

**ASSESSMENT OF LOCALIZED PAIN SENSITIVITY OVER THE TRANSTIBIAL
RESIDUAL LIMB AND ITS VARIABILITY AMONG MALE VETERANS WITH
AMPUTATION**

By © Kamiar Ghoseiri

A Thesis submitted to the School of Graduate Studies In partial fulfillment of the requirements
for the degree of

Master of Science (Kinesiology)

School of Human Kinetics and Recreation

Memorial University of Newfoundland

July 2020

St. John's Newfoundland and Labrador

Abstract

Localization of pain sensitization has clinical importance, however, rarely been assessed in amputees. The objective of this study was to investigate the sensitivity of pain over the residual limb and its variability among veterans with transtibial amputation. Pain sensitivity in 12 locations was explored twice in 19 veteran amputees using pressure algometry. The lowest pressure pain threshold (PPT) and pressure tolerance (PT) was recorded at the distal end of the residual limb (20.5 and 33 Ncm⁻², $p=0.13$), and the highest PPT and PT was recorded at the mid-patellar tendon (73.4 and 94.3 Ncm⁻², $p=0.03$). There was a significant moderate correlation ($r=0.48-0.52$) between pressure pain and daily hours of prosthesis use. A localized pattern for sensitivity to pain over the transtibial residual limb was obtained that can be used to improve the transtibial socket design and fit as well as the selection of prevention, evaluation, and treatment methods.

Acknowledgements

First of all, I would like to express my sincere gratitude to my supervisor Professor Duane Button for the continuous support of my M.Sc. study and research, for his always positive attitude, kindness, patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I never left his office without a firm belief and trust in myself and the work that we started. I am grateful to Duane for the consultation and helpful comments that enlighten the best decision at the time for the future of my research activity and career.

I would like to thank all my lecturers and instructors including Professors Duane Button, Kevin Power, Daniel Fuller, Fabien Basset, and Jeannette Byrne for their endless efforts, encouragements, and insightful comments that all aimed to teach me the knowledge and skills required for a master program in Kinesiology.

My sincere thanks also go to Professors Duane Button, Anne-Marie Sullivan and Kim Cullen, for offering me the teaching assistant positions, which gave me the real feel and experience of academia position in Canada. I am thankful to Mr. John Cullen and Ms. Nicole Bishop for their supportive and positive attitude in accepting me as their lab assistant for the Biomechanics course.

I thank Professor Kevin Power and all of my friends in the Human Neurophysiology Lab at the School of Human Kinetics and Recreation for the great opportunities of brainstorming, discussion, and fun.

Last but not the least, I would like to thank my wife, Mrs. Ahlam Bavi for her patience during the hard time of graduate study in another province, and for her countless support during all times I was not at her side.

Table of Contents

Abstract	II
Acknowledgements	III
List of Tables	VI
List of Figures.....	VII
List of Abbreviations and Symbols	VIII
Chapter 1: Review of Literature	1
1.1: Introduction.....	1
1.2. Limb Amputation Statistics.....	2
1.3. Amputations in Veterans Population.....	3
1.4. Post-Amputation Management.....	4
1.5. Issues of Current Transtibial Prostheses.....	6
1.6. Pain Definition and Classification.....	9
1.7. Post-Amputation Pain	10
1.8. Pain Management After Amputation.....	15
1.9. Pressure Algometry	18
1.10. Conclusion.....	22
1.11. References	23
Chapter 2: Co-authorship Statement	40
Chapter 3: Localized Pain Sensitivity over the Transtibial Residual Limb among Male Veteran Amputees.....	41
3.1. Abstract	42
3.2. Keywords	43
3.3. Introduction	43
3.4. Material and Methods.....	45
3.4.1. Participants.....	45
3.4.2. Pressure Algometry.....	46

3.4.3. Sites of PPT and PT	47
3.4.4. Experimental Set Up	47
3.4.5. Data and Statistical Analysis.....	48
3.5. Results	49
3.5.1. Clinical and Demographic Characteristics of Participants.....	49
3.5.2. Reliability of Pressure Algometry Measurements	50
3.5.3. Pain Sensitivity over the Transtibial Residual Limb.....	50
3.5.4. Pain Variability in Pressure Algometry Sites and Among Participants with Transtibial Amputation	50
3.5.5. Relationship of Pain Sensitivity with Clinical and Demographic Characteristics of Participants	51
3.6. Discussion	52
3.6.1. Pain Sensitivity over the Transtibial Residual Limb.....	52
3.6.2. Pain Variability in Pressure Algometry Sites and Among Participants with Transtibial Amputation	54
3.6.3. Relationship of Pain Sensitivity with Clinical and Demographic Characteristics of Participants	55
3.6.4. Study Limitations.....	55
3.6.5. Opportunities for Future Research.....	56
3.7. Conclusions	57
3.8. Acknowledgments	57
3.9. Disclosure.....	58
3.10. References	58
3.11. Appendix A: Research Ethics Certificate	62

List of Tables

Table 1. Clinical and demographic characteristics of participants (N=19).....	63
Table 2. The levels (Mean±SD) of pressure pain threshold (PPT) and pressure tolerance (PT) for twelve sites over transtibial residual limb	65
Table 3. The values (Mean±SD) of pressure pain threshold (PPT) and pressure tolerance (PT) during two trials and overall pain value for each participant.....	66
Table 4. Variability of pressure pain threshold (PPT) and pressure tolerance (PT) at algometry sites (Part A) and among participants (Part B).....	67
Table 5. The results of correlation assessment between mean of pressure pain threshold (PPT) and pressure tolerance (PT) with clinical and demographic characteristics of participants	68

List of Figures

Figure 1. Exoskeletal (A) and endoskeletal (B) designs of the transtibial prosthesis	69
Figure 2. Digital algometer.....	70
Figure 3. Twelve sites for transtibial residual limb pain assessment	71
Figure 4. Pressure pain threshold at different sites over the transtibial residual limb	72
Figure 5. Pressure tolerance at different sites over the transtibial residual limb.....	73

List of Abbreviations and Symbols

ANOVA	Analysis of variance
BMI	Body mass index
CNS	Central nervous system
IASP	International Association for the Study of Pain
ICC	Intraclass correlation coefficient
JMERC	Janbazan Medical and Engineering Research Center
MRI	Magnetic resonance imaging
PPT	Pressure pain threshold
PT	Pressure tolerance
SD	Standard deviation
TENS	Transcutaneous electrical nerve stimulation
VMAF	Veterans and Martyrs Affair Foundation

Chapter 1: Review of Literature

1.1: Introduction

Hundreds of thousands of people experience severe morbidities, traumatic injuries, and disorders that lead to a limb amputation each year.¹ Moreover, an increasing number of combats and armed conflicts in recent decades were associated with increased casualties² and the number of survived military service members with limb amputations.³⁻⁵ Lower limb amputations, particularly at the below knee (transtibial) level accounts for the majority of amputations in military service members.⁶

Pain is a common devastating impairment after limb amputation that affects the person for the remainder of their life.^{7,8} Pain in the remaining part of the amputated limb (residual limb) and in the amputated part of the limb (phantom limb) is two general kinds of pain in people with amputation. Amputees who suffer residual limb pain may avoid participating in physical and social activities, which consequently, may endanger their general health and quality of life.^{9,10} Little information regarding sources of residual limb pain, its associated factors and quantification methods are available in the literature. Controlling residual limb pain has therapeutic and rehabilitative significance. However, quantification of pain over the residual limb is challenging due to its direct contact to the prosthetic socket, biomechanics of the interface, and fluctuating size (i.e. volume and shape) of the residual limb over short and long terms.¹¹ Although there are numerous studies that focus on the residual limb-socket interface pressure measurements and estimation,¹²⁻¹⁴ the number of studies with focus on pain sensitivity of the residual limb are few.^{15,16}

Pain sensitivity can be measured through pressure pain algometry, which is the quantification of pressure (force) applied to the skin to cause pain over specific points in the body.¹⁷ This study explores the sensitivity of pressure pain threshold and pain tolerance over the transtibial residual limb. Furthermore, it investigates the variability of pain among transtibial amputees, and evaluates the relationship of clinical and/or demographic characteristics of transtibial amputees with their pain sensitivity. A potential application for determination of localized pain over the transtibial residual limb, could be improving the prosthetic socket design and fit, as well as the selection of prevention, evaluation, and treatment methods for the residual limb pain.

1.2. Limb Amputation Statistics

Limb amputation is globally increasing due to growing number of traumas (e.g. accidents and wars), vascular pathologies, and advancing surgical and therapeutic techniques to surviving patients from previous mortality conditions.^{1,18} It is difficult to get prevalence estimates of amputation due to limited and incomplete national and international disability databases.¹⁹ In 2009, it was reported that globally about 30 million people were living with limb loss.²⁰ In the United States, nearly 1.6 million amputees are living based on 2005 reports.²¹ Furthermore, based on the healthcare data from 1988 through 1996, dysvascular amputation accounted for 82% of limb loss discharges with 27% increase in rate over all years.²² However, more recent studies reported that the prevalence of limb loss exclusively due to peripheral arterial disease and diabetes are decreasing and instead a cumulative illness burden from different disorders and diseases leads amputation rates.²³ In United Kingdom it has been reported that trauma stands at

second rank following dysvascular etiology for lower limb amputations. However, for upper limb amputations, trauma is still the first etiologic rank.²⁴ It is estimated that amputee population in United States will increase to 3.6 million by 2050.²¹ In Canada, there were 44,430 new lower limb amputations from 2006 to 2012 with increasing numbers each year.²⁵ In the United Kingdom about 55,000 to 60,000 patients are living with limb loss and congenital deficiencies who use rehabilitation services.²⁶ Moreover, in United Kingdom there is about 5000 new referrals to prosthetic service centers each year.²⁶ Lower limb amputation is the main level of amputation and subsequently the transtibial amputation accounts for more than 50% of lower limb amputations.²⁴ Regardless of amputation cause, age, gender, and race are affecting the prevalence of amputations.^{23,27} These statistics could indicate high demands for amputee care and prostheses in near future. It could be estimated that the need for prostheses, orthoses, and other assistive devices is increasing. Nearly 30 million people in Africa, Asia, and Latin America suffer from a kind of physical disability and require such assistive devices.¹⁹

1.3. Amputations in Veterans Population

An increasing number of combats and armed conflicts in recent decades was associated with an increase in casualties.² Although improvement of protective gears and medical practices has greatly decreased war-related mortality rates, the number of survived military service members with limb amputation has increased.³⁻⁵ Based on a governmental report in 2015 for the United States, there were 1,645 veterans who suffered an amputation during war against terrorism.²⁸ Reports of the United Kingdom indicated there were 234 veterans who sustained an amputation during service through

Iraq, Afghanistan or other regions from 2001 through 2015.²⁹ The reason of limb loss in military servicemen could be attributed to combat traumas or training accidents, traumas occurring when serving off-duty, and systematic and chronic illnesses especially in former personnel.³⁰ For the Iraq-Iran war, it was reported that about 90% of amputations happened due to land mine explosions.³¹ Lower limb amputations, particularly at the below knee level account for the majority of amputations in military service members.⁶ Based on the report of the Iranian Veterans and Martyrs Affairs Foundation (VMAF), there were 11,570 veterans who sustained lower limb amputations during Iraq-Iran war.³² The veteran amputee population differs from general amputee population due to their multiple associated disorders and injuries. Psychological, cardiac, nervous, gastrointestinal, respiratory, and musculoskeletal disorders can be found at different levels among many veterans.^{32,33} In addition, back pain, joint pain, osteoarthritis, and phantom limb pain are long-term health issues in veterans.^{5,34}

1.4. Post-Amputation Management

Limb amputation is a devastating experience that can physically and psychologically affect the life style of a person. Impaired mobility, limited exercise and social activity, depression, post-traumatic stress disorder, and usually the systematic comorbidities are general sequelae to lower limb amputation that are well-known as “post-amputation syndrome”.³⁵ Post-amputation syndrome in lower limb amputees can be sub-divided into three categories: amputated limb issues (e.g. surgical wound healing, post-amputation pain, skin disorders, and musculoskeletal disorders), contralateral side to the amputated limb issues (e.g. osteoarthritis of the lower limb joints, and excess energy

expenditure) and systematic problems (e.g. balance and gait abnormality, low back pain, psychological disorders, handicaps and limited social participation, and decreased life expectancy).³⁵

