorded trials, a gravity correction trial was completed to measure the moment due to gravity of the lower leg and foot leg at rest in the position for each of the exercises. Gravity correction allows for an accurate representation of force produced by the leg muscles. For knee extension trials in supine, the gravity correction was added to the measured torque. For knee flexion trials in supine, the gravity correction was subtracted from the measured torque. All exercise trials were held for three seconds; exercises were repeated a maximum of one extra time in addition to the two trials collected if the maximum torque values differed by more than 10%.

3.3 Data Processing

EMG data was processed and time-normalized to the gait cycle and amplitude-normalized to the MVIC for each muscle (Hubley-Kozey et al., 2006, 2013) using custom programs written in MATLAB version 7.4 (Mathworks, Natick, Massachusetts, USA). To identify gait cycles and allow for the synchronization of EMG to the appropriate window of data, heel strike and toe-off timing were extracted from force plate and motion data (Hubley-Kozey et al., 2006; Landry et al., 2007). The human gait cycle is divided into two main components: the stance phase and the swing phase, referring to what the tested leg is doing at that point in the cycle; the human gait cycle is illustrated in *Figure 3.4.* The stance phase incorporates approximately the first 60% of the gait cycle, from heel strike terminating in toe-off of the tested leg. Toe-off is followed by the swing phase, which is approximately 40% of the gait cycle, terminating in heel strike of the tested leg, which is also the marker of a new gait cycle and the start of the next stance phase. Separating these two phases and identifying gait cycles was key in this study, as the muscle activation features used in the analysis of this work were calculated using percentages of the gait cycle to determine discrete values. First heel contact and toe-off for each trial were defined using force plate data. First heel strike was determined as the first frame of data in which the vertical signal exceeded a 5 Newton threshold; this was verified using optical data. Toe-off was determined from the force plate data as the first frame in which the vertical signal falls below the 5 Newton threshold. Second heel contact was determined from motion data only and was assigned to the frame with the first negative acceleration peak in ankle marker displacement after linear interpolation of the data.

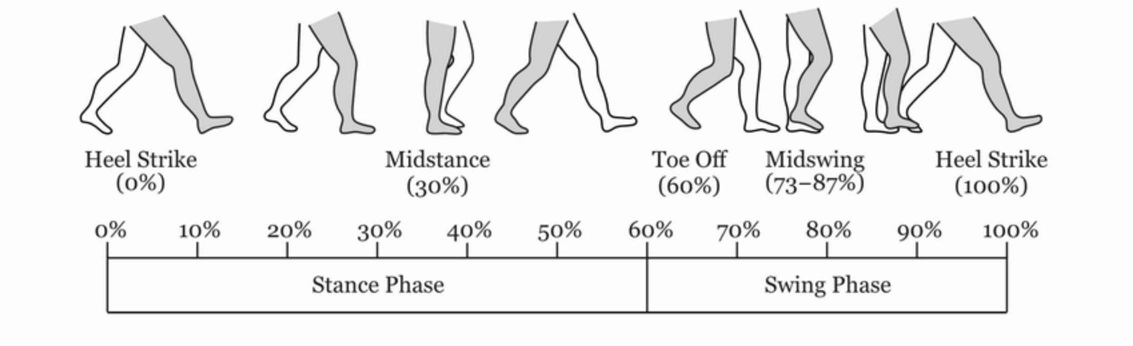

Figure 3. 4: Phases of the human gait cycle. Percentages represent average amount of time spent in that phase. Figure from Sherratt et al., 2021.

Walking speed for each gait trial was calculated by dividing stride length by stride time and represented in meters per second (m/s). Self-selected walking speed- the key outcome was calculated as the average speed for all test trials for each participant (Landry et al., 2007). WS_CHANGE SCORE was calculated using *Equation 1* and self-selected walking speed pre- and post- TKA as input values. Descriptions of interpretation for walking speed data are included in Table 3.1.

Equation 1: CHANGE SCORE = Post-TKA score – Pre-TKA score, where *scores* included Self-Selected Walking Speed, discrete EMG features, and absolute and mass-normalized KF and KE muscle strength.

Table 3. 1: Interpretation of pre-TKA scores and pre-post TKA improvements in outcome variable of self-selected walking speed.

Outcome Variable	High Pre-TKA Value Interpretation	Change Score for Improvement	Improvement Change Score Interpretation	Improvement Change Score Implication
Self-Selected Walking Speed (m/s)	Faster walking speed, better overall function	Positive	Increase in walking speed	Improved overall function post TKA

Raw EMG signals for MVIC and gait trials were assessed for quality using data plots that were inspected to ensure there were periods when EMG was active and inactive and to identify noise in the EMG data. Fast Fourier analyses were performed where necessary and noise spikes were removed using an inverse Fast Fourier Transform filter. Raw EMG signals were band pass filtered (20-500Hz), corrected for participant bias, full wave rectified, and low pass filtered using a 4th order Butterworth filter at 6Hz. The maximal activation during a 100ms moving average window for each muscle during any exercise was taken as the maximal voluntary isometric contraction (MVIC) values for those muscles (Astephen Wilson et al., 2017; Hubley-Kozey et al., 2010; Rutherford et al., 2011a). Spline interpolation was used to time normalize each walking trial waveform to 100% of the gait cycle, with 101 data points. Each waveform was then amplitude normalized to percent of MVIC using the amplitude determined from MVIC exercises. This is done by dividing activation amplitude values by the MVIC amplitude value and then multiplying by 100. Waveforms for all successful trials (~5-7) were then added together for each muscle to create an ensemble average muscle activation curve over one cycle for each muscle for each participant.

The first set of independent variables included discrete muscle activation amplitude and prolonged activity features for KE and KF during gait. The discrete metrics used as independent variables in this study are consistent with overall amplitude and prolonged activation features previously examined (Astephen Wilson et al., 2017; Hatfield et al., 2021b, 2021a), and are linked to key joint moment features that are predictive of OA progression and TKA outcomes (Hatfield et al., 2021b). The independent variable that was used for analysis to represent prolonged activity was the early stance peak to mid-stance mean difference (ES-MSD). The independent variable representing overall amplitude was the stance phase root mean square (RMS Stance) amplitude. *Figure 3.5* illustrates how these features can be interpreted in an EMG waveform.

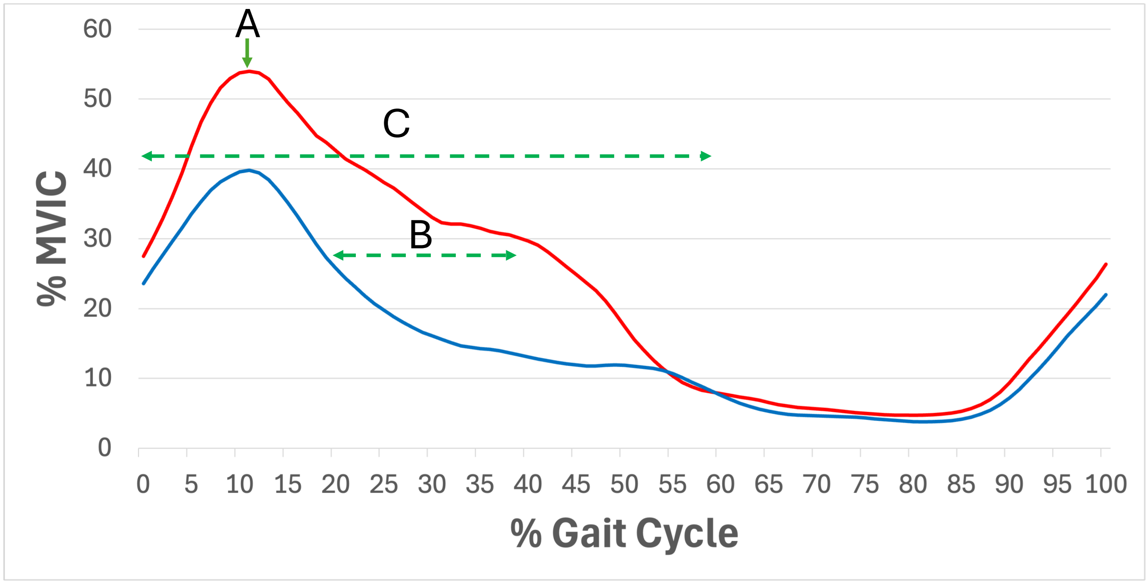

Figure 3. 5: VL EMG waveforms demonstrating where discrete metrics were extracted from; A- early stance peak (0-25%), B-mid-stance average (21-40%), and RMS Stance (0-60%) amplitudes are taken from. Waveform in red has higher overall activation, represented by a larger RMS stance, and more prolonged activation, represented by a smaller ES-MSD.

All discrete EMG measures were reported as a %MVIC. ES-MSD was calculated by identifying the maximum amplitude in the first 25% of the gait cycle and subtracting the average amplitude from 21 to 40% of the gait, to provide a difference measure for each muscle. RMS Stance was determined by calculating the root mean square amplitude over the stance phase of the gait cycle. The pre-TKA and the post-TKA values for each EMG discrete metric for all four muscles were used to calculate the pre-post TKA EMG Change Scores using *Equation 1.* Table 3.2 describes the interpretation of both pre-TKA and EMG Change Score values for RMS Stance and ES-MSD independent variables.

Table 3. 2: Interpretation of pre-TKA scores and pre-post TKA improvements in independent variables

Independent Variable	**High Pre-TKA Value Interpretation**	**Change Score for Improvement**	**Improvement Change Score Interpretation**
RMS Stance (%MVIC)	More overall muscle activity during stance	Negative	Reduction in overall magnitude muscle activation during stance
ES-MSD (%MVIC)	Less prolonged muscle activity during stance	Positive	Increase in difference between early stance peak and mid-stance mean muscle activation
KE and KF Strength (Nm or Nm/kg)	Greater muscle strength	Positive	Increase in torque produced against dynamometer

Muscle strength was the second set of independent variables. Custom MATLAB programs were used to calculate the maximum torque, in Nm, over a one-second steady state window from the two recorded trials. The maximum torque was determined from exercises *i* and *ii*, as the measure of strength for KE and KF respectively. These values were normalized to the body mass of the participant and are represented in units of Nm/Kg. Mass- normalized KE strength at 45° flexion and KF strength at 15° flexion were the primary strength variables analyzed in this study, with absolute strength analyzed as a secondary variable. Pre- and post- TKA strength was recorded, and KE STRENGTH_CHANGE SCORES and KF STRENGTH_CHANGE SCORES were calculated using *Equation 1.* Descriptions of interpretation for pre-TKA and change score values of strength measures as independent variables are included in Table 3.2.

3.4 Data Analysis

Statistical analyses were competed using SPSS Statistics software (IBM, Chicago, Illinois, USA). Descriptive statistics for the Study Sample included means and standard deviation calculated for age, height, mass and BMI, and percentages of sexes and KL grades as well as median KL grade. Mean and standard deviation were calculated for pre-TKA and the post-TKA measures for walking speed, KE and KF strength, and discrete EMG metrics; the ES-MSD and RMS Stance values.

For Objective 1, linear regression models were created to determine whether pre-TKA and pre-post TKA CHANGE SCOREs for KE and KF muscle function features were associated with and explain significant variance in pre-post TKA changes in walking speed. Normality checks were run on each of the predictor and outcome variables, using histograms and normal Q-Q plots to check normality graphically, and Shapiro-Wilks tests to assess the statistical normality, before inputting each variable into a model. Assumptions of linearity and homoscedasticity were assessed for each variable using residuals plots. Pearson product correlations were used to assess the direction of the relationship between predictor and outcome variables and to determine significant correlations. For each model, R squared values were calculated to determine how much variance the predictor variable was explaining in the outcome variable. The condition of independence was satisfied as each data point included in the model was from a different participant. Pre-TKA and pre-post TKA CHANGE SCORES for KF and KE muscle activation discrete metrics: RMS Stance and ES-MSD, and absolute and mass-normalized KF and KE strength were included as independent variables in linear regression models for the outcome variable WS CHANGE SCORE.

