Varus-Valgus Knee Laxity and Biomechanical Function in Patients with Severe Osteoarthritis and after Total Knee Arthroplasty

DISSERTATION

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Abstract

Over 50 million adults in the United States report doctor-diagnosed osteoarthritis (OA), which includes almost 50% of all people over the age of 65. There are no current treatments to stop the progression of OA; therefore, joint replacement is generally considered the final step to improve function and reduce pain in weight bearing joints. Increased varus-valgus laxity has been reported in participants with knee OA compared to controls, while passive stability is a major concern for orthopaedic surgeons during total knee arthroplasty (TKA). The purpose of this dissertation is to better understand the role of passive varus-valgus laxity on biomechanical, clinical and self-reported function in individuals with severe OA and following TKA.

Chapter 1 provides background information on tibiofemoral OA and TKA, while outlining the impact of knee stability on disease progression and outcomes. Chapter 2 is a systematic review of the literature containing varus-valgus laxity measurements in patients with OA. This research unearthed consistent findings indicating increased varus-valgus laxity is a characteristic of knee joints with OA. Large variances exist in reported varus-valgus laxity and may be due to differences in measurement devices. The remaining chapters include experimental data collected before, during, and after TKA from study volunteers. Chapter 3 assessed passive varus-valgus laxity in 30 osteoarthritic knees and found greater laxity was significantly associated with more varus-valgus
excursion during gait ($R^2=0.34$, $p=0.002$). However, no relationship was observed between passive varus-valgus laxity and knee flexion strength, perceived instability, or any Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales. Chapter 4 investigated the relationship between passive varus-valgus laxity and active stability of the knee joint provided by muscle activation and co-contraction. This analysis utilized data from 22 knees and found no relationship between active stability measures and passive laxity. There was also no association between active stability measures and varus-valgus excursion during gait, knee strength, and perceived instability. Chapter 5 quantified varus-valgus laxity intra-operatively and identified relationships to biomechanical and surgical outcomes. Thirty three knees were included in this analysis and laxity of the replaced joint was significantly associated with knee strength (extension $p=0.027$; flexion $p=0.024$) and KOOS quality of life ($p=0.046$). However, knee laxity was unrelated to a majority of the biomechanical, clinical performance and self-reported outcome measures. Relationships were also found between the change in varus-valgus laxity and the overall varus-valgus laxity in the osteoarthritic and replaced knee joint.

The main purpose of this research was to identify the contribution of soft-tissue knee stabilizers to biomechanical, clinical, and self-reported function in participants with severe OA and after TKA. Identifying the impact of passive and active knee stability on function may allow for improved surgical techniques and altered treatment and rehabilitation strategies for patients. The information presented in this dissertation improves the basic understanding regarding the influence of passive varus-valgus laxity on function. This work will help in achieving the long-term goal of improving patient function and reducing the costs and disability associated with knee OA and TKA.
I would like to dedicate this dissertation to my dogs

Maddy and Jersey

for keeping me sane and never making me drink alone.
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First off, I would like to thank my advisor, Ajit Chaudhari. Over the past 5 years he has spent a lot of time and energy mentoring me on what it takes to be a great scientist. I still have a lot to learn, but I would not have made it this far without him. I would also like to thank the other members of my dissertation committee; Alan Litsky, Laura Schmitt and Rob Siston. They each brought an expertise to this work which vastly improved its quality and greatly enhanced my understanding of what it takes to be a well-rounded biomechanist.

I also thank our orthopaedic surgeons, Matt Beal, Jeff Granger and Andy Glassman, for help recruiting subjects, testing patients in the operating room, and taking the time to answer my clinical and surgical questions. The work presented in this dissertation is a culmination of a true team effort and I would be remiss to not mention the enormous contributions of Erin Hutter, Jackie Lewis, Joe Ewing, and Jeff Pan.

Many others have been instrumental in getting me to this point of my life. My family, friends, teachers, military mentors and labmates each had a part in my growth and development over the years and for that I am truly lucky. I would like to thank the NIH for funding this research project, and also thank The Ohio State University Graduate School and the Pat Tillman Foundation for additional financial support. This project
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1.1 Tibiofemoral Osteoarthritis

1.1.1 Background and Prevalence

Osteoarthritis (OA) is a degenerative joint disease which affects articular cartilage and the underlying bone. It can cause abnormal bony growth, increased friction between articular surfaces, and inflammation; all of which can contribute to pain during motion. OA is the leading cause of chronic disability and up to 87% of people 55-65 years of age exhibit radiographic signs of OA in the hands, knees, hips, or spine (Meulenbelt, Bijkerk et al. 1997). In the United States, 52.5 million adults have doctor-diagnosed arthritis (Barbour, Helmick et al. 2013) and of those, 25 million are projected to have arthritis-attributable activity limitations by the year 2030 (Hootman and Helmick 2006). The total cost of arthritis and other rheumatic conditions was $128 billion in the United States in 2003 (Yelin, Cisternas et al. 2007).

OA in the hip and knee joint are primary causes of disability, due to their role in ambulation. In the early 1990s, radiographic knee OA was seen in 37.4% of the US population over age 60, while symptomatic knee OA was found in 12.1% of the same group (Dillon, Rasch et al. 2006). The total number of adults with OA is projected to increase 40% from 2005 to 2030, with almost one third of cases found in those 45-64 years of age (Hootman and Helmick 2006). The increasing prevalence of OA and the associated costs and disability make it imperative to better understand the impact of the disease and how treatments can be improved. There is currently no cure for OA and new strategies are needed for prevention and management of this disease. This dissertation
will be focused on end-stage knee osteoarthritis, as it is currently the leading cause of disability in the United States (2009).

1.1.2 OA Incidence and Progression Hypotheses

Incidence and progression of OA is generally thought to be multi-factorial in nature, but there exist multiple hypotheses outlining potential mechanisms of joint degeneration. Andriacchi et al. hypothesized that gait mechanics influenced both healthy knee cartilage and the incidence and progression of osteoarthritis (Andriacchi, Koo et al. 2009). In Figure 1.1, healthy cartilage loading is shown on the left where cartilage structure and biology can balance the loads during repetitive walking. The initiation of OA may be associated with some change such as increased age or obesity, knee injury or cartilage defect, alteration to the knee joint mechanics or change in kinematic laxity. Once this change occurs, the repetitive walking loads are too large for the cartilage to handle. This results in pain and clinical OA over time, and eventually cartilage degeneration and severe OA.
Figure 1.1: Healthy cartilage homeostasis is maintained by the magnitude of the repetitive cyclic loads during walking, and cartilage is thicker in regions with higher loads during walking. The initiation of osteoarthritis (OA) is associated with a change (due to injury, increased laxity, neuromuscular changes, aging, or increased obesity) in the normal balance between the mechanics of walking and the cartilage biology and structure. Once cartilage starts to degrade, it responds negatively to load and the rate of progression of osteoarthritis increases with loading. Figure and caption from Andriacchi et al. (Andriacchi, Koo et al. 2009)
The prevalence of OA in obese patients has led some to speculate that the increased body mass may overload weight-bearing joints and cause cartilage degeneration (Sowers and Karvonen-Gutierrez 2010). However, in healthy populations, heavier individuals tend to have thicker knee cartilage (Shepherd and Seedhom 1999). Cartilage has been shown to need a certain level of applied loading to maintain thickness, with joint immobilization and paralysis leading to rapid cartilage atrophy (Akeson, Amiel et al. 1987)(Vanwanseele, Eckstein et al. 2003; Vanwanseele, Eckstein et al. 2004). Increased cartilage thickness does not seem to be related to activity (Eckstein, Faber et al. 2002; Eckstein, Hudelmaier et al. 2006; Gratzke, Hudelmaier et al. 2007), even though cartilage loading between active and control groups is larger than any potential increase seen between normal weight and obese individuals during activities of daily living. The mechanical stimulus is clearly important in cartilage health, and OA is not simply a case of wearing out articular cartilage due to moderate increases in body mass or activity. However, increased loading in conjunction with other mechanical and metabolic risk factors may lead to joint degeneration (Sowers and Karvonen-Gutierrez 2010). Excessive varus or valgus knee alignment has been shown to amplify the risk of developing OA (Sharma, Lou et al. 2000; Sharma 2007; Sharma, Chmiel et al. 2013) (Hunter, Sharma et al. 2009), and this is thought to be due to the large increases in load on the medial or lateral compartment respectively.

Injury to the chondral surface is another possible mechanism of OA initiation, due to the lack of blood flow and restorative capacity of cartilage (Figure 1.2). Cartilage defects have been shown to increase stress concentrations in the surrounding cartilage surface (Buckwalter, Mow et al. 1994; Guettler, Demetropoulos et al. 2004). The sudden
increase in magnitude may be above and beyond what the cartilage can accommodate, causing cell death in the area surrounding the defect. Cartilage is aneural and symptoms may be delayed until there is subchondral bone involvement, making it difficult to identify the original cartilage injury that may lead to OA initiation.
Individuals who experience an anterior cruciate ligament (ACL) rupture also have a much larger likelihood of developing OA, with up to 51% of knees exhibiting radiographic OA 12 years after injury date (Lohmander, Ostenberg et al. 2004). This increased risk of OA may be due to changes in knee kinematics during *in vivo* motion and altered cartilage loading patterns (Andriacchi, Mundermann et al. 2004; Chaudhari, Briant et al. 2008). After ACL rupture, altered femoral anterior-posterior translation on the tibia during knee extension (Barrance, Williams et al. 2007) and increased internal...
rotation during gait have been identified (Andriacchi and Dyrby 2005). Cartilage thickness varies on the articular surface and tends to be thicker in areas that receive the highest loadings during gait (Figure 1.3) (Andriacchi, Mundermann et al. 2004). The thickest cartilage is seen where the femur and tibia contact during heel strike of gait and healthy subjects (Andriacchi, Mundermann et al. 2004). Following ACL injury there is an instantaneous shift in kinematics which can alter the cartilage contact patterns and load the joint in a way not previously adapted. In the years following ligament injury the cartilage may be unable to adapt to these changes in knee kinematics and cartilage loading patterns, resulting in a degenerative process. Altered passive laxity of other knee ligaments have also been proposed to alter knee kinematics and potentially initiate OA and lead to further cartilage degeneration.
Figure 1.3: Left – Superior views of thickness maps of the healthy articular cartilage of the femur and tibia, derived from MRI. Right – The thickest regions of the femoral cartilage (outlined) align with the thickest regions of the tibial cartilage at full extension. Modified from Andriacchi et al. (Andriacchi, Mundermann et al. 2004), with permission. Figure reproduced from Chaudhari et al (Chaudhari, Briant et al. 2008).

1.1.3 Treatment Options

Aerobic and resistance exercise programs can reduce pain symptoms and improve function in older adults with knee osteoarthritis (Ettinger, Burns et al. 1997). Physical therapy also showed improvements in function, however patients with worse OA severity had smaller improvements in function, indicating diminishing returns as OA severity increases (Fransen, Crosbie et al. 2001). The relief of symptoms and improvement in function, while important to patient quality of life, are not addressing the underlying cartilage degeneration. The improvements also tend to be modest and given the inability
for cartilage to self-heal, these treatments are generally used in an attempt to postpone subsequent options.

Oral medications such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to manage pain associated with mild OA, but there are no current drug therapies to slow the progression of cartilage breakdown. Intra-articular corticosteroids have been widely used since the 1950s to help reduce joint inflammation, which can decrease pain and improve poor joint mobility associated with OA (Snibbe and Gambardella 2005). Hyaluronic acid injections are also commonly used to increase the viscosity and elastic properties of the synovial joint fluid. Osteoarthritic joints produce lower levels of hyaluronic acid compared to normal joints (Snibbe and Gambardella 2005), however a recent systematic review and meta-analysis conducted by Arrich et al. concluded that intra-articular hyaluronic acid has not been proven clinically effective and may be associated with a greater risk of adverse events (Arrich, Piribauer et al. 2005). These therapy options focus on treating the symptoms of OA and not the underlying cause of painful bone on bone articulation due to degenerated cartilage.

Arthroplasty is the most common elective end-stage treatment for severe OA. It involves removing the damaged cartilage and underlying bone and replacing it with metal and polyethylene components (Figure 1.4). Uni-compartmental knee arthroplasty only removes the cartilage from the knee compartment that is damaged, thus preserving native joint surface where possible. Total knee arthroplasty removes and replaces the joint surfaces on both the medial and lateral compartments, while sometimes resurfacing the patella. These procedures are generally successful in reducing the disabling pain associated with severe OA, by replacing the bone-on-bone joint interaction with
prosthetic components. These prosthetic components are similar to cartilage in that they are aneural, therefore reducing the potential for painful sensation during knee joint articulation and loading.

1.2 Total Knee Arthroplasty

1.2.1 Background and Prevalence

Total Knee Arthroplasty (TKA) has been steadily increasing over the past 20 years as a final resort treatment for severe osteoarthritis. There are currently over 700,000 TKAs performed in the United States per year (2012) and that number is estimated to increase to approximately 3.5 million annually by 2030 (Kurtz, Ong et al. 2007). The direct costs of a single TKA are approximately $20,000 compared to non-surgical treatment, but these are offset by societal savings of almost $40,000 in reduced indirect costs such as increased employment and earnings (Ruiz, Koenig et al. 2013). Given this analysis, TKA is generally considered a cost effective procedure, but the projected cost for TKA in 2015 was over $45 billion (Kurtz, Ong et al. 2007).

1.2.2 Procedure

TKA is performed to replace severely damaged articular surfaces to reduce pain and improve function. According to the American Academy of Orthopaedic Surgeons, the arthroplasty procedure consists of four basic steps. The damaged cartilage surfaces and underlying bone are removed on the femur and tibia (Figure 1.4). Metal implants are cemented in place to recreate the distal femur geometry and proximal tibia. The articular surface of the patella is often cut and replaced with a polyethylene component. Lastly a polyethylene spacer is inserted between the metal femoral and tibial components to
provide a low friction knee joint interface. The condylar knee replacement surgery was developed in the early 1970s (Ranawat 2002); since then surgical strategies, techniques and implanted components have evolved but the general concept has remained the same.

Figure 1.4: Left – Illustration of severe osteoarthritis. Right – Arthritic cartilage and underlying bone has been removed and resurfaced with metal implants on the femur and tibia. A plastic spacer has been placed in between the implants. The patellar surface can be resurfaced with a plastic button, but it is not shown for clarity (Foran 2011).

Successful joint replacement depends on a multitude of factors including patient population, pre-operative joint condition, implant design and selection, surgical techniques and procedures, and rehabilitation protocols. Restoring frontal plane alignment has been considered one of the most important surgeon controlled factors, and excessive post-operative varus or valgus alignment increases revision risk (Fang and
Soft tissue balancing is often necessary to adjust knee stiffness in flexion and extension when restoring the knee’s mechanical alignment. If accurate soft tissue balancing is not achieved, this can result in instability or tightness for the patient and asymmetric loading distribution in the medial and lateral compartments of the knee (Wasielewski, Galat et al. 2005).

1.2.3 Surgical Outcomes

Implant survivorship 10 years following TKA is 94% for patients older than 70 years of age but only 83% for patients 55 years old or younger (Rand, Trousdale et al. 2003). Patients younger than 65 years old are projected to account for over 50% of primary and 60% of revision TKAs by 2030, so it is of growing importance to identify the factors which lead to successful functional outcomes and long term survivorship (Kurtz, Lau et al. 2009). TKA is generally considered successful at reducing pain associated with end stage OA, but 1 in 8 patients report moderate to severe pain 1 year after surgery (Brander, Stulberg et al. 2003). Many patients are unable to perform activities of daily living such as climbing stairs, standing up from a chair, stretching/strengthening exercises, gardening and recreational sports (Weiss, Noble et al. 2002). TKA patients on average also walk and climb stairs slower than controls, while exhibiting knee extensor strength deficits 1 year after surgery (Walsh, Woodhouse et al. 1998). 52% of TKA patients self-report limitations during functional activities vs. 22% for age/gender matched controls with no knee disorders (Noble, Gordon et al. 2005). Restoring strength and developing normal movement patterns are important aspects of all rehabilitation protocols and generally considered the last step to a successful TKA.
outcome (Petterson, Mizner et al. 2009) (Yoshida, Mizner et al. 2013). While it is clear that TKA can provide pain relief and improve function, not all outcomes are ideal. There is a need to better understand the underlying factors relating to function in order to improve patient outcomes.

1.2.4 Surgical Variables and Variation

There are many variables to consider when planning and executing a joint replacement. The complexity and interactions between these variables make every patient distinct, which is one reason why many of the decisions are dependent on the orthopaedic surgeon. Clinical examinations are used in conjunction with experience to come up with a pre-operative plan for each patient (Gustke 2005). Knee stability is assessed manually and can help guide the implant prosthesis selection (Kannus and Jarvinen 1988; Kannus and Jarvinen 1989). Three potential prosthesis designs are commonly chosen depending on knee stability and include: cruciate-retaining, posterior stabilized and constrained designs. Cruciate-retaining prostheses keep the posterior cruciate ligament intact to provide anterior-posterior stability, while the posterior stabilized designs use a cam/spine mechanism to prevent anterior translation of the femur on the tibia. Studies have not found any significant difference in outcomes dependent on cruciate retaining or posterior stabilized implant choice (Kolisek, McGrath et al. 2009)(Tanzer, Smith et al. 2002)(Clark, Rorabeck et al. 2001)(Bolanos, Colizza et al. 1998), although biomechanical differences in contact patterns have been noted (Most, Zayontz et al. 2003)(Komistek, Scott et al. 2002). In constrained implants, the femur and tibia are rigidly linked together with a hinge mechanism. These are not expected to last as long as
other designs due to the increased mechanical stress on the hinged element and the
greater transfer of force to the fixation and implant interface (Hodge and Chandler
implants are generally reserved for patients with ligamentous insufficiency (Sculco 1989)
or for use during a revision due to instability (Inglis and Walker 1991). There are also
gender specific designs, rotating tibial bearings, and cemented/cementless fixation
methods. Many of these choices are dependent on the pre-operative assessment and the
surgeon’s familiarity with the specific surgical procedure associated with each design.

Radiographic images are used to select the initial implant sizes and in some
instances used to assist the surgeon in deciding what the appropriate bone cut angles will
be in the operating room (Gustke 2005). Depending on the amount and location of bone
loss and corresponding varus or valgus deformity, the frontal plane bone cuts can be
adjusted to realign the knee joint in a more neutral position. These images will also
potentially show bony deformities which could alter surgical technique and identify
patients with osteoporosis or poor bone quality.

Soft tissue balancing is a process where orthopaedic surgeons attempt to achieve
adequate soft tissue tension to restrain the knee joint. Achieving a balanced knee is
considered crucial for long term success and patient satisfaction (Mihalko, Saleh et al.
2009). The “gap technique” is a common method employed to achieve balance and
utilizes the clear space concept to estimate ligamentous tension (Martin 1960)(Griffin,
Insall et al. 2000)(Insall, Binazzi et al. 1985). Following the femoral and tibial bone cuts,
the surgeon attempts to achieve a rectangular shaped gap between the bones that is equal
in size when the leg is extended and flexed (Figure 1.5). Equal sized gaps relate to the
length of the collateral ligaments and assume equal length will produce equal force throughout full range of motion. If the gaps are not equal in size, the surgeon can release part of the collateral ligaments or other soft tissue to achieve “balance.” While this assumption that equal gaps produce a balanced medial/lateral force makes intuitive sense, there are other factors that will affect the ligamentous force and therefore the balance of the knee.

Figure 1.5: The surgical gap technique is used to achieve equal sized rectangular gaps in extension and flexion. This technique is thought to approximate the stability of the knee joint during the entire range of motion (Griffin, Insall et al. 2000).
1.2.5 Surgical Navigation

In the operating room, the surgeon has the opportunity to adjust bone cut angles, implant type and other surgical factors depending on the condition of the exposed knee joint. These changes are mainly due to the look and feel of the knee joint and the surgeon’s experience on what he or she thinks will produce the best result. Soft tissue balancing is often done following the bone cuts or after the trial implants are fitted to see how the joint moves thru full range of motion. The patient’s hips and body are generally covered by surgical dressing and drapes and it is challenging to identify the mechanical axis of the knee with the patient in this position. Anatomical knee alignment can be measured with a goniometer, but this is rarely used in clinical practice as the surgeons only have a small area of the femur and tibia visible. One study found that only 25% of orthopaedic surgeons could visually align a synthetic bone model of the femur and tibia within 3 degrees of varus-valgus and 5 degrees of full extension, even with the entire model femur and tibia visible (Shetty, Mullaji et al. 2011). This highlights the precision and accuracy needed by surgeons to achieve knee alignments within such a small tolerance and how difficult that is to achieve on every patient. Surgical navigation systems can assist the surgeon by providing real-time information of the alignment of the femur and tibia in the operating room.

Surgical navigation systems provide a potential method to measure knee motion during TKA, by using computers and motion capture technology. This technology can assist in the determination of knee alignment and bone cut angles in the operating room (Figure 1.6). Post-operative mechanical alignment has been shown to be better with
surgical navigation compared to traditional alignment jigs (Bathis, Perlick et al. 2004)(Chauhan, Scott et al. 2004)(Haaker, Stockheim et al. 2005), with a decrease in the number of alignment outliers outside of +/- 3 degrees (Jenny and Boeri 2001)(Saragaglia, Picard et al. 2001)(Hart, Janecek et al. 2003)(Stockl, Nogler et al. 2004). Surgical navigation is a useful tool in assisting the surgeon in achieving a neutral knee alignment and reducing the number of outliers, but more work is necessary to better understand other factors that contribute to a successful knee replacement.

Figure 1.6: Example of surgical navigation utilizing motion capture to measure tibiofemoral alignment to assist surgeons in making bone cuts (2014).
1.3 Knee Stability

1.3.1 Components of Stability

The knee is the largest joint in the body and requires a high degree of mobility and the ability to support large loads during dynamic activity. The primary axis of rotation for the knee provides flexion-extension, but other rotations and translations occur on a smaller scale (Dyrby and Andriacchi 2004). There is a lack of bony support between the femur and tibia, which increases the need for stabilizing forces from other anatomical structures. External joint loading from ground reaction forces, gravity, and movement dynamics must be balanced by internal joint loading to remain dynamically stable (Figure 1.7). This is necessary to allow force transmission while maintaining joint congruency and the appropriate primary and secondary rotations and translations. Joint reaction forces, shown in Figure 1.7, are one component of balancing the external moments. (Andriacchi 1994) These contact forces and passive soft tissue forces such as the articular capsule, ligaments, and menisci are reactive in nature and are produced depending on the collective loading and percentages applied to other structures. Muscles which cross the knee joint are considered active soft tissue, since they can actively modulate the amount of force produced. The combination of joint contact forces, passive soft tissue and active muscle forces stabilize the knee during dynamic tasks. Maintaining both the primary and secondary motions of the knee requires a concerted effort between these three stabilizing systems and is important to joint function and health. (Schipplein and Andriacchi 1991)
Figure 1.7: Force balance between external (A) and internal (B) loads. The external moments and forces acting at the knee can be measured in the laboratory during walking. Internal loads acting in soft tissue ($F_s$), muscle ($F_m$), lateral joint surface ($R_l$), and medial joint surface ($R_m$) can be calculated. Approximately 70% of the total force ($R_l + R_m$) acts on the medial compartment. Figure reproduced from Andriacchi et al. (Andriacchi 1994).
1.3.2 Passive Stabilizers

The passive stabilizers of the knee include the joint capsule, menisci and ligaments. The articular joint capsule consists of fibrous tissue that surrounds the articular surfaces, with a main function of providing lubricating synovial fluid. Menisci are vital to distributing contact force between the femur and tibia and augment knee stability by improving joint congruency. The four major ligaments are generally considered the principal passive stabilizers of the knee. This includes the anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL) and lateral collateral ligament (LCL) shown in Figure 1.8. These ligaments provide varying amounts of restraint depending on the anatomical attachment points and the relative position of the femur and tibia. The ACL primarily restricts anterior motion of the tibia with respect to the femur while the PCL primarily restricts posterior tibial translation. (Markolf, Mensch et al. 1976) The MCL and LCL restrict motion in the frontal plane, primarily valgus and varus motion respectively. (Markolf, Mensch et al. 1976) Ligament injuries have been found to alter knee laxity (Lundberg and Messner 1997)(Kannus 1988) and also alter kinematics during gait (Andriacchi and Dyrby 2005).
1.3.3 Active Stabilizers

Active stabilizers are muscles that cross the knee joint and can modulate the amount of force acting across the knee. The major muscle groups that stabilize the knee are the quadriceps, hamstrings, and gastrocnemii. These muscles apply force to the pelvis, femur or tibia to resist gravity and produce locomotion. Active stability of the knee joint can be increased through co-contraction of agonist/antagonist muscle pairs. For a given movement or joint moment requirement there are many different muscle force solutions which can satisfy those conditions, due to the opposing action and redundancy of muscles in the lower extremity. For example, if a certain internal knee extension
moment is required one possible solution would be for the quadriceps to provide the exact force to create the necessary internal knee extension moment. In this scenario, the hamstrings and gastrocnemii must produce zero force, since any forces from these muscles would produce an internal knee flexion moment and counteract a portion of the required internal knee extension moment. Another solution to an identical movement could be to produce excess quadriceps force and also contract the hamstrings and gastrocnemii, resulting in an equivalent net joint moment. This second scenario would still provide the net moment required, while increasing the joint reaction forces and stability due to the co-contraction. Given the redundant nature of muscles and opposing actions of certain muscle groups, many muscle activation strategies can be utilized to achieve the same net joint moment with varying amounts of active joint stability.

1.3.4 Laxity

Clinical laxity is often assessed by manually manipulating the femur and tibia and grading the amount of relative motion in different planes. This examination procedure is largely subjective and reliability depends on the proficiency and experience of the examiner (Markolf, Mensch et al. 1976). Rotational laxity can be measured in varus-valgus and internal-external rotation and translational laxity is usually only measured in the anterior-posterior direction. This dissertation will focus on varus-valgus laxity, which is commonly assessed in patients with perceived instability, malalignment and osteoarthritis (Lewek, Rudolph et al. 2004)(Tallroth and Lindholm 1987; Brage, Draganich et al. 1994; Sharma, Lou et al. 1999; Lewek, Rudolph et al. 2004; van der

Laxity is often measured at one specific applied load but a continuous measure of force and displacement can help characterize the behavior of passive knee structures and give a more detailed description of knee stability (Markolf, Mensch et al. 1976). A sample from a cadaver study can be seen in Figure (1.9), where varus-valgus laxity is displayed as a continuous variable depending on the moment applied to the knee (Hutter, Granger et al. 2013). In the example shown in Figure 1.9, 10 Nm of varus and valgus load resulted in varus-valgus laxity of approximately 10 degrees of rotation, while 20 Nm of load increased the laxity to approximately 18 degrees. This experimental varus-valgus data illustrates how increased load results in larger rotation.
Figure 1.9: A sample of varus-valgus knee laxity from a cadaver study with continuous measures of applied moment and rotation (Hutter, Granger et al. 2013).

1.3.5 Measurement Devices and Techniques

Knee laxity can be quantified discretely at specific loads or using continuous measurement of load-displacement curves. Stress radiography is one method of stability testing, which applies a load or moment to the knee joint and measures the relative change in position of the femur and tibia from radiographic images (Tallroth and Lindholm 1987). Relative change in position can be measured in the angular rotation of the long bones (Miyazaki, Uchida et al. 2012) (Ishii, Noguchi et al. 2009), or it can be quantified by a change in joint space of the medial and/or lateral compartment (Lewek,
Another measurement technique is to attach a subject’s lower extremity into an apparatus that can measure varus-valgus knee angle (Brage, Draganich et al. 1994)(Sharma, Lou et al. 1999)(van der Esch, Steultjens et al. 2005). A load can then be applied in the varus and valgus direction and the total varus-valgus rotation would be a measurement of laxity. However, these techniques have the limitation that they typically cannot measure force or displacement continuously, and they do not directly visualize bones. This leaves potential for soft-tissue movement to influence angular measurements. Another method for quantifying laxity resolves the problems of continuous displacement measurement and soft-tissue obscuring bony motion by using surgical navigation technology to measure tibiofemoral motion (Siston, Goodman et al. 2007)(Jenny, Boeri et al. 2008). These systems generally screw motion trackers into the femur and tibia, while the patient is under anesthesia. Applying force to the subject’s leg with an instrumented handle allows for the continuous measurement of force and displacement, which can fully characterize passive knee stability (Figure 1.10) (Siston, Maack et al. 2012). Although invasive in nature, this approach solves the issues of accurately tracking bony motion without any artifact from soft tissue while removing the possibility of muscular guarding.
1.4 Statement of Purpose

Tibiofemoral OA is a growing problem, and joint replacement is a surgical option to reduce pain and improve function which is rapidly increasing in popularity. While joint replacement removes the affected cartilage and contact surface between the femur and the tibia, a majority of the soft tissue structures of the knee remain. The main purpose of this research is to identify the contribution of soft-tissue knee stabilizers to biomechanical,
clinical, and self-reported function in osteoarthritic knee joints and after TKA. Identifying the impact of passive and active knee stability on function may allow for improved surgical techniques and altered treatment and rehabilitation strategies for patients with severe OA and following TKA.

