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Individuals who use lower-limb prostheses have increased risks of developing overuse injuries and experiencing falls compared to the general population. This is often attributed to individuals loading, or weighting, their prosthetic limb less than their intact limb. Quantifying musculoskeletal and biomechanical symmetry between prosthetic and intact limbs could help clinicians evaluate risks of developing overuse injuries and experiencing falls. However, these relationships have not been determined.

The objective of this dissertation is to quantify musculoskeletal and biomechanical symmetry and determine their relationships to overuse injuries and falls in individuals with unilateral lower-limb loss. This objective has two specific aims: 1) evaluate musculoskeletal symmetry associated with risks of developing overuse injuries, and 2) determine the relationship between wearable sensor-derived walking symmetry values and falls.

Musculoskeletal symmetry was quantified in skeletal properties (e.g. fracture risk via dual x-ray absorptiometry), hip and knee joint space (e.g. osteoarthritis via x-rays), and thigh muscle

architecture (e.g. atrophy via cross-sectional area) in four anatomical donors and thirty post-mortem CT scans.

Biomechanical symmetry was quantified in twenty-two individuals who use unilateral lower-limb prostheses. Wearable sensors called inertial measurement units were compared to the gold standard of motion capture in the first five individuals. The relationship between number of falls, clinical outcome measures, and gait symmetry will be assessed to determine if gait symmetry could supplement clinical outcome measures to evaluate fall risk.

Impaired musculoskeletal symmetry suggests amputated limbs, particularly those with diabetes, had higher indications of distal femur fracture risk and more thigh muscle atrophy compared to intact limbs. Compared to healthy and diabetic control groups, individuals with amputation had higher indications of osteoarthritis and muscle atrophy bilaterally. Biomechanical studies suggest data derived from inertial measurement units were comparable to motion capture, and the Four Square Step test was associated with 12-month retrospective falls. Findings could help clinicians proactively evaluate overuse injury and fall risks in this population.

QUANTIFYING MUSCULOSKELETAL AND BIOMECHANICAL SYMMETRY TO IDENTIFY INJURY AND FALL RISKS IN INDIVIDUALS WHO USE LOWER-LIMB PROSTHESES

DISSERTATION

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By

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INTRODUCTION

Individuals who have major lower-limb loss or absence, defined as occurring at or above the tarsometatarsal joint, experience a wide variety of adverse health outcomes. For individuals in this population who use a unilateral lower-limb prosthesis, two prevalent adverse health outcomes are increased risks of developing overuse injuries, such as osteoarthritis, and experiencing falls. Despite advances in healthcare technology, these adverse health outcomes are still treated after they occur, rather than prospectively monitored to help prevent the adverse health outcome from occurring. In order to reduce the prevalence of overuse injuries and falls in this population, more research is needed to establish evidence-based clinical guidelines to help prospectively evaluate these risks.

Individuals in this population typically display less symmetry between prosthetic and intact limbs compared to the general population. This has been attributed to changes in musculoskeletal and biomechanical loading, with less load on the prosthetic limb than the intact limb. Symmetry is typically considered a major goal of prosthetic rehabilitation, but there is no objective way to quantify symmetry in clinical practice. Decreased musculoskeletal and biomechanical symmetry between prosthetic and intact limbs may be associated with greater incidences of overuse injuries and falls, but this relationship has not been directly determined. Further, a large portion of individuals in the amputee population are older or diabetic, but this is not reflected in populations typically included in musculoskeletal and biomechanical research. To directly determine these relationships, musculoskeletal and biomechanical symmetry must first be quantified.

Lower-limb musculoskeletal health influences walking biomechanics, which in turn influences lower-limb musculoskeletal health. Examining both the influence of musculoskeletal symmetry on overuse injury risk (e.g. hip and knee joint space narrowing as indications of osteoarthritis) and biomechanical symmetry on fall risk (e.g. ankle range of motion associated with number of falls) offers a broader perspective on proactively evaluating and reducing these risks. Further, a large portion of individuals in the amputee population are older or diabetic, but this is not reflected in populations typically included in musculoskeletal and biomechanical research.

While previous musculoskeletal research has focused on incidence of overuse injuries, underlying anatomical adaptations have largely been ignored. Quantifying anatomical characteristics that are indicators of overuse injuries in a way that is non-invasive (e.g. x-ray or CT scans) could allow for prospective identification of a decline in musculoskeletal health. Further, examining musculoskeletal properties in anatomical donors and post-mortem CT scans can allow us to examine musculoskeletal properties not feasible in living individuals (e.g. physiological cross-sectional area via muscle dissection). The ability to capture these musculoskeletal properties in more detail can allow for a more accurate representation of the adaptations of certain musculoskeletal properties, which can then help inform future directions for studies in living individuals.

While previous biomechanics research has focused on assessing the relationship between clinical outcome measures (e.g. Timed Up and Go) and number of retrospective falls, only one study has recently assessed prospective fall risk in this population. Further, none have attempted to determine the relationship between walking symmetry and number of falls, though this has been shown in individuals with other lower-limb pathologies (e.g. stroke). Additionally, while studies have recently begun using wearable sensors called inertial measurement units to quantify gait in clinical practice, none have directly compared inertial measurement unit data to the gold standard of motion capture. Validating the use of inertial measurement units in clinical practice and using them to determine the relationship between walking symmetry and prospective fall risk could help inform a clinical guideline for fall risk prediction.

Therefore, this dissertation sought to quantify musculoskeletal and biomechanical symmetry between prosthetic and intact limbs to determine relationships to overuse injuries and fall risks. Specifically, this dissertation aimed to: 1) quantify musculoskeletal symmetry to determine musculoskeletal properties vulnerable to overuse injuries, such as osteoarthritis or femoral fractures, and 2) quantify biomechanical symmetry to determine if gait assessment can supplement clinical measures to determine fall risk. Findings could help establish clinical guidelines to proactively assess and reduce risks of overuse injuries and falls.

Different terminology for this population exists depending on whether individuals have congenital limb absence, had an amputation, or used a prosthesis, as well as their level of limb difference. In this dissertation, musculoskeletal studies refer to anatomical donors as individuals with amputation, since amputation surgery was recorded for each individual. Biomechanical studies refer to living individuals as unilateral prosthesis users, since each participant used a unilateral prosthesis. The phrase ‘limb loss or absence’ is used to generally refer to all individuals in this dissertation, regardless of etiology or prosthesis use. The term transtibial refers to individuals who have limb loss below the knee or use a below-knee prosthesis, while transfemoral refers to individuals who have limb loss above the knee or use an above-knee prosthesis.

Section 1 contains three review manuscripts that summarize recent literature surrounding musculoskeletal symmetry, biomechanical symmetry, and clinical evaluation of fall risk in this population. Section 2 contains three musculoskeletal studies that investigated anatomical differences between amputated and intact lower-limbs to inform risks of overuse injuries. Section 3 contains two biomechanical studies that validated wearable sensors against the gold standard of motion capture systems and investigated whether biomechanical symmetry from these wearable sensors can help evaluate fall risk in clinical practice. At the time of submitting this dissertation, Chapters 5 and 8 are the only chapters that are not published (Chapters 1 and 4), accepted (Chapter 2), or in review (Chapters 3, 6, and 7).

SECTION 1: LITERATURE REVIEWS

CHAPTER 1

A REVIEW OF MUSCULOSKELETAL ADAPTATIONS IN INDIVIDUALS FOLLOWING MAJOR LOWER-LIMB AMPUTATION

CHAPTER 2

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CHAPTER 1

A REVIEW OF MUSCULOSKELETAL ADAPTATIONS IN INDIVIDUALS FOLLOWING MAJOR LOWER-LIMB AMPUTATION

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Abstract

Structural musculoskeletal adaptations following amputation, such as bone mineral density (BMD) or muscle architecture, are often overlooked despite their established contributions to gait rehabilitation and the development of adverse secondary physical conditions. The purpose of this review is to provide a summary of the existing literature investigating musculoskeletal adaptations in individuals with major lower-limb amputations to inform clinical practice and provide directions for future research.

Google Scholar, PubMed, and Scopus were searched for original peer-reviewed studies that included individuals with transtibial or transfemoral amputations.

Summary data of twenty-seven articles indicated reduced BMD and increased muscle atrophy in amputees compared to controls, and in the amputated limb compared to intact and control limbs. Specifically, BMD was reduced in T-scores and Z-scores, femoral neck, proximal tibia, and bone mineral content. Muscle atrophy was evidenced by decreased thigh cross-sectional area, decreased quadriceps thickness, and increased amounts of thigh fat.

Overall, amputees have impaired musculoskeletal health. Future studies should include dysvascular etiologies to address their effects on musculoskeletal health and functional mobility. Moreover, clinicians can use these findings to screen increased risks of adverse sequelae such as fractures, osteopenia/porosis, and muscular atrophy, as well as target specific rehabilitation exercises to reduce these risks.

Keywords: anatomy, physiology, remodeling, symmetry, limb loss

Introduction

Major lower-limb amputations occurring proximal to the tarsometatarsal joint are experienced by a variety of adults, ranging from young veterans with traumatic etiologies to elderly individuals with dysvascular etiologies[1]. Gait adaptations post-amputation lead to changes in loading and muscle recruitment strategies[2], which influences asymmetries between amputated and intact limbs. Specifically, less force is transmitted through the amputated limb compared to the intact limb, resulting in musculoskeletal remodeling[3,4]. These adaptations often result in adverse clinical sequelae in this population, such as osteopenia and muscle atrophy, which may influence functional mobility and quality of life[5, 6].

Structural musculoskeletal properties are defined in this manuscript as anatomical or physiological components, such as bone mineral density (BMD) and muscle architecture. Structural musculoskeletal properties have been understudied despite their known contributions to gait and rehabilitation post-amputation[7]. Several original research articles exist on the epidemiology or prevalence of outcomes associated with structural musculoskeletal properties[8, 9], and existing literature reviews address the clinical presentations such as leg strengthening exercise[6], low back pain[10], and walking ability[11, 12]. A review by Gailey et al. (2015) discussed musculoskeletal factors associated with negative secondary health effects, such as osteopenia, but only two of forty-four articles discussed structural musculoskeletal properties[5]. A current review dedicated to structural musculoskeletal adaptations following amputation is lacking from the literature.

Since studies have found increased risks of osteopenia and muscle atrophy[13, 14] along with increased adverse events such as falls and fractures[15, 16] in the amputee population, a better understanding of the underlying structural changes can broaden the range of clinical solutions to increase symmetry between prosthetic and intact limbs and assess these risks. A summary of findings could also provide evidence to proactively monitor musculoskeletal health to predict fracture or fall risks, as well as inform recommendations of specific rehabilitation exercises.

Therefore, this review aims to summarize literature investigating structural musculoskeletal adaptations in individuals with unilateral major lower-limb amputations to inform clinical practice and provide directions for future research.

Methods

A search was performed on Dec 1st, 2021 in Google Scholar, PubMed, and Scopus to encompass peer-reviewed original research articles of structural musculoskeletal adaptations in individuals post-amputation, such as BMD and muscle architecture. References from included studies were also examined for inclusion.

The following search terms were used:

> Google Scholar: musculoskeletal OR muscle OR skeletal OR bone OR physiol* OR anatom* AND amput* AND below-knee OR "below knee" transtibial OR above-knee OR "above knee" transfemoral OR leg OR lower-limb OR lower limb

> PubMed: ((((soft tissue injuries[MeSH Terms]) OR ((muscle, skeletal[MeSH Terms]) AND (pathology[MeSH Subheading])) OR ((muscular atrophy[MeSH Terms]) AND

(pathology[MeSH Subheading])) OR ((adiposity[MeSH Terms]) AND (physiology[MeSH Subheading])) OR (adipose tissue[MeSH Terms])) OR (bone mineral density[MeSH Terms] OR bone mineral densit*[Title/Abstract] OR bone densit[Title/Abstract] OR BMD[Title/Abstract])) AND ((((amputees[MeSH Terms]) OR (amputation[MeSH Terms])) OR (amput*[Title/Abstract])) AND ((below-knee OR transtibial OR trans-tibial OR above-knee OR transfemoral OR trans-femoral OR leg OR lower-limb OR lower limb OR "above knee" OR "below knee") OR ((extremities, lower[MeSH Terms])))))

Scopus: musculoskeletal OR muscle OR skeletal OR bone OR physiol* OR anatom* AND amput* AND below-knee OR “below knee” transtibial OR above-knee OR “above knee” transfemoral OR leg OR lower-limb OR lower limb

Original research articles were included if they investigated underlying structural musculoskeletal properties, defined as anatomical or physiological components (e.g. BMD, muscle architecture), in the lower-limbs of individuals of any age after transtibial or transfemoral amputation surgery. Title screening excluded articles that did not include individuals with amputation or were not original research studies (e.g. literature reviews). Abstracts were excluded if they were not peer-reviewed or if they were case reports, defined as less than five participants. Full-text articles were excluded if they were not available in English, used computer modeling in place of participant testing, or did not contain structural musculoskeletal methodology. For example, while skin morphology is an important consideration[17], it was not the purpose of this review.

MGF adapted and applied search terms from a librarian at the University of North Texas Health Science Center and performed title screening. MGF, SK, and WN performed abstract and full-text screening. MGF and SK discussed all articles that passed full-text screening to ensure inclusion of appropriate articles and to ensure data was summarized accurately.

Results

A total of twenty-seven studies were included after applying inclusion and exclusion criteria [Figure 1]. All studies are summarized in Table 1 and are grouped by whether they utilized skeletal (n=15, where n represents the number of studies) or muscular (n=12) methodology. Bemben et al. (2017) and Cavedon et al. (2021) were the only studies that utilized both skeletal and muscular methodology and both primarily utilized skeletal methodology[18, 19].

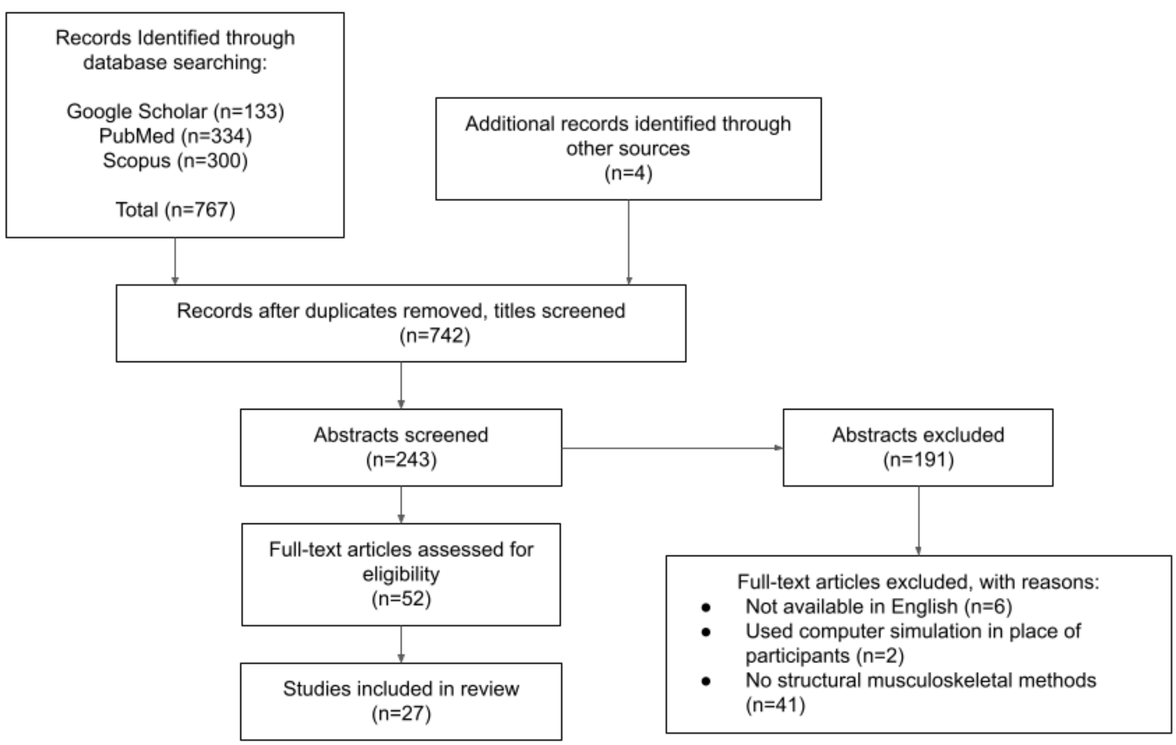

Figure 1: Flow diagram of the inclusion process.

Table 1: Summary of Included Studies

	Author, Year	Title	Participants With Amputation	Methods	Time Points	Comparison
Skeletal	Bemben et al. (2017)	Acute bone changes after lower limb amputation resulting from traumatic injury	8 TT; Mean age 35.4 (SD 11.1); All traumatic etiologies	DXA measured BMD for total body, lumbar spine, femoral neck, proximal femur; pQCT measured residual limb volumetric BMD, stress-strain index, and muscle cross-sectional area	prior to prosthesis fitting; 6 months post-prosthesis; 12 months post-prosthesis; additional blood draw occurred at time of surgery	amputated vs intact limbs; over time points
	Cavedon et al. (2021)	Body composition and bone mineral density in athletes with a physical impairment	18 total 7 TT and 11 TF Mean age 34.4; All athletes of at least two years in adaptive sports	DXA measured whole-body and regional: total mass, lean mass, fat mass, % fat mass, fat mass/lean mass, BMC, and BMD	cross-sectional; inclusion stated all athletes of at least two years in adaptive sports	amputated vs intact limbs; amputee group vs spinal cord injury group vs control group
	Haket et al. (2017)	Periprosthetic cortical bone remodeling in patients with an osseointegrated leg prosthesis	27 TF with osseointegration; 21 males, 6 females Mean age 48 (range 23-68); Mean TSA 18 years (range 2-45)	DXA measured BMD at the femoral neck (DXA only included 24 patients); X-ray measured periprosthetic cortical thickness;	immediately post-op; 1 year post-op; 2 years post-op	amputated vs intact; time points
	Hansen et al. (2019)	Changes in periprosthetic bone mineral density and bone turnover markers after osseointegrated implant surgery: A cohort study of 20 transfemoral amputees with 30-month follow-up	19 TF with osseointegration; 12 males, 7 females; Mean age 49 (SD 11.17)	DXA measured BMD in lumbar spine, proximal femur and seven periprosthetic regions (zones 1-7 may or may not be similar to other studies)	pre-op (2-21 days before surgery), and 1, 3, 6, 7, 9, 12, 18, 24 and 30 months after the S1 surgery or until implant was removed	amputees vs controls; removed OI implant over nonremoved OI implant; over time points
	Hoyt et al. (2021)	Femoral Neck Hounsfield Units as an Adjunct for Bone Mineral Density After Combat-Related Lower Extremity Amputation	26 individuals with 30 amputations total; 17 TT amputations and 13 TF amputations; All males; Mean age 26.4 (range 22-29); All traumatic etiologies	DXA measured BMD at femoral neck; CT measured Hounsfield units at femoral neck	cross-sectional; inclusion criteria stated DXA and CT scans within 6 months of each other; DXA scans taken 5-11 months post-injury (mean 6 months)	correlation b/t hounsfield units from CT scans and BMD from DXA scans

	Ramírez et al. (2011)	Analysis of bone demineralization due to the use of exoprosthesis by comparing Young's modulus of the femur in unilateral transfemoral amputees	20 TF; 3 females and 17 males; Mean age 44.6 (range 23–71); Mean TSA 10.9 years; All used SACH foot and mechanical monocentric knee	CT measured Young's Modulus (no BMD data presented- just correlations)	cross-sectional; no inclusion criteria stated	amputated vs intact proximal femur at three locations= femoral neck, metaphysis just below lesser trochanter, and proximal quarter of the diaphysis
	Royer and Koenig (2005)	Joint loading and bone mineral density in persons with unilateral, trans-tibial amputation	9 TT; 8 male 1 female; Mean age 41.7 (SD 10.6); Mean TSA 16.7 years (STD 10.9); All used ESAR feet; 4 traumatic etiologies, 1 diabetic, 2 congenital, 1 blood clot, 1 infection;	DXA measured BMD in proximal femur and tibia	cross-sectional	amputated vs intact vs averaged matched control limb value
	Rush et al. (1994)	Osteopenia in patients with above knee amputation	16 TF; All male; Mean age 48 range (23-66) All ischial weight bearing sockets; 9 suction sockets and 7 silesian belt suspension; 8 traumatic etiologies, 6 cancer, 2 vascular	DXA measured BMD for L2 and femoral neck	cross-sectional; inclusion says prosthesis users for over 5 years	amputated vs intact; amputee group vs controls

	Sherk et al. (2008)	BMD and bone geometry in transtibial and transfemoral amputees	14 total; 7 TT (5 males and 2 females); Mean age 43.4 (SD 6.0); 7 TF (6 males and 1 female); Mean age 45.7 (SD 5.7); TSA (14.7 TT and 15.5 TF), and hours/day of prosthesis wear (15 TT and 11 TF); 11 traumatic etiologies, 1 secondary to diabetes, 1 secondary to circulation issues, and 1 secondary to osteomyelitis; both groups had similar numbers of years wearing a prosthesis (14.4 TT and 15.4 TF),	DXA measured areal BMD of the dual proximal femur, lumbar spine, and total body; pQCT measured volumetric BMD and bone geometry at the distal ends of both limbs	cross-sectional; inclusion stated ambulatory with a prosthesis for at least 6 months	amputated vs intact limbs; group comparisons for both levels and two groups of nonamputee controls (one transtibial control group and one transfemoral control group)
	Smith et al. (2009)	A study of bone mineral density in adults with disability	52 lower-limb amputees (no further details)	DXA measured BMD for total lumbar spine, femoral neck, total proximal femur	cross-sectional; inclusion stated they had to have their disability for at least 3 months	amputees vs other groups with musculoskeletal deficits (e.g. spinal cord injury)
	Smith et al. (2011)	A study of BMD in lower limb amputees at a national prosthetics center	52 total; 24 TT; 19 TF; 8 bilateral; 1 hip disarticulation; 39 males and 13 females Mean age 61.9 (SD 12.8)	DXA measured BMD in lumbar spine, femoral neck, and proximal femur	cross-sectional	amputated vs intact; male vs female
	Thomson et al. (2019A)	Proximal Bone Remodeling in Lower Limb Amputees	48 total with osseointegration;	DXA measured BMD at lumbar spine and femoral neck	pre-op; 1 year post-op; and 3 years post-op	amputated vs intact limbs; between

		Reconstructed With an Osseointegrated Prosthesis	15 TT (12 males and 3 females) and 33 TF (22 males and 11 females); Mean age 51 (SD 13.5); TF group split into 2 groups depending on presence of femoral neck lag screw			amputation level/femoral neck screw groups; over time points
	Thomson et al. (2019B)	Radiographic Evaluation of Bone Remodeling Around Osseointegration Implants Among Transfemoral Amputees	28 TF with osseointegration; 15 received integral leg prosthesis (10 male and 5 female) and 13 received osseointegration prosthetic limb type A (8 male and 5 female); Mean age 48 years (SD 12.4)	X-rays measured bone density, longitudinal bone coverage, and bone width	about 6 months post-op (0.4 with STD of 0.5 years); about 3 years post-op(3.0 with STD of 0.8 years)	7 femoral (inverse Gruen) zones; between osseointegration implant groups; over time points
	Tugcu et al. (2009)	Muscle strength and bone mineral density in mine victims with transtibial amputation	15 TT; All male; Mean age 26.2 (SD 3.9); Mean TSA 57.9 months (SD 47.5) All traumatic etiologies; All PTB sockets	DXA measured BMD at femoral neck, Ward's triangle, total femur, and total tibia	cross-sectional	amputated vs intact
	Yaziciogl u et al. (2008)	Osteoporosis: A factor on residual limb pain in traumatic trans-tibial amputations	36 TT; All male; Mean age 26.8 (SD 3.5); Mean TSA 62.8 months (SD 37); All traumatic etiologies	DXA measured BMD for femoral neck, Ward's triangle, total hip, and proximal tibia	cross-sectional	amputated vs intact
Muscular	Bramley et al. (2021)	Changes in Tissue Composition and Load Response After Transtibial Amputation Indicate Biomechanical Adaptation	10 TT; (6 males and 4 females); Mean age 41 (range 25-62); Mean TSA 7.5 years; 2 chronic regional pain disease etiologies, 2 congenital, 5 traumatic, 1 vascular; Mean daily socket use 12.5 hours (range 6-16)	MRI measured fatty infiltration of limbs	cross-sectional	amputated vs intact vs control

	de Palma et al. (2011)	Involvement of the muscle-tendon junction in skeletal muscle atrophy: an ultrastructural study	15 TT Group A= 12 elderly (mean age 79 years; range 65-85) 10 males and 2 females; 10 vascular etiologies, 1 osteomyelitis, 1 cancer Group B= 3 healthy young adults (mean age 32 range 25-35); All male; All traumatic etiologies	Histology measured fiber structures; EM measured base/perimeter ratio in musculotendinous junction	cross-sectional	Group A vs B
	George et al. (2021)	Circumference Method Estimates Percent Body Fat in Males U.S. Service Members with Lower Limb Loss	47 total; 23 unilateral TT; 4 bilateral TT; 14 unilateral TF; 3 bilateral TF; 3 TT/TF; Mean age 27.6 years (SD 5.7)	DXA measured percent body fat	cross-sectional	amputees vs controls
	Henson et al. (2021)	Understanding lower limb muscle volume adaptations to amputation	12 total; 6 unilateral TT; mean age 33.7 years (SD 1.9); mean TSA 7.5 years 6 bilateral TF; mean age 31.8 years (SD 2.9); mean TSA 7.2 years; All male; All traumatic etiologies; All used dynamic response feet; All TF used MPKs	MRI measured gross skeletal measurements and muscle volume	cross-sectional	amputated vs intact (in TT) vs control
	Jaegers et al. (1995)	Changes in hip muscles after above-knee amputation	12 TF; Mean age 38.2 (SD of 18); TSA 3- 35 years (mean 9.4); 7 traumatic etiology and 5 osteosarcomic etiology	MRI measured femur and muscle volume	cross-sectional; inclusion said at least 2 years post-amputation	amputated vs intact vs control

	Onat et al. (2016)	Ultrasonographic assessment of the quadriceps muscle and femoral cartilage in transtibial amputees using different prostheses	38 TT; 13 using vacuum suspension; 11 male and 2 female; Mean age 41.9 years with SD 11.8; TSA 10.8 years; Prosthesis use 5.6 years); 25 using pin-lock suspension; 20 males and 5 females; Mean age 40.6 years with SD 11.6; Mean TSA 16.3 years; prosthesis use 6.6 years)	Ultrasound of femoral cartilage thickness (intercondylar area, lateral femoral condyle, medial femoral condyle) and quadriceps muscle thickness (rectus femoris, vastus intermedius, vastus intermedius, and vastus medialis)	cross-sectional; inclusion states at least 6 months of prosthesis use	amputated vs intact limbs; two suspension groups
	Putz et al. (2017)	Structural changes in the thigh muscles following trans-femoral amputation	12 TF; 6 males and 6 females; Mean age 44.1 at amputation (range 21-69); All cancer	MRI measured fatty infiltration and degeneration at the middle and distal end of specific muscles within the residual limb	about 1 year post-op (avg 10.6 months SD 12.6); about 2 years post-op (avg 25.6 months SD 21.4); 12 patients included at time 1 but only 7 patients included at time 2	middle vs end of residual limb; time points
	Renström et al. (1983)	Thigh muscle atrophy in below-knee amputees	10 TT; 8 males and 2 females; Mean age 56; 4 vascular etiologies, 2 infection, 4 trauma; Mean TSA 24 months (SD 37)	Histology measured fast and slow-twitch fibers, fiber sizes, and fiber area; CT measured mean fiber area of muscles in the thigh; measuring tape determined cross-sectional area of the thigh	cross-sectional	amputated vs intact; type 1 vs 2 fibers
	Schmalz et al. (2001)	Selective thigh muscle atrophy in trans-tibial amputees: an ultrasonographic study.	17 TT; 15 male and 2 female; Mean age 47 (SD 18); 14 traumatic etiologies, 1 due to infection, 1 due to tumor, and 1 due to venous thrombosis;	Ultrasound measured cross-sectional area and thickness of the quadriceps femoris, sartorius, gracillis, semitendinosus, and biceps femoris	cross-sectional; demographics state at least 6 months of prosthesis use (range 0.5 - 19 years with median of 5 years)	amputated vs intact vs control limb

			All had patellar tendon bearing prostheses			
	Sharma et al. (2019)	Fast and slow myosin as markers of muscle regeneration in mangled extremities: a pilot study	15 lower-limb amputees (no level details); All trauma	Histology measured fast and slow myosin in residual limb	during amputation surgery, at 7 day follow-up	fast vs slow myosin; time points
	Sherk et al. (2010)	Interlimb muscle and fat comparisons in persons with lower-limb amputation	12 total 7 TT; Mean age 43.4 (SD 15.8) 5 TF; Mean age 38.5 (SD 10.6)	DXA measured thigh and lower-leg fat mass and bone-free lean body mass; qQCT measured muscle cross-sectional areas and fat cross-sectional areas of the end of residual and intact limbs with thresholding technique to determine the composition of fat vs muscle	cross-sectional; inclusion states ambulatory for at least 6 months	amputated vs intact limbs; amputee vs control groups
	Sibley et al. (2020)	The effects of long-term muscle disuse on neuromuscular function in unilateral transtibial amputees	9 TT; All male; Mean age 40.3 (SD 8.5); All traumatic etiologies	Ultrasound of the vastus lateralis measured muscle thickness, pennation angle, and fascicle length	cross-sectional; inclusion states amputation performed at least 6 months prior	amputated vs intact vs control

Table 1: Studies are categorized by skeletal or muscular methodologies. All individuals with amputation were unilaterally affected unless otherwise specified. Mean age is in years unless otherwise specified. Abbreviations: TT= transtibial, TF= transfemoral, SD= standard deviation, TSA = time since amputation, DXA= Dual Energy X-ray Absorptiometry, pQCT= peripheral quantitative computed tomography, BMD= bone mineral density, CT= computed tomography, MRI= magnetic resonance imaging, MPKs= microprocessor knees.

Participant Demographics: Included studies were composed of transtibial amputees (n=10), transfemoral amputees (n=7), both (n=9), or unclear (n=2). The majority of studies included twenty participants with amputation or less (n=18). Eleven studies included females. Fifteen studies included individuals with traumatic etiology, with eight of those exclusively studying individuals with traumatic etiologies. In contrast, only a few studies included individuals with etiologies due to dysvascular issues (n=6), cancer (n=7), or congenital limb deficiency (n=2). Most studies had a mean participant age of 40- 49 years (n=13). Few studies recorded time since amputation (n=9), activity level (n=7), prosthetic wear time (n=7), or prosthetic componentry (n=8).

Comparisons: There were a wide variety of comparisons conducted across all studies. While most studies compared each individual's amputated limb to their intact limb (n=18), some also compared individuals with amputations to control groups of individuals without amputations (n=11) or individuals with spinal cord injury (n=2). Subgroups of individuals with amputation (n=9) were also compared by transtibial and transfemoral (n=4), osseointegration type (n=3), prosthetic suspension (n=1), and age (n=1). Studies were either cross-sectional (n=20) or compared data collected at multiple time points (n=7). Of these seven studies, two-time points (n=3), three-time points (n=3), and ten-time points (n=1) were compared.

Methodology & Parameters: Studies employed a variety of methodologies to measure skeletal and muscular properties. The studied parameters were inconsistent across studies, but those reported by a minimum of two or more studies are summarized in Table 2 and 3 for skeletal and muscular properties, respectively.

Table 2: Summary of Mean Skeletal Data

	Study	TT Group	TF Group	Amp Group (level unknown)	Control Group	TT Limb	Intact Limb	TF limb	Intact Limb	Amp Limb (level unknown)	Intact Limb	Control Limb
T-Scores	***Femoral neck***											
	Smith et al. (2011)	-	-	-	-	-	-	-	-	-1.91 male, -2.63 female	-1.3 male, -1.96 female	-
	Tugcu et al. (2009)	-	-	-	-	-0.4	0.8	-	-	-	-	-
	Yazicioglu et al. (2008)	-	-	-	-	-0.69	0.35	-	-	-	-	-
	Hip											
	Tugcu et al. (2009)	-	-	-	-	-0.5	1.1	-	-	-	-	-
	Yazicioglu et al. (2008)	-	-	-	-	-0.88	0.59	-	-	-	-	-
	Ward's triangle											
	Tugcu et al. (2009)	-	-	-	-	0.3	1.5	-	-	-	-	-
	Yazicioglu et al. (2008)	-	-	-	-	-0.12	0.84	-	-	-	-	-
Z-Scores	***Lumbar spine***											
	Smith et al. (2011)	-	-	-	-	-	-	-	-	-	0.11 male, 0.63 female	-

	Study	TT Group	TF Group	Amp Group (level unknown)	Control Group	TT Limb	Intact Limb	TF limb	Intact Limb	Amp Limb (level unknown)	Intact Limb	Control Limb
	Thomson et al. (2019A)	0.466	0.19 without femoral lag screw, -0.3 with	0.163	-	-	-	-	-	-	-	-
	Femoral neck											
	Smith et al. (2011)	-	-	-	-	-	-	-	-	-0.38 male, 0.19 female	-1.01 male, -0.48 female	-
	Thomson et al. (2019A)	-	-	-	-	-0.32	0.4428	-2.309 without femoral lag screw, -2.291 with	0.0476 without femoral lag screw, 0.3273 with	-	-	-
BMD (g/cm^2)	***Whole-body***											
	Bemben et al. (2017)	1.271 pre, 1.279 6MO, 1.271 12MO	-	-	-	-	-	-	-	-	-	-
	Cavedon et al. (2021)	1.2	1.15		1.17*	-	-	-	-	-	-	-
	Sherk et al. (2008)	1.272	1.227	-	1.275 for TT controls, 1.264 for TF controls	-	-	-	-	-	-	-

Study	***TT Group***	***TF Group***	***Amp Group (Level Unk).).***	***Control Group***	***TT Limb***	***Intact Limb***	***TF Limb***	***Intact Limb***	***Amp Limb (Level Unk.)***	***Intact Limb***	***Control Limb***
Lumbar spine											
Bemben et al. (2017)	1.266 pre, 1.244 6MO, 1.257 12MO	-	-	-	-	-	-	-	-	-	-
Hansen et al. (2019)	-	1.13	-	1.18	-	-	-	-	-	-	-
Sherk et al. (2008)	1.296	1.241	-	1.336 for TT controls 1.441 for TF controls	-	-	-	-	-	-	-
Smith et al. (2009)	-	-	0.994	-	-	-	-	-	-	-	-
Smith et al. (2011)	-	-	1.039 male, 0.865 female	-	-	-	-	-	-	-	-
Thomson et al. (2019A)	1.3164	1.268 without femoral lag screw 1.173 with femoral lag screw	1.261	-	-	-	-	-	-	-	-
Femoral neck											
Bemben et al. (2017)	-	-	-	-	1.087 pre, 0.996 6MO, 0.984 12MO	1.119 pre, 1.087 6MO, 1.095 12MO	-	-	-	-	-

Study	TT Group	TF Group	Amp Group (level unknown)	Control Group	TT Limb	Intact Limb	TF limb	Intact Limb	Amp Limb (level unknown)	Intact Limb	Control Limb
Haket et al. (2017)	-	-	-	-	-	-	0.68 preop, 0.67 12MO, 0.69 24MO		-	-	-
Rush et al. (1994)	-	-	-	-	-	-	0.68	1.01	-	-	-
Sherk et al. (2008)	-	-	-	-	1.015	1.077	0.704	1.064	-	-	1.072 for TT, 1.146 for TF
Smith et al. (2009)	-	-	0.724	-	-	-	-	-		-	-
Smith et al. (2011)	-	-	-	-	-	-	-	-	0.672 male, 0.556 female	0.753 male, 0.632 female	-
Thomson et al. (2019A)	-	-	-	-	0.9747	1.072	0.709 without femoral lag screw, 0.6725 with	1.016 without femoral lag screw, 1.01 with	0.783	1.031	-
Tugcu et al. (2009)	-	-	-	-	1.01	1.55	-	-	-	-	-
Yaziciog lu et al. (2008)	-	-	-	-	0.97	1.11	-	-	-	-	-

Study	***TT Group***	***TF Group***	***Amp Group (Level Unk).).***	***Control Group***	***TT Limb***	***Intact Limb***	***TF Limb***	***Intact Limb***	***Amp Limb (Level Unk.)***	***Intact Limb***	***Control Limb***
Ward's triangle											
Tugcu et al. (2009)	-	-	-	-	0.99	1.15	-	-	-	-	-
Yazicioglu et al. (2008)	-	-	-	-	0.94	1.06	-	-	-	-	-
Proximal femur											
Bemben et al. (2017)	-	-	-	-	0.862 pre, 0.734 6MO, 0.739 12MO	0.904 pre, 0.911 6MO, 0.912 12MO	-	-	-	-	-
Hansen et al. (2019)	-	-	-	-	-	-	0.66	1.03	-	-	1.04
Royer and Koenig, (2005)	-	-	-	-	0.82*	0.94*	-	-	-	-	0.92*
Sherk et al. (2008)	-	-	-	-	0.817	0.93	0.527	0.937	-	-	0.915 for TT, 0.904 for TF
Smith et al. (2009)	-	-	0.897	-	-	-	-	-	-	-	-
Smith et al. (2011)	-	-	-	-	-	-	-	-	0.807 male, 0.617 female	0.947 male, 0.738 female	-
Proximal tibia											
Royer and Koenig, (2005)	-	-	-	-	0.75*	1.09*	-	-	-	-	0.99*

	Study	TT Group	TF Group	Amp Group (level unknown)	Control Group	TT Limb	Intact Limb	TF limb	Intact Limb	Amp Limb (level unknown)	Intact Limb	Control Limb
	Tugcu et al. (2009)	-	-	-	-	0.56	0.86	-	-	-	-	-
	Yazicioglu et al. (2008)	-	-	-	-	0.6	0.95	-	-	-	-	-
volumetric BMD (mg/cm^3)	***Total***											
	Bemben et al. (2017)	-	-		-	-		-	-	701.1 pre, 564.9 6MO, 551.3 12MO	788.3 pre, 722.1 6MO, 798.1 12MO	-
	Sherk et al. (2008)	-	-		-	512.3	757.3	462.7	812.3	-	-	749.7 for TT controls, 927.7 for TF controls

Table 2: Summary of skeletal data reported in at least two studies included in this review. Asterisk (*) indicates value was estimated from a graph. Dash (-) indicates data was not reported. Abbreviations: TT= transtibial, TF= transfemoral, BMD= bone mineral density, MO= months.

Table 3: Summary of Mean Muscle and Fat Data

	Study	TT Group	TF Group	Control Group	TT Limb	Intact Limb	TF Limb	Intact Limb	Amputated Limb (level unknown)	Intact Limb	Control Limb
Cross-sectional area (mm^2 or % compared to intact limb or % atrophy)	***Thigh***										
	Bemben et al., (2017)	-	-	-	-	-	-	-	6324.8 pre, 4117.8 6MO, 3554.7 12MO	6479.1 pre, 69(20.5 6MO, 6515.5 12MO	-
	Renstrom et al., (1983)	-	-	-	86%	-	-	-	-	-	-
	Sherk et al., (2010)	-	-	-	1621.3mm^2	5320.4mm^2	4818.9mm^2	17122.8mm^2	-	-	5675.9 mm^2 TT, 17,028.3 mm^2 TF
	Sartorius										
	Jaegers et al., (1995)	-	-	-	40.1% atrophy compared to intact	-	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	88.30%	-	-	-	-	-	-
	Gracilis										
	Jaegers et al., (1995)	-	-	-	24.6% atrophy compared to intact	-	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	95.10%	-	-	-	-	-	-

	Study	TT Group	TF Group	Control Group	TT Limb	Intact Limb	TF Limb	Intact Limb	Amputated Limb (level unknown)	Intact Limb	Control Limb
	Semitendinosus										
	Jaegers et al., (1995)	-	-	-	44.3% atrophy compared to intact	-	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	91.90%	-	-	-	-	-	-
	Biceps femoris (long head)										
	Jaegers et al., (1995)	-	-	-	32.9% atrophy compared to intact	-	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	92.00%	-	-	-	-	-	-
Thickness (mm or % compared to intact limb)	***Vastus lateralis***										
	Onat et al., (2016)	-	-	-	9.63mm	11.06mm	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	80.20%	-	-	-	-	-	-
	Sibley et al., (2020)	-	-	-	15.4mm	26.3mm	-	-	-	-	25.0mm
	Rectus femoris										
	Onat et al., (2016)	-	-	-	15.6mm	17.63mm	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	84.30%	-	-	-	-	-	-
	Vastus medialis										
	Onat et al., (2016)	-	-	-	11.6mm	17.04mm	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	76.20%	-	-	-	-	-	-

	Study	TT Group	TF Group	Control Group	TT Limb	Intact Limb	TF Limb	Intact Limb	Amputated Limb (level unknown)	Intact Limb	Control Limb
	Vastus intermedius										
	Onat et al., (2016)	-	-	-	12.23mm	16.66mm	-	-	-	-	-
	Schmalz et al., (2001)	-	-	-	69.60%	-	-	-	-	-	-
Fat Mass (%)	***Whole-Body % Fat Mass***										
	Cavedon et al., (2021)	21.47	21.45	16*	-	-	-	-	-	-	-
	Sherk et al., (2010)	33.5	32.4	24.2 TT controls 25.5 TF controls	-	-	-	-	-	-	-
	George et al., (2021)	uni 23.1; bi 23.1	uni 23.4; bi 17.2	19.5							
	Affected Thigh % Fat Mass										
	Cavedon et al., (2021)	26.5	34.58	-	-	-	-	-	-	-	-
	Sherk et al., (2010)	38*	42*	30.0 TT controls, 29.0 TF controls*	-	-	-	-	-	-	-
	Intact Thigh % Fat Mass										
	Cavedon et al., (2021)	20.66	21.72	-	-	-	-	-	-	-	-
	Sherk et al., (2010)	36*	33*	30.5 TT controls, 28.5 TF controls*	-	-	-	-	-	-	-

Table 3: Summary of muscle and fat data reported in at least two studies included in this review. Asterisk (*) indicates value was estimated from a graph. Dash (-) indicates data was not reported. Abbreviations: TT= transtibial, TF= transfemoral, uni= unilateral limb loss, bi= bilateral limb loss.

The majority used dual x-ray absorptiometry (DXA) (n=13) to measure T-scores of the femoral neck (n=3), hip (n=2), and Ward's triangle (n=2), and Z-scores of the lumbar spine (n=2), and femoral neck (n=2). The same methodologies were utilized to report bone mineral density (BMD) in parameters of whole-body (n=3), lumbar spine (n=6), femoral neck (n=10), Ward's triangle (n=2), proximal femur (n=6), proximal tibia (n=3), and volumetric BMD (n=2). Other methodologies utilized to obtain the above properties were peripheral quantitative computed tomography (pQCT) scans (n=2), computed tomography (CT) scans (n=2), and x-rays (n=2).

Muscular methodologies utilized for each parameter were even less consistent. Histology (n=3) was employed to measure the fiber structures, fiber composition/size, ultrasound was employed to measure various muscle thicknesses the vastus lateralis (n=3), rectus femoris (n=2), vastus medialis (n=2), and vastus intermedius (n=2). MRI (n=4) was used in measuring fatty degeneration as well as femur and muscle volume, DXA (n=3) was utilized to measure whole-body, thigh, and lower-leg fat mass, qQCT (n=1) for muscle and fat CSA at the end of each limb. Muscle fiber typing could not be summarized in Table 3, because all four studies examined different muscles or properties[6, 20-22].

Discussion

Despite varying methodologies and reported parameters, studies agreed amputees compared to control groups and the amputated limb compared to the intact had reduced BMD and increased muscle atrophy. Specifically, reduced BMD was found in multiple parameters, T-scores and Z-scores, whole-body, lumbar spine, femoral neck, Ward's triangle, proximal femur, and proximal tibia. Additionally, muscle atrophy was found in parameters of decreased thigh cross-sectional area (CSA) and quadriceps thickness with higher ratios of fat to muscle within the thigh. Overall, the correlation between altered structural parameters (e.g. reduced BMD and increased muscle atrophy) with adverse clinical outcomes, such as increased risks of fractures, osteopenia, osteoporosis, and reduced mobilities in this population was repeatedly reported by multiple studies.

Skeletal Adaptations

The majority of articles included in this review investigated BMD using DXA, which is the gold standard for screening osteopenia and osteoporosis but is rarely used in post-amputation management[23]. Consistently, these studies revealed that individuals with amputations compared to control groups, and amputated limbs compared to intact/control limbs had reduced BMD. Moreover, there was increased prevalence of osteopenia or osteoporosis in amputees, shown by a lower T- and Z-scores[15, 24-27]. In accordance with the World Health Organization classification, an individual's T-score is a comparison of their bone density to a healthy individual of the same sex who is 30 years of age, while a Z-score compares an individual's bone density to an individual of the same age and sex[28]. Therefore, T-scores are only sex-matched, while Z-scores are age and sex-matched.

Studies consistently found reduced BMD in the femoral neck and Ward's triangle in amputated limbs compared to intact limbs[24-27, 29]. Ward's triangle is a small space within the femoral neck, located between the principal compressive, secondary compressive, and primary tensile trabeculae. BMD of Ward's triangle is a region of initial bone loss[30], with low BMD and high flexing strain [31] and is accepted as a sensitive indicator of osteoporosis[32]. Femoral neck BMD was reduced in amputated limbs regardless of amputation level. Ward's triangle BMD was only reported by two studies in individuals with transtibial amputation, and both indicated reduced BMD in the amputated limb. Overall, it is important to note that femoral neck and proximal femur BMD represents the greatest predictive power of fracture at that site[24, 33] indicating that individuals with amputations are at an increased risk of femoral neck fractures compared to controls.

In congruence with the femoral neck and Ward's triangle results, the proximal femur (femoral neck, trochanter, total hip) and proximal tibia had reduced BMD compared to the intact limb and controls across studies. Three studies that reported proximal tibia BMD all compared transtibial limbs to intact limbs and found reduced BMD on the amputated limb[25, 26, 34]. Royer and Koenig also included limbs from a control population, with values in between amputated and intact limbs. This finding further supports that the amputated limb is underused, and the intact limb is overused compared to control limbs. Reduced amputated limb BMD in the proximal tibia could be a factor in the development of intact limb knee osteoarthritis, which is prevalent in this population[34, 35].

All studies that reported whole-body or lumbar BMD found that BMD was most preserved in controls, followed by individuals with transtibial amputations, then individuals with transfemoral amputations. In a longitudinal study, whole-body and lumbar BMD over time in individuals with transtibial amputations had recovered baseline values at the 12-month follow-up despite having reduced values at the 6-month follow-up[18], suggesting a rehabilitation and adaptation period over the first six months post-amputation, consistent with the findings in the lower limb BMD.

The two studies that reported volumetric BMD both found reduced values on the amputated limb compared to the intact limb[18, 36]. Volumetric BMD, defined as BMC per volume of bone, can only be measured through computed tomography and is considered a more accurate measure of BMD compared to areal BMD[37-39]. Individuals with transfemoral amputation had greater reductions in volumetric BMD on the amputated limb than those with transtibial amputation[36]. These studies, again, highlight the importance of knee joint sparing, when possible, and show structural adaptations occur within the first six months after the amputation.

Overall, these studies suggest that those with an amputated limb suffer from loss of BMD in their amputated limb as well as central whole-body and lumbar regions, but have potential to reach baseline with proper rehabilitation. Proactive skeletal screening post-amputation may help identify and reduce the prevalent risks of osteopenia and osteoporosis in this population through targeted rehabilitation exercises to increase loading at the affected limbs. In addition, decreasing the time between amputation and ambulation with a prosthesis within the first six months could be critical to maintaining bone health.

<u>Muscular Adaptations</u>

Studies that investigated muscular adaptations found a decrease in thigh CSA and quadriceps thickness, an increase in amounts of thigh fat, and more muscle fiber atrophy in the amputated limb compared to the intact limb.

Thigh muscle CSA was reduced in the amputated limb compared to the intact limb in three studies, despite reporting data in different units[2, 18, 40]. Only one study to include a control group and found control limbs had similar CSA values to intact limbs in both individuals with transtibial and transfemoral amputations[2]. Reduced thigh CSA and volume indicates reduced ability to generate force, which can impede push-off during gait[14, 41] and contribute to the asymmetry between limbs[42].

All three studies that reported quadriceps muscle thickness found reduced quadriceps muscle thickness in the amputated limb compared to the intact limb[20, 43, 44], indicating reductions in quadriceps strength. Additionally, the intact limb had greater thickness compared to the control limb, which aligns with many previous studies that have found that individuals will compensate by overusing their intact limb[20]. The quadriceps are important in prosthetic control, particularly in terms of knee extension for stability and hip flexion for prosthetic clearance throughout gait, regardless of amputation level. Therefore, lack of quadriceps strength could potentially increase the prevalence of gait deviations and fall risk.

Fat mass was consistently greater in individuals with amputation compared to controls, especially in the thighs. Studies conflicted on whether individuals with transfemoral amputation had similar or greater fat mass compared to individuals with transtibial amputation, which may have been due to differences in included participants. Regardless of amputation level, thigh fat mass can be an important factor in achieving optimal prosthetic socket fit and effective prosthetic control[2]. Quantifying fat mass can inform prosthetic modeling and fitting, as well as gait rehabilitation exercises to improve functional prosthesis use.

Although the muscle architecture data could not be included in Table 3 due to the wide range of studied muscle groups and reported parameters, structural changes in fiber type, pennation angle, and fascicle length, are important indicators of muscle atrophy[20-22, 40]. Despite lack of consistency in methodology across studies, findings include a complete reduction in fast-twitch compared to slow-twitch fibers in the amputated limb within seven days[21], and a reduction in slow-twitch fibers[40] and shorter fascicle length[20] in the vastus lateralis of the amputated limb compared to the intact limb. Additionally, elderly individuals with vascular etiologies of transtibial amputation had split muscle fibers, fiber atrophy, reduced cross-sectional fiber area and length, and adipose tissue in the gastrocnemius compared to younger individuals with traumatic etiologies[22]. Fiber atrophy and shorter fascicle lengths in the amputated limb indicate impaired ability to generate force, which can impede gait.

Overall, these studies suggest that amputated limbs had less thigh CSA and quadriceps thickness, more thigh fat, and more muscle fiber atrophy with shorter fascicle lengths compared to the intact limb, which could impact gait through reduced knee stabilization and decreased propulsion. Proactive screening for lower limb muscular atrophy along with targeted exercises to specific thigh muscles could help prevent muscle atrophy reduction, and lead to increased symmetry between amputated and intact limbs.

<u>Clinical Considerations</u>

Osteopenia and osteoporosis: Studies in this review found increased risks of fractures, osteopenia, and osteoporosis, particularly at the femoral neck and distal end of the amputated limb. This aligns with retrospective studies in this population[15, 45], and agrees with previous literature that decreased loading results in reduced BMD[34, 46]. Coupled with muscle atrophy, which has also been associated with decreased loading, this population is particularly vulnerable to local and generalized osteoporosis[13, 25, 26, 29]. Clinicians could focus on recommending targeted rehabilitation exercises that increase weight-bearing load through the amputated limb, particularly within the first six months post-amputation.

Osseointegration: Individuals with osseointegration may not experience the same reductions in bone health as individuals who use traditional prostheses. After 30 months, individuals with removed implants had reduced BMD, but individuals with non-removed implants had BMD values normalized to baseline values[47]. Regarding preservation of femoral neck Z-scores in individuals with osseointegration, studies were inconsistent with results ranging from decreased, no significant change, and increased Z-scores. Differences in findings may be explained by amputation levels of included participants or different time points for follow-up measurements[27, 48, 49]. Maintenance or increase of BMD may be evidence of more activity on the prosthetic limb or more frequent ambulation[27]. Two studies agreed periprosthetic cortical thickness around the implant increased over two years[24, 49]. Muscles contribute to femur stabilization with osseointegrated implants more than with a traditional prosthetic socket, which may lead to increased periprosthetic cortical thickness[48, 49]. Due to the loading differences between osseointegration and traditional prosthetic sockets, individuals with osseointegration may not experience the same declines in BMD. However, localized bone declines in the femoral neck and distal end as stated above could put individuals at increased risk of periprosthetic fracture and surgery, potentially resulting in more proximal amputation levels.