Rehabilitation is a purposeful process to enable persons with disabilities to regain their functional independence at the mental, physical, psychological, and social levels.³⁶ Post-amputation rehabilitation is an intervention based on educational and problem-solving clinical views that aims to lessen multimodal issues of amputees and to help them regain their functional independence.²⁴ Immediately after amputation surgery, post-amputation management starts and continues for the remainder of the amputee's life. The most important tasks of post-operative amputation management are to rapidly heal the wound, control edema, control pain, prevent joint contracture, control the shape and volume of the residual limb (stump), rapid rehabilitation to resume the independence of the patient in daily activities, and prevention of depression.⁸ Chronic pain is a secondary disabling condition after amputation surgery that negatively affects the quality of life, impedes rehabilitation, and diminishes prosthesis use in these patients. Living with chronic pain can affect the outlook, personality and relationships of an amputee.³⁷ Following the intensive post-operative care, the rehabilitation process continues with main focus on improving function and comfort in amputee.⁸ The residual limb gradually matures in volume and shape when inflammations are suppressed and wound sites healed. Gradually, the preliminary soft and interim prostheses are replaced with rigid and permanent (final) prostheses, which provide transferring patient's load and help to sturdy their mobility. It was reported that lack of prosthesis use after amputation is a predictor of post-amputation pain.³⁸

1.5. Issues of Current Transtibial Prostheses

Transtibial prostheses are categorized based on their general design as exoskeletal or endoskeletal (Figure 1). The exoskeletal prosthesis has a hard outer shell that provides structural strength and cosmetic appearance. Endoskeletal prosthesis has a modular structure shaped by assembling different components that finally covered by a cosmetic foam.³⁹ An ordinary endoskeletal transtibial prosthesis includes a prosthetic socket, suspension system, pylon, foot and ankle components.³⁹

Socket is the main component of the prosthesis that surrounds the residual limb and primarily provides structural coupling, control, and proper transfer of forces and motions at its interface with residual limb.⁴⁰ Stable mechanical coupling between residual limb and prosthesis is a prerequisite for the sense of stability for the amputee during standing and walking. Such stability sense is achievable by high interface stresses over the skin of the transtibial residual limb that is not intended to tolerate the stresses of weight bearing, i.e. unlike the skin of the sole of the foot.¹ The interface of the residual limb-socket is under two kinds of compressive stresses: perpendicular (i.e. pressure) and tangential to the skin surface (i.e. shear). Stresses higher than a certain level and duration cause skin breakdown and consequently lead to discomfort and pressure ulcer.¹ The response of the skin to pressure is reduction of perfusion that can lead to ischemia and tissue necrosis. It was shown that under static loading the muscle tissue, due to higher vascularity and metabolic demand, is more vulnerable to tissue necrosis than skin. Therefore, it would be highly probable that someone may have deep soft tissue injury while there is no skin manifestation. With respect to shear stress, the response of skin

depends on how stress is applied. Friction and tangential are two common kinds of shear stresses at the residual limb-socket interface that can lead to blister formation and reduced local stress concentration, respectively.⁴¹

A major problem of most prosthetic sockets is their inability to adapt to the short term and long term changes of the shape and volume of the residual limb. Short term (diurnal) changes are cyclic and happen on a daily basis from morning to the evening due to movement of the extracellular fluid.^{42,43} During walking, hard walls of the socket act as a pump to push fluid out of the interstitial spaces leading to shrinkage of the residual limb over the course of a day. However, doffing prosthesis removes the rigid constraint over the residual limb, and resting for sufficient time will allow it to return to the primary size.⁴² With respect to long term changes, they happen over weeks or months mainly due to a variety of reasons including large weight changes, maturation of the residual limb, changes in vascular condition of the amputee, and even muscle atrophy.¹ Usually, long term changes of the residual limb are not easily reversible and force the amputee to change the prosthetic socket.

Socket comfort directly impacts function and extent of prosthesis use in amputees.^{44,45} Suspension system refers to the components that aim to keep prosthesis retention and provide safe and well-functioning prosthesis by suspending that over the residual limb.⁴⁶ Good prosthesis suspension requires a snug total contact fit that consequently limits ventilation and air circulation at socket-skin interface. Limited ventilation and low moisture permeability of the prosthetic socket walls contribute in increasing the residual limb skin temperature and perspiration accumulation inside prosthetic socket. These consequences could negatively affect the quality of life,

prosthesis suspension, prosthesis use and activity level. Moreover they cause discomfort, skin irritation, skin maceration, friction blisters, infection, unpleasant odor, and an unpleasant environment for bacterial invasion to hair follicles of the residual limb.^{44,47-61}

Residual limb skin care is important to a great extent such that any skin irritation could endanger load bearing and prosthesis use in spite of appropriate socket fit.^{59,62,63} Skin problems that easily could be seen in amputees include those with mechanical sources (epidermoid, cysts, calluses, verrucous hyperplasia), allergic reactions (inflammation, eczema, contact dermatitis, rash), and fungal or bacterial infections.^{58,64,65} The incidence of at least one skin problem is estimated to be between 34-74%.⁵⁰ Therefore, key factors in successful use of prosthesis include skin integrity of the residual limb, its health and hygiene.^{66,67} Skin irritation, ulceration, dermatitis, are major sources of the residual limb pain and besides excessive sweating are common complaints of amputees who use prostheses for their daily activities.^{68,69} Legro et al in their survey determined that from the amputees' point of view, prevention of skin blisters is one of their three most important issues in prosthesis use.⁶⁰ Intermittent pressure and shear stresses relief when followed by exercises could lead to remodeling and adaptation of the soft tissues to repetitive stresses.¹

Using a socket is not the sole method to link the residual limb to prosthesis. Osseointegration is another method used for the linkage and its popularity is increasing in North America and some parts of Europe. However, due to potential risks of infection and periprosthetic fracture, and high cost of the associated surgery, this method has not been globally accepted.⁷⁰ Therefore, using the prosthetic socket is still the main method for linkage between the residual limb and prosthesis.

1.6. Pain Definition and Classification

Pain has been defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”.⁷¹ Pain is a dichotomous phenomenon that acts like a double-side sword that may help us in the short term following injury but disables us when it becomes chronic and long term stimulation.⁷² Pain is a devastating impairment that decreases the quality of life of a person.^{7,8} Debilitating pain can present the community with extra costs in treatment and lost productivity of patients.⁷³ Although complex and under debate, four mechanism-based classifications of pain are available based on the dominant neurophysiological events that lead to pain generation and its maintenance. These mechanisms are: nociceptive, peripheral neuropathic, central sensitisation, and psychosocial.^{74,75} Nociceptive pain refers to pain attributed to the activation of peripheral receptive terminals of the primary afferent neurons in response to painful thermal, mechanical, or chemical (pro-inflammatory chemicals released in response to injury or pathology, as well as lowering of tissue pH in response to tissue ischemia due to static loading) stimuli.⁷⁵ Peripheral neuropathic pain is attributed to the pain arising from a primary lesion or dysfunction in the peripheral nervous system.⁷⁶ Central sensitisation pain refers to neurophysiological dysfunctions in the central nervous system (at the cellular level within spinal cord and/or supraspinal centers) that lead to pain sensation.⁷⁷ In other words, central sensitisation pain is attributed to amplification of neural signalling and regulation of the nociceptive system in different ways including enhanced synaptic excitability, reduced synaptic inhibition,

lowered receptors' thresholds of activation, and expanded receptive fields of the central neurons, which all elicit pain hypersensitivity.⁷⁷⁻⁷⁹ The net effect of the central sensitization is recruitment of sub-threshold inputs to the nociceptive receptors to generate an augmented action potential output.⁷⁹ Central sensitization happens as a result of plastic changes in properties of the central neurons, which consequently leads to hypersensitivity of the sensory receptors. Therefore, central sensitization pain is not reliant on presence, intensity, or duration of the noxious stimuli. It happens independently in presence of normal input to the nociceptive receptors.⁷⁹ Psychosocial pain refers to pain arising from cognitive, affective, behavioural, and social factors that modulate experience and perception of pain. For instance, the self-reported intensity of pain might be different in presence of a friend during experimental pain assessment.⁷²

Another classification for pain is acute, post-operative, neuropathic, terminal (e.g. cancerous), psychogenic, and chronic.⁸⁰ Acute pain is an immediate response to an injury or illness and will gradually resolve during healing process; however, chronic pain has a persistent nature characterized by lasting for more than 6 months and even for many years.^{71,81}

1.7. Post-Amputation Pain

Pain in the residual limb may prevent amputees from participating in physical and social activities; consequently, their general health and quality of life may be jeopardized.^{9,10} Post-amputation pain is highly prevalent and challenging for treatment regardless of time since amputation.^{27,82} In a national survey of 914 amputees in the United States, almost all (95%) amputees reported experiencing at least one kind of

amputation-related pain in the last month.⁸² The pathophysiologic basis of post-amputation pain can be described by supraspinal, spinal, and peripheral mechanisms.²⁷ Supraspinal mechanisms involve cortical reorganization of the brain map, where sprouting neurons from adjacent maps invade the deafferented brain map.⁸³ The upper limit of somatosensory cortical maps reorganization for a short-term deafferentation is about 1-2 millimeters mediolaterally, however, for the long-term deafferentation, it exceeds greatly from the upper limit.⁸⁴ It was reported that descending inhibition decreases with deafferentation and there is the possibility that some CNS structures like dorsal column nuclei, thalamus, cortex, and reticular formation are involved in pathogenesis of pain.⁸⁵ Spinal mechanisms involve reorganization at the dorsal horn when afferent signals from a peripheral nerve ceases. Loss of the afferent input to the dorsal horn associated with decreased impulses from the brainstem reticular formation, as well as absence of inhibitory effect for sensory input from the amputated part, which consequently leads to increased autonomous activity of the dorsal horn neurons known as sensory epileptic discharges.^{27,85,86} This process occurs in detail by a series of plastic changes occurring at the dorsal horn including death of many dorsal root ganglion cells, some trans-synaptic changes, decreased myelination, neuropeptide level changes, biochemical changes in the dendritic tree, and some sprouting of neurons within the dorsal horn.^{27,85,87} Finally, peripheral mechanisms involve initiation of axonal inflammation after injury, regeneration of axon, sprouting nerves, and increased abnormal afferent inputs.^{27,85} Axonal regeneration associated with changes in expression of transduction molecules, up-regulation of voltage-sensitive sodium channels, and down-regulation of potassium channels that all together produce areas with high excitability or

ectopic electrogenesis and lead to increased non-functional crosstalk between axons.⁸⁵ Residual limb pain and phantom limb pain are two general kinds of chronic pain in amputee patients that can be largely attributed to the supraspinal and peripheral mechanisms, respectively.^{27,82,88} Residual limb pain is usually a nociceptive pain associated with irritation or inflammation in the residual limb caused by external (e.g. surgery, misfit socket) or internal (e.g. referral pain from other body-parts) stimulations.⁸⁹ Residual limb pain could be associated with the surgical procedure due to physical damage to the body tissues, especially at its distal end.⁸⁹ In some cases, the residual limb pain is neuropathic and associated with a neural deficit such as a neuroma formation.^{81,90,91} Overall, the six most common causes of the residual limb pain are attributed to the prosthogenic (i.e. misfitting of a prosthesis), neurogenic, arthrogenic, sympathogenic, referred, and abnormal residual limb tissues.⁸⁵ The prosthogenic cause of the residual limb pain refers to problems with the fit and design of a prosthetic socket (e.g. when the socket walls are too tight or too loose or have inappropriate trim lines and rims), distal end weight bearing design, and an inappropriate suspension system.^{43,85} The neurogenic cause of the residual limb pain refers to the neurotmesis following amputation and development of the neuromas.⁹² Neuromas are sensitive and can trigger in response to muscle activation, external forces, and even without any internal or external stimuli.⁹² Arthrogenic residual limb pain is pain arising from a joint (e.g. from knee osteoarthritis) or its diseased adjacent soft tissues like tendons, ligaments, and synovial membranes.^{93,94} Sympathetically maintained pain is fairly common and could be another cause of the residual limb pain with clinical features of a neuropathic pain like burning, shooting, and stabbing.⁸⁵ Radiculopathy, myofascial pain and pain arising from

facet joints of the vertebra, and muscle could be other sources of the residual limb pain.^{27,95-97} Myofascia, which is a dense connective tissue innervated by sensory neurons (nociceptors), responds to injury, postural stress, and inactivity by bonding to other tissues that consequently, leads to formation of hypersensitive tender spots.⁹⁷ Therefore, adhesive myofascial spots can be a source of the residual limb pain. Smith et al (1999) found from a survey of 92 lower limb amputees that back pain was prevalent among amputees and could be more bothersome than phantom limb pain and residual limb pain.⁹⁸ The residual limb tissues including fat, bone, muscle, and skin could lead to painful conditions. Some of the most reported abnormalities include bony exostoses, heterotrophic ossification, soft tissue scars and ulcers, fat in atrophied muscles, osteomyelitis and residual graft infections, ischemia and hematoma.^{27,85,92} The majority of patients after a partial or complete amputation of a limb may feel that the amputated part of the body is still present and suffer from pain. Phantom limb pain is a neuropathic pain located at the missing body part and is thought to result from alterations in the central and peripheral nervous system.^{73,81,82,89,99} The first medical description of phantom pain goes back to the sixteenth century when a French military surgeon, Ambroise Pare, noticed recurrent complaints of severe pain at the missing part of the amputated limb.⁸⁹ In spite of the ample literature on phantom pain, there is no consensus on the exact mechanism of such a feeling. In the literature, phantom pain has been attributed to genetic background, memories, neuromas (the painful end branches of a cut nerve), peripheral/spinal dysfunction, supraspinal and central plasticity, and cortical re-mapping.^{100,101} The existence of pre-amputation pain, stress, depression and other emotional triggers can increase the risk of phantom pain. Moreover, physical factors (e.g.