1.5 Outline of Upcoming Chapters

Chapter 2 is a systematic review of the literature measuring frontal plane laxity in patients with OA. This outlines varus-valgus laxity in the context of the amount of laxity in OA knees versus controls, by radiographic OA severity, frontal plane knee alignment, sex difference, and clinical and self-reported function. Chapter 3 assesses passive varus-valgus knee laxity in participants with severe knee OA and investigates associations with varus-valgus knee motion during gait, clinical measures of performance, and self-reported instability and function. Chapter 4 focuses on the relationship between active and passive knee stability in patients with severe OA. Average muscle activations and co-contractions are measured during gait, and we examine potential associations with passive laxity, varus-valgus knee motion during gait, clinical performance measures, and self-reported function. Chapter 5 explores the effect of laxity in the replaced knee joint and attempts to identify relationships to function after surgery. We investigate 33 replaced knee joints and test for associations between laxity and change in laxity and biomechanical, clinical and self-reported outcomes 6 months after TKA. Lastly, Chapter 6 outlines the contributions of this dissertation and identifies future research.
Chapter 2: Tibiofemoral osteoarthritis and varus-valgus laxity – a systematic review
2.1 Abstract

Objective: The purpose of this study was to systematically review and synthesize the literature measuring varus-valgus laxity in individuals with tibiofemoral osteoarthritis (OA). Specifically, we aimed to identify varus-valgus laxity differences between persons with OA and controls, by radiographic disease severity, by frontal plane knee alignment, by sex, and if there was a relationship to clinical performance and self-reported function.

Method: We executed a systematic search of peer-reviewed research articles in PubMed, Scopus and CINAHL to identify all existing literature regarding knee osteoarthritis and objective measurement of varus-valgus laxity in-vivo. 36 articles were identified that met the inclusion criteria and data were extracted.

Results: Varus-valgus laxity was significantly greater in individuals with OA compared to controls in a majority of studies, while no study found laxity to be significantly greater in controls. Varus-valgus laxity of the knee was reported in persons with OA and varying degrees of frontal plane alignment, disease severity, clinical performance and self-reported function but no consensus finding could be identified. Females with knee OA appear to have more varus-valgus laxity than males. Meta-analysis was not possible due to the heterogeneity of the subject populations and differences in laxity measurement devices, applied loading, and laxity definitions.

Conclusions: Increased varus-valgus laxity is a characteristic of knee joints with OA. Large variances exist in reported varus-valgus laxity and may be due to differences in measurement devices. Prospective studies on joint laxity are needed to identify if increased varus-valgus laxity is a causative factor in OA incidence and progression.
2.2 Introduction

Osteoarthritis (OA) is the leading cause of disability in the United States, affecting over 50 million adults (2009). OA is a multifactorial disease, with the mechanical environment of the joint playing a key role in cartilage synthesis and degeneration. Cartilage thickness varies by compartment in the knee joint (Jones, Glisson et al. 2000; Eckstein, Winzheimer et al. 2001) and, in healthy knees, increased cartilage thickness is seen on the regions experiencing the largest loads (Carter and Wong 2003; Andriacchi, Mundermann et al. 2004). However, in subjects with OA, larger loading is associated with less cartilage thickness and worsening disease severity (Sharma, Hurwitz et al. 1998; Andriacchi, Mundermann et al. 2004; Andriacchi and Mundermann 2006; Andriacchi, Koo et al. 2009). This paradoxical response to loading may be due to changes in the mechanical environment of the knee, such as altered joint laxity. Altered laxity may change knee kinematics and shift cartilage contact to areas that are not well conditioned, leading to a cycle of cartilage degeneration with increased loading (Figure 2.1) (Sharma, Lou et al. 1999; Andriacchi, Mundermann et al. 2004; Scarvell, Smith et al. 2005; Chaudhari, Briant et al. 2008).
Figure 2.1: An illustration of a framework for the initiation and progression of OA (I) Abnormal motion causes a shift in the contact location to a region not conditioned to high loads. Note: abnormal motion can result from a traumatic event such as ACL injury or chronic changes to the musculoskeletal system that occur with aging (Idiopathic knee). (II) Matrix damage to the superficial collagen network follows a shift to a load bearing regions that cannot adapt to changes in load bearing. (III) Friction increases following fibrillation of the collagen network. (IV) The maximum tangential force (Ft) that can be transmitted through the contact surface will increase following an increase in friction (µ). In addition, Ft will increase as the normal force Fn increases. (V) Shear stress transferred to the matrix will increase following degenerative changes and is dependent on the compressive force Fn. (VI) Lowering the compressive force can lower the shear force transferred to the matrix and potentially slow the rate of cartilage degeneration. Reproduced with permission from Andriacchi et al. 2004 (Andriacchi, Mundermann et al. 2004)
In order to investigate the potential link between laxity and OA, several techniques have been used to assess knee joint laxity. Clinically, knee laxity is graded during a physical exam by manually applying a force to the tibia while stabilizing the femur in an unloaded position. Manual testing is subjective by nature, and the reliability of clinical varus-valgus laxity in patients with knee OA is poor (Cushnaghan, Cooper et al. 1990). Consequently a variety of devices have been developed in an attempt to quantify laxity with greater accuracy and precision. Tallroth and Lindholm (1987) first measured in-vivo varus-valgus laxity in osteoarthritic knees utilizing stress radiographs (Tallroth and Lindholm 1987). A device applied a varus or valgus load to the knee and the change in medial and lateral joint space widths was recorded. Brage et al. measured angular rotation of the tibia with respect to the femur with a goniometer while varus and valgus loading was applied (Brage, Draganich et al. 1994). Multiple other frontal plane knee laxity devices have subsequently been developed in order to quantify varus-valgus knee laxity by measuring a change in joint space or angular rotation with applied load. These devices enable the statistical testing of hypothetical quantitative links between knee laxity and OA.

The purpose of this study was to assess the relationship between varus-valgus laxity and tibiofemoral OA, by systematically reviewing and synthesizing the available literature. Specifically, we aimed to identify varus-valgus laxity differences between each of the following: subjects with OA and controls; by radiographic disease severity; by frontal plane knee alignment; by sex; and by clinical performance and self-reported function.
2.3 Method

2.3.1 Search Terminology

We executed a systematic search of peer reviewed research articles in the search engines PubMed, Scopus and CINAHL published between January 1, 1966 and Jan 24, 2014. Our intent was to identify all existing literature regarding knee osteoarthritis and varus-valgus laxity. The search strategy used three combined terms to identify articles with “knee OR tibiofemoral”, “osteoarthritis OR OA OR degenerative joint disease OR joint degeneration”, and “stability OR instability OR laxity”. The results from these three searches were combined with AND statements and further filtered for articles in English with human subjects. This search strategy and results from one of the three search engines used (PubMed) are shown in Table 2.1.
<table>
<thead>
<tr>
<th>Search Number</th>
<th>Search Term Combination</th>
<th>Items Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search 1</td>
<td>knee OR tibiofemoral</td>
<td>111542</td>
</tr>
<tr>
<td>Search 2</td>
<td>osteoarthritis OR OA OR degenerative joint disease OR joint degeneration</td>
<td>66911</td>
</tr>
<tr>
<td>Search 3</td>
<td>stability OR instability OR laxity</td>
<td>350477</td>
</tr>
<tr>
<td>Combined Search</td>
<td>Search 1 AND Search 2 AND Search 3</td>
<td>1599</td>
</tr>
<tr>
<td>Final Search</td>
<td>Filter only English and human subjects</td>
<td>1125</td>
</tr>
</tbody>
</table>

The final search was limited to articles published before January 24, 2014. A similar search strategy was used in Scopus and CINAHL.

Table 2.1: Search strategy to identify manuscripts from PubMed.

2.3.2 Study Selection

The inclusion criteria for studies in this systematic review were:

- Peer reviewed, primary research articles published in English between January 1, 1966 and January 24, 2014
- Human subjects
- Confirmed radiographic tibiofemoral OA
- Measurement of varus-valgus displacement on a continuous scale

The exclusion criteria were:

- Cadaver studies
- Case reports
- Subjective, clinical assessment of varus-valgus laxity
• Laxity only measured following a bone, ligament, or meniscal alteration made in the operating room to assess the surgical knee procedure (e.g. osteotomy or arthroplasty)

2.3.3 Data Extraction

The following information was extracted from each selected article if available: total number of subjects with OA, total number of knees investigated, number of male and female subjects, age, radiographic severity of osteoarthritis, laxity testing method, quantified varus-valgus laxity, total number of controls, and load applied and knee flexion angle during testing.

2.3.4 Quality Assessment

Quality assessments were completed on the selected articles utilizing the study quality assessment tools developed for a systematic evidence review by the NIH Lifestyle Work Group (Eckel, Jakicic et al. 2014). These tools had separate checklists and instructions for observational cohort/ cross-sectional studies and case-control designs.

2.4 Results

2.4.1 Selected Study Characteristics

The flow diagram of article selection and exclusion is shown in Figure 2.2 per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati et al. 2009). Exclusion criteria were applied in the order listed on Figure 2.2. Abstracts from 2056 articles were reviewed following the database search. The full text of 103 articles was further examined and 36 articles met the inclusion criteria outlined in the methods section. Of the 36 selected studies, 4 were
prospective trials, 15 were cohort-control designs and the remaining 17 were cross-sectional studies. Laxity was a primary variable of interest in 29 of the selected studies. Two studies received a quality assessment of poor with respect to the reporting of varus-valgus laxity in subjects with OA (Pai, Rymer et al. 1997)(Sharma, Pai et al. 1997). This was due to a lack of detail on the method of objective laxity measurement. It was decided to leave these articles in the systematic review for completeness, but not include them in any meta-analysis which may be executed.
Figure 2.2: Flow diagram of selected studies for the systematic review. Anterior-posterior (AP).
The selected studies were categorized by topic with respect to OA and varus-valgus laxity for this systematic review: OA versus controls (N=16); radiographic OA severity (N=7); frontal plane knee alignment (N=4); sex differences (N=1); and clinical and self-reported measures of function (N=16). Eight studies did not fit into the categories above but quantified varus-valgus knee laxity in subjects with OA. The extracted data for these studies can be found in supplementary Table A1 in the Appendix.

Varus-valgus laxity was quantified utilizing 10 different testing devices. These studies measured total varus-valgus laxity (N=18), separate varus or valgus laxity (N=6), specific medial and lateral compartment joint space (N=10), or combined joint space translation (N=2). The units of measure were degrees of varus/valgus angular excursion or mm of joint space. Some studies applied a force directly to the knee (N=10) while others applied the load away from the knee joint center to create a moment (N=23). Load application method was not reported in 3 selected studies and the magnitudes of applied loading were variable between articles. Several of the devices are listed in Tables 2.2 and 2.3, with the details for each study found in supplementary Table A1 in the Appendix.

Laxity definitions were not consistent between studies and, in some cases, it was not possible to identify when the same subjects were included in multiple manuscripts. Study populations were also not homogeneous by severity of radiographic OA and predominant compartment affected by the disease. Furthermore, the devices used to quantify laxity varied in varus or valgus motion was measured and load applied during testing. Due to these inconsistencies, a meta-analysis was not possible. A qualitative overview of findings for each topic can be seen in Table 2.4.
2.4.2 OA versus Controls

Sixteen studies included varus-valgus laxity of a control group. Of these studies, 11 found a significant increase in some measure of laxity in the OA group compared to controls (Pai, Rymer et al. 1997; Sharma, Lou et al. 1999; Wada, Kawahara et al. 2002; Lewek, Rudolph et al. 2004; Lewek, Ramsey et al. 2005; Lewek, Scholz et al. 2006; Rudolph, Schmitt et al. 2007; Schmitt and Rudolph 2007; Ishii, Noguchi et al. 2009; Miyazaki, Uchida et al. 2012; Kumar, Manal et al. 2013), 3 found no difference (Brage, Draganich et al. 1994; Wada, Imura et al. 1996; Creaby, Wrigley et al. 2010), and 2 did not report any statistics between groups as this was not the focus of those manuscripts (Sharma, Pai et al. 1997; Sharma, Song et al. 2010). In the studies which found increased laxity, 4 reported increased total varus-valgus laxity (Pai, Rymer et al. 1997; Sharma, Lou et al. 1999; Wada, Kawahara et al. 2002; Ishii, Noguchi et al. 2009), 6 had increased medial, but not lateral, compartment laxity in subjects with medial knee OA (Lewek, Rudolph et al. 2004; Lewek, Ramsey et al. 2005; Lewek, Scholz et al. 2006; Rudolph, Schmitt et al. 2007; Schmitt and Rudolph 2007; Kumar, Manal et al. 2013), and one found increased total varus-valgus laxity after stair climbing but not before activity (Miyazaki, Uchida et al. 2012). Quantified varus-valgus angular laxity and joint space laxity results from these 16 studies are shown in Table 2.2 and Table 2.3, respectively.
Table 2.2: Studies reporting angular laxity for OA and control groups. Varus-valgus (VV); medial (Med); Lateral (Lat); Compartment (Compart); Kellgren-Lawrence (KL); Osteoarthritis (OA).

<table>
<thead>
<tr>
<th>Author</th>
<th>Laxity measurement technique</th>
<th>OA Groups</th>
<th>Control Groups</th>
<th>OA Quantified Angular Laxity (deg)</th>
<th>Controls Quantified Angular Laxity (deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brage 1994</td>
<td>Genucom Knee Analysis System 12.2 Nm load</td>
<td>Bilateral OA: n=22 (43 knees) Mild = 10 Moderate = 15 Severe = 18</td>
<td>Age matched: n = 9 (18 knees)</td>
<td>Mild OA = 15 (4.8) Moderate OA = 10.9 (3.9) Severe OA = 10.4 (3.6)</td>
<td>Controls = 11.3 (3)</td>
</tr>
<tr>
<td>Wada 1996</td>
<td>Genucom Knee Analysis System 8 Nm load</td>
<td>Bilateral Medial OA: n = 34 (68 knees) KL Grade 1 = 15 KL Grade 2 = 16 KL Grade 3 = 19 KL Grade 4 = 18</td>
<td>Elderly: n =12 (24 knees)</td>
<td>KL Grade 1 = 11.5 (5.4) KL Grade 2 = 11.9 (4.3) KL Grade 3 = 15.1 (5.1) KL Grade 4 = 15.9 (5.4)</td>
<td>Controls = 12 (3.8)</td>
</tr>
<tr>
<td>Sharma 1999</td>
<td>Custom VV device 12 Nm load</td>
<td>Varied OA: n=164 (328 knees) KL Grade 0/1 = 39 KL Grade 2 = 154 KL Grade 3 = 84 KL Grade 4 = 51</td>
<td>Older: n = 24 Young: n=25</td>
<td>KL Grade 0/1 = 4.9 (0.35) KL Grade 2 = 4.4 (0.16) KL Grade 3 = 5.1 (0.22) KL Grade 4 = 5.7 (0.30)</td>
<td>Elderly controls =3.4 (1.1) young controls =2.9 (1.0)</td>
</tr>
<tr>
<td>Wada 2002</td>
<td>Genucom Knee Analysis System 8 Nm load</td>
<td>Varied Medial OA: n=38 (38 knees) Prior to TKA</td>
<td>Age matched: n=23</td>
<td>OA = 15 (7.9)</td>
<td>Controls = 12 (4.0)</td>
</tr>
<tr>
<td>Ishii 2009</td>
<td>TELOS VV stress radiograph 150 N load</td>
<td>Varied OA: n=102 (120 knees) KL Grade 2 = 1 KL Grade 3 = 30 KL Grade 4 = 89</td>
<td>Controls: n=not reported</td>
<td>Median [25% 75%] Varus laxity = 8 [6,9] Valgus laxity = 0 [0,2]</td>
<td>Median [25% 75%] Varus laxity = 4 [3,4] Valgus laxity = 2 [0.25,3]</td>
</tr>
</tbody>
</table>
Table 2.2 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Laxity measurement technique</th>
<th>OA Groups</th>
<th>Control Groups</th>
<th>OA Quantified Angular Laxity (deg)</th>
<th>Controls Quantified Angular Laxity (deg)</th>
</tr>
</thead>
</table>
| Creaby 2010 | VV modified Kin-Com           | Varied Medial OA: n = 127 (127 knees) | Age matched: n = 32 (32 knees) | Mild OA: Varus = 10.5 (3.6)  
Valgus = 9.6 (3.2)  
Total = 20.1 (6.4)  
Moderate OA: Varus = 9.2 (2.7)  
Valgus = 8.8 (2.4)  
Total = 18.0 (4.7)  
Severe OA: Varus = 8.5 (2.7)  
Valgus = 9.2 (2.9)  
Total = 17.7 (5.4) | Varus = 10.7 (3.7)  
Valgus = 8.4 (3.2)  
Total = 19.2 (6.5) |
| Sharma 2010 | Custom VV device 12 Nm load | Varied OA: n = 950 (1307 knees)  
KL Grade 2 or 3  
Alignment: Neutral: n = 232  
Varus: n=550  
Valgus: n = 168 | Without OA: n = 1752 (2958 knees)  
KL Grade 0 or 1  
Alignment: Neutral: n = 688  
Varus: n=725  
Valgus: n = 339 | Alignment: Neutral = 3.9 (2.5)  
Varus = 3.8 (2.5)  
Valgus = 4.4 (2.6) | Alignment: Neutral = 4.1 (2.6)  
Varus = 3.9 (2.5)  
Valgus = 3.8 (2.7) |
| Miyazaki 2012 | Custom VV Stress Radiograph 22.1 Nm load | Bilateral Medial OA: n = 46 (92 knees)  
KL Grade 2 = 40 knees  
KL Grade 3 = 32 knees  
KL Grade 4 = 20 knees | Age matched: n = 22  
KL Grade 0 = 20 knees  
KL Grade 1 = 24 knees | Pre-exercise  
KL Grade 2 = 6.18 (1.78)  
KL Grade 3/4 = 5.99 (2.81)  
Post-exercise  
KL Grade 2 = 8.85 (2.00)  
KL Grade 3/4 = 8.55 (3.44) | Pre-exercise  
KL Grade 0/1 = 6.98 (1.77)  
Post-exercise  
KL Grade 0/1 = 8.17 (2.18) |
<table>
<thead>
<tr>
<th>Author</th>
<th>Laxity measurement technique</th>
<th>OA Groups</th>
<th>Control Groups</th>
<th>OA Quantified Joint Space Laxity (mm)</th>
<th>Controls Quantified Joint Space Laxity (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pai 1997</td>
<td>Method not reported Load not reported</td>
<td>Bilateral OA: n = 30 (60 knees) (8 male, 22 female) KL Grade 2 = 20 KL Grade 3 = 26 KL Grade 4 = 14</td>
<td>Elderly: n = 29 (58 knees) (12 male, 17 female) KL Grade 0 = 58</td>
<td>Medial and Lateral compartments combined. <em>Bilateral OA:</em> Right = 2.4 (1.8) Left = 2.2 (1.8)</td>
<td>Medial and Lateral compartments combined. <em>Elderly controls:</em> Right = 1.1 (1.1) Left = 0.8 (1.2)</td>
</tr>
<tr>
<td>Sharma 1997</td>
<td>Method not reported Load not reported</td>
<td>Unilateral OA: n = 28 (28 knees) (13 male, 15 female) KL Grade 0 = 6 unaffected KL Grade 1 = 22 unaffected KL Grade 2 = 7 KL Grade 3 = 12 KL Grade 4 = 9</td>
<td>Elderly: n = 29 (58 knees) (13 male, 16 female) KL grade 0 = 29</td>
<td>Medial and Lateral compartments combined. <em>Unilateral OA:</em> Affected limb= 3.1 Unaffected limb= 1.3</td>
<td>Medial and Lateral compartments combined. <em>Elderly controls:</em> Right = 1.3 Left = 0.8</td>
</tr>
<tr>
<td>Lewek 2004</td>
<td>TELOS VV stress radiograph 150 N load</td>
<td>Varied Medial OA: n=12 (6 male, 6 female)</td>
<td>Age matched: n=12 (6 male, 6 female)</td>
<td>Med compart = 5.1 (1.5) Lat compart = 3.6 (1.6)</td>
<td>Med compart = 3.2 (1.0) Lat compart = 4.3 (1.3)</td>
</tr>
</tbody>
</table>

Table 2.3: Studies reporting joint space laxity for OA and control groups. Varus-valgus (VV); medial (VV); Lateral (Lat); Compartment (Compartment); Kellgren-Lawrence (KL): Osteoarthritis (OA).
Table 2.3 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Laxity measurement technique</th>
<th>OA Groups</th>
<th>Control Groups</th>
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<th>Controls Quantified Joint Space Laxity (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewek 2005</td>
<td>TELOS VV stress radiograph 150 N load</td>
<td>Varied Medial OA: n=21 (14 male, 7 female)</td>
<td>Age matched: n=19 (12 male, 7 female)</td>
<td>Med compart = 5.0 (1.7)</td>
<td>Med compart = 3.3 (0.9) Lat compart = 4.1 (1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral Medial OA: n=15 (30 knees) (9 male, 6 female)</td>
<td>Age matched: n=15 (30 knees) (9 male, 6 female)</td>
<td>Med compart = 4.9 (1.8) Lat compart = 3.5 (1.5)</td>
<td>Med compart = 3.2 (0.9) Lat compart = 4.0 (1.4)</td>
</tr>
<tr>
<td>Lewek 2006</td>
<td>TELOS VV stress radiograph 150 N load</td>
<td>Varied Medial OA: n =15 (15 knees) (8 male, 7 female)</td>
<td>Middle aged: n=15 (15 knees) (8 male, 7 female) Older: n=14 (14 knees) (4 male, 10 female)</td>
<td>Med compart = 4.77(1.72) Lat compart = 3.56 (1.65)</td>
<td>Middle age controls: Med compart = 3.12 (0.95) Lat compart = 4.20 (1.27) Older controls: Med compart = 3.05 (0.76) Lat compart = 3.63 (1.34)</td>
</tr>
</tbody>
</table>
Table 2.3 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Laxity measurement technique</th>
<th>OA Groups</th>
<th>Control Groups</th>
<th>OA Quantified Joint Space Laxity (mm)</th>
<th>Controls Quantified Joint Space Laxity (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitt 2007</td>
<td>TELOS VV stress radiograph 150 N load</td>
<td>Varied Medial OA: n=28 (28 knees) (14 male, 14 female) KL Grade 2 = 17 KL Grade 3 = 8 KL Grade 4 = 3</td>
<td>Age matched: n=26 (26 knees) (13 male, 13 female) KL Grade 0 = 26</td>
<td>Mean (95% CI) Med compart = 4.23 (3.57 4.89) Lat compart = 2.77 (2.28 3.27)</td>
<td>Mean (95% CI) Med compart = 2.76 (2.38 3.14) Lat compart = 3.52 (3.04 4.00)</td>
</tr>
<tr>
<td>Kumar 2013</td>
<td>TELOS VV stress radiograph 150 N load</td>
<td>Varied Medial OA: n= 16 (16 knees) (8 male, 8 female) KL &gt;= 2 Controls: n = 12 (12 knees) (6 male, 6 female) KL &lt;= 1</td>
<td>Controls: n = 12 (12 knees) (6 male, 6 female) KL &lt;= 1</td>
<td>Mean (95% CI) Med laxity = 5.5 (4.6, 6.4) Lat laxity = 3.4 (2.7, 4.1)</td>
<td>Mean (95% CI) Med laxity = 3.3 (2.4, 4.2) Lat laxity= 4.7 (3.2, 5.1)</td>
</tr>
</tbody>
</table>
2.4.3 Radiographic OA Severity

Varus-valgus laxity stratified by severity level of OA was reported in 7 articles. Three studies found a significant difference between OA severity levels (Brage, Draganich et al. 1994; Sharma, Lou et al. 1999; van der Esch, Steultjens et al. 2005), while 4 found no difference in laxity by severity level (Tallroth and Lindholm 1987; Wada, Imura et al. 1996; Creaby, Wrigley et al. 2010; Miyazaki, Uchida et al. 2012). In the studies that found a significant result, Brage et al. found knees with mild OA to have more laxity than moderate or severe OA groups, 15 (4.8)° vs. 10.9 (3.9)° and 10.4 (3.6)° respectively (Brage, Draganich et al. 1994). In this study, mild OA was indicated by the presence of osteophytes but less than 50% loss of joint space. Sharma et al. found the opposite relationship between OA severity and laxity. Subjects with Kellgren-Lawrence (KL) Grade 2 exhibited significantly less laxity than subjects with KL Grade 3 or 4, 4.4 (0.16)° vs. 5.1 (0.22)° and 5.7 (0.30)° respectively (Sharma, Lou et al. 1999). van der Esch et al. reported knees with a small amount of joint space narrowing to have more laxity than knees without joint space narrowing (van der Esch, Steultjens et al. 2005).

2.4.4 Frontal Plane Knee Alignment

Four studies measured laxity categorized by frontal plane alignment. Two found significant differences between aligned/malaligned and least/most varus aligned groups (van der Esch, Steultjens et al. 2005; Lim, Hinman et al. 2008), while the other 2 studies did not run any statistical tests comparing alignment groups (Eriksson, Sadr-Azodi et al. 2010; Sharma, Song et al. 2010). van der Esch et al. found that malaligned knees, characterized by greater than 5 degrees of mechanical varus or valgus alignment, had
significantly increased total laxity compared to aligned knees, 9.4 (3.9)° vs. 6.6 (3.9)° respectively (van der Esch, Steultjens et al. 2005). However, no statistical difference was found between the total laxity of the varus malaligned group and the valgus malaligned group (van der Esch, Steultjens et al. 2005). Lim et al. reported that the most varus aligned group had significantly less varus laxity when compared to the group with the least varus alignment, 4.9 (2.0)° vs. 6.5 (2.5)° (Lim, Hinman et al. 2008). Eriksson et al. only tested medial joint space changes in varus knees and lateral joint space changes for valgus knees thus a comparison could not be made (Eriksson, Sadr-Azodi et al. 2010). Sharma et al. reported similar total laxities for subjects with neutral, varus, and valgus alignments, 4.1 (2.6)°, 3.9 (2.5)°, 3.8 (2.7)° respectively, but did not test for any difference between alignment groups (Sharma, Song et al. 2010).

2.4.5 Sex difference

Only one study reported the laxity of males and females with OA separately. van der Esch et al. found females to have significantly more varus-valgus laxity than males, 7.7 (2.9)° vs 4.6 (2.2)° respectively (van der Esch, Steultjens et al. 2007). Another study selected in the systematic review found women to have larger varus-valgus laxity than men in healthy controls (Sharma, Lou et al. 1999).