Muscle strength: Studies that investigated structural muscle properties in this review found reduced thigh CSA, indicative of reduced force production. This finding aligns with many studies that have measured muscle contraction strength or force generation and absorption during gait[50]. The reduced ability of the amputated limb to produce force can impede gait and factor into the development of secondary health conditions, such as osteoarthritis[5, 51-53]. Studies in this review also found reduced quadriceps strength and increased thigh fat mass in the amputated limb, so exercises that increase quadriceps strength and reduce thigh fat mass could be goals prioritized in rehabilitation. Additionally, daily socket use was found to be negatively correlated with adipose infiltrating muscle in one study[54], indicating less daily socket use was associated with more muscle atrophy. This supports the importance of daily prosthesis use to limit residual limb atrophy.

Level of amputation: Studies that directly compared individuals with transtibial and transfemoral amputations typically found a greater degree of BMD reduction and muscle atrophy in individuals with transfemoral amputations[2, 19, 27, 36]. This aligns with numerous studies in this population that have found individuals with transfemoral amputations are more affected than individuals with transtibial amputations due to more proximal functional loss[5]. Therefore, individuals with transfemoral amputations have more structural and functional limitations than individuals with transtibial amputations, generally resulting in decreased musculoskeletal health. Less force is transferred to the body, particularly the femur, because force is transferred through the prosthetic socket to soft tissue and the ischial tuberosity. Force passes through more soft tissue in a transfemoral prosthesis compared to a transtibial prosthesis, due to amputation surgery and prosthesis design[36].

Time since amputation: Nearly all studies that measured multiple time points found significantly reduced BMD and increased muscle atrophy within six months or one year following amputation surgery. Findings suggest six months for skeletal rehabilitation and one year for muscular rehabilitation post-amputation may be a critical threshold of time to strengthen musculoskeletal health in rehabilitation[18, 55], but more research across multiple time points is needed.

Regional differences within the amputated limb: Studies that directly compared regional differences in musculoskeletal architecture along the amputated limb found reduced BMD and increased muscle atrophy at the distal end of the amputated limb compared to proximal or middle sections[2, 36, 55]. Throughout the proximal femur, found the lowest Young's Modulus values and BMD at the femoral neck and the highest values at the proximal quarter diaphysis of the femur[56]. These results suggest the femoral neck and distal end of the amputated limb may be important regions to monitor musculoskeletal health and target in rehabilitation.

Participant demographics: Findings in this review are not representative of the majority of individuals with amputations. The majority of participants included in the studies were adults between 18- 65 years of age with traumatic etiologies. However, 42% of individuals with limb loss are 65 years of age or older regardless of etiology, and 54% have dysvascular etiologies, such as diabetes mellitus and peripheral artery disease that have been associated with increased bone loss, fracture risks, osteoporosis/penia[1, 57-62]. Additionally, studies rarely compared results by amputated limb length, time since amputation, activity level, or prosthetic wear time, and findings typically conflicted. Additionally, two studies found significant differences between prosthetic wear time and BMD, but in different parameters[24, 36]. More research is needed to generalize findings to the majority of individuals in this population.

Clinical outcome measures: While all twenty-seven manuscripts included in this review stated clinical considerations, only two collected clinical outcome measures[27, 44].Clinical outcome measures included the Houghton survey to assess prosthetic use[44], as well as the 6-Minute Walk Test and Timed Up and Go[27]. However, the Houghton scores were not tied to findings in the study, and pre-osseointegration surgery 6-Minute Walk Test scores were positively correlated with BMD values at one-year follow-up. Thus, there is not yet a body of evidence that demonstrates how structural adaptations may potentially influence clinical outcome measure performance aside from one study in individuals with osseointegration. More research is needed to directly correlate structural findings summarized throughout this review to clinical outcome measure scores, as an indicator of functional mobility.

Limitations and Potential for Future Work

This review only summarized structural musculoskeletal properties, defined as anatomical or physiological components such as BMD and muscle architecture, published in the English language. Several articles measured other parameters, such as muscle activation using electromyography or muscle strength using dynamometers. These relationships should also be considered to understand how musculoskeletal architecture relates to functional mobility.

Future research can include larger sample sizes of participants with a variety of demographics, such as time since amputation and activity level. Additionally, studies can include participants that reflect the majority of individuals with limb loss, such as individuals who are older or have dysvascular etiologies. Including these individuals can also provide evidence to differentiate the effects of musculoskeletal adaptations due to amputation, aging, and dysvascular conditions such as diabetes. One study stated inclusion of individuals with congenital deficiencies, which were only two of nine participants, and did not compare etiologies[34]. Individuals with a congenital deficiency may have differences in musculoskeletal architecture than individuals who undergo amputation, but no current literature has compared individuals with congenital etiologies to other etiologies.

Future work can also compare parameters such as time since amputation, prosthetic componentry, and activity level to provide a variety of musculoskeletal health expectations based on these factors. Multiple time points were compared by several studies, but more work is needed to confirm critical thresholds that could be important landmarks in rehabilitation. Additionally, few studies measured the same musculoskeletal parameters or included raw values, especially in terms of muscular adaptations, which made results difficult to compare across studies. This population also has a combination of a high risk of falls and fractures and lower BMD on the amputated hip. Proactive assessment of fracture risk and prevention could be an initial crucial piece of long-term care in this population[24]. More work is needed to confirm findings by studies included in this review, investigate muscle architecture, and translate findings to clinical outcome measure performance.

Conclusion

This review summarized literature investigating structural musculoskeletal adaptations in individuals with major unilateral lower-limb amputations to inform clinical considerations and guide directions for future research. Findings in this review aligned with findings from non-anatomical studies that have suggested increased risks of fractures, osteopenia, osteoporosis, and muscle atrophy. BMD was reduced in individuals with amputation compared to controls and amputated limbs compared to intact limbs in T-scores and Z-scores, whole-body, lumbar spine, femoral neck, Ward's triangle, proximal femur, proximal tibia, and BMC. These findings indicate increased risks of experiencing fractures, osteopenia, and osteoporosis, particularly in the femoral neck and amputated limb. Amputated limbs also had more muscle atrophy compared to the intact limb, specifically in parameters of decreased thigh CSA and quadriceps thickness with more thigh fat and muscle fiber atrophy. These findings were more pronounced in individuals with transfemoral amputations compared to transtibial amputations, and in individuals with amputations compared to control groups. Studies that measured multiple time points indicated the first six months to one-year post-amputation may be a critical threshold for musculoskeletal rehabilitation. Musculoskeletal adaptations could eventually be screened by clinicians to inform rehabilitation techniques and improve functional mobility. However, more research is needed to directly inform clinical outcome measure performance and functional mobility.

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Chapter 1 Linkage

Chapter 1 informed decisions for the all three studies listed under 'Section 2: Musculoskeletal Symmetry.'

Specifically, findings from Chapter 1 highlighted the need to investigate the underlying mechanisms behind changes in anatomy post-amputation. Specifically, how these changes could be used as indicators of femoral fracture risk, hip and knee osteoarthritis, and muscle atrophy. Additionally, Chapter 1 showed no anatomical donors with amputation had been studied in prior literature. Including anatomical donors can allow for more detailed musculoskeletal data collection (e.g. whole muscle dissection to calculate physiological cross-sectional area), that could not reasonably be performed in living individuals. We also discovered from personal experience that anatomical donors could provide an alternative method of data collection in instances when human participant data collection is restricted, such as global pandemics.

CHAPTER 2

NORMALIZATION OF KINEMATIC WALKING SYMMETRY DATA TO INFORM CLINICAL CONSIDERATIONS FOR INDIVIDUALS WHO USE LOWER-LIMB PROSTHESES

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Abstract

Introduction: Individuals who use unilateral transtibial or transfemoral prostheses have negative secondary health effects associated with decreased kinematic (e.g., spatiotemporal and joint angle) walking symmetry between prosthetic and intact limbs. Research studies have quantified kinematic walking symmetry, but studies can be difficult to compare owing to the inclusion of small sample sizes and differences in participant demographics, biomechanical parameters, and mathematical analysis of symmetry. This review aims to normalize kinematic walking symmetry research data across studies by level of limb loss and prosthetic factors to inform considerations in clinical practice and future research.

Methods: A search was performed on March 18, 2020, in PubMed, Scopus, and Google Scholar to encompass kinematic walking symmetry literature from the year 2000. First, the most common participant demographics, kinematic parameters, and mathematical analysis of symmetry were identified across studies. Then, the most common mathematical analysis of symmetry was used to recalculate symmetry data across studies for the five most common kinematic parameters.

Results: Forty-four studies were included in this review. The most common participant demographics were younger adults with traumatic etiology who used componentry intended for higher activity levels. The most common kinematic parameters were step length, stance time, and sagittal plane ankle, knee, and hip range of motion. The most common mathematical analysis was a particular symmetry index equation.

Conclusions: Normalization of data showed that symmetry tended to decrease as level of limb loss became more proximal and to increase with prosthetic componentry intended for higher activity levels. However, most studies included 10 or fewer individuals who were active younger adults with traumatic etiologies.

Clinical Relevance: Data summarized in this review could be used as reference values for rehabilitation and payer justification. Specifically, these data can help guide expectations for magnitudes of walking symmetry throughout rehabilitation or to justify advanced prosthetic componentry for active younger adults under 65 years of age with traumatic etiologies to payers.

Introduction

Evaluating lower-limb walking symmetry can help clinicians establish functional limitations, track changes over time, and assess effectiveness of rehabilitation techniques.[1] Walking symmetry between prosthetic and intact limbs is often viewed as a measure of improved rehabilitation in individuals who use unilateral lower-limb prostheses (IULLPs),[2] such as transtibial and transfemoral prostheses. Walking symmetry has been associated with increased balance,[3–5] decreased fall risk,[6] and decreased risk of developing musculoskeletal overuse injuries such as osteoarthritis.[7] Confidence in walking and balance tasks have been shown to improve community participation and quality of life.[6,8] Therefore, increasing walking symmetry has the potential to improve functional mobility and quality of life in IULLPs.

Several reviews have discussed walking symmetry in IULLPs. In 2004, a review examined the influence of prosthetic componentry on kinematics, kinetics, and electromyography.[9] Reviews on lumbopelvic parameters,[10] standing balance,[4] and the influence of muscle strength on balance[5] also exist. Reviews on gait training[15] and suspension systems[11] have been shown to influence walking symmetry, and a review in 2011 identified the most common kinematic parameters studied in IULLPs.[12] However, a review normalizing kinematic walking symmetry data across studies to inform clinical considerations in this population is lacking from the literature. Normalized walking symmetry data summarized from research in IULLPs can provide quantitative baseline characteristics to better inform clinical decision making.

Translating research findings into clinical care was identified as a 2020 research priority by the American Academy of Orthotists and Prosthetists, highlighting the importance of narrowing the barrier that exists between research data and clinical application.[13] However, research studies have been difficult to compare, posing a barrier to translating research findings into clinical practice. Research studies typically have small sample sizes and differences in objectives, participant demographics, kinematic parameters, and mathematical analysis of symmetry.[14] As a result, consensus among clinical practitioners has largely been based on observational effects rather than research findings.[9] In order to translate kinematic walking symmetry research findings into clinical care, data needs to be comparable, which can be achieved by normalizing research data across studies. Normative, or reference, values for symmetry have not been identified across current literature, and could provide clinicians evidence-based rehabilitation targets by level of limb loss and payer justification for certain prosthetic componentry.

Therefore, the objective of this review was to normalize kinematic walking symmetry data in IULLPs by level of limb loss and prosthetic factors to inform considerations in clinical practice and future research. The most common participant demographics, kinematic parameters, and mathematical analysis of symmetry were identified. Then, data were normalized across studies using the most common mathematical analysis of symmetry for the five most common parameters identified in this review. Considerations for designing future kinematic walking symmetry studies are also provided to help promote clinical translation.

Methods

A search was performed on March 18th, 2020 in PubMed, Scopus, and Google Scholar to encompass literature from the year 2000. References from identified studies were also examined for inclusion.

The following search terms were used:

PubMed: (spatiotemporal) AND transtibial OR transfemoral AND prosth* AND unilateral AND symmetry OR asymmetry; (kinematic) AND transtibial AND prosth* AND unilateral AND symmetry OR asymmetry

Scopus: interlimb AND kinematic AND prosth* AND symmetry AND unilateral AND transtibial OR "below knee" OR transfemoral OR "above knee"

Google Scholar: kinematic OR spatiotemporal AND prosth* AND symmetry OR asymmetry OR "symmetry index" AND unilateral AND transtibial OR "below knee" AND transfemoral OR "above knee" AND gait OR ambulation -running -sprinting -powered -stair -ramp -incline -slope

Studies were selected based on the following inclusion criteria (Fig. 1):

- Adult population (defined as 18 or older) who used unilateral transtibial or transfemoral prostheses
- Kinematic symmetry data was reported between the prosthetic and intact limbs
- Participants walked on a level surface (ground or treadmill)

Studies were excluded based on the following criteria:

- Case reports (defined as less than 5 participants)
- Conference papers

- Novel development or testing of prosthetic components not commonly prescribed in clinical practice
- Participants performed movement tasks other than walking (e.g. stairs, running)
- Computer modeling was used in place of participant testing

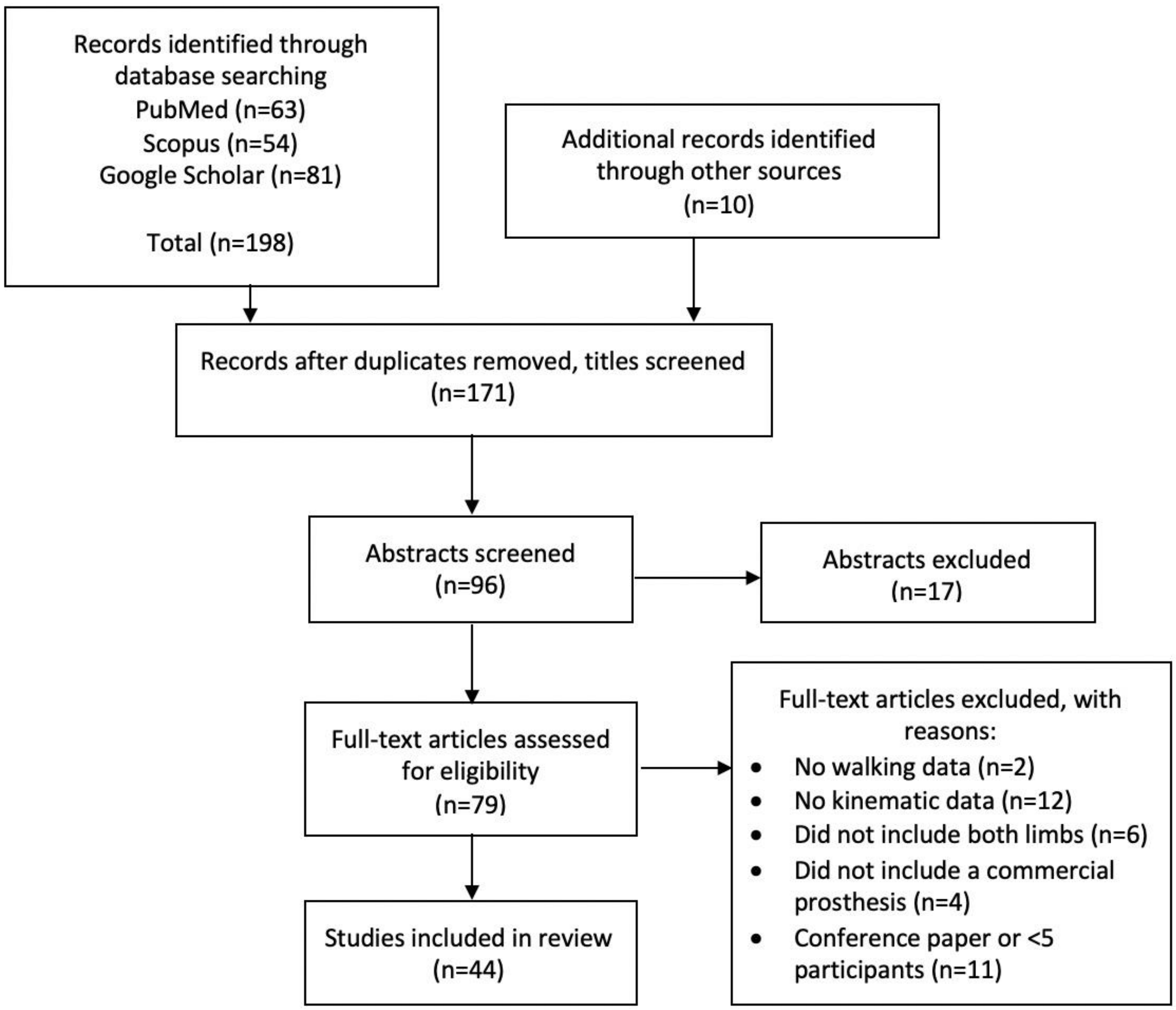

Fig. 1: Flow diagram of inclusion process.

Many studies included in this review investigated parameters other than kinematics such as kinetics, energy consumption, or patient preference. Several studies also investigated movement tasks other than walking such as traversing stairs or inclines, navigating turns, or performing sit-to-stand transitions. Only the portions of each study that met the inclusion criteria were discussed in this review.

The most common participant demographics, kinematic parameters, and mathematical analysis of symmetry were identified across studies. Findings by level of limb loss and prosthetic factors were then determined by using the most common mathematical analysis of symmetry identified in this review to recalculate symmetry data across studies for the five most common kinematic parameters in this review.

Normalizing data typically involves recalculating values to a range between 0 and 1.[15] This review normalized data to a range between 0 and 100% between-limb symmetry across studies. Several conversions were made to report results consistently. All spatiotemporal units were converted to meters (m) and seconds (s). The most common mathematical analysis of symmetry in this review was Eq. 1, which provides asymmetry percentages.

$$\frac{I - P}{0.5 * (I + P)} * 100$$

Eq. 1

I represents the intact limb and P represents the prosthetic limb. Perfect symmetry is a value of 0% and perfect asymmetry is a value of either 100% if intact limb values are greater or -100% if prosthetic limb values are greater. Therefore, an absolute value of 100 – Eq. 1 was used to provide symmetry percentages, resulting in 100% representing perfect symmetry and 0% representing perfect asymmetry.

Out of the 44 studies included in this review, 34 studies could be converted to normalized symmetry values. The remaining ten studies could not be normalized because symmetry was examined through ratio scales or waveform analysis, and did not provide prosthetic and intact limb values necessary for recalculation using Eq. 1.[15–24]

Results

This review included 44 studies after applying inclusion and exclusion criteria. Table 1 summarizes each study by objective, participant demographics, prosthetic componentry of participants, kinematic parameters measured, and mathematical analysis of symmetry. Results are reported in the following sections: participant demographics, kinematic parameters, and mathematical analysis of symmetry.

Table 1: Summary of Included Studies

Author, Year	Objectives	Participants	Prosthesis Components	Kinematic Parameters	Assessment of Symmetry
1. Astrom and Stenstrom, 2004	Investigate effects of using a polyurethane liner on gait and socket comfort	7 TT (4M 3F); Vascular (4), Nonvascular (3); Age (mean 46, range 23-71 years)	Prescribed silicone liners: Iceross(5), EVA(2); polyurethane liner used for study; Feet: Conventional (5), Flex(2)	Spatiotemporal: WS, StepL, StepT, SLS; Joint angles: Knee ROM during step period, Knee ROM at LR, Knee varus/valgus during stance	((I-P)/ (.5*(I+P)) *100
2. Bai et al., 2017	Kinematic and biomimetic assessment of a hydraulic ankle/foot (Echelon) compared with a fixed prosthetic ankle/foot (Esprit)	5 TF (all M); Age (range 27-65 years): 12 Controls (5M 7F); Age (mean 26 SD 2 years)	Knee: KX06(2), Linx(2), IP(1); Feet: Echelon VT(1), Elan(2), Linx(2); fitted with Echelon (hydraulic) and Esprit (fixed) for study	Spatiotemporal: WS, StepL, StanceT, StrideL; Joint angles: Ankle PF peak, Ankle DF peak, Ankle MS Eversion	Statistical comparison
3. Bateni and Olney, 2002	Identify kinematic characteristics of gait in TT and compare results to other studies	5 TT (all M); Trauma(all); Age (range 32-77 years)	Foot: SAFE foot (all)	Spatiotemporal: WS, StrideL, StrideT, StanceT, DLS Time; Joint angles: Knee ROM, Hip ROM	Statistical comparison
4. Carse et al., 2020	Identify differences in gait symmetry between NA and established unilateral TF mechanical knee users and characterize common gait deviations in TF group	60 TF or KD IULLPs (49M 11F); Trauma(32), Infection(7), PAD w/o diabetes(7), PAD w/ diabetes(1), Tumor(8), Other(5); Age (mean 51.1 SD 15.2 years); K2(10), K3(31), K4(18); 10 Controls (5M 5F)	Sockets: IsC(37) Quad(19), Distal end bearing(4); Suspension: Seal-in(18), Total suction(15), Pin(9), Waist belts(13), Other(5) Knee: Polycentric(20), Hydraulic yielding(15), Stance (weight) activated(19), Single axis (alignment controlled)(1), Hand operated knee lock(2), Semi-automatic knee lock(1), Fluid controlled hydraulic(1), Other(1)	WS, StepL, StepT, BoS, COM deviation	Ratio

5. Chow et al., 2006	Investigate effects of anteroposterior translations and tilts in prosthesis alignment on gait symmetry	7 TT (6M 1F); Age (range 32-58 years)	Sockets: PTB and SACH; some originally used exoskeletal designs; all used endoskeletal designs for study	Spatiotemporal: StepL, StanceT; Joint angles: Knee Flex at LR, Time to Knee Flex at LR, Max Knee Flex during Swing, Time to Max Knee Flex during Swing, Knee ROM	(I-P) /(.5*(I+P))*100; absolute value
6. Clemens et al., 2020	Measurement of gait symmetry and repeatability using IMUs	128 total IULLPs; 65 TT (34M and 31F) Age (mean 51 SD 14.1 years) 63 TF (27M and 36F) Age (mean 47.9 SD 16.2 years)	NR	Thigh: Segmental Symmetry Score (SSS) and Segmental Repeatability Score (SRS); Shank: Segmental Symmetry Score and Segmental Repeatability Score; sagittal angular velocities of the thigh and shank	$100 - (100 * x/y)$ where x is the average Angular Velocity Difference value, and y is the threshold of symmetry
7. Cutti et al., 2018	Determine reference values for gait temporal asymmetry	60 K3-K4 total IULLPs; Trauma(all); 23 TT Age (mean 44 SD 14 years); 37 TF Age (mean 46 SD 10 years): 10 Controls	Knee: Mechanical (12- including TotalKnee 2100(5), 3R60(2), Mauch(2)), C-leg (25); Feet: Vari-flex or Vari-flex LP foot, 1C40, Truestep, Esprit	StepT, StanceT	Ratio; StepT= I/P, StanceT= I/P
8. Darter et al., 2013	Investigate if home-based treadmill training improves gait performance in established unilateral TF MPK users	8 TF; Trauma or Cancer; Age (mean 41.4 SD 12.1 years)	Knee: MPKs	StepL, StanceT	Ratio; StepL= longer/shorter, StanceT = P/I

9. Darter et al., 2017	Investigate locomotor adaptability on a split belt treadmill	10 TT (all M); Trauma(all); Age (mean 32.2 range 23-39): 8 Controls	Suspension: Suction with sleeve(8), Pin lock(1), Elevated vacuum(1) Feet: Vari-flex XC(5), Soleus Tactical(3), Re-flex Rotate(1), Kinterra(1)	StepL, StanceT, Limb Excursion	(fast-slow)/ (fast + slow)
10. De Asha and Buckley, 2015	Investigate effects of walking speed on minimum toe clearance, and the temporal relationship between minimum clearance and peak swing-foot velocity	10 TT (all M) Age (mean 48 SD 11.7 years)	Feet: Esprit	Minimum toe-ground clearance, Peak Swing Velocity	Statistical comparison
11. Gholizadeh et al., 2014	Investigate effects of suction and pin/lock suspension systems on gait performance	10 TT; Trauma(5) Diabetes(5); Age (mean 45.8 SD 14.4 years); K2(4) K3(6)	Each participant used each suspension: Iceross Dermo Liner with pin lock, Iceross seal-in suction; Feet: Flex foot	Spatiotemporal: WS, StepL, StrideL, StanceT and SwingT; Joint Angles: Hip Position IC, Max Hip Ext, Hip ROM, Knee Position IC, Max Knee Flex Stance, Max Knee Flex Swing, Knee ROM, Ankle Position IC, Max Ankle PF Stance, Max Ankle PF Swing, Max Ankle DF Stance, Ankle ROM	((I-P) / (.5*(I+P))) *100

12. Gholizadeh et al., 2020	Compare effects of unity suspension system on gait between vacuum on and off conditions	12 TT (11M 1F); Trauma(8), Diabetes(3), Infection(1); Age (mean 57.2 SD 15.3 years); K3(10) and K4(2)	Suspension: Pin-lock(9), Suction(2); fit with Unity elevated vacuum suspension and Pro-flex XC foot for study	Spatiotemporal: WS, StepL, Step width, StepT, StrideL, StrideT, StanceT, SwingT, SLS Time, DLS Time; Joint Angles: Hip ROM, Peak Hip Flex early Stance, Knee ROM, Peak Knee Flex Swing, Knee Flex IC, Ankle ROM, Peak Ankle PF early Stance, Peak Ankle DF Stance	((I-P) / (.5*(I+P))) *100
13. Graham et al., 2007	Compare gait symmetry between conventional (Multiflex) and ESAR(Vari-flex) prosthetic feet in high-functioning TF	6 TF (all M): Age (range 34-50)	Knee: Blatchford stabilized with pneumatic swing phase control(1), IP (5); Feet: Multiflex(all); Foot changed to Vari-flex for study	Spatiotemporal: StepL, StanceT; Joint Angles: Ankle DF Late Stance, Knee Flex Midswing, Hip Flex Late Swing, Hip Ext Late Stance, Transverse Pelvic Rotation	Ratio
14. Hak et al., 2014	Determine if stepping asymmetry might be functional in terms of gait stability	10 TT (9M 1F); Trauma(8), Dysvascular(1), Other(1); Age (range 21-66)	Socket: TSB(1) PTB(9); Feet: Axtion(1), Elite VT(1), 1C40(3), Vari-flex EVO(2), Fusion(1), Celsus(1), Propiofoot(1)	StepL, FFP, Trunk Progression	(I / ((I+P)/2)*100
15. Hekmatfard et al., 2013	Investigate effects of four prosthetic mass conditions on spatiotemporal knee kinematics	10 TF (all M); Trauma(all); Age (range 27.2-60)	Socket: IC; Suspension: belt; Knee: single axis w/ ext. assist; Foot: single axis	WS, Cadence, walking distance, StepL, StrideL, Step speed, gait cycle duration, Stance T, SwingT, COM	Statistical comparison

16. Highsmith et al., 2010	Determine differences in spatiotemporal parameters between transtibial and transfemoral IULLPs	15 total IULLPs; 7 TT (all M); Trauma(3), PVD(3), Tumor(1); Age (range 32-70 years) 8 TF (all M); Trauma(all); Age (range 21-72 years)	Suspension: shuttle lock(7- all TT), suction(6), seal-in (2) Knees: C-Leg(6), Rheo(1), Plie(1); Feet: Trustep(1), Proprio(1), Perfect stride II(1), Vari-flex(2), Renegade(2), Ceterus(1), 1C40(2), Reflex-VSP(1), ESAR foot where brand not indicated(2), Journey(1), Luxon Max(1)	WS, Cadence, StepL, Step width, StepT	((I-P) / (I+P))
17. Houdijk et al., 2018	Compare StepL symmetry and MoS between Vari-flex to SACH prosthetic feet	15 TT (all M); Trauma(all); Age (mean 55.8 SD 11.1 years); K3(all)	all originally used ESAR foot; Feet: Variflex vs SACH foot	StepL, backward MoS	Statistical comparison
18. Johansson et al., 2005	Compare kinematics between the Mauch hydraulic knee, C-Leg MPK, and Rheo MPK	8 TF LLPs (7M 1F); Trauma(3), Infection(2), Cancer(2), Congenital(1); Age (range 29-54 years)	Suspension: suction(6), silesian belt(1), pin-lock(1)	WS, StepL, StepT, SLS Time, DLS Time	Statistical comparison
19. Kahle and Highsmith, 2014	Compare gait, balance, and subjective analysis between IsC and brimless TF socket designs with vacuum assisted suspension	10 TF (8M 2F); Trauma(7), PVD(2), Sarcoma(1); Age (mean 42.9 years)	Same liner, pump, knee, and foot utilized in both conditions; Knee: SAFE(1), C-leg(9); Feet: ESAR	WS, StepL, StepT, BoS width, SLS Time, DLS Time, Swing Time, StanceT	((I-P) / (I+P))

20. Kaufman et al., 2012	Compare gait asymmetry between TF of mechanical and MPKs	15 TF (12M 3F); Trauma(7), Cancer(6), PVD(1), Congenital(1); Age (mean 42 range 26–57 years); K3 and K4: 20 NA (9M 11F); Age (mean 26 SD 9 years)	Knee: session one with mechanical fluid controlled knee prosthesis (Mauch SNS(11), CaTech(2), Black Max(1), Total Knee 2000(1)); session 2 with Otto Bock C-Leg; Feet: kept same; Luxon Max(5), Dynamic Plus(1), College Park(1), Axtion(8)	Hip Stance, Hip Swing, Knee Stance, Knee Swing, Ankle Stance, Ankle Swing	Entire waveform analysis; singular value decomposition; subtracted the mean value from every value in the waveform
21. Keklicek et al., 2019	Compare gait variability and symmetry between trained individuals TT and TF	25 total IULLPs; 14 TT (12M 2F); 11 TF (4M 7F); Trauma(all): 14 Controls (8M 6F)	Knee: mechanical knee joint (Otto Bock 3R15); Feet: dynamic (Otto Bock 1D10) for both TT and TF Amps	StepL, StepL % Variability, StanceT, Ambulation Index Score (relative to 100 based on foot-to-foot time distribution ratio and average step cycle)	Statistical comparison
22. Kovac et al., 2010	Investigate spatial, temporal and kinematic characteristics in traumatic TT amputee gait	12 TT (all M); Trauma(all); Age (mean 40.25 SD 6 years): 12 Controls; Age (mean 37.46 SD 5.25 years)	Feet: Dynamic foot(7), Greissenger foot(2), Flex foot(2)	WS, Cadence, StepL, StrideL, StrideT, Swing Velocity, StanceT, SwingT, DLS Time	Statistical comparison
23. Marinakis, 2004	Compare interlimb symmetry in the early rehabilitation stage between two different prosthetic feet (Greissenger Plus and SACH)	9 TT (all M); Trauma (all); Age (mean 54.3 years SD 2.1 years): 13 Controls (all M); Age (mean 52.3 years SD 11.3 years)	PTB socket with removable prosthetic liner (all); used Greissenger Plus and SACH for study	Spatiotemporal: WS, Cadence, StepL, StepT, StanceT, StrideT, %StrideT (division of StanceT by the StrideT and multiplied by 100); Joint Angles: Hip ROM, Knee ROM, Ankle ROM	Method 1: 100* min(P,I)/max(P,I); Method 2: 100-((100*(P-I)) /(.5*(P+I))) for absolute difference; Method 3: 100- (P-I)(*50/max(P,I)-min(P,I)))
24. Mattes et al., 2000	Investigate walking symmetry after matching prosthetic and intact limb inertial properties	6 TT; Age (mean 35 SD 12 years); Trauma(3), Blood Clot(1), Cancer(1), Congenital(1)	NR	StepL, SwingT, StanceT	((P-I) / (.5*(P+I))) *100

25. Mishra et al., 2019	Compare kinematic gait symmetry between the Jaipur knee joint to each participant's prescribed prosthesis	11 TF (9M 2F); Age (mean 45 range 26-66 years); Trauma(8), PVD(2), Cancer(1)	Knee: Jaipur used in study; prescribed prostheses NR	Hip ROM, Knee ROM, Ankle ROM; all separated into swing and stance	Entire waveform analysis; singular value decomposition; subtracted the mean value from every value in the waveform
26. Moore, 2016	Compare StanceT asymmetry between hydraulic ankle units(Avalon for K2 and Echelon for K3) and previous prescription	13 total IULLPs; 7 TT; 6 TF; K3(6) K2(7)	Feet: K2 level= originally used Multiflex(12). K3 level= on the Multiflex(3), Javelin(2), Dynamic Response (1), Re-flex VSP(1), Seattle Lite-foot(1), Elite Blade(1), 1D10(1); Echelon (K3) and Avalon (K2) feet for study	StanceT	Statistical comparison
27. Morgan et al., 2016[83]	Compare effects of a concurrent cognitive task on walking between TF MPK users and NA	14 TF (9M 5F); Trauma(8) Tumor(3) Vascular(1) Infection(2); Age (mean 53.8 SD 13.6 years): 14 Controls	Suspension: suction, seal-in, or pin-locking liners; Knee: all MPK= C-Leg, Genium, X2	WS, Cadence, Step Width, StepT, StrideL	Absolute value of the difference between right and left
28. Moylan et al., 2015	Investigate effects of increased prosthetic mass on gait symmetry in dysvascular TF	10 TF (9M 1F); PVD(all); Age (mean 64 range 52-78 years); No assistive device(2), Cane(3), Walker(3), Rollator(2)	Suspension: suction(3), silesian belt(7); Knee: Mauch SNS(4), Locked(6) Foot: SACH(4), Single axis(4), Multi-axis(2)	StepL, StepT, Step Width, SLS Time	((I-P) / (I+P))
29. Nadollek et al., 2002	Investigate the relationship between quiet stance ability, strength of the hip abductor muscles, and gait	22 TT; PVD(10), Diabetic complications(12); Age (mean 71.7 range 54-86 years)	Socket: PTB or patella tendon supracondylar prosthesis; Suspension: cuff, silicone liner, or shuttle lock	WS, Cadence, StepL, StrideL, Stance: Swing Ratio, DLS Time	Statistical comparison

30. Nolan et al., 2003	Compare WS gait symmetry between TF, TT, and NA	8 total IULLPs; 4 TT Age (mean 29 SD 18.9 years); 4 TF Age (mean 31.5 SD 10.9 years); Trauma(all): 6 Controls (32.2 SD 9.3 years)	Knee: hinge knee prosthesis with SACH foot(all TF); Feet: SACH foot(all TT)	StepT, StanceT, SwingT	(I-P)/ (.5*(I+P)) *100; absolute value
31. Orekhov et al., 2019	Investigate knee joint biomechanics in gait, cycling, and elliptical training	10 TT (7M 3F); Age (mean 32.2 SD 6.7 years): 10 Controls; Age (range 20-26 years)	Foot: Vari-Flex; (8) originally used this foot	Max MS Knee Flex Angle (and timing), Max Swing Knee Flex Angle (and timing)	Statistical comparison
32. Petersen et al., 2010	Compare gait symmetry between the C-leg MPK and hydraulic 3R60 in TF	5 TF (4M 1F); Trauma(3), Cancer(2); Age (range 26-48 years)	Socket: IsC(4), Stump end bearing socket(1); Knee: C-leg and 3R60 (all originally used C-Leg but had past experience with hydraulic knees) Feet: Pacifica LP(1), Renegade(1), C-Walk(1), Axtion(1), Flex-foot(1)	StepL, StanceT, SLS Time, Temporal Symmetry % (calculated from duration of stance phase), Spatial Symmetry % (calculated from step length)	((I-P)/ (.5*(I+P)) * 100; absolute value
33. Roerdink et al., 2012	Determine if StepL asymmetry should be measured in conjunction with FFP and trunk progression	3 TT (2M 1F); Vascular(1), Trauma (2); Age (range 29-68): 7 TF (1F 6 M); Vascular(4), Trauma(3); Age (range 50-68)	Knees= 3R60(2), OFM1(1), 3R33(1), Hybrid Knee N1-C311(1), 3R106(1), C-leg(1); Feet: Multiflex(2), 1D10/1D11(4), 1C30 Trias(1), Vari-flex with EVO(1), Flex-Foot Assure(1), C-Walk 1C40(1)	StepL, FFP, Trunk Progression	((P-I)/(P+I)) * 100

34. Rowe, 2014	Determine if music improves self-regulated walking in terms of cadence and gait symmetry in TT with nontraumatic amputations	17 TT (15M 2F); Vascular(10), Congenital(5), Complications following trauma(2); Age (mean 52.2 SD 12.9 years)	Participants using microprocessor or carbon fiber spring feet not included	WS, Cadence, StepL, StepT, SLS Time	((P-I)/ (.5*(P+I))) *100
35. Schaarschmidt et al., 2012	Compare gait symmetry between the C-Leg MPK and the hydraulic 3R80 in TF	5 TF; Trauma(all); Age (mean 42.6 SD 13.4 years)	Knees: C-Leg (all, all had prior experience with mechanical knees) Feet: C-Walk	StepT, StanceT, SLS Time, DLS time	((P-I)/ (.5*(P+I))) *100
36. Segal et al., 2006	Compare gait symmetry between the C-Leg MPK and the Mauch SNS hydraulic knee after 3 month acclimation periods with each knee	8 TF (7M 1F); Age (mean 29 years) 6 Controls (all M)	Socket: thermoplastic(4),carbon fiber(4); Suspension: pin(6), suction(2); Knees: C-Leg (all), Mauch SNS (all); Feet of C-Leg users: Dynamic Plus(5), C-Walk(1), LuXon Max(2); Feet of Mauch SNS users: Seattle Lite Foot(5), Flex Walk Foot(3)	Spatiotemporal: WS, StepL; Joint Angles: Max Knee Flex in early stance, Knee Flex at opposite heel strike, Max Knee Flex during Swing	Statistical comparison
37. Sjodahl et al., 2002	Compare gait in the sagittal plane before and after special gait re-education	9 TF (5M 4F); Trauma or Tumor; Age (mean 33 range 16-51 years): 18 total Controls; 9 Controls (all M); Age (mean 33 range 21-47 years): 9 NA (all F); Age (mean 39 range 25-52 years)	Socket: IsC(3), Quad(6) Knee: Total knee mechanical(3), Aqua pend pneumatic(3), T-Ling pneumatic(1), Mauch knee hydraulic(1), Vaxjo knee hydraulic(1) Feet: Seattle foot(2), Flex foot(6), Multiflex(1), Multiaxis Vaxjo foot(1)	Spatiotemporal: WS, Cadence, StepL, SLS Time, DLS Time; Joint Angles: Hip Flex ROM, Knee Flex ROM, Ankle ROM	Statistical comparison

38. Smith and Martin, 2013	Investigate effects of prosthetic mass distribution on walking symmetry	6 TT (5M 1 F); Trauma(5) Congenital bone disease(1); Age (mean 47 SD 16 years)	Feet: Genesis(1), College Park(3), Flex-foot(2)	StanceT, SwingT, Max Knee Angular Velocity during Swing, Max Thigh Angular Velocity during Swing	((P-I) / (.5*(P+I))) *100
39. Supan et al., 2010	Investigate effects of a Talux prosthetic foot on gait parameters of nonvascular TT	10 TT (7M 3F); Nonvascular(all); Age (range 34-62 years)	Talux (3 originally used Talux)	Spatiotemporal: WS, Cadence, StepL, StepT, %SLS, StanceT; Joint Angles: Hip Position at IC, Hip Max Ext, Hip ROM, Knee Position at IC, Knee Max Flex at Stance, Knee Max Ext at Stance, Knee Max Swing Flex, Knee ROM, Ankle Position at IC, Ankle Max PF at Stance, Ankle Max DF at Stance, Ankle Max PF at Swing, Ankle ROM, Foot Progression Angle at IC, Foot Progression Angle Min at Swing, Foot Progression Angle ROM	Statistical comparison
40. Svoboda and Janura, 2007	Investigate effects of prosthetic alignment (DF and PF) and prosthetic foot length changes (shorter and longer) on temporal symmetry of I and P limbs	11 TT (all M); Age (mean 58 SD 9.47 years)	Feet: all dynamic feet characterized by a smooth rollover during gait and intended for second level activity users	StanceT, SwingT, %Stance (StanceT/duration of gait cycle)	((I-P) / (I+P)) * 100

41. Uchytil et al., 2014	Compare spatiotemporal parameters between the Rheo MPK and the Mauch SNS hydraulic knee in TF	8 TF (4M 4F); Age (mean 38.2 SD 6.1 years); K3(all) 10 Controls (8M 2F); Age (mean 27.6 SD 5.2 years)	All used ischial containment and SACH foot; Knees: Rheo MPK, Mauch SNS hydraulic knee	StepL, StepT, StanceT, SwingT	((I-P)/ (.5*(I+P)) * 100
42. Uchytil et al., 2017	Compare pelvis and lower limb joint angles in TF Rheo MPK and hydraulic knee joint users	11 TF (6M 5F); Trauma(3), Cancer(7), ; Age (mean 39.2 SD 10.1 years): 10 Controls (8M 2F); Age (mean 27.6 SD 5.2 years)	All used IsC socket and SACH foot; Knee: Rheo MPK, Hydraulic	Pelvis: Min Pelvic Tilt, Min Pelvic Obliquity, Max Pelvic Obliquity, Max Rot; Hip: Flex IC, Max Ext in Stance, Max Flex in Swing, Max Add in Stance, Max Abd in Swing, Max Int Rot in Stance, Max Ext Rot in Swing; Knee: Flex at IC, Max Flex during LR, Max Ext Stance, Max Flex Swing, Max IR in Stance, Max ER in Swing	((I-P) / (I+P)) * 100

43. Xu et al., 2017	Investigate effects of vacuum level on gait characteristics in TT of elevated vacuum suspension	9 TT; Trauma(5), Vascular(1), Other(3); Age (mean 51.1 SD 16.1 years); K3(7) and K4(2): 9 Controls; Age (mean 27.8 SD 3.7 years)	all originally used elevated vacuum suspension	Spatiotemporal: WS, Cadence, StepL, StepT, StanceT, SLS Time, DLS Time; Joint Angles: Hip Ext Stance, Hip Abd Swing, Hip ER Swing, Hip ROM Sagittal, Hip ROM Frontal, Hip ROM Transverse, Knee Flex Swing, Knee ROM Sagittal, Knee ROM Frontal, Knee ROM Transverse, Ankle DF Stance, Ankle PF Swing, Ankle ROM Sagittal	Statistical comparison
44. Yang et al., 2018	Compare gait patterns between two different shapes of ESAR prosthetic feet: 1C30 Trias and 1C60 Triton (has split forefoot and heel wedge) in TT	10 TT; Age (mean 63.8 SD 2.49 years); K2(4) and K3(6)	1C30 Trias, 1C60 Triton; none originally used ESAR feet	Spatiotemporal: WS, Cadence, StepL, Step Width, StanceT, SwingT; Stance: Swing Ratio Joint Angles: Hip Ext at TS, Hip Flex at Midswing, Knee Flex at TS, Knee Flex at Midswing, Ankle PF at IC, Ankle DF at MS, Ankle PF at TS, Ankle Pronation at early MS, Ankle Supination at onset of Preswing	Statistical comparison

Table 1. Overview of 44 studies included in this review.

Abbreviations: TT= individuals who use transtibial prostheses, TF= individuals who use transfemoral prostheses, IULLPs= individuals who use unilateral lower-limb prostheses, M= male, F= female, I= intact, P= prosthetic, SD= standard deviation, ESAR= energy storage and return, PTB= patellar tendon bearing, SACH= solid ankle cushion heel, MPK= microprocessor knee, IsC= ischial containment, WS= walking speed, StepL= step length, StepT= step time, StrideL= stride length, StrideT= stride time, StanceT= stance time, SwingT= swing time, SLS= single limb support, DLS= double limb support, BoS= base of support, MoS= margin of stability, FFP= forward foot placement, COM= center of mass, ROM= range of motion, Min= minimum, Max= maximum, PF= plantarflexion, DF= dorsiflexion, Flex= flexion, Ext= extension, Add= adduction, Abd= abduction, IR= internal rotation, ER= external rotation, IC= initial contact, MS= midstance, LR= loading response, TS= terminal stance.

Liner manufacturer: Iceross (Ossur, Reykjavik, Iceland).

Knee manufacturers: KX06, Linx, IP, CaTech, Black Max (Blatchford, USA, Canada, and UK); Jaipur Knee (BMVSS organization, Jaipur, India); Hybrid Knee N1-C311 (Nabtesco, Kobe, Japan); Rheo, Total Knee 2000, Total Knee 2100, Mauch SNS, OFM (Ossur, Reykjavik, Iceland); C-leg, Genium, X2, 3R60, 3R15, 3R33, 3R106, Aqua Knee (Ottobock, Duderstadt, Germany); SAFE (ST&G, California, USA).

Foot manufacturers: Foot manufacturers: Echelon, Echelon VT, Elan, Linx, Esprit, Multiflex, Javelin, Elite Blade, Avalon (Blatchford, USA, Canada, UK); Celsus, Truestep, Soleus Tactical (College Park, MI, USA); Genesis II (MICA Manufacturing Corp, WA, USA); Kinterra, Pacifica LP, Renegade (Freedom Innovations, CA, USA); Vari-flex, Vari-flex LP, Vari-flex XC, Vari-flex EVO, Pro-flex XC, Propiofoot, Reflex VSP, Reflex Rotate, Flex-foot, Flex-foot Assure, Talux (Ossur, Reykjavik, Iceland); Axtion, 1C30 Trias, 1C60 Triton, 1C40 C-Walk, 1D10, 1D11, Greissenger Plus, LuXon Max (Otto Bock, Duderstadt, Germany); Seattle Lite-foot (Trulife, USA, Canada, UK, Ireland); Fusion (Willowwood, OH, USA).

Participant Demographics

The highest number of IULLPs in a single study were 128,[25] followed by 60 in two studies.[15,16] However, 84.1% of studies included 15 or less IULLPs, and 61.4% of studies included 10 or less IULLPs. Half of studies included both females and males (n=22, where n indicates the number of studies) and several studies only included males (n=12) or did not report sex (n=10). The mean age of IULLPs ranged from 29.0 to 71.7 years. IULLPs with traumatic etiologies were included in over twice as many studies (n = 31) as those with vascular etiologies (n=15). Eleven studies did not report the etiology of participants.

Functional activity levels are assigned to IULLPs based on ambulation potential, and defined by Medicare as K-levels (K0-K4).[26] No studies included in this review had IULLPs at K0 or K1 functional activity levels. Therefore, this review defines lower functional activity as K2, and higher functional activity as K3 or K4. Only six studies included at least one IULLP at a lower functional activity level of K2,[15,17,18,27–29] while the remaining studies included IULLPs at higher functional levels of K3 or K4.

Kinematic Parameters

The most common spatiotemporal parameters were step length (n=31) and stance time (n=27). The most common joint angle parameters were sagittal plane range of motion (RoM) at the hip (n=12), knee (n=16), and ankle (n=12). Few studies investigated all five of these parameters (n=8).

The most common equipment used to assess symmetry was motion capture (n=29), followed by the GaitRite system (n=5), instrumented insoles (n=2), instrumented treadmills (n=3), and inertial measurement units (IMUs) (n=1).

Mathematical Analysis of Symmetry

Symmetry index equations were most commonly used to assess interlimb symmetry (n= 20). The most common equation, which provides an asymmetry value, was Eq. 1 (n=6). Many studies did not directly calculate symmetry, but used statistical comparison (n=16), ratio scales (n=5), waveform analysis (n=2), or developed their own measures of symmetry (n=1) to examine differences between limbs.

Findings by Level of Limb Loss and Prosthetic Factors

Findings by level of limb loss and prosthetic factors are summarized by differences between limbs in metric units (seconds, meters, degrees) in Table 2 and normalized symmetry percentages in Table 3. Individual study values used to calculate summaries in Tables 2 and 3 can be found in Supplementary Data Tables. Individuals who used unilateral transtibial prostheses were most frequently included (n=27), followed by individuals who used unilateral transfemoral prostheses (n=25), and individuals without limb loss were included as a control group in 15 studies. Individuals without limb loss tended to have the most symmetry, followed by individuals who used transtibial prostheses, then individuals who used transfemoral prostheses.

Half of studies included in this review investigated the influence of prosthetic factors on symmetry (n=22). Specifically, these studies investigated prosthetic factors of as suspension (n=5), alignment (n=2), foot componentry (n=6), and knee componentry (n=9). Suspension and alignment studies compared liners (n=1), transfemoral socket designs (n=1), transtibial suspension methods (n=3), and transtibial alignments (n=2). Foot componentry studies compared energy storage and return (ESAR) to non-ESAR feet (n=3), two different shapes of ESAR feet (n=1), and hydraulic feet to non-hydraulic feet (n=2). Knee componentry studies compared hydraulic knees to microprocessor knees (MPKs; n=5).

Table 2: Differences Between Prosthetic and Intact Limbs

Summary	Step Length Differences (m):	Stance Time Differences (s):	Stance Time Differences (% gait cycle):	Overall Hip RoM Differences (°):	Overall Knee RoM Differences (°):	Overall Ankle RoM Differences (°):
Ranges by Level of Limb Loss	Control= 0.003 - 0.01 TT= 0.01 – 0.12 TF= 0.008 – 0.164	Control= 0.001 - 0.02 TT= 0.01 – 0.04 TF= 0.01 - 0.24	Control= 0.71 TT= 0.07 – 5.15 TF= 5.0 – 20.7	Control= NR TT= 0.63 – 3.05 TF= 3.72 - 19.0	Control= 1.5 TT= 1.43 – 14.6 TF= 1.01 – 16.7	Control= NR TT= 0.8 – 12.2 TF= 2.4 - 7.7
Ranges by Prosthetic Feet	SACH= 0.05 ESAR= 0.01 – 0.13	SACH= NR ESAR= 0.04 – 0.07	SACH= NR ESAR= 0.3 – 8.0	SACH= NR ESAR= 0.63 – 1.47	SACH= NR ESAR= 1.43 – 3.19	SACH= NR ESAR= 2.4 – 12.2
Ranges by Prosthetic Knees	Hydraulic= 0.04 – 0.09 MPKs= 0.03 –0.07	Hydraulic= 0.07 – 0.11 MPKs= 0.03 – 0.13	Hydraulic= 7.4 MPKs= 5.3	Hydraulic= 8.75 MPKs= 3.72	Hydraulic= 1.01 – 13.4 MPKs= 1.26 – 16.74	Hydraulic= NR MPKs= NR

Table 2: Summary of studies (31 total) that reported raw values for prosthetic and intact limbs or differences between limbs in meters (m), seconds (s), % of the gait cycle, or degrees (º) for step length, stance time, or overall sagittal range of motion (RoM) at the hip, knee, and ankle. Studies that measured stance time either reported values in seconds or % of the gait cycle, so these are reported separately. Results are taken from level ground walking conditions at self-selected walking speeds. Baseline conditions and intermediate walking speeds were chosen if multiple conditions or speeds were tested. Normalized symmetry percentages calculated from these raw values are reported in Table 3. NR= not reported, TT= individuals who use unilateral transtibial prostheses, TF= individuals who use unilateral transfemoral prostheses, IULLPs= individuals who use unilateral lower-limb prostheses, SACH= solid ankle cushion heel, ESAR= energy storage and return, MPK= microprocessor knee.

Table 3: Normalized Symmetry Percentages

	Step Length (% Symmetry from m)	Stance Time (% Symmetry from s)	Stance Time (% Symmetry from % gait cycle)	Overall Sagittal Hip RoM (% Symmetry from °)	Overall Sagittal Knee RoM (% Symmetry from °)	Overall Sagittal Ankle RoM (% Symmetry from °)
Ranges by Level of Limb Loss	Control= 97.0 – 99.6 TT= 81.3 – 98.0 TF= 66.4 – 98.5	Control= 97.2 – 99.8 TT= 78.9 – 98.8 TF= 74.5 – 98.4	Control= 98.6 TT= 81.3 - 99.9 TF= 58.6 – 91.6	Control= NR TT= 85.7 – 99.8 TF= 55.0 – 91.9	Control= 96.2 TT= 70.8 – 97.8 TF= 70.5 – 98.2	Control= NR TT= 23.7 – 96.1 TF= 53.2 – 83.2
Ranges by Prosthetic Feet	SACH= NR ESAR= 81.6 – 97.3	SACH= 78.9 ESAR= 97.0	SACH= NR ESAR= 87.1 – 99.5	SACH= 85.7 ESAR= 89.0 – 98.5	SACH= 84.9 ESAR= 91.4 – 97.8	SACH= 23.7 ESAR= 44.5 – 83.2
Ranges by Prosthetic Knees	Hydraulic= 86.6 – 94.2 MPKs= 90.3 – 95.9	Hydraulic= 74.7 – 91.2 MPKs= 71.4 – 96.0	Hydraulic= 88.2 MPKs= 91.6	Hydraulic= 82.6 MPKs= 91.6	Hydraulic= 77.8 – 98.2 MPKs= 70.5 – 97.7	Hydraulic= NR MPKs= NR

Table 3: Summary of studies (34 total) that could be converted to percentages using 100- Eq. 1. Studies that measured stance time either reported values in seconds or % of the gait cycle, so these are reported separately. Results are taken from level ground walking conditions at self-selected walking speeds. Baseline conditions and intermediate walking speeds were chosen if multiple conditions or speeds were tested. NR= not reported, TT= individuals who use unilateral transtibial prostheses, TF= individuals who use unilateral transfemoral prostheses, IULLPs= individuals who use unilateral lower-limb prostheses, SACH= solid ankle cushion heel, ESAR= energy storage and return, MPK= microprocessor knee.