Objective 2 aimed to determine whether a combination of muscle function features better predicted the pre-post TKA outcomes than the univariate models. To address Objective 2, stepwise multiple regression models were created for the outcome variable to determine whether there was a combination of muscle function features from Objective 1 that best predicted WS CHANGE SCORE. Normality checks were run on each variable included in the models. In order to have a sufficient sample size, the model followed the rule of thumb of $N > 50 + 8p$, stating that for regression models, a sample size (N) of at least 50 is required for one independent variable, and that for every additional independent variable (p), at least 8 more observations are required for a sufficient sample size (Wilson Van Voorhis & Morgan, 2007).

For all multiple regression models, the independent variables used in the model were selected based on which combinations created models that explained the most variance in each outcome variable. Variables were added to the models if the significance value of the F-statistic of the model would be equal to or less than 0.05 with the addition of the variable; the predictor variable that would result in the smallest significance value was the variable chosen to be added at each step in the model. Variables were removed if the significance value of the F-statistic would be equal to or greater than 0.10 with the addition of the variable and models stopped adding variables when the addition of all variables would result in an F-statistic significance value equal or greater than 0.10. Multiple regression models were created in stages. The multiple regression model was first created with the entry of strength and EMG variables into stepwise selection for their own separate models; models were then created with the entry of both strength and EMG variables into the stepwise selection for the same model; finally, models were created with the entry of all strength and EMG variables, as well as anthropometric data, into stepwise selection. Anthropometric data added as independent variable options for stepwise selection included age, mass, height, body mass index, pre-post TKA change in mass, and pre-post TKA change in body mass index. Creation of the multiple regression models additionally examined whether these anthropometric features had significant influence on variance explained by the models, as these features have previously been shown to influence patient-reported outcomes following TKA and could provide information that can improve the models created in this study (Pronk et al., 2021; Van Onsem et al., 2016; Vissers et al., 2020).

Multicollinearity was avoided by using stepwise selection of the models, and tolerance and Variance Inflation Factors were checked to ensure multicollinearity was not present between the variables selected for the model. Before the creation of multiple regression models, outliers were assessed for both sample subgroups using boxplots for each predictor variable. Any values more than one and a half times the interquartile range outside of the first and third quartiles were identified and tracked in a table. Consistent outliers were flagged and trends in outliers for each variable were assessed. After the creation of each model, checks were run using Cook’s Distance and leverage plots to ensure the models were not skewed by outliers. Further, residuals were checked for normality, linearity, and homoscedasticity using residuals plots to ensure the models met these assumptions.

To address Objective 3, the above procedures for creating and assessing the univariate and multivariate models were conducted on the male and female participants from the Study Sample separately. The goal was to explore whether there were differences between sexes that would provide evidence that sex specific models should be created or that sex should be included in models.

Chapter 4: Results- Objectives 1 & 2

4.1. Participants and Available Data

The results for *Objectives 1 and 2* related to muscle function and post-TKA walking speed outcomes are reported in this chapter, including the univariate (Objective 1) and multivariate (Objective 2) analyses. Figure 4.1 illustrates the selection of participant data into this sample, including the reason for exclusion from the sample, herein referred to as the Study Sample. Of 150 participants who met the study criteria, data from 107 participants were included in this study, given they had pre- and post-TKA walking speed and pre- and post-TKA muscle strength and/or muscle activity data. The Study Sample includes 46 male and 61 female participants. Average time from pre-TKA to post-TKA data collection for the Study Sample was 435 ± 131 days (1.2 ± 0.36 years). Pre-TKA Kellgren-Lawrence grades ranged from 1-4, with a median grade of 3. Surgeons followed typical standard-of-care at the time of surgery, which included different implant types, but differences associated with implant type were assumed to be small on the key outcomes in the current study. From the surgical data, 80% of participant data included the name of the surgeon; 56% of these surgeries were performed by two surgeons, and the rest were done by five others. Of the 63% of participants with available implant manufacturer data, 45% received Stryker implants, and 40% received Zimmer implants; the remaining 15% used implants from Smith & Nephew or Wright Medical.

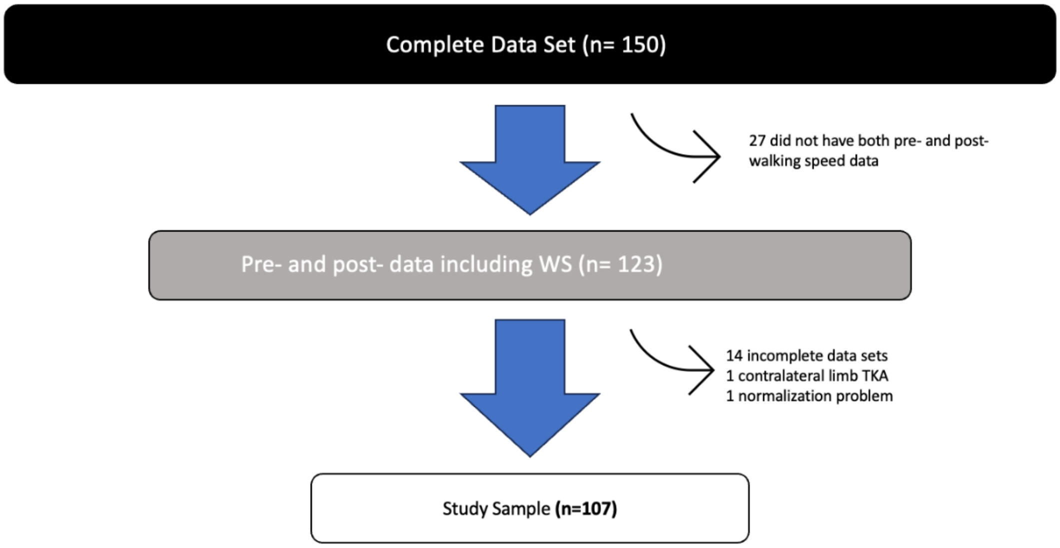

Figure 4. 1: Schematic illustrating the selection of data into the Study Sample. The number of excluded participants and reasons for exclusion are provided.

The pre- and post-TKA mean and standard deviation for all predictor variables, key anthropometric measures, and walking speed for the total Study Sample and for the male and female participants from the Study Sample separately are presented in *Table 4.1*. The pre- and post-TKA EMG ensemble average waveforms over the gait cycle for the Study Sample for VL, VM, LH and MH are displayed in *Figure 4.2*.

Table 4. 1: Pre-TKA and post-TKA descriptive statistics for demographics, outcomes, and muscle function predictor variables, mean ± SD for Study Sample (n=107) and for males (n= 46) and females (n= 61) separately.

	Pre-TKA	**Post-TKA**	**Pre-TKA Males**	**Post-TKA Males**	**Pre-TKA Females**	**Post-TKA Females**
Age (years)	63.8 ± 7.6	65.0 ± 7.5	64.7 ± 8.35	65.9 ± 8.2	63.1 ± 6.9	64.3 ± 7.0
Mass (kg)	93.1 ± 18.1	94.0 ± 20.0	98.2 ± 16.4	100.6 ± 19.0	89.3 ± 18.4	89.1 ± 19.4
Height (m)	1.68 ± 0.10	1.68 ± 0.10	1.76 ± 0.08	1.76 ± 0.08	1.61 ± 0.07	1.61 ± 0.07
BMI (kg/m^2)	33.2 ± 5.9	33.4 ± 6.2	31.8 ± 4.9	32.4 ± 5.3	34.2 ± 6.4	34.1 ± 6.8
WOMAC Total Score	47.9 ± 14.7	15.2 ± 12.6	45.8 ± 13.5	16.3 ± 12.9	49.2 ± 15.2	14.6 ± 12.6
Walking Speed (m/s)	0.91 ± 0.21	1.08 ± 0.18	0.92 ± 0.21	1.09 ± 0.20	0.90 ± 0.22	1.07 ± 0.17
VL RMS	36.6 ± 22.0	23.9 ± 12.0	27.9 ± 12.0	22.4 ± 12.2	43.1 ± 25.3	25.1 ± 11.9
VL ES-MSD	26.5 ± 22.7	26.6 ± 16.2	17.3 ± 12.5	25.6 ± 17.8	33.4 ± 26.0	27.4 ± 15.0
VM RMS	39.3 ± 25.3	26.0 ± 15.2	29.5 ± 15.8	22.2 ± 14.9	47.2 ± 28.7	29.1 ± 14.8
VM ES-MSD	26.5 ± 18.4	29.5 ± 18.1	17.8 ± 13.4	26.2 ± 17.6	33.5 ± 18.9	31.1 ± 18.4
LH RMS	35.6 ± 20.7	24.8 ± 18.5	36.1 ± 20.4	25.0 ± 14.5	35.3 ± 21.0	24.7 ± 21.4
LH ES-MSD	27.8 ± 20.5	28.3 ± 23.3	26.8 ± 20.0	29.1 ± 19.8	28.5 ± 21.0	27.7 ± 25.9
MH RMS	19.0 ± 14.2	18.0 ± 11.8	16.4 ± 11.3	15.2 ± 7.9	21.0 ± 15.8	20.2 ± 13.7
MH ES-MSD	24.1 ± 19.9	29.4 ± 23.8	19.5 ± 13.9	26.8 ± 18.5	27.6 ± 23.0	31.3 ± 27.0
KF15-Abs.	33.5 ± 28.4	40.3 ± 27.2	50.9 ± 34.9	57.2 ± 32.7	20.3 ± 10.1	27.4 ± 10.4
KF15-Norm.	0.35 ± 0.25	0.42 ± 0.23	0.51 ± 0.30	0.56 ± 0.27	0.23 ± 0.12	0.31 ± 0.12
KE45-Abs.	78.0 ± 35.8	96.1 ± 38.7	105.2 ± 33.7	121.5 ± 40.9	57.3 ± 20.2	76.8 ± 22.7
KE45-Norm.	0.84 ± 0.33	1.03 ± 0.32	1.06 ± 0.28	1.20 ± 0.30	0.67 ± 0.25	0.90 ± 0.28

Note. RMS and ES-MSD are recorded in % MVIC. Absolute (Abs.) and mass-normalized (Norm.) strength values are recorded in Nm and Nm/kg, respectively. Missing participant data numbers from the Study Sample are as follows: VL- 4, VM- 8, LH- 1, MH- 4, KE45 strength- 5, KF15 strength- 10, WOMAC Total Score- 45.