2.4.6 Clinical and Self-Reported Function

Varus-valgus laxity and a measure of clinical or self-reported function were reported in 16 studies (Sharma, Pai et al. 1997; Sharma, Hayes et al. 1999; Wada, Kawahara et al. 2002; Sharma, Cahue et al. 2003; Sharma, Dunlop et al. 2003; Lewek, Scholz et al. 2006; van der Esch, Steultjens et al. 2006; Rudolph, Schmitt et al. 2007;
Schmitt and Rudolph 2007; Lim, Hinman et al. 2008; Schmitt, Fitzgerald et al. 2008; Schmitt and Rudolph 2008; van der Esch, Steultjens et al. 2008; Holla, van der Leeden et al. 2012; Knoop, van der Leeden et al. 2012; van der Esch, Knoop et al. 2012). Of these studies, only 7 statistically tested for a relationship between varus-valgus laxity and function. Sharma et al. found greater laxity was associated with a weaker relationship between low extremity strength and physical function (Sharma, Hayes et al. 1999). Physical function was characterized in this study by chair stand rate and self-reported activity limitations, which was quantified by the Western Ontario and McMaster Universities Arthritis Index – Physical Function subscale (WOMAC – PF). This study also found greater varus-valgus laxity was modestly associated with worse WOMAC – PF score, but there was no significant association with laxity and chair-stand rate. In a subsequent study which tested over a 3 year period, Sharma et al. found greater varus-valgus laxity significantly increased the likelihood of a poor WOMAC-PF outcome, however varus-valgus laxity was not related to chair stand rate (Sharma, Cahue et al. 2003). van der Esch et al. found greater varus-valgus laxity to be moderately associated with faster 100m walking time and less lower extremity strength (van der Esch, Steultjens et al. 2006), yet no direct association was found between varus-valgus laxity and WOMAC – PF. Laxity and muscle strength both significantly explained the variance in WOMAC –PF in a multivariate regression, with greater laxity and strength improving WOMAC – PF. In a separate multivariate regression, varus-valgus laxity did not contribute to 100m walking time, but the interaction between varus-valgus laxity and muscle strength significantly reduced time needed to complete task. Holla et al. found more laxity to be significantly associated with less activity limitations (WOMAC – PF)
but not significantly associated with the timed stair-climbing test, in a multivariate regression including strength (Holla, van der Leeden et al. 2012). In two separate studies, Schmitt et al. found no significant differences in varus or valgus laxity between groups separated by self-reported perception of instability (Schmitt, Fitzgerald et al. 2008; Schmitt and Rudolph 2008). Knoop et al. also found high varus-valgus joint laxity was not associated with self-reported perception of instability (Knoop, van der Leeden et al. 2012).
<table>
<thead>
<tr>
<th>Topic</th>
<th># Total Studies</th>
<th>Study Findings</th>
<th>Qualitative Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA vs Controls</td>
<td>16</td>
<td>11 studies found increased laxity in OA vs Controls</td>
<td>11/14 studies found a significant difference between groups when tested</td>
</tr>
<tr>
<td>OA Severity</td>
<td>7</td>
<td>3 studies showed differences between OA severities with conflicting results</td>
<td>No consensus could be reached</td>
</tr>
<tr>
<td>Alignment</td>
<td>4</td>
<td>2 studies found altered laxity depending on alignment, but no common finding</td>
<td>No consensus could be reached</td>
</tr>
<tr>
<td>Clinical and Self-Reported Function</td>
<td>16</td>
<td>4 studies found conflicting results between laxity and clinical performance and self-reported activity limitations.</td>
<td>No consensus could be reached with varus-valgus laxity and clinical performance or activity limitations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 studies found laxity was unrelated to perceived instability.</td>
<td>Varus-valgus laxity was unrelated to perceived instability in 3 studies.</td>
</tr>
<tr>
<td>Sex Differences</td>
<td>1</td>
<td>Females found to have more varus-valgus laxity than males</td>
<td>Only one study tested varus-valgus laxity in OA males vs OA females, but females have been found to have higher laxity in other populations and joints</td>
</tr>
</tbody>
</table>

Table 2.4: Overview of systematic review findings with qualitative summary.
2.5 Discussion

The purpose of this study was to systematically review and synthesize the literature measuring varus-valgus laxity in subjects with tibiofemoral OA. Varus-valgus laxity has been hypothesized to influence cartilage health, but given the variance in reported laxity, it is difficult to draw conclusions from the literature as a whole. Specifically, we aimed to identify varus-valgus laxity differences between subjects with OA and controls, by radiographic disease severity, by frontal plane knee alignment, by sex, and if there was a relationship to clinical performance and self-reported function. Reported varus-valgus laxity varied greatly between studies using the 10 separate testing devices, and it is very difficult to compare studies measuring joint space change to those quantifying angular rotation. Large variations were also found when comparing similar devices measuring angular rotation. Paradoxically, total varus-valgus laxity was often smaller using devices which applied larger loads about the knee joint. These results may be due to differences between testing devices or differences in subject populations. Variance in OA severity between studies is likely not the cause of this paradoxical relationship, since this phenomenon of greater laxity with less applied load still exists between similar levels of OA, as demonstrated on Table 2.2. The following considerations have been previously identified as necessary to improve laxity measurement and reduce variation compared to the clinical examination: measure at a consistent knee flexion angle; reduce soft tissue artifact; reduce muscular guarding during manipulation; and accurately measure the applied load and the tibiofemoral motion (Markolf, Mensch et al. 1976; Cushnaghan, Cooper et al. 1990; Noyes, Cummings et al.)
1991; Sharma, Lou et al. 1999). Of these considerations, there do not appear to be drastic differences or shortcomings between testing devices that could explain the reported variations. A “gold standard” of laxity measurement is necessary to validate devices and potentially allow for meta-analyses.

Subjects with OA exhibited some measure of increased frontal plane laxity compared to controls, in 11 of the 14 papers that statistically tested for a difference. Across the comparisons made in the 36 systematically selected studies, this finding was the most consistent. The majority of studies were not designed in a manner to distinguish if altered varus-valgus laxity leads to OA, but altered laxity was present in subjects with OA. This finding lends support to the theory that altered varus-valgus laxity is a component of OA and more research is needed to identify if cartilage degeneration is due to a change in joint contact patterns resulting from altered laxity (Andriacchi, Mundermann et al. 2004; Chaudhari, Briant et al. 2008).

In the 7 articles that reported laxity based on severity of OA the results and conclusions were conflicted. Brage et al. and van der Esch et al. found knees with more severe radiographic OA exhibited less laxity (Brage, Draganich et al. 1994; van der Esch, Steultjens et al. 2005), while Sharma et al. found increasing laxity with increasing disease severity, after an initial decrease in laxity from KL Grade 0/1 to KL Grade 2 (Sharma, Lou et al. 1999). The formation of osteophytes tend to stabilize the knee (Pottenger, Phillips et al. 1990; Jenny, Boeri et al. 2008) and radiographic scales use combinations of osteophyte formation, joint space narrowing, and bone deformity to characterize severity of OA. The increased laxity seen in subjects with early radiographic signs of OA suggests
that osteoarthritic changes may develop after an initial increase in laxity, in an effort to control excessive knee joint motion.

In subjects with severe OA, laxity is hypothesized to increase due to cartilage degeneration and bone erosion. This may create “pseudo-laxity” by reducing the distance between ligament attachment points (Kolstad, Sahlstedt et al. 1980; Lewek, Rudolph et al. 2004) and lead to greater measured laxity in subjects with severe OA. However the trend of increased laxity in subjects with severe OA was only found in 1 of the 3 studies. The findings identified in this systematic review are not consistent and additional research is necessary to clarify the relationship between laxity and OA severity.

Static alignment changes may result from combined bone erosion and ligament adaptation, which could lead to unbalanced laxity in the varus and valgus directions. The two studies that statistically tested for differences in laxity by alignment found conflicting results (van der Esch, Steultjens et al. 2005; Lim, Hinman et al. 2008). These studies did not use the same definitions for malalignment and laxity measurement was varied, so it is difficult to compare results and form a consensus. Lim et al. reported that the most varus aligned group had significantly less varus laxity when compared to the group with the least varus alignment (Lim, Hinman et al. 2008), while van der Esch found no statistical difference was found between the total laxity of the varus malaligned group and the valgus malaligned group (van der Esch, Steultjens et al. 2005). The separation of varus and valgus laxity may be necessary when including subjects with predominantly medial or lateral knee OA in the same analysis. Alignment changes are often accompanied by increased disease severity in the medial or lateral compartment; however a laxity difference by predominant knee compartment with OA was not statistically tested by any
study in this systematic review. Frontal plane malalignment has been shown to be a driving factor in osteoarthritis incidence and progression (Sharma, Song et al. 2010), which is likely due to larger frontal plane moments (Sharma, Hurwitz et al. 1998; Baliunas, Hurwitz et al. 2002; Hurwitz, Ryals et al. 2002; Andriacchi, Mundermann et al. 2004). Consistently large frontal plane moments may cause a progressive change in medial and lateral collateral ligament lengths, due to the increased internal forces necessary to balance the external moments (Andriacchi 1994). This change in collateral ligament lengths, depending on if the malalignment was varus or valgus, may affect the varus and valgus knee laxity differently but this relationship has yet to be established.

Females exhibited higher varus-valgus laxity compared to men in both OA subjects (van der Esch, Steultjens et al. 2007) and controls (Sharma, Lou et al. 1999). While not part of this review, several studies indicate that females also have increased generalized laxity throughout all joints in the body compared to males (Larsson, Baum et al. 1987; Silman, Day et al. 1987; Jansson, Saartok et al. 2004; Quatman, Ford et al. 2008), which may be related to hormonal status (Wojtys, Huston et al. 2002). Hypermobility has been associated with OA (Bird, Tribe et al. 1978; Jonsson and Valtysdottir 1995; Jonsson, Valtysdottir et al. 1996) and females have higher rates of hypermobility (Scher, Owens et al. 2010) and knee OA (Srikanth, Fryer et al. 2005). Increased joint laxity may be an unmodifiable risk factor for women but more research is needed to rule out other sex differences as the cause of increased OA prevalence in females.

Function was quantified alongside varus-valgus laxity using clinical performance measures, chair-stand rate and 100m walk test, and self-reported function, with the
WOMAC – PF and perception of instability. Clinical performance measures were tested in four studies (Sharma, Hayes et al. 1999; Sharma, Cahue et al. 2003; van der Esch, Steultjens et al. 2006; Holla, van der Leeden et al. 2012), but greater laxity was only significantly related to faster walking speed in one (van der Esch, Steultjens et al. 2006).

Self-reported activity limitations were also tested in these four studies, each resulting in a significant association with laxity (Sharma, Hayes et al. 1999; Sharma, Cahue et al. 2003; van der Esch, Steultjens et al. 2006; Holla, van der Leeden et al. 2012), however the results were conflicting. Sharma et al. found more activity limitations in two studies (Sharma, Hayes et al. 1999; Sharma, Cahue et al. 2003) while van der Esch et al. and Holla et al. found reduced activity limitations in participants with greater laxity (van der Esch, Steultjens et al. 2006; Holla, van der Leeden et al. 2012). These contrary results may be due to differences in subject populations, with one group based in the United States and the other in the Netherlands, but the influence of laxity testing device may also have an impact. van der Esch et al. (van der Esch, Steultjens et al. 2006) designed their laxity testing device from Sharma et al. (Sharma, Lou et al. 1999), but used a smaller magnitude of frontal plane knee moment during testing, 7.7 Nm vs 12 Nm. Even with a decrease in applied load, larger mean varus-valgus laxity was reported with this device compared to the two Sharma et al. manuscripts. A device validation protocol would be necessary to identify the source of this variation. The only consistent finding was between varus-valgus laxity and self-reported instability, in which 3 studies found no significant relationship (Schmitt, Fitzgerald et al. 2008; Schmitt and Rudolph 2008; Knoop, van der Leeden et al. 2012).
Limitations in current testing procedures have been identified during this systematic review and recommendations are listed in order to improve varus-valgus laxity measurement and reporting. The majority of varus-valgus laxity measurement techniques use a single applied load level to calculate varus and valgus laxity. The degree of laxity measured is inherently dependent on the load applied to the knee joint, however the lack of a standard for applied load makes it difficult to compare or consolidate data across studies in order to perform any meta-analyses. A more detailed assessment of joint stability can be found by measuring applied force and relative tibiofemoral kinematics on continuous scales (Markolf, Mensch et al. 1976; Siston, Maack et al. 2012). With this approach, load-displacement curves can be plotted and varus and valgus laxity can be found at any selected load level below that maximally applied. The increased radiation dose necessary to employ this technique when measuring joint space width using fluoroscopy is a major drawback, but for angular rotation measures of laxity it involves no additional risk to subjects. This method has the ability to characterize knee stability at multiple load points, and at specific varus or valgus knee angles in order to identify how joint stiffness changes with displacement. This technique would also allow for comparisons and potential meta-analyses of laxity quantified at any load level below the maximum load applied.

Muscular guarding during varus-valgus laxity examination has been identified as one of the major sources of variation during a physical examination in subjects with OA (Markolf, Mensch et al. 1976; Sharma, Hayes et al. 1999; Sharma, Lou et al. 1999; Creaby, Wrigley et al. 2010). Despite these concerns, attempts to control muscle activity were only mentioned in 6 of the included studies (Brage, Draganich et al. 1994; Sharma,
Hayes et al. 1999; Sharma, Lou et al. 1999; Lim, Hinman et al. 2008; Ishii, Noguchi et al. 2009; Creaby, Wrigley et al. 2010). Two studies state that the testing device was designed to reduce incomplete muscle relaxation, but do not go into detail on how this was evaluated (Sharma, Hayes et al. 1999; Sharma, Lou et al. 1999). Three studies mention instructing the subject to relax completely during testing (Brage, Draganich et al. 1994; Ishii, Noguchi et al. 2009; Creaby, Wrigley et al. 2010), but only one study attempted to measure the amount of guarding (Lim, Hinman et al. 2008). Lim et al identified irregular traces of varus-valgus angular displacement in real-time and repeated tests when they occurred. This article also suggests electromyography of muscles crossing the knee joint as a potential quality control measure during laxity testing, but this was not measured in any of the selected studies. It is possible that subjects with increased pain or higher perception of instability may guard their knees by co-contracting muscles more during testing, therefore making it difficult to gauge true passive laxity. Increased muscular co-contraction has been seen during dynamic motion in subjects with higher perceived instability (Schmitt and Rudolph 2008) and similar co-contraction could be stabilizing the knee and reducing the magnitude of measured varus-valgus laxity.

Anesthetizing subjects before measurement is another potential solution which completely eliminates muscular guarding, although this adds significant complication to the measurement procedure. Subjects were under general anesthesia in 3 studies where varus-valgus laxity was measured in osteoarthritic knees prior to joint arthroplasty (Pottenger, Phillips et al. 1990; Siston, Goodman et al. 2007; Jenny, Boeri et al. 2008). Anterior knee laxity has been found to increase during unconscious measurement in subjects following anterior cruciate ligament disruption (Highgenboten, Jackson et al. 1999; Sharma, Lou et al. 1999; Lim, Hinman et al. 2008; Ishii, Noguchi et al. 2009; Creaby, Wrigley et al. 2010).
1992), and it is plausible that varus-valgus laxity would increase as well when muscular forces crossing the knee are completely eliminated. While recording muscle activation would provide an estimate of muscular guarding, anesthetizing subjects may be the only way to eliminate muscular guarding during varus-valgus laxity testing.

All varus-valgus laxity research to date has measured laxity at a single time point in subjects with OA. Prospective studies are needed to identify how laxity changes with OA progression. This information is critical to identifying what compensations are necessary to function and how those affect disease development. This could potentially lead to alternative treatment strategies, such as surgical ligament balancing or bracing to manage patients with OA based on individualized laxity and biomechanical analysis.

Limitations of this review include those inherent in the reported studies, which were primarily observational in nature. Laxity definitions were not consistent between studies and, in some cases, it was not possible to identify when the same subjects were included in multiple manuscripts. Subject populations and measurement devices were also not homogeneous between studies. OA classification scales varied and the predominant knee compartment with OA was not consistently reported, which added to the difficulty merging subjects with similar disease states. The etiology of OA, whether traumatic or degenerative in nature, was not specified in the included studies and therefore could not be assessed. Lastly, there is potential for selection bias due to excluding studies that were not published in English, although subject populations from multiple continents are included in this review.
2.6 Conclusions

Varus-valgus laxity was significantly larger in subjects with OA compared to controls in a majority of studies, and no study found laxity to be larger in controls. Varus-valgus laxity of the knee was investigated in subjects with osteoarthritis and varying degrees of frontal plane alignment, disease severity, clinical performance and self-reported function but no consensus finding could be identified. Females appear to have more varus-valgus laxity than males. Large variances in varus-valgus laxity were found between studies and this may be due to differences in testing device. Identifying standardized ways to measure load and varus-valgus displacement as continuous variables, along with controlling for muscular guarding, will help characterize all aspects of knee joint stability. This could potentially lead to meta-analyses and identify which aspects of knee joint stability are related to the incidence and progression of OA.
Chapter 3: Passive varus-valgus knee laxity and its relationship with varus-valgus knee excursion during gait, clinical performance, perceived instability and function in patients with severe osteoarthritis
3.1 Abstract

Objective: Increased varus-valgus laxity has been reported in participants with knee OA compared to controls. However, the majority of previous investigations do not report truly passive joint laxity, as their tests have been performed on conscious participants who may be guarding against motion with muscle contraction during laxity evaluation. The purpose of this study was to investigate how a measure of passive knee laxity, recorded when the participant is under anesthesia, is related to varus-valgus excursion during gait, clinical measures of performance, perceived instability and self-reported function in participants with severe OA.

Design: We assessed passive varus-valgus knee laxity in 29 participants (30 knees) with severe OA. Subjects also completed gait analysis, clinical assessment of performance (six-minute walk: 6MW, stair climbing test: SCT, isometric knee strength), and self-reported evaluations of function (perceived instability, Knee Injury and Osteoarthritis Outcome Score: KOOS).

Results: Greater varus-valgus laxity was significantly associated with more varus-valgus excursion during gait ($R^2=0.34$, $p=0.002$). Significant associations observed between larger laxity and greater isometric knee extension strength ($p=0.014$), farther 6MW distance ($p=0.033$) and better SCT time ($p=0.046$). No relationship was observed between passive varus-valgus laxity and isometric knee flexion strength, perceived instability, or any of the KOOS subscales.

Conclusion: Varus-valgus excursion during gait was positively associated with passive varus-valgus laxity. The observed association between laxity and gait is consistent with
previously described theories of altered gait kinematics and the pathomechanics of knee OA. Passive varus-valgus laxity was also associated with better scores in clinical performance measures.

3.2 Introduction

Over 50 million adults in the United States report doctor-diagnosed osteoarthritis (OA), which includes almost 50% of all people over the age of 65. (Barbour, Helmick et al. 2013) Knee OA is regularly characterized by pain, a loss of cartilage, formation of osteophytes and a reduction in joint space (Kellgren and Lawrence 1957; Hurwitz, Sharma et al. 1999). Clinical symptoms associated with severe knee OA are muscle weakness (Messier, Loeser et al. 1992; Lewek, Rudolph et al. 2004), perceived instability(Fitzgerald, Piva et al. 2004; Schmitt, Fitzgerald et al. 2008), and increased knee pain (Hurwitz, Sharma et al. 1999); these symptoms contribute to reduced function(Hurley, Scott et al. 1997). Increased varus-valgus laxity has been reported in individuals with knee OA compared to controls (Pai, Rymer et al. 1997; Sharma, Lou et al. 1999; Wada, Kawahara et al. 2002; Lewek, Rudolph et al. 2004; Rudolph, Schmitt et al. 2007; Schmitt and Rudolph 2007; Ishii, Noguchi et al. 2009; Kumar, Manal et al. 2013). Altered knee stability and kinematics have been hypothesized as a cause of OA initiation and progression; however there are no current treatments to stop the progression of knee OA.

Knee joint laxity is a quantitative measure of knee stability which measures the passive tibiofemoral motion under load. Increased laxity may result in greater motion between articular surfaces of the femur and tibia, which could increase shear stress and
alter articular loading patterns (Andriacchi, Mundermann et al. 2004). These changes may result in the cartilage being loaded in ways it is not adapted to withstand and cause irreversible cartilage damage. Alternately, the loss of joint space from damaged cartilage could reduce the distance between ligament attachment points and increase laxity as a consequence. Along with the potential for passive varus-valgus knee laxity to alter knee kinematics during gait and initiate a cycle of cartilage degeneration and OA, laxity may also directly influence clinical and self-reported function. van der Esch et al. found greater varus-valgus laxity to be moderately associated with faster 100m walking time and less lower extremity strength (van der Esch, Steultjens et al. 2006), yet no direct association was found between varus-valgus laxity and self-reported physical function. Alternately, Sharma et al. found greater varus-valgus laxity significantly increased the likelihood of a poor WOMAC-PF outcome, however varus-valgus laxity was not related to chair stand rate (Sharma, Cahue et al. 2003). However, the majority of previous investigations do not report truly passive joint laxity, as their tests have been performed on conscious participants. These study participants may be guarding against motion with muscle contraction during laxity evaluation (Markolf, Mensch et al. 1976) (Lim, Hinman et al. 2008) (Sharma, Lou et al. 1999), which could influence the results on the impact of varus-valgus laxity on function.

Identifying the factors which are associated with degraded function in people with severe OA is an essential step in understanding the mechanisms underlying knee function. Quantifying strictly passive varus-valgus laxity may give insight into the effect of knee function and assist in the development of novel treatment strategies to improve function, slow disease progression, and postpone joint replacement. The purpose of this
study was to investigate how passive varus-valgus knee laxity, recorded when the participant is under anesthesia, is related to varus-valgus excursion during gait, clinical measures of performance, perceived instability and self-reported function in participants with severe OA. Specifically, we hypothesized that larger passive varus-valgus knee laxity would be associated with more varus-valgus excursion during the weight acceptance phase of gait, poorer clinical performance, an greater perception of instability and reduced self-reported function.

3.3 Methods

3.3.1 Participants

Thirty three participants (34 knees) were recruited by The Ohio State University orthopaedic surgeons and participated in this study after providing IRB approved consent. Participants were diagnosed as having predominantly medial compartment tibiofemoral osteoarthritis and were scheduled for primary TKA within the following eight weeks. The exclusion criteria for this study were as follows: Body Mass Index (BMI) > 45; inability to walk 10 meters without an assistive device; surgeon diagnosed predominantly lateral compartment OA; or revision TKA. Four participants were dropped from the study due to the following reasons: sterilization error prohibited intra-operative data collection (n=2); technical difficulties during pre-operative motion analysis testing resulted in a lack of available data (n=2). The demographics of the twenty nine included participants (30 knees) are shown in Table 3.1. Gait, clinical assessments and self-report surveys were administered 25.5 ± 23.9 days prior to surgery. Varus-valgus laxity was measured intra-operatively on the osteoarthritic joint before any bone cuts were made.
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>10</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Age, years</td>
<td>58.6 ± 8.7</td>
<td>58.7 ± 7.0</td>
<td>58.6 ± 7.46</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.79 ± 0.06</td>
<td>1.61 ± 0.06</td>
<td>1.67 ± 0.10</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>100.9 ± 16.7</td>
<td>88.9 ± 12.9</td>
<td>93.0 ± 15.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.6 ± 4.8</td>
<td>34.2 ± 4.3</td>
<td>33.3 ± 4.6</td>
</tr>
<tr>
<td>Number of knees analyzed</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Involved limb, no. (right/left)</td>
<td>6 / 4</td>
<td>7 / 13</td>
<td>13 / 17</td>
</tr>
<tr>
<td>KL grade, no. (I / II / III / IV)</td>
<td>0 / 0 / 4 / 6</td>
<td>0 / 2 / 13 / 5</td>
<td>0 / 2 / 17 / 11</td>
</tr>
</tbody>
</table>

Table 3.1: Characteristics of participants with knee osteoarthritis. Values are the mean ± standard deviation unless otherwise noted. Body Mass Index (BMI); Kellgren-Lawrence (KL).

3.3.2 Motion Analysis of Gait

Marker data were collected at 150Hz using 10 Vicon MX-F40 cameras [Vicon; Oxford, UK] and filtered using a 4th order Butterworth filter at 6Hz. Ground reaction forces were recorded at 1500Hz from Bertec 4060-10 force plates [Bertec Corp; Columbus, Ohio] and used to identify heel contact and toe-off time points in the gait cycle. A modified point-cluster technique marker set (Andriacchi, Alexander et al. 1998) (Jamison, Pan et al. 2012) was used with additional iliac crest and upper body Plug-In Gait markers (Figure 3.1A). A functional hip joint center was estimated using the markers on the thigh during a star-arc motion. (Camomilla, Cereatti et al. 2006) Custom Bodybuilder [Vicon Motion Systems, Ltd., Oxford, UK] and MATLAB [Mathworks, Inc., Natick, MA] scripts calculated full body kinematics (Figure 3.1B and 3.1C).
Figure 3.1: A) Movement analysis was completed using a modified point-cluster marker set. B) A static calibration pose estimated the location of the femur and tibia utilizing a functional hip joint center and anatomical markers placed on the following bony landmarks; medial and lateral femoral epicondyles, medial and lateral tibial plateaus, and medial and lateral malleoli. C) Tracking marker clusters on the thigh and shank were used to quantify joint kinematics during dynamic activity. Varus-valgus excursion was calculated as the difference between peak varus and valgus knee angle during the weight acceptance phase of gait.

Frontal plane excursion was calculated as the difference between peak knee varus and peak knee valgus angle during the weight acceptance phase of gait. Weight acceptance was defined as the time period between initial contact and peak knee flexion during stance phase of the involved limb. Ensemble averages for each variable were calculated over four trials of gait at a self-selected speed.

3.3.3 Clinical Assessment The primary clinical performance measures were isometric knee strength, the six-minute walk test (Enright 2003; Terwee, Mokkink et al. 2006) (6MW) and the timed stair climbing test (Van Nostrand, Kjelsberg et al. 1968; Rejeski, Ettinger et al. 1995) (SCT). Knee extension and flexion strength were quantified
with a Biodex System 3 dynamometer [Biodex Medical Systems; Shirley, NY] during a maximal voluntary isometric contraction (MVIC). Each participant was seated upright with the involved limb at 60 degrees of knee flexion. Two maximal contractions for each knee extension and knee flexion were separated by 30 seconds. The maximal torque produced during extension and flexion were recorded and normalized by each participant’s mass (Nm/kg). 6MW was measured as the distance a participant could walk around a 90 meter indoor track in the six minute time limit (Enright 2003; Enright, McBurnie et al. 2003). Participants were instructed to walk as far as possible in a safe manner. They were encouraged to not take any breaks or use a walking aid unless necessary to complete the test. SCT was measured as the time necessary to ascend and descend a 12 step staircase (Ettinger, Burns et al. 1997; Rejeski, Brawley et al. 1997; Almeida, Schroeder et al. 2010). The participants were instructed to complete the task as quickly as possible in a safe manner. They were encouraged to not use the handrail unless necessary to complete the test.

Tibiofemoral radiographic severity was assigned using the Kellgren-Lawrence (KL) grading system (Kellgren and Lawrence 1957). Two fellowship-trained, musculoskeletal radiologists (JP & AR) graded each participant by consensus. All radiographs were obtained in the same unit and consisted of bilateral anterior, bilateral posterior, lateral, and axial patellar views.

Standing, frontal-plane knee alignment was found during the motion analysis calibration trial. An estimated functional hip joint center(Camomilla, Cereatti et al. 2006), the midpoint of markers on medial and lateral femoral epicondyles markers and the midpoint of markers on the medial and lateral malleoli were used to estimate frontal
plane mechanical knee alignment. Positive values indicate a varus knee angle. Similar methods have shown good correlation with standing radiographic alignment ($R^2=0.83$, $p<0.0001$)(Blazek, Asay et al. 2013). Self-selected gait speed was calculated in the middle of the 10m walkway during motion analysis from the mean velocity of markers on the pelvis.

### 3.3.4 Self-Reported Evaluations

Participants’ perceived knee instability was assessed from a question in the Knee Outcome Survey – Activities of Daily Living Scale(Irrgang, Snyder-Mackler et al. 1998). The question read “To what degree does giving way, buckling, or shifting of the knee affect your daily activity?” and was scored on a 6 point scale. The designated responses and associated scores are as follows: 0 indicated that instability prevented all activity; 1 indicated that instability affected activity severely; 2 indicated that instability affected activity moderately; 3 indicated that instability affected activity slightly; 4 indicated that instability did not affect activity; and a score of 5 indicated no instability.

Reported function was assessed from four subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos Roos et al. 1998). These subscales included questions focused on pain, symptoms, activities of daily living and knee-related quality of life. The subscale related to sport and recreation was collected for each participant, however the questions were not applicable to the majority of patients electing for TKA and therefore the score was not reported. Standardized answers to each question are provided and assigned a score from 0 to 4. These scores are normalized for each
subscale, with a normalized score of 0 indicating extreme symptoms and 100 indicating no symptoms.