Discussion

The objective of this review was to normalize kinematic walking symmetry data in IULLPs by level of limb loss and prosthetic factors to inform considerations in clinical practice and future research. Symmetry tended to decrease as the level of limb loss became more proximal, and increase with more advanced prosthetic foot and knee componentry. However, it should be noted studies primarily included ten or less individuals who were less than 65 years of age, had traumatic etiologies, and ambulated at higher functional levels of K3 or K4. While these findings are not novel, this review provides normative symmetry values by level of limb loss and prosthetic componentry, as well as considerations for future research in this population, such as including larger sample sizes and individuals who are over 65 years of age, have diabetic etiologies, and ambulate at K2 functional levels to reflect clinical considerations for the majority of IULLPs.

Participant Demographics

Functional activity level, age, and etiology can influence decisions regarding rehabilitation goals in IULLPs. Most IULLPs included in this review were individuals who were less than 65 years of age, had traumatic etiologies, and ambulated at higher functional levels of K3 or K4.

The six studies that included at least one IULLP at a lower functional level of K2 provided normalized symmetry values of 86.2- 97.2% for step length, 92.2- 99.5% for stance time, 96.4- 97.1% for hip RoM, 77.0- 97.8% for knee RoM, and 44.5- 96.1% for ankle RoM. These values were in line with studies that did not include K2 participants, which is not surprising considering few participants were classified as K2 in each of these studies.

General literature has found that walking symmetry declines with age in individuals without limb loss from ≥90% to 80-85% in individuals over 65 years of age.[30,31] Many individuals with limb loss are over 65 years of age, and vascular etiologies are the primary cause of amputation.[32] Yet, IULLPs 65 years of age or older with vascular etiologies were only included in twelve and fifteen studies, respectively. Only two studies exclusively included older IULLPs with vascular etiologies, with mean ages of 64 and 71.7 years.[17,28] One study could not be normalized, and the other only measured step length in individuals who used transtibial prostheses, providing normalized symmetry values of 96.6%. In contrast, ten studies exclusively included IULLPs with traumatic etiologies with mean ages ranging 30 to 45 years across studies.[16,22,23,33–39] Normalized symmetry values ranged 89.5- 98.5% for step length, 74.5- 98.4% for stance time, 92.9% for hip RoM, and 87.9% for knee RoM, which were comparable to individuals without limb loss.[16,23,34,35]

Therefore, IULLPs who are older adults, have vascular etiologies, or ambulate at lower functional activity levels may differ compared to IULLPs that were included in this review. Collecting kinematic walking symmetry data from individuals with these demographic characteristics can help inform clinical considerations in a way that accurately represents the majority of IULLPs.

Kinematic Parameters

The most commonly investigated parameters identified in this review, specifically step length, stance time, and knee RoM, were in line with a previous review of individuals who used transtibial prostheses.[12] Future studies could include these parameters to improve comparison of findings across studies.

Mathematical Analysis of Symmetry

The most common mathematical analysis of symmetry in this review were symmetry index equations (n= 18), with the most common equation being Eq. 1 (n=6), or a derivation of Eq. 1 (n=4). This equation was first described by Robinson et al. (1987) and then Herzog et al. (1989) in individuals without limb loss using right and left limbs, rather than prosthetic and intact limbs. Therefore, when applying this equation to IULLPs, it is up to the authors whether to use the prosthetic or intact limb as the reference value. Three studies instead calculated the absolute value of Eq. 1 to obtain only positive values.[35,40,41] Absolute values eliminate the need for a reference value, but also eliminate the distinction of which limb had higher or lower values. In this case, researchers could include both absolute percent symmetry values alongside the original data values (Table 2 & Table 3) to ease comparisons across studies.[42]

Additionally, one study used three different analyses for calculating symmetry with various statistical significance depending on the equation used,[43] and one developed symmetry scores based on thigh and shank angular velocity data collected from inertial measurement units.[25] These symmetry values were consistent with studies including similar demographics. Until these newly developed equations are consistently used or considered a better representation of symmetry, it is suggested that future studies analyze kinematic walking symmetry data using Eq. 1, in addition to the newly developed equations, to ease comparisons of findings across studies.

Findings by Level of Limb Loss

In agreement with research prior to 2000,[48–51] individuals without limb loss tended to show the most symmetrical gait with values over 90% (97.0- 99.8%), followed by individuals who used transtibial prostheses (70.8- 98.5%), while individuals who used transfemoral prostheses tended to show the least symmetrical gait (53.2- 98.5%).

Spatiotemporal Parameters

Step lengths tended to be longer on the prosthetic limb compared to the intact limb, with more symmetry in individuals who used transtibial prostheses than transfemoral prostheses. Two studies in this review suggested step length differences between prosthetic and intact limbs might be functional compensations to preserve backward margin of stability during double limb support.[48,49]

Stance times tended to be shorter on the prosthetic limb compared to the intact limb, with more symmetry in individuals who used transtibial prostheses than transfemoral prostheses. Three studies in this review compared stance time symmetries, and found the greatest symmetry in individuals without limb loss, followed by individuals who used transtibial prostheses (89.7- 93.4%), and then individuals who used transfemoral prostheses (58.6- 74.5%).[16,34,35] However, individuals without limb loss and individuals who used transtibial prostheses tended to have similar amounts of symmetry in studies included in this review. Individuals who used transfemoral prostheses tended to have the widest range of symmetry across studies with the lowest minimum values.

Joint Angle Parameters

In a study of seventy-eight individuals without limb loss, the ankle was the least symmetrical joint (88.0- 94.0%) compared to the knee (96.0- 98.0%) and hip (96.0- 98.0%).[50] The ankle was also the least symmetrical joint for all IULLPs in this review (Table 3). Transtibial values for normalized symmetry averaged 64.7% (23.7- 96.1%) at the ankle compared to 87.7% (70.8-97.8%) at the knee and 97.8% (85.7- 99.8%) at the hip. Transfemoral values for normalized symmetry averaged 68.2% (53.2- 83.2%) at the ankle compared to 86.0% (70.5- 98.2%) at the knee and 73.3% (55.0- 91.9%) at the hip. The prosthetic foot had less ankle plantarflexion compared to the intact limb in individuals who used transtibial prostheses.[43,51–54] This agrees with previous research,[55–57] and supports the idea that the intact limb may compensate for lack of plantarflexion in the prosthetic foot.[14,58–62]Ankle symmetry was not reported in any study included in this review for individuals without limb loss.

Findings by Prosthetic Factors

Prosthetic factors are discussed by studies that examined suspension and alignment, foot componentry, and knee componentry. The influence of suspension and alignment findings on symmetry were inconclusive for the five normalized kinematic parameters. ESAR and hydraulic feet tended to show increased symmetry compared to non-ESAR and non-hydraulic feet.[18,19,37,43,51] MPKs tended to show increased symmetry compared to non-MPKs.[16,20,41,63,64]

Suspension and Alignment

Spatiotemporal Parameters

Suspension systems are typically considered the most critical part of a prosthesis, since it provides direct contact between an individual’s prosthesis and residual limb. Individuals who used transtibial prostheses had decreased gait variability when participants wore a polyurethane liner compared to their previous liner, but had no difference in step length or stance time symmetry.[65] Individuals who used transfemoral prostheses had more symmetrical step lengths with a wider base of support while wearing an ischial containment socket (98.0%) compared to a brimless socket with vacuum suspension (92.0%).[66] Individuals who used transtibial prostheses showed increased step length and stance time symmetry, though not statistically significant, with suction suspension (93.2%) compared to pin-lock suspension (86.2%),[29] and increased step lengths with vacuum suspension (91.9- 95.8%) compared to without vacuum (91.5%).[54,67,68]

Prosthetists optimize prosthetic alignment by observing an individual's gait, and make prosthetic adjustments to increase symmetry between prosthetic and intact limbs. Misalignment of the prosthesis can negatively influence gait and cause residual limb irritation. One study found stance time symmetry was consistent across alignment conditions,[40] but another found stance time was least symmetrical during the optimal alignment condition.[69] Both investigated individuals who used transtibial prostheses. Differences in findings may be explained by prosthetic design and foot componentry. In the study that found stance time symmetry was consistent across alignment conditions,[40] some participants typically ambulated with an exoskeletal prosthesis, but used an endoskeletal prosthesis for the study. Participants in this study also used SACH feet, while participants used ESAR feet in the study that found stance time was least symmetrical during the optimal alignment condition.[69]

Joint Angle Parameters

Transtibial suspension studies found almost identical hip RoM symmetry across pin-lock, suction, and vacuum suspensions.[29,67] Astrom and Stenstrom (2004) found no differences in knee symmetry when participants used polyurethane liners compared to their prescribed liners. Chow et al. (2006) determined knee flexion at loading response had the least relevance in determining acceptable alignment. One study found pin-lock suspension (84.4%)showed significantly increased knee joint symmetry compared to suction suspension (77.0%),[29] and one study found differences in knee RoM between vacuum on (97.0%) and off (97.6%) conditions were almost identical.[54,67] Ankle symmetry had less than a 1% difference between pin-lock and suction suspensions,[29] and almost identical values between vacuum on and off conditions.[54,67]

Foot Componentry

Spatiotemporal Parameters

Studies agreed ESAR and hydraulic feet increased step length and stance time symmetry compared to non-ESAR and non-hydraulic feet.[16,18,19,37,43,51] Yang et al. (2018) found the ESAR foot with split forefoot and heel wedge (97.3%) slightly increased step length symmetry compared to an ESAR foot without those features (94.2%). Moore (2016) results could not be normalized, but found hydraulic feet significantly increased symmetry in comparison to non-hydraulic feet regardless of whether participants used transtibial or transfemoral prostheses, or ambulated at lower or higher functional activity levels.

Joint Angle Parameters

Hip, knee, and ankle symmetry increased when individuals who used transtibial prostheses ambulated with an ESAR foot compared to a SACH foot. The ankle showed the most prominent differences between ESAR (63.5%) and SACH (23.7%) feet.[43] Findings were consistent across three different equations Marinakis (2004) used to calculate results. Yang et al. (2018) showed the ESAR foot with split forefoot and heel wedge (60.8%) increased ankle dorsiflexion symmetry between limbs compared to the ESAR foot without those features (44.5%) throughout the gait cycle. Bai et al. (2017) found the non-hydraulic foot (83.2%) had increased ankle symmetry compared to the hydraulic foot (53.2%) throughout the gait cycle.

__Knee Componentry__

Spatiotemporal Parameters

Several studies found participants had increased step length symmetry with MPKs compared to hydraulic knees[64,70] while other studies found no significant differences.[41,71] These conflicting findings may be explained by prosthesis accommodation times. Studies that found significant differences had accommodation times of 3 months or stated each participant used the prosthetic knee for at least two years prior to testing, while studies that found no significant differences had accommodation times of 1 week or 10 hours. A previous review concluded proper accommodation times are important in determining findings that are reflective of long-term use and allowing clinicians to make appropriate prosthetic decisions.[72]

Stance time symmetry findings were also conflicting. One study found MPKs increased stance time symmetry compared to hydraulic knees,[41] while another found the opposite,[39] and two other studies found no significant differences.[64,71] Conflicting findings may be explained by selection of hydraulic knee componentry. The study that found MPKs increased stance time symmetry tested hydraulic 3R60 knees (Ottobock, Duderstadt, Germany), while the study that found the opposite tested hydraulic 3R80 knees (Ottobock, Duderstadt, Germany), and both studies with no significant differences tested hydraulic Mauch SNS knees (Ossur, Reykjavik, Iceland). Conflicting step length and stance time findings were in line with a clinical practice guideline stating spatiotemporal parameters may not be primary indications for prosthetic knee joint selection due to comparable symmetries among knees.[73]

Joint Angle Parameters

MPKs (91.6%) tended to increase hip RoM symmetry compared to non-MPKs (82.6%), but showed similar amounts of knee RoM symmetry with MPKs (70.5- 97.7%) compared to non-MPKs (77.8- 98.2%).[20,63,64] One study using waveform analysis found MPKs had more stance phase symmetry in all three joints compared to a variety of non-MPKs, though findings were not statistically signifcant.[20] Another study found MPKs had more symmetry in all three joints across the gait cycle compared to hydraulic knees, with most increased symmetry at the hip.[63] Finally, participants had more knee angle symmetry with MPKs compared to hydraulic knees after three-month acclimation periods to each knee. No studies that compared prosthetic knee componentry reported ankle symmetry or RoM.

Clinical Considerations

Walking symmetry is not typically quantified in clinical practice. Instead, prosthetists use observational gait analysis to observe kinematic symmetry parameters, such as step length or joint RoM, to make prosthetic adjustments and inform treatment plans. Effectiveness of using observational gait analysis can be dependent on subjective factors such as practitioner experience, user fatigue, or time allotted for the appointment. Observational gait analysis could be supplemented by translating kinematic walking symmetry research findings into clinical practice.

Motion capture was most commonly used to measure kinematic parameters in this review. While motion capture typically quantifies symmetry in research settings, it can be impractical to use in clinic for several reasons: high costs, lack of portability, and the need for specialized personnel.[14] Some studies used equipment such as gait mats or inertial measurement units to collect data outside of research lab settings. As portable and wearable equipment becomes more ubiquitous and cost effective, clinicians and researchers may find this equipment more practical.

Clinicians can use normalized data summarized in this review, particularly the Table 2 summary of differences between prosthetic and intact limbs in metric units, as reference values for step length, stance time, and sagittal plane hip, knee, and ankle range of motion. These values provide evidence-based data that can be used to guide thresholds of symmetry in rehabilitation and justify ESAR feet and MPKs for active adults under 65 years of age with traumatic etiologies to insurance payers.

Limitations and Future Research

This review focused on kinematic symmetry due to ease of translation to observational gait analysis in clinical practice, and several researchers have noted kinematics alone should not be the sole determinant of gait symmetry.[16,74] The majority of studies included in this review measured parameters other than kinematics such as kinetics, muscle strength, patient preference, or energy consumption, which should also be assessed. Furthermore, this review only included studies that measured walking. Other movement tasks such as sit-to-stand transitions, turns, and navigating inclines, declines, or uneven terrain are also important activities of daily living that should be examined in future research.

Several considerations can be applied to future studies regarding information collected from participants. Length of time since amputation was often assumed to reflect gait consistency. However, gait consistency could also be influenced by prosthetic socket or alignment changes, regardless of a participant's time since amputation. Collecting the date since last prosthetic fitting, adjustment, or alignment, may be a more accurate way to determine the consistency of a participant's gait pattern than time since amputation. Additionally, testing clinically appropriate components with adequate accommodation time is necessary to determine findings that accurately inform clinical decisions.

Considerations for data collection and analysis could also be applied to future research. Future studies could use normalized values provided in this review as a reference for their findings, and include the most common kinematic parameters and mathematical analysis of symmetry identified in this review to improve comparisons across studies. Studies could include larger sample sizes of IULLPs with a wide variety of demographics, which may be more feasible as portable and wearable equipment becomes more ubiquitous.

Several topics for future research were identified in this review. Collecting pelvic and trunk symmetry could improve understanding of gait deviations that contribute to commonly reported secondary health conditions such as low back pain in IULLPs.[10,75,76] No studies included in this review directly examined differences in gait symmetry by age or etiology, examined ankle symmetry in individuals who used transfemoral prostheses, or compared componentry intended for individuals with lower activity levels.

Conclusions

This review normalized kinematic walking symmetry data in IULLPs by level of limb loss and prosthetic factors to provide considerations for clinical practice, and also provided considerations to promote clinical translation in future research. Individuals without limb loss had the most symmetry, followed by individuals who used transtibial prostheses, then individuals who used transfemoral prostheses in step length, stance time, and lower limb sagittal RoM parameters.

Componentry intended for individuals with higher activity levels, such as ESAR feet and MPKs, tended to increase symmetry. However, the majority of studies included ten or less individuals young adult IULLPs with traumatic etiologies who used componentry intended for higher activity levels. Clinicians can use normalized values in this study to guide thresholds for walking symmetry during rehabilitation, and future research can include larger sample sizes of larger sample sizes and individuals who are older, have vascular etiologies, or use componentry intended for lower activity levels to help promote translation of research findings into clinical practice for the majority of IULLPs. Identifying reference values reflective of the majority to IULLPs could ultimately help clinicians elevate the standard of care for individuals with lower-limb loss.

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Chapter 2 Linkage

Chapter 2 informed decisions for both studies listed under ‘Section 3: Biomechanical Symmetry.’

Chapter 2 findings highlighted the need for a standard measure of spatiotemporal and kinematic symmetry in this population. Specifically, this review helped inform the following decisions in both biomechanical studies: to recruit underrepresented populations in this field of research (older individuals with diabetes), the equation to use to calculate symmetry (most commonly used in articles included in the review), and which spatiotemporal and biomechanical measures to collect (stance time, ankle, knee, and hip sagittal plane kinematics). This review also provided comparison data for our findings in Chapter 8.

CHAPTER 3

CLINICAL EVALUATION OF FALL RISKS IN OLDER ADULTS WHO USE LOWER-LIMB PROSTHESES: A SCOPING REVIEW

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Abstract

Background: Falls are prevalent among the general population of older adults and those who use a lower-limb prosthesis at any age, potentially placing older adults who use lower-limb prostheses at greater risks of falls. An abundance of literature has informed evidence-based clinical protocols to evaluate fall risk in the general population of older adults. However, no reviews or evidence-based clinical protocols exist to evaluate fall risk in lower-limb prosthesis users. This scoping review sought to determine assessments, defined as clinical outcome measures and gait parameters, associated with fall risk in this population to determine if a systematic review is warranted and help inform an evidence-based clinical protocol.

Methods: Google Scholar, PubMed, and Scopus were searched on April 19th, 2022 to include peer-reviewed original research. Included articles reported relationships between falls and clinical outcome measures or gait parameters in older adults who use transtibial or transfemoral prostheses. Clinical outcome measures included self-reported questionnaires and functional mobility tests. Gait parameters included spatiotemporal, kinematic, and kinetic data during walking and stair negotiation.

Results: Nineteen articles were included. Clinical outcome measure scores, gait parameter data, and cutoff scores by fall status (non-fallers, single fallers, recurrent fallers) were summarized. The Timed Up and Go was the clinical outcome measure most frequently found to be significantly associated with falls, but only in two of eight articles. Four gait parameters in walking kinetics and ten parameters in stair ascent were significantly associated with falls, but only in one article each.

Conclusions: The majority of articles found no clinical outcome measure or gait parameter alone was effective at determining fall risks in this population. Future research should evaluate a combination of assessments and collect prospective fall data to move towards establishing an evidence-based protocol to evaluate fall risk in older adults using lower-limb prostheses.

Key words: amputee, mobility, limb loss, balance, prosthesis

Introduction

Older adults in the general population have high fall risks,[1] as well as adults who use lower-limb prostheses.[2–4] Adults 18 years of age or older with lower-limb amputation have similar or higher fall risks compared to adults 65 years of age or older in the general population.[6,10] In both of these populations, falls have been associated with a wide variety of negative secondary health effects, such as diminished mobility, social activity, and fall-related injury.[1,5–9] Therefore, combined fall risk factors of older age and prosthesis use may make older adults who use prostheses more vulnerable to falls than either risk factor alone.[11] Further, older adults are estimated to be 42% of the amputee population, and numbers are expected to increase with the prevalence of peripheral vascular disease and type 2 diabetes.[12] As the prevalence of older adults who rely on lower-limb prostheses increases, the need for effective fall risk screening in this population increases.

Established evidence-based clinical protocols exist to evaluate fall risk in older adults in the general population, based on evidence from systematic reviews and meta-analyses.[13–16] However, no evidence-based clinical protocol exists to effectively evaluate fall risk in older adults who use lower-limb prostheses, or adults at any age,[11,17–19] despite falls being one of the most prevalent and costly concerns in this population.[20–22] While several studies have associated poor balance with older age in adults who use lower-limb prostheses,[23,24] older adults are typically underrepresented in amputation and prosthesis user literature surrounding musculoskeletal and biomechanical adaptations.[25,26]

No literature reviews have summarized assessments associated with fall risk in older adults who use lower-limb prostheses. Clinical outcome measures that are self-reported questionnaires (e.g.

Activities-Specific Balance Confidence (ABC)) or functional mobility tests (e.g. Timed Up and Go (TUG)) are clinically feasible ways to potentially evaluate fall risk, but there is still no consensus on collecting clinical outcome measures for general prosthetic rehabilitation.[27] Additionally, walking on level terrain has been identified as the most common activity when falls occur in adults who use lower-limb prostheses, and falls often involve the prosthesis.[2,28] Therefore, gait assessments while walking on level terrain may be useful to evaluate fall risk in this population. For instance, recent studies have suggested clinically feasible ways (e.g. mobile phone applications) to measure gait parameters during clinic visits in adults who use lower-limb prostheses.[29–31] Further, studies in non-prosthetic populations have suggested gait assessments may be stronger indicators of fall risk than clinical outcome measure scores[32,33] or could supplement clinical outcome measure scores[34,35] to improve fall risk screening. Thus, we also examine the literature surrounding gait analysis to determine if gait data would be useful to evaluate fall risk in older adults who use lower-limb prostheses.

Determining clinical outcome measures and gait parameters associated with fall risk in older adults who use lower-limb prostheses could provide a reference for clinicians and researchers to improve fall risk screening and move towards an evidence-based clinical protocol. However, this literature has yet to be summarized. The objective of this scoping review is to determine which, if any, clinical outcome measures or gait parameters have been associated with fall risk in older adults who use lower-limb prostheses in previous literature.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) guideline was followed, according to their published checklist (Supplemental Document 1).[36]

A search was performed on April 19th, 2022 in Google Scholar, PubMed, and Scopus to encompass all previous peer-reviewed original research articles of falls in older adults who use transtibial or transfemoral prostheses. References were also examined for inclusion.

The following search terms were used:

Google Scholar: amput* AND fall* OR balance AND older OR elderly AND above-knee OR below-knee OR transfemoral OR transtibial OR lower-limb OR leg

PubMed: ("fall"[Title/Abstract]) OR balance[Title/Abstract] AND older[Title/Abstract] OR elderly[Title/Abstract] AND ((((amputees[MeSH Terms]) OR (amputation[MeSH Terms])) OR (amput*[Title/Abstract])) AND ((below-knee OR transtibial OR trans-tibial OR above-knee OR transfemoral OR trans-femoral OR leg OR lower-limb OR lower limb OR "above knee" OR "below knee") OR ((extremities, lower[MeSH Terms])))))

Scopus: (amput* AND fall* OR balance AND older OR elderly AND above-knee OR below-knee OR transfemoral OR transtibial OR lower-limb OR leg)

Articles were included if they reported original research on falls in older adults who used transtibial or transfemoral prostheses. Original research on falls was defined as studies that distinguished groups by fall status (e.g. non-fallers, single fallers, recurrent fallers) or reported number of falls. MGF intended to define studies involving older adults as having a mean age of 65+ years, but only

4 articles met this criterion. Fifty-five years is the upper mean age limit of other studies in this population with large sample sizes (50-55 years), so older adults were defined as having a mean participant age of 55 years or older.[37–39]

Titles of articles were excluded if they did not include adults who used transtibial or transfemoral prostheses or were not original research (e.g. literature reviews). Abstracts of articles were excluded if they were not peer-reviewed or included less than five participants. Full-text articles were excluded if they were not available in English, did not report fall data, did not include adults with a mean age of at least 55 years, or did not report clinical outcome measure scores or gait data.

MGF applied search terms, screened titles, and screened abstracts. MGF and SCM independently screened full-texts. MGF and SCM discussed and resolved any differences in screening, so both authors agreed on the final list of included articles. Screening and data synthesis were completed manually in Microsoft Excel (version 6.6.27, 2016, Washington, USA). MGF extracted and summarized all data. Statistical significance was defined as either: 1) significance between fall data and clinical outcome measures or gait parameters (e.g. lower number of falls associated with improved Timed Up and Go times), or 2) significance in clinical outcome measure scores or gait parameters between groups by fall status (e.g. a difference in Timed Up and Go times between non-fallers and fallers). Thresholds for statistical significance were defined by each article, which was $p \leq 0.05$ for standard statistical tests. No articles assessed clinical significance, so clinical significance was not reported or discussed in this review. A review protocol was not registered for this project.

Results

Article Demographics:

Nineteen articles were included in this review.[5,10,40–56] Figure 1 depicts the inclusion process, and Supplemental Table 1 summarizes the included articles. Articles included ≤10 participants (n=3, where n is the number of articles), 16-30 participants (n=8), 31-50 participants (n=5), and 51 or more participants (n=3). Articles reported only clinical outcome measures (n=9), only gait parameters (n=4), or both (n=6). Clinical outcome measures and gait parameters that were reported by at least two articles in this review are summarized in Supplemental Tables 2 and 3, respectively. Articles reported the number of falls (n=9), or distinguished participant groups by non-fallers and fallers (n=11) or single and recurrent fallers (n=4). Only one article collected prospective fall data.[41] Six articles found significance between fall data and clinical outcome measures or gait parameters, summarized in Table 1.

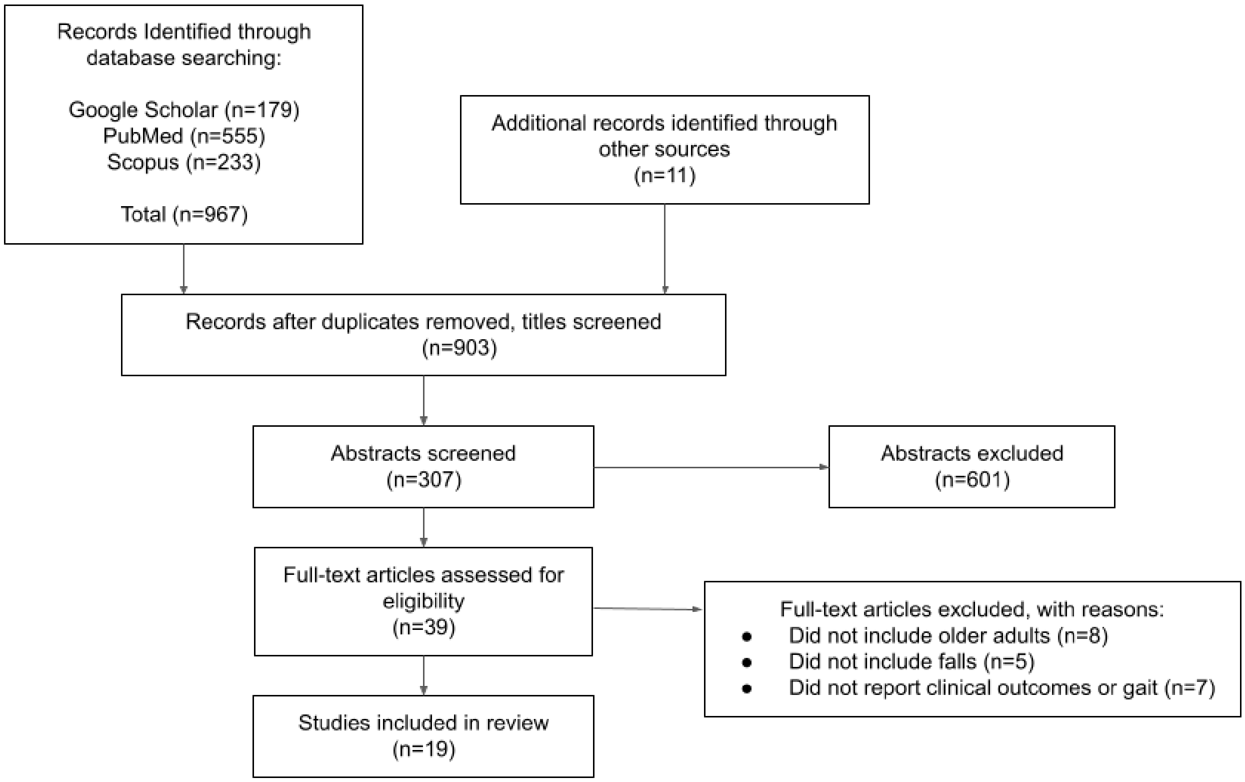

Figure 1: Flow diagram of the inclusion process.

Table 1: Significant Associations with Falls

		Study and population	Population	Summary or Cutoff Score
Clinical Outcomes	***Self-Reported Questionnaires***			
	SF-36	Barnett et al. 2013	TT	Higher falls efficacy was significantly associated with improved SF-36 scores
	LCI-advanced	Dite et al. 2007	TT	Score of 15 distinguished single and recurrent fallers
	mFES	Jayaraman et al. 2021	TF	Higher falls efficacy while using MPKs as opposed to using non-MPKs
	Functional Mobility			
	BBS	Wong et al. 2015	TT & TF	Better balance was significantly associated with greater fall risk
	TUG	Dite et al. 2007	TT	19s to distinguish single and recurrent fallers
	TUG	Hakim et al. 2018	TT & TF	10.03s to distinguish nonfallers and fallers
	FSST	Dite et al. 2007	TT	24s to distinguish single and recurrent fallers
	AMPPRO	Hakim et al. 2018	TT & TF	41.7 to distinguish nonfallers and fallers
	180 degree turn test	Dite et al. 2007	TT	3.7s turn time and 6 steps to distinguish single and recurrent fallers
	TUG, FSST, 12-month retrospective falls	Sawers and Hafner 2022	TT	Model that combined these assessments was significantly better than a null model at predicting the number of 6-month prospective falls
Gait Parameters	***Walking Kinetics***			
	peak vGRF 1 (braking)	Vanicek et al. 2009	TT	Fallers had greater first peak vertical force on the prosthetic limb than nonfallers
	Load rate	Vanicek et al. 2009	TT	Fallers had greater load rate on the prosthetic limb than nonfallers
	A1 (ankle power)	Vanicek et al. 2009	TT	Fallers had smaller ankle absorption power burst in terminal stance on the intact limb than nonfallers

	H2 (hip power)	Vanicek et al. 2009	TT	Fallers had greater power absorption burst in stance on the intact limb than nonfallers
	Stair Ascent (step over step)			
	Speed (m/s)	Vanicek et al. 2010	TT	Fallers ascended steps significantly faster than nonfallers
	Peak hip extension	Vanicek et al. 2010	TT	Fallers had less hip extension on the trailing (prosthetic) limb than nonfallers
	Knee flexion foot clearance	Vanicek et al. 2010	TT	Fallers had more knee flexion on the leading (intact) limb than nonfallers
	Knee flexion overall ROM	Vanicek et al. 2010	TT	Fallers had less knee flexion on the trailing (prosthetic) limb than nonfallers
	Pelvic tilt pull-up	Vanicek et al. 2010	TT	Fallers had less anterior pelvic tilt on the trailing (prosthetic) limb than nonfallers
	Peak vertical 1 (loading phase)	Vanicek et al. 2010	TT	Fallers had greater peak vertical 1 than nonfallers
	Low vertical 2 (midstance phase)	Vanicek et al. 2010	TT	Fallers had less low vertical 2 than nonfallers
	Peak vertical 3 (pre-swing phase)	Vanicek et al. 2010	TT	Fallers had greater peak vertical 3 than nonfallers
	Hip extensor moment weight acceptance	Vanicek et al. 2010	TT	Fallers had greater hip extensor moment on the leading (intact) limb than nonfallers
	Ankle plantarflexor moment forward continuance	Vanicek et al. 2010	TT	Fallers had greater ankle plantarflexor moment on the leading (intact) limb than nonfallers

Table 1: Clinical outcome measures and gait parameters reported to have statistically significant relationships to falls. Abbreviations: TT= transtibial, TF= transfemoral, SF-36= 36-Item Short Form, LCI= Locomotor Capabilities Index, BBS= Berg Balance Scale, TUG= Timed Up and Go, AMPPRO= Amputee Mobility Predictor.

Participant Demographics:

Detailed participant demographics can be found in Supplemental Table 1. Included articles evaluated adults who used transtibial prostheses (n=8), transfemoral prostheses (n=5), or both (n=6). The majority of articles primarily included adults with dysvascular etiologies (n=9), as well as traumatic (n=5), cancer (n=2), and congenital (n=1). Four articles did not report etiologies. Fifteen articles had mean participant ages of 55-65 years, and the remaining four articles had mean ages of 65+ years. Fifteen articles included at least one female.

Clinical Outcome Measures:

Clinical outcome measures (n=15) were subcategorized in this review by self-reported questionnaires (n=5) and functional mobility tests (n=8) (Supplemental Table 2). The TUG was the most commonly reported measure (n=8) and was found to be significantly different (n=2 of 8) between fall status groups (non-fallers vs fallers, as well as single vs recurrent fallers) (Table 1). Additionally, the following had significance with falls in one article: 36-Item Short Form (SF-36, n=2, significant in n=1), advanced version of the Locomotor Capabilities Index (LCI-advanced, n=2, significant in n=1), Berg Balance Scale (BBS, n=3, significant in n=1), Four Square Step Test (FSST, n=3, significant in n=1), and the 180 degree turn test (n=1, significant in n=1) (Table 1).

Gait Parameters:

Gait parameters were reported for walking (n=6), stair ascent (n=1) and stair descent (n=1), and categorized in this review by spatiotemporal (n=9), kinematic (n=4), and kinetic (n=4) parameters (Supplemental Table 3). Walking kinetics (n=2, significant in n=1) and stair ascent (n=1, significant in n=1) were the only gait parameters significantly associated with falls (Table 1).

Discussion

This scoping review sought to determine which clinical outcome measures and gait parameters were associated with fall risk in older adults who use lower-limb prostheses. Clinical outcome measure scores, gait parameter data, and cutoff scores by fall status were difficult to summarize due to differences among articles in population, assessments, and reported fall data. The TUG was the most commonly reported clinical outcome measure, but was only significantly associated with falls in two of eight articles. Gait parameters that significantly distinguished fallers and non-fallers included four kinetic parameters during walking and ten spatiotemporal, kinematic, and kinetic parameters during stair ascent. However, walking kinetics and stair ascent were only each reported by one article. Most articles found no clinical outcome measure or gait parameter alone was effective at determining fall risk in this population. A combination of assessments and collecting prospective fall data may be necessary to establish an evidence-based clinical protocol for fall risk evaluation in this population.

<u>Clinical Outcome Measures and Fall Risk:</u>

Studies that have collected both self-reported questionnaires and functional mobility tests suggest functional mobility tests are stronger indicators of fall risk in both older adults and adults who use lower-limb prostheses.[15,56] However, the self-reported questionnaires that were found to be significantly associated with falls in this review in Table 1 could potentially supplement functional mobility tests to improve fall screening. Additionally, an article that was excluded from this review due to a mean age of 47.1 years found ABC (self-reported measure of balance confidence) and PLUS-M scores (self-reported measure of mobility for prosthesis users), but not TUG times, were significantly different in non-dysvascular fallers who used transtibial and transfemoral prostheses compared to non-fallers.[57] If these findings are generalizable to older lower-limb prosthesis users, ABC and PLUS-M self-report may be useful self-report measures to evaluate fall risk.

The TUG, a functional walking test including rising from a chair and sitting, has been extensively used to assess fall risk in the general population of older adults.[16,58–61] TUG cutoff times ranging from 12 - 14 seconds have been adopted as standards in clinical practice to distinguish non-fallers from fallers.[14,62] In this review, the TUG was the most evidence-supported clinical outcome measure or gait parameter to evaluate fall risk, but was only significant in two of eight articles that included the TUG. Articles that did not find significance included smaller sample sizes of transfemoral prosthesis users (10, 12, and 27 participants),[54–56] or included a majority or all transtibial prosthesis users with mean ages of 65.[42,51] These findings suggest the TUG alone may not be an effective screening tool for this population, particularly adults 65 years and older.

The FSST, a functional outcome that involves stepping over four canes in a specific order, has also been found to be useful in predicting falls in the general population of older adults.[63] However, only one article in this review found significance between the FSST and fall risk. An article that was excluded from this review due to a mean age of 48.7 years, established FSST cutoff scores for fall risk in lower-limb prosthesis users.[64] This article found cutoff scores for the TUG (8.17 seconds) and FSST (8.49 seconds) were stronger indicators of falls than the BBS (score of 50.5), a functional measure of balance tasks, or ABC (score of 80.2). If findings are generalizable to older adults who use lower-limb prostheses and dysvascular individuals, FSST and TUG times, may be valuable assessments to evaluate fall risk in this population.

A combination of clinical outcome measures is likely necessary to improve fall risk screening. Reviews in the general population of older adults have recommended the TUG,[15,59] or any clinical outcome,[14] not be used in isolation to assess fall risk. Similarly, one article included in this review determined no combination of functional tests effectively predicted 6-month prospective falls in adults who used transtibial prostheses.[41] Rather, 12-month retrospective fall history combined with TUG and FSST times were most effective at predicting 6-month prospective falls.[41] If findings are replicated and generalizable to a larger number of older adults who use lower-limb prostheses, this combination of assessments could become an evidence-based clinical protocol to screen fall risk in this population.

Walking Parameters and Fall Risk:

No spatiotemporal or kinematic walking parameters were found to be significantly associated with fall data. However, only two articles directly measured this relationship. Recent research in other populations with lower-limb pathologies, such as stroke, have found significance of spatiotemporal and kinematic data (e.g. fallers had reduced walking speed and stride length, greater double limb support and stride time, and reduced kinematic coordination compared to non-fallers) with fall risk.[65–67] More research is needed to determine if spatiotemporal or kinematic parameters could also be associated with fall risk in older adults who use lower-limb prostheses.

During level-ground walking, one article identified four kinetic parameters that significantly distinguished non-fallers and fallers.[46] Findings in Table 1 indicate clinicians should focus on improving eccentric ankle and hip strength in the intact limb and weight transfer to single support of the prosthetic limb.[46] As force data becomes more feasible to collect in clinical settings, it will be increasingly important to determine if these findings are generalizable to a larger portion of this population.

Stair Parameters and Fall Risk:

The only article on stair ascent found kinematic and kinetic parameters significantly distinguished non-fallers and fallers.[47] The researchers suggested their findings (listed in Table 1) may indicate that non-fallers were more cautious than fallers when ascending stairs.[47] This research group reported stair descent in the same participants, but significance could not be measured due to a combination of reduced sample size and multiple stair descent strategies.[48] While not significant, findings indicate that similar to stair ascent, fallers descended steps faster than non-fallers.[48] Perhaps a clinical outcome measure that records time taken to negotiate stairs could distinguish fallers and non-fallers.

Evaluation of gait parameters during stair negotiation may be more difficult to translate directly into clinical settings than walking data, as stairs are less common than walkways in clinical practice. Still, findings that are generalizable to a larger number of older adults who use lower-limb prostheses could provide justification for the integration of short staircases into clinical practice for fall risk screenings. Few studies have examined activities of daily living besides walking to evaluate fall risk, and could be more sensitive at evaluating fall risk than walking measures.

Limitations:

Several limitations of this scoping review should be noted. Only articles available in English were included. The definition of older adults in this review as a mean participant age of 55 years influenced which articles were ultimately included. However, lowering the mean age threshold to 48 years would have only included two more articles.[17,57] Five of the nineteen articles included examined the relationship between MPKs and fall risk. MPKs are computerized prosthetic knees that measure and respond to an individual's gait in real time, and have been shown to be associated with reduced fall risk in previous literature. However, the relationship between MPKs and falls has been examined recently,[68,69] and was outside the scope of this review. Inpatient falls, fall-related injuries, and near-falls were outside the scope of this review, but are prevalent and could be captured in questionnaire assessments.[8,28,70] Risk factors for inpatient falls and fall-related injury include older adult inpatients, dysvascular etiologies and using two or more medications.[8,9,71] It is logical to conclude these risk factors would be similar among community-dwelling ambulators, but should be directly examined in future work.

Future Research:

Further research is needed to assess generalizability of assessments beyond single studies to a larger portion of older adults who use lower-limb prostheses. Specifically, TUG and FSST clinical outcome measures, as well as kinetic data during walking and the ten significant gait parameters during stair ascent. Additionally, future research can examine if spatiotemporal and kinematic gait parameters could also be indicators of fall risk in this population. Neither spatiotemporal or kinematic parameters were found to be significant in this review, but have been found to be significant in other populations of older adults (e.g. stroke). Gait parameters with significance were only examined in older adults who used transtibial prostheses, so future research can also determine if these findings are generalizable to older adults who use transfemoral prostheses. More evidence can warrant a systematic review and meta-analysis to establish evidence-based clinical protocols for fall risk screening in this population.

The majority of articles included in this review only collected retrospective fall history. Collecting retrospective fall history can shorten the time required for data collection, since it requires no participant follow-up. However, collecting retrospective fall history is less accurate than prospective fall occurrence due to issues with participant recall and gait adjustments after falls to increase stability.[15] The ability to predict future fall risk using prospective data can allow for more appropriate clinical interventions to reduce fall risk.

Based on findings in this review and in the general population of older adults, a combination of clinical outcome measures and gait parameters is likely necessary to determine associations with retrospective fall history and predict future fall risk. Researchers can collect multiple assessments and analyze their combined effectiveness at predicting fall risk, beginning with the assessments summarized in Table 1 as having significance, as a bridge to determining clinical significance in terms of fall risk screening and prediction.

Conclusion

This scoping review summarized clinical outcome measures and gait parameters associated with fall risk in older adults who use lower-limb prostheses. The authors conclude a systematic review is not yet warranted due to differences among articles in population, assessments, and reported fall data. Despite differences among articles, the majority found no clinical outcome measure or gait parameter alone was effective at determining fall risks. Future research can determine a combination of clinical assessments and collect prospective fall data to move towards establishing an evidence-based clinical protocol to screen fall risk in this population.

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Chapter 3 Linkage

Chapter 3 provided context for both studies listed under ‘Section 3: Biomechanical Symmetry.’

Chapter 3 findings showed the importance of developing a clinical protocol to evaluate fall risk in individuals of any age who use lower-limb prostheses, particularly older individuals. This scoping review helped inform decisions regarding which clinical outcome measures and gait parameters to include in Chapter 8.

SECTION 2. MUSCULOSKELETAL SYMMETRY

CHAPTER 4

SKELETAL ASYMMETRIES IN ANATOMICAL DONORS WITH LOWER-LIMB AMPUTATIONS

CHAPTER 5

STRUCTURAL AND PHYSIOLOGICAL PLASTICITY IN THIGH MUSCULATURE IN DIABETIC MALE ANATOMICAL DONORS WITH LOWER-LIMB AMPUTATION

CHAPTER 6

MUSCULOSKELETAL HEALTH IN ANATOMICAL DONORS WITH LOWER-LIMB AMPUTATIONS: COMPARISON TO DIABETIC AND HEALTHY CONTROLS

CHAPTER 4

SKELETAL ASYMMETRIES IN ANATOMICAL DONORS WITH LOWER-LIMB AMPUTATIONS

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Key words: Amputations-Lower Extremity, Prosthetics, Bone Diseases

Individuals with lower-limb amputations experience asymmetrical musculoskeletal loading that has been associated with gait asymmetry, increased fall risk, and overuse injuries.[1] To the authors' knowledge, this is the first case series to examine skeletal properties in anatomical donors, or cadavers, with lower-limb amputations as opposed to living individuals. Many biomechanical modeling systems rely on cadaveric data for a gold standard, so it is important to ensure findings in cadavers with lower-limb amputation reflect findings in living individuals with lower-limb amputation.

This case series investigated how prosthesis use following lower-limb amputation in cadavers influenced skeletal properties. Previous research in living individuals has found prolonged bone unloading of the residual limb can lead to significant bone loss[2-4] and atrophy[5] in the residual limb, as well as osteoarthritis in the intact limb.[6] Therefore, we expected each donor's most compromised limb would show decreased bone mineral density (BMD)[2] and bone mineral content (BMC),[3] more tissue fat,[5] thinner femoral diaphysis width,[4] and wider acetabular and knee joint space[6] compared to their most intact limb.

Four donors with transtibial lower-limb amputation secondary to diabetes from the Willed Body Program at the University of North Texas Health Science Center were included in this study (Table 1). All donors used a prosthesis. Each donor's most compromised limb was the limb with transtibial amputation, except Donor 1, who had a transfemoral amputation. X-rays and dual energy x-ray absorptiometry (DXA) scans were taken within three days of receiving of each donor, and donors were stored at 37^{o}F when data was not actively being collected.

Table 1: Donor Demographics and Results

	Donor 1	**Donor 2**	**Donor 3**	**Donor 4**
Sex	Male	Male	Male	Male
Age (years)	61	67	63	64
Weight (kg)	72.6	108.9	95.3	63.5
Amputation Level	R Transtibial 2017	R 1st Metatarsal 2010	R Transtibial 2018	R Transmet 2004/5
	L Transfemoral 2019	L Transtibial 2016	L Intact	L Transtibial 2012
DEXA % Difference				
BMD	-36.64%	-31.81%	-32.24%	-19.28%
BMC	-22.66%	-32.94%	-64.50%	-34.47%
Tissue % Fat	38.80%	51.82%	39.45%	49.40%
T-score	-3.2	-1.1	-1.2	-1.5
Z-score	-0.7	-1.7	-1.7	-0.6
X-ray % Difference				
Acetabular Joint Space	Hip replacements	6.12%	3.31%	10.10%
Femoral Diaphysis Width	-4.84%	0.80%	4.44%	-6.63%
Knee Joint Space	Left knee absent	43.80%	33.70%	32.74%

Table 1: Perfect symmetry between limbs is 0%. Negative percent differences indicate lower values on the most compromised limb compared to the most intact limb. R and L indicate right and left limbs, respectively.

The same individual trained to operate the DXA scanner (GE Lunar Prodigy, GE Healthcare, Madison, WI, USA) set parameters for each total body scan, which provided BMD, BMC, and percent tissue fat for each lower limb. Unequal limb lengths caused reduced values on each donor's compromised limb. For accurate comparison, both limb lengths were measured from the greater trochanter, and values for each donor's most compromised limb were adjusted as a percentage of their most intact limb:

$$\left(\frac{most\ compromised\ limb\ length}{most\ intact\ limb\ length}\right) x100$$

The same two individuals took X-rays of the hip joint, femoral midshaft, and knee joint for each donor using a mobile C-Arm (9600, GE OEC Medical Systems Inc., Salt Lake City, UT, USA). A radiopaque ruler was included in X-ray images to calibrate measurements taken in ImageJ software.[7] The same individual collected all measurements in ImageJ. Femoral diaphysis width was measured across the widest point of the femoral midshaft at six different points, and acetabular joint space was measured from the femoral head to the acetabulum at six different points. Knee joint space was measured from the distal end of the femur to the proximal end of the tibia at six different points: three on the medial compartment and three on the lateral compartment. Joint space measurements were used as indicators of osteoarthritis, which is known to result in joint narrowing.[1] Measurements were averaged for each final value.

Each donor's most intact limb was used as a control to compare their most compromised limb. Asymmetry was assessed using percent differences between limbs:[8]

$$\left[1-\left(\frac{most\ intact\ limb}{most\ compromised\ limb}\right)\right]\ x\ 100$$

Limb differences less than 10% were considered symmetrical, since this is considered symmetrical in the able-bodied population, and has been a threshold of gait symmetry in individuals with lower-limb amputation.[9]

Each donor's most compromised limb had decreased BMD (19.3-36.6%) and BMC (11.5-64.5%),[2-3] more tissue fat (38.8-51.8%),[5] and wider knee joint space (9.1-53.3%)[6] (Table 1; Figure 1). Despite large variability between donors, this case series found similar percent differences in BMD and BMC as reported in fifty-two living individuals with transtibial or transfemoral limb loss.[3] T-scores and Z-scores were also similar to previous research,[2-3] and indicated osteopenia for three donors and osteoporosis for one donor according to the World Health Organization's classification.[10]

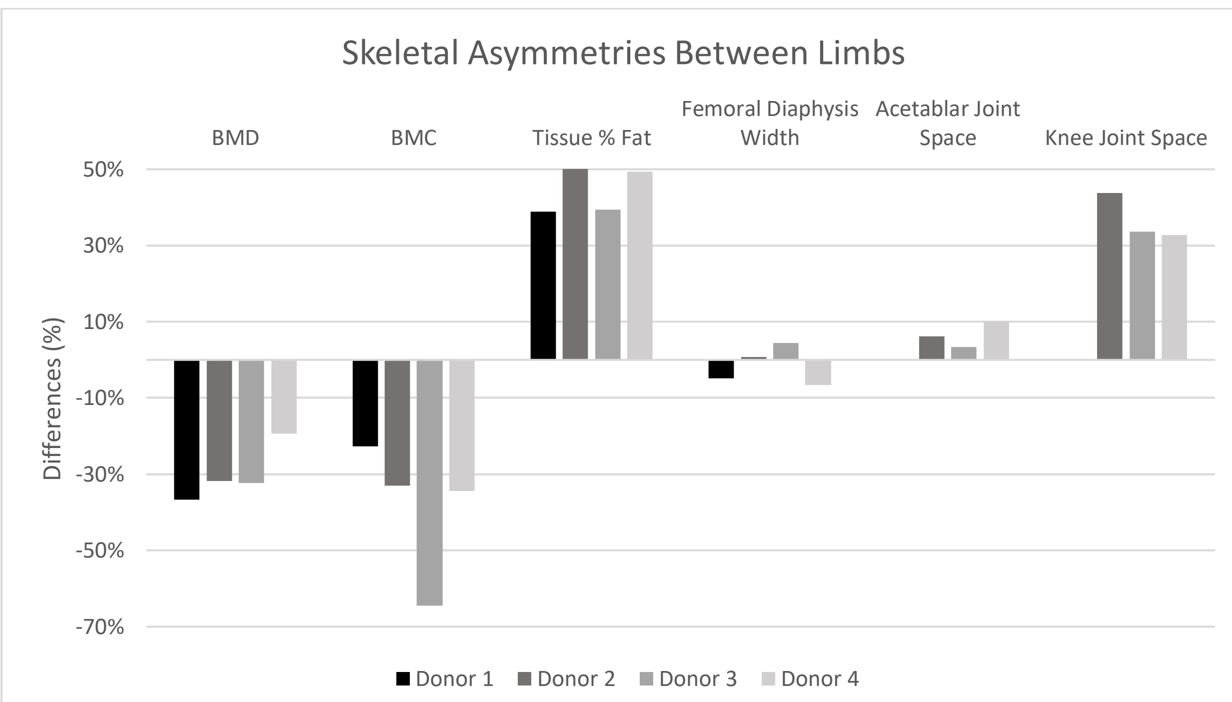

Figure 1: Percent differences between limbs where perfect symmetry is 0%. Negative percent differences indicate lower values on the donor's most compromised limb compared to their most

intact limb. Donor 1 had bilateral total hip replacements and only one remaining knee, so acetabular and knee joint space could not be calculated.

Two donors had thinner femoral diaphysis width (4.8-6.6%), while two donors had wider femoral diaphysis width (0.8-4.4%) on their most compromised limb. Each donor had wider acetabular joint spaces (3.3-10.1%) on their most compromised limb. However, both femoral diaphysis width and acetabular joint spaces had 10% differences or less, potentially due to the inclusion of only one donor with transfemoral amputation. Unlike previous research,[3] those with more proximal amputation levels or increased time since amputation did not show more asymmetry. This could be due to our small sample size and heterogeneous donor demographics, since only one donor had transfemoral amputation and only one donor had amputations occurring beyond the last five years.

We observed lower BMD and BMC, more tissue fat, and wider knee joint space in each donor's most compromised limb, consistent with findings in living individuals with lower-limb amputation. However, percentages of asymmetry varied widely between donors. Differences in activity level or use of assistive devices could have influenced results. Future research could include larger sample sizes of donors with longer time since amputation, compare findings to individuals who are older and diabetic without amputation, or investigate other known anatomical risk factors associated with falls and overuse injuries.

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Chapter 4 Linkage

Chapter 4 examined skeletal symmetry in anatomical donors with lower-limb amputation, while Chapter 5 examined muscular symmetry in the same anatomical donors. Thus, Chapter 5 expands the tissue composition results from Chapter 4 by examining more specific indications of muscle atrophy: physiological cross-sectional area and muscle fiber type ratios.

CHAPTER 5

STRUCTURAL AND PHYSIOLOGICAL PLASTICITY IN THIGH MUSCULATURE IN DIABETIC MALE ANATOMICAL DONORS WITH LOWER-LIMB AMPUTATION

Intended submission as a clinical letter pending final histological results

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Abstract

Background: Musculoskeletal remodeling occurs in both intact and amputated limbs, but has rarely been investigated from structural and physiological perspectives. Indicators of muscle atrophy, such as physiological cross-sectional area and ratios of slow to fast-twitch muscle fibers, can help inform targeted rehabilitation exercises in this population.