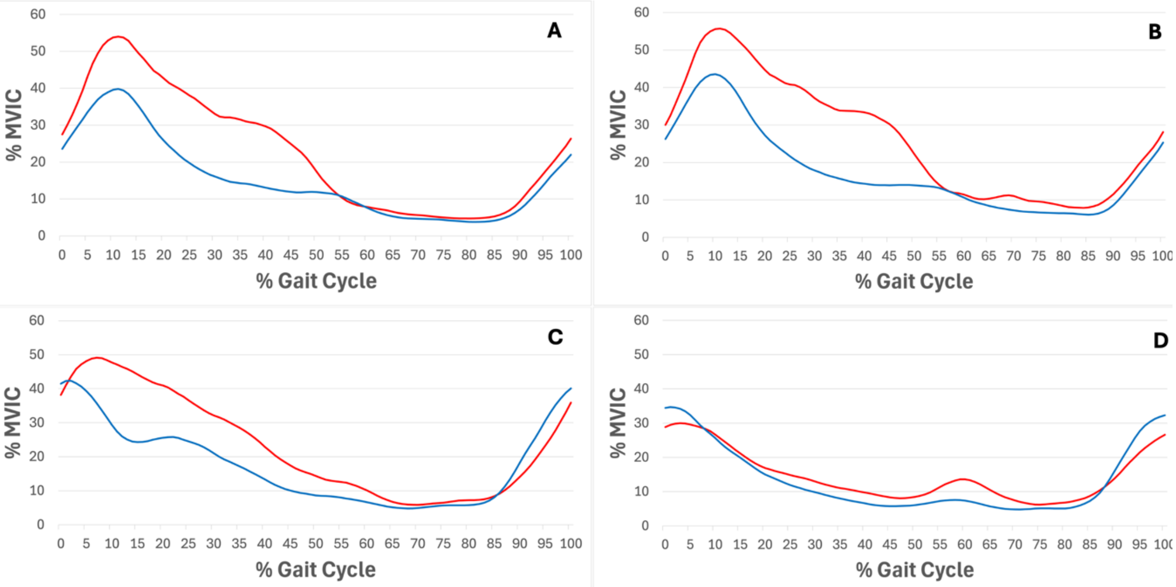

Figure 4. 2: Pre- (red) and post- (blue) TKA ensemble average EMG waveforms for Study Sample (n= 107) for VL (A), VM (B), LH (C), and MH (D) muscles. X axis is percent of the total gait cycle and Y axis is percent of maximal voluntary isometric contraction.

4.2. Univariate Analysis (Objective 1)

Assumptions related to linear regression were checked before running the analysis. The outcome variable WS CHANGE SCORE satisfied all assumptions for linear regression. None of the EMG activity predictor variables were normally distributed, but all met the assumptions of linearity and homoscedasticity when assessed using residuals plots. There were seven EMG activity variables that had significant ($p<0.05$) correlations with WS CHANGE SCORE. *Table 4.2* displays the correlation coefficients and variance explained for the EMG activity variables that had significant correlations ($p<0.05$) with WS CHANGE SCORES, along with the interpretations based on direction of the correlations. For both VL and VM, pre-TKA ES-MSD and ES-MSD CHANGE SCORE had significant negative and positive correlations respectively with WS CHANGE SCORE, R^2 ranging from four to eight percent. Pre-TKA ES-MSD for LH and MH, and LH RMS CHANGE SCORE had significant negative correlations with WS

CHANGE SCORE, R^2 ranging from five to six percent. See *Appendix A- Table 1* for correlation coefficient, variance explained, and p values for all EMG activity predictor variables.

Table 4. 2: Pearson product moment correlations (r) and variance explained (R2), and interpretation of correlations for lateral and medial vasti (VL, VM) and hamstring (LH, MH) EMG activity variables (% MVIC) that have significant ($p<0.05$) correlation with pre-post TKA change in walking speed (m/s).

Variable	***r***	***R^2***	***Interpretation***
Pre-TKA VL ES-MSD	-0.19	0.04	Smaller ES-MSD pre-TKA: more pre-TKA prolonged VL activity associated with larger increase in walking speed post-TKA
Δ VL ES-MSD	0.25	0.06	Increase in ES-MSD post-TKA: reduction in prolonged VL activity associated with larger increase in walking speed post-TKA
Pre-TKA VM ES-MSD	-0.22	0.05	Smaller ES-MSD pre-TKA: more pre-TKA prolonged VM activity associated with larger increases in walking speed post-TKA
ΔVM ES-MSD	0.28	0.08	Increase in ES-MSD post-TKA: reduction in prolonged VM activity associated with increase in walking speed
Δ LH RMS Stance	-0.23	0.05	Decrease in RMS Stance post-TKA: reduction in overall LH activity associated with increase in walking speed post TKA
Pre-TKA LH ES-MSD	-0.21	0.05	Smaller ES-MSD pre-TKA: more pre-TKA prolonged LH activity associated with larger increases in walking speed post-TKA
Pre-TKA MH ES-MSD	-0.25	0.06	Smaller ES-MSD pre-TKA: more pre-TKA prolonged MH activity associated with larger increases in walking speed post-TKA

Note. Interpretation based on the direction of the correlation. ***Δ*** represents all CHANGE SCORE variables. RMS= root mean squared amplitude, ES-MSD = early stance peak to mid stance amplitude difference.

Example waveforms and scatter plots for three significant correlations are found in Figures 4.3 to 4.5. *Figure 4.3* illustrates high and low pre-TKA VM ES-MSD waveforms (A), and the scatterplot for the association with WS CHANGE SCORE (B). This figure shows a trend toward more pre-TKA prolonged VM activity (blue dashed waveform) being associated with greater increase in walking speed pre-post TKA. VM ES-MSD CHANGE SCORE had the largest Pearson product moment correlation coefficient and the most variance explained among the EMG activity variables for the outcome of WS CHANGE SCORE (*Table 4.2)*. *Figure 4.4* illustrates the pre- and post-TKA waveforms for the VM ES-MSD CHANGE SCORE with the largest positive and largest negative values (A), and the positive association between VM ES-MSD CHANGE SCORE and WS CHANGE SCORE (B). This figure shows that an increase in the difference measure, representing a change from more prolonged activity pre-TKA (red dashed line) to less prolonged activity post-TKA (blue dashed line), was associated with a trend toward an increase in speed. The only RMS Stance variable that had a significant ($p<0.05$) correlation with WS CHANGE SCORE was the LH RMS CHANGE SCORE.

Figure 4.5 illustrates the pre- and post- TKA waveforms for the LH RMS CHANGE SCORE with the largest positive and largest negative values (A), and negative association between LH RMS CHANGE SCORE and WS CHANGE SCORE (B). The large decrease in the pre- (red) versus post- (blue) dotted waveforms shows the greater reduction in overall amplitude, and the trend toward an improvement in walking speed.

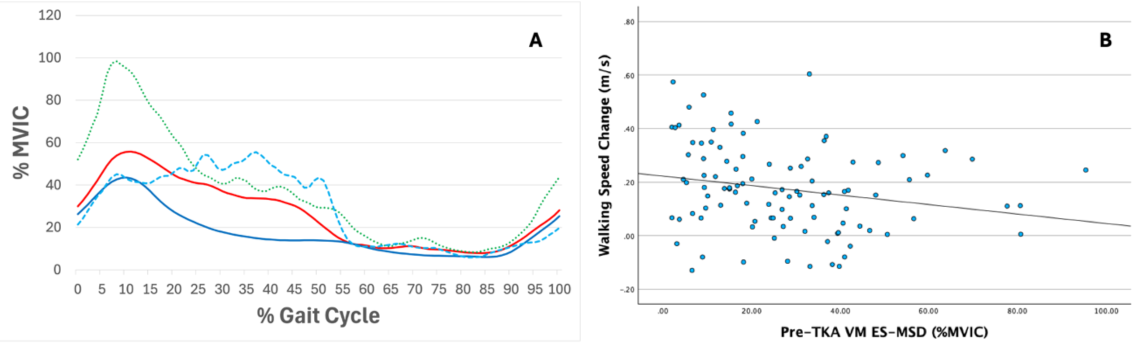

Figure 4. 3: (A) Pre- (red) and post- (blue) TKA ensemble average VM waveforms for Study Sample (n= 107) and pre-TKA ensemble average VM waveforms for the five participants with the largest (dotted green) and five participants with the smallest (dashed light blue) pre-TKA ES-MSD values from the Study Sample. (B) Scatterplot with trendline illustrating the association between pre-TKA VM ES-MSD and WS CHANGE SCORE.

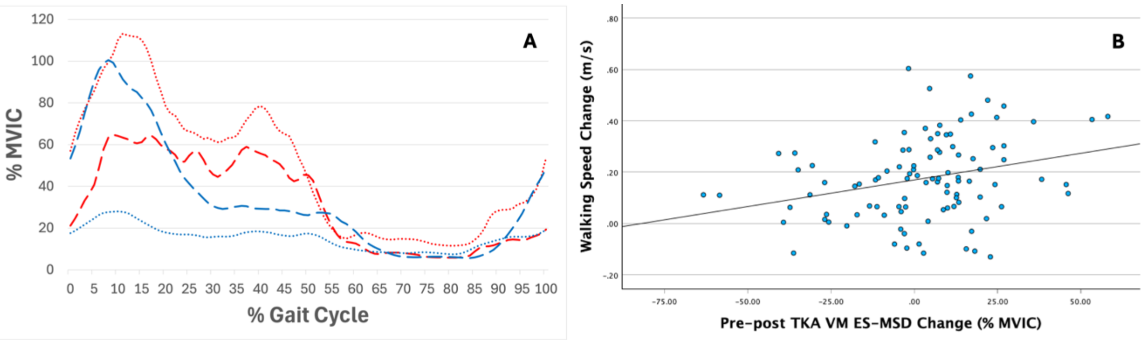

Figure 4. 4: (A) Pre- (red) and post- (blue) TKA ensemble average VM waveforms for the five participants with the largest negative (dotted line) and five participants with the largest positive (dashed line) ES-MSD CHANGE SCORE from the Study Sample. (B) Scatterplot with trendline illustrating the association VM ES-MSD CHANGE SCORE and WS CHANGE SCORE.

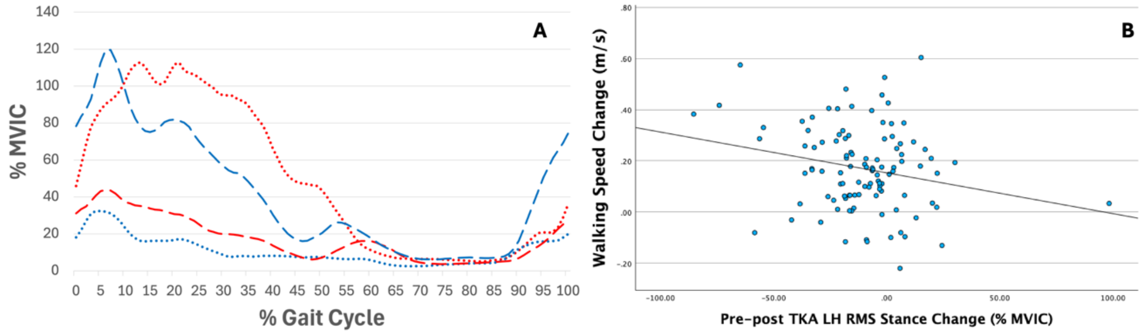

Figure 4. 5: (A) Pre- (red) and post- (blue) TKA ensemble average LH waveforms for the five participants with the largest negative (dotted line) and five participants with the largest positive (dashed line) LH RMS Stance CHANGE SCORE from the Study Sample. (B) Scatterplot with trendline illustrating the association between LH RMS Stance CHANGE SCORE and WS CHANGE SCORE.