3.3.5 Intra-operative Data Collection

To characterize passive knee joint laxity under anesthesia we quantified the load-displacement relationship of the knee in the frontal plane. Joint laxity of the native osteoarthritic knee was assessed with minimal disruption to the joint structures by performing the measurements after exposing the distal femur and proximal tibia but prior to any bone, ligamentous, or meniscal alterations associated with a standard total knee arthroplasty. Kinematics were collected intra-operatively utilizing a validated custom navigation system during the total knee arthroplasty procedure (Siston, Giori et al. 2006) (Siston, Maack et al. 2012). The knee was opened with a standard medial para-patellar approach and the tibiofemoral joint was exposed. Retro-reflective marker clusters were rigidly attached to the distal femur and proximal tibia with cortical bone screws. The hip joint center was estimated from the femoral cluster motion during hip circumduction (Siston and Delp 2006). Anatomical landmarks on the femur and tibia were located using a stylus integrated with the motion capture system by the orthopaedic surgeon. The anatomical coordinate system of the femur was defined using the hip joint center, anterior-lateral attachment point of the posterior cruciate ligament, and the medial and lateral epicondyles (Siston, Giori et al. 2006). The anatomical coordinate system of the tibia was defined using the midpoint of the tibia spine, the most medial and lateral points on the tibial plateau, and the most medial and lateral aspects of the malleoli (Siston, Giori et al. 2006). The custom surgical navigation system recorded relative tibiofemoral
kinematics from the motion of the marker clusters and their relationship to the previously defined anatomical coordinate systems.

The orthopaedic surgeon applied loads to a modified Alvarado boot, which rested in a low-friction track of a custom knee stability testing device (Siston, Maack et al. 2012), using a force application handle (Figure 3.2). The handle was instrumented with a tension-compression load cell and linked to the custom surgical navigation system. The orthopaedic surgeon alternately applied load in the varus and valgus direction until firm end points in motion were reached with the knee fully extended, while manually restricting motion of the femur. The maximal load was determined on an individual basis to ensure patient safety. Varus and valgus moments were calculated about the previously defined knee joint center, using the data from the load cell and the surgical navigation system. This procedure was repeated until a minimum of 3 trials were completed, each with an applied varus and valgus load. Continuous measurement of tibiofemoral kinematics and load were collected.
Figure 3.2: Passive varus-valgus testing completed intra-operatively with a custom knee stability device and surgical navigation system. The orthopaedic surgeon applies load in the varus and valgus direction with an instrumented handle, while manually restricting motion of the femur. Marker clusters screwed into the femur and tibia track kinematics with a motion capture camera.

A varus-valgus load-displacement curve was calculated for three trials of alternating varus and valgus load (Figure 3.3). A third order polynomial was fit to the raw data for each trial. Laxity was calculated as the difference in varus-valgus knee angle when the knee was loaded with 10 Nm of varus and 10 Nm of valgus torque. Each participant’s overall varus-valgus laxity is determined from the average of these three trials. Figure 3.3 illustrates how laxity was defined by presenting the recorded load-displacement data for a single trial of one participant. This participant’s varus-valgus excursion was not centered on mechanical zero alignment, which can be expected in participants with predominantly medial compartment OA and a varus deformity.
Figure 3.3: Example case of intra-operative load-displacement data and varus-valgus laxity calculation. Moment applied by the surgeon (Y axis) and frontal plane knee angle (X axis) were measured with a surgical navigation system and knee stability device. A 3rd order polynomial was then fit to the raw data for each trial. Varus-valgus laxity was calculated as the angular difference between a 10 Nm varus and 10 Nm valgus applied load. Each participant’s overall varus-valgus laxity was the average of the laxity calculated in three intra-operative load-displacement trials. Varus-valgus laxity is generally not centered on zero degrees, due to the varus deformity observed in our participant population.

3.3.6 Statistics

Male and female participants were analyzed together in order to maintain statistical power with our skewed sex distribution. Pairwise correlations were used to describe the relationship between varus-valgus laxity and the gait, clinical and self-
reported variables of interest. Pearson correlations were used to test for associations between variables that were normally distributed as collected or after log transformation (e.g. SCT). Spearman correlations were used between variables that were categorical or could not be transformed to fit normality constraints. A general linear regression model was used in conjunction with the direct correlations to allow for the investigation of covariates where appropriate. A p-value alpha = 0.05 was chosen to indicate statistical significance.

3.4 Results

The means and standard deviations for the variables of interest in the 30 knees (29 participants) are summarized in Table 3.2. Correlation coefficients are shown to identify the relationship between varus-valgus laxity and the gait, clinical and self-reported variables. SCT time was transformed using the natural logarithm to fit normality constraints. Spearman correlations were used for testing the association of varus-valgus laxity with perceived instability and radiographic OA severity, due to the categorical and non-normal distribution of these variables.
<table>
<thead>
<tr>
<th></th>
<th>Mean ± Standard Deviation</th>
<th>Correlation Coefficient</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Intra-operative knee stability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varus-valgus laxity, deg</td>
<td>5.0 ± 2.6</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Gait analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varus-valgus excursion, deg</td>
<td>5.2 ± 2.1</td>
<td>0.582</td>
<td>0.001***</td>
</tr>
<tr>
<td><strong>Clinical measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA radiographic severity (KL grade)</td>
<td>3.3 ± 0.6</td>
<td>0.012†</td>
<td>0.948</td>
</tr>
<tr>
<td>Standing alignment, deg (+ varus)</td>
<td>5.4 ± 3.5</td>
<td>-0.100</td>
<td>0.600</td>
</tr>
<tr>
<td>Self-selected gait speed, m/s</td>
<td>1.0 ± 0.2</td>
<td>0.364</td>
<td>0.048*</td>
</tr>
<tr>
<td>Knee ext strength, Nm/kg</td>
<td>1.0 ± 0.5</td>
<td>0.444</td>
<td>0.014*</td>
</tr>
<tr>
<td>Knee flex strength, Nm/kg</td>
<td>0.6 ± 0.3</td>
<td>0.225</td>
<td>0.233</td>
</tr>
<tr>
<td>6 minute walk, m</td>
<td>385.8 ± 90.2</td>
<td>0.389</td>
<td>0.033*</td>
</tr>
<tr>
<td>Stair climbing test, sec</td>
<td>24.7 ± 12.7</td>
<td>-0.367‡</td>
<td>0.046*</td>
</tr>
<tr>
<td><strong>Self-reported evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived instability, no.</td>
<td>2.3 ± 1.3</td>
<td>0.113†</td>
<td>0.558</td>
</tr>
<tr>
<td>KOOS pain</td>
<td>47.1 ± 20.2</td>
<td>0.099</td>
<td>0.604</td>
</tr>
<tr>
<td>KOOS symptoms</td>
<td>42.5 ± 9.2</td>
<td>-0.219</td>
<td>0.246</td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>56.1 ± 23.0</td>
<td>0.079</td>
<td>0.678</td>
</tr>
<tr>
<td>KOOS QOL</td>
<td>24.7 ± 20.2</td>
<td>-0.015</td>
<td>0.938</td>
</tr>
</tbody>
</table>

Table 3.2: Results for variables of interest and association to passive varus-valgus laxity. Osteoarthritis (OA), Kellgren-Lawrence (KL), extension (ext), flexion (flex), Knee injury and Osteoarthritis Outcome Score (KOOS), Activities of Daily Living (ADL), Quality of Life (QOL). †indicates Spearman correlation. ‡indicates data was transformed. Asterisks indicate significant association *(p<0.05) **(p<0.01) ***(p<0.001)
3.4.1 Gait Analysis

Greater varus-valgus laxity correlated with more varus-valgus excursion during gait ($R^2=0.34$, $p=0.001$). A scatterplot of this result can be seen below in Figure 3.4, with experimental male data shown as blue crosses and female data shown as red squares. This result confirms our hypothesis that greater passive laxity would result in larger varus-valgus motion during gait in participants with severe OA.

Figure 3.4: Varus-valgus laxity was significantly associated with varus-valgus excursion during the weight acceptance phase of gait ($R^2=0.34$, $p=0.001$)
3.4.2 Clinical Measures

A significant association was observed between larger varus-valgus laxity and greater normalized isometric knee extension strength (Figure 3.5 & Table 3.2. R²=0.20, p=0.014). In contrast, there was no relationship between normalized isometric knee flexion strength and varus-valgus laxity in this cohort (Table 3.2). Significant associations were also observed between larger varus-valgus laxity and farther 6MW distance (R²=0.15, p=0.033) and faster SCT time (R²=0.13, p=0.046). To further investigate the relationship between varus-valgus laxity and clinical performance measures, we executed a linear regression analysis with varus-valgus laxity as the response and 6MW, SCT (log transformed), knee extension strength and knee flexion strength as predictors. Only knee extension strength showed a trend with varus-valgus laxity, (R²=0.29, adj R² = 0.17, p=0.053). Greater varus-valgus laxity and faster self-selected gait speed were significantly correlated (R²= 0.13, p=0.048), although laxity and radiographic severity and standing alignment were unrelated. Self-selected gait speed, radiographic severity and standing alignment were not designated as a primary clinical performance measure a priori, and therefore not included in our multiple linear regression of clinical performance measures.
Figure 3.5: Scatter plot of the association between greater varus-valgus laxity and more knee extension strength ($R^2=0.20$, $p=0.014$)

3.4.3 Perceived Instability and Self-Reported Function

Perceived instability was not normally distributed, so a Spearman correlation was used to test for an association. No relationship was observed between varus-valgus laxity and perceived instability (Table 3.2 $R^2=0.03$, $p=0.385$). There was also no relationship observed between laxity and any of the four KOOS subscales (Table 3.2).
3.5 Discussion

The aims of this study were to identify how passive varus-valgus knee laxity associated with varus-valgus excursion during gait, clinical performance, instability and self-reported function in participants with severe medial knee OA. Varus-valgus excursion during gait was the only variable that was significantly associated with passive varus-valgus laxity. This relationship conflicts with previous findings by van der Esch et al., which found no correlation between varus-valgus laxity and varus-valgus excursion during the loading response phase of gait (van der Esch, Steultjens et al. 2008). Even with comparatively less laxity measured in the current study, 5.0 (2.6) degrees vs. 7.58 (3.25) degrees, we recorded larger varus-valgus excursion during gait, 5.2 (2.1) degrees vs. 3.24 (1.73) degrees. These contradictory findings may be due to key differences in the OA severity and laxity testing methodology between studies. Our participants all had severe OA and were awaiting a TKA, while a large percentage of the knees studied by van der Esch (67%) were diagnosed with mild OA (KL grade 1). We measured laxity at a 10 Nm varus and valgus knee moment while the subjects were anesthetized, compared to 7.7 Nm and conscious in van der Esch’s study. We also performed our knee laxity assessment at full extension while van der Esch et al. measured laxity at 20 degrees of knee flexion. Previous work has found varus-valgus laxity to increase with increasing flexion angle (Markolf, Mensch et al. 1976), so this could be influencing the magnitude of varus-valgus laxity reported. One reason we quantified passive laxity at full extension is because the largest loads during gait are seen during heel strike, when the knee is near full extension. We believe it is important to characterize the mechanical properties of the knee when it is
loaded most, as this will likely influence cartilage degeneration to the greatest degree. Surgeons also typically assess knee stability in full extension, so laxity testing of the knee in this position quantified their subjective assessment. Our device also accounted for the three dimensional rotations of the knee during laxity testing and calculated the applied moment using the anatomical coordinate system of the femur and tibia (Siston, Maack et al. 2012). Other laxity measurement devices that do not use three dimensional motion capture and anatomical defined coordinate systems have the potential for artifact when calculating the applied varus or valgus load. Differences in OA demographics, knee flexion angle during laxity testing, and 3D laxity calculations during measurement may explain why our varus-valgus laxity magnitude was smaller, even while varus-valgus excursion during gait was larger.

It has been theorized that altered joint laxity may increase shear stress on cartilage and shift joint contact patterns during dynamic activity (Andriacchi, Mundermann et al. 2004). Our observation that greater laxity is associated with larger varus-valgus excursion is consistent with this theory. While we did not explicitly measure knee contact patterns, differences in varus-valgus excursion and alignment likely influence cartilage loading patterns. These changes may load areas of cartilage in a way not previously conditioned to and incite a degenerative process. Contributors to active knee stability may also play an important role in constraining the knee joint in this population, but additional work is necessary to identify any relationship between active stability and varus-valgus excursion or passive laxity.

Varus-valgus laxity also exhibited positive correlation with greater knee extension strength, self-selected gait speed, and better 6MW distance and SCT times. Gait speed,
6MW and SCT scores have been previously linked to knee extension strength, and in this study the knee extension strength was moderately correlated with each; gait speed $R^2=0.38$, $p<0.001$; 6MW $R^2=0.48$, $p < 0.001$; and SCT $R^2=0.29$, $p=0.002$. To identify if any of these factors were independently associated with varus-valgus laxity, a linear regression analysis was performed with knee extension strength, knee flexion strength, self-selected gait speed, 6MW and SCT all entered as factors. Only knee extension strength showed a trend in this multi-factor analysis, so strength may be driving the other trends between clinical performance and laxity. While we do not have in-vivo data on healthy laxity utilizing our knee stability device, due to the invasive nature, previous research has been performed on cadavers without OA. Varus-valgus laxity of the cadaveric knee was only 2.7 (0.5) degrees (Hutter, Granger et al. 2013), compared to 5.0 (2.6) degrees in our OA participants, which is consistent with previous work indicating more varus-valgus laxity in OA populations compared to controls. While greater laxity was associated with larger strength in this cohort, it does not appear that this is due to a more normal amount of laxity.

The literature on laxity and self-reported function is conflicting, but our results showed no relationship between these two variables in OA participants immediately prior to joint replacement. Schmitt et al. and van der Esch et al. also found no relationship between laxity and self-reported outcomes (Schmitt, Fitzgerald et al. 2008) (van der Esch, Knoop et al. 2012). Holla et al. observed a significant association between greater laxity and better physical function gauged from the Western Ontario and McMaster osteoarthritis index (WOMAC-PF) (Holla, van der Leeden et al. 2012). However, Sharma et al. observed better WOMAC-PF scores in the low laxity group compared to high laxity
group, and a modest association between greater laxity and worse WOMAC-PF ($R^2=0.04$) (Sharma, Hayes et al. 1999). These previous studies included participants with varied severity of knee OA, whose results may not be applicable to individuals with severe OA. Our study was the only to include unconscious measurement of varus-valgus laxity, therefore reducing the possibility of muscular guarding. The custom knee stability device and three-dimensional surgical navigation system also removes the artifact which tibial internal/external rotation can have on moment calculations (Siston, Maack et al. 2012). This allowed for measurement of the true varus or valgus moment applied relative to the anatomical coordinate system of the knee. In study participants with severe OA, there was no evidence that varus-valgus laxity is associated with the KOOS subscales, and more work is needed to identify knee stability factors which influence self-reported function.

With the lack of correlation between passive knee stabilizers and symptoms of instability, we preliminarily investigated the potential for muscle strength to compensate for greater passive laxity and actively stabilize the joint. We found the normalized isometric knee extension strength was significantly different between participants with varying levels of instability (One-way ANOVA $R^2 = 0.40$, $P=0.013$), with participants reporting severe and moderate instability exhibiting the lowest levels of knee extension strength. To further investigate the connection between instability and strength, we categorized our participants into two groups for each variable. Participants reporting moderate to severe instability (Score 1-2) were first separated from those reporting slight or less instability (3-5). Each instability group was further broken down by strength level, using the overall study population’s mean value of 1.0 Nm/kg as our cutoff. The number
of participants and varus-valgus laxity of each group can be seen in Table 3.3. 11 of the 13 participants with a strength level of less than 1.0 Nm/kg reported moderate or severe instability. In those reporting moderate/severe instability with isometric knee strength over 1.0Nm/kg, their passive laxity was approximately 3 degrees larger than that of the weaker group with similar instability. Schmitt et al. previously reported no differences in quadriceps strength between OA patients reporting varied perceived instability (Schmitt, Fitzgerald et al. 2008); however the instability groups differed from the current study. This previous work grouped patients into 3 groups; one group with instability that affected activity (slight, moderate, severe instability), another with instability not affecting activity, and the third with no instability. Schmitt et al. also had approximately 19% of patients reporting moderate or severe instability, compared to over half of the participants in the current study. The differences in OA severity and instability grouping may explain the varied results between studies and the effect of quadriceps strength on perceived instability. Self-reported knee instability also has previously been linked to activity limitations (van der Esch, Knoop et al. 2012) and patient surveys of function (Schmitt, Fitzgerald et al. 2008), but the mechanism for knee instability is not well understood in participants with OA. Laxity was unrelated to self-reported instability in this study and in previous investigations (Schmitt, Fitzgerald et al. 2008) (van der Esch, Knoop et al. 2012) (van der Esch, Knoop et al. 2012)
Table 3.3: Participant distribution and laxity by perceived instability and knee extension strength.

<table>
<thead>
<tr>
<th>Instability Grouping</th>
<th>Knee Extension Strength</th>
<th>number of participants</th>
<th>Varus-Valgus Laxity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/Severe</td>
<td>&lt;1.0 Nm/kg</td>
<td>11</td>
<td>3.9° +/- 2.6°</td>
</tr>
<tr>
<td></td>
<td>&gt;1.0 Nm/kg</td>
<td>5</td>
<td>6.9° +/- 1.6°</td>
</tr>
<tr>
<td>Slight or Less</td>
<td>&lt;1.0 Nm/kg</td>
<td>2</td>
<td>5.2° +/- 2.7°</td>
</tr>
<tr>
<td></td>
<td>&gt;1.0 Nm/kg</td>
<td>12</td>
<td>5.5° +/- 0.4°</td>
</tr>
</tbody>
</table>

One possible explanation for this result is that there may be a certain level of strength necessary to control the knee joint during activities of daily living. The sensation of instability may be due to this lack of strength in some participants with OA. For those reporting instability without strength deficits, passive laxity may be the source of their issues. The potential interplay between passive laxity and strength may be useful to physicians and physical therapists that are treating patients for reported instability. It may also be of use to orthopaedic surgeons, who desire to better estimate joint laxity in participants with severe OA for surgical planning. For subjects who report moderate or severe instability, stronger patients had on average 77% more passive varus-valgus laxity than the weaker group. More research is necessary to confirm these results in a larger sample and identify the predictive power of instability and quadriceps strength to laxity.

Limitations of this study include the potential influence of soft-tissue artifact during motion analysis testing. In order to match typical demographics of patients with OA electing for TKA, we included those with a relatively high BMI. To mitigate the
issues of soft tissue artifact during gait analysis, we utilized a point cluster technique marker set (Andriacchi, Alexander et al. 1998) and functional hip joint center algorithm (Camomilla, Cereatti et al. 2006) when calculating joint kinematics during gait. Combined, these techniques reduced the effect of individual marker motion and eliminated the reliance on regression equations to calculate hip joint centers from pelvis markers. Another limitation is the heterogeneity of our participant’s contralateral limb. One patient had both knees replaced and both sets of data were included in this analysis, while other subjects had previous contralateral knee replacements or varying degrees of OA in the contralateral limb. This may influence our measures of function and make it difficult to assess the impact of only passive laxity on biomechanical, clinical and self-reported outcomes. Another potential limitation was the choice to use self-selected walking speed rather than a single standard speed across participants. However, in this cohort it would have been difficult to standardize speed due to the variation of function and pain in the participants before TKA. Moreover, in this cohort gait speed was unrelated to varus-valgus excursion ($R^2=0.02$, $p=0.41$). Lastly, the degree of active stability from muscle activation patterns was not investigated in this analysis. Muscle forces likely play an important role in knee joint stability, given the large frontal plane moments measured during walking. Future work should attempt to identify the relationship between passive and active knee stabilizers in participants with severe OA.
3.6 Conclusion

This study investigated the relationship between passive varus-valgus laxity and varus-valgus excursion, clinical performance measures, and self-reported instability and function. Varus-valgus excursion was significantly related to passive varus-valgus laxity. There were also significant associations between greater laxity and better clinical performance, however no association was found between laxity and self-reported instability or function. Knee extension strength may play a role in a participant’s perception of instability, but more work is needed to clarify and confirm this relationship and identify the potential connection to passive laxity. Increased laxity has been reported in subjects with OA, and it has been theorized that this may shift cartilage loading patterns and lead to OA. Our observation that greater laxity is associated with more varus-valgus excursion is consistent with this theory.

3.7 Acknowledgements

We would like to thank the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Award Number R01AR056700) for funding this research. We would also like to thank Jason Payne, MD and Alan Rogers, MD for their assistance in grading the radiographic OA severity and Andrew Glassman, MD, MS for his help recruiting participants.
Chapter 4: Active and passive knee stability in participants with severe OA
4.1 Abstract

Objective: Increased varus-valgus knee laxity has been reported in individuals with knee OA compared to controls, and a reduction in passive knee stability may require increased active stability to be provided by muscles crossing the knee joint. The primary purpose of this study was to identify the relationship between active knee stability, quantified by average quadriceps activation (avgQUAD) and average co-contraction indices (avgCCI) during gait, and passive varus valgus laxity, measured under general anesthesia, in participants with severe OA. The secondary purpose was to investigate the association between active stability and knee varus-valgus excursion during gait, isometric knee strength, and perceived instability.

Methods: We measured passive varus-valgus laxity in 20 participants (22 knees) with severe medial compartment OA. Subject’s also completed gait analysis, knee strength assessments, and reported their perception of knee instability. Spearman correlations were used to analyze the association among variables.

Results: Measures of active stability during either pre-stance or weight acceptance were unrelated to passive varus-valgus laxity, varus-valgus excursion, knee strength, or perceived instability.

Conclusion: Measures of active stability were not associated with passive varus-valgus laxity, even after the potential for muscular guarding during varus-valgus laxity examination was eliminated. There was also no relationship identified between any active stability measure and varus-valgus excursion during gait, isometric knee strength, or perceived instability. More research is needed to assess the interaction between active
and passive stabilizers in OA patients during gait, and the extent of co-contraction differences between OA and matched-controls while utilizing a simple reference activity for normalization.

4.2 Introduction

Osteoarthritis (OA) is the most common form of arthritis (Felson and Zhang 1998) and the largest single cause of disability in the United States (2009). The knee joint is most frequently affected (Oliveria, Felson et al. 1995) and approximately 700,000 people per year undergo knee replacement surgery in the United States (2012). Mechanical stress has been suggested to be the most important risk factor in knee OA (Visser, de Mutsert et al. 2014) and increased laxity has been hypothesized to alter the loading conditions of knee cartilage (Andriacchi, Mundermann et al. 2004). Increased laxity could change joint kinematics and cartilage contact patterns, which may initiate cartilage degeneration and OA. Increased knee laxity has been reported in individuals with knee OA compared to controls (Pai, Rymer et al. 1997; Sharma, Lou et al. 1999) (Wada, Kawahara et al. 2002; Lewek, Rudolph et al. 2004; Lewek, Ramsey et al. 2005; Lewek, Scholz et al. 2006; Rudolph, Schmitt et al. 2007; Schmitt and Rudolph 2007; Ishii, Noguchi et al. 2009; Kumar, Manal et al. 2013)(Dissertation Chapter 2), and a reduction in passive knee stability may require increased active stability to be provided by muscles crossing the knee joint (Schipplein and Andriacchi 1991; Lewek, Rudolph et al. 2004). The combination of shifted cartilage contact patterns and increased muscle activity may increase cartilage loading and lead to degeneration, worsening OA.

Passive stability in the knee joint is primarily provided by ligaments, and varus-valgus laxity is commonly used to estimate the passive stability provided by the medial and lateral collateral ligaments. Laxity has been measured in participants with OA using various devices (Tallroth and Lindholm 1987; Brage, Draganich et al. 1994; Sharma, Hayes et al. 1999; Siston, Goodman et al. 2007), which quantify tibiofemoral displacement under a given load. During conscious measurement of laxity, muscles which cross the knee have the potential to activate and guard the knee during testing (Sharma, Lou et al. 1999; Lim, Hinman et al. 2008). Muscular guarding may reduce the magnitude of measured laxity and it is currently unknown how large of an effect this plays in laxity measurement in the OA population (Markolf, Mensch et al. 1976). In order to get a more accurate measure of passive laxity all muscle forces must be eliminated, which can be accomplished by performing measurements while participants are under general anesthesia (Pottenger, Phillips et al. 1990; Siston, Goodman et al. 2007). This technique is ideal for identifying the passive knee laxity without any confounding aspects of structures that contribute to active knee stability.

While increased muscle activity, which contributes to active knee stability, has been reported in cohorts with knee OA, these results may be confounded by muscle weakness or altered activation. Higher muscle activity has been hypothesized to assist in the active stability of the knee in populations with greater passive laxity (Andriacchi 1994; Lewek, Rudolph et al. 2004)(Hirokawa, Solomonow et al. 1991). This neuromuscular strategy may reduce knee motion and oppose lateral knee joint opening
instigated by large adduction moments during gait (Schipplein and Andriacchi 1991). Previous studies have normalized the muscle activity to a maximal contraction (Childs, Sparto et al. 2004)(Lewek, Rudolph et al. 2004)(Hortobagyi, Westerkamp et al. 2005) (Rudolph, Schmitt et al. 2007)(Hubley-Kozey, Deluzio et al. 2008)(Heiden, Lloyd et al. 2009) (Hubley-Kozey, Hill et al. 2009) (Zeni, Rudolph et al. 2010) or to the peak activity measured during gait (Schmitt and Rudolph 2008). However, normalizing muscle activity by these techniques may have an undesirable influence on results due to participants with OA often exhibiting dysfunctional muscle activation (Hortobagyi, Garry et al. 2004), reduced strength (O'Reilly, Jones et al. 1998), and altered gait patterns (Astephen, Deluzio et al. 2008). A similar muscle activity percentage may represent drastically varied levels of muscle force produced between individuals with OA and compared to controls. Normalizing EMG to a submaximal task, which requires approximately similar force between individuals, may better estimate knee forces in pathological populations and has been suggested for clinical populations who are unable to attempt maximal efforts (Lehman and McGill 1999).

The primary purpose of this study was to identify the relationship between measures of active knee stability and passive knee laxity in participants with severe OA. We focused on increased quadriceps activation and co-contraction indices of antagonist muscle pairs for the measures of active knee stability, due to their potential to resist varus-valgus knee motion. We hypothesized that greater passive knee laxity would be associated with higher quadriceps muscle activity and co-contraction indices (normalized to a submaximal reference activity). Other potential variables which may be related to active stability were included as secondary analyses: knee varus-valgus excursion during
gait, isometric knee strength, and perceived instability. Lastly, we hypothesized that muscle activations and measures of active stability would be significantly different in pre-stance than during the weight acceptance phase of gait.