Objective: Identify differences in physiological cross-sectional area and ratios of slow to fast-twitch muscle fibers between intact and amputated limbs.

Methods: Gluteus maximus, sartorius, rectus femoris, and biceps femoris long head muscles were dissected from intact and amputated limbs of three unembalmed donors with transtibial lower-limb amputation. Physiological cross-sectional area for all muscles and ratios of slow to fast-twitch muscle fibers of the antagonist muscle pair (rectus femoris and biceps femoris long head), were calculated.

Results: The amputated limb biceps femoris long head had smaller physiological cross sectional areas than the intact limb across donors (18.1-68.6%). Histological results of slow-to-fast twitch muscle fiber ratios in the rectus femoris and biceps femoris are pending final analysis.

Conclusions: Targeting the intact limb biceps femoris in rehabilitation exercises might help improve musculoskeletal symmetry in this population. Histology results can help inform whether exercises targeting slow or fast twitch muscle fibers would be most beneficial.

Key words: amputation, rehabilitation, exercise, muscle, atrophy, symmetry

Introduction

Individuals with lower-limb amputations often have muscular asymmetries from loading prosthetic and intact limbs differently during ambulation.[1] Decreased loading in the residual limb post-amputation can result in structural and physiological muscle changes such as atrophy, architecture, and fiber phenotype.[1,2]

However, few studies have examined individuals' muscular status post-amputation from structural and physiological perspectives.[3-6] A thorough search of the relevant literature yielded no prior studies investigating muscular properties in donors, or cadavers, with lower-limb amputation aside from our previous study.[7] Measuring muscular asymmetries in anatomical donors can improve our understanding of underlying function in a way that would be difficult or impossible in living individuals.

For instance, physiological cross-sectional area (PCSA) is an established equation used to measure the maximum force a muscle can generate, and is an indicator of muscle atrophy.[8] Since muscle weight, pennation fiber angle, and length of muscle fibers is needed to calculate PCSA, dissection of whole muscles is most accurate, but not possible in living individuals. Additionally, slow-twitch fibers are trained by low weight exercises with a high number of repetitions, while fast-twitch fibers are trained by high weight exercises with a low number of repetitions.[2] Ratios of slow-twitch to fast-twitch muscle fibers can be used to determine if selective atrophy of muscle fiber types has occurred.[2] One study found selective atrophy of slow-twitch fibers in amputated limbs compared to intact limbs,[4] which aligns with studies that have examined unloading effects during space flight.[2] Therefore, PCSA can indicate which muscle should be targeted in rehabilitation due to having the least symmetry between prosthetic and intact limbs, and muscle fiber type ratios can indicate what type of exercise would be most beneficial to increase symmetry.

Previously, we examined skeletal asymmetries in these donors and found each donor's most compromised limb, compared to their most intact limb, had: less bone mineral density and bone mineral content, more tissue fat, and wider knee joint space.[7] This case series aimed to translate biological findings of muscular properties into considerations to help inform specific rehabilitation exercises to increase thigh muscle symmetry in living individuals with lower-limb amputations. We hypothesized each donor's most compromised limb would show more muscle atrophy compared to their most intact limb. Specifically, we expected each donor's most compromised limb, compared to the intact limb, would show: 1) smaller physiological cross-sectional area (PCSA), and 2) fewer and smaller slow-twitch muscle fibers.

Methods

Three unembalmed donors with transtibial lower-limb amputation secondary to diabetes from the Willed Body Program at the University of North Texas Health Science Center were included in this study (Table 1). Our previous study that examined skeletal asymmetries included four donors, but one donor had to be excluded from this study due to having a communicable blood disease. All donors used a prosthesis, but no information on mobility could be provided. Each donor's most compromised limb had a transtibial amputation, except Donor 1, who also had a transfemoral amputation. Muscles were dissected within three days of receiving each donor. Donors were stored at 37^{o}F when data was not actively being collected.

Four muscles were dissected from each limb of each donor: the gluteus maximus, sartorius, rectus femoris, and the biceps femoris long head. The biceps femoris long head was chosen, as opposed to the short head, because of its role in hip extension.

To collect the PCSA of each muscle, muscle mass and fiber lengths were measured using a hanging scale and calipers, respectively. Muscles were photographed (Nikon D5600 body with an AF-S Micro NIKKOR 60mm f/2.8G ED lens) to collect pennation angles in ImageJ software.[9] An average of three weights, five caliper measurements, and three pennation angles were taken to determine final values for each muscle. PCSA was calculated using the following formula, with recommended muscle density of 1.067g/cm^{-3}:[10]

$$\frac{\text{muscle mass x} \cos(\textit{pennation angle})}{\text{fiber length } x \textit{ muscle density}}$$

Eq. 1

The sartorius was the only parallel muscle dissected. Cross-sectional area is used for parallel muscles instead of PCSA, since parallel muscles do not contain pennation angles. Therefore, the sartorius was measured using the same equation as above, excluding the factor of pennation angle.

Asymmetry between compromised and intact limbs were assessed using an established equation of percent differences between limbs:[10]

Eq. 2

$$\text{abs}\left(\left(\frac{I-R}{(I+R)*0.5}\right)*100\right)$$

Limb differences less than 10% were considered symmetrical, since this is considered symmetrical in the able-bodied population, and has been a threshold of gait symmetry in individuals with lower-limb amputation.[10]

Based on our PCSA results, we also performed histological analysis to determine differences in slow-twitch to fast-twitch muscle fiber type ratios. Ratios were determined in terms of density and cross sectional area in the two antagonist thigh muscles: rectus femoris and biceps femoris long head. Samples were fixed in paraffin wax. Immunohistochemical (IHC) staining was used to identify the percentage of fibers containing the fast-twitch, or type II, isoform of myosin heavy chain (MHC). A 3,3'Diaminobenzidine (DAB) staining kit (Abcam ab64238) was used to differentiate slow-twitch from fast-twitch muscle fibers. Microscope slides were imaged using a brightfield microscope (Meiji Techno MT5300L) with 10x objective, and images were uploaded to ImageJ software. Histology results are pending analysis.

Results and Discussion

Table 1 contains donor demographics and PCSA results. Histology results, when analyzed, will be added into the final manuscript submission. Figure 1 depicts muscles that were dissected to obtain PCSA results. Figure 2 is a graphical depiction of PCSA results.

Table 1: Donor Demographics and PCSA Results

	Donor 1	**Donor 2**	**Donor 3**
Sex	Male	Male	Male
Age (years)	61	67	64
Weight (kg)	72.6	108.9	63.5
Amputation Level	R Transtibial 2017	R 1st Metatarsal 2010	R Transmetatarsal 2004/5
	L Transfemoral 2019	L Transtibial 2016	L Transtibial 2012
CSA % Differences Between Limbs			
Gluteus Maximus	60.4%	37.1%	-45.9%
Sartorius	3.5%	1.4%	33.9%
Rectus Femoris	-22.5%	-66.1%	26.2%
Biceps Femoris Long Head	68.6%	67.9%	18.1%

Table 1: Donor demographics and percent differences between most compromised and most intact limbs. Perfect symmetry is 0%. Clinically significant symmetry, based on previous research, was considered ≤ 10%. Negative percent differences indicate lower values on the most compromised limb compared to the most intact limb. R and L indicate right and left limbs, respectively. CSA indicates cross-sectional area.

The only muscle with PCSAs consistently smaller or larger across donors was the biceps femoris long head, with 18.1-68.6% larger PCSAs on each donor's most compromised limb compared to the most intact limb. Differences between limbs were largely driven by pennation angle, as opposed to muscle mass or fiber lengths, for each muscle. Larger biceps femoris long head PCSAs on each donor's most intact limb indicates more atrophy in the hamstrings on each donor's most compromised limb compared to their most intact limb. This is consistent with previous studies in living individuals that found more hip extension and power generation on the intact limb to maintain stability and forward progression during ambulation.[11,12]

Conclusions

PCSA findings suggest the biceps femoris long head was the most asymmetrical of the muscles we examined. The biceps femoris long head had larger PCSAs in the intact limb compared to the most compromised limb. This aligns with the few prior anatomical studies that have examined thigh muscle atrophy in this population, as well as biomechanics studies in living individuals that have observed increased compensatory hip extension mechanisms. Histology findings of slow to fast-twitch fiber ratios will help determine which types of exercise might be most beneficial to exercise the biceps femoris long head. Future research could include more donors or examine muscle biopsies in living individuals to assess the generalizability of our findings. Additionally, since intact limbs also undergo changes in loading, comparing individuals with amputation to controls without amputation can provide a more accurate view of loading influences on muscle changes.

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Chapter 5 Linkage

Chapter 5 concluded musculoskeletal findings from anatomical donors. The desire to increase our sample size and compare our findings in individuals with lower-limb amputation to diabetic and healthy control groups led us to perform the study in Chapter 6. Utilizing the New Mexico Decedent Image Database allowed us to determine if findings in Chapters 4 and 5 were generalizable, and how findings compared to diabetic and healthy controls without amputation.

CHAPTER 6

MUSCULOSKELETAL HEALTH AFTER LOWER-LIMB AMPUTATION: DIFFERENTIATING INFLUENCES OF AMPUTATION AND DIABETES IN DECEASED MALE INDIVIDUALS

In Review

on October 2, 2022

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Abstract

Background: Individuals with lower-limb amputations, many of whom have type 2 diabetes, experience impaired musculoskeletal health. This study: 1) compared residual and intact limbs of diabetic and non-diabetic individuals with amputation to identify structures vulnerable to injury, and 2) compared findings to diabetic and healthy control groups to differentiate influences of amputation and diabetes on musculoskeletal health.

Methods*:* Postmortem CT scans of three groups, ten individuals each, were included: 1) individuals with transtibial or transfemoral amputations, half with diabetes 2) diabetic controls, and 3) healthy controls. Hip and knee joint spaces, cross-sectional thigh muscle and fat areas, and cross-sectional bone properties (e.g. area, thickness, geometry) were measured. Wilcoxon Signed-Rank and Kruskal-Wallis tests assessed statistical significance. Asymmetry percentages between limbs assessed clinical significance.

Findings*:* Residual limbs of individuals with amputation, particularly those with diabetes, had significantly less thigh muscle area and thinner distal femoral cortical bone compared to intact limbs. Compared to control groups, individuals with amputation had significantly narrower joint spaces, less thigh muscle area bilaterally, and thinner proximal femoral cortical bone in the residual limb. Diabetic individuals with amputation had the most clinically significant asymmetry.

Interpretation*:* Individuals with amputation showed an increased risk of thigh muscle atrophy and femoral fracture in their residual limb compared to both their intact limb and the control populations, and an increased risk of osteoarthritis in their residual limb compared to control

populations. The combined effect of amputation and diabetes may increase the risk of thigh muscle atrophy. Larger sample sizes of living individuals are needed to assess generalizability of findings. Quantifying musculoskeletal properties and differentiating influences of amputation and diabetes could help direct rehabilitation techniques.

Key words: amputee, limb loss, leg, atrophy, prosthesis, physiology

1. Introduction

Forces acting on the human body during gait help maintain musculoskeletal health. Individuals with lower-limb amputation (IWAs) experience increased forces on the intact limb and reduced forces on the amputated, or residual, limb while walking with a prosthesis (1). Chronic over or underuse of musculoskeletal structures leads to musculoskeletal remodeling, which can contribute to asymmetries between residual and intact limbs (2). These asymmetries have been associated with adverse health outcomes such as increased risks of hip and knee osteoarthritis (2,3), thigh muscle atrophy (4), and femoral fracture (5).

While gait asymmetries between residual and intact limbs have been studied extensively in this population, little attention has been paid to underlying structural musculoskeletal adaptations that have been associated with gait deviations (2). Understanding structural musculoskeletal properties in this population could help reduce these risks by improving rehabilitation foci and improving clinical screening metrics. Specifically, these risks may be assessed by quantifying structural musculoskeletal properties, such as narrower hip and knee joint spaces to indicate osteoarthritis (6), reduced muscle mass and fat tissue area to indicate muscle atrophy (7), and reduced cross-sectional bone properties and moment of inertia to indicate fracture risk (8).

Type 2 diabetes is a common comorbidity of IWAs (9) and is also associated with increased risks of hip and knee osteoarthritis, thigh muscle atrophy, and femoral fracture risk (10-12). However, diabetic IWAs are underrepresented in musculoskeletal literature (2, 13). Determining how lower-limb amputation and diabetes differentially influence these risks can help inform rehabilitation techniques according to diabetic status in this population. As healthcare technology improves, quantifying musculoskeletal properties by pathology could help clinicians assess typical levels of musculoskeletal health, and implement rehabilitation exercises to reduce risks of hip and knee osteoarthritis, thigh muscle atrophy, and femoral fracture.

Therefore, this study quantified influences of amputation and diabetes on musculoskeletal parameters indicative of hip and knee osteoarthritis, thigh muscle atrophy, and femoral fracture risk. Our first aim was to determine if significant differences exist between residual and intact limbs of IWAs. We hypothesized that residual limbs, compared to intact limbs, would have significantly wider hip and knee joint spaces, reduced thigh muscle mass, and reduced cross-sectional bone properties (e.g. area, thickness, geometry). Our second aim was to compare IWA findings to diabetic and healthy control groups to differentiate interactions between amputation and diabetes on musculoskeletal health. We hypothesized IWAs, compared to diabetic and healthy control groups, would have significantly narrower hip and knee joint spaces, reduced muscle mass, and reduced cross-sectional bone properties. Overall, we expected diabetic IWAs would show the most impaired musculoskeletal health, followed by non-diabetic IWAs, diabetic controls, then healthy controls.

2. Methods

2.1 Study Population

Deidentified data of deceased individuals did not require ethics approval from the North Texas Regional Institutional Review Board. Computed tomography (CT) scans from deceased individuals were obtained with permission from the New Mexico Decedent Image Database (NMDID) (14) from June to October 2021. The NMDID used a Phillips Brilliance Big Bore 16 slice CT scanner with Z-position accuracy of ± 0.25mm and resolution of up to 24Lp/cm. Three groups were included: transtibial or transfemoral IWAs (half with diabetes), diabetic controls without amputation, and healthy controls without amputation.

IWAs were identified by searching for males 40-90 years of age with relevant causes of death (e.g. diabetes) or record of lower limb surgery, as indicated by the NMDID records. IWAs were included if they had limb loss upon visual inspection of scout images, and excluded if they had advanced decomposition. A total of 10 IWAs were found in the NMDID database as of October 10th, 2021. Diabetic and healthy controls were sex, age, and BMI-matched to the identified IWAs. Healthy controls were excluded if they had: amputation, diabetes, advanced body decomposition, cancer, or an age or BMI outside the range of identified IWAs. Diabetic controls were excluded for any of the above criteria, except diabetes.

2.2 Sample Demographics

In total, thirty males 42-79 years of age with BMIs of 19.7-48.9 kg/m^2 were included. BMIs for IWAs were adjusted according to equations in previous literature (18). IWAs were added to the study until no more could be found, which resulted in ten IWAs. Five IWAs had a diagnosis of diabetes, and five did not have a diagnosis of diabetes. Therefore, ten diabetic controls and ten healthy controls were included in this study. Summary (Table 1) and individual (Table S1) demographics are provided. Two IWAs were affected bilaterally. For these individuals, the residual limb refers to the most proximally amputated limb and the intact limb refers to the most distally amputated limb. Supplemental tables present all raw data (Tables S2 and S3) and p-values (Tables S4 and S5).

Table 1: Summarized demographics

	Sex	Age (years)	BMI (kg/m^2)	Time from Death to Scan (days)	Race	Ethnicity	Primary Cause of Death	Side/Level of Amputation
Healthy Controls (n=10)	All M	57.50 ± 11.17	30.93 ± 8.05	61.20 ± 130.42	All White	4 of 10 Hispanic, Latino, or Middle Eastern	All Natural	N/A
Diabetic Controls (n=10)	All M	54.00 ± 9.18	29.22 ± 6.89	26.20 ± 38.71	9 White; 1 Native American	2 of 10 Hispanic, Latino, or Middle Eastern	All Diabetes	N/A
All IWAs (n=10)	All M	61.90 ± 11.05	31.08 ± 9.76	23.11 ± 15.83	7 White; 1 Black or African American; 1 Hispanic; 1 Native American	5 of 10 Hispanic, Latino, or Middle Eastern	5 Diabetes; 2 Natural; 3 Sepsis	5 unilateral TT; 3 unilateral TF; 1 bilateral TT; 1 bilateral TF
Diabetic IWAs (n=5)	All M	67.00 ± 11.00	30.61 ± 11.51	14.00 ± 4.24	3 White; 1 Hispanic; 1 Native American	1 of 5 Hispanic, Latino, or Middle Eastern	2 Natural; 3 Sepsis	3 unilateral TT; 2 unilateral TF
Non-diabetic IWAs (n=5)	All M	56.80 ± 9.42	31.55 ± 9.01	30.40 ± 18.20	1 Black or African American; 4 White	0 of 5 Hispanic, Latino, or Middle Eastern	All Diabetes	3 unilateral TT; 2 unilateral TF;
***p*-values between Healthy Controls, Diabetic Controls, and All IWAs**		0.18	0.95	0.08				

Table 1: Summarized demographic characteristics of all individuals included in this study as reported in the New Mexico Decedent Image Database. Means ± standard deviations. Abbreviations: IWAs= individuals with lower-limb amputation, TT= transtibial, TF= transfemoral, N/A= not applicable.

2.3 Joint Space, Tissue Area, and Femur Morphology

CT scans were imported into 3D Slicer software (version 4.10) for the following bilateral measurements (15). CF measured all musculoskeletal properties in the IWAs. CF and WN were each randomly assigned to measure all musculoskeletal properties in half of the diabetic controls and half of the healthy controls.

Hip and knee joint spaces were measured from femoral head to acetabulum, and from femoral to tibial condyles, respectively. Fourteen measurements were averaged per hip and knee joint space, divided equally between anterior and posterior aspects or medial and lateral aspects, respectively.

Cross-sectional thigh muscle and fat tissue areas were measured at the femoral midshaft, defined as 50% of overall femur length. Within the midshaft slice, muscle and fat were identified using the threshold function within the Segmentation Editor module. Tissue areas were calculated using the Segmentation Statistics module.

Femur lengths were measured from greater trochanter to lateral condyle in intact limbs, and from greater trochanter to the lateral aspect of the distal end in residual limbs. Femoral head diameters were measured from anterior to posterior aspects and medial to lateral aspects. These two dimensions were averaged and expressed as a ratio of anterior-posterior to medial-lateral diameter. Femoral neck widths were measured superoinferiorly at the narrowest aspect. Femoral diaphysis width was measured anteroposteriorly at the midshaft.

2.4 Femur Geometry

Cross-sectional bone properties were also measured for the femur. CT scan slices were loaded into the BoneJ plugin (version 2) for Fiji to quantify cortical bone thickness and moment of inertia (16). Three slices per femur were used: the proximal (25% of total femoral length), middle (50%), and distal (75%) femoral shaft. The slice was cropped to enclose the cortical bone and converted into an 8-bit image. The grayscale threshold range was adjusted to encompass the bone while excluding air and soft tissue. Threshold values were imputed into the Slice Geometry module of BoneJ to calculate biomechanical properties of the bone at the specified cross-section.

2.5 Repeatability Study

A repeatability study was conducted to ensure intra and inter-observer reliability between CF and WN's control group measurements. CF and WN were assigned the same three scans, and collected all measurements three times with at least 24 hours between each collection. Intra- and inter-observer reliability of CF and WN were determined using paired and unpaired t-tests, respectively. Percent differences in measurements were also calculated. No significant differences were found, and all reliability measurements differed by less than 10%.

2.6 Statistics

NCSS Statistical Software (2021, LCC, Kaysville, UT, USA) was used for statistical analysis (17). Missing data points (e.g. knee joint space absent due to transfemoral amputation) were not included. For Aim 1, Wilcoxon Signed-Rank tests assessed differences between residual and intact limbs of IWAs, right and left limbs of diabetic controls, and right and left limbs of healthy controls. For Aim 2, Kruskal-Wallis tests with assessed differences between groups. Bonferroni corrections were used to reduce risks associated with Type 1 (false-negative) errors in our small sample size.

Right and left limbs were averaged for diabetic and healthy controls to provide a single limb value. Two Kruskal-Wallis tests were performed: 1) compared the intact limbs of IWAs to diabetic and healthy controls, and 2) compared the residual limbs of IWAs to diabetic and healthy controls. Mann-Whitney p-values were performed for significant Kruskal Wallis group comparisons. All significance levels were set at $\alpha \leq 0.05$.

2.7 Calculation of Asymmetry

Asymmetry between limbs was calculated to assess clinical significance. A threshold of 10% asymmetry is considered a clinically relevant threshold, where 0% is perfectly symmetrical and 100% is perfectly asymmetrical (13). Asymmetry percentages were calculated using the following equation:

Eq. 1 $$\mathrm{abs}\left(\left(\frac{I-R}{(I+R)*0.5}\right)*100\right)$$

For IWAs, I represents the intact limb value and R represents the residual limb value. For diabetic and healthy controls, the left limb value replaced I and the right limb value replaced R.

3. Results

3.1 Joint Space, Tissue Area, and Femur Morphology

3.1.1 Between-Limb Comparisons

Data are presented in Table 2 and Figure 1. Healthy controls had significantly different knee joint spaces (p=0.032) between right and left limbs. IWAs had significantly less muscle tissue area (p=0.010) in residual limbs compared to intact limbs. Diabetic IWAs also showed this significance in muscle tissue area (p=0.031). Diabetic controls had significantly different anterior-posterior femoral head width between right and left limbs (p=0.014), and significant differences in femoral head ratio (p=0.032). Healthy controls had significantly different femoral diaphysis widths (p=0.019) between right and left limbs.

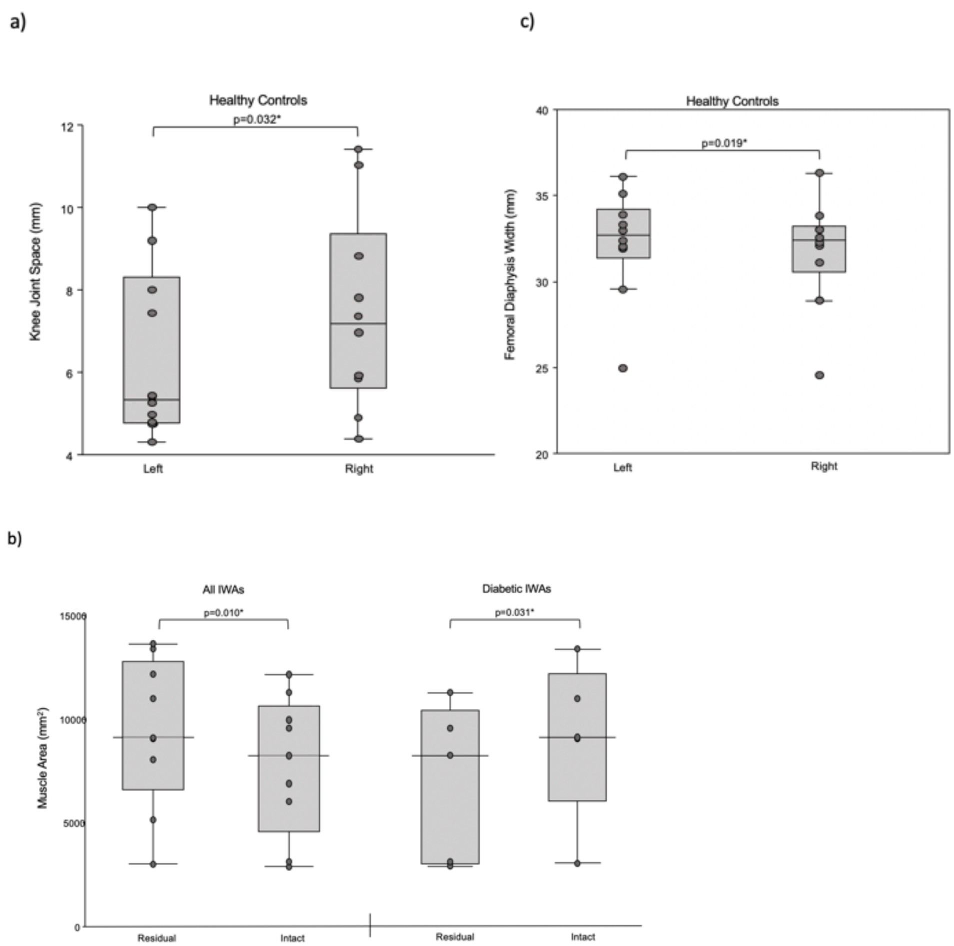

Figure 1: Between-limb comparisons with statistical significance for: a) joint space, b) tissue area, and c) femur morphology.

Table 2: Between-Limb Comparisons of Joint Space, Tissue Area, and Femur Morphology

	Hip Joint Space (mm)	**Knee Joint Space (mm)**	**AP Femoral Head Width (mm)**	**ML Femoral Head Width (mm)**	**Femoral Head Ratio (AP/ML)**	**Femoral Neck Width (mm)**	**Femoral Diaphysis Width (mm)**	**Muscle Area (mm^2)**	**Fat Area (mm^2)**
Healthy Controls (n=10)									
Left	3.80 ± 1.66	6.41 ± 2.07	46.46 ± 4.66	46.78 ± 4.51	0.99 ± 0.04	31.76 ± 4.03	32.23 ± 3.13	12530.90 ± 2655.17	8999.39 ±7546.05
Right	3.77 ± 1.47	**7.44 ± 2.40***	46.15 ± 3.98	47.86 ± 5.36	0.97 ± 0.04	31.99 ± 4.62	**31.72 ± 3.13***	12182.84 ± 2339.91	8964.95 ±6950.44
Direction of Asymmetry	L > R	L< R	L > R	L< R	L > R	L< R	L > R	L > R	L > R
Asymmetry	0.69%	**14.85%**	0.67%	2.29%	2.69%	0.72%	1.59%	2.82%	0.38%
Diabetic Controls (n=10)									
Left	3.65 ± 2.03	6.30 ± 1.77	43.22 ± 3.17	44.91 ± 4.20	0.96 ± 0.03	31.20 ± 2.94	31.98 ± 3.21	10295.51 ± 2445.49	9686.75 ±6617.29
Right	3.80 ± 2.29	6.45 ± 2.16	**44.84 ± 3.91***	45.32 ± 3.75	**0.99 ± 0.02***	32.05 ± 2.98	32.24 ± 3.75	10052.81 ± 2989.30	9492.07 ±6571.87
Direction of Asymmetry	L< R	L< R	L< R	L< R	L< R	L< R	L< R	L > R	L > R
Asymmetry	4.07%	2.33%	3.66%	0.89%	2.58%	2.70%	0.83%	2.39%	2.03%
IWAs (n=10)									
Intact	1.75 ± 0.42	4.02 ± 0.97	47.21 ± 2.88	49.41 ± 3.88	0.96± 0.04	35.50 ± 3.60	34.27 ± 7.90	9398.17 ± 3620.11	6755.21 ±4758.96
Residual	1.59 ± 0.42	3.78± 0.94	46.86 ± 3.63	48.70 ± 3.41	0.96 ± 0.06	33.57 ± 3.40	33.09 ± 6.26	**7791.61 ± 3333.84***	7213.73 ±5059.76
Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int > Res	Int < Res	Int > Res	Int > Res	Int > Res	Int < Res

Asymmetry	9.56%	5.93%	0.75%	1.46%	0.61%	5.58%	3.48%	**18.69%**	6.57%
Diabetic IWAs (n=5)									
Intact	1.79 ± 0.48	3.62 ± 1.10	46.53 ± 1.89	48.39 ± 2.89	0.96 ± 0.04	35.08 ± 4.08	35.70 ± 12.36	9745.16 ± 3870.95	7040.71 ±2763.96
Residual	1.80 ± 0.49	3.79 ± 1.24	46.49 ± 4.34	48.76 ± 4.10	0.95 ± 0.05	31.64 ± 3.20	34.00 ± 9.61	8761.36 ± 2815.49	7663.18 ±3723.55
Direction of Asymmetry	Int < Res	Int < Res	Int > Res	Int < Res	Int > Res	Int > Res	Int > Res	Int > Res	Int < Res
Asymmetry	0.37%	4.83%	0.08%	0.76%	0.91%	**10.30%**	4.90%	**10.63%**	8.47%
Non-diabetic IWAs (n=5)									
Intact	1.70 ± 0.41	4.51 ± 0.59	47.89 ± 3.73	50.43 ± 4.780	0.95 ± 0.05	35.92 ± 3.47	33.12 ± 2.57	9120.58 ± 3841.30	6526.81 ±6278.47
Residual	1.38 ± 0.24	3.77 ± 0.82	47.22 ± 3.25	48.63 ± 3.06	0.97 ± 0.06	35.50 ± 2.56	32.37 ± 2.76	**7015.81 ± 3819.82***	6854.17 ±6359.25
Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int > Res	Int < Res	Int > Res	Int > Res	Int > Res	Int < Res
Asymmetry	**21.01%**	**17.90%**	1.41%	3.63%	2.13%	1.17%	2.28%	**26.09%**	4.89%

Table 2: Between-limb comparisons of 3D Slicer data: joint space, tissue area, and femur morphology. Means with standard deviations. For healthy and diabetic control groups, right and left limbs were compared. For amputees, intact and residual limbs were compared. Wilcoxon-Signed Rank tests were used to assess significance. The significance level was set $\alpha \leq 0.05$. An asterisk (*) indicates a significant difference between limbs. Direction of asymmetry indicates which limb had greater mean values. Asymmetry indicates the amount of asymmetry between limbs where 0% is perfectly symmetrical and 100% is perfectly asymmetrical. Abbreviations: IWAs= individuals with lower-limb amputation, Int= intact limb, Res= residual limb, SD= standard deviation, AP= anterior-posterior, ML= medial-lateral.

Healthy controls had clinically significant knee joint space asymmetry (14.85%). Non-diabetic IWAs had clinically significant hip (21.01%) and knee (17.90%) joint space asymmetry. IWAs had clinically significant muscle area (18.69%) asymmetry, higher in diabetic (26.09%) compared to non-diabetic (10.63%) IWAs.

3.1.2 Between-Group Comparisons

Data are presented in Table 3 and Figure 2. Mann-Whitney post hoc comparisons for significant differences are presented in Table S6. Compared to diabetic and healthy controls, IWAs had significantly narrower hip joint space on intact (p=0.002) and residual (p<0.001) limbs, narrower knee joint space on intact (p<0.001) limbs, and wider femoral diaphysis on the intact limb (p=0.023). Compared to healthy controls, IWAs had significantly narrower knee joint space on residual (p<0.001) limbs, and reduced muscle area on intact (p=0.013) and residual (p=0.011) limbs.

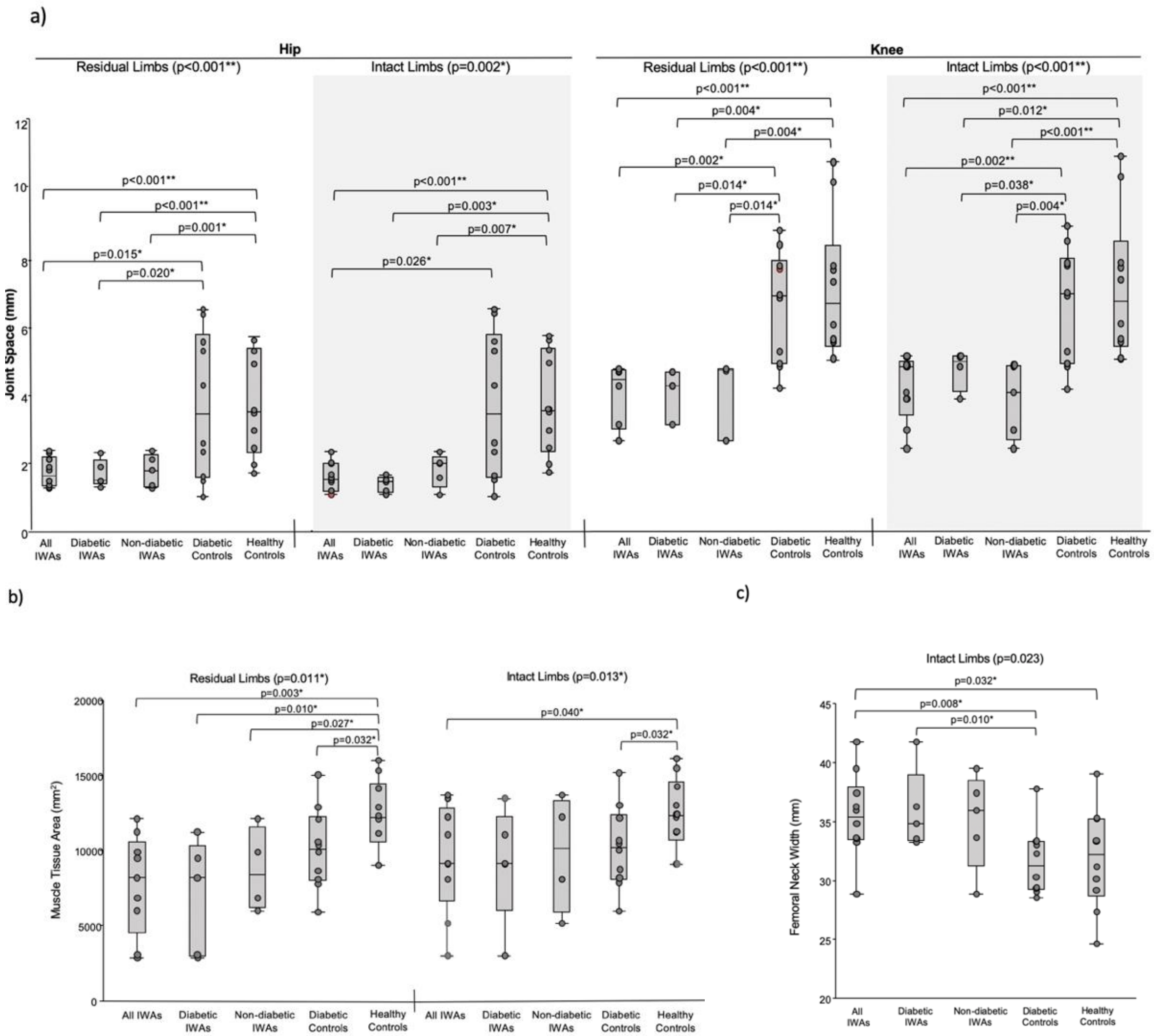

Figure 2: Between-group comparisons with statistical significance for: a) joint space, b) tissue area, and c) femur morphology. Gray boxes provided to help visually distinguish graphs.

Table 3: Between-Group Comparisons of Joint Space, Tissue Area, and Femur Morphology

	Hip Joint Space (mm)	**Knee Joint Space (mm)**	**AP Femoral Head Width (mm)**	**ML Femoral Head Width (mm)**	**Femoral Head Ratio (AP/ML)**	**Femoral Neck Width (mm)**	**Femoral Diaphysis Width (mm)**	**Muscle Area (mm^2)**	**Fat Area (mm^2)**
Healthy Controls (n=10)									
Right and Left Averaged	3.78 ± 1.56	6.93 ± 2.24	46.31 ± 4.32	47.32 ± 4.93	0.98 ± 0.04	31.87 ± 4.32	31.98 ± 3.13	12356.87 ± 2497.54	8982.17 ± 7248.25
Diabetic Controls (n=10)									
Right and Left Averaged	3.72 ± 2.16	6.37 ± 1.97	44.03 ± 3.54	45.11 ± 3.97	0.98 ± 0.02	31.62 ± 2.96	32.11 ± 3.48	10174.16 ± 2717.39	9589.41 ± 6594.58
All IWAs (n=10)									
Intact	**1.75 ± 0.42†‡**	**4.02 ± 0.97*†‡**	47.21 ± 2.88	49.41 ± 3.88	0.96 ± 0.04	**35.49 ± 3.60†‡**	34.27 ± 7.90	**9398.17 ± 3620.11†‡**	6755.21 ± 4758.96
Residual	**1.59 ± 0.42*†‡**	**3.78± 0.94*†**	46.86 ± 3.63	48.70 ± 3.41	0.96 ± 0.06	**33.57 ± 3.40**	33.09 ± 6.26	**7791.61 ± 3333.84†‡**	7213.73 ± 5059.76
Diabetic IWAs (n=5)									
Intact	1.79 ± 0.48	**3.62 ± 1.10*†‡**	46.53 ± 1.89	48.39 ± 2.89	0.96 ± 0.04	**35.08 ± 4.08†‡**	35.70 ± 12.36	**9745.16 ± 3870.95†‡**	7040.71 ± 2763.92
Residual	1.80 ± 0.49	3.79 ± 1.24	46.49 ± 4.34	48.76 ± 4.10	0.95 ± 0.05	31.64 ± 3.20	34.00 ± 9.61	8761.36 ± 2815.49	7663.19 ± 3723.55
Non-diabetic IWAs (n=5)									

Intact	1.71 ± 0.41	4.51 ± 0.59	47.89 ± 3.73	50.43 ± 4.78	0.95 ± 0.05	**35.92 ± 3.47†‡**	33.12 ± 2.57	**9120.58 ± 3841.30†‡**	6526.81 ± 6278.47
Residual	**1.38 ± 0.24*†‡**	3.77 ± 0.82	47.22 ± 3.25	48.63 ± 3.06	0.97 ± 0.06	35.50 ± 2.56	32.37 ± 2.76	**7015.81 ± 3819.82†‡**	6854.17 ± 6359.25
***p*-values (Healthy vs Diabetic vs Intact Limbs of All IWAs)**	**0.002***	**<0.001****	0.16	0.08	0.26	**0.02***	0.13	**0.01***	0.39
***p*-values (Healthy vs Diabetic vs Residual of All IWAs)**	**<0.001****	**<0.001****	0.25	0.13	0.32	0.13	0.49	**0.01***	0.45

Table 3: Between-group comparisons of 3D Slicer data for joint space, tissue area, and femur morphology. Means with standard deviations. For healthy and diabetic control groups, left and right limb values were averaged together. Kruskal-Wallis tests with Bonferroni corrections were used to assess significance. The significance level was set α ≤ 0.05. Bold text indicates p-values less than or equal to 0.05. Asterisks (*) indicate a *p*-value < 0.01, daggers (†) indicate significant differences compared to healthy controls, and double daggers (‡) indicate significant differences compared to diabetic controls. Abbreviations: IWAs= individuals with lower-limb amputation, SD= standard deviation; AP= anterior-posterior, ML= medial-lateral.

3.2 Femur Geometry

3.2.1 Between-Limb Comparisons

Data are presented in Table 4 and Figure 3. IWAs had significantly higher standard deviation cortical bone thickness (*p*=0.037), which indicates higher variability in cortical bone thickness, at the femoral midshaft in residual limbs compared to intact limbs. Healthy controls had significantly different maximum moments of inertia (*p*=0.025) at the proximal femur between right and left limbs. Diabetic controls had significantly different maximum (*p*=0.040) and standard deviation (*p*=0.025) thicknesses at the distal femur between right and left limbs.

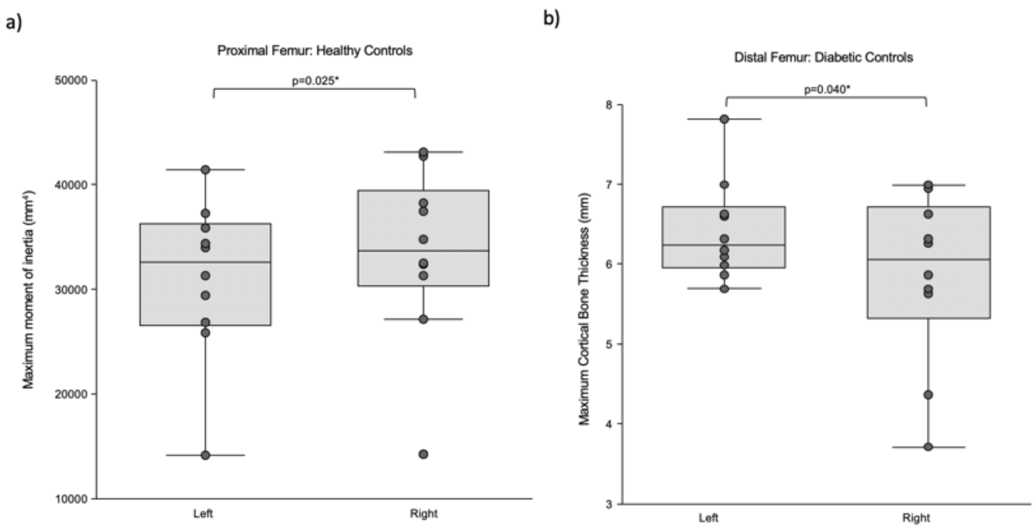

Figure 3: Between-limb comparisons with statistical significance for a) proximal femur geometry and b) distal femur geometry. Gray boxes provided to help visually distinguish graphs.

Table 4: Between-Limb Comparisons of Femur Geometry

		CSA (mm^2)	Imin (mm^4)	Imax(mm^4)	Max Thick 2d (mm)	Mean Thick 2d (mm)	SD Thick 2d (mm)
Proximal Femoral Shaft 25%	**Healthy Controls (n=10)**						
	Left	504.04 ± 72.67	41620.00 ± 10665.26	31075.98 ± 7636.79	9.03 ± 1.30	7.77 ± 0.78	0.95 ± 0.30
	Right	518.22 ± 81.44	43648.46 ± 10596.43	**33416.99 ± 8402.86***	9.21 ± 1.34	7.82 ± 0.95	0.946 ± 0.26
	Direction of Asymmetry	L < R	L < R	L < R	L < R	L < R	L > R
	Asymmetry	2.78%	4.76%	7.26%	2.05%	0.72%	0.33%
	Diabetic Controls (n=10)						
	Left	534.63 ± 93.24	46211.27 ± 13618.75	33446.60 ± 10213.37	9.98 ± 2.03	8.25 ± 1.46	1.22 ± 0.46
	Right	533.19 ± 110.94	46473.42 ± 16509.03	32798.82 ± 11755.50	10.15 ± 1.70	8.28 ± 1.38	1.39 ± 0.43
	Direction of Asymmetry	L > R	L < R	L < R	L < R	L < R	L < R
	Asymmetry	0.27%	0.57%	1.96%	1.68%	0.37%	**13.39%**
	IWAs (n=10)						
	Intact	511.98 ± 131.01	50951.37 ± 23625.27	39999.50 ± 18084.10	8.68 ± 1.55	7.09 ± 1.32	1.08 ± 0.33
	Residual	476.20 ± 166.52	50354.88 ± 28305.25	37878.45 ± 18401.54	8.09 ± 1.97	6.44 ± 1.78	1.09 ± 0.27
	Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int > Res	Int > Res	Int < Res
	Asymmetry	7.24%	1.18%	5.45%	6.98%	9.60%	0.60%
	Diabetic IWAs (n=5)						

	Intact	544.52 ± 171.81	55105.06 ± 32701.87	43929.45 ± 25212.90	9.08 ± 1.36	7.54 ± 1.49	0.99 ± 0.22
	Residual	490.86 ± 201.76	52716.32 ± 39078.84	41062.19 ± 25648.81	8.19 ± 1.72	6.66 ± 1.63	1.01 ± 0.15
	Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int > Res	Int > Res	Int < Res
	Asymmetry	**10.37%**	4.43%	6.75%	**10.39%**	**12.41%**	2.26%
	Non-diabetic IWAs (n=5)						
	Intact	479.44 ± 80.33	46797.68 ± 11970.79	36069.56 ± 7843.88	8.27 ± 1.77	6.65 ± 1.10	1.18 ± 0.42
	Residual	461.53 ± 145.42	47993.45 ± 16173.26	34694.70 ± 8870.45	7.99 ± 2.40	6.23 ± 2.10	1.17 ± 0.36
	Direction of Asymmetry	Int > Res	Int < Res	Int > Res	Int > Res	Int > Res	Int > Res
	Asymmetry	3.81%	2.52%	3.89%	3.36%	6.50%	0.82%
Middle Femoral Shaft 50%	**Healthy Controls (n=10)**						
	Left	492.86 ± 72.24	40155.28 ± 10382.12	29080.35 ± 8266.14	10.21 ± 0.91	8.02 ± 0.73	1.39 ± 0.28
	Right	503.13 ± 81.09	41944.95 ± 11718.68	29984.94 ± 8619.12	10.47 ± 1.43	8.13 ± 0.87	1.44 ± 0.45
	Direction of Asymmetry	L < R	L < R	L < R	L < R	L < R	L < R
	Asymmetry	2.06%	4.36%	3.06%	2.48%	1.26%	4.07%
	Diabetic Controls (n=10)						
	Left	525.26 ± 89.01	42877.95 ± 16659.48	30743.20 ± 10097.47	10.53 ± 1.15	8.49 ± 0.84	1.35 ± 0.45
	Right	506.13 ± 98.12	41817.58 ± 16253.89	29336.44 ± 10457.54	10.06 ± 1.39	8.16 ± 1.18	1.33 ± 0.30

	Direction of Asymmetry	L > R	L > R	L > R	L > R	L > R	L > R
	Asymmetry	3.71%	2.50%	4.68%	4.57%	4.04%	1.69%
	IWAs (n=10)						
	Intact	511.53 ± 154.98	48656.50 ± 30624.77	36209.66 ± 22120.00	8.64 ± 1.66	7.29 ± 1.52	1.13 ± 0.26
	Residual	474.15 ± 169.90	46070.47 ± 32146.77	33372.45 ± 21112.44	9.03 ± 2.53	6.99 ± 1.81	**1.33 ± 0.35***
	Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int < Res	Int > Res	Int < Res
	Asymmetry	7.59%	5.46%	8.16%	4.39%	4.14%	**16.80%**
	Diabetic IWAs (n=5)						
	Intact	555.07 ± 209.72	55105.68 ± 43469.35	41416.50 ± 30843.46	9.51 ± 1.75	7.98 ± 1.81	1.16 ± 0.20
	Residual	514.22 ± 218.10	54975.60 ± 47994.16	39025.22 ± 31171.98	9.86 ± 2.58	7.36 ± 1.65	1.54 ± 0.37
	Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int < Res	Int > Res	Int < Res
	Asymmetry	7.64%	0.24%	5.95%	3.66%	8.09%	**28.49%**
	Non-diabetic IWAs (n=5)						
	Intact	467.99 ± 72.93	42207.32 ± 10800.85	31002.82 ± 9045.13	7.78 ± 1.12	6.60 ± 0.86	1.10 ± 0.30
	Residual	442.08 ± 138.43	38946.37 ± 14018.11	28850.23 ± 10255.95	8.37 ± 2.57	6.70 ± 2.06	1.17 ± 0.26
	Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int < Res	Int < Res	Int < Res
	Asymmetry	5.69%	8.04%	7.19%	7.28%	1.55%	6.23%
Distal Femoral Shaft	**Healthy Controls (n=10)**						

75%	Left	382.22 ± 58.28	48118.49 ± 14337.67	37968.37 ± 11143.22	5.55 ± 0.90	4.63 ± 0.59	0.61 ± 0.18
	Right	390.46 ± 61.91	50445.11 ± 16873.66	39463.18 ± 12036.90	5.91 ± 0.83	4.73 ± 0.55	0.69 ± 0.14
	Direction of Asymmetry	L < R	L < R	L < R	L < R	L < R	L < R
	Asymmetry	2.13%	4.72%	3.86%	6.29%	2.11%	**10.87%**
	Diabetic Controls (n=10)						
	Left	397.60 ± 34.27	46510.46 ± 15166.72	38368.07 ± 15022.90	6.41 ± 0.63	5.07 ± 0.53	0.77 ± 0.19
	Right	382.83 ± 69.19	46991.59 ± 16047.99	37397.42 ± 15990.31	**5.84 ± 1.07***	4.78 ± 0.79	**0.62 ± 0.17***
	Direction of Asymmetry	L > R	L < R	L > R	L > R	L > R	L > R
	Asymmetry	3.79%	1.03%	2.56%	9.38%	5.91%	**21.53%**
	IWAs (n=10)						
	Intact	390.91 ± 114.06	58415.07 ± 36624.33	45178.18 ± 26176.32	5.61 ± 1.00	4.52 ± 0.99	0.70 ± 0.18
	Residual	374.98 ± 139.14	59347.39 ± 42489.22	47885.19 ± 31837.10	5.43 ± 1.05	4.29 ± 0.84	0.78 ± 0.24
	Direction of Asymmetry	Int > Res	Int < Res	Int < Res	Int > Res	Int > Res	Int < Res
	Asymmetry	4.16%	1.58%	5.82%	3.18%	5.15%	**10.20%**
	Diabetic IWAs (n=5)						
	Intact	408.86 ± 150.75	60167.10 ± 48199.65	47110.09 ± 35097.36	5.82 ± 1.26	4.82 ± 1.29	0.80 ± 0.15
	Residual	351.26 ± 181.41	57004.36 ± 57054.68	45708.57 ± 43083.92	5.44 ± 1.17	4.10 ± 0.99	0.90 ± 0.16
	Direction of Asymmetry	Int > Res	Int > Res	Int > Res	Int > Res	Int > Res	Int < Res

	Asymmetry	**15.15%**	5.40%	3.02%	6.78%	**16.13%**	**11.73%**
	Non-diabetic IWAs (n=5)						
	Intact	368.50 ± 56.45	56225.05 ± 21628.47	42763.29 ± 13067.91	5.34 ± 0.67	4.15 ± 0.28	0.58 ± 0.14
	Residual	406.59 ± 78.06	62471.43 ± 22528.35	50787.37 ± 15308.74	5.42 ± 1.11	4.56 ± 0.67	0.61 ± 0.24
	Direction of Asymmetry	Int < Res	Int < Res	Int < Res	Int < Res	Int < Res	Int < Res
	Asymmetry	9.83%	**10.53%**	**17.15%**	1.52%	9.29%	5.81%

Table 4: Between-limb comparisons of BoneJ data for femur geometry. Means with standard deviations of the proximal, middle, and distal femoral shafts. For healthy and diabetic control groups, right and left limbs were compared. For amputees, intact and residual limbs were compared. Wilcoxon-Signed Rank tests were used to assess significance. The significance level was set $\alpha \leq 0.05$. An asterisk (*) indicates a significant difference between limbs. Direction of asymmetry indicates which limb had greater mean values. Asymmetry indicates the amount of asymmetry between limbs where 0% is perfectly symmetrical and 100% is perfectly asymmetrical. Abbreviations: IWAs= individuals with lower-limb amputation, Int= intact limb, Res= residual limb, CSA= cross-sectional area, Imin= minimum moment of inertia, Imax= maximum moment of inertia, Max= maximum, SD=standard deviation, Thick= cortical bone thickness.

At the proximal femur, non-diabetic IWAs had clinically significant cross-sectional area (10.37%), maximum (10.39%), and mean (12.41%) cortical bone thickness asymmetry. At the femoral midshaft, IWAs and diabetic IWAs had clinically significant standard deviation cortical bone thickness asymmetry (16.80% and 28.49%, respectively). At the distal femur, IWAs and non-diabetic IWAs had clinically significant standard deviation cortical bone thickness asymmetry (10.87% and 21.53%, respectively). Further, at the distal femur, diabetic IWAs had clinically significant cross-sectional area (15.15%), mean (16.13%), and standard deviation (11.73%) cortical thickness asymmetry. Additionally, non-diabetic IWAs had clinically significant asymmetry in minimum (10.53%) and maximum (17.15%) moments of inertia.

3.2.2 Between-Group Comparisons

Data are presented in Table 5 and Figure 4. Mann-Whitney post hoc comparisons for significant differences are presented in Table S6. At the proximal femur, residual limbs of IWAs had significantly narrower mean cortical thickness (p=0.027) than diabetic and healthy controls. At the femoral midshaft, residual limbs of diabetic IWAs had significantly narrower maximum (p=0.004) and mean (p=0.017) cortical thickness than diabetic and healthy controls. At the distal femur, residual limbs of non-diabetic IWAs had significantly higher standard deviation cortical thickness (p=0.020) than all groups.