KE45-Abs. CHANGE SCORE, KE45-Norm. CHANGE SCORE, and KF15-Norm. CHANGE scores were normally distributed. All strength predictor variables met the assumptions of linearity and homoscedasticity when assessed using residuals plots. There were 91 outliers from 1652 EMG activity data points, approximately 6% of the total sample (*see Appendix B- Table 1*). Most outliers for vasti muscle RMS Stance and ES-MSD were female (45/48); with outliers more evenly distributed between sexes for hamstring EMG predictor variables. There were 27 outliers from 800 muscle strength data points, approximately 3% of the total data in the sample. All outliers for muscle strength predictor variables in the Study Sample were males with medial OA (*see Appendix B-Table 2*). The muscle strength variables with the most outliers were pre-TKA KF15-Abs. and pre-TKA KF15-Norm., with nine outliers each; the same nine participants were outliers for both absolute and mass-normalized pre-TKA KF strength predictor variables. There were no significant correlations (p>0.05) between WS CHANGE SCORE and any of the strength variables, including pre-TKA and pre-post TKA changes of both KF and KE strength (*see Appendix A- Table 2*). Variance explained in WS CHANGE SCORE by strength variables ranged from zero to three percent.

4.3. Multivariate Models (Objective 2)

The multiple regression model created using stepwise variable selection from all strength and EMG predictor variables included four variables and explained 24% of the variance in WS CHANGE SCORE. See Table 4.3. The model included 4 variables: VM ES-MSD CHANGE SCORE as the variable explaining the most variance, then pre-TKA MH ES-MSD, VL RMS Stance CHANGE SCORE and VL ES-MSD CHANGE SCORE, in order. The multiple correlation coefficients and variance explained for each model created in the stepwise process are displayed in *Table 4.3*, along with equations for each. Including only strength variables as predictors in stepwise selection yielded no model, and the addition of anthropometric variables (age, height, pre-TKA mass, pre-post TKA mass change, BMI, pre-post TKA BMI change) into stepwise variable selection did not change the model.

Table 4. 3: Multiple correlation coefficients (R) and variance explained (R2) with equations for multivariate regression models that explained the most variance in change in walking speed (in m/s) pre-post TKA.

Model	***R***	***R^2***	***Equation***
1	0.283	0.08	***Δ Walking Speed= 0.166 + (0.002 x Δ VM ES-MSD)***
2	0.368	0.136	***Δ Walking Speed= 0.213 + (0.002 x Δ VM ES-MSD) - (0.002 x Pre-TKA MH ES-MSD)***
3	0.436	0.190	***Δ Walking Speed= 0.189 + (0.003 x Δ VM ES-MSD) - (0.002 x Pre-TKA MH ES-MSD) - (0.002 x Δ VL RMS Stance)***
4	0.491	0.242	***Δ Walking Speed= 0.170 + (0.002 x Δ VM ES-MSD) - (0.002 x Pre-TKA MH ES-MSD) - (0.003 x Δ VL RMS Stance) + (0.002 x Δ VL ES-MSD)***

Note. ***Δ*** represents all predictors where a pre-post TKA change score was used. RMS= root mean squared amplitude, ES-MSD = early stance peak to mid stance amplitude difference.

This model fulfilled the assumption of sample size, as four predictor variables would require a sample size of at least 74 participants according to the rule of thumb used, and N=107 exceeds this. Leverage vs Cook's distance plot confirmed that the final model was not significantly skewed by any outliers, and residuals plots confirmed the normality, linearity, and homoscedasticity of the residuals from the model. Pearson product moment correlations and Variance Inflation Factors ranging from 1.000 to 2.043 confirmed that multicollinearity was not present between the variables used in the final model.

In summary, both pre- and pre-post TKA CHANGE SCOREs for muscle activity were significantly correlated with WS CHANGE SCORE, with the largest variance explained by VM ES-MSD CHANGE SCORE at 8%. Four muscle activity features, one pre-TKA variables and three CHANGE SCORE variables, explained 24% of the variance in WS CHANGE SCORE, a 16% increase over the highest univariate model. No muscle strength variables were significantly correlated with WS CHANGE SCORE or selected into the multivariate models.

Chapter 5: Results- Objective 3

The results for *Objective 3* related to muscle function and post-TKA walking speed outcomes separated by sex are reported in this chapter, including the univariate and multivariate analyses. The pre- and post-TKA mean and standard deviation of all predictor variables, key anthropometric measures, and walking speed for males and females of the Study Sample separately are presented in *Table 4.1*. The pre- and post-TKA EMG ensemble average waveforms over the gait cycle of VL, VM, LH and MH for the males and females from the Study Sample are displayed in *Figure 5.1*.

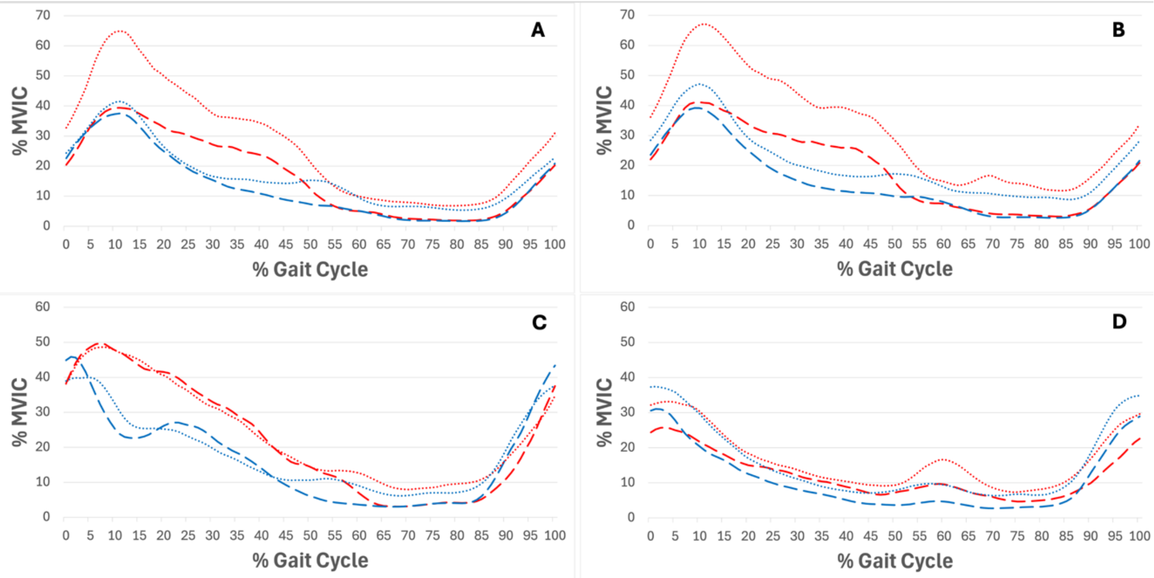

Figure 5. 1: Pre- (red) and post- (blue) TKA ensemble average EMG waveforms for the males (dashed lines) and females (dotted lines) from the Study Sample (n= 107) for VL (A), VM (B), LH (C), and MH (D) muscles. X axis is percent of the total gait cycle and Y axis is percent of maximal voluntary isometric contraction.

5.1 Univariate Analysis

When separated by sex, the Study Sample data presented unique significant correlations with independent when compared to the results of the Total Study Sample. *Table 5.1* includes the correlation coefficients and variance explained for the independent variables that had significant ($p<0.05$) correlations with WS CHANGE SCORE, and the interpretations for each. Pre-TKA VL ES-MSD ($r=-0.33$), VL ES-MSD CHANGE SCORE ($r=0.43$), pre-TKA VM ES-MSD ($r=-0.31$) and VM ES-MSD CHANGE SCORE ($r=0.38$) were significantly correlated with WS CHANGE SCORE for males. Pre-TKA MH ES-MSD was the only muscle activity feature significantly correlated with WS CHANGE SCORE for females ($r=-0.30$). *Figures 5.2* and *5.3* provide a visual comparison of differences in the strength of the associations using scatterplots with trendline for the data separated by sex. For VL ES-MSD CHANGE SCORE and WS CHANGE SCORE, illustrated in Figure 5.2, the males have a steeper positive trendline compared to the female data as captured by the significant correlation for the males. In *Figure 5.3* the associations between pre-TKA MH ES-MSD and WS CHANGE SCORE shows a steeper negative trendline for females than males, as captured by the significant correlation for the females. No EMG activity variables had significant correlations that had opposite polarity between sexes. *Appendix C- Table 1* includes the correlation coefficients, variance explained and significance values for all the EMG activity variables for all four muscles.

The only significant correlation for muscle strength was KE45-Norm. CHANGE SCORE, which was significantly ($p<0.05$) correlated with WS CHANGE SCORE for males ($r= 0.42$) as found in Table 4.4. *Appendix C- Table 2* includes the correlation coefficients, variance explained, and significance values for all strength variables analysed, separated by sex, showing no other significant correlations.

Table 5. 1: Pearson product moment correlations (r) and variance explained (R^2) for lateral and medial vasti (VL, VM) and hamstring (LH, MH) EMG activity (in % MVIC) and strength variables (in Nm/kg) that have significant ($p<0.05$) correlation with change in walking speed (in m/s) pre-post TKA, (46 males, 61 females).

Variable	***Sex***	***r***	***R^2***	***Interpretation***
Pre-TKA VL ES-MSD	Male	**-0.33**	**0.11**	Smaller ES-MSD pre-TKA: More pre-TKA prolonged VL activity associated with larger increases in walking speed post-TKA for males
	Female	-0.16	0.03	
Δ VL ES-MSD	Male	**0.43**	**0.19**	Increase in ES-MSD post-TKA: reduction in prolonged VM activity associated with larger increases in walking speed post-TKA for males
	Female	0.19	0.04	
Pre-TKA VM ES-MSD	Male	**-0.31**	**0.09**	Smaller ES-MSD pre-TKA: More pre-TKA prolonged VM activity is associated with larger increases in walking speed post-TKA for males
	Female	-0.21	0.04	
Δ VM ES-MSD	Male	**0.38**	**0.15**	Increase in ES-MSD post-TKA: reduction in prolonged VM activity post-TKA is associated with larger increases in walking speed for males
	Female	0.24	0.06	
Pre-TKA MH ES-MSD	Male	-0.18	0.03	
	Female	**-0.30**	**0.09**	Smaller ES-MSD pre-TKA: More pre-TKA prolonged MH activity is associated with larger increases in walking speed post-TKA for females
Δ KE45-Norm.	Male	**0.42**	**0.17**	Increase in KE45-Norm. post-TKA: increase in KE muscle strength is associated with larger increases in walking speed for males
	Female	-0.02	~0.00	

Note. Interpretation based on the direction of the correlations. Significant correlations ($p<0.05$) identified in **bold**. *Δ* represents all predictors where a pre-post TKA change score was used. RMS= root mean squared amplitude, ES-MSD = early stance peak to mid stance amplitude difference. Missing data values from Study Sample are as follows: pre-TKA VL- 2, post-TKA VL- 4, pre-TKA VM- 6, post-TKA VM- 8, pre- and post-TKA LH- 1, pre- and post-TKA MH- 4.

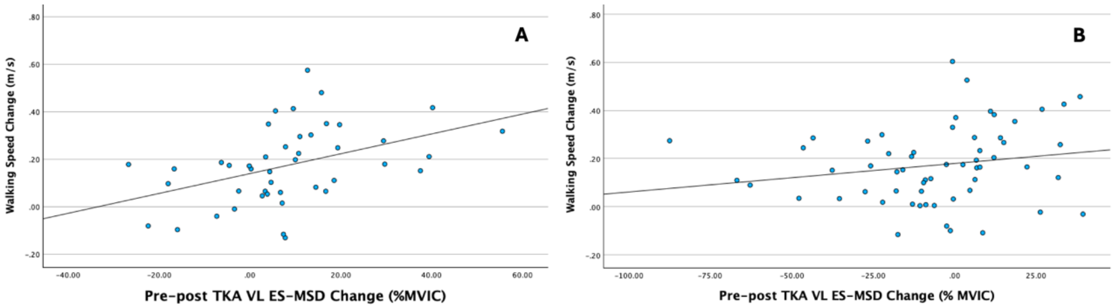

Figure 5. 2: Scatterplots with trendline illustrating the association between VL ES-MSD CHANGE SCORE and WS CHANGE SCORE for males (A) and females (B) from the Study Sample.