4.3 Methods

4.3.1 Patients with Osteoarthritis

33 individuals (35 knees) initially enrolled in this study after providing IRB approved consent. Participants had predominantly medial compartment tibiofemoral osteoarthritis, as determined by the orthopaedic surgeon, and were awaiting total knee arthroplasty (TKA). Preoperative movement analyses were also completed during separate sessions before each surgery. The exclusion criteria for participants in this study were as follows: Body Mass Index (BMI) > 45 kg/m$^2$; predominantly lateral compartment OA; inability to walk without an assistive device; or revision TKA. Accuracy of gait kinematics and signal transmission of muscle activity is reduced with excessive adiposity, which was the reason for excluding participants with BMI > 45. Since differences in knee stability are likely between individuals with predominantly medial and lateral knee osteoarthritis, we decided to reduce variability and focus on the subset of patients with medial knee OA electing for TKA. Participants who were unable to walk without an assistive device were also excluded, since this would impact kinematics, kinetics and muscle activations during gait and make inter-participant comparisons less straightforward. Bi-lateral TKA patients were not excluded from this study, as we did not control for knee joint health of the contralateral limb. For the two patients who were enrolled for both osteoarthritic knee joints, the surgeries were staged
245 and 124 days apart to allow for recovery and retesting before second TKA. Previous analysis has been completed on this cohort of participants with severe OA (Dissertation Chapter 3). Thirteen participants were excluded from this analysis for the following reasons: not enough gait trials recorded to calculate ensemble averages (n=2); technical difficulty transmitting muscle activation signals (n=3); substandard EMG signal with significant movement artifacts observed during quality assessment (n=6); and sterilization errors precluding intra-operative laxity testing (n=2). Radiographic OA severity was independently assigned by consensus using the Kellgren-Lawrence (KL) grading system by two fellowship-trained, musculoskeletal radiologists (JP & AR). The KL grade was evaluated after the decision to schedule surgery, for demographic purposes. Demographics for the 20 participants (22 knees) included in the subsequent analyses are shown in Table 4.1.
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, no.</td>
<td>7</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.3 ± 9.6</td>
<td>59.9 ± 6.0</td>
<td>59.0 ± 7.3</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.80 ± 0.07</td>
<td>1.61 ± 0.05</td>
<td>1.68 ± 0.11</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>103.0 ± 17.9</td>
<td>88.4 ± 11.4</td>
<td>93.5 ± 15.3</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>31.9 ± 5.0</td>
<td>34.0 ± 4.2</td>
<td>33.3 ± 4.5</td>
</tr>
<tr>
<td>Knees analyzed, no.</td>
<td>7</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Tested limb, no. (right/left)</td>
<td>3 / 4</td>
<td>7 / 8</td>
<td>10 / 12</td>
</tr>
<tr>
<td>KL grade, no. (I / II / III / IV)</td>
<td>0 / 0 / 4 / 3</td>
<td>0 / 0 / 11 / 4</td>
<td>0 / 0 / 15 / 7</td>
</tr>
<tr>
<td>Gait speed, m/s</td>
<td>1.04 ± 0.24</td>
<td>0.96 ± 0.27</td>
<td>0.98 ± 0.26</td>
</tr>
</tbody>
</table>

Table 4.1: Demographics of participants with osteoarthritis. Values are the mean ± standard deviation unless otherwise noted. Number (no.); Body Mass Index (BMI); Kellgren-Lawrence (KL);

4.3.2 Isometric Knee Strength

Isometric knee extension and flexion strength were observed with a Biodex System 3 dynamometer [Biodex Medical Systems; Shirley, NY] during a maximal voluntary isometric contraction (MVIC). Each participant was seated upright with the involved limb at 60 degrees of knee flexion. Two 5-second maximal contractions for each knee extension and knee flexion were separated by 30 seconds. The maximal torque produced during extension and flexion were recorded and normalized by each participant’s mass (Nm/kg).

4.3.3 Perceived Instability

Participants’ perceived knee instability was assessed from a question in the Knee Outcome Survey – Activities of Daily Living Scale (Irrgang, Snyder-Mackler et al.)
The question read, “To what degree does giving way, buckling, or shifting of the knee affect your daily activity?” and was scored on a 6 point scale. The designated responses and associated scores are as follows: 0 indicated that instability prevented all activity; 1 indicated that instability affected activity severely; 2 indicated that instability affected activity moderately; 3 indicated that instability affected activity slightly; 4 indicated that instability did not affect activity; and a score of 5 indicated no instability.

4.3.4 Movement analysis

Participants walked along a 10 m path at a self-selected speed. Ground reaction forces were sampled at 1500 Hz from multiple force plates embedded in the floor [4060-10; Bertec Corp; Columbus, OH]. Trials with 2 foot strikes on consecutive force plates were recorded and analyzed. Marker data was collected at 150 Hz utilizing 10 motion-capture cameras [MX-F40; Vicon; Oxford, UK]. A modified point-cluster technique (Andriacchi, Alexander et al. 1998) (Jamison, Pan et al. 2012) marker set was used in conjunction with a functional hip joint center (Camomilla, Cereatti et al. 2006). Kinematic variables were found over the weight acceptance phase of gait (WA), which was defined as the time period from initial heel contact to peak knee flexion (Jamison, Pan et al. 2012). Varus-valgus excursion was calculated as the difference between peak knee varus angle and peak knee valgus angle. Ensemble averages were found over four trials of gait per participant.

Wireless surface electromyography (EMG) [Telemyo DTS; Noraxon USA, Inc; Scottsdale, AZ] was measured on the involved limb in participants with severe OA. The EMG signals from the following muscles were recorded: rectus femoris (RF); vastus...
medialis (VM); vastus lateralis (VL); semimembranosus (SM); long head of the biceps femoris (BF); medial gastrocnemius (MG); lateral gastrocnemius (LG); and soleus (SO). Electrode locations were shaved, cleaned and lightly abraded with alcohol pads. Pregelled (Ag/AgCl), surface electrodes [A10011; Vermed, Inc; Bellows Falls, VT] with an inter-electrode distance of 42mm were placed on the most prominent aspect of each muscle belly and oriented parallel to the muscle fibers. Raw EMG data were recorded at 1500Hz and a high pass, zero-lag 4th order Butterworth filter was applied at 10Hz to reduce the effect of motion artifact. The EMG data were then subsequently full wave rectified and RMS filtered with a 20ms smoothing window.

Three separate tasks were used as submaximal reference activities to normalize EMG signals. Seated, unweighted, uni-lateral knee extension was used to normalize the RF, VM, and VL. Standing, unweighted, uni-lateral knee flexion was used to normalize SM and BF. Standing bi-lateral ankle plantarflexion was used to normalize MG, LG, and SO. For each task, participants performed 4 repetitions in sync with verbal commands to maintain consistency. EMG was manually inspected during these normalization tasks to ensure adequate transmission of muscle activity which reflected the patient motion. After the filtering and rectification, the highest 500ms running average for each muscle was used for normalization (Jamison, McNally et al. 2013).

We investigated muscle activity during two separate phases of the gait cycle. Pre-contact (PRE) was defined as 100ms before heel strike of the investigated limb and weight acceptance (WA) defined from initial contact to peak knee flexion (Jamison, Pan et al. 2012). Processed EMG signals were visually inspected for valid transmission and signal artifact during gait. Recorded muscle activities with no visual contraction
amplitudes or non-physiological spikes, likely due to motion artifact of the sensors, were noted and removed from further analysis. Four trials of gait were used to calculate ensemble averages for the muscle activations during each phase of gait. They are expressed as a percentage of the EMG measured during each normalization activity.

4.3.5 Active Stability Measures

The average quadriceps activation (avgQUAD) and average co-contraction indices (avgCCI) were used as active stability measures for their potential to stabilize the knee joint during gait. avgQUAD was found by calculating the mean of RF, VM, and VL muscle activity during each phase and avgCCIs were calculated using the following equation (Rudolph, Axe et al. 2000) for the following antagonist muscle pairs: quadriceps and hamstring (QH); quadriceps and gastrocnemii (QG); vastus medialis and semimembranosus (MQH); vastus lateralis and biceps femoris (LQH); vastus medialis and medial gastrocnemius (MQG); and vastus lateralis and lateral gastrocnemius (LQG).

\[
avgCCI = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{lower \ EMG_i}{higher \ EMG_i} \times (lower \ EMG_i + higher \ EMG_i) \right)
\]

Equation Average co-contraction index (avgCCI) was calculated using the relatively lower and higher EMG signals for antagonistic muscles.
This co-contraction formula accounts for the relative magnitude and timing of the agonist/antagonist muscle pairs. When calculating the avgCCI for each antagonist muscle pair, n denotes the number of frames for each phase of gait. For the QH and QG avgCCI, which include multiple muscles for each input, all the normalized muscle activity for each group were averaged before the lower or higher EMG designation. In the cases where the recording for one of the individual muscle activations was not valid, the avgCCI was not calculated for that specific participant.

4.3.6 EMG Normalization Comparison

To our knowledge, the chosen submaximal EMG normalization technique has not been used previously in an OA population. However, increased co-contraction indices in OA participants have been reported previously (Childs, Sparto et al. 2004; Lewek, Rudolph et al. 2004) (Rudolph, Schmitt et al. 2007) (Hubley-Kozey, Hill et al. 2009) (Heiden, Lloyd et al. 2009) (Zeni, Rudolph et al. 2010) (Schmitt and Rudolph 2007) (Dissertation Chapter 3). Participants with severe OA also often exhibit dysfunctional muscle activation (Hortobagyi, Garry et al. 2004), reduced strength (O'Reilly, Jones et al. 1998), and altered gait patterns (Astephen, Deluzio et al. 2008), so normalizing muscle activity by maximal techniques may have an undesirable influence on results. In preparation for this study’s analysis, we performed an additional analysis to identify the correlation of gait EMG when normalizing with submaximal reference tasks versus normalizing to maximal voluntary isometric contractions (MVIC). MVICs were performed on a Biodex System 3 dynamometer [Biodex Medical Systems; Shirley, NY]. The setup details for normalizing the quadriceps and hamstrings are described above.
(Section 4.3.2). For the plantarflexor MVIC test, the hip was flexed approximately 90 degrees while the knee was slightly bent. The knee was supported and secured to the attachment for the seat, and the ankle was set at 15 degrees of plantar flexion. We recorded 2 maximal contractions with verbal encouragement, instructing the participant to point the toe as hard as possible. Each maximal contraction was 5 seconds in length, and separated by 15 seconds of rest. The MVIC EMG signals were rectified and filtered similarly to the submaximal reference activity EMG, and the highest 500ms running average was used for MVIC normalization.

All participants who had accurate EMG signals for every recorded muscle during submaximal reference activities, MVICs, and during the WA phase of gait were included in this comparison. A total of 11 participants fit the criteria (4 male: 7 female, age = 57.9 ± 7.2 years, height = 1.69 ± 0.10 m, mass = 88.3 ± 8.8 kg, BMI = 31.0 ± 3.4 kg/m²). Participants were excluded for the following reasons: EMG not measured during MVIC (n=5); plantarflexor MVIC not completed due to time constraints (n=3), EMG artifact for individual muscles during WA (n=3). Six of the EMG variables did not meet normality constraints for submaximal or MVIC normalization techniques (Anderson-Darling p<0.05), therefore the median and interquartile range (IQR) are reported in Table 4.2. Spearman correlation coefficients were calculated and the results with associated p-values are shown in Table 4.2.
Table 4.2: Subset (n=11) analysis of EMG during gait, utilizing two normalization activities. Maximal voluntary isometric contraction (MVIC); Interquartile range (IQR); Average (Avg); Co-contraction index (CCI). Significant associations are designated with asterisks: *(p <0.05); **(p<0.01).

<table>
<thead>
<tr>
<th>Weight acceptance phase of gait</th>
<th>Normalization Task</th>
<th>Submaximal Reference</th>
<th>MVIC</th>
<th>Spearman Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>Rectus Femoris</td>
<td>RF</td>
<td>69.1%</td>
<td>46.0%</td>
<td>47.4%</td>
</tr>
<tr>
<td>Vastus Medialis</td>
<td>VM</td>
<td>72.4%</td>
<td>96.4%</td>
<td>45.2%</td>
</tr>
<tr>
<td>Vastus Lateralis</td>
<td>VL</td>
<td>91.0%</td>
<td>82.1%</td>
<td>53.9%</td>
</tr>
<tr>
<td>Semimembranosus</td>
<td>SM</td>
<td>35.4%</td>
<td>28.2%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Biceps Femoris</td>
<td>BF</td>
<td>123.7%</td>
<td>132.7%</td>
<td>98.5%</td>
</tr>
<tr>
<td>Med Gastrocnemius</td>
<td>MG</td>
<td>15.1%</td>
<td>19.0%</td>
<td>29.0%</td>
</tr>
<tr>
<td>Lat Gastrocnemius</td>
<td>LG</td>
<td>22.8%</td>
<td>32.3%</td>
<td>43.0%</td>
</tr>
<tr>
<td>Soleus</td>
<td>SO</td>
<td>28.5%</td>
<td>18.3%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Avg Quadriceps Activation</td>
<td>avgQUAD</td>
<td>87.8%</td>
<td>63.3%</td>
<td>49.8%</td>
</tr>
<tr>
<td>Avg Quad/Ham CCI</td>
<td>QH avgCCI</td>
<td>1.328</td>
<td>0.829</td>
<td>0.496</td>
</tr>
<tr>
<td>Avg Quad/Gastroc CCI</td>
<td>QG avgCCI</td>
<td>0.263</td>
<td>0.297</td>
<td>0.611</td>
</tr>
<tr>
<td>Avg Medial Quad/Ham CCI</td>
<td>MQH avgCCI</td>
<td>0.451</td>
<td>0.476</td>
<td>0.329</td>
</tr>
<tr>
<td>Avg Lateral Quad/Ham CCI</td>
<td>LQH avgCCI</td>
<td>1.296</td>
<td>0.964</td>
<td>0.449</td>
</tr>
<tr>
<td>Avg Medial Quad/Ham CCI</td>
<td>MQG avgCCI</td>
<td>0.180</td>
<td>0.274</td>
<td>0.284</td>
</tr>
<tr>
<td>Avg Lateral Quad/Gastroc CCI</td>
<td>LQG avgCCI</td>
<td>0.259</td>
<td>0.515</td>
<td>0.592</td>
</tr>
</tbody>
</table>
The median percent activation was larger for RF, VM, VL, SM, and BF using the submaximal normalization, while percent activation for MG, LG, and SO was larger using the MVIC. Correlation coefficients ranged from 0.409 to 0.855, with 12/15 variables significantly related. For a majority of EMG variables (8/15) the two techniques were strongly correlated ($R \geq 0.7$). Also of note, the activations for all three plantarflexors during MVIC were smaller than that measured during the submaximal reference activity, which results in higher percent activations for the MG, LG, and SO when normalizing to the MVIC. This result highlights a main limitation of using MVICs in pathological populations, as it is unlikely all OA participants are producing true maximal contractions. This analysis compared the submaximal normalization technique to MVIC technique and found significant associations for 12 of 15 EMG variables.

4.3.7 Intra-operative Laxity Measurement

To characterize knee joint laxity we measured the load-displacement relationship of the knee in the frontal plane. Joint laxity of the native osteoarthritic knee was quantified immediately prior to total knee arthroplasty, before any bone, ligamentous, or meniscal alterations, and with minimal disruption to the joint structures. Each participant was under general anesthesia, which eliminated the potential for muscular guarding during laxity testing. Kinematics were collected intra-operatively utilizing a validated custom navigation system during the total knee arthroplasty procedure (Siston, Giori et al. 2006; Siston, Maack et al. 2012). Applied varus and valgus moments were measured with a custom knee stability testing device. Load was applied with a force application handle instrumented with a tension-compression load cell, which was integrated with the
surgical navigation system (Siston, Maack et al. 2012). A third order polynomial was fit to the raw data for three trials of varus and valgus load applied to the knee. Laxity was calculated as the difference in varus-valgus knee angle when the knee was loaded with 10 Nm of varus and valgus moment, respectively. Each participant’s overall varus-valgus laxity was the average value found in these three trials. A more detailed description of the methods used to calculate varus-valgus laxity in this cohort has been previously published (Siston, Giori et al. 2006; Siston, Maack et al. 2012)(Dissertation Chapter 3).

4.3.8 Statistics

Statistical analysis was performed using Minitab Statistical Software (Version 17; Minitab Inc.; State College, PA). Non-parametric statistics were chosen after an initial inspection of the data revealed 15 out of the 28 EMG variables were not normally distributed (Anderson-Darling test; p <0.05). Spearman correlations were used to analyze the relationship between avgQUAD / avgCCIs and passive varus-valgus laxity, varus-valgus excursion, knee extension strength, knee flexion strength, and perceived instability. Mann-Whitney U tests were used to identify significant differences between the PRE and WA phase for the muscle activations and active stability measures. Significance was set at alpha = 0.05.

4.4 Results

Muscle activations and avgCCIs, normalized by submaximal tasks, during the PRE and WA gait phases are shown in Table 4.3. Due to the non-normal distribution of a majority of the muscle activation and active stability variables, the medians and the first and third quartiles are reported. The number of samples utilized for each muscle
activation and avgCCIs are displayed in Table 4.3. There was a significant difference in avgQUAD activation between PRE and WA (p-value < 0.001), 42.4% median activation vs 90.4% median activation respectively. QH avgCCI was also larger during weight acceptance than 100ms prior to initial contact (0.63 [0.43] PRE vs. 1.15 [0.65] WA, p=0.002). The magnitudes and difference between QG avgCCI were not as large and not significantly different from one another (0.19 [0.21] PRE vs. 0.26 [0.28] WA, p=0.063). MQH avgCCI was the only active stability measure that was larger during PRE, however the difference was quite small and not statistically significant (0.59 [0.49] PRE vs. 0.57 [0.61] WA, p=0.953). In contrast, LQH avgCCI was almost 3 times larger during WA than PRE (0.55 [0.63] PRE vs. 1.51 [0.74], p=0.002). LQH avgCCI was also significantly larger than MQH avgCCI during WA (p=0.005), but not during PRE (p=0.784). Contrary to the medio-lateral QH differences, MQG avgCCI was significantly different between PRE and WA (0.13 [0.20] PRE vs. 0.24 [0.22] WA, p=0.034), but not for LQG avgCCI (0.22 [0.22] PRE vs. 0.30 [0.36] WA, p=0.070).
<table>
<thead>
<tr>
<th>Muscle / Active Stability Measure</th>
<th>Phase</th>
<th>n</th>
<th>Median</th>
<th>IQR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectus Femoris</td>
<td>Pre</td>
<td>22</td>
<td>30.7%</td>
<td>29.1%</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>22</td>
<td>65.5%</td>
<td>32.3%</td>
<td></td>
</tr>
<tr>
<td>Vastus Medialis</td>
<td>Pre</td>
<td>22</td>
<td>52.8%</td>
<td>30.2%</td>
<td>0.001**</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>22</td>
<td>95.8%</td>
<td>71.6%</td>
<td></td>
</tr>
<tr>
<td>Vastus Lateralis</td>
<td>Pre</td>
<td>22</td>
<td>43.8%</td>
<td>31.9%</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>22</td>
<td>108.5%</td>
<td>54.4%</td>
<td></td>
</tr>
<tr>
<td>Semimembranosus</td>
<td>Pre</td>
<td>22</td>
<td>50.8%</td>
<td>37.8%</td>
<td>0.286</td>
</tr>
<tr>
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<td>22</td>
<td>41.7%</td>
<td>32.6%</td>
<td></td>
</tr>
<tr>
<td>Biceps Femoris</td>
<td>Pre</td>
<td>19</td>
<td>99.9%</td>
<td>76.9%</td>
<td>0.243</td>
</tr>
<tr>
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<td>19</td>
<td>118.0%</td>
<td>97.4%</td>
<td></td>
</tr>
<tr>
<td>M Gastrocnemius</td>
<td>Pre</td>
<td>22</td>
<td>10.7%</td>
<td>14.9%</td>
<td>0.015*</td>
</tr>
<tr>
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<td>WA</td>
<td>22</td>
<td>18.7%</td>
<td>14.9%</td>
<td></td>
</tr>
<tr>
<td>L Gastrocnemius</td>
<td>Pre</td>
<td>21</td>
<td>16.7%</td>
<td>17.8%</td>
<td>0.050*</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>21</td>
<td>23.1%</td>
<td>20.8%</td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>Pre</td>
<td>21</td>
<td>12.9%</td>
<td>14.2%</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>21</td>
<td>32.0%</td>
<td>28.0%</td>
<td></td>
</tr>
<tr>
<td>avgQUAD</td>
<td>Pre</td>
<td>22</td>
<td>42.4%</td>
<td>24.0%</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>22</td>
<td>90.4%</td>
<td>46.3%</td>
<td></td>
</tr>
<tr>
<td>QH avgCCI</td>
<td>Pre</td>
<td>19</td>
<td>0.63</td>
<td>0.43</td>
<td>0.002**</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>19</td>
<td>1.15</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>QG avgCCI</td>
<td>Pre</td>
<td>21</td>
<td>0.19</td>
<td>0.21</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>21</td>
<td>0.26</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>MQH avgCCI</td>
<td>Pre</td>
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<td>0.59</td>
<td>0.45</td>
<td>0.953</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>22</td>
<td>0.57</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>LQH avgCCI</td>
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<td>0.55</td>
<td>0.63</td>
<td>0.002**</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>19</td>
<td>1.51</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>MQG avgCCI</td>
<td>Pre</td>
<td>22</td>
<td>0.13</td>
<td>0.20</td>
<td>0.034*</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>22</td>
<td>0.24</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>LQG avgCCI</td>
<td>Pre</td>
<td>21</td>
<td>0.22</td>
<td>0.22</td>
<td>0.070</td>
</tr>
<tr>
<td></td>
<td>WA</td>
<td>21</td>
<td>0.30</td>
<td>0.36</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.3: Muscle and active stability distributions during pre stance and weight acceptance. Interquartile range (IQR); Medial (M); Lateral (L); Average quadriceps activation (avgQUAD); Average co-contraction index (avgCCI); Quadriceps (Q); Hamstring (H); Gastrocnemii (G). Significant differences are designated with asterisks: *(p<0.05), **(p<0.01), *** (p<0.001).
The intra-operative, kinematic, clinical, and self-reported variables of interest are shown in Table 4.4. Mean and standard deviation are shown for all variables. We did not test for differences between males and females, as this was not the primary purpose and the distribution was skewed with less than half as many male as female participants. Passive varus-valgus laxity, varus-valgus excursion, knee strength and perceived instability for these participants have been previously published in a separate manuscript investigating the effect of passive laxity on biomechanical and clinical function (Dissertation Chapter 3).

<table>
<thead>
<tr>
<th></th>
<th>Male (n=7)</th>
<th>Female (n=15)</th>
<th>Overall (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive varus-valgus laxity, deg</td>
<td>3.6 ± 1.8</td>
<td>5.1 ± 2.6</td>
<td>4.7 ± 2.4</td>
</tr>
<tr>
<td>Varus-valgus excursion, deg</td>
<td>3.8 ± 1.6</td>
<td>5.4 ± 2.0</td>
<td>4.9 ± 2.0</td>
</tr>
<tr>
<td>Knee extension strength, Nm/kg</td>
<td>1.12 ± 0.37</td>
<td>1.08 ± 0.48</td>
<td>1.09 ± 0.44</td>
</tr>
<tr>
<td>Knee flexion strength, Nm/kg</td>
<td>0.66 ± 0.26</td>
<td>0.55 ± 0.20</td>
<td>0.58 ± 0.22</td>
</tr>
<tr>
<td>Perceived instability, no.</td>
<td>3.0 ± 0.6</td>
<td>2.4 ± 1.5</td>
<td>2.6 ± 1.3</td>
</tr>
</tbody>
</table>

Table 4.4: Intra-operative, kinematic, clinical, and self-reported variables of interest for patients with severe OA.
Spearman correlations were used to analyze the association between normalized active stability measures and the five variables of interest for the severe OA group. The resulting correlation coefficients and p-values are reported in Table 4.5. There was no relationship between any active stability measure and passive varus-valgus laxity, during either PRE or WA. There was also no relationship between any active stability measure and secondary variable of interest.
Table 4.5: Spearman’s rank order correlations between the active stability measures and the primary and secondary variables of interest.
4.5 Discussion

The primary purpose of this study was to identify the relationships between passive knee laxity and active knee stability during walking in participants with severe OA. Contrary to our hypothesis, we found no associations between passive knee laxity and average quadriceps activity (avgQUAD) or any of the co-contraction indices during gait. The interactions between passive soft tissue tension and active muscle forces are critical to knee stability during gait (Andriacchi 1994)(Schipplein and Andriacchi 1991), but no connection was revealed in this analysis. Stability of the knee joint may necessitate a more complex control strategy to modulate passive, active, and joint reaction forces than the proposed active stability measures. Lewek et al. previously found a relationship between medial joint laxity and the co-contraction of vastus medialis and medial gastrocnemius (MQG) (Lewek, Rudolph et al. 2004), but differences between that study and ours confound any direct comparison of the results. Lewek et al. also quantified laxity differently, by measuring joint space change with stress radiography, and reported medial and lateral laxity separately. In contrast, we measured the total varus-valgus angular rotation under load in each direction while the participant was under anesthesia. The normalization procedures and period of gait cycle used to calculate CCIs also differed. Lewek et al. also combined OA and control subjects in their analysis, so the differences between the two groups may be driving the association between greater laxity and more co-contraction. Our results, using just participants with severe OA, identified no association between active stability measures during gait and passive varus-valgus laxity.
One of our secondary hypotheses was that active stability measures would be related to varus-valgus excursion during weight acceptance. Excessive knee motion may provide feedback that triggers altered control of the knee joint, potentially increasing the amount of muscle activity to actively stabilize the joint and compensate for the increased motion (Baratta, Solomonow et al. 1988). However, we did not find any relationships between active stability measures and varus-valgus excursion during WA. We have previously published data with this cohort identifying a relationship between larger varus-valgus excursion during gait and greater passive varus-valgus laxity ($r = 0.582$, p-value = 0.001) (Dissertation Chapter 2). That previous result combined with the current result suggest that passive structures may be the primary restraint to frontal plane motion in patients with severe OA (Baratta, Solomonow et al. 1988), although other specific measures of active stability must be further investigated. In an effort to identify what other factors are related to varus-valgus excursion in osteoarthritic knees, we explored the difference between the peak knee varus and valgus moments during weight acceptance. The difference in peak varus-valgus moment and varus-valgus excursion were highly correlated, with a Pearson correlation coefficient of $r = 0.724$, p-value<0.001. The difference in peak varus and valgus moment may potentially be driving the knee through a range of passive laxity, with little stabilizing influence from quadriceps activation or antagonist co-contraction during WA.

We identified no active stability measure related to strength with our submaximal reference activity normalization, which utilized tasks with comparable muscle forces to compare patients with OA. We further explored the effect of our normalization technique by testing the association between knee extension strength and the active stability
measures when using MVIC for EMG normalization. MVIC-normalized QH, LQH, and MQH avgCCI during WA were significantly correlated to knee extension strength (QH \( R=-0.625, \ p=0.007 \); LQH \( R=-0.495, \ p=0.043 \); MQH \( R=-0.630, \ p=0.007 \)). Each of the previous 3 co-contraction indices displayed an inverse relationship to strength, indicating that stronger individuals used less QH, LQH, and MQG avgCCI. However, this may be misleading when comparing participants, as differences in muscle activation are not inherently related to force differences when using MVIC normalization. The differences in co-contraction found with MVIC normalization could be the result of different isometric strength levels between our participants. This is the main reason we chose to use submaximal references tasks as it may reduce the influence of strength on active stability calculations. With the difficult producing maximal contractions, submaximal reference tasks require a consistent amount of force between participants and may allow for better comparisons.

No significant association was observed between active stability measures and perceived instability in this study. Schmitt et al. previously found differences in co-contraction between OA groups who perceive their knee to be stable or moderately/severely unstable (Schmitt and Rudolph 2008), however in the current study we found no association between perceived instability and active stability measures. This, inconsistent result could be due to differences in perceived instability reported by participants in the current study compared to Schmitt and Rudolph (2.6 ± 1.3 vs. 3.9 ± 1.2). Schmitt and Rudolph also investigated co-contraction indices during a perturbed gait task, where the floor shifted laterally underneath the subject. This may have altered muscle activity from standard gait and could explain why differences are reported.
between studies. In the current study, participants reported a range from severe instability to no instability, however no relationship was uncovered that linked any active stability measure to our participant’s perceived instability.

The participants in this study exhibited larger lateral co-contraction compared to medial co-contraction during WA, which may be a normal strategy to stabilize the adduction moment during WA (Lewek, Rudolph et al. 2004). Schipplein and Andriacchi found that 65% of OA patients were predicted to have lateral knee joint opening when no antagonistic muscle activity or passive soft tissue pre-tension was applied (Schipplein and Andriacchi 1991). They also predicted that the minimum muscle forces, by definition utilizing no antagonist co-contraction, were not sufficient to balance the external adduction moment during gait (Schipplein and Andriacchi 1991). In our participants, we observed large amounts of LQH avgCCI during WA, approximately 3 times larger than what was calculated for the MQH avgCCI. This lateral co-contraction may be an adaptation to balance the large external knee adduction moments common in subjects with severe medial compartment OA and varus deformity.