referred sensation), psychological factors (e.g. thinking about the amputation), and weather-induced factors (e.g. temperature fluctuations) can trigger phantom pain.¹⁰¹ Phantom pain in 50% of the cases is intermittently episodic versus a constant pain. Episodes of intermittent phantom pain can range from hours, days, weeks, and years, to decades.¹⁰² Although phantom limb pain typically happens in the first six months after amputation surgery, several studies reported its high occurrence years after amputation surgery.^{86,102,103}

Residual limb pain and phantom limb pain are prevalent after amputation surgeries. Kooijman et al, determined that the prevalence of phantom limb pain and residual limb pain is 51% and 47%, respectively.¹⁰⁴ Sherman et al found that 78% of their participant amputees had complaints of phantom pain.¹⁰² The prevalence of phantom pain is higher in women, as well in amputees with upper extremity amputations. The range of prevalence for the residual limb pain and phantom limb pain after upper extremity amputation was reported from 7% to 49% and 30% to 79%, respectively.¹⁰⁵ In another study, the rate of phantom limb pain and residual limb pain was reported 71% and 78%, respectively among veterans who were injured in the war zones of the Kurdistan.¹⁰⁶ One of the main sources of residual limb pain is skin dermatoses ranging from 34 to 74% in amputees.^{90,107} Yang and her coauthors reported existence of residual limb pain in 61.5% of their 247 participant amputees.⁹¹ It has been shown that many amputees who suffer from phantom limb pain, also report residual limb pain as a result of the difficulty in distinguishing between these two different types of pain.¹⁰⁴ Sherman and Sherman (1983) found 61% of 648 veteran amputees with residual limb pain also suffered from phantom limb pain. However, in those without phantom limb pain, 39% had residual limb pain.³⁸

Indeed, in the majority of amputees, phantom limb pain and residual limb pain coexist and have a significant correlation in their intensity.^{27,38} In addition to residual limb pain and phantom limb pain, many people with amputation experience ambiguous pain in their residual limb.^{5,34} Moreover, environmental, social, and economic factors can influence the intensity of post-amputation pain in veterans.¹⁰⁶

1.8. Pain Management After Amputation

A variety of pain management strategies of the healthy and intact persons were applied over the past few decades with different success rates in amputees. Still, there are many potential techniques and strategies that can be applied to alleviate post-amputation pain. Pain management after amputation can be classified into three categories, which include medical, non-medical, and surgical treatments. Surgical treatment is an invasive method that is usually considered as the last choice. Cordotomy, root lesions, targeted nerve implantation and targeted muscle reinnervation are common surgical procedures to prevent or decrease stump and phantom pains.¹⁰⁸⁻¹¹⁰ Targeted nerve implantation and targeted muscle reinnervation are based on the same principles of transferring the resected nerve and rely on a surgically denervated muscle to reinnervate instead of neuroma formation.¹⁰⁸ In spite of high similarity of the two procedures there are some differences between them. Targeted muscle reinnervation is distinct due to employment of much more formal and proximal nerve transfers into defined muscle segment to obtain robust muscle signals.¹⁰⁸ The longevity of pain relief after surgical treatment is not high and usually the neuroma will grow again after surgery.^{101,111,112} Motor cortex stimulation as an intracranial and invasive method, when delivered in the awakened situation during

operation, was shown to have promising results in treatment of post-amputation pain. This technique needs prior functional MRI to localize the pain site over the cortex and then directly triggering the reorganization cortical map.²⁷ It was reported that pain relief after this technique lasted from 6 months to 10 years after amputation.²⁷ The brain has the ability to inhibit the transmission of pain signals monoaminergically using monoamine transmitters like norepinephrine and serotonin.¹¹³ Therefore, many medications can be used to alter the distribution of monoamines in body and affect pain perception.¹¹⁴ Although the most effective treatment for pain is medication therapy, it is associated with some drawbacks due to the drug side-effects.²⁷ It has been reported that antibody-based medications (e.g. tumor necrosis factor alpha inhibitor and anti-nerve growth factor antibody) are the most safe and efficient treatment for the post-amputation pain.¹¹⁵ Contrary to great drawbacks of medical and surgical treatments, non-medical treatments show some promising results. The most common non-medical treatments are using soft and rigid dressings to provide pain and edema control and prevent joint contracture.¹¹⁶ In addition, physical, massage, heat/cold, vibration and electroshock therapies, transcutaneous electrical nerve stimulation (TENS), acupuncture, hypnosis, and biofeedback (virtual reality methods such as mirror box therapy) are common for pain management.^{73,85} In addition to these non-medical treatments, some psychological and behavioral treatments have been introduced and proved to be effective for phantom pain relief. The mechanism of action of these treatments is invoking neural plasticity in amputees.²⁷ Energy medicine by focusing on psychological trauma of the amputation, is a novel treatment for phantom pain.¹¹⁷ As a general consensus, the best outcome for phantom pain treatment can be obtained when physical, psychological and behavioral

treatments replace or substitute afferent signals from amputated limb.¹⁰¹ Although there are many conflicts in outcome results of non-medical treatments, they are more acceptable due to their few drawbacks. Using assistive devices/technologies and exercise therapy are examples of non-medical treatments to control pain.^{110,118,119} Usually a combination of different treatments can be used to alleviate pain after amputation. Moreover, in comparison to expanded body of evidence for pain management in healthy and intact people, there are limited practical and scientific reports for pain management in people with amputation. For example, the best practical massage and exercise technique to alleviate pain in amputees has not been established.¹²⁰ However, it was reported in healthy individuals that massage therapy and mechanical pressure can neurologically, physiologically, and mechanically alleviate pain by inducing analgesic effects, increasing blood flow, and rearranging the muscle structure (fibers, connective tissues, and blood vessels), respectively.⁹⁷ Similarly, myofascial release techniques were shown to be effective in pain reduction by promoting soft tissue extensibility, optimal muscle function, arterial dilation and vascular plasticity, and increased range of motion.⁹⁷ Conclusively, nonpharmacological approaches to alleviate pain need to be developed and tested in amputee people. Exercise, cognitive-behavioral therapies, yoga, acupuncture, chiropractic, and massage were previously used in intact population with different success rates of alleviating chronic pain.^{97,119,120} Further investigations of these approaches are warranted in amputees to alleviate their pain.

1.9. Pressure Algometry

Pain is inherently subjective and its intensity is reliant on a person's report.¹²¹ Albeit self-reported pain intensity is valuable, it's not a pure representation of the severity of pain. Indeed, self-reported pain intensity is a combination of the physiological, psychological, social, and health-related features of a person that make its interpretation difficult.¹²² Traditional ways to determine pain intensity by interview or self-administration filling out of paper forms are to some extent inefficient and time consuming.¹²¹ In a focused systematic review by veteran affair's pain measurement outcomes workgroup, it was shown that majority of the outcome measures of the musculoskeletal chronic pain had no key psychometric properties (minimal important difference, responsiveness, validity, and test-retest reliability).¹²³ Objective pain assessment methods are more desirable and can be done using computers and technologies. In this way, researchers and clinicians can accelerate pain assessment in shorter time with higher accessibility.^{121,122} Thermal, electrical, chemical, and mechanical stimuli are different modalities that can be used for evaluation of pain perception.¹²⁴ Mechanical stimulus is the most favorable modality by researchers and clinicians and used frequently in mechanical pain assessments.^{124,125} Quantitative sensory testing, which works based on the determination of the pain threshold or stimulus response curves after sensory processes, is a valuable tool for the diagnosis, phenotype determination, and management of the post-amputation pain.²⁷

Pressure algometry is a reliable and responsive method to quantify pain by applying controlled pressure to a specific point of the body.^{122,126} Cuff algometry, pressure algometry, and computerized algometry are different methods to determine the

pressure pain threshold. Computerized algometry delivers indentation pressure using a mechanical arm and eliminates the operator effects on reaction time, randomisation of algometry points, alignment and rate of the indentation.¹²⁷ Although pressure algometry and computerized algometry have comparable reliabilities, pressure algometry is inexpensive, more convenient to use, and more frequently available in research and clinical settings.¹²⁷

Pressure algometry can be used to assess the sensation of different underlying tissues depending on the size of the algometer tip. For instance, the algometer tips of 0.2 mm can be used for the measurement of the intra-epidermal nerve endings.¹²⁸ However, it was reported that algometers with tip size of 1.6 mm or above can provide the summation of sensation from deeper tissues.¹²⁹ Algometers with tip sizes of 0.5 cm², 1 cm², and 2 cm² are the most commonly used algometer tips since they imitate the surface area of one or two finger tips.^{130,131} For reasons of simplicity, handheld digital algometer with a 1-cm² application surface area (Figure 2) is a frequently used device for pressure algometry.¹³⁰ However, training for applying constant pressure, especially over multiple testing is required for efficient use of this device.¹²⁴ The most reported pressure rate for the handheld algometer ranges from 0.05 to 20 Ns⁻¹, while higher pressure rates may induce error in reading lower thresholds, as well as response time error and increased pressure peak and anxiety in repetitions.^{124,132}

The pressure pain threshold (PPT) is the lowest pressure an individual perceives as pain and discomfort.¹⁶ In other words, it's the point at which a non-painful pressure stimulus turns into a painful pressure sensation.¹²⁶ Pressure tolerance (PT) is the highest pressure that someone can tolerate (i.e. the pressure has become painful).¹⁶ Vanderweeen

et al (1996) in a pressure algometry experiment over 14 trigger points of 30 patients with unilateral chronic pain found that painful body part is more sensitive to pressure than its contralateral side and PPT is higher in males than in the females.¹³³ Moreover, they found that pressure tenderness was different over individual trigger points.¹³³ Great variability (inter-individual differences) in PPT was reported in healthy individuals during pressure algometry.^{134,135} It was reported that PPT values decrease in the cephalic direction for trigger points over the spine as well as in the distal direction for trigger points over the upper limb.^{133,134} Interestingly, it was reported that nerve tissue had lower PPT values than adjacent muscle tissue.¹³⁴ In another study in healthy individuals it was found that PPT decreased orderly during pressure algometry over nail bed to bony prominences to muscles.¹³⁵ Moreover, except over muscles the lower limbs had higher PPT values than upper limbs.¹³⁵ It was reported that great variability in PPT across healthy individuals can be anticipated, which normally deviates less than a factor of two of the group mean. With respect to the within subject variability, the PPT values have high reproducibility, which normally deviates less than 30% in repetitions.¹³⁵

Quantification of pain over the residual limb is challenging due to its direct contact to prosthetic socket, biomechanics of the interface, and fluctuating size (i.e. volume and shape) of the residual limb over short and long terms.¹¹ Although there are numerous studies that focus on the residual limb-socket interface pressure measurements and estimation,¹²⁻¹⁴ the numbers of studies with focus on pain sensitivity of the residual limb skin are few.^{15,16} Pain sensitivity in amputees can be measured through skin indentation method by pressure pain algometry.¹⁷ Lee et al (2005) and Zhang and Lee (2006) used the indentation method in eight patients with transtibial amputation to

evaluate pain threshold and tolerance at 11 regions over the transtibial residual limb.^{15,16} However, these studies did not include algometry for the distal end of the residual limb as a potential painful site of the transtibial residual limb.