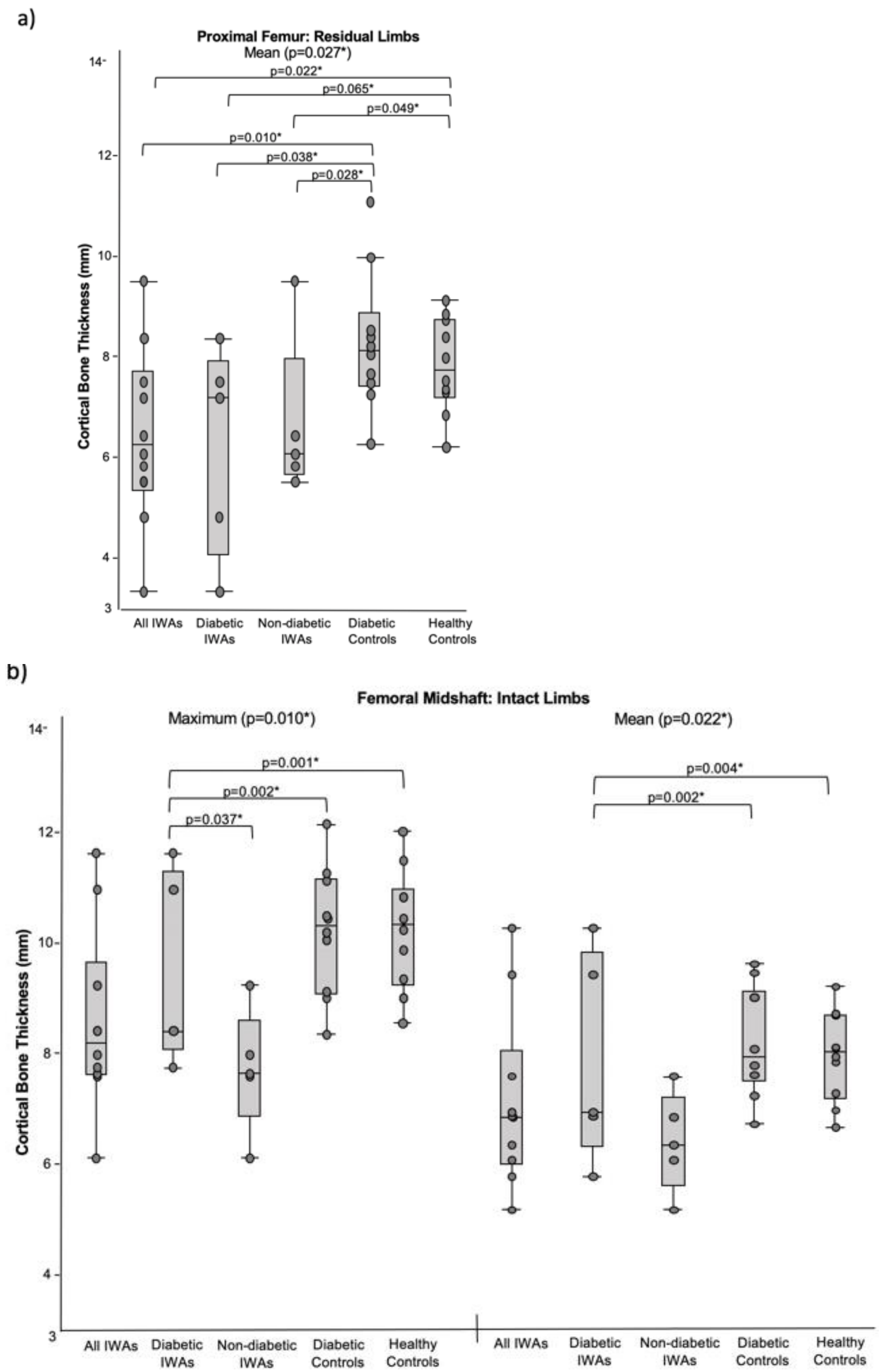

Figure 4: Between-group comparisons with statistical significance for: a) proximal femur geometry, and b) distal femur geometry.

Table 5: Between-Group Comparisons of Femur Geometry

		CSA (mm^2)	Imin (mm^4)	Imax (mm^4)	Max Thick 2d (mm)	Mean Thick 2d (mm)	SD Thick 2d (mm)
Proximal Femoral Shaft 25%	**Healthy Controls (n=10)**						
	Right and Left Averaged	511.13 ± 77.05	42634.23 ± 10630.84	32246.49 ± 8019.83	9.12 ± 1.32	7.79 ± 0.87	0.95 ± 0.28
	Diabetic Controls (n=10)						
	Right and Left Averaged	533.91 ± 102.09	46342.35 ± 15063.89	33122.71 ± 10984.43	10.07 ± 1.87	8.27 ± 1.42	1.30 ± 0.44
	All IWAs (n=10)						
	Intact	511.98 ± 131.01	50951.37 ± 23625.27	39999.50 ± 18084.10	8.68 ± 1.55	7.09 ± 1.32	1.08 ± 0.33
	Residual	476.20 ± 166.53	50354.88 ± 28305.25	37878.45 ± 18401.54	8.09 ± 1.97	**6.44 ± 1.78†‡**	1.09 ± 0.27
	Diabetic IWAs (n=5)						
	Intact	544.52 ± 171.81	55105.06 ± 32701.87	43929.45 ± 25212.90	9.08 ± 1.36	7.54 ± 1.49	0.99 ± 0.22
	Residual	490.86 ± 201.76	52716.32 ± 39078.84	41062.19 ± 25648.81	8.19 ± 1.72	6.66 ± 1.63	1.01 ± 0.15
	Non-diabetic IWAs (n=5)						
	Intact	479.44 ± 80.33	46797.68 ± 11970.79	36069.56 ± 7843.88	8.27 ± 1.77	6.65 ± 1.10	1.18 ± 0.42
	Residual	461.53 ± 145.42	47993.45 ± 16173.26	34694.70 ± 8870.45	7.99 ± 2.40	6.23 ± 2.10	1.17 ± 0.36
Middle Femoral Shaft 50%	**Healthy Controls (n=10)**						
	Right and Left Averaged	498.00 ± 76.67	41050.11 ± 11050.40	29532.64 ± 8442.63	10.34 ± 1.17	8.07 ± 0.80	1.42 ± 0.37

	Diabetic Controls (n=10)						
	Right and Left Averaged	515.69 ± 93.56	42347.76 ± 16456.68	30039.82 ± 10277.51	10.30 ± 1.27	8.33 ± 1.01	1.34 ± 0.38
	All IWAs (n=10)						
	Intact	511.53 ± 154.98	48656.50 ± 30624.77	36209.66 ± 22119.99	8.64 ± 1.66	7.29 ± 1.52	1.13 ± 0.26
	Residual	474.15 ± 169.90	46070.47 ± 32146.77	33372.45 ± 21112.44	9.03 ± 2.53	6.99 ± 1.81	1.33 ± 0.35
	Diabetic IWAs (n=5)						
	Intact	555.07 ± 209.72	55105.68 ± 43469.35	41416.50 ± 30843.46	9.51 ± 1.75	7.98 ± 1.81	1.16 ± 0.20
	Residual	514.22 ± 218.10	54975.60 ± 47994.16	39025.22 ± 31171.98	9.86 ± 2.58	7.36 ± 1.65	1.54 ± 0.37
	Non-diabetic IWAs (n=5)						
	Intact	467.99 ± 72.93	42207.32 ± 10800.85	31002.82 ± 9045.13	**7.78 ± 1.12†‡**	6.60 ± 0.86‡	1.10 ± 0.33
	Residual	442.08 ± 138.43	38946.37 ± 14018.11	28850.23 ± 10255.95	8.37 ± 2.57	6.70 ± 2.06	1.17 ± 0.26
Distal Femoral Shaft 75%	**Healthy Controls (n=10)**						
	Right and Left Averaged	386.34 ± 60.01	49281.80 ± 15605.66	38715.78 ± 11590.06	5.73 ± 0.87	4.68 ± 0.57	0.65 ± 0.16
	Diabetic Controls (n=10)						
	Right and Left Averaged	390.22 ± 51.73	46751.03 ± 15607.36	37882.75 ± 15506.61	6.13 ± 0.85	4.92 ± 0.66	0.69 ± 0.18
	All IWAs (n=10)						
	Intact	390.91 ± 114.06	58415.07 ± 36624.33	45178.18 ± 26176.32	5.61 ± 1.00	4.52 ± 0.99	0.70 ± 0.18

	Residual	374.98 ± 139.14	59347.39 ± 42489.22	47885.19 ± 31837.10	5.43 ± 1.05	4.29 ± 0.84	0.78 ± 0.24
	Diabetic IWAs (n=5)						
	Intact	408.84 ± 150.75	60167.10 ± 48199.65	47110.09 ± 35097.36	5.82 ± 1.26	4.87 ± 1.29	0.80 ± 0.15
	Residual	351.26 ± 181.41	57004.36 ± 57054.68	45708.57 ± 43083.92	5.44 ± 1.17	4.10 ± 1.00	0.90 ± 0.16
	Non-diabetic IWAs (n=5)						
	Intact	368.50 ± 56.45	56225.05 ± 21628.47	42763.29 ± 13067.91	5.34 ± 0.67	4.15 ± 0.28	0.58 ± 0.14
	Residual	406.59 ± 78.06	62471.43 ± 22528.35	50787.37 ± 15308.74	5.42 ± 1.11	4.56 ± 0.67	**0.61 ± 0.24†‡**

Table 5: Between-group comparisons of BoneJ data for femur geometry. Means with standard deviations of the proximal, middle, and distal femoral shafts. For healthy and diabetic control groups, left and right limb values were averaged together. For amputees, intact and compromised limbs were compared separately. Kruskal-Wallis tests with Bonferroni corrections were used to assess significance. The significance level was set $\alpha \leq 0.05$. Bold text indicates p-values less than or equal to 0.05. Asterisks (*) indicate a p-value < 0.01, daggers (†) indicate significant differences compared to healthy controls, and double daggers (‡) indicate significant differences compared to diabetic controls. Abbreviations: IWAs= individuals with lower-limb amputation, CSA= cross-sectional area, Imin= minimum moment of inertia, Imax= maximum moment of inertia, Max= maximum, SD=standard deviation, Thick= cortical bone thickness.

4. Discussion

Obtaining large cohorts of CT scans in living individuals with amputations can be challenging. Using the NMDID to collect musculoskeletal data from deceased individuals with amputations could help inform which properties might be most beneficial to examine in living individuals. To our knowledge, this was the first study to use CT scans to quantify musculoskeletal health in individuals with amputation, compare findings to diabetic and healthy controls, and is of the largest sample sizes to examine musculoskeletal health from an anatomical perspective in individuals with amputation. Findings aligned with other musculoskeletal methodologies, (e.g. MRI, ultrasound) and risk factors in living individuals.[2] Residual limbs of IWAs had higher indications of thigh muscle atrophy and distal femoral fracture risk compared to intact limbs. Compared to control groups, IWAs had higher indications of muscle atrophy and osteoarthritis bilaterally, along with proximal femoral fracture risk on the residual limb. Intact limbs of IWAs had wider femoral necks, indicative of increased femoral loading compared to diabetic and healthy controls. Diabetic IWAs tended to show the most impaired musculoskeletal health. Findings align with previous literature surrounding risk factors of hip and knee osteoarthritis, thigh muscle atrophy, and femoral fracture risk in living individuals with amputation. Future research should examine larger sample sizes of living individuals to determine if findings are generalizable.

4.1 Hip and Knee Osteoarthritis

Individuals who are unilateral lower-limb prosthesis users are more likely to develop hip and knee osteoarthritis on the intact limb, compared to the residual limb and nonamputee (1). Prosthesis users rely on their intact limb, resulting in more biomechanical load, narrow joint space, and accelerated cartilage degeneration (1). IWAs showed narrower hip and knee joint spaces bilaterally compared to controls, in line with prior work on the prevalence of osteoarthritis in the IWAs population compared to the general population (1). However, in contrast with previous work (18-19), neither hip or knee joint space were significant between residual and intact limbs of IWAs. This may be due to our limited sample size. Pain from osteoarthritis can reduce mobility and quality of life (20), and eventually result in total hip or knee replacement. Recommended exercises for IWAs with osteoarthritis include improving core strength, balance, and flexibility to reduce gait deviations (21). Ensuring appropriate prosthetic alignment and gait training, as well as implementing proactive joint screenings, may help reduce risks of osteoarthritis.

4.2 Thigh Muscle Atrophy

Thigh atrophy can hinder prosthetic control (22) and balance (23). IWAs, particularly those with diabetes, showed more thigh muscle atrophy in residual limbs compared to intact limbs. IWAs also showed more thigh muscle atrophy bilaterally compared to diabetic and healthy controls. Findings align with work in living IWAs that used other methodologies (e.g. ultrasound, MRI) (4, 24-25). Elevated blood sugar levels, as seen in type 2 diabetes, may be associated with muscle atrophy (26), which may explain why diabetic IWAs had the most thigh muscle atrophy. No significant differences in fat mass were found in any group, in contrast with previous work (24, 27-28). Thigh muscle strengthening within the first year post-amputation may be a critical window to maintaining muscular health in IWAs (29). Rehabilitation exercises should target thigh muscle strength bilaterally, particularly in diabetic IWAs. Shortening time between amputation to physical therapy and ambulation may also help prevent muscle atrophy.

4.3 Femoral Fractures

Falls and fall-related injuries are prevalent in IWAs, so preventing fall-related fractures are of particular concern in this population (34). In alignment with prior work, intact limbs of IWAs, compared to controls, had wider femoral necks and thinner cortical bone at the proximal femur (30-31). Clinical significance among diabetic and non-diabetic IWAs suggest femoral adaptations may differ according to diabetic status. In nonamputees, proximal and distal femoral diaphysis are most adaptive to changes in biomechanical loading (32). This may also occur in IWAs, as our findings and previous literature have shown thinner cortical bone and increased fracture rates at the proximal and distal femoral diaphysis (31, 33). Proactive skeletal screening, rehabilitation exercises to promote residual limb loading, and earlier ambulation may help maintain skeletal health.

4.4 Control Groups

Significant differences within diabetic and healthy controls may have been driven by leg dominance and outliers. Right or left leg dominance is associated with the corresponding hand dominance of the individual (35). Diabetic controls tended to have larger left-side values on the left limb for gross and cross-sectional data. Healthy controls tended to have larger values on the right limb for all cross-sectional data. These tendencies in leg dominance, combined with outliers, may underlie significant differences between right and left limbs in both control groups.

4.5 Influence of Diabetes

Despite having no statistical significance between diabetic and non-diabetic IWAs, diabetic IWAs showed the most clinical significance in hip and knee joint space as well as muscle tissue area. Diabetic IWAs also had the most impaired musculoskeletal health in several parameters, including knee joint space bilaterally, intact limb femoral neck width, and thinner intact femoral midshaft cortical bone. These trends suggest additive effects of amputation and diabetes on impaired musculoskeletal health, despite a lack of statistical significance. Clinicians should still consider other diabetic complications, such as retinopathy and peripheral neuropathy, which can lead to fall-related fractures (36).

4.6 Limitations and Future Work

A major limitation of this study was the amount of medical history information available from the NMDID. While potential confounding factors of musculoskeletal health were excluded (e.g. cancer, advanced body decomposition), information on prosthesis use was absent. For instance, all of the IWAs had a confirmed amputation surgery, but no record of time since amputation, diabetic onset, prosthesis use, or activity level. Therefore, musculoskeletal findings could not be assessed by these factors. This study included individuals with unilateral and bilateral amputations, as well as transtibial and transfemoral amputations, so findings should not be applied to one subset of amputation level.

Several properties on two individuals could not be measured, since the limb was outside the frame of the CT scan, detailed in Supplemental Table 1. Similarly, several femoral properties could not be measured in individuals with transfemoral amputation. Further, while time between death and CT scan typically ranged between 10 and 30 days, two of the control individuals were scanned over 100 days after death. While this time delay could theoretically have influenced findings, outliers were not observed in these individuals.

The authors located, to the best of our knowledge, all available scans of IWAs in the database for this study. Future work can differentiate quadriceps and hamstring atrophy, include a larger sample size to assess the generalizability of our findings as individuals are added to the database, or compare our results to CT scans of living individuals. Additionally, application of findings are limited to males. Future work could examine effects of aging or include females, particularly to examine additive effects of osteoporosis risk due to hormonal changes during menopause.

5. Conclusion

This study is currently among the largest sample sizes of musculoskeletal health in this population, and is the first to use CT scans of deceased individuals. While musculoskeletal health has been assessed in prior literature, few studies have collected anatomical properties underlying musculoskeletal health risks prevalent in this population. Findings aligned with previously reported health risks in living individuals. Residual limbs of IWAs had higher indications of muscle atrophy and fracture risk at the distal femur compared to intact limbs. IWAs, compared to control groups, had higher indications of muscle atrophy and osteoarthritis bilaterally, as well as higher indications of fracture risk at the proximal femur on the residual limb. Proactive musculoskeletal screenings, targeted rehabilitation exercises, shortening time from amputation to ambulation, and ensuring optimal prosthetic fit and alignment could help clinicians reduce these risks. Musculoskeletal adaptations from amputation and diabetes tended to show an additive effect, but were not statistically significant. Larger sample sizes and living individuals should be included in future work to assess generalizability of findings.

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Chapter 6 Linkage

Chapter 6 concludes the musculoskeletal section in this dissertation. This section quantified musculoskeletal symmetry in deceased individuals with amputation and discussed how findings could be used to evaluate injury risks posed by femoral fractures, hip and knee osteoarthritis, and muscle atrophy. The next section quantifies biomechanical symmetry in living individuals who use unilateral lower-limb prostheses and discusses how findings could be used to evaluate fall risk.

SECTION 3: BIOMECHANICAL SYMMETRY

CHAPTER 7

ARE INERTIAL MEASUREMENT UNITS A VIABLE OPTION FOR INDIVIDUALS WHO USE UNILATERAL LOWER-LIMB PROSTHESES?

CHAPTER 8

PRELIMINARY DATA: RELATIONSHIP BETWEEN RETROSPECTIVE FALLS WITH CLINICAL OUTCOME MEASURES AND WALKING SYMMETRY IN INDIVIDUALS WHO USE LOWER-LIMB PROSTHESES

CHAPTER 7

ARE INERTIAL MEASUREMENT UNITS A VIABLE OPTION FOR INDIVIDUALS WHO USE UNILATERAL LOWER-LIMB PROSTHESES?

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Abstract

Introduction: Inertial measurement units (IMUs) may be viable options to collect gait data in clinics. This study compared IMU to motion capture data in individuals who use unilateral lower-limb prostheses.

Methods: Participants walked with lower-body IMUs and reflective markers in a motion analysis space. Sagittal plane hip, knee, and ankle waveforms were extracted for the entire gait cycle. Discrete points of peak flexion, peak extension, and range of motion were extracted from the waveforms. Stance times were also extracted to assess the IMU software's accuracy at detecting gait events. IMU and motion capture-derived data were compared using absolute differences and root mean square error (RMSE).

Results: Five individuals (n=3 transtibial; n=2 transfemoral) participated. IMU prosthetic limb data was similar to motion capture (RMSE: waveform ≤5.65°; discrete point ≤9.62°; stance ≤0.10s). However, one transfemoral participant had larger differences at the microprocessor knee joint (RMSE: waveform ≤13.28°; discrete ≤30.55°) from IMU magnetometer interference. Intact limbs tended to have minimal differences between IMU and motion capture data (RMSE: waveform ≤9.15°; discrete ≤9.90°; stance ≤0.03s).

Conclusion: Findings suggest IMUs can collect data similar to motion capture systems in sagittal plane kinematics and stance time in this population.

Key words: amputee, validation, kinematic, prosthesis, biomechanics

Introduction

Motion capture equipment is considered the gold standard for collecting gait data, but is impractical to use in clinical practice for several reasons: high costs, lack of portability, and the need for specialized personnel.[1] Clinicians, such as prosthetists and physical therapists, evaluate prosthetic alignment and gait deviations using visual observation. Therefore, the patient's quality of rehabilitation can be subject to factors such as clinician experience, time allotted for the appointment, and patient fatigue. Existing low-cost and portable wearable sensors called inertial measurement units (IMUs) could provide an objective method for practical real-time clinical measurements of gait that could inform rehabilitation recommendations.[2] However, IMUs must first be compared to motion capture equipment to determine their validity in prosthetic limbs.

Numerous studies have validated IMUs against motion capture systems in healthy individuals.[3] Several studies have also validated IMUs against motion capture systems in individuals with various lower-limb pathologies, such as stroke,[4] Parkinson's Disease,[5] and knee osteoarthritis.[6] In individuals with unilateral lower-limb loss, recent studies have used IMUs to measure symmetry and repeatability,[7,8] coronal plane kinematics,[9] pose estimation,[10] sensory feedback,[11] spatiotemporal parameters (e.g. stance time),[12] walking speed in daily life,[13] and compare IMU algorithms to detect gait events.[14–17] However, no previous literature has directly compared IMU-derived data to motion capture in individuals who use lower-limb prostheses, aside from a 2014 case study in a transfemoral user that found IMU-derived knee and ankle flexion data was within 4 degrees of motion capture data.[18] Comparison of IMU-derived data to motion capture in this population can provide supporting evidence for use in prosthetic practice, provide comparisons for future IMU-derived data to motion capture data from previous studies, and ensure prosthetic componentry does not interfere with IMU data collection.

Lower-limb kinematic (e.g. joint angle) and stance time data have been associated with adverse clinical events, such as falls, in individuals who use lower-limb prostheses.[19] However, these gait parameters rely on force plates or motion capture gait event detection to calculate,[20] which makes data collection in clinics infeasible. Commercially available IMUs have the ability to detect gait events, yet no research has directly compared these data to motion capture. The ability to measure lower-limb sagittal plane kinematics and stance time of prosthesis users in clinical practice could aid prosthetists and physical therapists with decisions regarding prosthetic alignment, targeted rehabilitation exercises, and potentially insurance justification.

Therefore, IMU-derived kinematic and temporal data were compared to motion capture in individuals who use unilateral lower-limb prostheses. Based on a recent meta-analysis in healthy controls,[3] we hypothesized IMU data on prosthetic limb, compared to motion capture, would show: 1) full gait cycle waveform root mean square errors at the hip, knee, and ankle $\leq 5.0°$, 2) peak parameters at the hip, knee, and ankle $\leq 15.0°$, and 3) stance durations ≤ 0.02 seconds (s). Findings could support the use of IMUs in clinical practice to collect lower-limb sagittal plane kinematics and stance time in this population.

Methods

Participants:

This study was approved under the North Texas Regional Institutional Review Board (#2020-048). Individuals who use unilateral transtibial or transfemoral prostheses were recruited from prosthetic clinics in the Dallas-Fort Worth metroplex to complete a single visit at the University of North Texas Health Science Center. Individuals were included if they were: between the ages of 18 and 95 years, walking with a prosthesis for at least one year, and able to walk independently for at least five minutes or 100 yards. Individuals were excluded if they had: pain, open wounds or discomfort on their lower limbs or trunk on the day of testing, limb loss or deficiency on other limbs, major musculoskeletal injury or surgery in the last year besides amputation or revision, or other comorbidities that would make standing, turning, or walking unsafe. All participants provided written informed consent to voluntarily participate, and permission to use images.

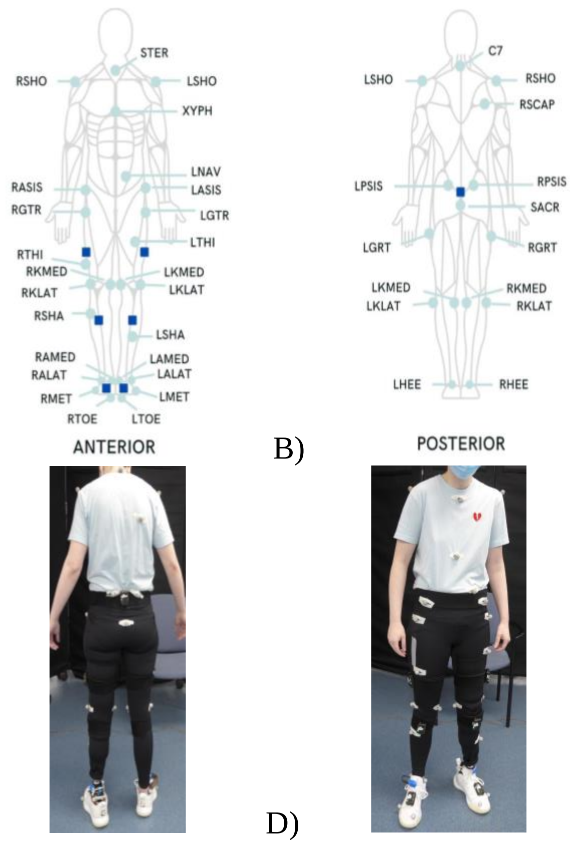
Equipment:

Seven IMU sensors (iSen, STT Systems, San Sebastian, Spain) were used in this study to collect and store lower-body IMU data within iSen software. Each IMU (46g) had a tri-axial accelerometer (±16g), gyroscope (±2000°/s), and magnetometer (±13G) with company-reported pitch/roll accuracy within 0.5° and heading accuracy within 2.0°. A 14-camera motion capture system (Cortex, Motion Analysis Corp, Santa Rosa, CA) was used to collect and store data from 32 reflective markers using a modified full-body Helen-Hayes marker set. All data was collected at a sampling rate of 100Hz.

Data Collection:

Demographic data were collected and managed using Research Electronic Data Capture (REDCap) software hosted at the University of North Texas Health Science Center.[21–23]

Participants also completed the following clinical outcome measures: Socket Comfort Score (SCS), Prosthetic Limb Users Survey of Mobility 12-Item Short Form (PLUS-M), and Amputee Mobility Predictor with Prosthesis (AMPPRO). Researchers placed IMUs and reflective markers on participants as shown in Figure 1.



A) B) C) D)

Figure 1: Equipment placement. Panels A and B depict the location of reflective markers (mint green circles) and IMUs (dark blue squares) on from anterior and posterior views. Panels C and D depict locations of reflective markers and IMUs on a participant. Abbreviations: STER= sternum; RSHO= right shoulder; LSHO= left shoulder; XYPH= xyphoid, LNAV= left offset navel; RASIS= right anterior superior iliac spine; LASIS= left anterior superior iliac spine; RGTR= right greater trochanter; LGTR= left greater trochanter; RTHI= right thigh; LTHI= left thigh; RKMED= right knee medial; LKMED= left knee medial; RKLAT= right knee lateral; LKLAT= left knee lateral; RSHA= right shank; LSHA= left shank; RAMED= right ankle medial; LAMED= left ankle

medial; RALAT= right ankle lateral; LALAT= left ankle lateral; RMET= right base of fifth metatarsal; LMET= left base of fifth metatarsal; RTOE= right toe; LTOE= left toe; C7= seventh cervical vertebrae; RSCAP= right scapula; RPSIS= right posterior superior iliac spine; LPSIS= left posterior superior iliac spine; SACR= sacrum; RHEE= right heel; LHEEL= left heel.

IMUs were secured to each participant as recommended by STT Systems for the lower-body model: one on the sacrum, one on each thigh, one on each shank, and one on each foot. IMUs were secured to body segments with elastic straps provided by STT Systems, excluding foot IMUs, which were secured directly to the dorsal aspect of the shoe with velcro. Additionally, for transfemoral prosthetic limbs, the thigh IMU was secured directly to the prosthesis using self-adherent wrap (Coban 1580 Series, 3M™, Saint Paul, MN) to prevent slippage. IMUs and reflective markers on the prosthetic limb were matched to the placement of the intact limb. Participants walked across 6 meters of level ground at their self-selected habitual walking speed for five trials.

<u>Data analysis:</u>

Figure 2 depicts the process used for data analysis. IMU data was processed to calculate joint angles and gait event detection within proprietary iSen software provided by STT Systems and exported to MATLAB for analysis. Motion capture data was processed using a custom MATLAB code based on Cortex definitions to derive joint angle data [Supplemental Document 1], with means and standard deviations in Supplemental Table 1. IMU and motion capture data were time-aligned and vertically aligned. Time alignment was necessary to ensure IMU and motion capture data were aligned at each point, since IMU and motion capture equipment were started at different times. Vertical alignment was necessary to minimize the effects of magnitude shifts, since IMUs can be subject to drift and were calibrated to 0 degrees at the start of each walking trial. For example, if the knees were slightly flexed 2 degrees during calibration, then the IMU calibration considered the 2 degrees of flexion as 0 degrees. While this error was minimized as much as possible by manually inspecting the participant at calibration, this is a limitation of utilizing IMUs with this type of calibration. Alignments were manually confirmed by MGF.

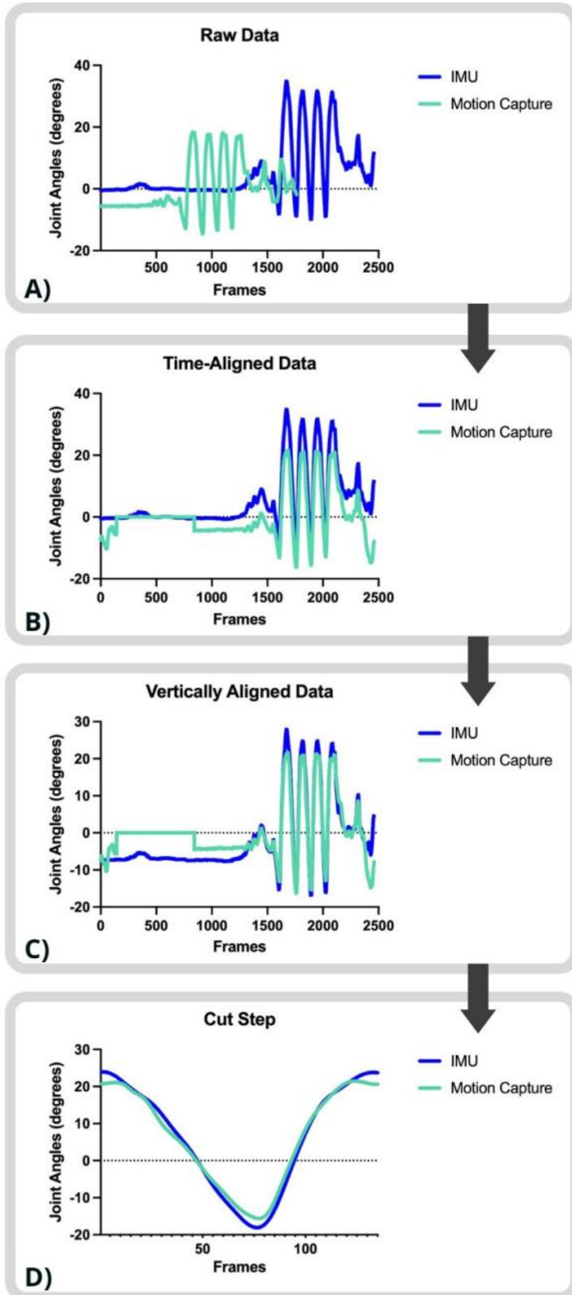


Figure 2: Data processing. The flow of IMU (dark blue) and motion capture (mint green) data processing. The left hip sagittal plane joint angles from a walking trial of a representative participant was used as an example. Data was exported to MATLAB (Panel A), time-aligned (Panel B), and vertically aligned (Panel C). Then, the middle step was extracted using initial contact gait events (Panel D). All data was processed using a custom MATLAB code and confirmed by visual inspection.

Three of the participant's five walking trials were selected for analysis. Typically, the first three trials were selected due to the last two trials showing evidence of IMU slippage distally on the thigh segment. Once three walking trials were selected, the middle step of each limb from each trial was extracted to minimize effects from the participant accelerating or decelerating, and to minimize IMU drift or distal slippage that tended to occur towards the end of the walking trial.

The step, for both IMU and motion capture-derived data, was defined as occurring between two initial contact events. For IMU-derived data, the step was extracted based on the automatic detection of gait events identified within iSen IMU software. Additionally, toe-off events were needed to calculate single and double limb support times, which were also automatically detected within iSen IMU software. For motion capture-derived data, the step was extracted based on the maximum distance between the sacrum marker and heel marker for each limb, and toe-off events to calculate single and double limb support times were extracted using the minimum distance between the toe marker for each limb and the sacrum marker.[24] MGF visually confirmed all gait events and cut steps were appropriate.

Lower-limb sagittal plane kinematic and stance time parameters were extracted from each cut step. Lower-limb sagittal plane waveforms at the hip, knee, and ankle, as well as peak flexion and extension values were extracted across the entire gait cycle. Range of motion was calculated from peak flexion and extension values. Stance time parameters included single and double limb support times for both prosthetic and intact limbs. These parameters were extracted from the middle step of three walking trials, then averaged. IMU and motion capture-derived data were then compared by calculating absolute differences in seconds and degrees. Additionally, root mean square error

(RMSE) across the entire waveform and at discrete points of peak flexion and extension at the hip, knee, and ankle during the entire gait cycle were also calculated. Throughout this manuscript, error and RMSE are defined as the difference between the IMU and motion capture data.

Results

Five individuals who use unilateral lower-limb prostheses (n=3 transtibial users; n=2 transfemoral users) participated in this study. Demographic characteristics are reported in Table 1. K-levels were determined based on normative AMP-PRO scores and prosthetic componentry. Absolute differences and group (transtibial and transfemoral) RMSE of discrete points between IMU and motion capture-derived data are reported for each participant in Table 2. Average RMSE values between IMU and motion capture-derived waveform data are reported for each participant in Table 3. Joint angle waveforms are depicted with RMSE values across the entire gait cycle for transtibial users in Fig 3 and transfemoral users in Figure 4.

Table 1: Participant Demographics

Participant	1	2	3	4	5
Age (yrs)	62.42	34.83	62.08	38.75	37.08
Height (cm)	185.42	172.72	182.88	167.64	167.64
Weight (kg)	141.52	56.70	72.12	89.58	54.43
Sex	M	F	M	M	F
TSA (yrs)	12.0	2.5	6.0	37.0	7.0
Etiology	Trauma	Trauma	Vascular	Congenital	Cancer
Res Limb Length (cm)	18.00	21.00	18.60	17.78	20.32
Level of Prosthesis	TT	TT	TT	TF	TF
K-Level	K3	K3	K2	K3	K3
Walking Speed (m/s)	0.64	0.63	0.65	0.77	1.06
SCS (out of 10)	7	8	9	9	7
PLUS-M	54	56	50	49	51

12-Item T-score					
AMPPRO	40	42	41	41	42
Time Using Prosthesis (years)	9.0	3.0	5.5	1.0	3.0
Components and Shoes	Ossur Proflex foot; vacuum suspension with a total of 8 ply socks; Merrell tennis shoes	Fillauer AllPro Sport foot; suction suspension with 2 ply socks and sleeve; Adidas tennis shoes	Kinterra K2 foot; suction suspension with 1 ply sock; Bicanno tennis shoes	Ossur Powered Knee with Ossur Cheetah Xplore foot; Iceross 5-ring suction suspension with 0 sock ply; Brooks tennis shoes	Ottobock C-leg 4 knee; Fillauer AllPro foot; magnetic system with vaccuum suspension; Brooks tennis shoes

Table 1: Participant demographics. Abbreviations: M= male; F= female; TSA- time since amputation; TT= transtibial; TF= transfemoral; SCS= Socket Comfort Score; PLUS-M= Prosthetic Limb Users Survey of Mobility; AMPPRO= Amputee Mobility Predictor; TUG= Timed Up and Go. Manufacturers: Liner manufacturer: Iceross (Ossur, Reykjavik, Iceland). Knee manufacturers: Powered Knee (Ossur, Reykjavik, Iceland); C-leg (Ottobock, Duderstadt, Germany); Foot manufacturers: Foot manufacturers: Kinterra (Freedom Innovations, CA, USA); Cheetah Xplore, ProFlex (Ossur, Reykjavik, Iceland); AllPro (Fillauer, Sollentuna, Sweden).

Table 2: Discrete Point Absolute Differences and RMSE

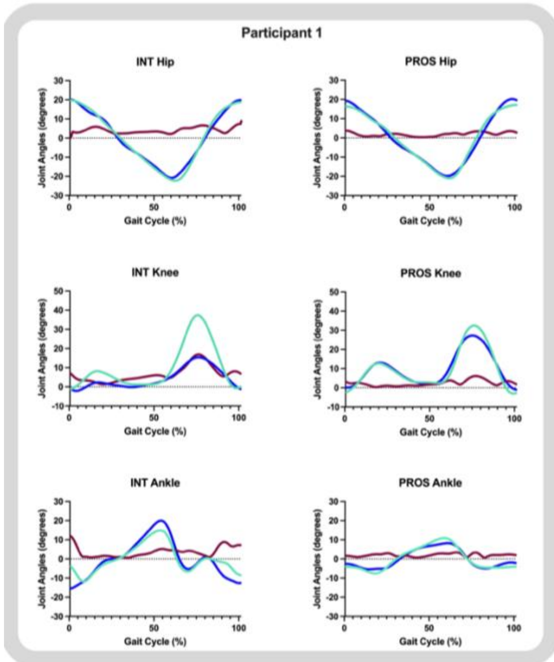
		Transtibial				Transfemoral		
		Participant 1	Participant 2	Participant 3	RMSE	Participant 4	Participant 5	RMSE
	Double Limb Support (s)	0.02	0.02	0.02	0.08	0.01	0.01	0.03
Intact Limb	Single Limb Support (s)	0.07	0.01	0.02	0.03	0.02	0.01	0.02
	Peak Hip Flex (∘)	0.56	1.20	2.39	2.23	9.47	0.87	0.97
	Peak Hip Ext (∘)	1.43	1.39	2.22	2.04	10.27	1.02	1.17
	Overall Hip ROM (∘)	0.87	0.20	4.61	4.14	19.76	1.89	1.93
	Peak Knee Flex (∘)	22.47	3.60	3.76	4.07	7.69	0.78	1.00
	Peak Knee Ext (∘)	0.97	6.59	0.80	4.56	1.19	0.94	1.02
	Overall Knee ROM (∘)	21.02	10.17	7.59	8.52	8.88	0.17	0.72
	Peak Ankle DF (∘)	5.06	0.63	2.53	2.63	0.27	2.05	2.39
	Peak Ankle PF (∘)	3.57	0.99	1.54	5.08	5.52	7.26	7.64
	Overall Ankle ROM (∘)	8.63	0.36	0.99	3.13	5.79	9.31	9.90
Prosthetic Limb	Single Limb Support (s)	0.04	0.01	0.02	0.04	0.02	0.02	0.10
	Peak Hip Flex (∘)	3.04	3.79	0.17	0.71	3.58	6.30	6.07
	Peak Hip Ext (∘)	1.15	4.47	3.40	3.68	8.16	1.93	3.43
	Overall Hip ROM (∘)	1.88	8.27	3.57	3.86	11.74	4.38	2.72
	Peak Knee Flex (∘)	5.25	0.68	7.37	7.57	9.76	1.79	2.76
	Peak Knee Ext (∘)	2.00	0.92	0.69	2.09	6.13	29.86	30.55
	Overall Knee ROM (∘)	7.25	0.23	9.38	9.62	15.90	28.07	28.08
	Peak Ankle DF (∘)	2.69	4.70	1.39	1.55	0.37	1.65	2.60
	Peak Ankle PF (∘)	2.21	6.69	2.50	2.78	0.57	0.97	3.19
	Overall Ankle ROM (∘)	4.89	0.23	3.88	4.27	0.21	5.26	5.70

Table 2: Absolute differences in seconds (s) and degrees (∘) for each participant. Root mean square error (RMSE) in seconds (s) and degrees (∘) for each group (transtibial and transfemoral). All values are an average of three walking trials. Abbreviations: Max= maximum, DF= dorsiflexion; PF= plantarflexion; ROM= range of motion, Flex= flexion, Ext= extension.

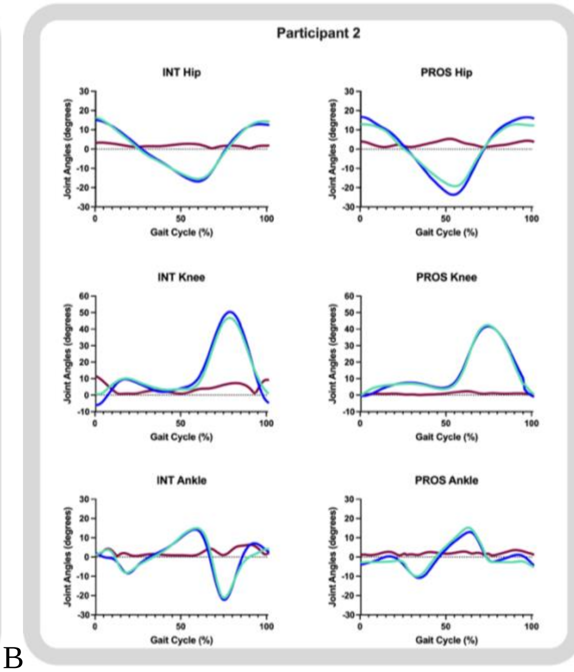
Table 3: Waveform Average RMSE Values

			Transtibial			Transfemoral	
			Participant 1	Participant 2	Participant 3	Participant 4	Participant 5
RMSE	Intact Limb	Hip (∘)	3.59	1.81	1.56	9.15	1.76
		Knee (∘)	5.85	0.95	2.45	7.81	1.85
		Ankle (∘)	3.17	2.33	2.62	2.35	3.49
	Prosthetic Limb	Hip (∘)	1.66	2.69	2.80	4.72	4.18
		Knee (∘)	2.02	4.95	3.19	5.65	13.28
		Ankle (∘)	1.83	1.96	1.24	0.98	1.67

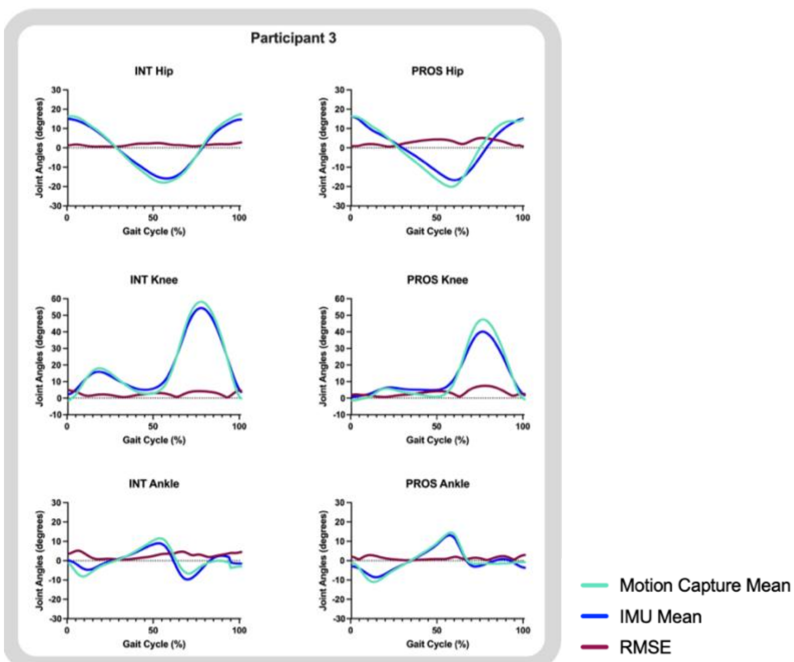
Table 3: Average root mean square error (RMSE) values in degrees (∘) for each participant over the entire gait cycle.



A)

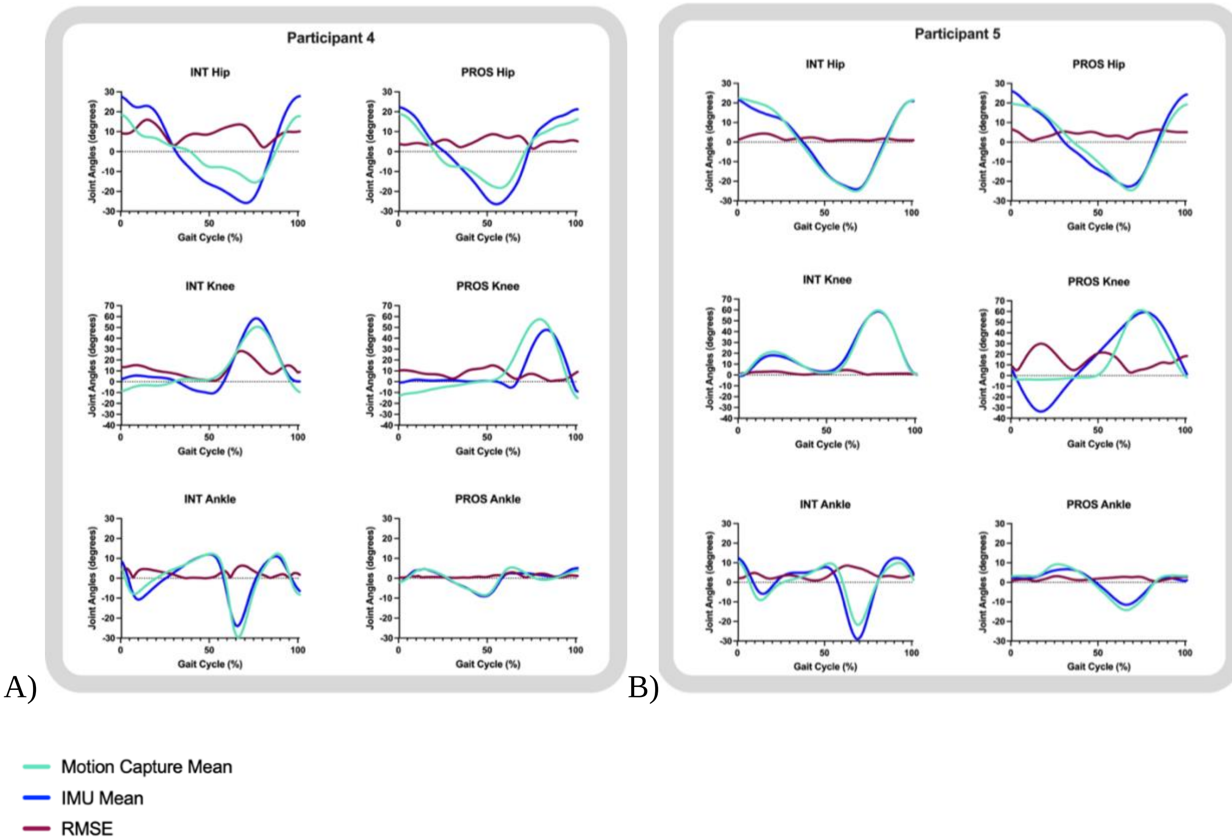


B



C)

Figure 3: Transtibial participant waveform data. Normalized to 100% of the gait cycle for each participant that used a transtibial prosthesis. Abbreviations: INT= intact limb; PROS= prosthetic limb; RMSE= root mean square error.



A) B)

Figure 4: Transfemoral participant waveform data. Normalized to 100% of the gait cycle for both participants that used a transfemoral prosthesis. Abbreviations: INT= intact limb; PROS= prosthetic limb; RMSE= root mean square error.

Transtibial Participants

Prosthetic limbs

Waveforms of prosthetic limbs in transtibial participants had RMSEs of ≤ 4.95° (Table 3) at hip, knee, and ankle joints. All three transtibial participants showed the highest prosthetic limb error at the knee joint (RMSEs 2.02°, 4.95°, and 3.19°, respectively), as opposed to hip or ankle joints (Table 3), driven by differences in maximum knee flexion values (Table 2, Figure 3). Double limb support times had RMSEs of ≤ 0.08s. For prosthetic limb support time, Participant 1 had a larger absolute difference (0.04s) than Participants 2 and 3 (0.01s, and 0.02s, respectively) (Table 2).

Intact limbs

Intact limbs tended to have higher error values than prosthetic limbs. With the exception of Participant 1's knee waveform (RMSEs ≤ 5.85°), intact limbs had RMSEs ≤ 2.45° (Table 3, Figure 3). All three transtibial participants showed the highest intact limb RMSEs at the knee joint, as opposed to hip or ankle joints. These were driven by differences in maximum knee flexion values for Participants 1 and 3, and maximum knee extension values for Participant 2 (Table 2, Figure 3). Participant 1 had a larger absolute difference in intact limb support time (0.07s) than Participants 2 and 3 (0.01s and 0.02s, respectively) (Table 2).

Transfemoral Participants

Prosthetic limbs

For both transfemoral participants, hip, knee, and ankle waveform RMSEs were all ≤ 9.15° (Table 3, Figure 4). However, Participant 5's prosthetic knee joint had higher error values of RMSE ≤ 13.28°, driven by differences in maximum knee extension values (Table 2, Figure 4). These higher prosthetic knee joint RMSEs in Participant 5 were caused by magnetometer interference, detailed in the discussion. Double limb support times had RMSEs of ≤ 0.03s and prosthetic limb support times had RMSEs of ≤ 0.10s (Table 2).

Intact limbs

Intact limbs tended to have higher error values than prosthetic limbs, particularly at the ankle joint (RMSEs ≤ 3.49°) (Table 3, Figure 4). Higher RMSE in ankle range of motion were driven by maximum ankle plantarflexion values (Table 2, Figure 4). Intact limb support times had RMSEs of ≤ 0.02s (Table 2).

Discussion

To our knowledge, this was the first study to directly compare gait data between IMUs and motion capture systems in unilateral lower-limb prosthesis users. IMUs provided similar prosthetic limb data compared to motion capture, with the exception of the microprocessor prosthetic knee joint in one transfemoral user due to magnetometer interference. Additionally, prosthetic limb RMSE tended to be less than intact limb RMSE and previous control data, which could be explained by: 1) differences in how the IMUs were secured to each limb (prosthetic with direct velcro and self-adherent wrap; intact with elastic straps), or 2) intact limb skin and muscle motion that does not occur on the prosthesis. Potentially for similar reasons, lower-limb kinematic IMU data was more similar to motion capture in the stance phase than the swing phase. Participant 1 had higher intact limb RMSE than the other two transtibial users, which may have been due to more IMU slippage and anatomical motion due to larger weight. Participant 4, a transfemoral user, had higher hip RMSE bilaterally compared to all other participants, which may have been due to increased compensatory motions from using a prosthesis from an age of two years old (as noted by the greatest time since amputation in Table 1). Overall, findings from this case series indicate IMUs could collect lower-limb sagittal plane kinematic and stance time data to inform rehabilitation. However, data across participants tended to vary widely, so comparisons across participants should be made with caution. Future studies should include a larger sample size to determine if findings are generalizable to a larger population of unilateral lower-limb prosthesis users. The portability of IMUs could allow researchers to include participants that have been underrepresented in gait literature (e.g. diabetes, older in age, less active) to better reflect the overall population of lower-limb prosthesis users.[20,25]

Prosthetic Limbs Compared to Previous Control Data

Prosthetic limbs had similar or less RMSE than healthy control participants in previous studies. A clinical threshold of 5 degrees (°) of error has been used for motion capture systems and recently applied to IMUs.[26,27] Recent meta-analysis[3] found multi-sensor waveform RMSEs in healthy controls at the hip (2.7 - 6.3°),[28–31] knee (0.7 - 4.6°),[28–30,32,33] and ankle (4.0 - 7.8°).[28–30,33] Compared to these values, prosthetic limbs in this study showed similar or lower RMSEs in transtibial participants at the hip (1.66 - 2.80°), knee (2.02 - 4.95°), and ankle (1.24 - 1.96°), and transfemoral participants at the hip (4.18 - 4.72°), and ankle (0.98° - 1.67°). However, transfemoral participant RMSEs at the prosthetic knee tended to be higher than previous control data (5.65° - 13.28°). Discrete points of peak flexion and extension RMSE in control limbs at each joint have ranged 2.7 - 15°.[34,35] Prosthetic limbs in this case series had similar or lower RMSEs of 1.55 – 9.38°, with the exception of the transfemoral prosthetic knee joint (≤ 30.55°) of Participant 5 due to magnetometer interference with the microprocessor knee. In the same meta-analysis, IMU single limb support times were 0.02s.[28,36–38] These values aligned with prosthetic limb support times in this case series of all participants (0.01s - 0.02s) except Participant 1 (0.07s), potentially due to increased IMU slippage and motion in the anatomical limb discussed later.

Prosthetic Limbs Compared to Intact Limbs

Control limb data mentioned above was similar to intact limb data in this case series. Therefore, prosthetic limbs also had similar or less RMSE than intact limbs, which may have been influenced by how the IMUs were secured to each limb. IMUs on the intact limb were typically secured using STT systems' recommended method of elastic straps, which allowed more slippage distally and movement between the IMU and individual's body segment. However, IMUs on the prosthetic limb were typically secured directly to the prosthesis with velcro and then wrapped tightly in self-adherent wrap to prevent slippage. Additionally, anatomical limbs produce skin and muscle motions that do not occur on the prosthesis. These findings are supported by a 2014 case study of a single transfemoral user that suggested the participant's intact limb RMSE was nearly four times higher than prosthetic limb RMSE due to skin and muscle motions.[18]

Transtibial Participant Comparisons

Participant 1 had the most conically shaped thigh of all participants, so increased IMU slippage down the thigh and anatomical motion could explain why they had higher RMSE values, particularly at the intact knee joint, than the other two transtibial participants. Of the three transtibial participants, Participant 2 was the youngest and had the highest mobility based on their PLUM-12 score, potentially explaining why they had the least RMSE at all joints. Participant 3 was the only participant that used a K2 level foot, which is classified by Medicare as typical for the limited community ambulator.[39] This difference in foot componentry may explain why Participant 3 had higher prosthetic limb RMSE at the knee and hip. They may have employed proximal compensation strategies to ensure prosthetic foot clearance, as well as intact limb compensations due to the reduced range of motion available in the prosthetic foot.