Previous studies normalizing EMG in OA populations have used maximal contractions (Childs, Sparto et al. 2004) (Lewek, Rudolph et al. 2004) (Hortobagyi, Westerkamp et al. 2005) (Rudolph, Schmitt et al. 2007) (Hubley-Kozey, Deluzio et al. 2008) (Heiden, Lloyd et al. 2009) (Hubley-Kozey, Hill et al. 2009) (Zeni, Rudolph et al. 2010) or peaks measured during gait (Schmitt and Rudolph 2008), both of which have important limitations when comparing between subjects. Investigations in healthy participants have found conflicting results as to the best normalization method to reduce intra-participant variability (Yang and Winter 1984; Knutson, Soderberg et al. 1994;
Burden and Bartlett 1999; Burden, Trew et al. 2003). However, Lehman and McGill state that normalizing to controlled, submaximal reference activities is helpful in clinical populations who are unable to attempt maximal efforts (Lehman and McGill 1999). Participants with severe OA exhibit large strength (O'Reilly, Jones et al. 1998) and reduced quadriceps activation (Hortobagyi, Westerkamp et al. 2005), which was our rationale for replacing maximal voluntary contractions with a less demanding task in this study. Using a simple reference activity allowed for a comparable amount of force produced between participants, which may reduce the confounding effect of maximal quadriceps inhibition and weakness on our results.

Limitations of this study include the following: The BMI of some OA participants may have impacted the ability to locate muscle bellies and transmit muscle activity. To account for this, we visually confirmed muscle activation during normalization tasks and quality controlled the EMG signals. If the signal did not qualitatively reflect the motion being produced, it was dropped from further analysis. Increased soft-tissue may also introduce artifact into the motion capture data collection. However, our use of the Point-cluster marker set and a functional hip joint center reduced these concerns. While we believe our EMG normalization technique provides improvement over MVICs in this population, it does not exactly estimate muscle forces and has limitations. Closed-chain bilateral ankle plantarflexion was chosen as the normalization task, which uses the entire body weight of each participant. Therefore OA participants with higher BMI may elicit a relatively larger muscle activity than those with lower BMI during the reference task. This could reduce the normalized muscle activation magnitudes of the plantarflexors calculated during dynamic activity, although EMG magnitudes are also likely larger.
during gait due to the increased mass. Mass differences are less likely to impact the normalization of the quadriceps and hamstrings, since the tasks used were open-chain knee extension and flexion, and the amount of force required to complete these tasks should be more similar between participants. Our participants walked with a large range of self-selected gait speeds [0.48 m/s 1.31 m/s], which is likely due to differences in pain and disability associated with knee OA. Faster gait speed has been associated with increased magnitude of all lower extremity joint moments (Landry, McKean et al. 2007) (Andriacchi and Strickland 1985) and increased EMG magnitudes (Yang and Winter 1985), but we did not control for speed in this study. Many participants would be unable to walk at a faster specified speed, while instructing others to walk at a slower than typical speed would likely alter gait kinematics, kinetics and EMG. Lastly, we did not separate males and females in this analysis. Our cohort was predominantly female, which was expected given the differences of OA prevalence by sex (Felson, Naimark et al. 1987). However we did not have enough male participants to power separate analysis. More research is needed to assess the extent of co-contraction differences between OA and matched-controls while utilizing a simple reference activity for normalization, as well as accounting for differences due to gait speed and sex.

4.6 Conclusion

While a greater contribution from active knee stability, specifically increased muscle activation or co-contraction of antagonist muscles, has been hypothesized to assist in stabilizing the knee in populations with greater passive laxity (Andriacchi 1994; Lewek, Rudolph et al. 2004) (Hirokawa, Solomonow et al. 1991), we did not find any
association between laxity and the active stability measures during gait evaluated in this study, even with eliminating the potential for muscular guarding during varus-valgus laxity examination. Varus-valgus excursion during weight acceptance, isometric knee strength and perceived instability were also unrelated to the active stability measures evaluate in this study. More research is needed to assess the interaction between active and passive stabilizers in OA patients during gait, and the extent of co-contraction differences between OA and matched-controls while utilizing a simple reference activity for normalization.

4.7 Acknowledgements

We would like to thank the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Award Number R01AR056700) for funding this research. We would also like to thank Jason Payne, MD and Alan Rogers, MD for their assistance in grading the radiographic OA severity and Andrew Glassman, MD, MS for his help recruiting OA participants.
Chapter 5: Intra-operative varus-valgus knee laxity and its relationship to biomechanical and surgical outcomes following TKA
5.1 Abstract

Objective: Many orthopaedic surgeons believe proper soft-tissue knee stability is important to a successful total knee arthroplasty (TKA). However there is little data guiding surgical decisions, as the current standard of care for gauging knee stability is qualitative and based on feel. Our purpose was to quantify varus-valgus knee laxity intra-operatively and identify relationships to post-surgical biomechanical and functional outcomes.

Methods: Thirty one individuals (33 knees) underwent laxity measurement of the native, osteoarthritic knee and replaced knee during surgery. Movement analysis during gait, clinical performance tests and self-reported evaluations were completed 6 months after surgery. Correlation coefficients identified associations between varus-valgus laxity and outcome measures.

Results: Varus-valgus laxity was 6.8 ± 3.4 degrees following TKA, which was an increase of 1.8 ± 3.5 degrees from the initial osteoarthritic measurement. Greater TKA laxity was associated with larger knee extension strength (p=0.027), larger knee flexion strength (p=0.024), and higher Knee Injury and Osteoarthritis Outcome Score (KOOS) quality of life subscore (p=0.046). Laxity in the osteoarthritic knee and replaced joint were significantly related to the change in varus-valgus laxity (OA p=0.043; TKA p<0.001).

Conclusion: Greater passive varus-valgus laxity was associated with better clinical performance on certain measures; however laxity was unrelated to the other biomechanical, clinical and self-reported outcome measures. A large range of varus-
valgus laxity and change in laxity was recorded in our subjects; surgical navigation systems may have the potential to reduce surgical variability and identify relationships between passive knee stability and patient outcomes.

5.2 Introduction

Total knee arthroplasty (TKA) is an increasingly common surgical procedure in the United States, with an estimated cost of $41 billion spent on approximately 700,000 TKAs performed annually (2012) (Kurtz, Ong et al. 2007). By 2030, this number is expected to increase to approximately 3.5 million procedures per year (Kurtz, Ong et al. 2007). Despite the high expense, TKA is considered a cost-effective treatment that provides long term benefits to society by reducing disability and increasing productivity (Ruiz, Koenig et al. 2013). Survivorship of knee implants is high, with over 90% success rate 10 years after surgery (Rand, Trousdale et al. 2003). However, approximately one in five primary TKA patients is not satisfied with the outcome (Bourne, Chesworth et al. 2010). Fifty-two percent (52%) of patients report limitations during functional activities after surgery (Noble, Gordon et al. 2005), with many patients unable to perform activities of daily living such as climbing stairs, gardening and recreational sports (Weiss, Noble et al. 2002).

and changes in ligament stiffness (Fishkin, Miller et al. 2002), which may alter the balance of load on the medial and lateral compartments of the knee (Sharma 2007). Postoperative knee stability is impacted by the amount of bone resected, size and alignment of implant components, soft-tissue properties, and pre-operative deformity. Surgical strategies such as the gap technique (Insall, Binazzi et al. 1985)(Griffin, Insall et al. 2000; Whiteside, Saeki et al. 2000; Boyer, Boublil et al. 2009; Lee, Park et al. 2010; Daines and Dennis 2014) or measured resection(Lee, Park et al. 2010; Daines and Dennis 2014) are used in an attempt to provide medio-lateral knee stability in extension and flexion. Equal sized rectangular gaps between the bone cuts of the femur and tibia, when the knee is in extension and flexion, are often referenced to approximate equal ligamentous force throughout the range of motion (Insall, Binazzi et al. 1985; Griffin, Insall et al. 2000). To achieve equal rectangular gaps, soft-tissue release techniques are often necessary to loosen the medial or lateral side of the knee joint. A knee joint that is too tight may not provide full range of motion for activities of daily living after surgery (Asano, Muneta et al. 2008), while too little passive ligamentous tension may cause instability of the knee prosthesis (Rodriguez-Merchan 2011). Knee stability is then assessed qualitatively with manual manipulations in the operating room after TKA components are installed (Bellemans, Ries et al. 2005; Siston, Goodman et al. 2007). Knee stability can also be adjusted after these manual manipulations based on the surgeon’s subjective assessment of how the knee feels, utilizing multiple techniques such as altering the implant sizes or performing additional soft-tissue releases. Despite the consensus regarding the importance of adequate knee stability, soft-tissue support is commonly only approximated by the gap technique or by feel during manipulation.
Varus-valgus knee laxity measurement is one way to quantitatively assess knee stability. Knee laxity has been previously defined as the amount of motion or angular rotation of the knee joint under load (Markolf, Mensch et al. 1976). Knee laxity assessments are commonly estimated from the subjective manipulation of the knee, but it is difficult to feel small changes in laxity or accurately estimate frontal plane knee angles. The magnitude of intra-operative varus-valgus laxity has been reported to be only 6.5 ± 2.3 degrees after TKA (Siston, Goodman et al. 2007). However orthopaedic surgeons deviated by 2.8 ±1.9 degrees when attempting to place a model femur and tibia in 0 degrees of mechanical frontal plane alignment (Shetty, Mullaji et al. 2011). Moreover, Shetty et al. did their study with the entire femur and tibia visible; it is likely much more difficult for surgeons to gauge changes in varus-valgus knee angle in the operating room, where the view of the femur and tibia is severely limited. Testing laxity in the operating room is also confounded by the surgeon’s ability to apply a consistent load to the knee joint. The magnitude of applied load may influence the amount of varus-valgus motion and there is no consensus on a standard loading magnitude in laxity assessments. These issues with subjective laxity assessments make it difficult to characterize intra-operative laxity after TKA or identify the impact of laxity on post-operative outcomes.

There is room for improvement in TKA outcomes, and many orthopaedic surgeons believe soft-tissue knee stability to be important to a successful surgery. With the advent of computer navigation systems, the potential exists to accurately measure kinematics in the operating room and calculate varus-valgus knee motion of the replaced knee joint. These new technologies allow for the quantification of knee laxity, which can then be statistically tested against patient outcomes. However, there is little published
data guiding surgical decisions on knee joint laxity and the current standard of care for gauging knee stability is qualitative and based on feel. Identifying the intra-operative factors that are related to function is an important step in improving patient outcomes.

Our purpose was to characterize intra-operative varus-valgus knee laxity, measured with surgical navigation and a knee stability testing device, and identify if laxity was related to post-operative biomechanical and clinical outcomes. We hypothesized that greater laxity in the knee joint, following implantation of TKA components, would be associated with more varus-valgus excursion during the weight acceptance phase of gait, poorer clinical performance, larger perception of knee instability and a worse self-evaluation of function.

5.3 Methods

5.3.1 Participants

Thirty-one individuals (33 knees) participated in this study after providing consent, which was approved by The Ohio State University institutional review board. Participants had predominantly medial compartment tibiofemoral osteoarthritis prior to primary TKA. The exclusion criteria for this study were as follows: Body Mass Index (BMI) > 45 kg/m²; inability to walk without an assistive device; predominantly lateral compartment OA; or revision TKA. Seven participants were dropped from the study for the following reasons: sterilization error prohibited intra-operative data collection (n=2); surgeon intra-operatively decided to use a constrained prosthesis (n=1); unable to obtain usable force data during gait (n=2); acute neurological condition prohibited follow up movement analysis testing (n=1); and participant refused to return for movement analysis
testing due to dissatisfaction with surgical result (n=1). Additionally, one participant was a statistical outlier on 4 of the 6 self-reported outcomes and only generated 0.18 Nm/kg of isometric knee extension torque. This lack of measured strength was not reflected in functional ability or net external joint moments generated during dynamic activity. Due to the combination of qualitative and quantitative discrepancies, this participant was dropped from further analysis. The demographics of the twenty-three included participants (25 knees) are shown in Table 5.1. Varus-valgus laxity was measured intraoperatively on the osteoarthritic joint before bone cuts and TKA components were implanted. Movement analysis, clinical assessments and self-reported surveys were administered 202 ± 40 days after surgery.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
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<td>15</td>
<td>23</td>
</tr>
<tr>
<td>Age, years</td>
<td>60.1 ± 8.2</td>
<td>60.0 ± 6.6</td>
<td>60.0 ± 7.0</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.78 ± 0.06</td>
<td>1.61 ± 0.07</td>
<td>1.67 ± 0.10</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>105.2 ± 20.2</td>
<td>89.2 ± 16.3</td>
<td>94.8 ± 18.9</td>
</tr>
<tr>
<td>BMI, kg/m^2</td>
<td>33.0 ± 5.9</td>
<td>34.2 ± 5.3</td>
<td>33.8 ± 5.4</td>
</tr>
<tr>
<td>Number of knees analyzed</td>
<td>8</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>Involved limb, no.</td>
<td>4/4</td>
<td>6/11</td>
<td>10/15</td>
</tr>
<tr>
<td>Pre-op standing alignment, degree (+ varus)</td>
<td>6.3 ± 3.3</td>
<td>4.1 ± 3.3</td>
<td>4.8 ± 3.4</td>
</tr>
<tr>
<td>Pre-op KL grade, no.</td>
<td>0/0/3/5</td>
<td>0/0/13/4</td>
<td>0/0/16/9</td>
</tr>
<tr>
<td>Follow up time, days</td>
<td>215 ± 57</td>
<td>197 ± 30</td>
<td>202 ± 40</td>
</tr>
</tbody>
</table>

Table 5.1: Study participant characteristics. Values are the mean ± standard deviation unless otherwise noted. Body Mass Index (BMI); Kellgren-Lawrence (KL).
5.3.2 Intra-operative Data Collection

Surgeries and intra-operative data collection were completed by three experienced orthopaedic surgeons (MB, AG, JG) at The Ohio State University Wexner Medical Center. The knee was opened with a standard medial para-patellar approach and the tibiofemoral joint was exposed. A posterior-stabilized implant [NexGen LPS Flex, Zimmer Inc., Warsaw, IN] was used in all patients, to eliminate potential inter-subject variability in posterior cruciate ligaments and their impact on knee stability. The distal femoral cut guide was set at 5 degrees of valgus for all participants, based on the intra-medullary cutting guide, to account for any varus alignment associated with predominantly medial knee OA. A measured resection technique was used by all surgeons, with soft-tissue releases made after bone cuts to achieve equal extension and flexion gaps.

To characterize passive knee joint laxity under anesthesia, we quantified the load-displacement relationship of the knee in the frontal plane. Kinematics were collected intra-operatively utilizing a validated custom navigation system (Siston, Giori et al. 2006) (Siston, Goodman et al. 2007). Retro-reflective marker clusters were rigidly attached to the distal femur and proximal tibia with cortical bone screws. The hip joint center was estimated from the femoral cluster motion during hip circumduction (Siston and Delp 2006). Anatomical landmarks on the femur and tibia were located by the orthopaedic surgeon using a stylus integrated with the motion capture system. The femoral origin was designated as the anterior-lateral attachment point of the posterior cruciate ligament. The anatomical coordinate system of the femur was defined using the hip joint center,
anterior-lateral attachment point of the posterior cruciate ligament, and the medial and lateral epicondyles (Siston, Giori et al. 2006). The origin of the tibia was defined by the midpoint of the tibial spine. The anatomical coordinate system of the tibia was defined using the midpoint of the tibial spine, the most medial and lateral points on the tibial plateau, and the most medial and lateral aspects of the malleoli (Siston, Giori et al. 2006). The custom surgical navigation system recorded relative tibiofemoral kinematics from the motion of the marker clusters and their relationship to the previously defined anatomical coordinate systems.

A complete description of the design and validation of the knee stability testing device is explained in Siston et al. (Siston, Maack et al. 2012), so only a brief description is provided here. Varus-valgus laxity was evaluated first on the osteoarthritic knee joint and then on the same knee after replacement components are installed. For the native osteoarthritic limb, laxity was measured before any bone cuts, ligament resections, or meniscal alterations were made. For the replaced knee, laxity was measured after the orthopaedic surgeon was satisfied with the fit and feel of the knee joint, and the replacement components installed. This allowed us to quantify the native osteoarthritic varus-valgus knee laxity, resultant varus-valgus laxity following TKA, and the change in laxity due to surgery.

The varus-valgus measurement process was the same in the OA knee and in the replaced knee. The orthopaedic surgeon applied loads to a modified Alvarado boot, which rested in a low-friction track of a custom knee stability testing device (Siston, Maack et al. 2012), using a force application handle (Figure 5.1). The handle was instrumented with a tension-compression load cell and linked to the custom surgical
navigation system. The orthopaedic surgeon alternately applied load in the varus and valgus direction until firm end points in motion, while manually restricting motion of the femur. The maximal load was determined on an individual basis to ensure patient safety. Varus and valgus moments were calculated about the defined femoral origin, using the data from the load cell and the surgical navigation system. This procedure was repeated until a minimum of 3 trials were completed, each with an applied varus and valgus load. Continuous measurement of tibiofemoral kinematics and load were collected. The time allotted to make intra-operative measurements was capped at 20 minutes to reduce risks associated with substantially longer periods under anesthesia and increased tourniquet time.
Figure 5.1: Passive varus-valgus testing completed intra-operatively with a custom knee stability device and surgical navigation system. The orthopaedic surgeon applies load in the varus and valgus direction with an instrumented handle, while manually restricting motion of the femur. Marker clusters screwed into the femur and tibia track kinematics with a motion capture camera. (Figure reproduced from Dissertation Chapter 3)

A varus-valgus load-displacement curve was calculated for three trials of alternating varus and valgus load (Figure 5.2). A third order polynomial was fit to the raw data for each trial. Laxity was calculated as the difference in varus-valgus knee angle when the knee was loaded with 10 Nm of varus and 10 Nm of valgus torque. Each participant’s overall varus-valgus laxity is determined from the average of these three trials. Figure 5.2 illustrates how laxity was defined by presenting the recorded load-displacement data for a single trial of one participant. This participant’s varus-valgus excursion was not centered on mechanical zero alignment, which can be expected in participants with predominantly medial compartment OA and a varus deformity.
Figure 5.2: Example of intra-operative load-displacement data and varus-valgus laxity calculation. Moment applied by the surgeon (Y axis) and frontal plane knee angle (X axis) were measured with a surgical navigation system and knee stability device. A 3rd order polynomial was then fit to the raw data for each trial. Varus-valgus laxity was calculated as the angular difference between a 10 Nm varus and 10 Nm valgus applied load. Each participant’s overall varus-valgus laxity was the average of the laxity calculated in three intra-operative load-displacement trials. Varus-valgus laxity is generally not centered on zero degrees, due to the varus deformity observed in our participant population. (Figure reproduced from Dissertation Chapter 3)
5.3.3 Movement Analysis of Gait

Movement analysis was completed on each participant before and after TKA. Marker data was collected at 150Hz using 10 Vicon MX-F40 cameras [Vicon; Oxford, UK] and filtered using a 4th order Butterworth filter at 6Hz. Ground reaction forces were recorded at 1500Hz from Bertec 4060-10 force plates [Bertec Corp; Columbus, Ohio] and used to identify heel contact and toe-off time points in the gait cycle. A modified point-cluster technique marker set (Andriacchi, Alexander et al. 1998) was used with additional iliac crest and upper body Plug-In Gait markers (Figure 5.3A). A functional hip joint center was estimated using the markers on the thigh during a star-arc motion. (Camomilla, Cereatti et al. 2006) Custom Bodybuilder [Vicon Motion Systems, Ltd., Oxford, UK] and MATLAB [Mathworks, Inc., Natick, MA] scripts calculated full body kinematics (Figure 5.3B and 5.3C).
Figure 5.3: A) Movement analysis was completed using a modified point-cluster marker set. B) A static calibration pose estimated the location of the femur and tibia utilizing a functional hip joint center and anatomical markers placed on the following bony landmarks; medial and lateral femoral epicondyles, medial and lateral tibial plateaus, and medial and lateral malleoli. C) Tracking marker clusters on the thigh and shank were used to quantify joint kinematics during dynamic activity. Varus-valgus excursion of the involved limb was calculated as the difference between peak varus and valgus knee angle during the weight acceptance phase of gait. (Figure reproduced Dissertation Chapter 3)

Weight acceptance (WA) was defined as the time period between initial contact (heel strike) and peak knee flexion during stance phase of the involved limb. Frontal plane excursion was calculated as the difference between peak knee varus and peak knee valgus angle during WA. Peak external knee adduction moment (pKAdM) was also found over WA, and normalized by body weight multiplied by height. Ensemble averages for each variable were calculated over four trials of gait at a self-selected speed.
5.3.4 Clinical Assessment

Tibiofemoral radiographic severity was assigned using the Kellgren-Lawrence (KL) grading system (Kellgren and Lawrence 1957). Two fellowship-trained, musculoskeletal radiologists (JP & AR) graded each participant by consensus. All radiographs were obtained in the same unit and consisted of bilateral anterior, bilateral posterior, lateral, and axial patellar views.

Standing, frontal-plane knee alignment was found during the motion analysis calibration trial. An estimated functional hip joint center (Camomilla, Cereatti et al. 2006), the midpoint of markers on medial and lateral femoral epicondyles markers and the midpoint of markers on the medial and lateral malleoli were used to estimate frontal plane mechanical knee alignment. Positive values indicate a varus knee angle. Similar methods have shown good correlation with standing radiographic alignment ($R^2=0.83$, $p<0.0001$) (Blazek, Asay et al. 2013). Self-selected gait speed was calculated in the middle of the 10 m walkway during motion analysis. The mean velocity of markers on the pelvis during both the right and left stance phases were averaged for four trials.

Clinical performance was gauged with isometric knee strength, the six-minute walk test (Enright 2003; Terwee, Mokkink et al. 2006) (6MW) and the timed stair climbing test (Van Nostrand, Kjelsberg et al. 1968; Rejeski, Ettinger et al. 1995) (SCT). Knee extension and flexion strength were found with a Biodex System 3 dynamometer [Biodex Medical Systems; Shirley, NY] during a maximal voluntary isometric contraction (MVIC). Each participant was seated upright with the involved limb at 60 degrees of knee flexion. Two 5 second maximal contractions, for each knee extension
and knee flexion, were separated by 30 seconds. The maximal torque produced during extension and flexion were recorded and normalized by each participant’s mass (Nm/kg). 6MW was measured as the distance a participant could walk around a 90 m indoor track in the six minute time limit. Participants were instructed to walk as far as possible in a safe manner. They were encouraged to not take any breaks or use a walking aid unless necessary to complete the test. SCT was measured as the time necessary to ascend and descend a 12 step staircase. The participants were instructed to complete the task as quickly as possible in a safe manner. They were encouraged to not use the handrail unless necessary to complete the test.

5.3.5 Self-reported Evaluations

Participants’ perceived knee instability was assessed from a question in the Knee Outcome Survey – Activities of Daily Living Scale (Irrgang, Snyder-Mackler et al. 1998). The question read, “To what degree does giving way, buckling, or shifting of the knee affect your daily activity?” and was scored on a 0 to 5 point scale. The designated responses and associated scores are as follows: 0 indicated that instability prevented all activity; 1 indicated that instability affected activity severely; 2 indicated that instability affected activity moderately; 3 indicated that instability affected activity slightly; 4 indicated that instability did not affect activity; and a score of 5 indicated no instability.

Reported function, specifically regarding the involved knee, was assessed from four subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos, Roos et al. 1998). These subscales included questions focused on pain, symptoms, activities of daily living (ADL) and knee-related quality of life (QOL). The subscale related to sport
and recreation was not applicable to the majority of participants in this cohort, and therefore not reported. Standardized answers to each question are provided and assigned a score from 0 to 4. These scores are normalized for each subscale, with a normalized score of 0 indicating extreme symptoms and 100 indicating no symptoms. The SF-36 questionnaire was also administered and the physical component score (PCS) and mental component score (MCS) used to gauge overall self-reported function (Ware and Sherbourne 1992; McHorney, Ware et al. 1993; McHorney, Ware et al. 1994)

5.3.6 Statistics

Male and female participants were analyzed together in order to maintain statistical power with our skewed sex distribution. Pairwise correlations were used to describe the association between varus-valgus laxity and gait, clinical and self-reported variables of interest. Pearson correlations were used to test for association between normally distributed variables. One male participant was missing SF-36 data, so all analyses on SF-36 include 24 individual knees. Perceived instability score is categorical and Spearman’s rank-order correlation was used. After initial inspection of each variable of interest, the Mental Component Score (MCS) of the SF-36 was found to be not normally distributed (Anderson-Darling p<0.05). Attempts to transform the data by natural log or square root to fit normality constraints were unsuccessful. Therefore a Spearman’s rank-order correlation was used to analyze any relationship between laxity variables and SF-36 MCS. Significance was set at alpha = 0.05.
5.3 Results

The mean and standard deviation for intra-operative knee laxity, movement analysis during gait, clinical measures, and self-reported evaluation is show in Table 5.2. Varus-valgus laxity was 6.8 ± 3.4 degrees following TKA, which was an increase of 1.8 ± 3.5 degrees from the initial osteoarthritic measurement of 5.1 ± 2.8 degrees. A one-sample t-test found the change in varus-valgus laxity to be significantly greater than zero (p=0.017). Standing varus knee alignment was significantly reduced from 4.8 ± 3.4 degrees in the osteoarthritic knee pre-surgery to -1.6 ± 3.5 degrees after surgery at 6 month follow-up (p-value < 0.001). The distributions of the other kinematic, kinetic, clinical and self-reported variables are shown in Table 5.2.

Correlations between varus-valgus laxity of the replaced knee joint and the other variables of interest are shown in Table 5.2. Varus-valgus laxity was significantly correlated to the change in varus-valgus laxity (R=0.680, p-value <0.001) (Figure 5.4). A trend was observed between laxity in the osteoarthritic knee and laxity after knee replacement (R=0.392, p-value=0.053). Varus-valgus laxity in the replaced knee joint was positively associated with knee extension strength (R=0.441, p-value=0.027), knee flexion strength (R=0.450, P=0.024), and KOOS QOL subscale (R=0.406, p-value=0.046).
<table>
<thead>
<tr>
<th>Intra-operative knee stability</th>
<th>TKA Varus-Valgus Laxity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± Standard Deviation</td>
</tr>
<tr>
<td>TKA varus-valgus laxity, °</td>
<td>6.8 ± 3.4</td>
</tr>
<tr>
<td>OA varus-valgus laxity, °</td>
<td>5.1 ± 2.8</td>
</tr>
<tr>
<td>Change in varus-valgus laxity, °</td>
<td>1.8 ± 3.5</td>
</tr>
</tbody>
</table>

| Gait analysis                  |                         |           |         |
| Varus-valgus excursion, °      | 4.2 ± 1.8                | 0.111     | 0.596   |
| Peak KAdM, %bw*ht              | 2.00 ± 0.94              | 0.025     | 0.906   |

| Clinical measures              |                         |           |         |
| Standing alignment, degrees (+ varus) | -1.6 ± 3.5            | -0.105    | 0.618   |
| Self-selected gait speed, m/s   | 1.15 ± 0.17              | 0.146     | 0.485   |
| Knee ext strength, Nm/kg        | 1.04 ± 0.40              | 0.441     | 0.027*  |
| Knee flex strength, Nm/kg       | 0.53 ± 0.23              | 0.450     | 0.024*  |
| 6 minute walk, m                | 469.3 ± 86.2             | 0.290     | 0.160   |
| Stair climbing test, sec        | 18.2 ± 6.2               | -0.370    | 0.069   |

| Self-reported evaluation        |                         |           |         |
| Perceived instability, no.      | 4.2 ± 1.0                | -0.105†   | 0.618   |
| KOOS pain                       | 80.4 ± 14.4              | 0.077     | 0.716   |
| KOOS symptoms                   | 53.6 ± 12.0              | -0.115    | 0.584   |
| KOOS activities of daily living | 84.8 ± 11.6              | 0.177     | 0.397   |
| KOOS quality of life            | 59.4 ± 19.1              | 0.403     | 0.046*  |
| SF-36 v2 - PCS                  | 46.8 ± 9.1               | 0.040     | 0.852   |
| SF-36 v2 - MCS                  | 55.2 ± 10.2              | 0.084†    | 0.695   |

Table 5.2: Results for variables of interest and association to passive varus-valgus laxity. Correlation coefficient (Corr Coef), osteoarthritis (OA), total knee arthroplasty (TKA), knee adduction moment (KAdM), percent body weight times height (%bw*ht), extension (ext), flexion (flex), Knee injury and Osteoarthritis Outcome Score (KOOS), physical component score (PCS), mental component score (MCS). †indicates Spearman correlation. Asterisks indicate significant association *(p<0.05) **(p<0.01) ***(p<0.001)
5.4. Discussion

This study accurately quantified varus-valgus laxity of the knee joint intraoperatively before and after TKA, utilizing custom surgical navigation and a custom stability testing device. On average there was a significant increase in varus-valgus laxity of 1.8 degrees ± 3.5 degrees (p=0.017) from the osteoarthritic to the replaced state. We found the measured range of varus-valgus laxity in the replaced knee joint across the participants to be 11.2 degrees, varying between 1.3 degrees to 12.5 degrees. In this study, we also investigated the relationship between intra-operative varus-valgus laxity and biomechanical, clinical and self-reported outcomes. Greater laxity in the replaced joint was related to larger knee strength and higher KOOS QOL subscale score, but we did not find consistent evidence linking varus-valgus laxity to other measures of function following TKA.