The relationship of amputees' clinical and demographic characteristics with existence and intensity of the post-amputation pain could provide better insight over potential risk factors to occurrence and progress of post-amputation pain. However, the selected variables and the methods of assessment were not always the same. In a survey study, it was reported that there was no relationship of post-amputation pain with reasons of amputation, experience of using prosthesis, pain sensitivity, age, and years after amputation surgery.³⁸ However, many studies lack the investigation of daily prosthesis use with residual limb pain or limb size fluctuations.^{15,16,38}

Classification of patients based on their phenotypic pain could provide better insight regarding the source of their pain and mechanism of their pain perception. It has been shown that individual variability in pain threshold and susceptibility can be attributed to the differences in genotypes or mutations in gene expression. This kind of information could be used to determine those with higher vulnerability to chronic pain development after amputation. Therefore, it would be possible to manage their pain by early therapeutic and clinical interventions.^{27,136-138} Another benefit of determination of pain variability among amputees is influencing the service delivery strategy and guiding policy making in order to increase the accessibility and extent of the delivered services to them.

1.10. Conclusion

Based on the gate control theory of pain, which was first introduced by Melzack and Wall (1965), signals which reach to the spinal cord and transmit to the supraspinal centers are modulated and controlled by other afferent signals and supraspinal centers, respectively.^{139,140} It means that while pain impulses are transmitting with unmyelinated and small myelinated fibers to the posterior horn of the spinal cord, simultaneous sensory inputs from larger myelinated fibers can disrupt or slow down the transmission of pain impulses.¹⁴⁰ By reduction of ascending nociceptive signals, the descending pain inhibitory mechanism will be more prominent leading to an analgesic effect.^{97,141} According to the gate control theory of pain, different kinds of physical stimuli can be applied to decrease pain perception in amputees. In this way, controlled pressure over the residual limb might have analgesic effect for post-amputation pain. This idea can describe why post-amputation pain was lower in those who used prosthesis earlier after amputation.³⁸ The pressure stimuli can be delivered to the residual limb by walls of a prosthetic socket during standing and walking. Therefore, the importance of a good design and fit of the prosthesis over the residual limb is evident. With respect to the transtibial residual limb, it has a heterogeneous structure consisting of different underlying tissues with different thicknesses, blood perfusion rates, metabolic activities, and stress characteristics.⁴⁸ Therefore, it seems reasonable to anticipate different behaviors of its soft tissue in response to physical stimuli at different locations. The knowledge of localized pain sensitivity and mechanisms that underlie pain perception in people with amputation could be used to improve the transtibial socket design and fit as well as the selection of prevention, evaluation, and treatment methods.

1.11. References

1. Sanders J. Stump-socket interface conditions. In: Bader DL, Bouten CVC, Colin D, Oomens CWJ, editors. *Pressure Ulcer Research: Current and Future Perspectives*. New York: Springer Berlin Heidelberg; 2005:129-147.
2. Burkle FM. The epidemiology of war and conflict. In: Antosia RE, Cahill JD, editors. *Handbook of bioterrorism and disaster medicine*. New York: Springer Science+Business Media; 2006:89-91.
3. Krueger CA, Wenke JC, Ficke JR. Ten years at war: comprehensive analysis of amputation trends. *J Trauma Acute Care Surg*. 2012;73(6 Suppl 5):S438-444.
4. Penn-Barwell JG, Roberts SA, Midwinter MJ, Bishop JR. Improved survival in UK combat casualties from Iraq and Afghanistan: 2003-2012. *J Trauma Acute Care Surg*. 2015;78(5):1014-1020.
5. Robbins CB, Vreeman DJ, Sothmann MS, Wilson SL, Oldridge NB. A review of the long-term health outcomes associated with war-related amputation. *Mil Med*. 2009;174(6):588-592.
6. Clasper J, Ramasamy A. Traumatic amputations. *Br J Pain*. 2013;7(2):67-73.
7. Penna A, Konstantatos AH, Cranwell W, Paul E, Bruscino-Raiola FR. Incidence and associations of painful neuroma in a contemporary cohort of lower-limb amputees. *ANZ J Surg*. 2018;88(5):491-496.
8. Smith DG. General principles of amputation surgery. In: Smith DG, Michael JW, Bowker JH, editors. *Atlas of amputations and limb deficiencies: surgical,*

prosthetic, and rehabilitation principles. Rosemont: American Academy of Orthopaedic Surgeons; 2004:21-30.

9. Lu C, Sun X, Wang C, Wang Y, Peng J. Mechanisms and treatment of painful neuromas. *Rev Neurosci*. 2018;29(5):557-566.
10. Zidarov D, Swaine B, Gauthier-Gagnon C. Quality of life of persons with lower-limb amputation during rehabilitation and at 3-month follow-up. *Arch Phys Med Rehabil*. 2009;90(4):634-645.
11. Sanders JE, Fatone S. Residual limb volume change: systematic review of measurement and management. *J Rehabil Res Dev*. 2011;48(8):949-986.
12. Dou P, Jia X, Suo S, Wang R, Zhang M. Pressure distribution at the stump/socket interface in transtibial amputees during walking on stairs, slope and non-flat road. *Clin Biomech (Bristol, Avon)*. 2006;21(10):1067-1073.
13. Al-Fakih EA, Abu Osman NA, Mahmad Adikan FR. Techniques for Interface Stress Measurements within Prosthetic Sockets of Transtibial Amputees: A Review of the Past 50 Years of Research. *Sensors (Basel)*. 2016;16(7):1119.
14. Sanders JE. Interface mechanics in external prosthetics: review of interface stress measurement techniques. *Med Biol Eng Comput*. 1995;33(4):509-516.
15. Zhang M, Lee WC. Quantifying the regional load-bearing ability of trans-tibial stumps. *Prosthet Orthot Int*. 2006;30(1):25-34.
16. Lee WC, Zhang M, Mak AF. Regional differences in pain threshold and tolerance of the transtibial residual limb: including the effects of age and interface material. *Arch Phys Med Rehabil*. 2005;86(4):641-649.

17. Fischer AA. Pressure tolerance over muscles and bones in normal subjects. *Arch Phys Med Rehabil.* 1986;67(6):406-409.
18. Spoden M, Nimptsch U, Mansky T. Amputation rates of the lower limb by amputation level – observational study using German national hospital discharge data from 2005 to 2015. *BMC Health Serv Res.* 2019;19(1):8.
19. Kurichi JE, Bates BE, Stineman MG. Amputation. In: Stone H, Blouin M, editors. *International encyclopedia of rehabilitation.* New York: Center for International Rehabilitation Research Information and Exchange (CIRRIE); 2013.
20. Eide AH, Øderud T. Assistive technology in low-income countries. In: Maclachlan M, Swartz L, editors. *Disability & international development.* New York: Springer; 2009:149-160.
21. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil.* 2008;89(3):422-429.
22. Dillingham TR, Pezzin LE, MacKenzie EJ. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. *South Med J.* 2002;95(8):875-883.
23. Varma P, Stineman MG, Dillingham TR. Epidemiology of limb loss. *Phys Med Rehabil Clin N Am.* 2014;25(1):1-8.
24. Devinuwara K, Dworak-Kula A, O'Connor RJ. Rehabilitation and prosthetics post-amputation. *Orthop Trauma.* 2018;32(4):234-240.
25. Imam B, Miller WC, Finlayson HC, Eng JJ, Jarus T. Incidence of lower limb amputation in Canada. *Can J Public Health.* 2017;108(4):e374-e380.

26. *National Amputee Statistical Database (NASDAB)*. Edinburgh (UK): Information Services Division NHSScotland; 2009.
27. Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. *J Pain Res*. 2013;6:121-136.
28. Fischer H. *A Guide to U.S. Military Casualty Statistics: Operation Freedom's Sentinel, Operation Inherent Resolve, Operation New Dawn, Operation Iraqi Freedom, and Operation Enduring Freedom*.
<https://fas.org/sgp/crs/natsec/RS22452.pdf>2015.
29. Head of Defence Statistics. *Quarterly Afghanistan and Iraq Amputation Statistics*.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/449400/AnnexA_20150730_DAY-RELEASE_Quarterly_Afghanistan_Iraq_Amputation_Statistics.pdf2015.
30. Caddick N, Cullen H, Clarke A, et al. Ageing, limb-loss and military veterans: a systematic review of the literature. *Ageing Soc*. 2018;39(8):1582-1610.
31. Ejtahed H-S, Soroush M-R, Hasani-Ranjbar S, et al. Prevalence of metabolic syndrome and health-related quality of life in war-related bilateral lower limb amputees. *J Diabetes Metab Disord*. 2017;16:17-17.
32. Zargar M, Araghizadeh H, Soroush MR, Khaji A. Iranian casualties during the eight years of Iraq-Iran conflict. *Rev Saude Publica*. 2007;41(6):1065-1066.
33. Pizarro J, Silver RC, Prause J. Physical and mental health costs of traumatic war experiences among Civil War veterans. *Arch Gen Psychiatry*. 2006;63(2):193-200.

34. Esfandiari E, Yavari A, Karimi A, Masoumi M, Soroush M, Saeedi H. Long-term symptoms and function after war-related lower limb amputation: A national cross-sectional study. *Acta Orthop Traumatol Turc.* 2018;52(5):348-351.
35. Kulkarni J. Post amputation syndrome. *Prosthet Orthot Int.* 2008;32(4):434-437.
36. Khasnabis C, Heinicke Motsch K, Achu K, et al. *Community-Based Rehabilitation: CBR Guidelines.* Geneva: World Health Organization; 2010.
37. Ehde DM, Smith DG. Chronic pain management. In: Smith DG, Michael JW, Bowker JH, editors. *Atlas of amputations and limb deficiencies: surgical, prosthetics, and rehabilitation principles.* Rosemont: American Academy of Orthopaedic Surgeons; 2004:711-726.
38. Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb pain among American veterans. Results of a trial survey. *Am J Phys Med.* 1983;62(5):227-238.
39. Nelson FRT, Blauvelt CT. Prosthetics and orthotics. In: Nelson FRT, Blauvelt CT, editors. *A manual of orthopaedic terminology.* Philadelphia: W.B. Saunders; 2015:189-207.
40. Klute GK, Kantor C, Darrouzet C, et al. Lower-limb amputee needs assessment using multistakeholder focus-group approach. *J Rehabil Res Dev.* 2009;46(3):293-304.
41. Husain T. An experimental study of some pressure effects on tissues, with reference to the bed-sore problem. *J Pathol Bacteriol.* 1953;66(2):347-358.
42. Aukland K. Distribution of body fluids: local mechanisms guarding interstitial fluid volume. *J Physiol (Paris).* 1984;79(6):395-400.

43. Golbranson FL, Wirta RW, Kuncir EJ, Lieber RL, Oishi C. Volume changes occurring in postoperative below-knee residual limbs. *J Rehabil Res Dev*. 1988;25(2):11-18.
44. Klute GK, Kallfelz CF, Czerniecki JM. Mechanical properties of prosthetic limbs: adapting to the patient. *J Rehabil Res Dev*. 2001;38(3):299-307.
45. Dumbleton T, Buis AW, McFadyen A, et al. Dynamic interface pressure distributions of two transtibial prosthetic socket concepts. *J Rehabil Res Dev*. 2009;46(3):405-415.
46. Wirta RW, Golbranson FL, Mason R, Calvo K. Analysis of below-knee suspension systems: effect on gait. *J Rehabil Res Dev*. 1990;27(4):385-396.
47. Kohler P, Lindh L, Bjorklind A. Bacteria on stumps of amputees and the effect of antiseptics. *Prosthet Orthot Int*. 1989;13(3):149-151.
48. Peery JT, Klute GK, Blevins JJ, Ledoux WR. A three-dimensional finite element model of the transibial residual limb and prosthetic socket to predict skin temperatures. *IEEE Trans Neural Syst Rehabil Eng*. 2006;14(3):336-343.
49. Naylor PF. The skin surface and friction. *Br J Dermatol*. 1955;67(7):239-246.
50. Visscher MO, Robinson M, Fugit B, Rosenberg RJ, Hoath SB, Randall Wickett R. Amputee skin condition: occlusion, stratum corneum hydration and free amino acid levels. *Arch Dermatol Res*. 2011;303(2):117-124.
51. Hachisuka K, Matsushima Y, Ohmine S, Shitama H, Shinkoda K. Moisture permeability of the total surface bearing prosthetic socket with a silicone liner: is it superior to the patella-tendon bearing prosthetic socket? *J UOEH*. 2001;23(3):225-232.