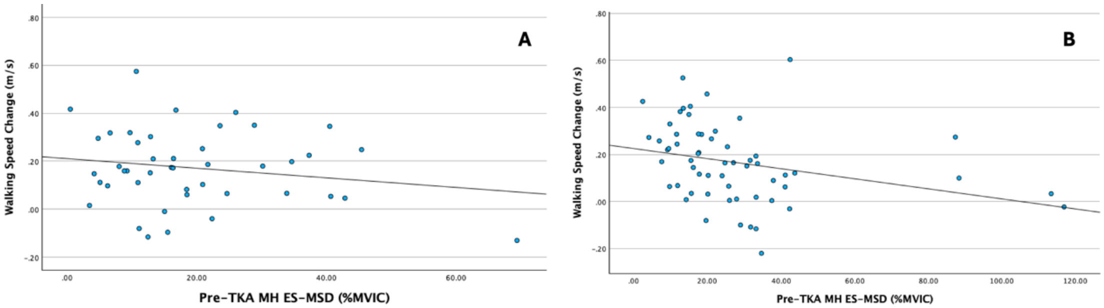

Figure 5. 3: Scatterplots with trendline illustrating between pre-TKA MH ES-MSD and WS CHANGE SCORE for males (A) and females (B) from the Study Sample.

5.2 Multivariate Models

Exploratory analysis selected different features in the multiple regression models that explained variance in WS CHANGE SCORE for males and females. Table 5.2 presents the models that were created for males and females separately by adding strength predictor variables only, EMG predictor variables only, and both strength and EMG predictor variables at the same time. The addition of anthropometric variables (age, height, pre-TKA mass, pre-post TKA mass change, BMI, pre-post TKA BMI change) into stepwise variable selection did not change the model for either sex.

When multivariate models were created with only strength variables, only one variable, KE45-Norm. change score, explaining 17% of variance in WS CHANGE SCORE, was included for male participants, and no model was created with only strength variables for the female participants. When multivariate models were created with only muscle activity variables, three independent variables were chosen for males; VL ES-MSD CHANGE SCORE, Pre-TKA VM ES-MSD, and Pre-TKA MH RMS Stance, explaining 39% of the variance in WS CHANGE SCORE; and one variable was chosen for the females, the Pre-TKA MH ES-MSD, which explained 9% of the variance in WS CHANGE SCORE. When including both strength and EMG variables in the selection for multivariate models, four variables were selected in the model for males, including VL ES-MSD CHANGE SCORE, KE45-Norm. CHANGE SCORE, KF15-Abs. CHANGE SCORE, and pre-TKA LH RMS Stance, in order, and explained 54% of the variance in WS CHANGE SCORE. The multivariate model created using both strength and EMG variables for the female participants included two variables pre-TKA MH ES-MSD and pre-TKA KF15-Abs., in order, explaining 17% of the variance in WS CHANGE SCORE for the female participants.

Table 5. 2: Multiple correlation coefficients (R) and variance explained (R^2) and equations for multivariate regression models that explained the most variance in change in walking speed (in m/s) pre-post TKA, separated by sex.

Model		***R***	***R^2***	***Equation***
Male- Strength only		0.417	0.174	***Δ Walking Speed= 0.147 + (0.213 x Δ KE45-Norm.)***
Male- EMG only	1	0.431	0.185	***Δ Walking Speed= 0.142 + (0.004 x Δ VL ES-MSD)***
	2	0.548	0.301	***Δ Walking Speed= 0.212 + (0.004 X Δ VL ES-MSD) – (0.004 x Pre-TKA VM ES-MSD)***
	3	**0.622**	**0.386**	***Δ Walking Speed= 0.296 + (0.005 x Δ VL ES-MSD) – (0.005 x Pre-TKA VM ES-MSD) – (0.003 x Pre-TKA MH RMS)***
Male- Strength & EMG	1	0.431	0.185	***Δ Walking Speed= 0.142 + (0.004 x Δ VL ES-MSD)***
	2	0.619	0.383	***Δ Walking Speed= 0.109 + (0.004 x Δ VL ES-MSD) + (0.227 x Δ KE45-Norm.)***
	3	0.692	0.479	***Δ Walking Speed= 0.114 + (0.005 x Δ VL ES-MSD) + (0.282 x Δ KE45-Norm.) – (0.003 x Δ KF15-Abs.)***
	4	**0.738**	**0.544**	***Δ Walking Speed= 0.042 + (0.005 x Δ VL ES-MSD) + (0.294 x Δ KE45-Norm.) – (0.003 x Δ KF15-Abs.) + (0.002 x Pre-TKA LH RMS)***
Female- EMG only		0.295	0.087	***Δ Walking Speed= 0.226 – (0.02 x Pre-TKA MH ES-MSD)***
Female- Strength & EMG		**0.413**	**0.170**	***Δ Walking Speed= 0.332 - (0.002 x Pre-TKA MH ES-MSD) - (0.005 x Pre-TKA KF15-Abs.)***

Note. ***Δ*** represents all predictors where a pre-post TKA change score was used. RMS= root mean squared amplitude, ES-MSD = early stance peak to mid stance amplitude difference.

In summary, different independent variables showed significant correlation with the outcome of WS CHANGE SCORE for males and females, and different multivariate regression models were created. For the male participant subset, both pre- and pre-post TKA CHANGE SCOREs for ES-MSD and one KE strength variable were significantly correlated with WS CHANGE SCORE, with the largest variance explained by VL ES-

MSD CHANGE SCORE at 19%. Two muscle activity features and two strength variables explained 54% of the variance in WS CHANGE SCORE, a 35% increase over the highest univariate model. For the female participant subset, one muscle activity variable, pre-TKA MH ES-MSD was significantly correlated with WS CHANGE SCORE, explaining 9% of variance. This feature, along with pre-TKA KF15-Abs. explained 17% of the variance in WS CHANGE SCORE, an 8% increase compared to the univariate model.

Chapter 6: Discussion

6.1. Objectives 1 & 2

The Study Sample is a combination of participants from the DOHM laboratory with subsets of data previously published, hence the average age of participants (63.8 ± 7.6 years) at pre-TKA was similar to previous TKA participants (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2010; Outerleys et al., 2021; Young-Shand et al., 2020) and on average, there was no difference in pre-TKA or changes in mass or BMI, and walking speed improved by ~0.2 m/s post-TKA, similar to previous findings (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2010; Outerleys et al., 2021; Young-Shand et al., 2020). Pre-TKA measures and increases in KE and KF strength and WOMAC Total Score pre-post TKA was also consistent with previous literature from our group on smaller samples (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2010).

The pre- and post-TKA waveforms for the VL, VM, LH, and MH of the participants in the Total Study Sample are visually similar to muscle activity waveforms from pre- and post-TKA literature (Astephen Wilson et al., 2015; Hubley-Kozey et al., 2010; Hubley-Kozey & Astephen Wilson, 2017). The RMS amplitudes, representing overall activity, decreased post-TKA for both vasti muscles and LH, but the MH were similar (19% MVIC pre-TKA and 18% MVIC post-TKA), consistent with previous findings based on Principal Component Analysis (PCA) of EMG activity features (Hubley-Kozey et al., 2010). The three and five percent MVIC increases post TKA in ES-MSD for VM and MH sites, respectively, represents a decrease in prolonged activity, and in part agree with the previous study, however decreases were reported for both medial and lateral muscle sites for PCA features characterizing prolonged activity during stance phase (Hubley-Kozey et al., 2010). The lack of pre-post changes in ES-MSD for lateral muscle sites pre-post TKA could be explained by additional participants in the current sample altering this relationship, or that the PCA features, and the difference measures are not well correlated. Overall, the study samples among these studies are similar with respect to the pre- and post- TKA characteristics found in Table 4.1.

The Total Study Sample presents novel findings about the associations between muscle strength and EMG activity and walking speed as an objective measure of overall function. By extracting discrete EMG metrics that represent prolonged activity and overall activity during stance phase of gait, results were able to identify muscle activity features among knee flexor and extensor muscles that had significant associations with walking speed change as an outcome of TKA.

6.1.1 Univariate Analysis (Objective 1)

Six out of eight prolonged activity (ES-MSD) variables had significant correlations with WS CHANGE SCORE, whereas only one of eight overall activity (RMS Stance) variables had a significant correlation with WS CHANGE SCORE. This suggests that prolonged activity of KE and KF muscles have stronger associations than overall amplitude of muscle activity with changes in overall function post-TKA. Since prolonged activity is associated with a stiff knee gait pattern (Hatfield et al., 2021b) it is reasonable that a reduction would improve dynamic knee joint function and subsequently overall function. This is consistent with previous work, which found prolonged activity measures of KE and KF muscles to be associated with both knee adduction and knee flexion moment difference features, and only MH overall activity to be significantly correlated with the KFM difference feature (Hatfield et al., 2021b); these moment difference features are associated with OA severity (Astephen et al., 2007, 2008) and progression to TKA (Hatfield et al., 2015b), and are thus representative of key changes in knee joint function for those with OA.

For all four muscles investigated, the significant negative correlations between pre-TKA ES-MSD and WS CHANGE SCORE indicate that smaller difference values, or more prolonged hamstring and vasti muscle activity during stance, before TKA was associated with greater improvements in walking speed post TKA. For both KE muscles, a positive correlation between ES-MSD CHANGE SCORE and WS CHANGE SCORE indicates that a greater reduction in prolonged KE activity after surgery was associated with larger increases in walking speed post-TKA. It is interesting to note that while pre-TKA ES-MSD had significant correlations with WS CHANGE SCORE for all four muscles, ES-MSD CHANGE SCOREs were only significant for the VL and VM (KE muscles). To summarize, more pre TKA prolonged activity for both KE and KF, and a greater reduction in post-TKA KE prolonged activity and LH overall activity were associated with improved overall function.

Interesting was that there were no significant correlations between any of the four strength measures and improvements in overall function based on WS CHANGE SCORE. These strength results were unexpected, given that significant associations between pre-TKA KE strength (Mizner et al., 2005b) and post-TKA changes in KE strength with functional outcomes were previously reported for the Time Up and Go, Stair Climbing Test and 6 Minute Walk Test (Mizner et al., 2011; Mizner et al., 2005a; Yoshida et al., 2008). However, these functional tasks previously tested, such as stair ascent and sit-to-stand, produce larger knee flexion moments, requiring greater KE strength in healthy (Rutherford et al., 2016), functionally impaired (Hughes & Myers, 1996), and OA afflicted (Mizner & Snyder-Mackler, 2005) older adults, compared to knee flexion moments during walking (Astephen et al., 2008; Mizner & Snyder-Mackler, 2005; Zeni & Higginson, 2009). For example, peak internal extensor moments were twice the amplitude during sit-to-stand compared to walking in post-TKA participants, requiring the KE muscles to generate a larger moment during sit-to-stand movements (Mizner & Snyder-Mackler, 2005). Typically, peak knee flexion moments for self-selected speed waking are approximately 0.5 Nm/Kg and decrease with increasing OA severity (Astephen et al., 2008; Zeni & Higginson, 2009), in contrast to 0.9 Nm/Kg for healthy older adults during a sit-to-stand task (Rutherford et al., 2016). These values support that a sufficient amount of KE strength is needed for walking but increases beyond that amount might have minimal additional effect on walking speed. Furthermore, the above measures only reflect the peak value and do not consider the increased co-activation and more prolonged activity, characteristic severe knee OA muscle activity patterns, that sometimes remain post-TKA (Hubley-Kozey et al., 2009; Zeni et al., 2010), and as illustrated in Figures 4.4 and 4.5, can get worse in some individuals.