Transemoral Participant Comparisons

The only study that has previously compared lower-limb sagittal plane kinematics between IMUs and motion capture was a 2014 case study that reported knee and ankle RMSEs in one transfemoral prosthesis user.[18] Compared to knee error in the 2014 case study (RMSEs: prosthetic ≤ 1.0°; intact ≤ 4.0°), participants in this case series had higher prosthetic knee error (RMSE ≤ 13.28°) and intact knee error (RMSE ≤ 7.81°). Additionally, compared to ankle error in the 2014 case study (RMSE ≤ 2.0° at the prosthetic and intact ankle), transfemoral participants in this case series had similar prosthetic ankle error (RMSEs ≤ 1.67°) but higher intact ankle error (RMSEs ≤ 3.47°). These differences between the 2014 case study and this case series may have been due to differences in IMU systems. Differences may have also been due to prosthetic foot componentry, as the prosthetic knee was the same as Participant 5, and the 2014 case study did not list the participant's prosthetic foot.

Participant 4 had larger differences between IMU and motion capture data during hip range of motion compared to all other participants, potentially due to proximal compensatory strategies from congenital prosthesis use. Further, Participant 5 had a large RMSE at the prosthetic knee joint due to a technical issue with the IMU magnetometer. The IMU magnetometers were disabled in Participants 4 and 5 to avoid interference with the microprocessor knees. Upon data analysis, MGF found the prosthetic knee data still looked as if the magnetometers were enabled, so data files were sent to the IMU company, iSen, for inspection. iSen staff concluded there still appeared to be magnetic interference, but could not explain why, since the display showed the magnetometers were disabled. After troubleshooting, our research group at the University of North Texas Health Science Center found the disabling of the magnetometers only took effect if data collection was initiated with the magnetometers disabled. Participant 4 was able to come in for retesting, while Participant 5 could not be retested due to time constraints. Thus, Participant 4's data was collected with the magnetometers actually disabled, while Participant 5's data was collected while the system incorrectly showed the magnetometers were disabled.

Limitations and Future Work

For clinical use, while the user interface was generally intuitive, experience with biomechanics data was still required in order to process and interpret IMU data. A second limitation is that motion capture data was collected using a marker set and modeling technique that makes inherent assumptions regarding body segments that do not typically hold true for prostheses (e.g. body segment lengths remain constant during movement). [40,41] However, differences between IMU and motion capture-derived data were present on both intact and prosthetic limbs, and RMSEs were typically higher in intact limbs compared to prosthetic limbs. This suggests both intact limb and prosthetic limb data was similarly represented, regardless of the motion capture marker set and modeling techniques used in this case series.

Future studies should include more participants to determine if our findings are generalizable to a larger sample of unilateral and bilateral lower-limb prosthesis users. Future work could also determine if IMU RMSEs are influenced by: the method in which they are secured to body segments (e.g. elastic strap compared to direct velcro), motion capture marker modeling techniques, or IMU company. These future directions could help inform a recommended clinical data collection protocol.

Conclusions

Findings from this case series suggest IMUs are capable of providing lower-limb kinematic and stance time data comparable to motion capture systems. Prosthetic limbs tended to have less error than intact limbs or previous control limb data, potentially due to increased movement of the IMUs on anatomical limbs. We suspect for similar reasons, IMU-derived lower-limb kinematic data tended to be more similar to motion capture-derived data in stance than swing. However, error varied across participants, suggesting comparisons within individuals may be more accurate. Future studies should include larger sample sizes to assess generalizability of findings in this case series. Clinicians and researchers could eventually use IMUs to collect gait data that better reflects real-world conditions in prosthesis users to help inform rehabilitation.

Declarations

Conflicting interests: The authors declare that they have no conflicting interests.

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Guarantor: MGF

Contributorship: Conceptualization: SCM, RMP; Data Curation: MGF; Formal Analysis: MGF; Funding Acquisition: MGF, SCM; Investigation: MGF; Methodology: SCM, RMP; Project Administration: MGF: Software: MGF, SCM; Supervision: SCM, RMP; Resources: RMP; Visualization: MGF; Writing- Original Draft Preparation: MGF; Writing- Review and Editing: SCM, RMP.

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Chapter 7 Linkage

Chapter 7 indicated the inertial measurement unit-derived data was similar to motion capture equipment in the parameters we intended to measure in Chapter 8 (stance time, sagittal plane kinematics at the ankle, knee, and hip). Thus, Chapter 7 provided evidence supporting our inertial measurement units could be used to carry out the study presented in Chapter 8. Chapter 8 will determine if inertial measurement units could supplement clinical outcome measures to evaluate fall risk. While the majority of data from Chapter 8 has been processed, we are awaiting 6-month prospective fall data from participants. Therefore, Chapter 8 presents preliminary results from the retrospective fall data.

CHAPTER 8

PRELIMINARY DATA: RELATIONSHIP BETWEEN RETROSPECTIVE FALLS WITH CLINICAL OUTCOME MEASURES AND WALKING SYMMETRY IN INDIVIDUALS WHO USE LOWER-LIMB PROSTHESES

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Abstract

Background: Despite technological advancements in healthcare, preventable overuse injuries, falls, and related detrimental secondary health effects remain treated post-occurrence rather than proactively identified and prevented. Among individuals who use unilateral lower-limb prostheses, falls have been associated with decreased walking symmetry between prosthetic and intact limbs. However, the relationship between falls and walking symmetry has not been directly determined. This study sought to determine if walking symmetry could distinguish non-fallers from fallers.

Methods: At the time of this dissertation, twenty-two participants who use a unilateral transtibial or transfemoral prosthesis were asked if they had fallen over the past year, completed clinical outcome measures (e.g. Timed Up and Go), and walked over level ground at their self-selected habitual walking speed with wearable sensors that collected kinematic and kinetic data. Walking symmetry between prosthetic and intact limbs was calculated overall and for peak ranges of motion at the hip, knee, and ankle, as well as peak ground reaction force during braking and propulsion. After the study visit, participants also reported number of falls every two weeks for a total of 6 months, but this data is still being acquired. Mann-Whitney U tests were used to assess statistical significance between retrospective non-fallers and fallers, and this analysis will be repeated with the prospective data.

Results: The Four Square Step Test was the only parameters that distinguished retrospective non-fallers and fallers ($p = 0.040$).

Conclusion: Findings can help determine which clinical outcome measure scores or gait asymmetry parameters, if any, could be clinically useful indicators to screen for fall risk in this population.

Introduction

Falls are prevalent in individuals who use unilateral lower-limb prostheses. Community-dwelling adults 18+ years of age with lower-limb amputation have similar or higher fall risks compared to older adults 65+ years of age without amputation.[1,2] Further, over 58% of individuals who use unilateral lower-limb prostheses fall per year, and up to 39% report multiple falls.[3–5] Falls in this population have been associated with injury,[2,3,5–7] decreased mobility,[8,9] and decreased quality of life.[10] Despite this knowledge, this population is still not effectively screened for fall risk,[11,12] and falls continue to be one of the most common concerns in this population.[13,14]

The relationship between falls and gait symmetry has not been directly determined. Studies have examined the relationship between fall occurrence and: clinical assessment scores,[15,16] muscle strength,[17] overuse injuries,[18] and quality of life.[10] Studies have also examined the relationship between gait symmetry and: clinical assessment scores,[19] muscle strength,[20] overuse injuries,[21] and quality of life.[22] Studies frequently state an association between falls and gait symmetry, however, none have directly examined this relationship. Directly examining this relationship is crucial in determining if gait symmetry could be a useful indicator of fall risk in clinical practice.

Recent studies in the general population of older adults have suggested walking symmetry could be used to predict fall risk,[23,25] but no practical equipment exists to measure walking symmetry in clinical practice. Kinematic (e.g. stance time, range of motion) and kinetic (e.g. ground reaction force) walking data is collected in research settings using motion capture and force plate equipment, respectively. This equipment is impractical to use in clinic for several reasons: high costs, lack of portability, and the need for specialized personnel.[26] Wearable sensors, such as inertial measurement units (IMUs) and pressure insoles, can provide objective values for real-time clinical measurements of kinematic and kinetic walking symmetry to predict fall risk. The portability of wearable sensors allows for data collection in large sample sizes, and does not require specific expertise to use or obtain valid and reliable data. Both IMU-derived kinematic data (see Chapter 7 of this dissertation) and pressure insole-derived kinetic data have been validated to measure walking symmetry in individuals who use unilateral lower-limb prostheses.[27]

Individuals who are stroke survivors and individuals who use unilateral lower-limb prostheses both have gait asymmetries due to unilateral limb differences. Therefore, gait asymmetries associated with fall risk in stroke survivors might be comparable to gait asymmetries in individuals who use unilateral lower-limb prostheses. In individuals with stroke, kinematic asymmetries in stance time and ankle range of motion in the sagittal plane, as well as kinetic asymmetries of peak propulsion force during walking, have recently been associated with increased fall risks.[28]

However, no literature has determined the relationship between kinematic parameters and fall risk in individuals who use unilateral prostheses. Our previous literature review of lists several kinetic parameters have been associated with fall risk in older adults who use unilateral prostheses,[29] but this has not been tested using wearable technology or in individuals who are not older adults. Further, most falls in the general population and individuals who use lower-limb prostheses occur due to tripping or slipping during level-ground walking.[30] Thus, since many falls occur during weight transfer between limbs, asymmetries between intact and prosthetic limbs in joint range of motion or peak ground reaction force during level-ground walking may be clinically useful indicators of fall risk.

Therefore, this study aims to determine if wearable sensor-derived walking asymmetry data can supplement clinical outcome measures to evaluate fall risk in individuals who use unilateral transtibial or transfemoral prostheses. We hypothesized sagittal plane gait asymmetry data can significantly distinguish non-fallers from fallers in this population, particularly in stance time, ankle range of motion, and peak propulsion based on literature in the stroke population. For clinical outcome measures and gait parameters that can significantly distinguish non-fallers and fallers, we will also determine cutoff scores that can be used in clinical practice.

Methods

Participants:

This study was approved under North Texas Regional Institutional Review Board (#2020-048). Individuals who used unilateral transtibial or transfemoral prostheses were recruited from prosthetic clinics in the Dallas-Fort Worth metroplex and the Amputee Coalition National Assembly. Individuals were included if they were: between the ages of 18 and 95 years, walking with a prosthesis for at least one year, and able to walk independently for at least five minutes or 100 yards. Individuals were excluded if they had: pain, open wounds or discomfort on their lower-limbs or trunk on the day of testing, limb loss or deficiency on other limbs, major musculoskeletal injury or surgery in the last year besides amputation or revision, or other comorbidities that would make standing, turning, or walking unsafe.

Equipment:

Seven IMU sensors (iSen, STT Systems, San Sebastian, Spain) were used in this study to collect and store lower-body IMU data within iSen software. Each IMU (46g) had a tri-axial accelerometer (±16g), gyroscope (±2000°/s), and magnetometer (±13G) with company-reported pitch/roll accuracy within 0.5° and heading accuracy within 2.0°. Pressure insoles (Loadsol, Novel, USA) were also used to collect ground reaction force data. Each insole contained three pressure sensors on the medial, lateral, and heel aspects of the foot. All data was collected at a sampling rate of 100Hz.

Data Collection:

Research Electronic Data Capture (REDCap) software hosted at the University of North Texas Health Science Center was used to collect and manage demographic data and scores on clinical outcome measures.[31-33] After demographic data was collected, the following self-report clinical outcome were completed:

1. Socket Comfort Score (SCS): One question that assesses an individual's socket comfort on a scale of 0 to 10, where higher scores indicate the greatest level of comfort.[34]
2. Patient Reported Outcomes Measurement Information System (PROMIS-29): Twenty-nine questions that measure an individual's quality of life with their prosthesis, where higher scores indicate greater quality of life.[35]
3. Prosthetic Limb Users Survey of Mobility (PLUS-M) 12-Item Short Form: 12 questions determine functional mobility, where higher scores indicate greater functional mobility.[36]
4. Activities-Specific Balance Confidence Scale (ABC): 16 questions assess balance confidence, where higher scores indicate greater balance confidence.[37]

Additionally, the following functional clinical outcome measures were completed:

2. Timed Up and Go (TUG) test: This test requires standing up from a chair, walking 3 meters in a straight line, turning around, and sitting back down in the same chair. This test is performed 3 times and averaged.[38]
3. Amputee Mobility Predictor with Prosthesis (AMPPRO): This requires participants to complete a 21-item list that involves static and dynamic activities while sitting, standing, transferring, and walking.[39]
4. Four Square Step Test (FSST): This requires participants to step forwards, backwards, and sideways over four canes arranged in a 'plus' sign (creating four squares). The test is performed 2 times and the faster time is used as the final score.[40]

AMPPRO scores, were used to determine participant K-levels, which were confirmed by prosthetic componentry. Retrospective fall and near-fall histories over the previous 12 months were also collected. Falls and near-falls were defined according to a 2022 study, which conducted a focus group to determine definitions meaningful to this population.[41] Falls were defined as "a loss of balance where your body landed on the ground or floor," and near-falls were defined as "a loss of balance where you caught yourself or recovered without landing on the ground or floor." Participants were asked if they had experienced a fall in the previous twelve months, and if so, how many they had experienced. Additionally, they were then asked to recall the fall they remembered best, and answered several additional questions outlined in the survey detailed in the 2022 study previously mentioned. For instance, questions asked whether or not the participant was wearing their prosthesis when they fell or nearly fell, if they experienced an injury, and the significance of the fall or near-fall. These questions were then repeated for near-falls. Then, researchers placed IMUs and pressure insoles on each participant as shown in Figure 1.

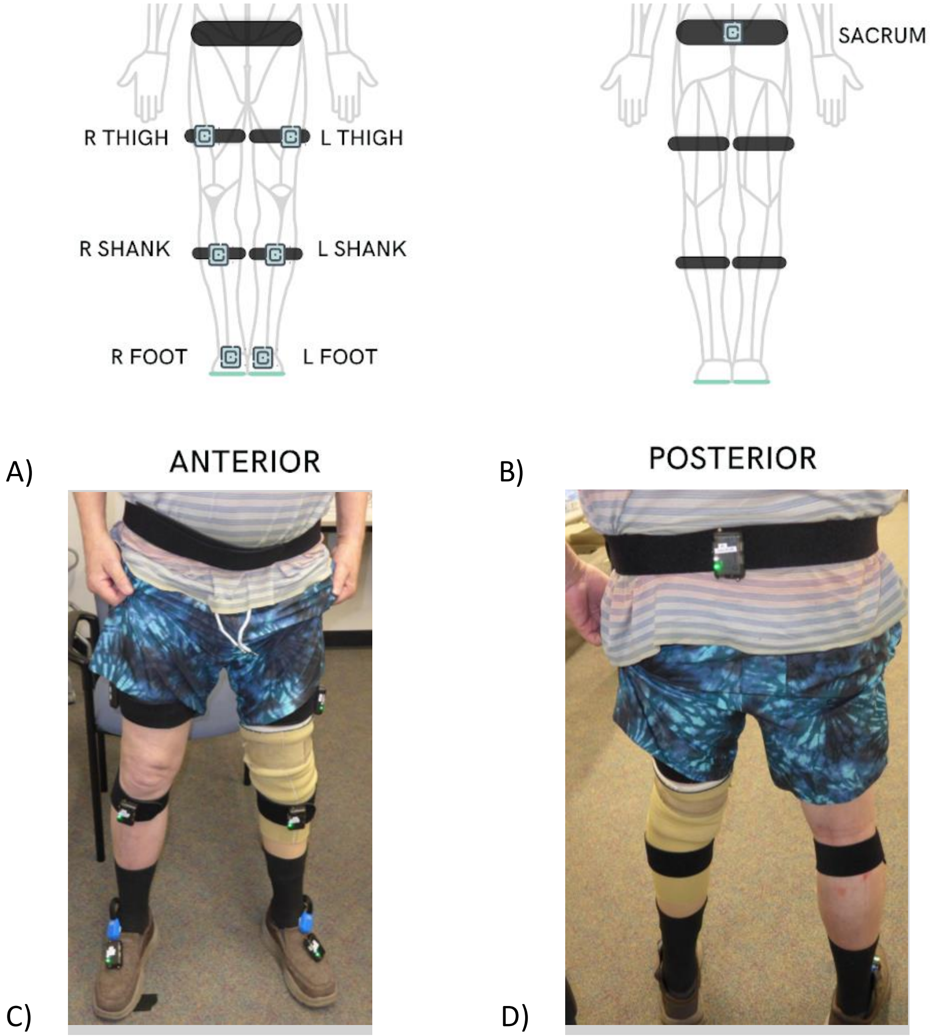

Figure 1: Anterior (panels A and C) and posterior (panels B and D) views of IMU and pressure insole equipment placed on a representative participant who uses a transtibial prosthesis.

IMUs were secured to each participant using recommendations from STT Systems for the lower-body model: one on the sacrum, one on each thigh, one on each shank, and one on each foot. IMUs were secured to body segments with elastic straps provided by STT Systems, except the IMUs on each foot, which were secured directly to the shoe with velcro. Additionally, the thigh IMU on transfemoral prosthetic limbs was secured directly to the prosthesis using self-adherent wrap (Coban 1580 Series, 3M™, Saint Paul, MN) to prevent sliding. For transfemoral participants, the IMU magnetometers were disabled during data collection to prevent magnetic interference from the microprocessor knees. Each participant was assessed by MGF for the proper size of pressure insoles, which were in standard US sizes. Pressure insoles were less than 3.4mm thick, worn bilaterally, and placed between the participant's foot and their shoe. Participants walked across 6 meters of level ground at their self-selected habitual walking speed for five trials.

After the data collection visit, participants were emailed a survey through REDCap every 2 weeks for a period of 6 months. The number of falls and near-falls over the 6-month period will be totaled to provide prospective fall and near-fall data for each participant. Since the majority of participants had their research visit in August 2022, we expect to have the majority of prospective fall and near-fall data by February 2023.

Data analysis:

IMU data was processed within proprietary iSen software provided by STT Systems, and ground reaction force data was processed within proprietary Loadsol software.

Three of the participant's five walking trials were selected for analysis, and the middle step of each limb from each trial was extracted. The middle step, for both IMU and pressure insole data, was defined as occurring between two initial contact events. For IMU-derived data, the middle step was extracted based on the automatic detection of gait events identified within iSen IMU software. Toe-off events were also needed to calculate single and double limb support times, which were also automatically detected within iSen IMU software. For Loadsol data, the middle step was extracted based on evidence of the first non-zero point (initial contact) and last non-zero point (toe-off).[26] Loadsol and IMU events were compared by MGF and were consistently within 2-3 frames (0.02- 0.03s) of each other. Once three walking trials were selected, the middle step of each limb from each trial was extracted to minimize effects from the participant accelerating or decelerating, and to minimize IMU drift or distal slippage that tended to occur towards the end of the walking trial. MGF visually confirmed all gait events and cut steps were appropriate.

Stance time and lower-limb sagittal plane kinematic parameters were extracted from each middle step of IMU data. Lower-limb sagittal plane waveforms at the hip, knee, and ankle, as well as peak flexion and extension values were extracted across the entire gait cycle. Range of motion was calculated from peak flexion and extension values. Stance time parameters included single and double limb support times for both prosthetic and intact limbs. For pressure insole data, ground reaction force parameters of peak braking and peak propulsive force were extracted from each cut step. Symmetry between intact and prosthetic limbs were calculated for all parameters using the equation below, and averaged across the three cut steps to provide final symmetry values. These parameters were extracted from the middle step of three walking trials, and the equation below was used to calculate symmetry between intact (I) and prosthetic (P) limbs.[42,43] The symmetry values from the three trials were averaged.

Eq. 1 $$abs\left(\frac{(I-P)}{(0.5*(I+P))} * 100\right)$$

For both retrospective and prospective fall data analysis, we intend to stratify participants into two groups, non-fallers and fallers. Shapiro-Wilks tests will be used to determine normality of the data. Assuming our data is non-parametric, significance between groups will be assessed using Mann-

Whitney U tests with a significance level set at $p \leq 0.05$ and Hedge's g will be used to determine effect sizes. Then, for each clinical outcome measure and gait parameter that is significant between non-fallers and fallers, cut-off scores will be determined using area under the curve and receiver operating characteristic (AUC/ROC) analysis. Spearman correlations will also be used to assess relationships between number of falls with clinical outcome scores and gait asymmetry. Once the authors have the prospective fall data for all participants, these tests will be repeated for prospective non-fallers and fallers.

Results

Preliminary demographic data are listed in Table 1, clinical outcome measure data are listed in Table 2, and gait data are listed in Table 3.

Table 1: Preliminary demographic characteristics stratified by fall status.

Demographics	**Non-Fallers (n=12)**	**Fallers (n=10)**	***p*-values**
Age (yrs)	57.5 ± 15.0	56.8 ± 13.8	0.461
Height (cm)	175.9 ± 8.8	173.0 ± 10.2	0.286
Weight (kg)	90.0 ± 25.4	92.1 ± 21.6	0.461
Sex	7 M / 5 F	8 M / 2 F	0.144
TSA (yrs)	19.0 ± 17.9	14.0 ± 14.3	0.265
Etiology	6 Tr / 2 Vasc / 3 Can / 1 Cong	4 Tr / 3 Vasc / 2 Can / 1 Cong	0.403
Residual Limb length (cm)	18.2 ± 4.0	17.3 ± 5.0	0.322
Level of Prosthesis Use	8 TT / 4 TF	7 TT / 3 TF	0.435
K-Level	9 K3 / 3 K2	8 K3 / 2 K2	0.497
Time using current prosthesis (yrs)	4.0 ± 2.6	3.3 ± 2.6	0.251
Last prosthetic adjustment (months)	3.1 ± 3.6	1.0 ± 0.5	0.185
# Retrospective Falls	0.0 ± 0.0	3.6 ± 4.2	**0.012***
# Retrospective Near-Falls	2.2 ± 1.1	8.2 ± 15.8	0.249

Table 1: Preliminary mean ± standard deviation data for the 22 participants that have been collected, stratified by retrospective non-fallers and fallers. K-levels were determined based on AMPPRO scores and prosthetic componentry. Abbreviations: TSA= time since amputation, M= male, F= female, Tr= trauma, Vasc= vascular, Can= cancer, Cong= congenital, TT= transtibial, TF= transfemoral.

Table 1 indicates non-fallers and fallers had similar demographic characteristics. However, while not significant, potentially notable differences in mean values between groups are: higher proportion of females in non-fallers (n=5) compared to fallers (n=2), longer time since last prosthetic adjustment in non-fallers (3.1 months) than fallers (1.0 month), and lower number of self-reported near-falls in non-fallers (2.2) compared to fallers (8.2).

Table 2: Preliminary clinical outcome measure data stratified by fall status.

Clinical Outcomes	**Non-Fallers (n=12)**	**Fallers (n=10)**	***p*-values**
SCS	8.7 ± 1.1	7.9 ± 2.3	0.268
PROMIS- Physical T-score	47.5 ± 6.7	45.0 ± 5.7	0.160
PROMIS- Anxiety T-score	44.8 ± 5.9	44.7 ± 5.9	0.470
PROMIS- Depression T-score	43.5 ± 4.6	43.6 ± 5.9	0.411
PROMIS- Fatigue T-score	46.8 ± 6.5	47.0 ± 8.1	0.286
PROMIS- Sleep T-score	45.4 ± 8.3	46.4 ± 7.3	0.371
PROMIS- Social T-score	55.0 ± 7.6	55.0 ± 6.3	0.500
PROMIS- Pain Interference T-score	47.8 ± 6.9	47.8 ± 7.0	0.472
PROMIS- Global Pain	1.6 ± 1.2	3.1 ± 2.5	0.089
ABC	8.4 ± 2.2	8.8 ± 0.6	0.234
PLUS-M 12 T-score	52.6 ± 4.6	50.2 ± 8.1	0.334
AMPPRO	41.3 ± 2.3	40.4 ± 3.2	0.303
TUG (s)	9.7 ± 1.8	11.1 ± 3.0	0.090
FSST (s)	12.7 ± 5.4	14.8 ± 3.4	**0.040***

Table 2: Preliminary mean ± standard deviation data for the 22 participants that have been collected, stratified by retrospective non-fallers and fallers. Bold *p*-value with asterisk (*) indicates significance. Abbreviations: SCS= Socket Comfort Score, PROMIS= Patient Reported Outcomes Measurement Information System, ABC= Activities Specific Balance Confidence Scale, PLUS-M= Prosthetic Limb Users Survey of Mobility, AMPPRO= Amputee Mobility Predictor with Prosthesis, TUG= Timed Up and Go, FSST= Four Square Step Test.

Table 2 indicates the FSST was the only clinical outcome measure that was statistically significant between non-fallers and fallers, with faster times in non-fallers (12.7s) compared to fallers (14.8s). While not statistically significant, non-fallers reported less pain in the PROMIS-Global Pain scale (1.6) than fallers (3.1). Additionally, non-fallers had faster TUG times (9.7s) compared to fallers (11.1s).

Table 3: Preliminary gait data stratified by fall status.

Gait Parameters	**Non-Fallers (n=12)**	**Fallers (n=10)**	***p*-values**
Walking Speed (m/s)	0.6 ± 0.23	0.5 ± 0.14	0.138
SLS Asymmetry (%)	67.6 ± 41.1	68.4 ± 42.4	0.487
Hip Flexion Asymmetry (%)	47.40 ± 41.32	46.47 ± 37.53	0.461
Hip Ext. Asymmetry (%)	67.57 ± 45.16	56.99 ± 28.31	0.387
Hip Overall Asymmetry (%)	47.38 ± 41.49	39.17 ± 21.98	0.461
Knee Flexion Asymmetry (%)	47.34 ± 40.07	47.14 ± 29.07	0.269
Knee Ext. Asymmetry (%)	81.74 ± 38.51	89.35 ± 47.56	0.436
Knee Overall Asymmetry (%)	43.17 ± 34.78	33.46 ± 24.46	0.337
Ankle Dorsi. Asymmetry (%)	48.13 ± 45.59	71.74 ± 45.43	0.079
Ankle Plantar. Asymmetry (%)	65.21 ± 42.60	73.79 ± 38.55	0.291
Ankle Overall Asymmetry (%)	45.72 ± 42.89	56.69 ± 38.91	0.209
Peak Braking Asymmetry (%)	44.04 ± 38.21	45.04 ± 51.37	0.286
Peak Propulsive Asymmetry (%)	35.33 ± 41.49	24.57 ± 17.44	0.517

Table 3: Preliminary mean ± standard deviation data for the 22 participants that have been collected, stratified by retrospective non-fallers and fallers. Abbreviations: SLS= Single Limb Support, Ext.= extension, Dorsi.= dorsiflexion, Plantar.= plantarflexion.

No significant differences in gait parameters were observed. While not statistically significant, non-fallers seemed to have notably less ankle dorsiflexion asymmetry (48.13%) than fallers (71.74%).

Discussion

Two recent studies have shown that three clinical outcome measures (TUG, FSST, AMPPRO) have strong relationships with retrospective falls in transtibial and transfemoral prosthesis users.[11,12] While only the FSST was statistically significant in this study, the PROMIS-Global Pain and TUG had the next lowest p-values (0.089 and 0.09, respectively). The FSST and TUG times in this study (up to 14.8s and 11.1s in fallers, respectively) were slower than the prior studies, which determined cutoff scores for the FSST and TUG of 8.49s and 8.47s, respectively. This may be due to the inclusion of individuals with older age, K2 level ambulation, and dysvascular etiologies in this study. Additionally, this study included 22 participants to date, while the two previous studies included 38 and 40 participants. Our power analysis indicated we should include 38 participants to detect statistical significance between non-fallers and fallers, so our study might be underpowered due to a lower sample size of 22 participants.

Non-fallers reported a longer time since last prosthetic adjustment, lower number of near-falls, more socket comfort, and less global pain than fallers. Collectively, this may indicate non-fallers experienced increased stability and comfort with their prosthesis than non-fallers. Additionally, participants in this study tended to show more gait asymmetry in stance time, as well as hip, knee, and ankle range of motion, compared to values from previous studies summarized in Chapter 2 (please note this study reports asymmetry values while Chapter 2 reports symmetry values). As mentioned previously, this study included a greater number of older individuals, K2 participants, and individuals with vascular etiologies than reported in previous literature, which might explain these differences. From Chapter 3 (Table 1), we expected peak braking ground reaction force would be able to distinguish non-fallers from fallers. However, this study showed similar values between non-fallers and fallers.

We also intend to measure prospective fall risk in this population, which has rarely been reported. Instead, retrospective fall history is typically collected, despite flaws of participant recall and the adjustment of gait to increase stability if the participant has experienced a fall.[23] However, only one study, published earlier this year, has examined the relationship between these clinical assessments and number of prospective falls.[24] Based on this study, we expect a combination of number of retrospective falls combined with PLUS-M scores will be able to distinguish prospective non-fallers and fallers. We also expect gait asymmetry parameters, particularly ankle range of motion based on research in the stroke population, will be able to distinguish prospective non-fallers from fallers. Examining the relationship between prospective falls with clinical assessments and walking symmetry could help identify strong clinical predictors of falls.

Conclusion

Preliminary results indicate the FSST time was the only clinical characteristic that could distinguish retrospective non-fallers from fallers. Upon the inclusion of more participants, analysis of all retrospective fall data, and acquisition of prospective fall data, we will determine if any additional clinical outcome measures or gait parameters can significantly distinguish retrospective non-fallers and fallers. Additionally, we will perform the same analysis to determine if any factors can distinguish prospective non-fallers from fallers. Findings can help clinicians proactively evaluate fall risk in this population.

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Author contributions: Conceptualization: MGF, CLM, SCM; Data Curation: MGF; Formal Analysis: MGF; Funding Acquisition: MGF, RMP, SCM; Investigation: MGF; Methodology: MGF, CLM, SCM; Project Administration: MGF, RMP, SCM: Software: MGF, SCM; Supervision: SCM; Visualization: MGF; Writing- Original Draft Preparation: MGF; Writing-Review and Editing: CLM, RMP, SCM.

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SUMMARY

Individuals who use lower-limb prostheses have increased risks of developing overuse injuries and experiencing falls. These risks have been attributed to decreased musculoskeletal and biomechanical symmetry between prosthetic and intact limbs, but this relationship not been directly examined. This dissertation sought to quantify musculoskeletal and biomechanical symmetry to determine their relationships to overuse injuries and falls in individuals with unilateral lower-limb loss or absence. Quantifying musculoskeletal and biomechanical symmetry could help clinicians move towards proactive monitoring of overuse injury and fall risk assessment in this population.

Findings:

<u>Literature Reviews:</u> Chapters 1-3 helped inform decisions for Aims 1 and 2. Chapter 1 summarized the limited amount of research that has investigated musculoskeletal health in individuals with lower-limb amputations, and directed our focus towards bone mineral density, muscle fiber types, and use of CT scans to collect data in Aim 1. Chapter 2 helped inform decisions to validated our inertial measurement units against motion capture in Chapter 7 and summarized results that served as normative values for symmetry in Chapter 8 of Aim 2. Chapter 3 determined which clinical outcome measures would be selected to evaluate fall risk and highlighted the need to collect both retrospective and prospective falls in Chapter 8.

<u>Aim 1:</u> Aim 1 sought to evaluate musculoskeletal symmetry in anatomical donors associated with risk of developing overuse injuries. Chapters 4 and 5 demonstrated amputated limbs in anatomical donors had indications of increased risks of lower-limb fracture, hip and knee osteoarthritis, and

muscle atrophy compared to intact limbs. These findings were supported by Chapter 6 using CT Scans from the New Mexico Decedent Image Database. Specifically, Chapter 6 found amputated limbs had increased indications of thigh muscle atrophy and distal femoral fracture compared to intact limbs. Further, Chapter 6 demonstrated increased indications of thigh muscle atrophy and osteoarthritis bilaterally compared to diabetic and healthy control limbs. Clinicians could eventually use quantified symmetry values from non-invasive patient scans (e.g., dual x-ray absorptiometry, CT, x-ray) to help inform risks of overuse injuries in this population.

Aim 2: Aim 2 sought to determine the relationship between wearable sensor-derived walking symmetry values and fall risk in living individuals. In Chapter 7, inertial measurement units were validated against the gold standard of motion capture in five individuals who used a unilateral transtibial or transfemoral prosthesis. Then, they were used in Chapter 8, along with pressure insoles, to determine if gait symmetry could supplement clinical outcome measures to evaluate fall risk. At the time of this dissertation, two more participants are scheduled for the study in Chapter 8, but data has not been collected. Clinical outcomes and gait parameters that significantly distinguished retrospective fallers and non-fallers over the previous year are still being analyzed. Prosthetists or physical therapists could use cutoff scores for self-repot or functional clinical outcomes, or gait parameters from wearable sensors, to assess 6-month prospective fall risk.

Overall: Impaired musculoskeletal symmetry observed in anatomical donors was in line with the high prevalence of femoral fractures, hip and knee osteoarthritis, and thigh muscle atrophy in this population. Specifically, thigh muscle atrophy in the biceps femoris long head seen in Chapter 5 is congruent with previous literature regarding asymmetries in hip extension in living individuals.

Preliminary results from Chapter 8 support also partially support this, with large asymmetry values in peak hip extension (mean of 67.57 in non-fallers and 56.99 in fallers) and overall hip range of motion (47.38 in non-fallers and 39.17 in fallers). Chapter 8 showed larger kinematic asymmetry values than reported in previous literature (symmetry values summarized in Chapter 2), which may be due to the inclusion of more participants who are K2 and/or older in age than in previous literature. Inertial measurement units were found to be a viable data collection tool to quantify gait, and clinicians may be able to use these, in combination with pressure insoles, to evaluate fall risk in this population. Future research could, within the same study, collect musculoskeletal symmetry and gait symmetry in larger samples of living individuals to further establish the relationship between musculoskeletal and gait health.

Future Directions:

Aim 1: Researchers could expand Aim 1 by increasing the sample size of donors or examining living individuals to determine if findings are generalizable. Additionally, researchers could lower the donor/database age criteria to differentiate age-related musculoskeletal changes, or examine females to determine potential contributions of menopause on impaired musculoskeletal health post-amputation. A larger sample size that includes a wider age range and females could help inform specific treatment plans for musculoskeletal monitoring and rehabilitation exercises by age, sex, comorbidities, or amputation level.

Aim 2: Prospective fall data is still being gathered and will help inform fall risk prediction. Researchers could also determine if data collected from a single inertial measurement unit (i.e. pelvis) was sensitive enough to distinguish fallers from non-fallers, which could further reduce the cost and labor for clinicians to implement fall risk evaluation. Future studies could determine if findings are generalizable to: a larger subset of the population by recruiting a more heterogeneous sample of lower-limb prosthesis users, or other wearable systems by evaluating inertial measurement units and pressure insoles from different companies.

Overall: Researchers could directly examine relationships between musculoskeletal and biomechanical symmetry by having participants complete a series of musculoskeletal evaluations (e.g. bone density scan, CT scan, wearable electromyography sensors), in addition to the clinical outcome measures and biomechanical gait evaluations reported in Chapter 8 within the same study. This dissertation was completed during the COVID-19 pandemic, which made a cross-disciplinary study difficult to accomplish. Determining relationships between musculoskeletal and biomechanical symmetry could potentially help clinicians evaluate musculoskeletal health based on gait symmetry or vice versa.

Final Thoughts:

While this dissertation examined musculoskeletal and biomechanical symmetry, these are only two potential factors that could influence risks of developing overuse injuries and experiencing falls. Clinicians and researchers should consider how other factors (e.g. fall self-efficacy, visual or vestibular impairments, living environment, medication use, motor control impairments resulting from neural damage, etc.) could influence risks of developing overuse injuries and experiencing falls, in addition to the musculoskeletal and biomechanical factors presented in this dissertation. Ensuring individuals are considered from a variety of perspectives helps inform a broader view of strategies to reduce adverse health outcomes in this population.

APPENDIX

APPENDIX A

IRB APPROVAL LETTER

3500 Camp Bowie Blvd
Fort Worth, TX 76107
NorthTexRegIRB@unthsc.edu
(817) 735-0409

DATE:	November 12, 2021
TO:	Rita Patterson, PhD
FROM:	North Texas Regional Institutional Review Board
PROJECT TITLE:	[1603361-4] Use of Wearable Inertial Sensors to Measure Walking Symmetry in Individuals with Lower Limb Pathologies
REFERENCE #:	2020-048
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	November 12, 2021
REVIEW TYPE:	Expedited Review

Thank you for your submission of Amendment/Modification materials for this project. The North Texas Regional Institutional Review Board has APPROVED the protocol modifications via Expedited review procedures under the provisions of 45 CFR 46.110(b)(1)(ii).This submission received Expedited review and approval based on applicable federal regulations.

The following modifications have been approved with this submission:

- Compensation for participants with lower limb loss
- Updated language to the study documents to provide flexibility in recruiting the three groups
- Updated protocol synopsis to reflect current key personnel
- Minor modifications to survey instruments to indclude addtional questions about falls for limb loss participants

The following items have been approved with your submission:

- Protocol Synopsis
- Recruitment materials (i.e. flyers and electronic annoucements for all 3 groups)
- Consent forms

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

You may ONLY use documents that have been IRB-approved and display IRB approval verification (print-stamping).

Please note that any revision to previously approved materials must be approved by the IRB prior to initiation. Please use the appropriate revision procedures for this activity.

All UNANTICIPATED PROBLEMS involving risks to subjects or others (UPIRSOs) and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office. Please use the appropriate reporting forms for this procedure. All FDA and sponsor reporting requirements should also be followed.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office within 10 business days of identifying the issue / complaint.

In addition, the Principal Investigator must notify the IRB immediately if any new potential Conflict of Interest arises.

Any research / key personnel involved in the study are also responsible for maintaining appropriate human subject protection educational training current.

If you have any questions, please contact Jessica Bird at 817-735-2081 or jessica.bird@unthsc.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within North Texas Regional Institutional Review Board's records.

APPENDIX B

QUESTIONNAIRES

Inclusion Exclusion Criteria Form

Date of Visit ________________________________

Inclusion Criteria

Is the participant an adult between the ages of 18 and 95?

◯ Yes ◯ No

Has the participant been walking on a prosthesis for at least one year?

◯ Yes ◯ No

Does the participant have unilateral limb loss between their ankle and hip?

◯ Yes ◯ No

Is the participant able to walk independently for at least 5 minutes or 100 yards?

◯ Yes ◯ No

Exclusion Criteria

Does the participant have bilateral lower-limb loss?

◯ Yes ◯ No

Does the participant have arm or foot amputations?

◯ Yes ◯ No

Does the participant currently have pain, open wounds, or discomfort in their lower-limbs or trunk?

◯ Yes ◯ No

Has the participant had major musculoskeletal injury or surgery in the last year besides amputation or revision?

◯ Yes ◯ No

Does the participant have visual deficits not corrected by eye glasses or contact lenses?

◯ Yes ◯ No

Does the participant have medical or health issues that would make walking, turning while walking, sitting/standing up from a chair without armrests difficult or unsafe?

◯ Yes ◯ No

Does the participant have cognitive impairments preventing ability to follow instructions?

◯ Yes ◯ No

Participant cannot understand the English language to give informed consent or follow instructions? (select no if participant can understand English)

◯ Yes ◯ No

Patient is ELIGIBLE for enrollment.

Patient is NOT ELIGIBLE for enrollment.

Examined by: __________________________________

Date: __________________________________

Participant Demographics

Please complete the survey below.

Thank you!

Please provide the following demographic information:

24)	Date of birth (DD/MM/YYYY e.g. 06/26/1992)	______________________________
25)	Level of prosthesis use on RIGHT side:	○ None ○ Transtibial ○ Transfemoral
26)	Level of prosthesis use on LEFT side:	○ None ○ Transtibial ○ Transfemoral
27)	How long have you used the prosthesis you are wearing? (e.g. ten years, two years, five years, etc.)	______________________________
28)	When was your last appointment with your prosthetist? (e.g. one month ago, two weeks ago, etc.)	______________________________
29)	Biological Sex	○ Male ○ Female
30)	Ethnicity	○ Hispanic or Latino ○ NOT Hispanic or Latino ○ Unknown/ Prefer not to answer
31)	Race	☐ American Indian/Alaska Native ☐ Asian ☐ Native Hawaiian or Other Pacific Islander ☐ Black or African American ☐ White ☐ Other ☐ Unknown/ Prefer not to answer
32)	Please provide us with an email address you check regularly. If you are part of the main study, a brief survey will be sent to the email address you provide every 2 weeks over a period of 6 months.	______________________________

Socket Comfort Score

Please complete the survey below.

Thank you!

On a 0-10 scale, if 0 represents the most uncomfortable socket you an imagine and 10 represents the most comfortable socket you can imagine...

33) How would you score the comfort of your socket at the moment?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ 8
- ○ 9
- ○ 10

34) How would you score the comfort of your socket over the last week?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ 8
- ○ 9
- ○ 10

PLUS-M

Please complete the survey below.

Thank you!

Please respond to all questions as if you were wearing the prosthetic leg you use most days. If you would normally use a cane, crutch, or walker to perform the task, please answer the questions as if you were using that device.

Please choose "unable to do" if you:
-would need help from another person to complete the task
-would need a wheelchair or scooter to complete the task, or
-feel the task may be unsafe for you

35) Are you able to walk a short distance in your home?
- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

36) Are you able to step up and down curbs?
- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

37) Are you able to walk across the parking lot?
- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

38) Are you able to walk over gravel surfaces?
- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

39) Are you able to move a chair from one room to another?
- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

40) Are you able to walk while carrying a shopping basket in one hand?
- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

41) Are you able to keep walking when people bump into you?
- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

ABC Scale

Please complete the survey below.

Thank you!

For each of the following activities, please indicate your level of self-confidence by choosing a number.

0% = No confidence
100% = Completely confident

How confident are you that you will not lose your balance or become unsteady when you...

---

48) Walk around the house?

○ 0%
○ 10%
○ 20%
○ 30%
○ 40%
○ 50%
○ 60%
○ 70%
○ 80%
○ 90%
○ 100%

---

49) Walk up or down stairs?

○ 0%
○ 10%
○ 20%
○ 30%
○ 40%
○ 50%
○ 60%
○ 70%
○ 80%
○ 90%
○ 100%

---

50) Bend over and pick up a slipper (or item) from the front of a closet floor?

○ 0%
○ 10%
○ 20%
○ 30%
○ 40%
○ 50%
○ 60%
○ 70%
○ 80%
○ 90%
○ 100%

---

51) Reach for a small can off a shelf at eye level?

○ 0%
○ 10%
○ 20%
○ 30%
○ 40%
○ 50%
○ 60%
○ 70%
○ 80%
○ 90%
○ 100%

52) Stand on your tiptoes and reach for something above your head?

◯ 0%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ 100%

53) Stand on a chair and reach for something?

◯ 0%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ 100%

54) Sweep the floor?

◯ 0%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ 100%

55) Walk outside the house to a car parked in the driveway?

◯ 0%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ 100%

56) Get into or out of a car?

◯ 0%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ 100%

57) Walk across a parking lot to the mall (store)?

- ◯ 0%
- ◯ 10%
- ◯ 20%
- ◯ 30%
- ◯ 40%
- ◯ 50%
- ◯ 60%
- ◯ 70%
- ◯ 80%
- ◯ 90%
- ◯ 100%

58) Walk up or down a ramp?

- ◯ 0%
- ◯ 10%
- ◯ 20%
- ◯ 30%
- ◯ 40%
- ◯ 50%
- ◯ 60%
- ◯ 70%
- ◯ 80%
- ◯ 90%
- ◯ 100%

59) Walk in a crowded mall where people rapidly walk past you?

- ◯ 0%
- ◯ 10%
- ◯ 20%
- ◯ 30%
- ◯ 40%
- ◯ 50%
- ◯ 60%
- ◯ 70%
- ◯ 80%
- ◯ 90%
- ◯ 100%

60) Are bumped into by people as you walk through the mall?

- ◯ 0%
- ◯ 10%
- ◯ 20%
- ◯ 30%
- ◯ 40%
- ◯ 50%
- ◯ 60%
- ◯ 70%
- ◯ 80%
- ◯ 90%
- ◯ 100%

61) Step onto or off an escalator while you are holding onto a railing?

- ◯ 0%
- ◯ 10%
- ◯ 20%
- ◯ 30%
- ◯ 40%
- ◯ 50%
- ◯ 60%
- ◯ 70%
- ◯ 80%
- ◯ 90%
- ◯ 100%

Retrospective Falls And Near-Falls

Please complete the survey below.

Thank you!

This survey asks about FALLS and NEAR-FALLS you have experienced in the past 12 months.

Please respond to all questions with the following definitions in mind:
• A FALL is a loss of balance where your body landed on the ground or floor.
• A NEAR-FALL is a loss of balance where you caught yourself or recovered without landing on the ground or floor.

If you report MULTIPLE falls or MULTIPLE near-falls, please answer the following questions for the fall or near-fall you REMEMBER BEST.

FALLS

Have you experienced a FALL in the past 12 months?	◯ Yes ◯ No
How many FALLS have you experienced in the past 12 months? Example: 2	______________________
Were you wearing your prosthesis when you fell? (Choose the best answer)	◯ Yes ◯ No ◯ Do not remember
In what direction did you fall? (Select ALL that apply)	☐ Forward ☐ Backward ☐ To the right ☐ To the left ☐ Straight down ☐ Do not remember
Did you experience an injury because of the fall?	◯ Yes ◯ No
Did you receive medical treatment because of the fall? (Choose the best answer)	◯ Self-administered treatment ◯ Treated but not taken to provider ◯ Treated and sent home the same day ◯ Hospitalized for 1 night ◯ Hospitalized for 2-3 nights ◯ Hospitalized for more than 3 nights ◯ Did not receive medical treatment ◯ Do not remember

Have you done any of the following because of the fall? (Select ALL that apply)	☐ Changed how you do certain activities ☐ Do certain activities less often ☐ Stopped doing certain activities altogether ☐ Rested more than usual ☐ Become more careful or cautious ☐ Pay more attention to your surroundings ☐ Began to use a cane, crutch, or walker ☐ Relied more on a cane, crutch, or walker ☐ Made safety modifications to your home ☐ Received physical help to perform activities ☐ None of these apply ☐ Do not remember
Did you experience any of the following changes after the fall? (Select ALL that apply)	☐ Less confident in your balance ☐ More afraid of falling ☐ Less confident in your prosthesis ☐ None of these apply ☐ Do not remember
On a scale of 0 (not significant at all) to 10 (extremely significant) how would you rate the fall? (Choose the best answer)	○ 0 (not significant at all) ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 (extremely significant)

NEAR-FALLS

Have you experienced a NEAR-FALL in the past 12 months?	○ Yes ○ No
How many NEAR-FALLS have you experienced in the past 12 months? Example: 2	______________________________
Were you wearing your prosthesis when you nearly fell? (Choose the best answer)	○ Yes ○ No ○ Do not remember
In what direction did you nearly fall? (Select ALL that apply)	☐ Forward ☐ Backward ☐ To the right ☐ To the left ☐ Straight down ☐ Do not remember
Did you experience an injury because of the near-fall?	○ Yes ○ No

Did you receive medical treatment because of the near-fall? (Choose the best answer)	◯ Self-administered treatment ◯ Treated but not taken to provider ◯ Treated and sent home the same day ◯ Hospitalized for 1 night ◯ Hospitalized for 2-3 nights ◯ Hospitalized for more than 3 nights ◯ Did not receive medical treatment ◯ Do not remember
Have you done any of the following because of the near-fall? (Select ALL that apply)	☐ Changed how you do certain activities ☐ Do certain activities less often ☐ Stopped doing certain activities altogether ☐ Rested more than usual ☐ Become more careful or cautious ☐ Pay more attention to your surroundings ☐ Began to use a cane, crutch, or walker ☐ Relied more on a cane, crutch, or walker ☐ Made safety modifications to your home ☐ Received physical help to perform activities ☐ None of these apply ☐ Do not remember
Did you experience any of the following changes after the near-fall? (Select ALL that apply)	☐ Less confident in your balance ☐ More afraid of falling ☐ Less confident in your prosthesis ☐ None of these apply ☐ Do not remember
On a scale of 0 (not significant at all) to 10 (extremely significant) how would you rate the near-fall? (Choose the best answer)	◯ 0 (not significant at all) ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 (extremely significant)

PROMIS-29 Profile/Battery v2.1

Please complete the survey below.

Thank you!

FINAL RESULTS

T-score ______________________________

Standard Error ______________________________

PFA11

Are you able to do chores such as vacuuming or yard work?

- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

PFA21

Are you able to go up and down stairs at a normal pace?

- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

PFA23

Are you able to go for a walk of at least 15 minutes?

- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

PFA53

Are you able to run errands and shop?

- ◯ Without any difficulty
- ◯ With a little difficulty
- ◯ With some difficulty
- ◯ With much difficulty
- ◯ Unable to do

PROMIS-29 Profile/Battery v2.1

FINAL RESULTS	
T-score	__________________________________
Standard Error	__________________________________

EDANX01	
In the past 7 days I felt fearful	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always

EDANX40	
In the past 7 days I found it hard to focus on anything other than my anxiety	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always

EDANX41	
In the past 7 days My worries overwhelmed me	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always

EDANX53	
In the past 7 days I felt uneasy	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always

PROMIS-29 Profile/Battery v2.1

FINAL RESULTS

T-score ______________________________

Standard Error ______________________________

EDDEP04

In the past 7 days
I felt worthless

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

EDDEP06

In the past 7 days
I felt helpless

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

EDDEP29

In the past 7 days
I felt depressed

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

EDDEP41

In the past 7 days
I felt hopeless

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

PROMIS-29 Profile/Battery v2.1

FINAL RESULTS

T-score ______________________________

Standard Error ______________________________

HI7

During the past 7 days:
I feel fatigued

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

FATEXP40

In the past 7 days
How fatigued were you on average?

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

FATEXP41

In the past 7 days
How run-down did you feel on average?

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

An3

During the past 7 days:
I have trouble starting things because I am tired

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

PROMIS-29 Profile/Battery v2.1

FINAL RESULTS

T-score

____

Standard Error

____

Sleep116

In the past 7 days
My sleep was refreshing.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

Sleep20

In the past 7 days
I had a problem with my sleep.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

Sleep44

In the past 7 days
I had difficulty falling asleep.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

Sleep109

In the past 7 days
My sleep quality was...

- ◯ Very poor
- ◯ Poor
- ◯ Fair
- ◯ Good
- ◯ Very good

PROMIS-29 Profile/Battery v2.1

FINAL RESULTS

T-score

____

Standard Error

____

SRPPER11_CaPS

I have trouble doing all of my regular leisure activities with others

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

SRPPER18_CaPS

I have trouble doing all of the family activities that I want to do

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

SRPPER23_CaPS

I have trouble doing all of my usual work (include work at home)

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

SRPPER46_CaPS

I have trouble doing all of the activities with friends that I want to do

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

PROMIS-29 Profile/Battery v2.1

FINAL RESULTS	
T-score	______________________
Standard Error	______________________

PAININ9	
In the past 7 days How much did pain interfere with your day to day activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much

PAININ22	
In the past 7 days how much did pain interfere with work around the home?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much

PAININ31	
In the past 7 days How much did pain interfere with your ability to participate in social activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much

PAININ34	
In the past 7 days How much did pain interfere with your household chores?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much

PROMIS-29 Profile/Battery v2.1

FINAL RESULTS

T-score

____

Standard Error

____

Global07

In the past 7 days
How would you rate your pain on average?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ 8
- ○ 9
- ○ 10

For Research Staff- Amputee Mobility Predictor w/ Prosthesis

Testee is seated in a hard chair with arms. The following maneuvers are tested while using the prosthesis. Advise the testee of each task or group of tasks prior to performance. Please avoid talking throughout the test. No task should be performed if either the tester or testee feels the item cannot be completed safely.