52. Klute GK, Rowe GI, Mamishev AV, Ledoux WR. The thermal conductivity of prosthetic sockets and liners. *Prosthet Orthot Int.* 2007;31(3):292-299.
53. Huff E, Ledoux W, Berge J, Klute G. Measuring residual limb skin temperatures at the skin-prosthesis interface. *J Prosthet Orthot.* 2008;20(4):170–173.
54. Kern U, Kohl M, Seifert U, Schlereth T. Botulinum toxin type B in the treatment of residual limb hyperhidrosis for lower limb amputees: a pilot study. *Am J Phys Med Rehabil.* 2011;90(4):321-329.
55. Hagberg K, Branemark R. Consequences of non-vascular trans-femoral amputation: a survey of quality of life, prosthetic use and problems. *Prosthet Orthot Int.* 2001;25(3):186-194.
56. Mak AF, Zhang M, Boone DA. State-of-the-art research in lower-limb prosthetic biomechanics-socket interface: a review. *J Rehabil Res Dev.* 2001;38(2):161-174.
57. Datta D, Vaidya SK, Howitt J, Gopalan L. Outcome of fitting an ICEROSS prosthesis: views of trans-tibial amputees. *Prosthet Orthot Int.* 1996;20(2):111-115.
58. Dudek NL, Marks MB, Marshall SC, Chardon JP. Dermatologic conditions associated with use of a lower-extremity prosthesis. *Arch Phys Med Rehabil.* 2005;86(4):659-663.
59. Vultee FE. Chemical control of hyperhidrosis of amputation stumps. *South Med J.* 1958;51(8):966-969.
60. Legro MW, Reiber G, del Aguila M, et al. Issues of importance reported by persons with lower limb amputations and prostheses. *J Rehabil Res Dev.* 1999;36(3):155-163.

61. Hachisuka K, Nakamura T, Ohmine S, Shitama H, Shinkoda K. Hygiene problems of residual limb and silicone liners in transtibial amputees wearing the total surface bearing socket. *Arch Phys Med Rehabil.* 2001;82(9):1286-1290.
62. Levy SW. Skin problems in the amputee. In: Smith DG, Michael JW, Bowker JH, editors. *Atlas of amputations and limb deficiencies.* Rosemont: American Academy of Orthopaedic Surgeons; 2004:701-710.
63. Barnes GH. Skin health and stump hygiene. *Artif Limbs.* 1956;3(1):4-19.
64. Meulenbelt HE, Geertzen JH, Jonkman MF, Dijkstra PU. Skin problems of the stump in lower limb amputees: 1. A clinical study. *Acta Derm Venereol.* 2011;91(2):173-177.
65. Susak Z, Minkov R, Isakov E. The use of Methenamine as an antiperspirant for amputees. *Prosthet Orthot Int.* 1996;20(3):172-175.
66. Hachisuka K, Nakamura T, Ohmine S, Shitama H, Shinkoda K. Hygiene problems of residual limb and silicone liners in transtibial amputees wearing the total surface bearing socket. *Arch Phys Med Rehabil.* 2001;82(9):1286-1290.
67. Butler K, Bowen C, Hughes AM, et al. A systematic review of the key factors affecting tissue viability and rehabilitation outcomes of the residual limb in lower extremity traumatic amputees. *J Tissue Viability.* 2014;23(3):81-93.
68. Ghoseiri K, Safari MR. Prevalence of heat and perspiration discomfort inside prostheses: literature review. *J Rehabil Res Dev.* 2014;51(6):855-868.
69. Meulenbelt HE, Geertzen JH, Dijkstra PU, Jonkman MF. Skin problems in lower limb amputees: an overview by case reports. *J Eur Acad Dermatol Venereol.* 2007;21(2):147-155.

70. Hoellwarth JS, Tetsworth K, Rozbruch SR, Handal MB, Coughlan A, Al Muderis M. Osseointegration for Amputees: Current Implants, Techniques, and Future Directions. *JBJS Rev.* 2020;8(3):e0043.
71. Special Interest Group on Pain of Urogenital Origin. Part III: pain terms, a current list with definitions and notes on usage. In: Merskey H and Bogduk N, editors. *Classification of Chronic Pain*. Seattle: IASP Press; 1994:209-214..
72. Tracy LM. Psychosocial factors and their influence on the experience of pain. *Pain Rep.* 2017;2(4):e602-e602.
73. Bloomquist T. Amputation and phantom limb pain: a pain-prevention model. *AANA J.* 2001;69(3):211-217.
74. Cameron MH. *Physical Assistive Technology in Low-Income Countries Agents in Rehabilitation*. 5th ed. St. Louis: Saunders; 2018.
75. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: Part 3 of 3: Symptoms and signs of nociceptive pain in patients with low back (\pm leg) pain. *Man Ther.* 2012;17(4):352-357.
76. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 2 of 3: symptoms and signs of peripheral neuropathic pain in patients with low back (\pm leg) pain. *Man Ther.* 2012;17(4):345-351.
77. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central

- sensitisation in patients with low back (\pm leg) pain. *Man Ther.* 2012;17(4):336-344.
78. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 2011;152(3 Suppl):S2-15.
 79. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain.* 2009;10(9):895-926.
 80. Benzon H, Raj PP, Rathmell JP, Wu CL, Turk DC, Argoff CE. *Practical Management of Pain.* 3rd ed. St. Louis: Mosby; 2000.
 81. Grobler L, Derman W, Blauwet CA, Chetty S, Webborn N, Pluim B. Pain Management in Athletes With Impairment: A Narrative Review of Management Strategies. *Clin J Sport Med.* 2018;28(5):457-472.
 82. Ephraim PL, Wegener ST, MacKenzie EJ, Dillingham TR, Pezzin LE. Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. *Arch Phys Med Rehabil.* 2005;86(10):1910-1919.
 83. Ramachandran VS, Rogers-Ramachandran D, Stewart M. Perceptual correlates of massive cortical reorganization. *Science.* 1992;258(5085):1159-1160.
 84. Pons TP, Garraghty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M. Massive cortical reorganization after sensory deafferentation in adult macaques. *Science.* 1991;252(5014):1857-1860.
 85. Davis RW. Phantom sensation, phantom pain, and stump pain. *Arch Phys Med Rehabil.* 1993;74(1):79-91.

86. Jensen TS, Krebs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation limb pain. *Pain*. 1985;21(3):267-278.
87. Abbadie C, Brown JL, Mantyh PW, Basbaum AI. Spinal cord substance P receptor immunoreactivity increases in both inflammatory and nerve injury models of persistent pain. *Neuroscience*. 1996;70(1):201-209.
88. Ghoseiri K, Allami M, Soroush MR, Rastkhadiv MY. Assistive technologies for pain management in people with amputation: a literature review. *Mil Med Res*. 2018;5(1):1.
89. Nikolajsen L, Jensen TS. Phantom limb pain. *Br J Anaesth*. 2001;87(1):107-116.
90. Lyon CC, Kulkarni J, Zimerson E, Van Ross E, Beck MH. Skin disorders in amputees. *J Am Acad Dermatol*. 2000;42(3):501-507.
91. Yang NB, Garza LA, Foote CE, Kang S, Meyerle JH. High prevalence of stump dermatoses 38 years or more after amputation. *Arch Dermatol*. 2012;148(11):1283-1286.
92. Singson RD, Feldman F, Staron R, Fechtner D, Gonzalez E, Stein J. MRI of postamputation neuromas. *Skeletal Radiol*. 1990;19(4):259-262.
93. Miller DI. Resultant lower extremity joint moments in below-knee amputees during running stance. *J Biomech*. 1987;20(5):529-541.
94. Andersen-Ranberg F, Jorgensen U. Meniscal tear in a below-knee amputee. *Acta Orthop Belg*. 1987;53(4):514-516.

95. Reiestad F, Kulkarni J. Role of myofascial trigger points in post-amputation pain: causation and management. *Prosthet Orthot Int*. 2013;37(2):120-123.
96. Lipton DE, Nagendran T. A rare cause of stump pain--herniated lumbar disc. A case report. *Ala Med*. 1989;58(7):39-40.
97. Aboodarda SJ, Spence AJ, Button DC. Pain pressure threshold of a muscle tender spot increases following local and non-local rolling massage. *BMC Musculoskeletal Disord*. 2015;16:265-265.
98. Smith DG, Ehde DM, Legro MW, Reiber GE, del Aguila M, Boone DA. Phantom limb, residual limb, and back pain after lower extremity amputations. *Clin Orthop Relat Res*. 1999;(361):29-38.
99. Dijkstra PU, Geertzen JH, Stewart R, van der Schans CP. Phantom pain and risk factors: a multivariate analysis. *J Pain Symptom Manage*. 2002;24(6):578-585.
100. Griffin SC, Tsao JW. A mechanism-based classification of phantom limb pain. *Pain*. 2014;155(11):2236-2242.
101. Giummarra MJ, Moseley GL. Phantom limb pain and bodily awareness: current concepts and future directions. *Curr Opin Anaesthesiol*. 2011;24(5):524-531.
102. Sherman RA, Sherman CJ, Parker L. Chronic phantom and stump pain among American veterans: results of a survey. *Pain*. 1984;18(1):83-95.
103. Limakatso K, Bedwell GJ, Madden VJ, Parker R. The prevalence of phantom limb pain and associated risk factors in people with amputations: a systematic review protocol. *Syst Rev*. 2019;8(1):17.

104. Kooijman CM, Dijkstra PU, Geertzen JH, Elzinga A, van der Schans CP. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain*. 2000;87(1):33-41.
105. Tintle SM, Baechler MF, Nanos GP, 3rd, Forsberg JA, Potter BK. Traumatic and trauma-related amputations: Part II: Upper extremity and future directions. *J Bone Joint Surg Am*. 2010;92(18):2934-2945.
106. Husum H, Resell K, Vorren G, et al. Chronic pain in land mine accident survivors in Cambodia and Kurdistan. *Soc Sci Med*. 2002;55(10):1813-1816.
107. Koc E, Tunca M, Akar A, Erbil AH, Demiralp B, Arca E. Skin problems in amputees: a descriptive study. *Int J Dermatol*. 2008;47(5):463-466.
108. Pet MA, Ko JH, Friedly JL, Mourad PD, Smith DG. Does targeted nerve implantation reduce neuroma pain in amputees? *Clin Orthop Relat Res*. 2014;472(10):2991-3001.
109. Souza JM, Cheesborough JE, Ko JH, Cho MS, Kuiken TA, Dumanian GA. Targeted muscle reinnervation: a novel approach to postamputation neuroma pain. *Clin Orthop Relat Res*. 2014;472(10):2984-2990.
110. Roux FE, Ibarrola D, Lazorthes Y, Berry I. Chronic motor cortex stimulation for phantom limb pain: A functional magnetic resonance imaging study: Technical case. *Neurosurgery*. 2001;48(3):681-688.
111. Sherman RA, Sherman CJ, Gall NG. A survey of current phantom limb pain treatment in the United States. *Pain*. 1980;8(1):85-99.

112. Prantl L, Schreml S, Heine N, Eisenmann-Klein M, Angele P. Surgical treatment of chronic phantom limb sensation and limb pain after lower limb amputation. *Plast Reconstr Surg*. 2006;118(7):1562-1572.
113. Marks DM, Shah MJ, Patkar AA, Masand PS, Park GY, Pae CU. Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. *Curr Neuroparmacol*. 2009;7(4):331-336.
114. Lamont LA, Tranquilli WJ, Grimm KA. Physiology of pain. *Vet Clin North Am Small Anim Pract*. 2000;30(4):703-728.
115. Katz N, Borenstein DG, Birbara C, et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. *Pain*. 2011;152(10):2248-2258.
116. Wu Y, Keagy RD, Krick HJ, Stratigos JS, Betts HB. An innovative removable rigid dressing technique for below-the-knee amputation. *J Bone Joint Surg Am*. 1979;61(5):724-729.
117. Leskowitz E. Phantom limb pain: an energy/trauma model. *Explore (NY)*. 2014;10(6):389-397.
118. Kern KU, Kohl M, Seifert U, Schlereth T. [Effect of botulinum toxin type B on residual limb sweating and pain. Is there a chance for indirect phantom pain reduction by improved prosthesis use?]. *Schmerz*. 2012;26(2):176-184.
119. Arango JE, Mazo JC, PeñaPalacio A. Rehabilitation system for phantom limb syndrome using brain-computer interface and augmented reality. *Iberian Journal of Information Systems and Technologies*. 2013;11:93-106.