Finding no significant correlations between KF strength variables and changes in walking speed after TKA was also unexpected, from a joint function perspective, but minimal literature exists that can be used for direct comparisons. Previous results using knee moment difference features as outcomes found that both KE and KF strength were significantly correlated with KFM features capturing a stiff knee gait, whereas only KF strength was correlated with the KAM feature capturing a stiff knee gait (Hatfield et al., 2021b).

Together these findings provide evidence that muscle activity patterns play a greater role than muscle strength in the recovery of overall function based on walking speed post TKA. However, the greatest variance explained by any one variable was 8%, so a combination of pre and pre-post TKA change variables may better highlight what muscle function features can best influence changes in overall function pre-post TKA.

6.1.2 Multivariate Models (Objective 2)

The multivariate models included features from both pre-TKA and pre-post TKA change in strength and muscle activity features to determine what combination of features would best explain changes in self-selected walking speed. The multiple regression model that explained the most variance selected four independent variables- VM ES-MSD CHANGE SCORE, pre-TKA MH ES-MSD, VL RMS STANCE CHANGE SCORE and VL ES-MSD CHANGE SCORE explaining 24% of the variance in WS CHANGE SCORE. A combination of decreased VL and VM prolonged activity and VL overall activity post-TKA plus more pre-TKA MH prolonged activity were associated with larger increases in walking speed post-TKA. These findings support that both pre-post TKA changes in KE muscle activity patterns and pre-TKA MH prolonged activity influence changes in overall function post TKA. Further, the lack of effect on the multivariate model of age, mass, height, and BMI indicates that these factors did not add explained variance to the model.

As expected, based on the univariate models, no model was created when only strength variables were entered as independent variables in stepwise multivariate regression, nor were strength variables selected to the model that included both strength and EMG variables. This is an important finding, as muscle strengthening has been a focus of pre- and post-TKA rehabilitation (Alrawashdeh et al., 2021; Konnyu et al., 2023), but many studies have begun to discuss the need to change biomechanics pre-post TKA, and that the surgery itself does make a significant change to frontal plane moment overall magnitude, and the sagittal plane moment, improving stiff knee gait, but not back to moderate OA or asymptomatic values (Hatfield et al., 2011; Outerleys et al., 2021). Since hip and knee OA are strong predictors of walking difficulties (King et al., 2018) and the amount of walking is associated with risk of functional limitations in those with or at-risk of knee OA (White et al., 2014), it is especially important that walking speed as a functional outcome be addressed in this population. Unlike the functional tasks that require standing up from a sitting position, that require KE muscle strength (Hughes & Myers, 1996; Mizner & Snyder-Mackler, 2005; Rutherford et al., 2016), walking relies on cyclic repetitions of highly coordinated muscle activity, which are altered with severe knee OA, including more coactivation and prolonged activity (Hubley-Kozey et al., 2010; Rutherford et al., 2011b, 2013; Zeni et al., 2010).

So while the results for the Total Sample did not find any strength variable that was significantly correlated or included in the multivariate models for pre-post TKA walking speed change, the prolonged activity features for the VM and LH were significantly correlated to the WS CHANGE SCORE outcome, consistent with the two prolonged activity features associated with a worse stiff knee gait pattern (Hatfield et al., 2021b), predictive of future TKA in those with moderate knee OA (Hatfield et al., 2021a), and with the patterns for some participants in the current study (Figures 4.3-4.5).

6.1.3 Summary and Implications

The results from both univariate and multivariate regression models provide evidence that pre-habilitation prior to TKA surgery with the goal to reduce prolonged activity of KE and KF muscles would likely not improve post-TKA functional outcomes with respect to greater improvements in walking speed after surgery. However, links between pre-TKA prolonged activity and negative outcomes such as implant migration (D. Wilson et al., 2012) and pain (Smith et al., 2004) indicate that there may be potential value with respect to pain and implant stability. Further, more severe muscle activity patterns, including prolonged activity of KF and KE muscles, have been associated poor joint function (Hatfield et al., 2021b) and predictive of progression towards TKA (Hatfield et al., 2021a). Thus, those with more prolonged muscle activity would have slower walking speeds pre-TKA, allowing for more potential to increase walking speed, indicative of improvement in function post-TKA. This theory is consistent with recent work investigating pre-post TKA changes in high and low-functioning gait biomechanics phenotypes, which found that the lower-functioning groups of participants demonstrated the greatest increases in walking speed and joint function features pre-post TKA, and the higher-functioning groups experienced little to no improvements in gait speed and joint function features pre-post TKA (Young-Shand et al., 2023).

The Study Sample findings indicate that improvements in muscle strength post-TKA were not associated with improvements in function based on walking speed, in contrast to strong associations with improvements in other functional tasks, such as sit-to-stand (Mizner et al., 2011; Mizner et al., 2005a, 2005b; Yoshida et al., 2008). This finding supports a shift in focus of pre-post TKA rehabilitation beyond strengthening leg muscles to improve walking function. Specifically, these findings would suggest that post-TKA neuromuscular training with the goal to reduce prolonged activity of VL and VM muscles during gait can help improve overall function outcomes post-TKA.

Although encouraging, only 24% of the variance in the post-TKA change in self-selected walking speed was accounted for by the multivariate model created. Seventy six percent of the variance was not explained by the variables entered and selected, which could be due to variability in the sample, the sensitivity of the muscle function variables entered, and other factors that may be important. One such factor that has shown to create variability pre- and post- TKA gait biomechanics is sex of participants (Astephen Wilson et al., 2015).

6.2. Objective 3

The average age of participants at pre-TKA were similar for males and females, mass and height were greater for males (~10kg and 0.15m) than females, resulting in similar BMIs, and minimal post-TKA changes were consistent with previous work (Astephen Wilson et al., 2015). WOMAC Total Score were similar between males and females, including 64 and 70% decreases respectively post-TKA, and are consistent with previous pre-post TKA reports of WOMAC (Hubley-Kozey et al., 2010). Pre-TKA waking speed was similar, as was the increase post-TKA (0.17 m/s) between males and females, consistent with previous work, although males in the previous study had an almost two-fold greater increase in walking speed pre-post TKA, but this was not significantly different (Astephen Wilson et al., 2015). Males had greater pre-TKA KE and KF strength, and both sexes had similar increases in both KE and KF strength pre-post TKA, consistent with previous work (Astephen Wilson et al., 2015).

Sex-separated average waveforms for VL, VM, and MH pre- and post-TKA (Figure 5.1) were similar to previous work; however, in the current study, male and female participants had overlapping pre TKA waveforms for the LH, whereas the previous study showed female participants had lower LH waveforms compared to male participants (Astephen Wilson et al., 2015). A potential explanation is that the current study did not exclude those with greater lateral compartment OA based on joint-space narrowing whereas the previous study did, and nine out of ten participants included in the current study that had lateral OA were female.

For both VL and VM, females had higher preoperative RMS stance amplitudes and larger decreases (approx. 18 % MVIC) than males (approx. 6-8 % MVIC) resulting in females having more similar post-TKA amplitudes to males. This is consistent with previous findings showing greater pre-TKA overall activity of quadriceps muscles for females and a significant sex by pre-post TKA interaction, where only females had a significant decrease post-TKA (Astephen Wilson et al., 2015). Males and females had similar pre-TKA LH and MH RMS stance and had similar decreases for both muscles, consistent with no significant difference between sexes, but a difference pre-post TKA found in Astephen Wilson et al. (2015).

The pre-post TKA increases in VL and VM ES-MSD for males, but decreases for females suggest that females had an increase in prolonged quadriceps activity, consistent with a gait feature characteristic of more severe OA (Hubley-Kozey et al., 2009; Zeni et al., 2010) and predictive of poor post-TKA outcomes (Smith et al., 2004; D. Wilson et al., 2012), and that males decreased their prolonged activity post-TKA. Despite pre-post TKA improvements in prolonged activity for males based on this feature, females have larger pre-TKA ES-MSD, primarily due to high pre-TKA peaks (65-70% MVIC) that drop to similar VL peaks and slightly higher peaks for VM than males post-TKA, consistent with previous findings (Astephen Wilson et al., 2015). Figure 5.1 shows that females have similar post-TKA prolonged activity as males for the VL, and slightly less post-TKA prolonged activity for the VM than males, perhaps illustrating the frailty of this value, which may help to explain the lack of significant correlations for females with muscle activity features. LH ES-MSD pre- and post-TKA were similar between males and females, consistent with their waveforms (Figure 5.1C) with only a slight (~2%) increase in this difference feature for male participants. Females had greater MH ES-MSD values both pre- and post-TKA, as seen in EMG waveforms (Figure 5.1D), but males had a greater pre-post TKA increase in MH ES-MSD, as they had smaller pre-TKA ES-MSD for MH, consistent with previous work (Astephen Wilson et al., 2015).

6.2.1 Univariate Analysis

The most striking finding when analyzing each sex separately was that five muscle function features had significant correlations with WS CHANGE SCORE for males and only one was significant for females. KE45-Norm. CHANGE SCORE was the only muscle strength variable that had a significant correlation with WS CHANGE SCORE for males, indicating that a greater increase in knee extensor strength was associated with greater increases in walking speed pre-post TKA. The five EMG features were all ES-MSD measures, representing prolonged activity, and included both pre-TKA and CHANGE SCORE variables. For males, the significant correlations were for vasti muscles only, including pre-TKA ES-MSD and ES-MSD CHANGE SCORE with WS CHANGE SCORE for males. The variance explained in WS CHANGE SCORE for these features ranged from 9 to 19%, which is greater than the variance explained for the features associated with WS CHANGE SCORE for the complete Study Sample. Overall, these findings support that greater increases in mass-normalized knee extensor strength, more pre-TKA prolonged activity of VL and VM muscles, and greater decreases in prolonged activity of VL and VM, were associated greater improvement in function, based on a larger increase in post-TKA walking speed for males who receive TKA.

For females, the only feature that was significantly correlated with WS CHANGE SCORE was pre-TKA MH ES-MSD, indicating that more pre-TKA prolonged activity of the MH was associated with greater improvement in function, based on a larger increase in walking speed post-TKA for females. The variance explained in WS CHANGE SCORE was 17%, which was about twice as much as this feature explained for the total Study Sample. Differences between sexes were expected given previous work that found differences in muscle strength, muscle activity, and joint biomechanics between males and females with knee OA (Hubley-Kozey et al., 2022; Kaufman et al., 2001; McKean et al., 2007), and in changes pre-post TKA (Astephen Wilson et al., 2015; Young-Shand et al., 2023). However, given the lower muscle strength, in particular KE strength, and higher and more prolonged activity during walking for females with severe knee OA, the expectation was that there would be muscle function features that explain more variance in functional improvements following TKA surgery for females.

These results provide preliminary evidence that there are quantifiable differences between males and females in the pre and pre-post muscle function features that influence changes in overall function following TKA surgery, and that these features explain more variance in males than females.