To better understand the significant relationships between TKA laxity and isometric strength and KOOS QOL, we investigated the pre-operative functional assessments and OA laxity. Relationships between OA laxity and function have been published previously (Dissertation Chapter 3); however the pre-operative variables for the 25 knees used in this analysis were examined separately and data presented here. Laxity of the osteoarthritic knees was also significantly related to pre-operative extension strength (R=0.510, p-value = 0.009) and a trend was observed with pre-operative flexion strength (R=0.366, p-value = 0.072). The intra-operative change in laxity was unrelated to post-operative knee strength, so it is possible that the post-operative relationship between TKA laxity and strength may be due to the pre-operative association observed in
our participant population. Isometric knee strength was also not significantly different from our pre-operative assessment (Paired T-Test: extension p-value = 0.549, flexion p-value = 0.160), so the influence of TKA laxity on strength may be minimal at 6 month follow up. However, KOOS QOL subscales did significantly improve following TKA (Paired T-Test: 95% confidence interval [26 43], p-value <0.001). Pre-operative varus-valgus laxity was unrelated to pre-operative KOOS QOL (R=0.079, p-value=0.707) (Figure 5.4), but significantly related at 6 month follow up (R=0.406, p-value=0.046) (Figure 5.5). Kuster et al. also reported a trend for greater range of motion and self-reported outcomes in more lax knee joints when compared to tighter knee joints (Kuster, Bitschnau et al. 2004). We did not find a relationship between laxity and any of the other gait, clinical or self-reported surgical outcome measures, therefore more research is needed between TKA laxity and varied measures of function before guiding clinical decisions on laxity of the replaced knee joint.
Figure 5.4: OA varus-valgus laxity was unrelated to pre-operative Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL) subscale (R=0.079, p-value=0.707).
Figure 5.5: TKA varus-valgus laxity was significantly related to post-operative Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL) subscale ($R=0.406$, $p$-value=0.046).

All participating surgeons were experienced in total knee replacements and executed the surgery within a personally acceptable range of qualitative knee stability. However, accurately and precisely evaluating knee laxity by hand is difficult and post-operative laxity depends on multiple factors. Varus-valgus laxity in the OA knee was significantly related to the change in varus-valgus laxity ($R^2= 0.17$, $p$-value=0.043) (Figure 5.6), with a negative correlation coefficient. OA knees with increased laxity had a reduction in the total varus-valgus laxity, while OA knees with smaller amounts of laxity
had increases. This indicates that as a group, our surgeons moved patients towards a middle ground of laxity as a group.

TKA varus-valgus laxity and change in laxity were also significantly related to each other, with the participants who had a larger change in laxity also tending to have more laxity overall after TKA ($R^2 = 0.46$, p-value<0.001) (Figure 5.7). This relationship may seem obvious and self-evident, but it is important to note that OA laxity exhibited a range of approximately 10 degrees in our cohort (Figure 5.6). If each patient’s TKA laxity was moved to a specific median value, there would be no relationship between the change in laxity and TKA laxity. However we found a stronger relationship between TKA laxity and change in laxity ($R^2 = 0.46$) than OA laxity and change in laxity ($R^2 = 0.17$). This result indicates that the magnitude of the change in laxity may be driving post-operative TKA laxity more so than initial OA laxity. Surgeons are moving patients toward the median laxity as a group, but they may be overcompensating for the initial OA laxity condition.
Figure 5.6: Experimental data for varus-valgus laxity in the native, osteoarthritic knee joint and the change in varus-valgus laxity from the OA to replaced knee joint. These variables were significantly related (R= -0.408, p-value=0.043) in our study participants. This figure illustrates how patients with greater OA laxity tended to have reductions in overall laxity in the replaced knee, while OA knees with less laxity had increases in post-operative laxity.
Figure 5.7: Experimental data for TKA varus-valgus laxity and the change in varus-valgus laxity from the OA to replaced knee joint. These variables were significantly related ($R=0.680$, p-value <0.001) in our study participants. This figure illustrates how patients with a positive change in laxity tended to have greater laxity than those with reductions of laxity in the operating room.
OA and TKA laxity are shown in Figure 5.8 as a quiver plot, with the change in laxity shown by the length of the arrows. While significant correlations were found between change in laxity and the OA and TKA laxity, this figure illustrates just how variable changes in laxity can be for subjects with similar initial OA laxity. The surgeons participating in this study have clinical practices that are focused on joint replacement surgery, so one can reasonably assume that they have an experienced feel for knee stability due to the volume of surgeries performed. For orthopaedic surgeons executing fewer total knee replacements, it is possible that subjective assessments of laxity may be more inconsistent.
Figure 5.8: Quiver plot with OA laxity on the x-axis and TKA laxity on the y-axis. The red squares and blue crosses are the OA laxity in females and males respectively, and the size of the arrow is the change in laxity in degrees. The tip of the arrow indicates the final laxity measured after TKA components were installed.
The change in varus-valgus laxity, from the osteoarthritic knee to the replaced joint, also varied from a reduction of 4.6 degrees to an increase of 6.7 degrees. However, a trend was also observed between laxity in the osteoarthritic knee and laxity after knee replacement ($R^2=0.15$, $p$-value=0.053), so while individual laxity changes varied drastically, pre-operative laxity accounted for approximately 15% of the variance in post-operative laxity.

In a previous study using the same cohort of participants, we found a relationship between varus-valgus laxity and varus-valgus excursion in the osteoarthritic knee joints; where greater varus-valgus laxity was significantly related to larger varus-valgus excursion during the weight acceptance phase of gait ($R^2=0.34$, $p$-value = 0.001) (Dissertation Chapter 3). We were expecting a similar relationship after joint replacement, but there was no significant association between these two variables post-operatively ($R^2=0.012$, $p$-value=0.596). It is possible that after TKA, patients do not need to rely on the passive stabilizers as much to restrict motion during gait. This could be due to changes in active knee stability or from a change in mechanical alignment of the knee joint. Another potential reason why a relationship was seen before, but not after TKA, may be the larger amount of time between TKA varus-valgus laxity measurement and follow up movement analysis. Some orthopaedic surgeons believe that stress relaxation occurs in a tighter joint post-operatively (Bellemans, D'Hooghe et al. 2006), while Sekiya et al. found a reduction in laxity from immediately after implantation to follow up examinations (Sekiya, Takatoku et al. 2009). Our participants came for follow up testing an average of 202 days after surgery, so it is possible the varus-valgus laxity changes following the intra-operative measurement. The soft-tissue structures which provide
passive stability may heal or adapt after TKA based on the new conditions within the knee. This could influence any potential relationship between our measured passive varus-valgus laxity and varus-valgus excursion during gait. More research is needed to identify the changes that occur to laxity in the months or years after surgery.

While surgical navigation was used as a measurement tool in this study, the surgeons were blinded to the results and did not use the data to make intra-operative decisions. While this study did not provide consistent evidence between laxity and all chosen outcome measures, a large range of post-operative varus-valgus laxity and changes in laxity were observed. There are currently no evidenced-based recommendations on the magnitude of varus-valgus laxity which achieves the best surgical outcomes; however technology may still be helpful in the operating room to assist surgeons with knee stability during total knee replacement. Surgical navigation has been previously shown to reduce the potential for alignment outliers (Siston, Giori et al. 2007) in particularly difficult cases. Surgical navigation, along with a knee stability testing device, may also be useful to reduce laxity outliers and assist surgeons who are not as experienced with qualitatively assessing knee stability during TKA.

Limitations of this study include the potential influence of soft-tissue artifact during motion analysis testing. Our participant population included those with a relatively high BMI, as we believe it is important to test a representative sample of the population and incorporate those that are most affected by OA. To mitigate the issues of soft tissue artifact during gait analysis, we utilized a point cluster technique marker set (Andriacchi, Alexander et al. 1998) and functional hip joint center algorithm (Camomilla, Cereatti et al. 2006) when calculating joint kinematics during gait. Combined, these techniques
reduced the effect of individual marker motion and eliminated the reliance on regression equations to calculate hip joint centers from pelvis markers. Another potential limitation was the choice to use self-selected walking speed rather than a single standard speed across participants. However, in this cohort it would have been difficult to standardize speed due to the variation of function in the participants following TKA. Moreover, in this cohort, gait speed was unrelated to varus-valgus laxity or change in laxity. Lastly, the degree of active stability from muscle activation patterns was not investigated in this analysis. Muscle forces likely play an important role in knee joint stability. Future work should attempt to identify the relationship between passive and active knee stabilizers in participants following TKA.

5.5 Conclusion

There are currently no quantitative evidenced-based data to guide how much laxity should be present intra-operatively following TKA component implantation. Greater varus-valgus laxity of the replaced knee joint was associated with larger knee strength and a higher score on the KOOS QOL subscale following surgery; however laxity was unrelated to the other biomechanical, clinical and self-reported outcome measures. A large range of varus-valgus laxity and change in laxity was recorded in our subjects; surgical navigation systems may have the potential to reduce surgical variability and identify relationships between passive knee stability and patient outcomes.
5.6 Acknowledgements

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Chapter 6: Research Findings and Future Work
6.1 Contributions

The main purpose of this research was to identify the contribution of soft-tissue knee stabilizers to biomechanical, clinical, and self-reported function in participants with severe OA and after TKA. Identifying the impact of passive and active knee stability on function may allow for improved surgical techniques and altered rehabilitation strategies for patients. A systematic review was first completed, to identify the previous literature on varus-valgus laxity in patients with OA. We then investigated the effect of knee stability using a longitudinal study design, where we tested individuals with severe OA before, during, and after TKA. The pre and post-operative testing sessions included biomechanical analysis, clinical performance measures and self-reported evaluations in an attempt to understand all aspects of patient function. Novel intra-operative measurements gauged knee stability among other surgical variables, to better understand surgical variability and quantify surgical technique. Our interdisciplinary approach, using a combination of advanced technology and comprehensive assessments, has never been previously attempted in individuals with OA and TKA. The major contributions of this work are listed below.

Increased varus-valgus laxity is a characteristic of knee joints with OA (Chapter 2).

Prospective studies on joint laxity are needed to identify if increased varus-valgus laxity is a causative factor in OA incidence and progression. Sixteen studies included varus-valgus laxity of a control group. Of these studies, 11 found a significant increase in some measure of laxity in the OA group compared to controls (Pai, Rymer et al. 1997;
Sharma, Lou et al. 1999; Wada, Kawahara et al. 2002; Lewek, Rudolph et al. 2004; Lewek, Ramsey et al. 2005; Lewek, Scholz et al. 2006; Rudolph, Schmitt et al. 2007; Schmitt and Rudolph 2007; Ishii, Noguchi et al. 2009; Miyazaki, Uchida et al. 2012; Kumar, Manal et al. 2013), 3 found no difference (Brage, Draganich et al. 1994; Wada, Imura et al. 1996; Creaby, Wrigley et al. 2010), and 2 did not report any statistics between groups as this was not the focus of those manuscripts (Sharma, Pai et al. 1997; Sharma, Song et al. 2010). Across the comparisons made in the 36 systematically selected studies, this finding was the most consistent. The majority of studies were not designed in a manner to distinguish if altered varus-valgus laxity leads to OA, but altered laxity was present in subjects with OA. This finding lends support to the theory that altered varus-valgus laxity is a component of OA and more research is needed to identify if cartilage degeneration is due to a change in joint contact patterns resulting from altered laxity (Andriacchi, Mundermann et al. 2004; Chaudhari, Briant et al. 2008).

Large variances exist in reported varus-valgus laxity and may be due to differences in measurement devices (Chapter 2).

Reported varus-valgus laxity varied greatly between studies using the 10 separate testing devices, and it is very difficult to compare studies measuring joint space change to those quantifying angular rotation. Large variations were also found when comparing similar devices measuring angular rotation. Paradoxically, total varus-valgus laxity was often smaller using devices which applied larger loads about the knee joint. These results may be due to differences between testing devices or differences in subject populations. Variance in OA severity between studies is likely not the cause of this paradoxical
relationship, since this phenomenon of increased laxity with less applied load still exists between similar levels of OA, as exhibited on Table 2.2. The following considerations have been previously identified as necessary to improve laxity measurement and reduce variation compared to the clinical examination: measure at a consistent knee flexion angle; reduce soft tissue artifact; reduce muscular guarding during manipulation; and accurately measure the applied load and the tibiofemoral motion (Markolf, Mensch et al. 1976; Cushnaghan, Cooper et al. 1990; Noyes, Cummings et al. 1991; Sharma, Lou et al. 1999). Of these considerations, there do not appear to be drastic differences or shortcomings between testing devices that could explain the reported variations. A “gold standard” of laxity measurement is necessary to validate devices and potentially allow for meta-analyses.

Passive varus-valgus laxity was linked to varus-valgus knee excursion (Chapter 3).

Greater varus-valgus laxity correlated with larger varus-valgus excursion during gait at a self-selected speed ($R^2=0.34$, $p=0.001$). It has been theorized that altered joint laxity may increase shear stress on cartilage and shift joint contact patterns during dynamic activity (Andriacchi, Mundermann et al. 2004). Our observation that greater laxity is associated with larger varus-valgus excursion is consistent with this theory. While we did not explicitly measure knee contact patterns, differences in varus-valgus excursion and alignment likely influence cartilage loading patterns. These changes may load areas of cartilage in a way not previously conditioned to and incite a degenerative process.
Greater varus-valgus laxity was associated to better measures of clinical performance, however no association was found between laxity and self-reported instability or function (Chapter 3).

Greater varus-valgus laxity was associated with larger knee extension strength, faster self-selected gait speed, farther 6MW distance and faster SCT times. To identify if any of these factors were independently associated with varus-valgus laxity, a linear regression analysis was performed with knee extension strength, knee flexion strength, 6MW and SCT all entered as factors. Only knee extension strength showed a significant association in this multi-factor analysis, so strength may be powering the other associations between clinical performance and laxity. While no correlation was found with perceived instability or the KOOS subscales, strength may play a role in a patient’s perception of instability.

Active stability was unrelated to passive varus-valgus laxity, varus-valgus excursion, knee strength, or perceived instability (Chapter 4).

Contrary to our hypothesis, we found no associations between passive knee laxity and average quadriceps activity (avgQUAD) or any of the co-contraction indices during gait. The interactions between passive soft tissue tension and active muscle forces are critical during gait (Andriacchi 1994)(Schippenlein and Andriacchi 1991), but no connection was revealed in this analysis. Stability of the knee joint may necessitate a more complex control strategy to modulate passive, active, and joint reaction forces than the proposed active stability measures. Active stability measures were calculated using a simple reference activity allowed for a comparable amount of force produced between
participants, which may reduce the confounding effect of maximal quadriceps inhibition and weakness on our results.

Intra-operative varus-valgus laxity, measured after TKA components are installed, was associated with knee strength and self-reported quality of life, but unrelated to the other biomechanical, clinical performance, and self-reported outcome measures (Chapter 5).

The current standard of care in evaluating knee stability in the operating room is qualitative, and there is little data guiding surgical decisions on knee joint laxity. Identifying the intra-operative factors that are related to function is an important step in improving patient outcomes. Post-operative varus-valgus laxity was associated with knee extension strength (R=0.441, p-value=0.027), knee flexion strength (R=0.450, P=0.024), and KOOS QOL subscale (R=0.406, p-value=0.046). Isometric knee strength was not significantly different from our pre-operative assessment to 6 month follow up testing (Paired T-Test: extension p-value = 0.549, flexion p-value = 0.160) and the intra-operative change in laxity was unrelated to knee strength. It is likely that the post-operative relationship between varus-valgus laxity and strength was due mainly to the pre-operative association between laxity and strength observed in our participant population. Pre-operative varus-valgus laxity was unrelated to pre-operative KOOS QOL (R=0.079, p-value=0.707) (Figure 5.6), but significantly related at 6 month follow up (Figure 5.7). This may indicate that patients prefer more varus-valgus laxity for better quality of life. However, the association between greater laxity and better function was not found in any of the other gait, clinical or self-reported surgical outcome measures, so more research in necessary before clinical recommendations on laxity can be supported.
Osteoarthritic knee laxity and replaced varus-valgus knee laxity are both significantly associated to the change in laxity measured intra-operatively, a large range of TKA laxity was observed (Chapter 5).

Varus-valgus laxity and change in laxity were significantly related to each other, with the participants who had a larger change in laxity also tended to have more laxity overall after TKA ($R^2 = 0.46$, p-value<0.001). Varus-valgus laxity in the OA knee was also significantly related to the change in varus-valgus laxity ($R^2= 0.17$, p-value=0.043) (Figure 5.5), with a negative correlation coefficient. For some OA knees with greater laxity, there was a reduction in the total varus-valgus laxity, while in other OA knees with a smaller amount of varus-valgus laxity, the change in laxity was positive to increase total laxity in the replaced joint. On average there was a significant increase in varus-valgus laxity of 1.8 degrees ± 3.5 degrees (p=0.017), with the measured range of post-operative varus-valgus laxity between 1.3 degrees to 12.5 degrees. Figure 5.5 illustrates how the orthopaedic surgeons in this study were able to achieve laxity changes toward a middle ground for the entire group of patients, based on their subjective feel of knee stability. However, given the large range in post-operative laxity, surgical navigation may be able to assist orthopaedic surgeons achieve more precise and accurate levels of knee stability in the operating room.
6.2 Future Work

The work presented in this dissertation has added to the knowledge of passive laxity in people with severe OA and TKA. However, in order to improve function and reduce disability in affected patients, more research needs to be performed. The following topics can build off the current research to further explore the impact of knee stability on function.

Long term surgical outcomes

We explored the relationship between passive varus-valgus knee laxity and function approximately 6 months after TKA. While this amount of time allows for improvements in function compared to pre-operative status, it may not be sufficient to see the complete recovery process. Two year outcomes have been designated as long term by many orthopaedic journals. While we are continuing to track study participants and have completed 2 year follow up assessments, we did not have a large enough sample to present that data in this dissertation. Revision rates are generally low with TKA; however approximately 10% of knee implants do not survive 10 years (Rand, Trousdale et al. 2003) and the percentage of revisions is higher in younger, more active patients. As more individuals are choosing TKA earlier in their life-span and our population is living longer, research on the influence of surgical variables and varus-valgus laxity on long term implant survival is necessary to adjust intra-operative decisions and potentially reduce revision rates.
Change in function from pre to post TKA

Chapter 5 investigated biomechanical function, clinical performance, and self-reported outcomes after TKA, but it did not account for pre-operative function. This is necessary to specifically investigate improvement following surgery and identify what factors are related to the largest improvements. Individuals choosing to undergo total joint replacement often have a large range of functional ability, so it is important to identify the pre-operative factors related to outcomes. This information can be used to better advise patients of the expected benefits during consultations and potentially alter intra-operative factors to achieve the greatest improvement. This information could also be used to guide rehabilitation protocols even before TKA, to ensure patients are going into surgery with the strength and function which allows for the best results.

Knee stability and biomechanical function during other dynamic tasks

Gait performed at a self-selected speed was chosen as the dynamic activity to analyze due to the importance for participants to stay mobile in their homes and community. Other tasks such as stair climbing, standing up from seated, squatting down and kneeling are also common activities of daily living and should be investigated. These other tasks may require greater degrees of strength and mobility compared to walking, and it is unknown how passive and active knee stability influence function in these activities. With the growing number of younger knee replacement recipients may, it may be of growing importance to investigate the effects of passive and active knee stability during running and jogging. The ability to stay physically active, and the effect that has
on the implanted knee components, are important outcome measures following joint replacement.

**Prospective study of varus-valgus laxity and OA initiation**

Increased varus-valgus laxity has been shown to be a characteristic of knees with OA, and altered laxity is hypothesized to be a cause of OA. A study prospectively measuring varus-valgus laxity and cartilage degeneration is necessary to identify if increases in varus-valgus laxity is a causative factor in OA incidence and progression.

**Varied subject populations**

This research has been performed on participants with predominantly medial compartment OA who are awaiting TKA. Knee stability is likely to differ between the participants tested in this dissertation and those with predominantly lateral compartment OA or people with varied severity of OA. Passive varus-valgus laxity is also a consideration in patients who undergo high tibial osteotomy, where a wedge of bone is removed to better align the knee joint. The contributions of knee stability to function may be different in each of these groups of patients with OA. Sex differences are also seen in laxity measurements, so it would be important to analyze mean and women separately to personalize knee stability for the individual patient.
Varied implant prosthesis designs

Posterior-stabilized prostheses from one orthopaedic device company were used on all study participants, in order to reduce the effect of differences between designs. Designs that retain the posterior-cruciate ligament are also common, and differences in kinematics and femoral rollback have been reported. The retention of an additional knee ligament will likely change some component of passive knee stability and may interact with active stability strategies during dynamic movement. Mobile bearing designs and curvature differences between implants could also impact stability and function.

Passive stability

Passive stability in the frontal plane was assessed by measuring laxity at 10 Nm varus and valgus load. Laxity can also be assessed at other loads below what the surgeon can safely apply. End range stiffness, measured by the slope of the load displacement curve, may be important to resisting motion during dynamic activity. Passive knee stability in other planes of motion, for example anterior-posterior and internal-external rotation were also measured intra-operatively but this data has not yet been investigated. Overall passive knee stability is not a single value such as varus-valgus laxity, but a complex interaction of restraint from a multitude of ligaments and other soft-tissue structures. Quantitative data measured intra-operatively is necessary to statistically test passive knee parameters against function and surgical outcomes.
Active stability

We utilized average quadriceps activation and co-contraction of antagonist muscle pairs as our active stability measures in this dissertation. Increased co-contraction has been reported in patients with OA and co-contraction is reduced following TKA. We found no association between these active stability measures and passive varus-valgus laxity in osteoarthritic knee joints; however other neuromuscular strategies could potentially provide stability for the knee joint. Investigation of muscle onset timing or simulations which can estimate actual muscle force would be beneficial in identifying why muscle activation is altered in OA patients and changes after TKA. The impact of rehabilitation and physical therapy on active stability is also unknown. Increased co-contraction has been hypothesized to increase load on the knee joint and contribute to cartilage degeneration with OA. Continued co-contraction after surgery may increase wear and reduce the lifespan of the polyethylene spacer and other components.

Attempting to reduce co-contraction, while not affecting overall knee stability may be able to slow OA progression and improve outcomes after TKA.

Passive laxity changes after TKA

Varus-valgus excursion was related to laxity in the native osteoarthritic knee but not in the replaced joint. One potential explanation is that laxity measured on the replaced joint intra-operatively may change over time. At our follow up assessments 6 months after surgery, the previously measured passive knee laxity is not accurate to the current conditions of the knee joint. Re-testing passive varus-valgus laxity, after the 6 month follow up assessment, is a simple way to measure and confirm if varus-valgus laxity
changes after TKA. However, this would require our volunteer participants to undergo another surgery on their involved limb. It may be difficult to find participants willing to complete another passive knee stability testing procedure, but this would be helpful in understanding how laxity if influenced by the healing and rehabilitation process following TKA. It would also inform surgeons on whether the laxity they feel in the operating room is the resultant laxity of the knee in-vivo following TKA.

6.3 Summary

Osteoarthritis (OA) is the leading cause of disability in the United States, affecting over 50 million adults (2009). The cause of knee OA is likely multifactorial, however mechanical factors have been suggested to be the most important risk factors (Visser, de Mutsert et al. 2014). Increased joint laxity has been hypothesized to initiate cartilage degeneration and lead to joint degeneration (Andriacchi, Mundermann et al. 2004; Andriacchi and Mundermann 2006; Chaudhari, Briant et al. 2008; Andriacchi, Koo et al. 2009). Increased varus-valgus laxity has been reported by 11 studies of patients with OA compared to controls (Dissertation Chapter 2); however the impact of laxity on knee function is still unclear. In Chapter 3 of this dissertation, we investigated associations between passive varus-valgus laxity and function. We identified greater passive laxity to be related to larger frontal plane motion during gait, in our participants with severe medial compartment OA. We also found a significant association between greater laxity and farther walking distance and larger knee extension strength. In Chapter 4, we investigated the potential for active knee stability to interact with passive knee laxity and influence function. However, no associations were found between active
stability measures and laxity or biomechanical, clinical, or self-reported variable of interest. These studies improve upon our understanding between the mechanisms behind varus-valgus knee laxity and biomechanical, clinical and self-reported function. More research is necessary to improve treatment strategies and potentially reduce risk factors associated with OA.