120. Shue S, Kania-Richmond A, Mulvihill T, Munk N. Treating individuals with amputations in therapeutic massage and bodywork practice: A qualitative study. *Complement Ther Med*. 2017;32:98-104.
121. Kroenke K. Pain measurement in research and practice. *J Gen Intern Med*. 2018;33(Suppl 1):7-8.
122. Mutlu EK, Ozdincler AR. Reliability and responsiveness of algometry for measuring pressure pain threshold in patients with knee osteoarthritis. *J Phys Ther Sci*. 2015;27(6):1961-1965.
123. Goldsmith ES, Taylor BC, Greer N, et al. Focused Evidence Review: Psychometric Properties of Patient-Reported Outcome Measures for Chronic Musculoskeletal Pain. *J Gen Intern Med*. 2018;33(1):61-70.
124. Melia M, Schmidt M, Geissler B, et al. Measuring mechanical pain: The refinement and standardization of pressure pain threshold measurements. *Behav Res Methods*. 2015;47(1):216-227.
125. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain*. 2009;10(6):556-572.
126. Pelfort X, Torres-Claramunt R, Sánchez-Soler JF, et al. Pressure algometry is a useful tool to quantify pain in the medial part of the knee: An intra- and inter-reliability study in healthy subjects. *Orthop Traumatol Surg Res*. 2015;101(5):559-563.

127. Koo TK, Guo JY, Brown CM. Test-retest reliability, repeatability, and sensitivity of an automated deformation-controlled indentation on pressure pain threshold measurement. *J Manipulative Physiol Ther.* 2013;36(2):84-90.
128. Treede RD, Rolke R, Andrews K, Magerl W. Pain elicited by blunt pressure: neurobiological basis and clinical relevance. *Pain.* 2002;98(3):235-240.
129. Kosek E, Ekholm J, Hansson P. Pressure pain thresholds in different tissues in one body region: The influence of skin sensitivity in pressure algometry. *Scand J Rehabil Med.* 1999;31(2):89-93.
130. Pongratz U, Licka T. Algometry to measure pain threshold in the horse's back: An in vivo and in vitro study. *BMC Vet Res.* 2017;13(1):80-80.
131. Stohler CS, Ashton-Miller JA. Servo-controlled stepped and ramped mechanical tissue algometry. *J Biomech.* 2007;40(7):1635-1640.
132. Jensen K, Andersen HO, Olesen J, Lindblom U. Pressure-pain threshold in human temporal region: Evaluation of a new pressure algometer. *Pain.* 1986;25(3):313-323.
133. Vanderweeen L, Oostendorp RA, Vaes P, Duquet W. Pressure algometry in manual therapy. *Man Ther.* 1996;1(5):258-265.
134. Kosek E, Ekholm J, Nordemar R. A comparison of pressure pain thresholds in different tissues and body regions: Long-term reliability of pressure algometry in healthy volunteers. *Scand J Rehabil Med.* 1993;25(3):117-124.
135. Rolke R, Andrews Campbell K, Magerl W, Treede RD. Deep pain thresholds in the distal limbs of healthy human subjects. *Eur J Pain.* 2005;9(1):39-48.

136. Nielsen CS, Price DD, Vassend O, Stubhaug A, Harris JR. Characterizing individual differences in heat-pain sensitivity. *Pain*. 2005;119(1-3):65-74.
137. Foulkes T, Wood JN. Pain genes. *PLoS Genet*. 2008;4(7):e1000086.
138. Indo Y, Tsuruta M, Hayashida Y, et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nat Genet*. 1996;13(4):485-488.
139. The gate control theory of pain. *Br Med J*. 1978;2(6137):586-587.
140. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150(3699):971-979.
141. Moayedi M, Davis KD. Theories of pain: from specificity to gate control. *J Neurophysiol*. 2013;109(1):5-12.

Chapter 2: Co-authorship Statement

My contributions to this thesis are outlined below:

- 1) With the assistance of Mr. Mohammad Yusuf Rastkhdiv (bachelor's student) and Mr. Mostafa Allami (researcher), I recruited all participants.
- 2) With the help of Mr. Mohammad Yusuf Rastkhdiv and Mr. Mostafa Allami, I collected all experimental data for this thesis.
- 3) I analyzed all data collected for this thesis.
- 4) I prepared the manuscript and thesis with the help and guidance of my supervisor, Professor Duane Button.
- 5) Drs. Phillip Page and Lars L. Andersen provided constructive feedback on the manuscript.

**Chapter 3: Localized Pain Sensitivity over the Transtibial Residual Limb among
Male Veteran Amputees**

Kamiar Ghoseiri^{1,2} (ORCID ID: 0000-0002-9813-6613), Mohammad Yusuf Rastkhadi²,
Mostafa Allami² (ORCID ID: 0000-0002-9683-3415), Phillip Page³, Lars L. Andersen⁴
(ORCID ID: 0000-0003-2777-8085), Duane C. Button¹ (ORCID ID: 0000-0001-6402-
8545)

¹School of Human Kinetics and Recreation, Memorial University of Newfoundland, St.
John's, Newfoundland, Canada

²Janbazan Medical and Engineering Research Center (JMERC), Tehran, Iran

³Doctor of Physical Therapy Program, School of Health Professions, Franciscan
University, Baton Rouge, Louisiana, USA

⁴National Research Centre for the Working Environment, Copenhagen, Denmark

*Correspondence: Duane C Button, *PhD, Professor, CSEP-CEP*

School of Human Kinetics and Recreation, Memorial University of Newfoundland, St.
John's, Newfoundland, Canada A1C 5S7

Tel: +1 709 864 4886

Fax: +1 709 864 3979

Email: dbutton@mun.ca

3.1. Abstract

Purpose: Residual limb pain is common and jeopardizes general health and quality of life in amputees. Localization of pain sensitization has clinical practice implications, however, rarely been assessed in amputees. The objective of this study was to investigate the sensitivity of pain over the residual limb and its variability among veterans with transtibial amputation.

Patients and methods: Pain sensitivity in 12 locations over transtibial residual limb was explored twice in 19 male veterans by determining their pressure pain threshold (PPT) and pressure tolerance (PT) using pressure algometry. Comparison of PPT and PT at each location within and between participants, and relationship of clinical and demographic characteristics with pain sensitivity were explored.

Results: There were significant differences ($p < 0.05$) between PPT and PT at mid-patellar tendon, medial tibial flare, and distal end of the tibia. The lowest PPT and PT (20.5 and 33 Ncm⁻², $p = 0.13$) was recorded at the distal end of the residual limb, and the highest PPT and PT (73.4 and 94.3 Ncm⁻², $p = 0.03$) was recorded at the mid-patellar tendon. There was a significant moderate correlation ($r = 0.48-0.52$) between pressure pain and daily hours of prosthesis use. There was no significant relationship between pressure pain and age, weight, height, body mass index (BMI), time after amputation, years of prosthesis use, and prosthesis type.

Conclusion: Pressure-sensitive and pressure-tolerant areas over residual limb and variability of pressure pain among transtibial amputees were identified. Schematic representation of localized pain over the transtibial residual limb and daily usage of

prosthesis could be considered to improve the transtibial socket design and fit as well as the selection of prevention, therapeutic, and pain management strategies.

3.2. Keywords

Amputation stumps, pain threshold, tolerance, variability of pain, pressure algometry

3.3. Introduction

According to the definition of the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.¹ Regardless of the exact cause, chronic pain is a devastating impairment that affects the whole life of a person.^{2,3} Although complex, pain can be classified in 3 areas: nociceptive, neuropathic, and psychosocial.⁴ Acute pain is an immediate response to an injury or illness and will gradually resolve during healing process; however, chronic pain has a persistent nature and may remain for many years.⁵

Residual limb pain and phantom limb pain are two general kinds of chronic pain in amputee patients.^{6,7} Residual limb pain is usually a nociceptive pain associated with irritation or inflammation in the residual limb caused by external (e.g. misfit socket) or internal (e.g. referral pain from other body-parts) stimulations.⁸ In some cases, the residual limb pain is neuropathic and associated with a neural deficit such as a neuroma formation.^{5,9,10} Phantom limb pain is a neuropathic pain located at the missing body part and is thought to result from alterations in the central and peripheral nervous system.⁵

However, the exact mechanisms underlying phantom limb pain have not been determined yet.¹¹ Neuropathic pain and post-surgical pain can lead to pain hypersensitivity, which may cause brain plasticity in pain sensation, trigger a transition from acute to chronic pain, and affect response to therapeutic techniques.^{12,13} In addition to residual limb pain and phantom limb pain, many people with amputation experience ambiguous pain in their residual limb.

Pain in the residual limb may prevent amputees from participating in physical activity; consequently, their general health and quality of life may be jeopardized.^{14,15} Information regarding sources of residual limb pain, associated factors, and quantification of pain could provide better insight for therapeutic and rehabilitative decision making.¹⁶ Quantification of pain over the residual limb is challenging due to its direct contact to prosthetic socket, biomechanics of the interface, and fluctuating size (i.e. volume and shape) of the residual limb over the short and long term.¹⁷ Although there are numerous studies that focus on the residual limb-socket interface pressure measurements and estimation,¹⁸⁻²⁰ the number of studies with focus on pain sensitivity of the residual limb skin are few.^{21,22}

PPT and PT have been used as measures of pain sensitivity by pressure algometry, which is the quantification of pressure (force) applied to the skin to cause pain over specific points in the body.^{23,24} Lee et al (2005) and Zhang and Lee (2006) used the pressure algometry in eight patients with amputation to evaluate PPT and PT at 11 regions over the transtibial residual limb.^{21,22} However, these studies did not include pressure algometry for the distal end of the residual limb as a potential painful site of the transtibial residual limb. Furthermore, these studies did not investigate a relationship of

the residual limb pain with daily prosthesis uses and limb size fluctuations. Daily fluctuations of the residual limb may lead to misfit issues in prosthesis users and consequently cause residual limb pain.²⁵ Approximately, a mature transtibial residual limb has daily fluctuations of -2% to 12% of its volume.¹⁷ As confirmed earlier in patients with knee osteoarthritis,¹³ there is a possibility that PPTs and PT of the residual limb at different locations were due to hypersensitivity of the residual limb and neuroplasticity changes in pain perception (central sensitization).¹² Therefore, investigation of residual limb pain outside of prosthetic interface could provide better insight about mechanisms of pain in people with amputation. The purpose of this study was to evaluate the pain sensitivity over the residual limb by PPT and PT to explore its diversity and location-dependent while there is no socket interface. In addition, this study evaluated the relationship of clinical and/or demographic characteristics with pain sensitivity in transtibial amputees.

3.4. Material and Methods

3.4.1. Participants

Participants were sampled from the database of the Veterans and Martyrs Affair Foundation (VMAF) among veterans with unilateral transtibial amputation who were living in the Hamadan province of Iran. Veterans were called by phone and after describing the aim, process, and benefits of the study, were invited to participate. From the 28 volunteers who responded, 19 met the inclusion criteria and enrolled into the study (post statistical power analysis: 60%). The inclusion criteria were intact skin of the

residual limb, at least 25 cm length of the residual limb, and daily prosthesis use. The exclusion criteria were the existence of mental disorders (n=8), addictions (n=1), and neurological deficits. All participants were male and their mean age was 49.53 ± 10.70 years. All aspects of the study were approved by the research ethics committee of the Veterans and Martyrs Affair Foundation (Tehran, IR) with the approval number of: IR.ISAAR.REC.1398.016 (Appendix A). Furthermore, consistent with the declaration of Helsinki, all aspects of the study and its aim were described to participants. Participants were informed that they were allowed to quit the study at any time. All participants gave written consent to participate in study.