6.2.2 Multivariate Models

The KE45-Norm. CHANGE score was the one variable selected when only strength variables were included as independent variables in stepwise multivariate model for males, explaining 17% of the variance in WS CHANGE SCORE. Including EMG activity variables as independent variables, three variables (VL ES-MSD CHANGE SCORE, pre-TKA VM ES-MSD, and pre-TKA MH RMS Stance) were selected, explaining almost 39% of the variance in WS CHANGE SCORE. When both strength and EMG variables were included together in the model, four variables were selected, with only the first two VL ES-MSD CHANGE SCORE and KE45-Norm. CHANGE SCORE consistent with the previous EMG only model. The KF15-Abs. CHANGE SCORE, and the pre-TKA LH RMS Stance, were two unique features, and together the four variables explained 54% of the variance in WS CHANGE SCORE. The third and fourth variables were unexpected based on their univariate association but are reasonable based on the three-feature EMG model given that the pre-TKA RMS Stance values for MH and LH explain similar amounts of variance, and KF15-Abs. is likely not strongly correlated with the other variables included in the model.

The addition of anthropometric variables (age, mass, height, BMI, mass change and BMI change) as independent variables in selection did not add any explained variance to the model. Overall, this final model indicates that change in both KF and KE strength, a reduction in prolonged activity of VL, and higher pre-TKA LH overall activity, are factors that influence pre-post TKA changes in self-selected walking speed for males who receive TKA.

For the female subset, as expected no model was made from strength-only variables, and the pre-TKA MH ES-MSD, was the only variable selected for the model made from EMG variables only, explaining 9% of the variance in WS CHANGE SCORE. The model that included strength and EMG variables selected pre-TKA values only, including pre-TKA MH ES-MSD and pre-TKA KF15-Abs., explaining 17% of the variance in WS CHANGE SCORE. Pre-TKA MH ES-MSD had a significant correlation to WS CHANGE SCORE, and was the first variable added to the model, indicating that more prolonged activity of MH pre-TKA was associated with greater increases in walking speed post-TKA. Pre-TKA KF15-Abs. was added, showing that lower non-mass-normalized knee flexor strength pre-TKA was associated with greater improvements in walking speed post-TKA. The addition of anthropometric variables (age, mass, height, BMI, mass change and BMI change) as independent variables in selection did not add any explained variance to the model. Overall, this model, which includes only pre-TKA variables from hamstring muscles, indicates that the pre-TKA strength and activity of the knee flexor muscles, the hamstrings, are key in the pre-post TKA changes in overall function for the female participants. Specifically, more severe activity patterns pre-TKA, characterized by more prolonged activity, and lower strength were associated with greater improvements in walking speed pre-post TKA.

These models suggest that a combination of features that influence pre-post TKA changes in overall function for male and female participants separately, many of which are different from those that were selected in the models for the Total Study Sample. These models are valuable for developing TKA rehabilitation protocol, as they highlight features that are significantly correlated to change in self-selected walking speed as a measure of overall function, and highlight features that, when targeted in conjunction with one another, can influence the greatest possible improvements. This allows clinicians to develop more effective rehabilitation protocols by using strategies to target different muscle function features depending on the sex of their patients. Hopefully, more customized, improved TKA rehabilitation protocol can help improve the overall outcomes of the procedure, which can improve the lives of individuals with OA and reduce the number of patients requiring TKA revision surgery.

6.3 Comparison of Total Study Sample and Sex-Separated Analysis

Overall, the correlations and percent variance explained for the independent variables with significant correlation to WS CHANGE SCORE were higher for the sex specific analysis ($|r|= 0.30-0.43$, $R^2=0.09-0.19$) compared to the analysis using the Total Study Sample ($|r|= 0.19-0.28$, $R^2= 0.04-0.08$), particularly for males. This means that the features that were significantly correlated for each of the two sexes are more reflective of the features that influence improvements in overall function for male and female patients post-TKA separately. Significant correlations between variables found for one sex but not the other can, in part, explain the lack of significant correlation between many independent variables with WS CHANGE SCORE for the Total Study Sample, as the association between variables can change when averaged among the whole group. For example, when looking at the male-only component of the Study Sample there was a correlation between KE45-Norm. CHANGE SCORE and WS CHANGE SCORE that explained 17% of the variance in WS CHANGE SCORE. The female component of the Study Sample did not have any significant correlation between KE45-Norm. CHANGE SCORE and WS CHANGE SCORE, and since this group made up more than half of the participants in the Study Sample, the Total Study Sample did not show any significant correlation with this variable.

Compared to the full group model, the sex-specific multiple regression models featured different variables. Most notably, while the full group model did not select any muscle strength features, both the male and female multivariate models selected strength variables. The Total Study Sample model included three change score variables for KE muscle activation patterns plus pre-TKA MH ES-MSD, which was the first feature selected for the multiple regression model for the females. Thus, the addition of this feature to the full-group model is expected, as there were more females in the sample (57%) and the average association among the whole group is influenced by the proportion of the females in the Total Study Sample. The only common feature between the multivariate model made for the male subset and the multivariate model made for the Total Study Sample was VL ES-MSD CHANGE SCORE, which was the first variable selected for the model made the male subset, but was the final variable added to the model made for the Total Study Sample.

The multivariate models created for each of the sexes were clearly different from one another, and from the multivariate model created for the Total Study Sample, which indicates that whole-group models may not extract the most influential features for many individuals. Overall, the multivariate model created for the Total Study Sample was a representation of the associations between muscle function features and change in self-selected walking speed for the average values of the whole group, and, for the most part, do not reflect the features that have the most impact for either of the sexes. This means that the features selected for the sex-separated models may be better targets for TKA rehabilitation as they can have a greater influence when implemented for the correct population.

6.4 Summary and Conclusions

The overall aim of this study was to determine whether pre-TKA and/or pre-post TKA changes in knee joint muscle function are associated with changes in overall function after TKA surgery in patients with severe knee osteoarthritis. The study examined knee muscle strength and muscle activation features to represent muscle function, and self-selected walking speed to represent overall function. Using linear models, the associations between independent variables and change in self-selected walking speed were examined, and then multivariate regression models were created to determine what combination of independent variables could explain the greatest amount of variance in post-TKA change in self-selected walking speed.

With respect to objective 1, findings support that muscle activity patterns representing prolonged activity and overall activity of knee extensor and knee flexor muscles explain significant variance in post-TKA changes in self-selected walking speed. Findings do not support a strong association between knee extensor or knee flexor muscle strength and change in self-selected walking speed pre-post TKA for a mixed sample of males and females. With respect to objective 2, findings support that a combination of knee extensor and knee flexor muscle activity features explain the most variance in changes in self-selected walking speed post-TKA.

Returning to the overarching hypothesis for objectives 1 and 2, results support that both pre-TKA values and pre-post TKA change scores of both knee extensor and flexor muscle activity patterns representing prolonged activity and overall activity explained significant variance in pre-post TKA changes in self-selected walking speed. However, results do not support the same conclusion for strength of knee extensor and knee flexor muscles, nor do they support that a combination of strength and muscle activity variables explain the most variance in pre-post TKA changes in self-selected walking speed. Further, multivariate models were only able to explain 24% of the variance in pre-post TKA changes in self-selected walking speed.

With respect to objective 3, the results determined that there were differences between males and females who undergo TKA surgery in which muscle function features explained significant variance in pre-post TKA changes in self-selected walking speed, and in the combinations of muscle function features that explain more variance in pre-post TKA changes in self-selected walking speed. These findings support the exploratory hypothesis for objective 3 and explain more variance than the non-sex separated models, with multivariate models explaining up to 54% of variance in pre-post TKA changes in self-selected walking speed for the male participant subset.

This study addressed a gap in the current literature by investigating the associations between the magnitude of changes in pre-post TKA measures of muscle function with the magnitude of change in an objective measure of overall function; this was done through a comprehensive examination of pre-TKA values and pre-post TKA changes in both knee extensor and knee flexor muscle strength and muscle activity patterns linked to poor outcomes in knee OA, and their association with pre-post TKA changes in walking speed. Further, this study investigated the sex-specific differences in these associations. Understanding these relationships is important in informing future

TKA rehabilitation protocol, as muscles can serve as modifiable targets for intervention, with the goal to improve the long-term outcomes of TKA.

6.5 Strengths and Limitations

This study presented novel findings on the association between muscle function features and pre-post TKA changes, using data collected from a clinical population using valid and reliable measures. With a sample size of 107 participants, this study included a robust sample of pre-post TKA data compared to previously published studies, which increases the generalizability of the results to the overall TKA patient population. The results of this study provide data on modifiable muscle function features that can serve as targets for future TKA rehabilitation protocol, which can improve the outcomes of TKA.

Despite this, there are limitations to this study that should be acknowledged. Due to the nature of this study as a secondary analysis, all values and information were to be interpreted in the context of only the notes and data provided. The main limitation to interpreting the findings of this study was that there was no information on whether participants took part in pre- or post-TKA rehabilitation. Thus, the main intervention was the total joint replacement, and we have no information on what individuals did, either supervised or unsupervised, related to exercise or physical activity pre- or post-TKA. The data do, however, clearly show that some participants improved muscle function features one-year after TKA, whereas some had worse muscle activation patterns (see Figures 4.4 and 4.5) and muscle strength after surgery. Thus, the associations found with this functional outcome indicate that these individuals with worse outcomes should be considered candidates for neuromuscular training to improve their walking gait.

Since this data was originally collected for use in two separate studies, not all the same variables were collected between studies, including which muscle strength exercises were performed and what PROM questionnaires were completed by participants. For example, there were several participants from the Study Sample who did not have WOMAC data (n= 45), leaving a much smaller sample for pre- and post- TKA data on WOMAC Total Score. However, the data from the current study did find similar changes to what has previously been reported in literature.

This study provided novel perspectives on sex-differences in muscle function features that influence pre-post TKA changes in overall function. However, due to small sample size when separated into groups based on sex, the multivariate regression models may be overtrained. This is particularly of concern for the model made for the male participants, as the complete model selected using both strength and EMG variables contained four variables, and there were only 46 male participants in the Study Sample. Thus, the findings need to be interpreted within the limitations posed by the study and the delimitations of the variables selected for this study.

6.6 Future Directions

The differences between males and females further support the need for implementing sex separated analysis for clinical studies on gait and muscle activity in the future, as the differences between sexes can change the interpretation of relationships between variables; this implication likely applies to other fields using clinical populations. Since recent systematic reviews have shown that one-size-fits-all approaches to rehabilitation are unable to produce systematic improvements in clinical outcomes (Alrawashdeh et al., 2021; Konnyu et al., 2023), future work should build on patient-specific research with the continued use of sex-separated analysis to improve rehabilitation practices.

To build on this study, an investigation of the robustness of the sex specific models should be performed, including the collection of more data, if necessary, to ensure that the multivariate models created have selected the features that most effectively impact changes in self-selected walking speed for each sex. Specifically, independent variables of potential interest for future study include KE45-Abs. CHANGE SCORE and pre-TKA KF15-Abs. for males and females respectively. While these variables were not correlated with WS CHANGE SCORE from the limited sample size in this study, results indicate that it is possible that with a larger sample size, these variables could be correlated with WS CHANGE SCORE. Further, both pre-TKA MH RMS Stance and MH RMS Stance CHANGE SCORE appeared to have associations with WS CHANGE SCORE with trends of opposite effect for the two sexes when separated, however these correlations were not significant, so future work should conduct a more robust analysis on these variables to see if significant associations arise.