128) Sitting balance: sit forward in a chair with arms folded across chest for 60s	◯ Cannot sit upright independently ◯ Can sit upright independently
129) Sitting reach: reach forward and grasp the ruler. (Tester holds ruler 12in beyond extended arms midline to the sternum)	◯ Does not attempt ◯ Cannot grasp or requires arm support ◯ Reaches forward and successfully grasps item
130) Chair to chair transfer: 2 chairs at 90 degrees. Patient may choose direction and use their upper extremities.	◯ Cannot do or requires physical assistance ◯ Performs independently, but appear unsteady ◯ Performs independently, appears to be steady
131) Arise from a chair: ask patient to fold arms across chest and stand. If unable, use arms or assistive device.	◯ Unable without help (physical assistance) ◯ Able, uses arms/assist device to help ◯ Able, without using arms
132) Attempts to arise from a chair (stopwatch ready): if attempt in #4 was without arms, then ignore and allow another attempt without penalty.	◯ Unable without help (physical assistance) ◯ Able, requires more than one attempt ◯ Able to rise first attempt
133) Immediate standing balance (first 5s): begin timing immediately.	◯ Unsteady (staggers, moves foot, sways) ◯ Steady using walking aid or other support ◯ Steady without walker or other support
134) Standing balance (30s) (stopwatch ready): for items #7 and #8, first attempt is without assistive device. If support is required, allow after first attempt.	◯ Unsteady ◯ Steady but uses walking aid or other support ◯ Standing without support
135) Single-limb standing balance (stopwatch ready): time the duration of single limb standing on the sound limb up to 30s. Grade the quality, not the time.	◯ Nonprosthetic side- Unsteady ◯ Nonprosthetic side- Steady but uses walking aid or other support for 30s ◯ Nonprosthetic side- Single limb standing without support for 30s
136) Single-limb standing balance (stopwatch ready): time the duration of a single limb standing on the prosthetic limb up to 30s. Grade the quality, not the time.	◯ Prosthetic side- Unsteady ◯ Prosthetic side- Steady but uses walking aid or other support for 30s ◯ Prosthetic side- Single limb standing without support for 30s
137) Standing reach: reach forward and grasp the ruler (Tester holds ruler 12in beyond extended arm(s) midline to the sternum).	◯ Does not attempt ◯ Cannot grasp or requires arm support on assistive device ◯ Reaches forward and successfully grasps item no support
138) Nudge test (subject at maximum position #7): with feet as close together as possible, examiner pushes firmly on subject's sternum with palm of hand 3 times (toes should rise).	◯ Begins to fall ◯ Staggers, grabs, catches self, or uses assistive device ◯ Steady

139) Eyes closed (at maximum position #7): if support is required grade as unsteady.	◯ Unsteady or grips assistive device ◯ Steady without any use of assistive device
140) Picking up objects off the floor (pick up a pencil from the floor placed midline 12in in front of foot).	◯ Unable to pick up object and return to standing ◯ Performs with some help (table, chair, walking aid, etc) ◯ Performs independently (without help from object or person)
141) Sitting down: ask patient to fold arms across chest and sit. If unable, use arm or assistive device.	◯ Unsafe (misjudged distance, falls into chair) ◯ Uses arms, assistive device, or not a smooth motion ◯ Safe, smooth motion
142) Initiation of gait (immediately after told to "go").	◯ Any hesitancy or multiple attempts to start ◯ No hesitancy
143) Step length and height: walk a measured distance of 12ft twice (up and back). "Marked deviation" is defined as extreme substitute movements to permit clearing the floor. Nonprosthetic foot.	◯ Does not advance a minimum of 12in ◯ Advances a minimum of 12in
144) Nonprosthetic foot clearance from previous question.	◯ Foot does not completely clear floor without deviation ◯ Foot completely clears floor without marked deviation
145) Prosthetic step length from previous question	◯ Does not advance a minimum of 12in ◯ Advances a minimum of 12in
146) Prosthetic foot clearance from previous question.	◯ Foot does not completely clear floor without deviation ◯ Foot completely clears floor without marked deviation
147) Step continuity.	◯ Stopping or discontinuity between steps (stop & go gait) ◯ Steps appear continuous
148) Turning: 180 degree turn when returning to chair.	◯ Unable to turn, requires intervention to prevent falling ◯ Greater than 3 steps but completes task without intervention ◯ No more than 3 continuous steps with or without assistive aid
149) Variable cadence: walk a distance of 12ft fast as safely as possible 4 times. (Speeds may vary from slow to fast and fast to slow, varying cadence.)	◯ Unable to vary cadence in a controlled manner ◯ Asymmetrical increase in cadence controlled manner ◯ Symmetrical increase in speed in a controlled manner
150) Stepping over obstacle: place a movable box of 4in. in height in the walking path.	◯ Cannot step over the box ◯ Catches foot, interrupts stride ◯ Steps over without interrupting stride

151) Stairs (must have at least 2 steps): try to go up and down these stairs without holding on to the railing. Don't hesitate to permit patient to hold on to rail. Safety first, if examiner feels that any risk is involved, then omit and score as 0.	◯ Ascending Unsteady, cannot do ◯ One step at a time, or must hold on to railing or device ◯ Steps over step, does not hold onto the railing or device
152) Assistive device selection: add points for the use of an assistive device if used for 2 or more items. If testing without prosthesis use of appropriate assistive device is mandatory.	◯ Bed bound ◯ Wheelchair ◯ Walker ◯ Crutches (axillary or forearm) ◯ Cane (straight or quad) ◯ None
153) AMPPRO Score	__________________________________

For Research Staff- Functional Measures Data Collection Sheet

Four Square Step Test:

General Information:
-The patient is instructed to stand in square 1 facing square number 2 (see figure below)
-The patient is required to step as fast as possible into each square in the following sequence: 2, 3, 4, 1, 4, 3, 2, and 1 requires the patient to step forward, backward, and sideway to the right and left
-Equipment required for the FSST includes a stopwatch and 4 canes.

Patient Instructions (derived from Dite and Temple 2002):
-"Try to complete the sequence as fast as possible without touching the sticks. Both feet must make contact with the floor in each square. If possible, face forward during the entire sequence."
-Demonstrate the sequence to the patient.
-Ask the patient to complete one practice trial to ensure the patient knows the sequence. Repeat the trial if the patient is unsuccessful at completing the sequence, loses balance, or contacts a cane during the trial.
-Two FSST are completed with the best time taken as the score.
-A score is still provided if the patient is unable to face forward during the entire sequence.

Scoring:
-the best time of two FSST is the score
-stopwatch starts when the first foot contacts the floor in square 2 stopwatch finishes when the last foot comes back to touch the floor in square 1

[Attachment: "Four Step Square Test Instructions.pdf"]

154) FSST Time (in seconds) ______________________________

155) FSST Time (in seconds) ______________________________

Place biomechanics equipment (e.g. IMUs, reflective markers, and/or pressure insoles) on participant. Ask them to walk in designated area/distance in a straight line and stop.

Inform participant they will be performing 5 trials at a comfortable walking speed, then 5 trials at a fast walking speed. Participants may take breaks between trials or choose not to complete all trials.

156) Walking Trial 1 Comfortable Walking Speed (in meters/second) ______________________________

157) Walking Trial 2 Comfortable Walking Speed (in m/s) ______________________________

158) Walking Trial 3 Comfortable Walking Speed (in m/s) ______________________________

159) Walking Trial 4 Comfortable Walking Speed (in m/s) ______________________________

160) Walking Trial 5 Comfortable Walking Speed (in m/s) ______________________________

161) Walking Trial 1 Fast Speed (in m/s) ______________________________

162) Walking Trial 2 Fast Speed (in m/s) __________________________________

163) Walking Trial 3 Fast Speed (in m/s) __________________________________

164) Walking Trial 4 Fast Speed (in m/s) __________________________________

165) Walking Trial 5 Fast Speed (in m/s) __________________________________

Timed Up and Go Test:
Begin by having the patient sit back in a standard arm chair and identify a line 3 meters, or 10 feet away, on the floor.

When I say "Go," I want you to:
1. Stand up from the chair.
2. Walk to the line on the floor at your normal pace.
3. Turn.
4. Walk back to the chair at your normal pace.
5. Sit down again

On the word "Go," begin timing.
3 Stop timing after patient sits back down.
4 Record time.

Participant will complete 3 trials, which will be averaged.

166) TUG Time (in seconds) __________________________________

167) TUG Time (in seconds) __________________________________

168) TUG Time (in seconds) __________________________________

169) TUG Average Score __________________________________

For Research Staff- Prosthetic Componentry

170) Height in feet and inches (5ft 6in) __________________________________

171) Weight in lbs (150lbs) __________________________________

172) Residual limb length in cm: __________________________________

PROSTHETIC COMPONENTRY

173) Prosthetic knee model: __________________________________

174) Prosthetic foot model: __________________________________

175) Shoe model: __________________________________

176) Shoe size: __________________________________

177) Suspension (vacuum, sleeve, skin fit, pin-lock, etc.): __________________________________

178) Sock ply: __________________________________

179) Comments: ____

Fall and Near-Fall Tracking

Please complete the survey below.

Thank you!

This survey asks about FALLS and NEAR-FALLS you have experienced in the past 2 weeks.

Please respond to all questions with the following definitions in mind:
• A FALL is a loss of balance where your body landed on the ground or floor.
• A NEAR-FALL is a loss of balance where you caught yourself or recovered without landing on the ground or floor.

If you report MULTIPLE falls or MULTIPLE near-falls, please answer the following questions for the fall or near-fall you REMEMBER BEST.

FALLS

Have you experienced a FALL in the past 2 weeks?	◯ Yes ◯ No
How many FALLS have you experienced in the past 2 weeks? Example: 2	______________________
Were you wearing your prosthesis when you fell? (Choose the best answer)	◯ Yes ◯ No ◯ Do not remember
In what direction did you fall? (Select ALL that apply)	☐ Forward ☐ Backward ☐ To the right ☐ To the left ☐ Straight down ☐ Do not remember
Did you experience an injury because of the fall?	◯ Yes ◯ No
Did you receive medical treatment because of the fall? (Choose the best answer)	◯ Self-administered treatment ◯ Treated but not taken to provider ◯ Treated and sent home the same day ◯ Hospitalized for 1 night ◯ Hospitalized for 2-3 nights ◯ Hospitalized for more than 3 nights ◯ Did not receive medical treatment ◯ Do not remember

Have you done any of the following because of the fall? (Select ALL that apply)	☐ Changed how you do certain activities ☐ Do certain activities less often ☐ Stopped doing certain activities altogether ☐ Rested more than usual ☐ Become more careful or cautious ☐ Pay more attention to your surroundings ☐ Began to use a cane, crutch, or walker ☐ Relied more on a cane, crutch, or walker ☐ Made safety modifications to your home ☐ Received physical help to perform activities ☐ None of these apply ☐ Do not remember
Did you experience any of the following changes after the fall? (Select ALL that apply)	☐ Less confident in your balance ☐ More afraid of falling ☐ Less confident in your prosthesis ☐ None of these apply ☐ Do not remember
On a scale of 0 (not significant at all) to 10 (extremely significant) how would you rate the fall? (Choose the best answer)	◯ 0 (not significant at all) ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 (extremely significant)

NEAR-FALLS

Have you experienced a NEAR-FALL in the past 12 months?	◯ Yes ◯ No
How many NEAR-FALLS have you experienced in the past 12 months? Example: 2	______________________________
Were you wearing your prosthesis when you nearly fell? (Choose the best answer)	◯ Yes ◯ No ◯ Do not remember
In what direction did you nearly fall? (Select ALL that apply)	☐ Forward ☐ Backward ☐ To the right ☐ To the left ☐ Straight down ☐ Do not remember
Did you experience an injury because of the near-fall?	◯ Yes ◯ No

Did you receive medical treatment because of the near-fall? (Choose the best answer)	◯ Self-administered treatment ◯ Treated but not taken to provider ◯ Treated and sent home the same day ◯ Hospitalized for 1 night ◯ Hospitalized for 2-3 nights ◯ Hospitalized for more than 3 nights ◯ Did not receive medical treatment ◯ Do not remember
Have you done any of the following because of the near-fall? (Select ALL that apply)	☐ Changed how you do certain activities ☐ Do certain activities less often ☐ Stopped doing certain activities altogether ☐ Rested more than usual ☐ Become more careful or cautious ☐ Pay more attention to your surroundings ☐ Began to use a cane, crutch, or walker ☐ Relied more on a cane, crutch, or walker ☐ Made safety modifications to your home ☐ Received physical help to perform activities ☐ None of these apply ☐ Do not remember
Did you experience any of the following changes after the near-fall? (Select ALL that apply)	☐ Less confident in your balance ☐ More afraid of falling ☐ Less confident in your prosthesis ☐ None of these apply ☐ Do not remember
On a scale of 0 (not significant at all) to 10 (extremely significant) how would you rate the near-fall? (Choose the best answer)	◯ 0 (not significant at all) ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 (extremely significant)

APPENDIX C

SUPPLEMENTAL TABLES

Chapter 2

Supplemental Data for Table 2

	Step Length (m)	Stance Time (s)	Stance Time (% gait cycle)	Overall Sagittal Hip RoM(°)	Overall Sagittal Knee RoM(°)	Overall Sagittal Ankle RoM(°)
Bai et al., 2017	Echelon (hydraulic foot)= 0.13 Esprit (non-hydraulic foot)= 0.12	NR	Echelon (hydraulic foot)= 8.0 Esprit (non-hydraulic foot)= 6.8	NR	NR	Echelon (hydraulic foot)= 7.7 Esprit (non-hydraulic foot)= 2.4
Bateni and Olney, 2002	NR	NR	4.2	2.6	7.7	NR
Clemens et al., 2020	NR	TT= 0.03 TF= 0.1	NR	NR	NR	NR
Darter et al., 2013	Pre-training= 0.13 Intermediate= 0.1 Post-training= 0.1	Pre-training= 0.12 Intermediate=0.12 Post-training= 0.09	NR	NR	NR	NR
Gholizadeh et al., 2014	Suction= 0.04 Pin-Lock= 0.08	NR	Suction= 3.3 Pin-Lock= 5.0	Suction= 1.1 Pin-Lock= 1.1	Suction= 14.6 Pin-Lock= 8.9	Suction= 1.0 Pin-Lock= 0.8

Gholizadeh et al., 2020	Vacuum suspension off= 0.05 Vacuum suspension on= 0.03	Vacuum suspension off= 0.02 Vacuum suspension on= 0.03	NR	Vacuum suspension off= 2.4 Vacuum suspension on= 3.1	Vacuum suspension off= 1.53 Vacuum suspension on= 1.88	Vacuum suspension off= 8.41 Vacuum suspension on= 8.22
Hak et al., 2014	0.02*	NR	NR	NR	NR	NR
Hekmatfard et al., 2013	Unweighted condition=: 0.01	NR	Unweighted condition= 13.0	NR	NR	NR
Highsmith et al., 2010	TT= 0.03 TF= 0.02	NR	NR	NR	NR	NR
Houdijk et al., 2018	SACH= 0.05 ESAR= 0.01					
Johansson et al., 2005	Mauch (hydraulic knee) = 0.05 C-Leg MPK= 0.03 Rheo MPK= 0.06	Mauch (hydraulic knee)= 0.09 C-Leg MPK= 0.1 Rheo MPK= 0.1	NR	NR	NR	NR
Keklicek et al., 2019	Control= 0.01 TT=	NR	Control=0.71 TT=	NR	NR	NR

	0.02 TF= 0.16		5.15 TF= 20.73			
Kovac et al., 2010	Control= 0.01 TT= 0.07	Control= 0.001s TT= 0.04s		NR	NR	NR
Mattes et al., 2000	Unweighted condition= 0.03*	Unweighted condition= 0.01*		NR	NR	NR
Moore, 2016	NR	K3 group: pre-Echelon foot= 0.07 post-Echelon foot= 0.05 K2 group: pre-Avalon foot= 0.06 post-Avalon foot= 0.04		NR	NR	NR
Nadollek et al., 2002	0.01	NR		NR	NR	NR
Nolan et al., 2003	NR	TT= 0.06				

		TF= 0.24				
Orekhov et al., 2019	NR	NR		NR	Control= 1.5* TT= 13.0*	NR
Petersen et al., 2010	3R60 (hydraulic knee)= 0.06 C-Leg MPK= 0.06	NR	3R60 (hydraulic knee)= 7.4 C-Leg MPK= 5.3	NR	NR	NR
Rowe, 2014	0.03	NR	NR	NR	NR	NR
Schaarschmidt et al., 2012	NR	Speed of 0.8m/s: 3R80 (hydraulic knee)= 0.07 C-Leg MPK=0.08 Speed of 1.1m/s: 3R80 (hydraulic knee)= 0.02 C-Leg MPK=0.01	NR	NR	NR	NR
Segal et al., 2006	Mauch (hydraulic knee)= 0.04	NR	NR	NR	Mauch knee= 1.26	NR

	C-Leg MPK= 0.03				C-Leg MPK= 13.39	
Sjodahl et al., 2002	Before gait training= 0.12 After gait training= 0.08	NR	Before gait training= 5.0 After gait training= 7.0	Before gait training= 18.0 After gait training= 19.0	NR	NR
Smith and Martin, 2013	NR	Baseline condition= 0.04*	NR	NR	Baseline condition = 10*	NR
Supan et al., 2010	Baseline condition= 0.07	NR	Baseline condition= 0.07	Baseline condition= 0.98	Baseline condition= 8.27	Baseline condition= 6.56
Svoboda and Janura, 2007	NR	Optimal alignment condition= 0.01	NR	NR	NR	NR
Uchytil et al., 2014	Control= 0.003 Mauch (hydraulic knee)= 0.09 Rheo MPK= 0.07	Control= 0.02 Mauch (hydraulic knee)= 0.07 Rheo MPK= 0.03	NR	NR	NR	NR
Uchytil et al., 2017	NR	NR	NR	Mauch (hydraulic knee)= 8.75 Rheo MPK= 3.72	Mauch (hydraulic knee)= 1.01 Rheo MPK= 16.7	NR

Xu et al., 2017	15 inHg condition= 0.06	NR	15 inHg Condition= 2.1	15 inHg condition= 1.3	15 inHg condition= 7.8	15 inHg Condition= 10.1
Yang et al., 2018	1C30 Trias (ESAR foot)= 0.04 1C60 Trias (ESAR split forefoot & heel wedge)= 0.02	NR	IC30 Trias= 0.3 1C60 Trias= 0.6	IC30 Trias= 0.63 1C60 Trias= 1.47	IC30 Trias= 3.19 1C60 Trias= 1.43	IC30 Trias= 9.27 IC60 Trias= 12.22
Summary	**Step Length Differences (m):**	**Stance Time Differences (s):**	**Stance Time Differences (% gait cycle):**	**Overall Hip RoM Differences (°):**	**Overall Knee RoM Differences (°):**	**Overall Ankle RoM Differences (°):**
Ranges by Level of Limb Loss	Control= 0.003 - 0.01 TT= 0.01 – 0.12 TF= 0.008 – 0.164	Control= 0.001 - 0.02 TT= 0.01 – 0.04 TF= 0.01 - 0.24	Control= 0.71 TT= 0.07 – 5.15 TF= 5.0 – 20.7	Control= NR TT= 0.63 – 3.05 TF= 3.72 - 19.0	Control= 1.5 TT= 1.43 – 14.6 TF= 1.01 – 16.7	CONTROL= NR TT= 0.8 – 12.2 TF= 2.4 - 7.7
Ranges by Prosthetic Feet	SACH= 0.05 ESAR= 0.01 – 0.13	SACH= NR ESAR= 0.04 – 0.07	SACH= NR ESAR= 0.3 – 8.0	SACH= NR ESAR= 0.63 – 1.47	SACH= NR ESAR= 1.43 – 3.19	SACH= NR ESAR= 2.4 – 12.2
Ranges by Prosthetic Knees	Hydraulic= 0.04 – 0.09 MPKs= 0.03 –0.07	Hydraulic= 0.07 – 0.11 MPKs= 0.03 – 0.13	Hydraulic= 7.4 MPKs= 5.3	Hydraulic= 8.75 MPKs= 3.72	Hydraulic= 1.01 – 13.4 MPKs= 1.26 – 16.74	Hydraulic= NR MPKs= NR

Table 2: Supplemental data for Table 2. Summary of studies (31 total) that reported raw values for prosthetic and intact limbs or differences between limbs in meters (m), seconds (s), % of the gait cycle, or degrees (º) for step length, stance time, or overall sagittal range of motion (RoM) at the hip, knee, and ankle. Studies that measured stance time either reported values in seconds or % of the gait cycle, so these are reported separately. Results are taken from level ground walking conditions at self-selected walking speeds. Baseline conditions and intermediate walking speeds were chosen if multiple conditions or speeds were tested. An asterisk (*) indicates values were estimated from a graph or chart because they were not explicitly stated in a table. Ranges by level of limb loss, prosthetic feet, and prosthetic knees are summarized from the 31 studies above in Table 2. NR= not reported, TT= individuals who use unilateral transtibial prostheses, TF= individuals who use unilateral transfemoral prostheses, IULLPs= individuals who use unilateral lower-limb prostheses, SACH= solid ankle cushion heel, ESAR= energy storage and return, MPK= microprocessor knee.

Supplemental Data for Table 3

	Step Length (% Symmetry from m)	Stance Time (% Symmetry from s)	Stance Time (% Symmetry from % gait cycle)	Overall Sagittal Hip RoM (% Symmetry from °)	Overall Sagittal Knee RoM (% Symmetry from °)	Overall Sagittal Ankle RoM (% Symmetry from °)
Astrom and Stenstrom, 2004	83 to "over 90%"^	82 to "over 90%"^	NR	NR	86 to "over 90%"^	NR
Bai et al., 2017	Echelon (hydraulic foot)= 81.6 Esprit (non-hydraulic foot)= 82.9	NR	Echelon (hydraulic foot)= 87.1 Esprit (non-hydraulic foot)= 89.1	NR	NR	Echelon (hydraulic foot)= 53.2 Esprit (non-hydraulic foot)= 83.2
Bateni and Olney, 2002	NR	NR	93.3	93.0	87.9	NR
Clemens et al., 2020	NR	TT= 95.8 TF= 87.2	NR	NR	NR	NR

Chow et al., 2006	Most symmetrical alignment= 97.9^ Avg. of all alignments= 88.5^	Most symmetrical alignment = 93.7^ Avg. of all alignments= 90.6^		NR	Most symmetrical alignment = 85.1^ Avg. of all alignments= 83.1^	NR
Darter et al., 2013	Pre-training= 78.9 Intermediate= 84.8 Post-training= 84.8	Pre-training= 84.6 Intermediate= 83.5 Post-training= 87.8	NR	NR	NR	NR
Darter et al., 2017	Baseline conditions: Control= 97.0* TT= 98.0*	Baseline conditions: Control= 98.0* TT= 92.0*	NR	NR	NR	NR
Gholizadeh et al., 2014	Suction suspension= 93.2 Pin-lock suspension= 86.2	NR	Suction suspension= 94.8 Pin-lock suspension= 92.2	Suction suspension= 97.1 Pin-lock suspension= 97.0	Suction suspension= 77.0 Pin-lock suspension= 84.4	Suction suspension= 95.3 Pin-lock suspension= 96.1

Gholizadeh et al., 2020	Vacuum suspension off= 91.5 Vacuum suspension on= 95.8	Vacuum suspension off= 97.4 Vacuum suspension on= 96.2	NR	Vacuum suspension off= 93.6 Vacuum suspension on= 91.7	Vacuum suspension off= 97.6 Vacuum suspension on= 97.0	Vacuum suspension off= 64.5 Vacuum suspension on= 65.0
Hak et al., 2014	96.7*	NR	NR	NR	NR	NR
Hekmatfard et al., 2013	Unweighted condition= 98.5	NR	Unweighted condition= 81.3	NR	NR	NR
Highsmith et al., 2010	TT= 95.4 TF= 97.1	NR	NR	NR	NR	NR
Johansson et al., 2005	Mauch (hydraulic knee)= 93.2 C-Leg MPK= 95.9 Rheo MPK= 91.7	Mauch (hydraulic knee)= 80.6 C-Leg MPK= 78.7 Rheo MPK= 79.2	NR	NR	NR	NR
Keklicek et al., 2019	Control= 97.6 TT= 95.5 TF= 66.4	NR	Control= 98.6 TT= 89.7 TF= 58.6	NR	NR	NR

Kahle and Highsmith, 2014	Ischial containment= 98.0^ Brimless socket w/ vacuum= 92.0^	Ischial containment= 94.0^ Brimless socket w/ vacuum= 92.0^	NR	NR	NR	NR
Kovac et al., 2010	Control= 98.4 TT= 89.6	Control= 99.8 TT= 94.9		NR	NR	NR
Marinakis, 2004	NR	Used 3 different equations (Symmetry Index 2) SACH foot= 78.9^ Greissenger (ESAR foot)= 97.0^	NR	Used 3 different equations (Symmetry Index 2) SACH foot= 85.7^ Greissenger (ESAR foot)= 89.0^	Used 3 different equations (Symmetry Index 2) SACH foot= 84.9^ Greissenger (ESAR foot)= 91.4^	Used 3 different equations (Symmetry Index 2) SACH foot= 23.7^ Greissenger (ESAR foot)= 63.5^
Mattes et al., 2000	Unweighted condition= 96.7*	Unweighted condition= 98.6*	NR	NR	NR	NR
Nadollek et al., 2002	96.6	NR	NR	NR	NR	NR

Nolan et al., 2003	NR	Control= 97.4 TT= 93.5 TF= 74.5	NR	NR	NR	NR
Orekhov et al., 2019	NR	NR	NR	NR	Control= 96.2* TT= 70.8*	NR
Petersen et al., 2010	3R60 (hydraulic knee)= 90.9 C-Leg MPK= 90.9	NR	3R60 (hydraulic knee)= 88.2 C-Leg MPK= 91.6	NR	NR	NR
Roerdink et al., 2012	Avg. of participants at comfortable walking speed= 94.9	NR	NR	NR	NR	NR
Rowe, 2014	95.3	NR	NR	NR	NR	NR

Schaarschmidt et al., 2012	NR	Speed of 0.8m/s: 3R80 (hydraulic knee)= 89.3 C-Leg MPK= 87.9 Speed of 1.1m/s: 3R80 (hydraulic knee)= 96.8 C-Leg MPK= 98.4	NR	NR	NR	NR
Segal et al., 2006	Mauch (hydraulic knee)= 94.2 C-Leg MPK= 95.7	NR	NR	NR	Mauch knee= 97.7 C-Leg MPK= 77.7	NR
Sjodahl et al., 2002	Before gait training= 82.1 After gait training= 91.0	NR	Before gait training= 91.6 After gait training= 88.4	Before gait training= 55.0 After gait training= 60.0	NR	NR
Smith and Martin, 2013	NR	Unweighted prosthesis: 95.6	NR	NR	Unweighted prosthesis: 83.3	NR

Supan et al., 2010	Baseline condition= 81.3	NR	Baseline condition= 99.9	Baseline condition= 97.6	Baseline condition= 83.8	Baseline condition= 71.2
Svoboda and Janura, 2007	NR	Optimal alignment condition= 98.8	NR	NR	NR	NR
Uchytil et al., 2014	Control= 99.6 Mauch (hydraulic knee)= 86.6 Rheo MPK= 90.3	Control= 97.2 Mauch (hydraulic knee)= 91.2 Rheo MPK= 96.0	NR	NR	NR	NR
Uchytil et al., 2017	NR	NR	NR	Mauch (hydraulic knee)= 82.6 Rheo MPK= 91.9	Mauch (hydraulic knee)= 98.2 Rheo MPK= 70.5	NR
Xu et al., 2017	15 inHg condition= 91.9	NR	15 inHg Condition= 96.7	15 inHg condition= 97.5	15 inHg condition= 88.6	15 inHg Condition= 62.5
Yang et al., 2018	1C30 Trias (ESAR foot)= 94.2 1C60 Trias (ESAR split forefoot & heel wedge)= 97.3	NR	IC30 Trias= 99.5 1C60 Trias= 99.0	IC30 Trias= 98.5 1C60 Trias= 96.4	IC30 Trias= 95.0 1C60 Trias= 97.8	IC30 Trias= 60.8 IC60 Trias= 44.5

Summary	Step Length (% Symmetry from m)	Stance Time (% Symmetry from s)	Stance Time (% Symmetry from % gait cycle)	Overall Sagittal Hip RoM (% Symmetry from °)	Overall Sagittal Knee RoM (% Symmetry from °)	Overall Sagittal Ankle RoM (% Symmetry from °)
Ranges by Level of Limb Loss	Control= 97.0 – 99.6 TT= 81.3 – 98.0 TF= 66.4 – 98.5	Control= 97.2 – 99.8 TT= 78.9 – 98.8 TF= 74.5 – 98.4	Control= 98.6 TT= 81.3 - 99.9 TF= 58.6 – 91.6	Control= NR TT= 85.7 – 99.8 TF= 55.0 – 91.9	Control= 96.2 TT= 70.8 – 97.8 TF= 70.5 – 98.2	Control= NR TT= 23.7 – 96.1 TF= 53.2 – 83.2
Ranges by Prosthetic Feet	SACH= NR ESAR= 81.6 – 97.3	SACH= 78.9 ESAR= 97.0	SACH= NR ESAR= 87.1 – 99.5	SACH= 85.7 ESAR= 89.0 – 98.5	SACH= 84.9 ESAR= 91.4 – 97.8	SACH= 23.7 ESAR= 44.5 – 83.2
Ranges by Prosthetic Knees	Hydraulic= 86.6 – 94.2 MPKs= 90.3 – 95.9	Hydraulic= 74.7 – 91.2 MPKs= 71.4 – 96.0	Hydraulic= 88.2 MPKs= 91.6	Hydraulic= 82.6 MPKs= 91.6	Hydraulic= 77.8 – 98.2 MPKs= 70.5 – 97.7	Hydraulic= NR MPKs= NR

Table 3: Supplemental data for Table 3. Summary of studies (34 total) that could be converted to percentages using 100- Eq. 1. Studies that measured stance time either reported values in seconds or % of the gait cycle, so these are reported separately. A circumflex symbol (^) indicates studies that used Eq. 1 or could be converted to Eq. 1, but are not in Table 2 because they did not include raw prosthetic and intact limb values. An asterisk (*) indicates prosthetic and intact limb values were estimated from a graph or chart. Ranges by level of limb loss, prosthetic feet, and prosthetic knees are summarized from the 34 studies above. NR= not reported, TT= individuals who use unilateral transtibial prostheses, TF= individuals who use transfemoral prostheses, IULLPs= individuals who use unilateral lower-limb prostheses, SACH= solid ankle cushion heel, ESAR= energy storage and return, MPK= microprocessor knee.

Chapter 3

Supplemental Table 1: Summary of Included Articles

	Author, Year	Title	Participants	Assessments	Fall Data
Clinical Outcomes	Cowley & Kerr 2001	Amputees and Tightropes: A Pilot Study to Measure Postural Control Post-Amputation	7 TT prosthesis users; mean age 64.6 yrs; 6 male, 1 female	FES, BBS, TUG	Falls and falls efficacy during 3 month study
	Dite et al. 2007	Clinical identification of multiple fall risk early after unilateral transtibial amputation	47 uni TT prosthesis users; Non-recurrent fallers= 27 participants mean age 65.2 ± 11.18 yrs, Recurrent fallers= 13 participants mean age 59.9 ± 14.28 yrs; 30 males, 17 females; PVD or diabetes= 26	LCI-advanced, TUG, FSST, 180 degree turn test	6 month retrospective falls
	Hakim et al. 2018	Identifying Fallers and nonfallers	40 uni total; 20 Non-fallers, 14 TT prosthesis users, 6 TF prosthesis users, 17 male, 3 female, mean age 56.9 ± 16.0 yrs, K2=4, K3=12, K4=4, 12 used assistive devices; 20 Recurrent Fallers, all TT prosthesis users, 12 male, 8 female, mean age 58.3 ± 15.9 yrs, K2=0, K3=13, K4=7, 8 used assistive devices	TUG, AMPPRO, Functional Reach, Single Limb Stance	Nonfallers and recurrent fallers grouped by 12 month retrospective falls
	Jayaraman et al. 2021	Using a microprocessor knee (C-Leg) with appropriate foot transitioned individuals	10 uni TF prosthesis users using a non-MPK; 4 male, 6 female; all dysvascular or diabetic; all K1 or K2;	mFES, PEQ-MS, BBS, TUG, AMPPRO, FSST, 10MWT, 6MWT	Falls efficacy via mFES only

	with dysvascular transfemoral amputations to higher performance levels: a longitudinal randomized clinical trial	mean age 63 ± 9 yrs; half the participants (n=5) were aged 69 and older; mean TSA 5.8 ± 8.1 yrs		
Lansade et al. 2018	Mobility and satisfaction with a microprocessor-controlled knee in moderately active amputees: A multi-centric randomized crossover trial	27 TF Non-MPK users completed the study; 25 uni, 2 bi TF-TT; mean age 64.5 ± 9.7 yrs; mean TSA 61.4 ± 85.5 yrs; etiologies= 14 vascular, 2 vascular diabetic, 4 trauma, 1 tumor, 1 infection; assistive devices= 7 none, 10 cane(s), 11 crutch(es)	SF-36v2, LCI-5, TUG, Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST) 2.0	Number of falls during study with non-MPK and MPK over 1 month
Mileusnic et al. 2017	Effects of a Novel Microprocessor-Controlled Knee, Kenevo, on the Safety, Mobility, and Satisfaction of Lower-Activity Patients with Transfemoral Amputation	23 TF total; 22 uni, 1 bi; mean age 63.2 ± 9.5 yrs; mean TSA 6.3 ± 8.9 yrs; 6 vascular, 5 infection, 1 cancer, 1 trauma (not all responded); 1 K1, 19 K2, 3 K3;	(n=11 for all outcomes) LCI-5, Houghton scale, PLUS-M	Number of falls during study and fear of falling
Miller et al. 2001	The influence of falling, fear of falling, and balance confidence on prosthetic mobility and social activity among individuals with a lower extremity amputation	435 total; mean age 62 ± 15.7 yrs; 319 TT; 309 males; 230 vascular; Nonfallers= 207, Fallers= 228	ABC, PEQ-MS, Houghton scale, Frenchay activities index	12 month retrospective falls

	Sawers & Hafner 2022	Performance-based balance tests, combined with the number of falls recalled in the past year, predicts the incidence of future falls in established unilateral transtibial prosthesis users	45 uni TT prosthesis users: Non-fallers= mean age 53.4 yrs; mean TSA 13.1 yrs; Single fallers= mean age 56.6 yrs and mean TSA 19.6 yrs; Recurrent fallers= mean age 55.7 yrs and mean TSA 6.6 yrs; 33 males and 12 females; 20 dysvacular, 25 non-dysvascular; 11 K1-K2, 34 K3-K4	SCS, PLUS-M, TUG, FSST, 10MWT, Narrow Beam Walking Test	12 month retrospective falls; 6 month prospective falls
	Wong et al. 2015	Balance ability measured with the Berg balance scale: a determinant of fall history in community-dwelling adults with leg amputation	54 uni/bi TT /TF 46 prosthesis users, 8 non-prosthesis users; mean age 56.8 yrs; 36 males, 18 females; Non-fallers= 25, Single fallers= 15, Recurrent fallers= 14	ABC, Houghton Scale, BBS	Nonfallers and fallers groups by 12 month retrospective falls
Gait Parameters	Schafer et al. 2018	A personalised exercise programme for individuals with lower limb amputation reduces falls and improves gait biomechanics: A block randomised controlled trial	15 total; Exercise group= mean age 60 ± 12 yrs, mean TSA 10 ± 17 yrs, 5 uni TF, 2 uni TT, 4 males, 3 females, 3 vascular, 1 trauma, 2 cancer, 1 infection; Control group= mean age 65 ± 16 yrs, mean TSA 19 ± 20 year, 5 uni TF, 3 uni TT, 7 males, 1 female, 2 vascular, 4 trauma, 1 cancer, 1 infection	spatiotemporal (stance time, SLS, DLS), kinematics (peak hip abd, hip add, hip flex, hip ext, knee flex, knee ext, ankle PF, ankle DF), kinetics (peak vertical GRF, peak braking force, peak propulsive force, peak sagittal plane moments, peak powers)	12 month retrospective falls at 1 year follow-up

	Vanicek et al. 2009	Gait patterns in transtibial amputee fallers vs. non-fallers: biomechanical differences during level walking	11 uni TT prosthesis users; 5 non-fallers= 2 females, 3 males, mean age 57 ± 21 yrs; 6 fallers= all male, mean age 56 ± 13 yrs	walking: spatiotemporal parameters (walking speed, double support, step length, step frequency, stance); peak vertical GRF; Hip ROM (extension, adduction stance, abduction swing, total sagittal, total frontal); Knee ROM (flexion in loading response, flexion in swing, total sagittal); Ankle ROM (dorsiflexion in terminal stance, ankle angle toe-off, planarflexion swing, total sagittal); Moments (hip, knee, and ankle waveforms); Kinetics (posterior braking, anterior propulsion, vertical 1, vertical 2, load rate, decay rate)	Nonfallers and fallers grouped by 9 month retrospective falls
	Vanicek et al. 2010	Lower Limb Kinematic and Kinetic Differences between Transtibial Amputee Fallers and Non-Fallers	11 uni TT prosthesis users; 5 non-fallers= 2 females, 3 males, mean age 57 ± 21 yrs; 6 fallers= all male, mean age 56 ± 13 yrs		Nonfallers and fallers grouped by 9 month retrospective falls
	Vanicek et al. 2015	Kinematic differences exist between transtibial amputee fallers and non-fallers during downwards step transitioning	11 uni TT prosthesis users; 5 non-fallers= 2 females, 3 males, mean age 57 ± 21 yrs; 6 fallers= all male, mean age 56 ± 13 yrs	stair ascent: spatiotemporal, kinematics, & kinetics	Nonfallers and fallers grouped by 9 month retrospective falls
Both Clinical Outcomes & Gait Parameters	Anderson et al. 2021	Falls After Dysvascular Transtibial Amputation: A Secondary Analysis of Falling Characteristics	69 TT; all 6mo to 5yrs after dysvascular amputation; Nonfallers= mean age 65.2 ± 8.6yrs, TSA, 1.3 ± 1.4yrs;	TUG, 2MWT, gait speed, step count	Nonfallers and fallers grouped by falls during 12 week study

		and Reduced Physical Performance	Fallers= mean age 63.7 ± 8.5yrs, TSA 1.1 ± 1.3yrs		
	Barnett et al. 2013	Temporal adaptations in generic and population-specific quality of life and falls efficacy in men with recent lower-limb amputations	7 TT prosthesis users; mean age 56.1 yrs; all male; 4 vascular, 3 nonvascular	mFES, , SF-36, PEQ, walking speed	Falls efficacy via mFES only
	Christiansen et al. 2020	Biobehavioral Intervention Targeting Physical Activity Behavior Change for Older Veterans after Nontraumatic Amputation: A Randomized Controlled Trial	31 total; 26 TT users, 5 TF users; mean age 65.7 ± 7.8 yrs; mean TSA 36.4 months; all male	FES-I, PEQ-MS, TUG, 2MWT, step counts, walking speed from 5MWT	Number of falls during 12 week study
	Hafner & Askew 2015	Physical performance and self-report outcomes associated with use of passive, adaptive, and active prosthetic knees in persons with unilateral, transfemoral amputation: Randomized crossover trial	12 uni TF prosthesis users; mean age 58.8 ± 6.1 yrs; mean TSA 28.9 ± 12.5 yrs; all males; all nonvascular etiologies; all K3; tested under 3 conditions= prescribed passive knee, adapative MPK, and active MPK	ABC, PEQ-MS, PROMIS-Physical Function, PROMIS-Fatigue, PROMIS- Global Health, Timed Stair Test, Timed Ramp Test, Outdoor Obstacle Course, StepWatch3 Activity Monitor	Number of falls during previous week for each knee condition
	Hordacre et al. 2015	Community activity and participation	46 uni TT prosthesis users; Non-fallers= 30, mean age 58.5 ± 13.3 yrs, 26 male, mean TSA 13.2 ± 19.1, 9 PVD, 11 trauma, 10 other, K1= 0, K2= 1, K3= 9, K4= 20; Fallers= 16, mean age	AMPPRO, step counts over 7 days using accelerometer and GPS	Nonfallers and fallers grouped by 12 month retrospective falls

			64.4 ± 13.5 yrs, 10 male, mean TSA 18.0 ± 19.2, 6 trauma, 1 other, K1= 1, K2= 3, K3= 4, K4= 8		
	Kaufman et al. 2018	Functional assessment and satisfaction of transfemoral amputees with low mobility (FASTK2): A clinical trial of microprocessor-controlled vs. non-microprocessor-controlled knees	50 uni TF tested using prescribed non-MPK and fit with MPK; all K2; mean age 69 yrs; tested at baseline with non-MPK, then 10 wks after using MPK, then 4 wks after reverting to non-MPK	PEQ, ActiGraph GTX3 wearable sensors= time spent sitting, upright activity, gait complexity (with MPK= significant decrease in time spent sitting, significant increase in time spent upright, gait complexity increased)	Number of falls during study with MPK and non-MPK

Supplemental Table 1: Summary of nineteen articles included in this review. Abbreviations: TT= transtibial, TF= transfemoral, uni= unilateral, bi= bilateral, TSA= time since amputation, PVD= peripheral vascular disease, ABC= Activities-Specific Balance Confidence scale, FES= Falls Efficacy Scale, SF-36= 36-Item Short Form, PEQ-MS= Prosthetic Evaluation Questionnaire Mobility Subscale, PEQ-A= Prosthetic Evaluation Questionnaire- Ambulation, LCI= Locomotor Capabilities Index, PLUS-M= Prosthetic Limb Users Survey of Mobility, BBS= Berg Balance Scale, TUG= Timed Up and Go, 2MWT= 2-minute walk test, AMPPRO= Amputee Mobility Predictor, FSST= Four Square Step Test, 10MWT= 10-meter walk test, SLS= single limb support, DLS= double limb support, ROM= range of motion, MPK= Microprocessor knee.

Supplemental Table 2: Clinical Outcome Measures Associated with Falls

			All participants (not distinguished by fall status)	**Non-Fallers**	**Fallers (not distinguished by single or recurrent falls)**	**Single Fallers**	**Recurrent Fallers**
Self-Reported Questionnaires	**ABC**	Hafner & Askew 2015	Active knee: 78.5= BL, 82.3= interv; Adaptive knee: 83.3= BL, 84.5= interv				
		Miller et al. 2001	62.8 ± 27.1				
		Sawers & Hafner 2022		3.15		3.07	2.78
		Wong et al. 2015		66.6 ± 30.5		61.2 ± 26.7	73.7 ± 19.5
	FES	Barnett et al. 2013 *(modified/14 items)*	75.7 ± 17.2= 1mo., 70.6 ± 17.5= 3mo., 78.4 ± 15.9= 6mo.				
		Christiansen et al. 2020 *(FES-I score out of 64)*	Group 1: 28.9= BL, 30.3= 12w, 27.5= 24w; Group 2: 28.0 BL, 32.5= 12w, 29.1= 24w				
		Cowley & Kerr 2001 *(unmodified/10 items)*	89.8= BL, 92.8= 6wks, 82.6= 3mo				
		Jayaraman et al. 2021 *(modified/14 items)*	7.78 ± 1.14= BL, Non-MPK = 8.51 ± 1.03, MPK = 9.33 ± 0.69				
	SF-36	Barnett et al. 2013	**60.8 ± 19.2= 1mo., 61.5 ± 19.3= 3mo., 68.2 ± 14.2= 6mo.***				
		Lansade et al. 2018 *(v2)*	Mental: Non-MPK= 53.3, MPK= 60.2; Physical:				

		Non-MPK= 44.1, MPK= 56.3				
PEQ-MS	Barnett et al. 2013 *(PEQ-A)*	74.5 ± 6.0= 1mo, 60.3 ± 14.9= 3mo, 71.4 ± 18.0= 6mo				
	Christiansen et al. 2020	Group 1: 2.5= BL, 2.4= 12w, 2.7= 24w; Group 2: 2.7= BL, 2.6= 12w, 2.7= 24w				
	Hafner & Askew 2015	Active knee: 2.9= BL, 2.9= interv; Adaptive knee: 3.1 BL, 3.2 interv				
	Jayaraman et al. 2021 *(PEQ-A)*	60.63 ± 18.75= BL, Non-MPK = 59.15 ± 19.31, MPK = 81.92 ± 18.74				
	Kaufman et al. 2018 *(PEQ-A)*	Non-MPK ~ 50.0, MPK ~ 45.0 (estimated from chart)				
	Miller et al. 2001		7.4		7.0	
LCI	Dite et al. 2007 *(LCI-advanced score out of 21)*				17.6 ± 4.2	12.9 ± 4.3
	Lansade et al. 2018 *(LCI-5)*	Non-MPK= 40.4 ± 7.6, MPK= 42.8 ± 6.2				
	Mileusnic et al. 2017 *(LCI-5)*	Non-MPK= 37.7 ± 11.2, MPK= 40.0 ± 12.7				
Houghton Scale	Mileusnic et al. 2017	Non-MPK= 7.0 ± 2.2, MPK= 8.0 ± 2.7				
	Miller et al. 2001		8.7		8.5	
	Wong et al. 2015		6.6 ± 4.8		6.4 ± 4.0	7.6 ± 3.1

	PLUS-M	Mileusnic et al. 2017	Non-MPK= 45.5 ± 7.0, MPK= 48.3 ± 10.7				
		Sawers & Hafner 2022		58.0		57.1	54.5
Functional Mobility	**BBS**	Cowley & Kerr 2001	38.3 BL, 44.3 6wks, 44.0 3mo				
		Jayaraman et al. 2021	37 ± 8= BL, Non-MPK = 39 ± 15, MPK = 44 ± 13				
		Wong et al. 2015				**36.3 ± 16.6***	**48.8 ± 5.9***
	TUG (s)	Christiansen et al. 2020	Group 1: 19.4= BL, 18.0= 12w, 15.3= 24w; Group 2: 14.9 BL, 14.8= 12w, 14.5= 24w				
		Cowley & Kerr 2001	34.1= BL, 14.4= 6wks, 17.0= 3mo				
		Dite et al. 2007				**16.2s ± 5.3***	**25s ± 6.9***
		Hafner & Askew 2015	Active knee: 11.1= BL, 13.7= interv; Adaptive knee: 11.5= BL, 10.6= interv				
		Hakim et al. 2018		10.7 ± 2.6*			**14.8 ± 7.3***
		Jayaraman et al. 2021	27.5 ± 15= BL, Non-MPK = 29.0 ± 16.3, MPK= 25.3 ± 14.1				
		Lansade et al. 2018	Non-MPK 23.1s ± 5.4, MPK= 19.4s ± 5.1				
		Sawers & Hafner 2022		9.4s		10.3s	10.4s
	2MWT	Anderson et al. 2021		313.9 ± 121.6	298.2 ± 111.5		

		Christiansen et al. 2020	Group 1: 97.7= BL, 85.5= 12w, 103.4= 24w; Group 2: 101.8 BL, 101.3= 12w, 103.3= 24w				
	AMPPRO	Hakim et al. 2018		**41.7 ± 3.1***			**36.9 ± 7.4***
		Hordacre et al. 2015		43.0 ± 3.2	39.6 ± 7.2		
		Jayaraman et al. 2021	31 ± 7= BL, Non-MPK = 35 ± 6, MPK = 36 ± 5				
	FSST (s)	Dite et al. 2007				**17.6 ± 8.3***	**32.6 ± 10.1***
		Jayaraman et al. 2021	17.4 ± 5.0= BL, Non-MPK = 19.6 ± 12.4, MPK = 16.8 ± 11.2				
		Sawers & Hafner 2022		9.1		9.4	8.6
	10MWT (s)	Jayaraman et al. 2021	9.7= BL, 7.8= Non-MPK, 7.3= MPK				
		Sawers & Hafner 2022		8.3		8.8	8.5

Supplemental Table 2: Clinical outcome measure scores reported by at least 2 included studies in this review. Means with standard deviations (±). Bold text with asterisk (*) indicates the study found a significant association with falls, further described in Table 4. All functional outcomes collected at comfortable walking speed. Abbreviations: ABC= Activities-Specific Balance Confidence scale, FES= Falls Efficacy Scale, SF-36= 36-Item Short Form, PEQ-MS= Prosthetic Evaluation Questionnaire Mobility Subscale, PEQ-A= Prosthetic Evaluation Questionnaire- Ambulation, LCI= Locomotor Capabilities Index, PLUS-M= Prosthetic Limb Users Survey of Mobility, BBS= Berg Balance Scale, TUG= Timed Up and Go, 2MWT= 2-minute walk test, AMPPRO= Amputee Mobility Predictor, FSST= Four Square Step Test, 10MWT= 10-meter walk test, BL= baseline, interv= intervention, MPK= Microprocessor knee, wks= weeks, mo= months.