3.4.2. Pressure Algometry

PPT and PT were evaluated by an examiner using a handheld digital algometer (FPIX 25, Wagner Instruments, Greenwich, Connecticut, USA). The instrument had a round, 1 cm^2 rubber tip to transfer examiner load to test sites over the skin. The PPT is the lowest pressure an individual perceives as pain and discomfort. PT is the highest pressure that someone can tolerate (i.e. the pressure has become painful).²² Participants were trained to respectively say “enough” for painful feeling and “stop” for intolerable pain feeling. Each site was evaluated 4 times, 2 for pain threshold and 2 for pain tolerance, all in the same order. The examiner was trained to apply a constant and gradually increasing load of 5 N s^{-1} at each test site until the participant felt pain. The amount of force was immediately recorded at the PPT and PT.

3.4.3. Sites of PPT and PT

Twelve sites that most often are rectified during transtibial socket fabrication²⁶ were marked by a certified prosthetist on the residual limb for pressure algometry. These sites were mid-patellar tendon, tibial tuberosity, midshaft of the tibia, medial tibial flare, fibular head, distal end of the tibia, distal end of the fibula, distal end of the residual limb, midshank of the fibula, anterolateral of the tibia, anteromedial of the tibia, and lateral side of the popliteus muscle (Figure 3).

3.4.4. Experimental Set Up

In this cross sectional study, the same researcher surveyed participants regarding their demographic and clinical characteristics (age, weight, height, BMI, time after amputation, years of prosthesis use, daily prosthesis use, and prosthesis type) using a researcher designed questionnaire. The researcher checked participant compatibility with study criteria and then measured their weight and height using a scale and a stadiometer, respectively to calculate their BMI. The examiner asked participants to show up at the morning at the lab, remove their prostheses and rest half an hour on a chair. Thereafter, the participants were asked to select one of the two small folded papers with hidden labels of supine or prone on them to determine their first position for pressure algometry measurements. Therefore, participants were randomly laid in a supine or prone position to provide access to different sites for pressure algometry. After pressure algometry of all sites were collected in the supine or prone position, the participant was moved to the other position and pressure algometry was collected again at all of the sites.

The same researcher chose marked assessment sites randomly by chance for pressure algometry. Each PPT algometry was followed by 30 seconds of rest before PT algometry. The PT algometry continued by applying further load beyond the recorded PPT until the participant said “stop”. The amount of pressure was visually recorded from the screen of the device immediately after the participant said “enough” (PPT) or “stop” (PT). At each test site, after 2 minutes rest, PPT and PT evaluations were repeated. All pressure algomeries were done in one session for each participant. Localized pain sensitivity was explored by PPT and PT comparison at each site. Moreover, variability of PPT and PT was explored among participants. Finally, the relationships of clinical and demographic characteristics with pain sensitivity were explored.

3.4.5. Data and Statistical Analysis

Clinical and demographic characteristics of participants, and their PPT and PT were measured. Statistical analyses were computed using SPSS software (Version 22.0, IBM Corp, New York, NY). The intra-day reliability of pressure algometry measurements was explored by calculating the intraclass correlation coefficient (ICC) of participants’ perceived pain during two trials, i.e. PPT and PT algometry. Independent t-tests were used to identify differences between PPT and PT at different sites over the residual limb. The significant difference between PPT and PT at each location could be an indicator of appropriateness of the site for load bearing. Contrary, non-suitability of the site for load bearing could be concluded from non-significant difference between PPT and PT. Hence, PPT and PT over the residual limb had homogeneity variances (Levene’s $p>0.05$), the variability in each measure was explored separately by parametric one-way

analysis of variance (ANOVA). Tukey post-hoc analysis was used to identify differences among multiple pressure algometry sites. Furthermore, due to non-homogeneity variances (Levene's $p < 0.05$), the variability of PPT and PT among participants were explored separately by non-parametric Kruskal-Wallis ANOVA. Pearson correlation coefficient and partial eta squared were calculated to explore potential relationship of PPT and PT values with numeric and nominate clinical and demographic variables, respectively. Significance for all data was defined as $p < 0.05$ and all data are reported as mean \pm SD.

3.5. Results

3.5.1. Clinical and Demographic Characteristics of Participants

The clinical and demographic characteristics of participants are shown in Table 1. Most of the participants were amputated nearly 26 years ago and had nearly 25 years of experience in prosthesis use. Daily prosthesis use was about 10 hours for most of the participants. Approximately, 60% of participants had a right-sided transtibial residual limb.

Research is generally difficult to conduct in veterans with a transtibial amputation because of their multiple injuries. In our sample, 37% of participants had cardiac, pulmonary or metabolic disorders or combination of these. Approximately, 70% of participants were retired or unemployed who preferred to receive compensation and pension from VMAF based on their disability rating. In respect to prosthesis type, exoskeletal prostheses were more prevalent (63%) than endoskeletal prostheses.

3.5.2. Reliability of Pressure Algometry Measurements

The reliability of pressure algometry measurements of participants' perceived PPT ($ICC_{(3,1)}=0.996$) and PT ($ICC_{(3,1)}=0.997$) was high.

3.5.3. Pain Sensitivity over the Transtibial Residual Limb

The results of PPT and PT, as well as their comparison for each of the twelve sites over the transtibial residual limb are presented in Table 2. There were differences between PPT and PT at all twelve pressure algometry sites. However, the results of independent t-test showed that differences were significant ($p<0.05$) for only three sites: mid-patellar tendon, medial tibial flare, and distal end of the tibia. Moreover, the mean difference between PPT and PT had a range of 11 to 21 Ncm^{-2} at different test sites over the transtibial residual limb. Figures 4 and 5 provide sensitivity and variability of pain over the transtibial residual limb at each pressure algometry site.

As presented in Figures 4 and 5, the lowest PPT and PT recorded at the distal end of the residual limb was 20.5 and 33 Ncm^{-2} ($p=0.13$) and the highest PPT and PT was recorded at the mid-patellar tendon, 73.4 and 94.3 Ncm^{-2} ($p=0.03$), respectively.

3.5.4. Pain Variability in Pressure Algometry Sites and Among Participants with Transtibial Amputation

The value of PPT and PT for each participant is presented in Table 3. The Levene's test for homogeneity of variances showed that PPT (*Levene statistic*=1.205, $p=0.285$) and PT (*Levene statistic*=0.538, $p=0.876$) had equal variances among pressure algometry sites. Therefore, parametric one-way ANOVA was used to explore variability

of PPT and PT over the residual limb. The results revealed there were significant differences among mean values of PPT ($F_{(11,216)}=5.279, p<0.05$) and PT ($F_{(11,216)}=7.190, p<0.05$) at different sites over transtibial residual limb. Tukey post-hoc analysis showed that the pressure algometry sites for the PPT and PT can be categorized in 6 and 5 distinctly significant limits, respectively (Table 4, part A).

Comparing participants, the Levene's test for homogeneity of variances showed that PPT ($p<0.05$) and PT ($p<0.05$) had unequal variances. Therefore, non-parametric Kruskal-Wallis one-way ANOVA test was used to compare variability of PPT and PT among participants. A Kruskal-Wallis one-way ANOVA test showed that there was a statistically significant difference in PPT ($\chi^2(18)=36.526, p=0.006$), and PT ($\chi^2(18)=36.676, p=0.006$) among participants. The mean rank of PPT and PT among participants are presented in Table 4, part B.

3.5.5. Relationship of Pain Sensitivity with Clinical and Demographic Characteristics of Participants

The results of Pearson correlation assessment of PPT and PT with clinical and demographic characteristics of participants are presented in Table 5. There were no significant correlations between pain sensitivity with participants' age, weight, height, BMI, time after amputation, and years of prosthesis use. However, daily hours of prosthesis use showed significant correlation with PPT ($r=0.52, p=0.02$) and PT ($r=0.48, p=0.04$).

3.6. Discussion

3.6.1. Pain Sensitivity over the Transtibial Residual Limb

PPT and PT were evaluated using pressure algometry at 12 sites over transtibial residual limb. The results confirmed variability of PPT and PT over the residual limb. The minimum of PPT and PT, as well as the maximum of PPT and PT were recorded at the distal end of the residual limb (20.5 and 33 Ncm⁻²) and mid-patellar tendon (73.4 and 94.3 Ncm⁻²), respectively. This finding is in agreement with Zhang and Lee (2006) and Lee et al (2005) who found that the maximum PPT and PT site was at the mid-patellar tendon; however, the site for the lowest PPT and PT differs in comparison to their studies. They showed that the distal end of the fibula had the minimum PPT and PT.^{21,22} Zhang and Lee (2006) and Lee et al (2005) evaluated pain at 11 sites over transtibial residual limb; however, our study explored pain at 12 sites. The distal end of the residual limb that had the lowest PPT and PT was an additional site evaluated in this study. During transtibial amputation surgery, a muscular flap should be added at the end of the residual limb below the tibia and fibula to provide muscular shock absorption, thus eliminating upward load transfer to residual bones. This flap forms the distal end of the residual limb approximately 3 to 5 cm below the distal end of the tibia and fibula. Our results showed that this flap had the lowest PPT and PT in transtibial residual limb, which was not assessed in previous reports.^{21,22,27}

To our knowledge, this study was the first to evaluate pain sensitivity at 12 locations over the transtibial residual limb, and explore differences between PPT and PT at each location. The results showed that the mean difference between PPT and PT at

each site over the transtibial residual limb had a range of 11 to 21 Ncm⁻², which was significant at mid-patellar tendon, medial tibial flare, and distal end of the tibia. This could be meant that these three sites had the highest pain tolerance (lowest pain hypersensitivity) of transtibial residual limb due to higher distance between their threshold and tolerance limits. On the other hand, the smaller differences at other sites between threshold and tolerance limits could be indicated as intolerable pain happens sooner after threshold limit. As indicated in Table 2, there were medium effect sizes ($r = \pm 0.3$) in difference between the PPT and PT for most locations over the transtibial residual limb. Therefore, in spite of non-significant differences between PPT and PT for most locations, the amputee's response to localized pressure over the transtibial residual limb is similar at most locations. These issues are more important in socket design, socket fit, and the pattern of pressure/shear distribution over the residual limb. Total surface bearing sockets, which were so popular among amputees and prosthetists were designed and fabricated by prosthetists to provide equal pressure/shear distribution over the residual limb. However, this design and fabrication process is continuously improving based on further evidences from residual limb behaviour under localized pressure.^{26,28} The present study further supports the use of pressure algometry (i.e. skin pressure algometry to induce mechanical stimulus) as a reliable method ($ICC_{(3,1)} > 0.995$) to assess PPT and PT of the residual limb.^{21,22,24}

3.6.2. Pain Variability in Pressure Algometry Sites and Among Participants with Transtibial Amputation

Variability tests showed there were significant differences between twelve pressure algometry sites over the transtibial residual limb. Moreover, post-hoc testing classified sites into four separate subclasses for PPT and PT. This finding revealed the complexity of the transtibial residual limb in respect to pressure pain responses, which could be related to the thickness and distribution of its underlying soft tissues, as well as localized hypersensitization.

In spite of design differences between present study and previous studies,^{21,22} the mean values of PPT and PT were closer to those of the Lee et al (2005) study.²² The mean PPT and PT values in present study versus Lee et al study were 45.2 Ncm⁻² versus 46.72 Ncm⁻², and 60.4 Ncm⁻² versus 61 Ncm⁻², respectively.²² However, Zhang and Lee (2006) reported higher values for PPT (56.72 Ncm⁻²) and PT (72.54 Ncm⁻²) in their study.²¹ Limited studies were focused on PPT and PT in amputee patients, however in healthy individuals great variability in PPT less than a factor of two of the group mean was reported.²⁹

There were significant differences in the variability of PPT and PT among participants. The highest PPT and PT was seen in participant #18. By exploring his clinical and demographic characteristics, we noticed this participant had the highest level of prosthesis use per day (18 h). On the other hand, the lowest PPT and PT was recorded in participant #3. Interestingly, this participant had the most recent amputation surgery and the lowest duration (experience) of prosthesis use (3 y). However, the correlation

between pain sensitivity and time after surgery as well as years of prosthesis use was not significant.

3.6.3. Relationship of Pain Sensitivity with Clinical and Demographic Characteristics of Participants

Our study found no significant relationships between pain sensitivity and participants' age, weight, height, BMI, time after amputation, or years of prosthesis use. In respect to age, our finding was in agreement with that of Ephraim et al (2005), and in disagreement with that of Lee et al (2005).^{6,22} The contrary finding of relationship between participant's age and residual limb pain can be attributed to differences in participants. In our study participants were younger and their amputation cause was trauma; however, Lee et al (2005) included traumatic, vascular, and osteosarcoma-related amputees.²²

There was a significant correlation between residual limb pain sensitivity and daily hours of prosthesis use ($p < 0.05$). This finding was likely related to daily fluctuations of the residual limb size. Interestingly, the type of prosthesis and the years of using prosthesis had no relationship with the PPT or PT.