Symptoms such as pain, stiffness, and instability remain an important factor when considering patient eligibility for TKA (Gademan et al., 2016; Riddle et al., 2018; Skou et al., 2016), and it can be important to consider what factors influence changes in these subjective outcomes. Future studies can investigate the associations between the muscle function features investigated in this study and other outcomes, such as PROMs, to see if different features play a role in pre-post TKA changes in symptoms. Beyond this research, next steps should involve the development of interventions that target the specific features highlighted by this work, and future studies should investigate the effectiveness of these targeted interventions in addressing the specific features they are designed for, and in improving overall TKA outcomes.

Amount and types of physical activity as well as any rehabilitation protocols that patients complete both pre- and post-TKA likely have significant influence on outcomes from TKA. Since both pre- and post-TKA features were associated with pre-post TKA changes in walking speed, and physical activity and rehabilitation programs can improve measured functional and patient reported outcomes following TKA (Alrawashdeh et al., 2021; Konnyu et al., 2023), it can be important to consider the effect of both pre- and post-TKA physical activity and rehabilitation on post-TKA outcomes, including changes in muscle function features. The present study did not collect any information from participants on these factors, and thus cannot consider in what ways they influence outcomes post-TKA. Future work collecting gait and/or muscle activity data pre- and post-TKA should aim to fill in this gap by collecting information on the level of activity and the amount of rehabilitation that participants engage in, including pre-TKA, and considering this information as part of analysis to get an idea of how different types of physical activity and rehabilitation can influence TKA outcomes.

The hope is that this research is a step towards the eventual development and implementation of standard-of-care rehabilitation to patients who receive TKA, which can help improve TKA outcomes, and reduce the number of TKA patients requiring revision surgery, thus lessening the load on the healthcare system. This can be done through the widespread knowledge translation of the results from this study and previous work to populations such as physicians and surgeons, practicing rehabilitation professionals, patients, and healthcare policy makers of the value of rehabilitation in improving the outcomes of TKA surgery, and how it can change the healthcare system.

Appendix A

Table 1. Pearson product moment correlations (r) variance explained (*R^2*), and significance values (p) for lateral and medial vasti (VL, VM) and hamstring (LH, MH) EMG activity predictor variables (% MVIC) with pre-post TKA change in walking speed (m/s).

Variable	*r*	*R^2*	*p*
Pre-TKA VL RMS Stance	0.05	~0.00	0.59
Δ VL RMS Stance	-0.06	~0.00	0.59
Pre-TKA VL ES-MSD	**-0.19**	**0.04**	**0.05**
Δ VL ES-MSD	**0.25**	**0.06**	**0.10**
Pre-TKA VM RMS Stance	0.11	0.01	0.28
Δ VM RMS Stance	~0.00	~0.00	0.95
Pre-TKA VM ES-MSD	**-0.22**	**0.05**	**0.03**
ΔVM ES-MSD	**0.28**	**0.08**	**0.01**
Pre-TKA LH RMS Stance	0.19	0.03	0.06
Δ LH RMS Stance	**-0.23**	**0.05**	**0.02**
Pre-TKA LH ES-MSD	**-0.21**	**0.05**	**0.03**
Δ LH ES-MSD	0.15	0.02	0.14
Pre-TKA MH RMS Stance	-0.04	~0.00	0.72
Δ MH RMS Stance	-0.07	0.01	0.48
Pre-TKA MH ES-MSD	**-0.25**	**0.06**	**0.1**
Δ MH ES-MSD	0.13	0.02	0.18

Note. Significant correlations ($p < 0.05$) identified in **bold**. ***Δ*** represents all predictors where a pre-post TKA change score was used. RMS= root mean squared amplitude, ES-MSD = early stance peak to mid stance amplitude difference. Missing data values from Study Sample are as follows: pre-TKA VL- 2, post-TKA VL- 4, pre-TKA VM- 6, post-TKA VM- 8, pre- and post-TKA LH- 1, pre- and post-TKA MH- 4.

Table 2. Pearson product moment correlations (r), variance explained (*R^2*), and significance values (p) for knee extensor (KE) and flexor (KF) muscle strength predictor variables with pre-post TKA change in walking speed (in m/s). Included are absolute (Abs.) strength values (Nm), and mass-normalized (N) strength values (Nm/kg).

Variable	*r*	*R^2*	*p*
Pre-TKA KE45- Abs.	-0.09	0.01	0.37
Δ KE45- Abs.	0.16	0.03	0.10
Pre-TKA KE45-Norm.	-0.12	0.01	0.24
Δ KE45-Norm.	0.18	0.03	0.07
Pre-TKA KF15- Abs.	-0.06	~0.00	0.53
Δ KF15- Abs.	~0.00	~0.00	0.98
Pre-TKA KF15-Norm.	-0.07	~0.00	0.50
Δ KF15-Norm.	0.03	~0.00	0.79

Note. No significant ($p < 0.05$) correlations found. ***Δ*** represents all predictors where a pre-post TKA change score was used. Missing data values from Study Sample are as follows: pre-TKA KE45 strength- 4, post-TKA KE45 strength- 5, pre-TKA KF15 strength- 9, post-TKA KF15 strength- 10.

Appendix B

Table 1. Outliers from Study Sample (N=107) for lateral and medial vasti (VL, VM) and hamstring (LH, MH) EMG activity predictor variables.

Variable	**Outliers (Number, Sex, OA compartment)**
Pre-TKA VL RMS	Four Female, Medial OA One Female, Lateral OA
Δ VL RMS	Seven Female, Medial OA One Female, Lateral OA
Pre-TKA VL ES-MSD	Four Female, Medial OA Two Female, Lateral OA
Δ VL ES-MSD	Two Female, Lateral OA Two Female, Medial OA One Male, Medial OA
Pre-TKA VM RMS	Five Female, Medial OA
Δ VM RMS	Six Female, Medial OA
Pre-TKA VM ES-MSD	Three Female, Medial OA
Δ VM ES-MSD	Six Female, Medial OA Two Female, Lateral OA Two Male, Medial OA
Pre-TKA LH RMS	One Female, Medial OA
Δ LH RMS	Two Female, Medial OA Four Male, Medial OA
Pre-TKA LH ES-MSD	Three Female, Medial OA Two Male, Medial OA
Δ LH ES-MSD	Three Female, Medial OA One Male, Medial OA

Variable	**Outliers (Number, Sex, OA compartment)**
Pre-TKA MH RMS	Five Female, Medial OA Five Male, Medial OA One Female, Lateral OA
Δ MH RMS	Four Male, Medial OA Two Female, Medial OA
Pre-TKA MH ES-MSD	Two Female, Medial OA Two Male, Medial OA One Female, Lateral OA
Δ MH ES-MSD	Three Female, Medial OA Two Male, Medial OA

Note. This subgroup includes 46 male and 61 female participants. RMS= root mean squared amplitude, ES-MSD = early stance peak to mid stance amplitude difference.

Table 2. Outliers from Study Sample (N= 107) for absolute (Abs.) and mass normalized (N) muscle strength predictor variables.

Variable	**Outliers (Number, Sex, OA compartment)**
Pre-TKA KE45- Abs.	One Male, Medial OA
Δ KE45- Abs.	One Male, Medial OA
Pre-TKA KE45-Norm.	One Male, Medial OA
Pre-TKA KF15- Abs.	Nine Male, Medial OA
Δ KF15- Abs.	Four Male, Medial OA
Pre-TKA KF15-Norm.	Nine Male, Medial OA
Δ KF15-Norm.	Two Male, Medial OA

Note. No outliers for *Δ* KE45-Norm. This subgroup includes 46 male and 61 female participants.

Appendix C

Table 1. Pearson product moment correlations (r), variance explained (R^2), and significance values (p) for lateral and medial vasti (VL, VM) and hamstring (LH, MH) EMG activity predictor variables (in % MVIC) with change in walking speed (in m/s) pre-post TKA, from the Study Sample separated by sex (46 males, 61 females).

Variable	***Sex***	***r***	***R^2***	***p***
Pre-TKA VL RMS Stance	Male	-0.02	~0.00	0.89
	Female	0.10	0.01	0.46
Δ VL RMS Stance	Male	0.01	~0.00	0.93
	Female	-0.09	0.01	0.49
Pre-TKA VL ES-MSD	Male	**-0.33**	**0.11**	**0.03**
	Female	-0.16	0.03	0.21
Δ VL ES-MSD	Male	**0.43**	**0.19**	**< 0.01**
	Female	0.19	0.04	0.14
Pre-TKA VM RMS Stance	Male	0.04	~0.00	**0.80**
	Female	0.16	0.03	0.24
Δ VM RMS Stance	Male	0.03	~0.00	**0.87**
	Female	-0.02	~0.00	0.88
Pre-TKA VM ES-MSD	Male	**-0.31**	**0.09**	**0.04**
	Female	-0.21	0.04	0.12
Δ VM ES-MSD	Male	**0.38**	**0.15**	**0.01**
	Female	0.24	0.06	0.08
Pre-TKA LH RMS Stance	Male	0.22	0.05	0.14
	Female	0.16	0.03	0.23
Δ LH RMS Stance	Male	-0.26	0.07	0.08
	Female	-0.21	0.04	0.12
Pre-TKA LH ES-MSD	Male	-0.17	0.03	0.27
	Female	-0.25	0.06	0.06
Δ LH ES-MSD	Male	0.17	0.03	0.27
	Female	0.13	0.02	0.32
Pre-TKA MH RMS Stance	Male	0.17	0.03	0.26
	Female	-0.14	0.02	0.31
Δ MH RMS Stance	Male	-0.24	0.06	0.12
	Female	0.05	~0.00	0.72
Pre-TKA MH ES-MSD	Male	-0.18	0.03	0.25
	Female	**-0.30**	**0.09**	**0.02**
Δ MH ES-MSD	Male	0.13	0.02	0.41
	Female	0.14	0.02	0.30

Note. Significant ($p<0.05$) correlations identified in **bold**. *Δ* represents all predictors where a pre-post TKA change score was used. RMS= root mean squared amplitude, ES-MSD = early stance peak to mid stance amplitude difference. Missing data values from Study Sample are as follows: pre-TKA VL- 2, post-TKA VL- 4, pre-TKA VM- 6, post-TKA VM- 8, pre- and post-TKA LH- 1, pre- and post-TKA MH- 4.

Table 2. Pearson product moment correlations (r), variance explained (R^2), and significance values (p) for knee extensor (KE) and flexor (KF) muscle strength predictor variables with change in walking speed (in m/s) pre-post TKA, separated by sex (46 males, 61 females).

Variable	*Sex*	*r*	R^2	*p*
Pre-TKA KE45- Abs.	Male	-0.22	0.05	0.15
	Female	-0.17	0.03	0.20
Δ KE45- Abs.	Male	0.30	0.09	0.05
	Female	0.03	~0.00	0.80
Pre-TKA KE45-Norm.	Male	-0.25	0.06	0.10
	Female	-0.17	0.03	0.21
Δ KE45-Norm.	Male	**0.42**	**0.17**	**<0.01**
	Female	-0.02	~0.00	0.99
Pre-TKA KF15- Abs.	Male	-0.08	0.01	0.60
	Female	-0.24	0.06	0.08
Δ KF15- Abs.	Male	-0.07	~0.00	0.68
	Female	0.11	0.01	0.45
Pre-TKA KF15-Norm.	Male	-0.08	0.01	0.60
	Female	-0.21	0.04	0.13
Δ KF15-Norm.	Male	0.01	~0.00	0.96
	Female	0.06	~0.00	0.64

Note. Significant ($p<0.05$) correlations identified in **bold**. ***Δ*** represents all predictors where a pre-post TKA change score was used. Absolute (Abs.) strength values are recorded in Nm, and mass-normalized (N) strength values are represented in Nm/kg.

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