Supplemental Table 3: Gait Parameters Associated with Falls

			All participants	**Non-Fallers**	**Fallers (not distinguished by single or recurrent)**	**Single Fallers**	**Recurrent Fallers**
Spatiotemporal	**Step counts**	Anderson et al. 2021		1669.7 ± 1386.2	1582.3 ± 1393.6		
		Christiansen et al. 2020	Group 1: BL= 1862, 12wks= 1609, 24wks= 1716; Group 2: BL= 1869, 12wks= 1897, 24wks= 1773				
		Hafner & Askew 2015	Active knee: BL= 2204.4, Interv= 1942.5; Adaptive knee: BL= 2238.9, Interv= 2041.4				
		Hordacre et al. 2015	2124				
	Walking speed (m/s)	Anderson et al. 2021		0.866 ± 0.308	0.825 ± 0.278		
		Jayaraman et al. 2021 *(calculated from 10MWT)*	BL= 1.0, Non-MPK= 1.3, MPK= 1.4				
		Kaufman et al. 2018	88% had < 0.5				
		Schafer et al. 2018	BL= 0.77, 12mo= 0.98				
		Sawers & Hafner 2022 *(calculated from 10MWT)*		1.2		1.8	1.1

		Vanicek et al. 2009		1.07 ± 0.2	1.19 ± 0.35		
	Step length	Schafer et al. 2018 *(m)*	BL: I= 0.52 ± 0.1, P= 0.55 ± 0.1; 12mo: 0.52 ± 0.1, P= 0.62 ± 0.1				
		Vanicek et al. 2009 *(% body height)*		I= 0.35 ± 0.1, P= 0.37 ± 0.1	I= 0.37 ± 0.1, P= 0.38 ± 0.1		
	Cadence (steps/min)	Schafer et al. 2018	BL: I= 97 ± 20, P= 109 ± 8; 12mo: 78 ± 16, P= 88 ± 16				
		Vanicek et al. 2009		I= 106 ± 8, P= 104 ± 10	I= 106 ± 9, P= 105 ± 6		
	DLS (%)	Schafer et al. 2018	BL= 31.4 ± 7, 12mo= 27.0 ± 3.7				
		Vanicek et al. 2009		30 ± 4	27 ± 7		
	Stance (%)	Schafer et al. 2018	BL: I= 71.3 ± 5.7, P= 59.7 ± 2.0; 12mo: I= 68.6 ± 4.8, P= 56.4 ± 3.2				
		Vanicek et al. 2009		I= 66 ± 3, P= 63 ± 3	I= 65 ± 4, P= 62 ± 3		
Kinematics ***(joint angles in degrees)***	**Peak hip adduction (stance)**	Schafer et al. 2018	BL: I= -0.7 ± 4.9, P= -7.2 ± 7.1; 12mo: I= -0.3 ± 5.7, P= -6.2 ± 4.7				
		Vanicek et al. 2009		I= 5.8 ± 5.4, P= 0.4 ± 2.4	I= 4.9 ± 5.4, P= 2.3 ± 3.8		
	Peak hip abduction (swing)	Schafer et al. 2018	BL: I= -9.7 ± 3.7, P= 4.7 ± 7.4; 12mo: I= 9.2 ± 6.9, P= 5.2 ± 6.7				

		Vanicek et al. 2009		I= -2.2 ± 5.5, P= -6.1 ± 1.9	I= -4.8 ± 4.8, P= -6.0 ± 4.2		
	Peak hip extension	Schafer et al. 2018	BL: I= -9.2 ± 9.1, P= -9.5 ± 14.0; 12mo: I=-22.2 ± 4.5, P= -23.5 ± 3.1				
		Vanicek et al. 2009		I= 0.6 ± 5.5, P= 6.6 ± 8.6	I= -1.3 ± 8.5, P= -0.7 ± 8.5		
	Peak knee flexion (loading response)	Schafer et al. 2018	BL: I= 4.0 ± 7.3, P= 0.8 ± 8.7; 12mo: I= 7.5 ± 9.2, P= 1.7 ± 10.0				
		Vanicek et al. 2009		I= 17.2 ± 3.2, P= 19.8 ± 13.5	I= 18.0 ± 4.4, P= 15.1 ± 4.6		
	Peak knee flexion (swing)	Schafer et al. 2018	BL: I= 56.7 ± 6.5, P= 40.3 ± 20.6; 12mo: I= 63.7 ± 4.0, P= 49.4 ± 14.8				
		Vanicek et al. 2009		I= 59.4 ± 3.8, P= 73.2 ± 13.5	I= 61.7 ± 5.1, P= 66.5 ± 7.8		
	Peak ankle dorsiflexion (terminal stance)	Schafer et al. 2018	BL: I= 17.0 ± 3.5, P= 14.5 ± 6.4; 12mo: I= 17.8 ± 2.7, P= 11.0 ± 4.2				
		Vanicek et al. 2009		I= 17.8 ± 2.7, P= 16.7 ± 3.9	I= 17.2 ± 4.2, P= 15.7 ± 2.3		

	Peak ankle plantarflexion	Schafer et al. 2018	BL: I= -12.2 ± 5.2, P= -9.9 ± 7.0; 12mo: I= -14.3 ± 2.8, P= -2.8 ± 3.5				
		Vanicek et al. 2009		I= -10.6 ± 6.8 P= 3.1 ± 2.9	I= -3.6 ± 8.0, P= 8.4 ± 2.2		
Kinetics	**Peak braking force (N/kg)**	Schafer et al. 2018	BL: I= -0.12 ± 0.07, P= -0.09 ± 0.05; 12mo: I= -0.16 ± 0.06, P= -0.10 ± 0.05				
		Vanicek et al. 2009		I= -0.20 ± 0.03, P= -0.10 ± 0.03	I= -0.18 ± 0.06, P= -0.12 ± 0.03		
	Peak propulsion force (N/kg)	Schafer et al. 2018	BL: I= 0.17 ± 0.04, P= 0.05 ± 0.04; 12mo: I= 0.20 ± 0.04, P= 0.09 ± 0.04				
		Vanicek et al. 2009		I= 0.17 ± 0.06, P= 0.13 ± 0.02	I= 0.16 ± 0.07, P= 0.12 ± 0.03		
	Peak vGRF 1 (loading response) (N/kg)	Schafer et al. 2018	BL: I= 0.97 ± 0.14, P= 1.01 ± 0.13; 12mo: I= 1.05 ± 0.16, P= 1.01 ± 0.16				
		Vanicek et al. 2009		**I= 1.14 ± 0.10, P= 1.01 ± 0.03***	I= 1.14 ± 0.28, **P= 1.10 ± 0.05***		
	Peak vGRF 2 (pre-swing) (N/kg)	Schafer et al. 2018	BL: I= 0.93 ± 0.09, P= 0.95 ± 0.07; 12mo: I=				

			1.06 ± 0.12, P= 0.90 ± 0.09				
		Vanicek et al. 2009		I= 1.07 ± 0.12, P= 0.98 ± 0.08	I= 1.02 ± 0.23, P= 1.06 ± 0.08		
	Hip extensor moment (loading reaponse) (Nm/kg)	Schafer et al. 2018	BL: I= 0.42 ± 0.26, P= 0.28 ± 0.48; 12mo: I= 0.61 ± 0.22, P= 0.52 ± 0.23				
		Vanicek et al. 2009 (estimated from graph)		I= -0.6, P= -0.6	I= -0.9, P= -0.75		
	Ankle plantarflexor moment (preswing) (Nm/kg)	Schafer et al. 2018	BL: I= 0.99 ± 0.28, P= 1.10 ± 0.35; 12mo: I= 1.33 ± 0.13, P= 1.08 ± 0.39				
		Vanicek et al. 2009 (estimated from graph)		I= 1.3, P= 0.8	I= 1.4, P= 1.2		
	H2 Power (W/kg)	Schafer et al. 2018	BL: I= -0.39 ± 0.20, P= -0.35 ± 0.21; 12mo: I= -0.46 ± 0.29, P= -0.74 ± 0.50				
		Vanicek et al. 2009 (estimated from graph)		**I= -0.2*, P= -0.5**	**I= -0.8*,** P= -0.5		
	H3 Power (W/kg)	Schafer et al. 2018	BL: I= 0.60 ± 0.33, P= 0.36 ± 0.19; 12mo: I= 0.99 ± 0.32, P= 0.87 ± 0.57				

		Vanicek et al. 2009 (estimated from graph)		I= 0.6, P= 0.7	I= 0.8, P= 0.8		
	A1 Power (W/kg)	Schafer et al. 2018	BL: I= -0.56 ± 0.22, P= -0.51 ± 0.29; 12mo: I= -0.86 ± 0.25, P= -0.67 ± 0.26				
		Vanicek et al. 2009 (estimated from graph)		**I= -1.0*, P= -0.5**	**I= -0.5*,** P= -0.4		
	A2 Power (W/kg)	Schafer et al. 2018	BL: I= 1.49 ± 0.60, P= 0.48 ± 0.29; 12mo: I= 2.81 ± 0.29, P= 0.50 ± 0.27				
		Vanicek et al. 2009 (estimated from graph)		I= 1.9, P= 0.4	I= 2.1, P= 0.4		

Supplemental Table 3: Gait parameters reported by at least 2 included studies in this review. Means with standard deviations (±). Bold text with asterisk (*) indicates the study found a significant association with falls. All Schafer et al. 2018 values depict the exercise group. 'Calculated by 10MWT' indicates the first author calculated walking speed from reported 10MWT times. 'Estimated from graph' indicates values were visually estimated from a graph. Abbreviations: DLS= double limb support, ROM= range of motion, BL= baseline, Interv= intervention, wks= weeks, mo= months, I= intact side, P=prosthetic side, H= hip power bursts, A= ankle power bursts.

Chapter 6

Supplemental Table 1: Detailed Demographics

	Sex	Age (years)	BMI (kg/m^2)	Race	Ethnicity	Primary Cause of Death	Side/Level of Amputation	Percent Residual Limb Length of Intact (%)
Healthy Controls								
	Male	50	24.31	White	Not Hispanic, Latino or Middle Eastern	Natural	N/A	N/A
	Male	62	24.36	White	Not Hispanic, Latino or Middle Eastern	Natural	N/A	N/A
	Male	56	25.1	White	Hispanic or Latino	Natural	N/A	N/A
	Male	59	25.91	White	Not Hispanic, Latino or Middle Eastern	Natural	N/A	N/A
	Male	76	26.79	White	Hispanic or Latino	Natural	N/A	N/A
	Male	74	28.58	White	Not Hispanic, Latino or Middle Eastern	Natural	N/A	N/A
	Male	60	35.39	White	Not Hispanic, Latino or Middle Eastern	Natural	N/A	N/A
	Male	44	40.78	White	Not Hispanic, Latino or Middle Eastern	Natural	N/A	N/A
	Male	44	48.14	White	Hispanic or Latino	Natural	N/A	N/A
	Male	50	29.9	White	Not Hispanic, Latino or Middle Eastern	Natural	N/A	N/A
Diabetic Controls								
	Male	58	21.57	White	Hispanic or Latino	Diabetes	N/A	N/A
	Male	60	24.93	White	Hispanic or Latino	Diabetes	N/A	N/A
	Male	47	26.09	White	Not Hispanic, Latino or Middle Eastern	Diabetes	N/A	N/A
	Male	71	23.88	White	Not Hispanic, Latino or Middle Eastern	Diabetes	N/A	N/A
	Male	51	27.32	White	Hispanic or Latino	Diabetes	N/A	N/A
	Male	52	34.46	White	Hispanic or Latino	Diabetes	N/A	N/A
	Male	43	33.83	Native American	Not Hispanic, Latino or Middle Eastern	Diabetes	N/A	N/A
	Male	46	36.08	White	Not Hispanic, Latino or Middle Eastern	Diabetes	N/A	N/A
	Male	47	41.94	White	Not Hispanic, Latino or Middle Eastern	Diabetes	N/A	N/A
	Male	65	22.1	White	Not Hispanic, Latino or Middle Eastern	Diabetes	N/A	N/A
IWAs								
Diabetic	Male	42	44.41	ck or African Ameri	Not Hispanic, Latino, or Middle Eastern	Diabetes	Bilateral TT	N/A- bilateral
	Male	59	24.43	White	Hispanic or Latino	Diabetes	Right TF	26.35
	Male	59	26.16	White	Not Hispanic, Latino, or Middle Eastern	Diabetes	Bilateral TF	N/A- bilateral
	Male	56	37.68	White	Not Hispanic, Latino, or Middle Eastern	Diabetes	Left TT	ND- femur not in frame
	Male	68	25.08	White	Not Hispanic, Latino, or Middle Eastern	Diabetes	Left TT	65.25
Non-Diabetic	Male	66	34.35	Hispanic	Hispanic or Latino	Sepsis	Right TT	59.28
	Male	50	48.88	White	Not Hispanic, Latino, or Middle Eastern	Natural	Right TF	ND- femur not in frame
	Male	74	25.97	White	Not Hispanic, Latino, or Middle Eastern	Natural	Right TF	44.98
	Male	66	24.11	Native American	Not Hispanic, Latino, or Middle Eastern	Sepsis	Right TT	60.64
	Male	79	19.72	White	Not Hispanic, Latino, or Middle Eastern	Sepsis	Left TT	67.41

Supplemental Table 1: Demographic characteristics of all individuals included in this study as reported in the New Mexico Decedent Image Database. Abbreviations: IWAs= individuals with lower-limb amputation, TT= transtibial, TF= transfemoral, ND= no data collected.

Supplemental Table 2: Raw Data for Joint Space, Tissue Area, and Femur Morphology

LEFT (Intact Limb for IWAs)

ID	Treatment	Age	BMI	Hip Joint Space (mm)	Knee Joint Space (mm)	AP Femoral Head (mm)	ML Femoral Head (mm)	Femoral Head Ratio (AP:ML)	Femoral Neck Width (mm)	Femoral Diaphysis Width (mm)	Muscle Area (mm^2)	Fat Area (mm^2)
112016	Healthy	62	24.35918367	3.562	4.7362	51.22	49.99	1.024604921	34.59	33.31	8051	5171.8
153971	Healthy	76	26.79493802	3.117	4.3116	49.89	47.83	1.043069203	35.85	33.9	11004.7	8232.04
190245	Healthy	50	29.9	1.557	4.782	48.94	51.16	0.956606724	38.82	36.11	15491.6	7868.49
135307	Healthy	50	24.3064887	1.944	5.249	51.97	49.36	1.052876823	29.57	35.13	14177.2	4375.61
161045	Healthy	56	25.10387812	2.079	8.01	38.84	39.66	0.979324256	25.82	24.96	8765.6	4213.89
126148	Healthy	59	25.90945695	6.172	7.446	47.65	50.88	0.936517296	32.8	31.94	12321.9	3507.91
106936	Healthy	74	28.58024691	3.513	5.417	44.9	47.11	0.953088516	29.85	32.37	12204.6	8946.05
148390	Healthy	60	35.3921538	5.34	10.013	40.38	39.84	1.013554217	33.37	32.05	12903.4	8845.38
115479	Healthy	44	40.78019596	5.128	9.198	48.87	49.73	0.982706616	29.4	32.96	15872.2	9304.98
101808	Healthy	44	48.141251	5.551	4.977	41.98	42.19	0.995022517	27.49	29.55	14516.8	29527.7
150158	Diabetic	58	21.56683432	1.648	4.748	39.49	39.9	0.989724311	29.23	28.39	6869.1	4422.16
169853	Diabetic	60	24.92565739	1.538	4.532	46.24	47.97	0.963935793	27.33	29.44	9670.8	6088.67
101413	Diabetic	47	26.09418283	2.555	7.859	44.27	46.05	0.961346363	29.49	37.77	10706.8	8181.76
[illegible]	Diabetic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	3027.95
[illegible]	Diabetic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	6447.3
[illegible]	Diabetic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	3582.95
[illegible]	Diabetic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	12337.8
[illegible]	Diabetic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	16783.7
[illegible]	Diabetic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	12360.9
[illegible]	Diabetic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	23634.3
[illegible]	Non-diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8729.33
[illegible]	Non-diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	3221.35
[illegible]	Non-diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9372.71
[illegible]	Non-diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	6839.44
[illegible]	Non-diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	Diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	6217.26
[illegible]	Diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4069.33
[illegible]	Diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4055.02
[illegible]	Diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1031.12
[illegible]	Diabetic IWA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	17261.3

RIGHT (Residual Limb for IWAs)

ID	Hip Joint Space (mm)	Knee Joint Space (mm)	AP Femoral Head (mm)	ML Femoral Head (mm)	Femoral Head Ratio (AP:ML)	Femoral Neck Width (mm)	Femoral Diaphysis Width (mm)	Muscle Area (mm^2)	Fat Area (mm^2)
112016	3.6074	5.9251	51.17	55.36	0.924313584	36.03	33.04	10050.3	5095.28
153971	2.81442	7.3631	48.19	50.81	0.948435347	34.57	32.29	11363.1	7970.66
190245	1.899	4.889	48.71	51.35	0.948588121	39.3	36.3	15261.5	8728.14
135307	1.996	4.369	50.66	52.3	0.968642447	32.7	33.81	10532.2	3505.25
161045	2.837	6.961	40.71	41.19	0.988346686	23.44	24.59	9393.37	4042.28
126148	5.07	7.807	45.39	50.64	0.896327014	33.79	31.12	10088.4	3713.83
106936	3.466	8.826	46.89	48.5	0.966804124	28.48	32.08	12117.7	10458.5
148390	4.557	11.418	43.38	43.24	1.003237743	33.46	32.55	12967.8	8325.51
115479	6.363	11.03	47.14	46.59	1.011805108	30.91	32.54	16228.5	10631.7
101808	5.093	5.843	39.28	38.6	1.01761658	27.18	28.89	13825.5	27178.3
150158	1.362	4.47	40.31	39.99	1.008002001	27.83	28.52	5060.67	4997.12
169853	1.722	3.349	48.97	49.15	0.996337742	30.77	30.04	10245.3	5194.16
101413	2.648	5.632	48.27	48.48	0.995668317	31.05	39.9	10095.8	7791.14
[illegible]	2.312	5.111	50.9	50.08	1.016373802	38.34	34.83	7763.06	3272.09
[illegible]	0.852	4.793	45.1	44.35	1.016910936	30.32	27.7	7923.66	6006.56
[illegible]	6.209	8.776	44.58	46.33	0.962227498	33.03	34.3	8321.76	3635.41
[illegible]	5.994	9.539	38.41	39.06	0.983358935	32.22	33.01	10216.2	11406.2
[illegible]	4.249	7.521	45.42	45.98	0.987820792	33.49	32.58	13155.9	16986.8
[illegible]	7.055	9.095	41.78	42.77	0.976852934	29.09	33.26	15260.1	12176.4
[illegible]	5.586	6.19	44.61	46.96	0.949957411	34.36	28.26	12485.6	23454.8
[illegible]	2.336	4.479	42.49	42.51	0.9995	29.33	26.77	12149.2	12019.7
[illegible]	2.022	2.365	47.11	50.11	0.9401	34.75	48.04	6047.7	3051.7
[illegible]	1.073		43.87	50.09	0.8758	28.85	32.06	9959.22	8602.14
[illegible]	1.995	4.54	45.36	47.52	0.9545	29.8	29.11	6889.3	6979.19
[illegible]	1.56		53.62	53.57	1.0009	35.47			
[illegible]	1.086	2.854	42.78	46.83	0.9135	38.54	35.26	11290.1	7303.15
[illegible]	1.656		47.02	49.31	0.9536	32.56	32.77	3117.56	4516.6
[illegible]	1.508	4.424	49.97	53.65	0.9314	37.16	34.71	8236.88	4455.57
[illegible]	1.466		45.62	45.95	0.9928	33.21	28.95	2890.7	596.846
[illegible]	1.19	4.022	50.72	47.42	1.0696	36.03	30.18	9543.81	17398.7

LEFT & RIGHT AVERAGED (Controls Only)

ID	Hip Joint Space (mm)	Knee Joint Space (mm)	AP Femoral Head (mm)	ML Femoral Head (mm)	Femoral Head Ratio (AP:ML)	Femoral Neck Width (mm)	Femoral Diaphysis Width (mm)	Muscle Area (mm^2)	Fat Area (mm^2)
112016	3.5847	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
153971	2.96571	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
190245	1.728	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
135307	1.97	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
161045	2.458	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
126148	5.621	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
106936	3.4895	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
148390	4.9485	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
115479	5.7455	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
101808	5.322	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
150158	1.505	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
169853	1.63	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
101413	2.6015	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	2.3345	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	1.02	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	6.405	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	5.312	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	4.2945	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	6.544	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	5.585	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]									
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[illegible]									

Supplemental Table 2: All raw 3D Slicer data for joint space, tissue area, and femur morphology. Abbreviations: IWAs= individuals with lower-limb amputation, SD= standard deviation, AP= anterior-posterior, ML= medial-lateral.

Supplemental Table 3: Raw Data for Femur Geometry

			LEFT (Intact Limb for IWAs)						RIGHT (Residual Limb for IWAs)						RIGHT & LEFT AVERAGED (Controls only)					
ID	Treatment	Regions	CSA (mm^2)	Imin (mm^4)	Imax(mm^4)	Max Thick 2d (mm)	Mean Thick 2d (mm)	SD Thick 2d (mm)	CSA (mm^2)	Imin (mm^4)	Imax(mm^4)	Max Thick 2d (mm)	Mean Thick 2d (mm)	SD Thick 2d (mm)	CSA (mm^2)	Imin (mm^4)	Imax(mm^4)	Max Thick 2d (mm)	Mean Thick 2d (mm)	SD Thick 2d (mm)
112016	Healthy	25%	536.24900	47795.033	34425.758	9.35200	7.91200	1.04600	515.60100	47679.521	32451.046	7.79300	7.34600	0.55500	525.925	47737.277	33438.402	8.5725	7.629	0.8005
112016	Healthy	50%	528.35400	39852.564	35573.012	9.48100	8.17200	1.12000	493.73800	35859.457	30810.981	9.35200	7.77200	0.94000	511.046	37856.0105	33191.9965	9.4165	7.972	1.03
112016	Healthy	75%	337.66100	44208.71	32787.616	4.67600	4.10100	0.57900	346.16300	41276.64	34486.852	4.92900	4.15600	0.53900	341.912	42742.675	33637.234	4.8025	4.1285	0.559
153971	Healthy	25%	455.91200	38147.743	26830.271	8.02100	6.77100	0.81500	473.50500	41109.678	31347.923	8.50800	6.83500	1.10700	464.7085	39628.7105	29089.097	8.2645	6.803	0.961
153971	Healthy	50%	430.77900	35516.89	23650.485	9.07900	6.91100	1.17200	434.29700	36130.607	24724.109	9.07900	6.78100	1.17300	432.538	35823.7485	24187.297	9.079	6.846	1.1725
153971	Healthy	75%	327.23100	43998.281	33862.054	4.48400	3.76800	0.54400	325.723	40867.963	37468.744	4.48400	3.80600	0.50400	326.477	42433.122	35665.399	4.484	3.787	0.524
190245	Healthy	25%	594.09200	52794.674	41451.383	10.78100	8.67500	1.32000	586.02000	50529.127	42769.897	10.78100	8.71300	1.23200	590.056	51661.9005	42110.64	10.781	8.694	1.276
190245	Healthy	50%	617.50000	56653.657	42533.725	11.50600	9.12500	1.45300	628.80100	60351.99	43315.198	12.70600	9.43300	1.93200	623.1505	58502.8235	42924.4615	12.106	9.279	1.6925
190245	Healthy	75%	489.15700	67401.221	55244.872	7.18800	5.53700	0.63600	494.00000	70072.774	58504.05	6.47900	5.51100	0.78500	491.5785	68736.9975	56874.461	6.8335	5.524	0.7105
135307	Healthy	25%	508.42300	43969.415	35905.361	9.50400	7.49500	1.13200	515.74700	43452.676	37456.465	9.11100	7.51600	0.96000	512.085	43711.0455	36680.913	9.3075	7.5055	1.046
135307	Healthy	50%	505.98100	49191.882	29270.288	11.04900	7.81300	1.73200	535.27800	48541.265	32143.417	10.00500	8.31200	1.14600	520.6295	48866.5735	30706.8525	10.527	8.0625	1.439
135307	Healthy	75%	428.46700	51059.528	44597.676	6.25000	5.13000	0.67900	457.15300	55653.3	49655.865	6.44200	5.36300	0.57100	442.81	53356.414	47126.7705	6.346	5.2465	0.625
161045	Healthy	25%	340.76800	18097.068	14138.023	6.99200	6.48100	0.65800	327.07900	17296.94	14260.918	6.99200	6.19900	0.81600	333.9235	17697.004	14199.4705	6.992	6.34	0.737
161045	Healthy	50%	345.65700	17546.263	11922.326	8.84400	7.33600	1.07100	326.59000	15379.582	11317.34	8.39100	6.93900	1.01100	336.1235	16462.9225	11619.833	8.6175	7.1375	1.041
161045	Healthy	75%	289.92200	19557.572	14835.758	5.04200	4.69400	0.42400	281.12200	17563.884	13192.064	5.93300	4.81100	0.74100	285.522	18560.728	14013.911	5.4875	4.7525	0.5825
126148	Healthy	25%	463.72200	37741.744	25873.299	7.64000	7.24600	0.45100	473.45100	39990.49	27213.908	9.00400	7.29700	0.77300	468.5865	3.89E+04	2.65E+04	8.322	7.2715	0.612
126148	Healthy	50%	445.07600	36779.258	24453.389	9.69800	7.36100	1.38400	463.72200	40327.716	23796.112	10.18700	7.49500	1.64100	454.399	38553.487	24124.7505	9.9425	7.428	1.5125
126148	Healthy	75%	353.46700	39451.556	31344.256	5.09300	4.36000	0.77100	384.27300	41247.54	32540.738	7.20300	5.07000	0.98800	368.87	40349.548	31942.497	6.148	4.715	0.8795
106936	Healthy	25%	581.32000	51477.421	37333.965	10.23400	8.72300	0.99000	558.27700	51166.04	38321.273	8.43900	7.96800	0.61700	569.7985	5.13E+04	3.78E+04	9.3365	8.3455	0.8035
106936	Healthy	50%	499.62100	42511.724	31290.336	10.23400	7.86700	1.38300	536.28100	46146.881	31584.756	11.57900	8.59600	1.60400	517.951	44329.3025	31437.546	10.9065	8.2315	1.4935
106936	Healthy	75%	384.40500	53149.897	39781.938	4.57700	4.40600	0.22600	399.06900	47217.611	38693.713	5.78900	4.84500	0.64200	391.737	50183.754	39237.8255	5.183	4.6255	0.434
148390	Healthy	25%	513.49100	37259.402	31342.33	10.66400	8.59500	1.42600	543.66200	41225.563	32466.832	10.77200	8.84400	1.22300	528.5765	3.92E+04	3.19E+04	10.718	8.7195	1.3245
148390	Healthy	50%	513.49100	44388.288	29208.751	10.98600	8.52000	1.98600	540.76100	47902.384	32678.267	12.18800	9.08500	2.29600	527.126	46145.336	30943.509	11.587	8.8025	2.141
148390	Healthy	75%	375.98000	51833.345	43225.11	6.09400	4.33600	0.73400	420.65600	50122.836	41688.516	6.09400	4.93600	0.71000	398.318	50978.0905	42456.813	6.094	4.636	0.722
115479	Healthy	25%	545.14600	52899.085	34033.646	8.34600	7.70500	0.77000	575.95200	55905.677	34754.561	9.82000	8.39200	0.92200	560.549	5.44E+04	3.44E+04	9.083	8.0485	0.846
115479	Healthy	50%	529.07300	44448.932	35346.11	10.35200	8.05600	1.30000	544.47600	46548.732	37575.213	11.45700	8.38200	1.63900	536.7745	45498.832	36460.6615	10.9045	8.219	1.4695
115479	Healthy	75%	422.58800	69498.889	48671.249	5.90100	4.44000	0.83500	404.50600	73077.738	47384.333	5.17600	4.13100	0.71900	413.547	71288.3135	48027.791	5.5385	4.2855	0.777
101808	Healthy	25%	501.23400	36018.384	29425.778	8.71900	8.06000	0.88500	612.88400	48128.908	43127.156	10.89800	9.11300	1.25700	557.059	4.21E+04	3.63E+04	9.8085	8.5865	1.071
101808	Healthy	50%	513.112	34663.313	27555.035	10.898	9.078	1.262	527.365	42260.857	31903.978	9.748	8.459	1.057	520.2385	38462.085	29729.5065	10.323	8.7685	1.1595
101808	Healthy	75%	413.34000	41025.937	35333.168	6.16500	5.50900	0.71200	391.96100	67350.808	41016.942	6.53900	4.64100	0.64700	402.6505	54188.3725	38175.055	6.352	5.075	0.6795
150158	Diabetic	25%	416.549	23148.509	18787.784	9.381	7.692	0.941	365.214	22281.663	12000.985	9.888	7.47	1.509	390.8815	22715.086	15394.3845	9.6345	7.581	1.225
150158	Diabetic	50%	403.837	22366.477	14076.16	9.888	8.22	0.964	351.524	19292.019	10833.371	8.506	7.27	1.226	377.6805	20829.248	12454.7655	9.197	7.745	1.095
150158	Diabetic	75%	357.88	23680.935	13767.557	6.992	6.342	0.597	329.523	24234.445	9346.118	6.992	5.833	0.678	343.7015	23957.69	11556.8375	6.992	6.0875	0.6375
169853	Diabetic	25%	507.047	42291.217	25012.71	10.272	8.271	1.237	519.943	42205.51	28480.36	10.719	8.387	1.465	513.495	42248.3635	26746.535	10.4955	8.329	1.351
169853	Diabetic	50%	503.53	30272.888	27393.768	9.805	8.901	0.799	533.426	35418.576	29213.264	10.719	9.276	0.97	518.478	32845.732	28303.516	10.262	9.0885	0.8845
169853	Diabetic	75%	375.743	36829.829	32678.696	6.314	4.919	0.653	413.258	40092.325	34802.756	6.314	5.486	0.648	394.5005	38461.077	33740.726	6.314	5.2025	0.6505
101413	Diabetic	25%	618.286	66960.468	46810.77	11.049	8.406	1.55	587.158	67543.844	42581.839	11.049	8.048	1.879	602.722	67252.156	44696.3045	11.049	8.227	1.7145
101413	Diabetic	50%	640.869	74725.569	45023.118	12.204	8.601	2.317	594.482	70734.043	40352.271	10.482	7.788	1.745	617.6755	72729.806	42687.6945	11.343	8.1945	2.031
101413	Diabetic	75%	447.388	71343.028	69008.481	6.629	4.603	0.862	422.363	67220.95	61741.17	5.634	4.415	0.703	434.8755	69281.989	65374.8255	6.1315	4.509	0.7825
165953	Diabetic	25%	659.79	65088.281	45491.469	11.375	9.51	1.634	690.308	73985.012	47171.666	11.9	9.97	1.567	675.049	69536.6465	46331.5675	11.6375	9.74	1.6005
165953	Diabetic	50%	663.452	60168.497	45132.431	11.375	9.869	1.259	624.39	54736.298	42434.018	11.049	9.151	1.588	643.921	57452.3975	43783.2245	11.212	9.51	1.4235
165953	Diabetic	75%	432.129	56103.638	48692.762	7.812	5.143	1.211	469.971	55736.25	49913.34	6.629	5.407	0.788	451.05	55919.944	49303.051	7.2205	5.275	0.9995
131646	Diabetic	25%	420.52	33856.06	21047.554	7.25	6.63	0.635	401.819	31853.834	20256.198	7.109	6.261	0.667	411.1695	32854.947	20651.876	7.1795	6.4455	0.651
131646	Diabetic	50%	387.161	21764.085	18169.001	8.291	6.975	0.846	379.58	21593.306	17217.136	8.531	6.836	0.96	383.3705	21678.6955	17693.0685	8.411	6.9055	0.903
131646	Diabetic	75%	346.726	27640.038	24253.461	5.688	5.015	0.495	296.689	26168.78	20398.693	5.688	4.3	0.545	321.7075	26904.409	22326.077	5.688	4.6575	0.52
188924	Diabetic	25%	510.216	48304.176	39942.946	7.812	6.919	0.594	523.567	50620.643	39788.832	8.053	7.252	0.704	516.8915	4.95E+04	3.99E+04	7.9325	7.0855	0.649
188924	Diabetic	50%	514.984	47709.436	30736.461	10.518	7.864	1.514	524.521	47244.793	34037.432	9.766	7.637	1.145	519.7525	4.75E+04	3.24E+04	10.142	7.7505	1.3295
188924	Diabetic	75%	422.478	53734.763	42456.583	5.859	4.98	0.769	415.802	56318.804	45687.747	5.859	4.653	0.69	419.14	5.50E+04	4.41E+04	5.859	4.8165	0.7295
168638	Diabetic	25%	463.028	44382.135	32792.647	8.301	6.56	1.133	511.949	40329	38049.075	9.68	7.663	1.207	487.4885	4.24E+04	3.54E+04	8.9905	7.1115	1.17
168638	Diabetic	50%	510.571	41930.351	31508.45	9.68	7.712	1.271	460.272	38878.855	27299.535	8.465	7.064	1.067	485.4215	40404.603	29403.9925	9.0725	7.388	1.169
168638	Diabetic	75%	384.479	35323.578	31866.422	5.986	5.297	0.707	265.276	33870.658	26698.308	3.712	3.273	0.454	324.8775	34597.118	29282.365	4.849	4.285	0.5805
117920	Diabetic	25%	512.123	38244.275	33140.337	8.735	7.755	0.893	502.586	35617.795	27026.806	9.766	8.197	1.357	507.3545	3.69E+04	3.01E+04	9.2505	7.976	1.125
117920	Diabetic	50%	520.706	43801.988	29383.683	11.389	8.514	1.669	461.578	39366.254	27336.917	9.766	7.314	1.41	491.142	4.16E+04	2.84E+04	10.5775	7.914	1.5395
117920	Diabetic	75%	374.794	53244.201	38563.914	6.176	4.373	0.768	370.026	63483.346	43662.925	4.367	4.043	0.224	372.41	5.84E+04	4.11E+04	5.2715	4.208	0.496
102676	Diabetic	25%	679.607	56390.424	43540.658	13.48	10.871	1.927	721.329	60990.162	46277.082	12.919	11.083	1.932	700.468	5.87E+04	4.49E+04	13.1995	10.977	1.9295
102676	Diabetic	50%	589.673	51207.612	37846.143	11.555	8.976	1.529	645.302	58622.108	41096.26	12.919	10.364	1.781	617.4875	5.49E+04	39471.2015	12.237	9.67	1.655
102676	Diabetic	75%	426.493	59403.898	47277.23	6.09	4.826	0.796	470.069	62865.881	51419.063	6.944	5.352	0.787	448.281	6.11E+04	4.93E+04	6.517	5.089	0.7915
141694	Diabetic	25%	559.121	43447.155	27899.167	12.163	9.927	1.612	507.995	39306.745	26355.318	10.43	8.512	1.614	533.558	4.14E+04	2.71E+04	11.2965	9.2195	1.613
141694	Diabetic	50%	517.785	34832.615	28162.746	10.636	9.308	1.311	486.239	32289.499	23544.174	10.43	8.879	1.361	502.012	3.36E+04	2.59E+04	10.533	9.0935	1.336
141694	Diabetic	75%	407.919	47800.71	35115.62	6.596	5.162	0.818	375.285	39924.5	30304.084	6.258	4.991	0.667	391.602	4.39E+04	32709.852	6.427	5.0765	0.7425
106139	Non-Diabetic IWAs	25%	445.45	39519.449	33722.198	8.027	6.319	1.21	378.54	34889.495	28381.521	7.04	5.505	1.177						
106139	Non-Diabetic IWAs	50%	469.613	35666.251	27855.956	8.477	7.109	1.046	428.103	30754.021	25313.238	9.197	6.756	1.523						
106139	Non-Diabetic IWAs	75%	311.01	38834.734	33857.707	4.723	3.832	0.608	281.272	33441.825	29228.211	4.723	3.566	0.795						
149800	Non-Diabetic IWAs	25%	587.373	65406.753	42896.487	10.41	8.131	1.491	615.55	67277.679	40364.555	10.41	8.359	1.508						
149800	Non-Diabetic IWAs	50%	577.62	59029.25	46037.903	9.311	7.725	1.104	555.945	53569.352	41985.082	11.212	8.302	1.596						
149800	Non-Diabetic IWAs	75%	446.49	87524.88	61926.399	5.889	4.427	0.448	493.09	87263.292	68115.938	6.246	4.96	0.747						
180518	Non-Diabetic IWAs	25%	794.225	108080.066	86212.864	10.621	8.925	1.176	844.531	120992.649	85371.373	11.18	9.505	1.016						
180518	Non-Diabetic IWAs	50%	894.837	131915.609	94402.878	11.043	9.48	1.114	833.098	126488.207	84627.111	13.637	9.754	2.047						
180518	Non-Diabetic IWAs	75%	605.196	142947.479	107798.463	6.296	5.184	0.996	621.965	142148.002	109807.546	6.984	5.577	0.836						
160926	Non-Diabetic IWAs	25%	454.938	44474.69	32541.818	7.813	6.402	0.781	449.216	42971.544	39582.342	7.813	6.416	0.826						
160926	Non-Diabetic IWAs	50%	405.343	32589.742	29870.43	7.813	5.999	1.052	454.938	38088.697	31418.208	8.735	6.941	1.149						
160926	Non-Diabetic IWAs	75%	254.651	30337.004	24173.475	4.367	3.348	0.8	265.142	31913.004	27125.32	4.367	3.428	0.849						
100065	Non-Diabetic IWAs	25%	379.779	22265.845	21195.65	8.477	6.665	1.034	349.421	22220.699	20953.855	7.871	5.817	1.131						
100065	Non-Diabetic IWAs	50%	390.311	28559.932	15396.071	8.477	7.033	1.07	340.748	24571.461	14742.32	7.871	5.994	1.458						
100065	Non-Diabetic IWAs	75%	343.226	27102.95	23851.382	6.297	5.063	0.887	236.665	20514.614	16673.189	5.676	3.818	1.133						
128438	Non-Diabetic IWAs	25%	648.194	61185.254	45974.719	10.482	9.39	0.738	432.587	42507.196	31021.868	7.031	6.054	0.902						
128438	Non-Diabetic IWAs	50%	615.235	46796.84	39557.143	11.719	10.287	1.514												
128438	Non-Diabetic IWAs	75%	530.091	61613.332	45869.411	7.412	6.654	0.725												
117549	Diabetic IWAs	25%	375.748	33142.907	24386.887	6.176	5.237	0.885	236.511	23224.848	19668.186	4.367	3.311	0.826						
117549	Diabetic IWAs	50%	378.609	30096.556	21958.11	6.176	5.42	0.856	216.484	18697.277	13726.931	4.367	3.232	0.905						
117549	Diabetic IWAs	75%	313.759	41305.661	32975.708	4.367	3.911	0.473												
156584	Diabetic IWAs	25%	519.753	49719.355	43555.895	9.766	7.094	1.714	545.502	51651.249	41961.567	9.766	7.487	1.471						
156584	Diabetic IWAs	50%	467.3	44626.389	28468.805	8.053	6.279	1.638	544.548	50825.022	31417.775	9.766	7.915	1.176						
156584	Diabetic IWAs	75%	367.165	42249.258	36441.618	5.524	4.358	0.702	385.284	43252.806	39098.548	5.859	4.926	0.757						
172930	Diabetic IWAs	25%	437.243	42189.954	36078.775	7.311	5.989	1.096	415.715	53696.554	36689.719	7.105	4.808	1.282						
172930	Diabetic IWAs	50%	435.016	36952.037	27403.488	7.706	6.545	1.065	480.299	36692.756	31084.519	8.616	7.605	1.06						
172930	Diabetic IWAs	75%																		
195499	Diabetic IWAs	25%	477.104	43529.412	33429.749	7.666	6.789	0.7	494.391	44116.894	34789.469	8.315	7.182	0.751						
195499	Diabetic IWAs	50%	481.426	40332.342	31145.798	7.666	7.02	0.816	413.145	34947.448	26036.852	7.889	6.449	1.094						
195499	Diabetic IWAs	75%	346.592	53820.397	39709.452	5.578	3.908	0.693	341.406	56898.198	45147.609	4.158	3.78	0.337						

Supplemental Table 3: All raw BoneJ data for femur geometry. Abbreviations: IWAs= individuals with lower-limb amputation, CSA= cross-sectional area, Imin= minimum moment of inertia, Imax= maximum moment of inertia, Max= maximum, SD=standard deviation, Thick= cortical bone thickness.

Supplemental Table 4: Joint Space, Tissue Area, and Femur Morphology *p*-values

	Hip Joint Space (mm)	Knee Joint Space (mm)	AP Femoral Head Width (	ML Femoral Head Width (	Femoral Head Ratio (AP/I	Femoral Neck Width (mm	Femoral Diaphysis Width	Muscle Area (mm^2)	Fat Area (mm^2)
Healthy Controls (n=10)	0.461	**0.032***	0.348	0.188	0.161	0.313	**0.019***	0.385	0.461
Diabetic Controls (n=10)	0.461	0.500	**0.014***	0.188	**0.032***	0.066	0.216	0.279	0.188
All IWAs (n=10)	0.161	0.422	0.313	0.279	0.348	0.077	0.151	**0.010***	0.213
Diabetic IWAs (n=5)	0.500	0.250	0.500	0.500	0.500	0.094	0.313	0.125	0.500
Non-diabetic IWAs (n=5)	0.157	0.250	0.313	0.219	0.313	0.393	0.219	**0.031***	0.156
Healthy vs Diabetic vs Intact Limbs of All IWAs	**0.002***	**< 0.001****	0.160	0.076	0.257	**0.023***	0.130	**0.013***	0.387
Healthy vs Diabetic vs Residual Limbs of All IWAs	**< 0.001****	**< 0.001****	0.250	0.134	0.324	0.130	0.488	**0.011***	0.450

Supplemental Table 4: All *p*-values for joint space, tissue area, and femur morphology. The significance level was set $\alpha \leq 0.05$. Abbreviations: IWAs= individuals with lower-limb amputation, SD= standard deviation; AP= anterior-posterior, ML= medial-lateral.

Supplemental Table 5: Femur Geometry *p*-values

			CSA (mm^2)	Imin (mm^4)	Imax(mm^4)	Max Thick 2d (mm)	Mean Thick 2d (mm)	SD Thick 2d (mm)
Table 3: Between-Limb Comparisons	**Proximal Femoral Shaft**	**Healthy Controls (n=10)**	0.216	0.116	**0.025***	0.304	0.313	0.461
	25%	**Diabetic Controls (n=10)**	0.423	0.439	0.348	0.207	0.385	0.097
		All IWAs (n=10)	0.188	0.500	0.116	0.097	0.101	0.385
		Diabetic IWAs (n=5)	0.156	0.219	0.219	0.087	0.157	0.313
		Non-diabetic IWAs (n=5)	0.500	0.219	0.157	0.286	0.342	0.500
	Middle Femoral Shaft	**Healthy Controls (n=10)**	0.116	0.116	0.116	0.154	0.279	0.216
	50%	**Diabetic Controls (n=10)**	0.188	0.116	0.097	0.080	0.461	0.279
		All IWAs (n=10)	0.248	0.213	0.102	0.065	0.410	**0.037***
		Diabetic IWAs (n=5)	0.313	0.438	0.188	0.125	0.875	0.063
		Non-diabetic IWAs (n=5)	0.406	0.219	0.156	0.219	0.406	0.313
	Distal Femoral Shaft	**Healthy Controls (n=10)**	0.188	0.385	0.080	0.091	0.161	0.254
	75%	**Diabetic Controls (n=10)**	0.141	0.423	0.216	**0.040***	0.188	**0.025***
		All IWAs (n=10)	0.469	0.407	0.344	0.466	0.407	0.289
		Diabetic IWAs (n=5)	0.313	0.188	0.313	0.420	0.438	0.188
		Non-diabetic IWAs (n=5)	0.250	0.250	0.125	0.500	0.250	0.500
Table 5: Between-Group Comparisons	**Proximal Femoral Shaft**	**Healthy vs Diabetic vs Intact Limbs of All IWAs**	0.414	0.485	0.443	0.133	0.066	0.172
		Healthy vs Diabetic vs Residual Limbs of All IWAs	0.259	0.431	0.482	0.053	**0.027***	0.127
	Middle Femoral Shaft	**Healthy vs Diabetic vs Intact Limbs of All IWAs**	0.389	0.498	0.498	**0.004***	**0.017***	0.110
		Healthy vs Diabetic vs Residual Limbs of All IWAs	0.409	0.482	0.500	0.098	0.097	0.307
	Distal Femoral Shaft	**Healthy vs Diabetic vs Intact Limbs of All IWAs**	0.473	0.489	0.494	0.218	0.144	0.109
		Healthy vs Diabetic vs Residual Limbs of All IWAs	0.275	0.356	0.349	0.202	0.174	**0.020***

Supplemental Table 5: All *p*-values for femur geometry. The significance level was set $\alpha \leq 0.05$. Abbreviations: IWAs= individuals with lower-limb amputations, CSA= cross-sectional area, Imin= minimum moment of inertia, Imax= maximum moment of inertia, Max= maximum, SD=standard deviation, Thick= cortical bone thickness.

Supplemental Table 6: Mann-Whitney *p*-values for post-hoc group comparisons

Significant Parameter (Kruskal-Wallis *p*-value)					
Hip Joint Space (p = 0.00	Healthy	Diabetic	All IWAs (Int)	Non-diabetic IWAs (Int)	Diabetic IWAs (Int)
Healthy					
Diabetic	0.398				
All IWAs (Int)	**< 0.001**	**0.026**			
Non-diabetic IWAs (Int)	**0.007**	0.065	0.4755		
Diabetic IWAs (Int)	**0.003**	0.277	0.4755	0.4585	
Hip Joint Space (p < 0.00	Healthy	Diabetic	All IWAs (Res)	Non-diabetic IWAs (Res)	Diabetic IWAs (Res)
Healthy					
Diabetic	0.398				
All IWAs (Res)	**< 0.001**	**0.015**			
Non-diabetic IWAs (Res)	**0.001**	0.083	0.212		
Diabetic IWAs (Res)	**< 0.001**	**0.020**	0.212	0.111	
Knee Joint Space (p < 0.0	Healthy	Diabetic	All IWAs (Int)	Non-diabetic IWAs (Int)	Diabetic IWAs (Int)
Healthy					
Diabetic	0.290				
All IWAs (Int)	**< 0.001**	**0.002**			
Non-diabetic IWAs (Int)	**< 0.001**	**0.004**	0.251		
Diabetic IWAs (Int)	**0.012**	**0.038**	0.219	0.143	
Knee Joint Space (p < 0.0	Healthy	Diabetic	All IWAs (Res)	Non-diabetic IWAs (Res)	Diabetic IWAs (Res)
Healthy					
Diabetic	0.2895				
All IWAs (Res)	**< 0.001**	**0.002**			
Non-diabetic IWAs (Res)	**0.004**	**0.014**	0.348		
Diabetic IWAs (Res)	**0.004**	**0.014**	0.348	0.350	
Femoral Neck Width (p =	Healthy	Diabetic	All IWAs (Int)	Non-diabetic IWAs (Int)	Diabetic IWAs (Int)
Healthy					
Diabetic	0.370				
All IWAs (Int)	**0.032**	**0.008**			
Non-diabetic IWAs (Int)	0.083	0.065	0.476		
Diabetic IWAs (Int)	0.056	**0.010**	0.476	0.459	
Muscle Area (p = 0.013)	Healthy	Diabetic	All IWAs (Int)	Non-diabetic IWAs (Int)	Diabetic IWAs (Int)
Healthy					
Diabetic	**0.032**				
All IWAs (Int)	**0.040**	0.453			
Non-diabetic IWAs (Int)	0.120	0.473	0.439		
Diabetic IWAs (Int)	0.065	0.477	0.447	0.453	
Muscle Area (p= 0.011)	Healthy	Diabetic	All IWAs (Res)	Non-diabetic IWAs (Res)	Diabetic IWAs (Res)
Healthy					
Diabetic	**0.032**				
All IWAs (Res)	**0.003**	0.106			
Non-diabetic IWAs (Res)	**0.027**	0.270	0.321		
Diabetic IWAs (Res)	**0.010**	0.103	0.344	0.278	
Proximal Femoral Shaft:	Healthy	Diabetic	All IWAs (Res)	Non-diabetic IWAs (Res)	Diabetic IWAs (Res)
Healthy					
Diabetic	0.685				
All IWAs (Res)	**0.022**	**0.010**			
Non-diabetic IWAs (Res)	**0.049**	**0.028**	0.475		
Diabetic IWAs (Res)	**0.065**	**0.038**	0.525	0.579	
Middle Femoral Shaft: Ma	Healthy	Diabetic	All IWAs (Int)	Non-diabetic IWAs (Int)	Diabetic IWAs (Int)
Healthy					
Diabetic	0.485				
All IWAs (Int)	0.010	0.014			
Non-diabetic IWAs (Int)	0.163	0.195	0.146		
Diabetic IWAs (Int)	**0.001**	**0.002**	0.147	**0.037**	
Middle Femoral Shaft: Me	Healthy	Diabetic	All IWAs (Int)	Non-diabetic IWAs (Int)	Diabetic IWAs (Int)
Healthy					
Diabetic	0.370				
All IWAs (Int)	0.038	0.022			
Non-diabetic IWAs (Int)	0.384	0.297	0.212		
Diabetic IWAs (Int)	**0.004**	**0.002**	0.212	0.111	
Distal Femoral Shaft: SD	Healthy	Diabetic	All IWAs (Res)	Non-diabetic IWAs (Res)	Diabetic IWAs (Res)
Healthy					
Diabetic	0.264				
All IWAs (Res)	0.044	0.067			
Non-diabetic IWAs (Res)	**0.007**	**0.007**	0.126		
Diabetic IWAs (Res)	0.469	0.469	0.084	**0.029**	

Supplemental Table 6: Mann-Whitney Comparisons for significant Kruskal-Wallis *p*-values. The significance level was set $\alpha \leq 0.05$. Abbreviations: IWAs= individuals with lower-limb amputations, Int= intact limb, Res= residual limb.

Chapter 7

Supplemental Table 1: Mean IMU and Motion Capture Data

		Participant 1		Participant 2		Participant 3		Participant 4		Participant 5	
		IMU	MoCap	IMU	MoCap	IMU	MoCap	IMU	MoCap	IMU	MoCap
	Double Limb Support (s)	0.26 ± 0.02	0.28 ± 0.02	0.24 ± 0.018	0.26 ± 0.07	0.20 ± 0.01	0.22 ± 0.07	0.25 ± 0.01	0.26 ± 0.02	0.22 ± 0.03	0.23 ± 0.13
Intact Limb	Single Limb Support (s)	0.69 ± 0.37	0.62 ± 0.01	0.53 ± 0.22	0.52 ± 0.16	0.58 ± 0.39	0.56 ± 0.42	0.43 ± 0.06	0.45 ± 0.10	0.49 ± 0.14	0.48 ± 0.13
	Hip Max Flex (∘)	20.31 ± 7.26	19.75 ± 3.40	15.00 ± 1.86	15.41 ± 2.41	15.04 ± 1.49	17.43 ± 0.86	18.36 ± 1.37	27.83 ± 0.47	21.48 ± 1.93	22.35 ± 0.80
	Hip Max Ext (∘)	-20.78 ± 4.89	-22.21 ± 7.88	-16.89 ± 1.34	-15.49 ± 2.29	-15.78 ± 0.80	-17.99 ± 1.78	-15.54 ± 0.48	-25.81 ± 1.71	-24.14 ± 1.26	-25.16 ± 1.13
	Hip ROM (∘)	41.09 ± 5.83	41.96 ± 5.18	31.89 ± 1.19	31.69 ± 5.43	30.83 ± 4.07	35.44 ± 4.31	33.89 ± 1.74	53.65 ± 1.49	45.62 ± 4.21	47.51 ± 3.01
	Knee Max Flex (∘)	15.47 ± 4.82	37.47 ± 2.92	50.41 ± 0.69	46.81 ± 12.61	54.39 ± 1.75	58.15 ± 1.99	50.60 ± 2.91	58.29 ± 3.59	58.71 ± 1.89	59.49 ± 1.06
	Knee Max Ext (∘)	-2.08 ± 0.52	-1.11± 2.84	-5.97 ± 1.18	0.62 ± 3.37	-2.31 ± 1.33	-1.51 ± 1.86	-9.54 ± 2.72	-10.73 ± 1,47	-0.77 ± 0.42	0.17 ± 0.40
	Knee ROM (∘)	17.55 ± 4.78	38.57 ± 1.83	56.37 ± 1.39	46.20 ± 11.15	52.08 ± 2.35	59.67 ± 2.10	60.14 ± 5.32	69.02 ± 5.02	59.49 ± 2.27	59.32 ± 0.92
	Ankle Max DF (∘)	19.96 ± 4.53	14.91 ± 2.76	14.89 ± 2.78	14.92 ± 7.44	9.03 ± 3.37	11.56 ± 0.38	12.26 ± 3.64	11.99 ± 0.32	12.39 ± 0.38	10.34 ± 0.91
	Ankle Max PF (∘)	-15.35 ± 1.72	-11.77 ± 1.98	-22.23 ± 1.29	-21.24 ± 1.04	-9.68 ± 0.39	-8.14 ± 1.85	-29.55 ± 4.66	-24.03 ± 1.93	-29.03 ± 2.51	-21.77 ± 1.25
	Ankle ROM (∘)	35.32 ± 4.34	26.68 ± 0.79	36.52 ± 1.72	36.16 ± 7.90	18.70 ± 2.24	19.69 ± 1.09	41.81 ± 8.29	36.02 ± 1.95	41.42 ± 2.50	32.11 ± 1.84
Prosthetic Limb	Single Limb Support (s)	0.64 ± 0.32	0.60 ± 0.003	0.48 ± 0.23	0.49 ± 0.13	0.61 ± 0.42	0.59 ± 0.433	0.47 ± 0.07	0.49 ± 0.06	0.51 ± 0.13	0.49 ± 0.05
	Hip Max Flex (∘)	20.16 ± 4.73	17.12 ± 4.75	16.72 ± 1.43	12.93 ± 0.25	16.13 ± 1.58	16.29 ± 0.58	18.65 ± 1.22	22.23 ± 0.37	25.93 ± 4.83	19.62 ± 0.48
	Hip Max Ext (∘)	-19.82 ± 5.34	-20.97 ± 5.91	-23.68 ± 0.55	-19.21 ± 4.95	-16.68 ± 0.71	-20.08 ± 0.37	-18.26 ± 2.84	-26.42 ± 0.97	-22.7 ± 4.90	-24.64 ± 1.35
	Hip ROM (∘)	39.98 ± 4.74	38.1 ± 1.42	40.41 ± 0.91	32.14 ± 4.97	32.81 ± 2.00	36.38 ± 0.95	36.91 ± 3.89	48.65 ± 0.59	48.65 ± 0.58	44.27 ± 0.87
	Knee Max Flex (∘)	27.27 ± 1.32	32.52 ± 1.39	41.77 ± 0.48	42.45 ± 10.05	40.12 ± 1.99	47.50 ± 1.07	57.48 ± 0.93	47.72 ± 4.74	59.47 ± 1.66	61.27 ± 0.90
	Knee Max Ext (∘)	-0.98 ± 4.82	-2.98 ± 0.74	-0.78 ± 0.79	0.14 ± 3.19	0.66 ± 0.53	-1.35 ± 1.55	-15.11 ± 3.27	-8.98 ± 2.29	-33.68 ± 0.42	-3.83 ± 0.71
	Knee ROM (∘)	28.25 ± 4.23	35.50 ± 0.66	42.54 ± 1.26	42.31 ± 9.29	39.46 ± 1.94	48.84 ± 1.92	72.59 ± 2.47	56.69 ± 0.10	93.16 ± 1.75	65.09 ± 0.51
	Ankle Max DF (∘)	8.25 ± 1.64	10.94 ± 1.22	12.98 ± 0.87	15.2 ± 1.75	13.12 ± 0.33	14.50 ± 0.40	5.48 ± 1.10	5.11 ± 0.79	6.72 ± 1.96	9.27 ± 0.87
	Ankle Max PF (∘)	-5.37 ± 1.96	-7.58 ± 1.29	-10.79 ± 0.12	-16.13 ± 9.97	-8.54 ± 1.17	-11.03 ± 0.67	-8.53 ± 0.68	-9.10 ± 0.56	-11.45 ± 1.08	-14.20 ± 0.74
	Ankle ROM (∘)	13.63 ± 0.66	18.52 ± 0.59	23.77 ± 0.98	25.19 ± 0.65	21.65 ± 0.81	25.54 ± 0.72	14.00 ± 1.61	14.21 ± 1.22	18.16 ± 0.91	23.42 ± 0.13

Supplemental Table 1: Mean spatial and kinematic values calculated from 3 walking trials of each limb for each participant in seconds (s) and degrees (∘). Abbreviations: DF= dorsiflexion; PF= plantarflexion; ROM= range of motion; Flex= flexion; Ext= extension.

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