There are no current treatments to stop the progression of OA; therefore, knee replacement is generally considered the final step to improve function and reduce pain associated with severe OA. Total knee arthroplasty (TKA) is an increasingly common surgical procedure in the United States, with over 700,000 performed annually (2012) at an estimated cost of $41 billion (Kurtz, Ong et al. 2007). Fifty-two percent (52%) of TKA patients report limitations during functional activities (Noble, Gordon et al. 2005), with many patients unable to perform activities of daily living such as climbing stairs, gardening and recreational sports (Weiss, Noble et al. 2002). The importance of surgical technique and precision to improved function are often emphasized, but it can be difficult to quantify these variables. Scientifically testing for cause and effect relationships between modifiable surgical variables and outcomes is paramount to improving standard of care and patient function. In Chapter 5 we tested the influence of passive varus-valgus laxity on function. We found greater passive varus-valgus laxity was associated with larger knee strength and a higher KOOS QOL subscore; however laxity was unrelated to the other biomechanical, clinical and self-reported outcome measures. A large range of varus-valgus laxity and change in laxity was recorded in our subjects; surgical navigation systems may be useful to reduce surgical variability and identify relationships between passive knee stability and patient outcomes.
This is the first combination of pre-operative, intra-operative, and post-operative laxity measurements tested against biomechanical, clinical and self-reported functional data in subjects with severe OA and following TKA. We were able to identify the impact of knee laxity on our chosen outcomes and demonstrated how technology can be used in the operating room to quantify pre-operative condition and surgical variables. This work will lead to further research on the impact of surgical decisions and develop cause and effect relationships to function.
### Appendix A – Extracted data from systematic review

<table>
<thead>
<tr>
<th>Author</th>
<th>Laxity measurement technique</th>
<th>Subject Groups</th>
<th>Quantified Laxity</th>
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</thead>
<tbody>
<tr>
<td>Tallroth 1987</td>
<td>TELOS VV stress radiograph 150 N applied load Knee flexion angle not reported</td>
<td>Varied OA: n = 26 (38 knees) (14 male, 12 female) Mean age = 59 range [36-75] slight OA = 13 moderate OA = 15 severe OA = 10</td>
<td>Joint Space Translation (mm) Weight-bearing compartment: Mean width in compression: 2.2 Mean width in widening: 6.8 Non-weight-bearing compartment: Mean width in compression: 5.1 Mean width in widening: 9.3 Percent Change in joint space of weight-bearing compartment compared to lying Slight OA: -17% standing, -37% compression, +62% widening Moderate OA: -28% standing, -46% compression, +88% widening Severe OA: -33% standing, -49% compression, +79% widening</td>
</tr>
<tr>
<td>Pottenger 1990</td>
<td>Stainless steel intramedullary goniometer Force applied until firm end point 20 degrees of knee flexion</td>
<td>Unicompartmental OA: n = 17 (20 knees) (5 male, 12 female) Mean age = 70.8 range [56-86] Prior to TKA medial compartment = 16 lateral compartment = 4</td>
<td>Angular Rotation (deg) Entire Group OA: 11.0 (0.7) Medial compartment OA: 10.6 (0.6) Lateral compartment OA: 12.3 (2.3) ACL present: 10.8 (0.8) ACL absent: 11.4 (1.4)</td>
</tr>
</tbody>
</table>

Table A.1: Extracted data from all selected studies in Dissertation Chapter 2 systematic review. Laxity reported in mean (standard deviation) unless otherwise noted. Varus-valgus (VV); Kellgren-Lawrence (KL): osteoarthritis (OA).
<table>
<thead>
<tr>
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<th>Laxity measurement technique</th>
<th>Subject Groups</th>
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<tbody>
<tr>
<td>Brage 1994</td>
<td>Genucom Knee Analysis System 12.2 Nm applied VV load 20 degrees of knee flexion</td>
<td>Bilateral OA: n=22 (43 knees) (sex not reported) Mean age = 65 range [45-85] Mild = 15 Moderate = 15 Severe = 18 Age matched controls: n = 9 (18 knees)</td>
<td>Angular Rotation (deg) Mild OA = 15 (4.8) Moderate OA = 10.9 (3.9) Severe OA =10.4 (3.6) Controls = 11.3 (3)</td>
</tr>
<tr>
<td>Wada 1996</td>
<td>Genucom Knee Analysis System 8 Nm applied VV load 20 degrees of knee flexion</td>
<td>Bilateral, medial OA: n = 34 (68 knees) (sex not reported) Mean age = 71 range [61-82] KL Grade 1 = 15 KL Grade 2 = 16 KL Grade 3 = 19 KL Grade 4 = 18 Elderly controls: n =12 (24 knees) (sex not reported) Mean age = 68 range [60-74]</td>
<td>Angular Rotation (deg) KL Grade 1 = 11.5 (5.4) KL Grade 2 = 11.9 (4.3) KL Grade 3 = 15.1 (5.1) KL Grade 4 = 15.9 (5.4) Controls = 12 (3.8)</td>
</tr>
<tr>
<td>Pai 1997</td>
<td>Measurement device not reported Load not reported Knee flexion not reported</td>
<td>Bilateral OA: n = 30 (60 knees) (8 male, 22 female) Mean age = 68.2 (8.3) KL Grade (2/2) = 20 KL Grade (2/3,3/2,3/3) = 26 KL Grade (2/4,3/4,4/2,4/3,4/4) = 14 Elderly controls: n = 29 (58 knees) (12 male, 17 female) Mean age = 71.3 (8.3) KL Grade 0 = 58</td>
<td>Joint Space Translation (mm) Medial and Lateral compartment translations combined. Bilateral OA: Right - 2.4 (1.8) Left - 2.2 (1.8) Elderly controls: Right - 1.1 (1.1) Left - 0.8 (1.2)</td>
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<tr>
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</thead>
</table>
| Sharma 1997 | Measurement device not reported | **Unilateral OA:** n = 28 (28 knees) (13 male, 15 female)  
Mean age = 65.5 (14.5)  
KL Grade 0 = 6 unaffected  
KL Grade 1 = 22 unaffected  
KL Grade 2 = 7  
KL Grade 3 = 12  
KL Grade 4 = 9  
Elderly controls: n = 29 (58 knees) (13 male, 16 female)  
Mean age = 71 (11.5)  
KL grade 0 = 29 | **Joint Space Translation (mm)**  
Medial and Lateral compartments combined.  
*Unilateral OA:*  
Affected limb= 3.1  
Unaffected limb= 1.3  
*Elderly controls:*  
Right = 1.3  
Left = 0.8 |
| Sharma 1999 | Custom VV testing device  
12 Nm applied load  
20 degrees of knee flexion | **Varied OA:** n=164 (328 knees) (no sex information)  
Mean age = 62.6 (11.5) range [33-91]  
Right:Left  
KL Grade 0 = 7 : 1  
KL Grade 1 = 12 : 19  
KL Grade 2 = 78 : 76  
KL Grade 3 = 42 : 42  
KL Grade 4 = 25 : 26 | **Angular Rotation (deg)**  
OA Right = 5.1 +/- 1.9  
OA Left = 4.6 +/- 1.8 |
| Sharma 1999 | Custom VV testing device  
12 Nm applied load  
20 degrees of knee flexion | **Varied OA:** n=164 (328 knees) (46 male, 118 female)  
Mean age = 62.6 (11.5) range [33-91]  
KL Grade 0/1 = 39  
KL Grade 2 = 154  
KL Grade 3 = 84  
KL Grade 4 = 51  
Older controls: n = 24 (10 male, 14 female)  
Mean age = 71.4 (8.3) range [53-85]  
Young controls: n=25 (no sex information)  
Age range [20-40] | **Angular Rotation (deg)**  
*OA:*  
KL Grade 0/1 = 4.9 (0.35)  
KL Grade 2 = 4.4 (0.16)  
KL Grade 3 = 5.1 (0.22)  
KL Grade 4 = 5.7 (0.30)  
*Controls:*  
Elderly controls = 3.4 (1.1)  
young controls = 2.9 (1.0) |

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</thead>
<tbody>
<tr>
<td>Wada 2002</td>
<td>Genucom Knee Analysis System 8 Nm applied load 20 degrees of knee flexion</td>
<td>Varied Medial OA: n=38 (38 knees) (3 male, 35 female) Mean age = 72.6 range [58-80] Prior to TKA Age matched controls: n=23 (2 male, 21 female) Mean age =71.5 [60-76]</td>
<td>Angular Rotation (deg) OA = 15 (7.9) Controls: 12 (4.0)</td>
</tr>
<tr>
<td>Sharma 2003</td>
<td>Custom VV testing device 12 Nm applied load 20 degrees of knee flexion</td>
<td>Varied OA: n=236 (sex not reported) Mean age = 68.6 (10.8) KL Grade &gt;=2</td>
<td>Angular Rotation (deg) at baseline: OA = 5.9 (2.9)</td>
</tr>
<tr>
<td>Sharma 2003</td>
<td>Custom VV testing device 12 Nm applied load 20 degrees of knee flexion</td>
<td>Varied OA= 237 (328 knees) (45 male, 126 female) Mean age = 64.0 (11.0) Right side : KL Grade 0 = 0 KL Grade 1 = 11 KL Grade 2 = 110 KL Grade 3 = 50 KL Grade 4 = 0</td>
<td>Angular Rotation (deg) at baseline: OA Right = 5.32 (2.03)</td>
</tr>
<tr>
<td>Lewek 2004</td>
<td>TELOS VV stress radiograph 150 N applied load 20 degrees of knee flexion</td>
<td>Varied Medial OA: n=12 (6 male, 6 female) Mean age = 50.3 (7.4) range [39-64] age matched controls: n=12 (6 male, 6 female) Mean age = 49.5 (6.1) range [40-62]</td>
<td>Joint Space Translation (mm) OA: Medial compartment= 5.1 (1.5) Lateral compartment = 3.6 (1.6) Control: Medial compartment = 3.2 (1.0) Lateral compartment = 4.3 (1.3)</td>
</tr>
<tr>
<td>Lewek 2005</td>
<td>TELOS VV stress radiograph 150 N applied load 20 degrees of knee flexion</td>
<td>Varied Medial OA: n=21 (14 male, 7 female) Mean age = 49.3 (7.0) range [39-64] age matched controls: n=19 (12 male, 7 female) Mean age = 49.3 (5.8) range [38-62]</td>
<td>Joint Space Translation (mm) OA: Medial compartment = 5.0 (1.7) Lateral compartment = 3.4 (1.7) Control: Medial compartment =3.3 (0.9) Lateral compartment = 4.1 (1.5)</td>
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</tr>
</thead>
<tbody>
<tr>
<td>van der Esch 2005</td>
<td>Custom VV testing device</td>
<td>Varied OA: n=35 (70 knees) (9 male, 26 female) Mean age = 66.5 (10.3) range [40-85] Categorized by joint space narrowing and osteophyte Joint Space Narrowing 0 = 13 Joint Space Narrowing 1 = 31 Joint Space Narrowing 2 = 16 Joint Space Narrowing 3 = 10 Osteophyte 0 = 9 Osteophyte 1 = 44 Osteophyte 2 = 14 Osteophyte 3 = 3</td>
<td>Angular Rotation (deg) Entire Group = 8.0 (4.1) JSN 0 = 5.3 (3.0) JSN 1 = 9.3 (4.7) JSN 2 = 8.0 (2.8) JSN 3 = 8.0 (3.7) Osteophyte 0 = 8.0 (3.7) Osteophyte 1 = 8.0 (3.9) Osteophyte 2 = 7.4 (3.2) Osteophyte 3 = 9.6 (3.0)</td>
</tr>
<tr>
<td>Lewek 2006</td>
<td>TELOS VV stress radiograph</td>
<td>Unilateral Medial OA: n= 15 (30 knees) (9 male, 6 female) Mean age = 48.7 (7.4) age matched control: n=15 (30 knees) (9 male, 6 female) Mean age = 48.4 (6.3)</td>
<td>Joint Space Translation (mm) OA: Involved medial compartment = 5.3 (1.5) Involved lateral compartment= 3.5 (1.5 ) Uninvolved medial compartment = 4.2 (1.8) Uninvolved lateral compartment = 4.2 (2.4) Controls: Medial compartment = 3.2 (0.9) Lateral compartment = 4.0 (1.4)</td>
</tr>
<tr>
<td>van der Esch 2006</td>
<td>Custom VV testing device</td>
<td>Varied OA: n = 86 (79 knees) (21 male, 65 female) Mean age = 63.9 (9.1) range [46-83] Right : Left KL Grade 0 = 7 : 5 KL Grade 1 = 7 : 11 KL Grade 2 = 39 : 35 KL Grade 3 = 24 : 20 KL Grade 4 = 2 : 8</td>
<td>Angular Rotation (deg) OA Left = 6.9 (3.4) OA Right = 6.9 (3.2)</td>
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</tr>
</thead>
</table>
| Rudolph 2007 | TELOS VV stress radiograph 150 N applied load 20 degrees of knee flexion                  | Varied Medial OA: n =15 (15 knees) (8 male, 7 female)  
Mean age = 49.2 range [39-57] young controls: n=15 (15 knees)  
(7 male, 8 female)  
Mean age = 20.6 range [18-25] middle aged controls: n=15 (15 knees)  
(8 male, 7 female)  
Mean age = 49.2 range [40-57] older controls: n=14 (14 knees)  
(4 male, 10 female)  
Mean age = 68.8 range [60-80] | Joint Space Translation (mm)  
Approximate laxity mean and SD measured from bar graph  
OA:  
Medial compartment = 4.77(1.72)  
Lateral compartment = 3.56 (1.65)  
Middle age controls:  
Medial compartment = 3.12 (0.95)  
Lateral compartment = 4.20 (1.27)  
Older controls:  
Medial compartment = 3.05 (0.76)  
Lateral compartment = 3.63 (1.34) |
| Schmitt 2007 | TELOS VV stress radiograph 150 N applied load 20 degrees of knee flexion                  | Varied Medial OA: n=28 (28 knees) (14 male, 14 female)  
Mean age = 60.4 range [39-78]  
KL Grade 2 = 17  
KL Grade 3 = 8  
KL Grade 4 = 3  
age matched control: n=26 (26 knees)  
(13 male, 13 female)  
Mean age = 58.5 [38-76]  
KL Grade 0 = 26 | Joint Space Translation (mm)  
Mean (95% confidence interval)  
OA:  
Medial compartment = 4.23 (3.57 4.89)  
Lateral compartment = 2.77(2.28 3.27)  
Controls:  
Control medial compartment = 2.76(2.38 3.14).  
Control lateral compartment = 3.52(3.04 4.00) |
| Siston 2007 | Custom surgical navigation Load applied to hard end point  
Maximal extension & 90 degrees of knee flexion  | Tricompartmental OA: n=24 (24 knees) (24 male, 0 female)  
Age not reported Prior to TKA | Separated Angular Rotation (deg)  
OA extension valgus = 3.9 (1.7)  
OA extension varus = 2.0 (1.2)  
OA flexion valgus = 2.5 (1.5)  
OA flexion varus = 0.6 (1.5)  
Total Angular Rotation (deg)  
OA extension = 5.9 (2.2) deg  
OA flexion = 3.1 (1.8) deg |

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Table A.1 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Laxity measurement technique</th>
<th>Subject Groups</th>
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</tr>
</thead>
<tbody>
<tr>
<td>van der Esch 2007</td>
<td>Custom VV testing device 7.7 Nm applied load 20 degrees of knee flexion</td>
<td>Varied OA: n=86 (172 knees) (male 21, female 65) Mean male age = 64 (7.3) Mean female age = 63 (10) Male/Female Right : Left KL Grade 0 = 0/7 : 0/5 KL Grade 1 = 2/5 : 2/9 KL Grade 2 = 15/24 : 9/26 KL Grade 3 = 3/21 : 6/14 KL Grade 4 = 0/2 : 3/5 KL Grade Missing = 1/1 : 6/6</td>
<td>Angular Rotation (deg) OA Male Left = 4.6 (2.5) OA Male Right = 4.6 (2.2) OA Female Left = 7.7 (3.3) OA Female Right = 7.8 (3.1)</td>
</tr>
<tr>
<td>Jenny 2008</td>
<td>Orthopilot surgical navigation Maximal manual valgus applied load Maximal knee extension Degrees of knee flexion not reported</td>
<td>Medial OA: n = 20 (20 knees) (sex not reported) (age not reported) Prior to TKA</td>
<td>Valgus Rotation (deg) OA alignment without applied load = 5.6 (3.1) OA alignment with applied valgus load = 1.4 (3.3) OA medial laxity = 4.2 (2.7)</td>
</tr>
<tr>
<td>Lim 2008</td>
<td>VV modified Kin-Com Leg moved passively 10 times from varus to valgus at 5 degrees per second. Varus and Valgus angles determined where 8Nm of passive resistance was reached. 20 degrees of knee flexion</td>
<td>Varied Medial OA: n=107 (107 knees) (48 male, 59 female) Mean age = 64.6 (8.4) Least Varus: n = 37 (37 knees) (13 male, 24 female) Mean age = 62.0 (8.9) KL Grade 2: 23 KL Grade 3: 8 KL Grade 4: 6 Moderate Varus: n = 36 (36 knees) (15 male, 21 female) Mean age = 63.5 (7.8) KL Grade 2: 9 KL Grade 3: 15 KL Grade 4: 12 Most Varus: n = 34 (34 knees) (20 male, 14 female) Mean age = 68.5 (7.5) KL Grade 2: 2 KL Grade 3: 6 KL Grade 4: 26</td>
<td>Angular Rotation (deg) Entire Group OA: Varus-Valgus Arc = 10.8 (4.3) Varus = 5.5 (2.3) Valgus = 5.3 (2.3) Least Varus OA Group: Alignment = 0.5 (1.6) Varus-Valgus Arc = 12 (4.9) Varus only = 6.5 (2.5) Valgus only = 5.6 (2.6) Moderate Varus OA Group Alignment = 4.2 (1.1) Varus-Valgus Arc = 10.0 (3.7) Varus only = 5.1 (2.0) Valgus only = 4.9 (2.0) Most Varus OA Group Alignment = 7.7 (1.7) Varus-Valgus Arc = 10.3 (4.0) Varus only =4.9 (2.0) Valgus only = 5.4 (2.2)</td>
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Table A.1 continued

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<thead>
<tr>
<th>Author</th>
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<tbody>
<tr>
<td>Schmitt</td>
<td>TELOS VV stress radiograph</td>
<td>Varied Medial OA: n=52 (52 knees)</td>
<td>Joint Space Translation (mm)</td>
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<tr>
<td>2008</td>
<td>150 N applied load</td>
<td>No instability; n=20 (12 male, 8 female)</td>
<td>No instability OA:</td>
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<tr>
<td></td>
<td>20 degrees of knee flexion</td>
<td>Mean age = 65.1 range [44-78]</td>
<td>Medial = 4.60 (1.47)</td>
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<td>KL grade 2 = 12</td>
<td>Lateral = 2.79 (1.20)</td>
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<td>KL grade 3 = 5</td>
<td>Mild instability OA:</td>
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<td>KL grade 4 = 3</td>
<td>Medial = 3.72 (1.42)</td>
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<td>Mild instability: n=12 (8 male, 4 female)</td>
<td>Lateral = 2.33 (1.04)</td>
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<td>Mean age = 54.7 range [40-71]</td>
<td>Instability affects function OA:</td>
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<td>KL grade 2 = 5</td>
<td>Medial = 4.48 (1.94)</td>
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<td>Lateral = 2.29 (1.14)</td>
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<td>KL grade 4 = 2</td>
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<td>KL grade missing = 2</td>
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<td>Instability affects function: n=20 (10 male, 10 female)</td>
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<td>Mean age = 62.9 [49-77]</td>
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<td>KL grade 2 = 8</td>
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<td>KL grade 3 = 6</td>
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<td>KL grade 4 = 6</td>
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</tr>
<tr>
<td>Schmitt</td>
<td>TELOS VV stress radiograph</td>
<td>Varied Medial OA: n = 20 (20 knees)</td>
<td>Joint Space Translation (mm)</td>
</tr>
<tr>
<td>2008</td>
<td>150 N applied load</td>
<td>OA Stable: n = 10 (male 5, female 5)</td>
<td>OA Stable:</td>
</tr>
<tr>
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<td>20 degrees of knee flexion</td>
<td>Mean age = 64.5 range [44-78]</td>
<td>Medial = 4.31 (1.16)</td>
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<td>KL grade 2 = 7</td>
<td>Lateral = 3.08 (1.42)</td>
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<td>KL grade 3 = 2</td>
<td>OA Unstable:</td>
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<td>KL grade 4 = 1</td>
<td>Medial = 4.54 (2.28)</td>
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<td>OA Unstable: n = 10 (male 6, female 4)</td>
<td>Lateral = 2.55 (1.28)</td>
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<td>Mean age = 64.7 range [49-77]</td>
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<td>KL grade 2 = 4</td>
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<td>KL grade 3 = 4</td>
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<td>KL grade 4 = 2</td>
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<tr>
<td>Sharma</td>
<td>Custom VV testing device</td>
<td>Varied OA: n = 153 (251 knees)</td>
<td>Angular Rotation (deg)</td>
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<tr>
<td>2008</td>
<td>12 Nm applied load</td>
<td>(sex not reported)</td>
<td>OA Medial = 2.52 (1.28)</td>
</tr>
<tr>
<td></td>
<td>20 degrees of knee flexion</td>
<td>Mean age = 66.4 (11.0)</td>
<td>OA Lateral = 4.14 (1.53)</td>
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<td></td>
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<td>KL grade 2 = 41%</td>
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<td>KL grade 3 = 33%</td>
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<td>KL grade 4 = 26%</td>
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<tr>
<td>van der Esch 2008</td>
<td>Custom VV testing device 7.7 Nm applied load 20 degrees of knee flexion</td>
<td>Varied OA: n=63 (125 knees) (male 15, female 48) Mean age = 60 (7.5) range [45-79] Right : Left KL grade 0 = 0 : 2 KL grade 1 = 45 : 39 KL grade 2 = 10 : 9 KL grade 3 = 6 : 11 KL grade 4 = 1 : 22</td>
<td>Angular Rotation (deg) OA Right = 7.81 (3.52) OA Left = 7.34 (2.96)</td>
</tr>
<tr>
<td>Ishii 2009</td>
<td>TELOS VV stress radiograph 150 N applied load maximal knee extension</td>
<td>Varied OA: n=102 (120 knees) (5 male, 115 female knees) Mean age = 72 range [56-83] KL grade 2 = 1 KL grade 3 = 30 KL grade 4 = 89 Controls: n=not reported (sex not reported) (age not reported)</td>
<td>Angular Rotation (deg) Angle measured using distal convex margin of the femoral condyles and outer margin of condyles of tibia. Median [25% 75%] OA: Varus laxity = 8 [6,9] Valgus laxity = 0 [0,2] Control: Varus laxity = 4 [3,4] Valgus laxity = 2 [0.25,3]</td>
</tr>
<tr>
<td>Creaby 2010</td>
<td>VV modified Kin-Com Leg moved passively 10 times from varus to valgus at 5 degrees per second. Varus and Valgus angles determined where 12Nm of passive resistance was reached. 20 degrees of knee flexion</td>
<td>Varied Medial OA: n = 127 (127 knees) Mild OA: n = 50 (23 male, 27 female) Mean age = 61.6 (7.1) Moderate OA: n = 45 (25 male, 20 female) Mean age = 65.2 (7.7) Severe OA: n = 32 (21 male, 11 female) Mean age = 66.4 (9.4) age matched controls: n =32 (32 knees) (15 male, 17 female) Mean age = 59.4 (6.9)</td>
<td>Angular Rotation (deg) Mild OA: Varus =10.5 (3.6) Valgus = 9.6 (3.2) Total = 20.1 (6.4) Moderate OA: Varus = 9.2 (2.7) Valgus = 8.8 (2.4) Total = 18.0 (4.7) Severe OA: Varus = 8.5 (2.7) Valgus = 9.2 (2.9) Total = 17.7 (5.4) Controls: Varus = 10.7 (3.7) Valgus = 8.4 (3.2) Total = 19.2 (6.5)</td>
</tr>
<tr>
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</table>
| Eriksson 2010 | Custom VV Stress Radiograph  
Force adjusted up to 10 kg max  
Full extension and 30 degrees flexion  
Smallest joint space in medial and lateral compartments compared to standard weight bearing films. | Varied OA: n = 60  
(60 knees)  
(23 male, 37 female)  
Mean age = 69 (8.9)  
Varus Knees: n = 43  
Valgus Knees: n = 17  
Contralateral: n=47  
(47 knees) | Joint Space Translation (mm)  
OA:  
Medial compartment standing = 2.6 (2.84)  
Varus in ext = 1.7 (2.37)  
Varus in flex =1.8 (2.38)  
Lateral compartment standing = 5.2 (3.52)  
Varus ext = 4.0 (2.85)  
Valgus flex = 3.3 (3.13)  
Varus OA knees only:  
Medial compartment standing = 1.3 (1.39)  
Varus ext = 0.5 (1.01)  
Varus flexion = 0.9 (1.33)  
Valgus OA knees only:  
Lateral compartment standing = 1.3 (1.53)  
Valgus ext = 0.8 (1.13)  
Valgus flexion = 0.1 (0.27)  
Contralateral Knees:  
Medial compartment standing = 3.8 (1.97)  
Varus in ext = 3.6 (2.32)  
Varus in flex = 3.1 (2.72)  
Valgus in ext = 6.4 (2.44)  
Valgus in flex = 7.3 (3.12)  
Lateral compartment standing = 5.0 (2.15)  
Varus in ext = 6.9 (2.83)  
Varus in flex = 7.3 (3.74)  
Valgus ext = 4.2 (2.18)  
Valgus flex = 4.0 (2.50) |

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Table A.1 continued

<table>
<thead>
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<tbody>
<tr>
<td><strong>Sharma 2010</strong></td>
<td>Custom VV testing device 12 Nm applied load 20 degrees of knee flexion</td>
<td>Varied OA: n = 950 (1307 knees) (474 male knees, 833 female knees) Mean age = 63.6 (7.8) One knee per subject reported KL Grade 2 or 3 Neutral alignment: n = 232 Varus alignment: n=550 Valgus alignment: n = 168 Without OA: n = 1752 (2958 knees) (1198 male, 1760 female knees) Mean age = 61.3 (7.8) One knee per subject reported KL Grade 0 or 1 Neutral alignment: n = 688 Varus alignment: n =725 Valgus alignment: n = 339</td>
<td>Angular Rotation (deg) Knees with OA: Neutral Alignment = 3.9 (2.5) Varus = 3.8 (2.5) Valgus = 4.4 (2.6) Knees without OA: Neutral Alignment = 4.1 (2.6) Varus = 3.9 (2.5) Valgus = 3.8 (2.7)</td>
</tr>
<tr>
<td><strong>Holla 2012</strong></td>
<td>Custom VV testing device 7.7 Nm applied load 20 degrees of knee flexion</td>
<td>Varied OA: n = 151 (151 knees) (male 31, female 120) Mean age = 58.5 (5.0) KL &lt; 2 =122 KL &gt;=2 = 29</td>
<td>Angular Rotation (deg) median [Interquartile range] OA = 11.1 [8.4-14.6]</td>
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<tr>
<td><strong>Knoop 2012</strong></td>
<td>Custom VV laxity testing device 7.7 Nm applied load 20 degrees of knee flexion</td>
<td>Varied OA: n = 283 (283 knees) (102 male, 181 female) Mean age = 61.6 (7.4) KL grade &gt;= 2 = 190 Reported instability OA: n = 191 (191 knees) (65 male, 126 female) Mean age = 62.1 (7.3) KL grade &gt;= 2 = 128 No instability OA: n = 92 (92 knees) (36 male, 56 female) Mean age = 60.6 (7.6) KL grade &gt;= 2 = 61</td>
<td>Angular Rotation (deg) Total group = 7.3 (4.0) Instability = 7.2 (3.9) No instability = 7.5 (4.1)</td>
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<tr>
<td>Miyazaki 2012</td>
<td>Custom VV Stress Radiograph</td>
<td>Bilateral Medial OA: n = 46 (92 knees) (0 male, 46 female)</td>
<td>Angular Rotation (deg)</td>
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<tr>
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<td>22.1 Nm applied loading</td>
<td>Mild OA: Mean age = 73.8 (9.2)</td>
<td>Pre-exercise</td>
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<td>20 degrees of knee flexion</td>
<td>Advanced OA: Mean age = 74.1 (7.9)</td>
<td>non OA = 6.98 (1.77)</td>
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<td>KL grade 2 = 40 knees</td>
<td>mild OA = 6.18 (1.78)</td>
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<td>KL grade 3 = 32 knees</td>
<td>advanced OA = 5.99 (2.81)</td>
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<td>KL grade 4 = 20 knees</td>
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<td>Age matched controls: n = 22</td>
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<td>Mean age = 71.8 (8.3)</td>
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<td>KL grade 0 = 20 knees</td>
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<td>KL grade 1 = 24 knees</td>
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<tr>
<td>van der Esch 2012</td>
<td>Custom VV testing device</td>
<td>Varied OA: n = 248 (496 knees) (87 male, 161 female) Mean age = 61.0 (7.9)</td>
<td>Angular Rotation (deg)</td>
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<td>7.7 Nm applied load</td>
<td>Right : Left: KL Grade 0 = 10 : 9</td>
<td>OA Right = 7.46 (3.92)</td>
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<td>20 degrees of knee flexion</td>
<td>KL Grade 1 = 87 : 86</td>
<td>OA Left = 7.36 (3.98)</td>
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<td>KL Grade 2 = 72 : 82</td>
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<td>KL Grade 3 = 49 : 47</td>
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<td>KL Grade 4 = 30 : 23</td>
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<td>KL Grade Missing = 0 : 1</td>
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<td>Kumar 2013</td>
<td>TELOS VV stress radiograph</td>
<td>Varied Medial OA: n= 16 (16 knees) (8 male, 8 female) Mean age = 65.2 (9.5)</td>
<td>Joint space translation (mm): mean (95% confidence interval)</td>
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<td>150 N applied load</td>
<td>KL &gt;= 2 Controls: n = 12 (12 knees) (6 male, 6 female) Mean age = 59.5 (10.4)</td>
<td>OA: Medial laxity = 5.5 (4.6, 6.4)</td>
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<td>20 degrees of knee flexion</td>
<td>KL &lt;= 1</td>
<td>Lateral laxity = 3.4 (2.7, 4.1)</td>
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<td>Control: Medial laxity = 3.3 (2.4, 4.2)</td>
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<td>Lateral laxity = 4.7 (3.2, 5.1)</td>
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<tr>
<td>van der Esch 2013</td>
<td>Custom VV testing device</td>
<td>Varied OA: n = 105 (105 knees) (male 32, female 73) Mean age = 61.4 (6.9)</td>
<td>Angular Rotation (deg)</td>
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<td>7.7 Nm applied load</td>
<td>KL grade 0 = 1</td>
<td>OA = 6.9 (2.8)</td>
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<td>20 degrees of knee flexion</td>
<td>KL grade 1 = 31</td>
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<td>KL grade 2 = 28</td>
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References