3.6.4. Study Limitations

There were several limitations in our study. Because this study was limited to veterans, the results may not be generalizable to other transtibial amputee populations due to complexity of the associated injuries and disorders in veterans. In addition, participation of just male veterans is another limitation due to substantial gender

differences in PPT and PT.³⁰ This study had no control on type of amputation surgery in respect to kind of nerve block to decrease the chance of neuroma formation, vascularity of the residual limb, tapering shape of the distal part of the residual tibia and/or fibula, distal flap of the soft tissue, and sutures, which all could influence the results.³¹ Hence, post-amputation edema in early months after surgery is an intervening parameter in inducing and increasing pain,³¹ care should be taken in comparing our findings with those amputees. Finally, the design of pain sensitivity and variability assessment in this study lacked consideration of potential daily fluctuations of the mature transtibial residual limb, which could potentially affect the results.¹⁷

3.6.5. Opportunities for Future Research

This study may also lead to opportunities for further research for interventions such as exercise that may improve pain sensitivity in lower extremity amputees.³² Desensitizing methods such as vibration therapy and specific exercises could increase PPT and PT over time;³³ therefore, an investigation about pain sensitivity and variation in people with amputation after exercise therapy is warranted. Furthermore, the current study did not compare pressure algometry of the contralateral intact side to the amputated side. A comparison between these limbs may provide better insight on underlying peripheral and central sensitizations in amputees, and further investigation with this regard is required. Following amputation, the residual limb is the interface of body with the environment and is responsible for transferring loads and movements. However, its structure is not well adapted to this responsibility. Therefore, further research on determination of safe and comfortable pressure limits of the transtibial residual limb

during activities of daily living with and without weight bearing is warranted. Such information could improve rehabilitation techniques for amputees by increasing their functionality and participation. Ultrasonography to quantify the depth of the residual limb tissue, and examining the relationship between residual tissue thickness and pain sensitivity may provide implications for salvage techniques. Pain assessment in a larger sample of amputees while controlling variations of the amputation surgery could provide better insight regarding threshold and tolerance limits.

3.7. Conclusions

PPT and PT over the transtibial residual limb identified the sensitivity of different anatomical locations of the residual limb to pain. Longer daily usage of the prosthesis led to increased pressure pain sensitivity; therefore, residual limb pain, daily usage of prosthesis, and the schematic representation of localized pain over the transtibial residual limb could be used to improve the transtibial socket design and fit as well as the selection of prevention, therapeutic, and pain management strategies. Improving the prosthetic socket design with the possibility of adaptation to the daily fluctuations of the residual limb could possibly alleviate pain in people with transtibial amputation.

3.8. Acknowledgments

The authors would like to sincerely thank the financial support of the Janbazan Medical and Engineering Research Center. Moreover, the authors would like to thank the Veterans and Martyrs Affairs Foundation for their cooperation with the study.

3.9. Disclosure

The authors declare that they have no competing interests.

3.10. References

1. Special Interest Group on Pain of Urogenital Origin. Part III: pain terms, a current list with definitions and notes on usage. In: Merskey H and Bogduk N, editors. *Classification of Chronic Pain*. Seattle: IASP Press; 1994:209-214.
2. Penna A, Konstantatos AH, Cranwell W, Paul E, Bruscino-Raiola FR. Incidence and associations of painful neuroma in a contemporary cohort of lower-limb amputees. *ANZ J Surg*. 2018;88(5):491-496.
3. Smith DG. General principles of amputation surgery. In: Smith DG, Michael JW, Bowker JH, editors. *Atlas of amputations and limb deficiencies: surgical, prosthetic, and rehabilitation principles*. Rosemont: American Academy of Orthopaedic Surgeons; 2004:21-30.
4. Cameron MH. *Physical Agents in Rehabilitation*. 5th ed. St. Louis: Saunders; 2018.
5. Grobler L, Derman W, Blauwet CA, Chetty S, Webborn N, Pluim B. Pain management in athletes with impairment: a narrative review of management strategies. *Clin J Sport Med*. 2018;28(5):457-472.
6. Ephraim PL, Wegener ST, MacKenzie EJ, Dillingham TR, Pezzin LE. Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. *Arch Phys Med Rehabil*. 2005;86(10):1910-1919.

7. Ghoseiri K, Allami M, Soroush MR, Rastkhadiv MY. Assistive technologies for pain management in people with amputation: a literature review. *Mil Med Res*. 2018;5(1):1.
8. Nikolajsen L, Jensen TS. Phantom limb pain. *Br J Anaesth*. 2001;87(1):107-116.
9. Lyon CC, Kulkarni J, Zimerson E, Van Ross E, Beck MH. Skin disorders in amputees. *J Am Acad Dermatol*. 2000;42(3):501-507.
10. Yang NB, Garza LA, Foote CE, Kang S, Meyerle JH. High prevalence of stump dermatoses 38 years or more after amputation. *Arch Dermatol*. 2012;148(11):1283-1286.
11. Aternali A, Katz J. Recent advances in understanding and managing phantom limb pain. *F1000Res*. 2019;8(F1000 Faculty Rev):1167.
12. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2-15.
13. Suokas AK, Walsh DA, McWilliams DF, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2012;20(10):1075-1085.
14. Lu C, Sun X, Wang C, Wang Y, Peng J. Mechanisms and treatment of painful neuromas. *Rev Neurosci*. 2018;29(5):557-566.
15. Zidarov D, Swaine B, Gauthier-Gagnon C. Quality of life of persons with lower-limb amputation during rehabilitation and at 3-month follow-up. *Arch Phys Med Rehabil*. 2009;90(4):634-645.
16. Pelfort X, Torres-Claramunt R, Sánchez-Soler JF, et al. Pressure algometry is a useful tool to quantify pain in the medial part of the knee: an intra- and inter-

- reliability study in healthy subjects. *Orthop Traumatol Surg Res*. 2015;101(5):559-563.
17. Sanders JE, Fatone S. Residual limb volume change: systematic review of measurement and management. *J Rehabil Res Dev*. 2011;48(8):949-986.
 18. Dou P, Jia X, Suo S, Wang R, Zhang M. Pressure distribution at the stump/socket interface in transtibial amputees during walking on stairs, slope and non-flat road. *Clin Biomech (Bristol, Avon)*. 2006;21(10):1067-1073.
 19. Al-Fakih EA, Abu Osman NA, Mahmad Adikan FR. Techniques for interface stress measurements within prosthetic sockets of transtibial amputees: a review of the past 50 years of research. *Sensors (Basel)*. 2016;16(7):1119.
 20. Sanders JE. Interface mechanics in external prosthetics: review of interface stress measurement techniques. *Med Biol Eng Comput*. 1995;33(4):509-516.
 21. Zhang M, Lee WC. Quantifying the regional load-bearing ability of trans-tibial stumps. *Prosthet Orthot Int*. 2006;30(1):25-34.
 22. Lee WC, Zhang M, Mak AF. Regional differences in pain threshold and tolerance of the transtibial residual limb: including the effects of age and interface material. *Arch Phys Med Rehabil*. 2005;86(4):641-649.
 23. Mikkelsen M, Latikka P, Kautiainen H, Isomeri R, Isomaki H. Muscle and bone pressure pain threshold and pain tolerance in fibromyalgia patients and controls. *Arch Phys Med Rehabil*. 1992;73(9):814-818.
 24. Fischer AA. Pressure tolerance over muscles and bones in normal subjects. *Arch Phys Med Rehabil*. 1986;67(6):406-409.

25. Pirouzi G, Abu Osman NA, Eshraghi A, Ali S, Gholizadeh H, Wan Abas WAB. Review of the socket design and interface pressure measurement for transtibial prosthesis. *ScientificWorldJournal*. 2014;2014:849073.
26. Foort J. The patellar-tendon-bearing prosthesis for below-knee amputees: a review of technique and criteria. *Artif Limbs*. 1965;9(1):4-13.
27. Pascale BA, Potter BK. Residual limb complications and management strategies. *Curr Phys Med Rehabil Rep*. 2014;2(4):241-249.
28. Engsberg JR, Sprouse SW, Uhrich ML, Ziegler BR, Luitjohan FD. Comparison of rectified and unrectified sockets for transtibial amputees. *J Prosthet Orthot*. 2008;18(1):1-7.
29. Rolke R, Andrews Campbell K, Magerl W, Treede RD. Deep pain thresholds in the distal limbs of healthy human subjects. *Eur J Pain*. 2005;9(1):39-48.
30. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. *J Pain*. 2009;10(5):447-485.
31. Prantl L, Schreml S, Heine N, Eisenmann-Klein M, Angele P. Surgical treatment of chronic phantom limb sensation and limb pain after lower limb amputation. *Plast Reconstr Surg*. 2006;118(7):1562-1572.
32. Vaegter HB, Hoeger Bement M, Madsen AB, Fridriksson J, Dasa M, Graven-Nielsen T. Exercise increases pressure pain tolerance but not pressure and heat pain thresholds in healthy young men. *Eur J Pain*. 2017;21(1):73-81.

33. Wahren LK. Changes in thermal and mechanical pain thresholds in hand amputees. A clinical and physiological long-term follow-up. *Pain*. 1990;42(3):269-277.

3.11. Appendix A: Research Ethics Certificate



Veterans and Martyrs Affairs Foundation (VMAF)

Research Ethics Certificate


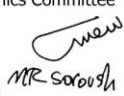
Approval ID:	IR.ISAAR.REC.1398.016	Approval Date:	2018-05-13
Evaluated by:	Veterans and Martyrs Affairs Foundation (VMAF)		
Status:	Approved		
Approval Statement:	<p>The project was found to be in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran.</p> <p>Notice:</p> <p>Although the proposal has been approved by the research ethics committee, meeting the professional and legal requirements is the sole responsibility of the PI and other project collaborators.</p> <p>This certificate is reliant on the proposal/documents received by this committee on 2018-05-13. The committee must be notified by the PI as soon as the proposal/documents are modified.</p>		
Proposal Title:	The investigation of the localized pain threshold and tolerance in transtibial residual limb of veterans		
Principal Investigator:	<p>Name: Kamiar Ghoseiri Email: kamiar_g@yahoo.com</p>		
<p>Dr. Seyed Mohammad Ali Shahidi Director of University/Regional Research Ethics Committee</p> <p>Veterans and Martyrs Affairs Foundation (VMAF)</p> 		<p>Dr. Mohammadreza Soroush Secretary of University/Regional Research Ethics Committee</p> <p>Veterans and Martyrs Affairs Foundation (VMAF)</p> 	

Table 1. Clinical and demographic characteristics of participants (N=19)

Variable	Data Range	Mean	Standard Deviation (SD)
Age	23-64	49.5	10.7
Weight (kg)	60-93	79.9	9.6
Height (cm)	156-205	171.7	9.9
BMI (kgm ⁻²)	22.1-34.7	27.2	3.3
Time after Amputation (y)	4-34	25.8	8.8
Years of Prosthesis Use (y)	3-34	25.3	8.9
Daily Prosthesis Use (h)	3.5-16	10.2	3.4
Employment Status*	E: n=5 *Un-E: n=14		
Amputation Side	R: n=11 L: n=8		
Associated Disorder	C: n=2 P: n=1 M: n=2 C+P: n=1 C+M: n=1		
Type of Prosthesis	Ex-P: n=11 En-P: n=5 En-S: n=3		

Notes:

Abbreviations: *Un-E, unemployed (retired or unemployed veterans and veterans who received compensation and pension from Veterans and Martyrs Affair Foundation

(VMAF) based on their disability rating considered unemployed; R, right side; L, left side; E, employed; C, cardiac disorder; M, metabolic disorder; P, pulmonary disorder; Ex-P, exoskeletal with polyfoam liner; En-P, endoskeletal with polyfoam liner; En-S, endoskeletal with silicone/gel liner.

Table 2. The levels (Mean±SD) of pressure pain threshold (PPT) and pressure tolerance (PT) for twelve sites over transtibial residual limb

Location of Assessment	Type of algometry		Independent t-test to compare PPT and PT					
	PPT (Ncm ⁻²)	PT (Ncm ⁻²)	Mean Difference (Ncm ⁻²)	<i>t</i>	<i>r</i> ⁺	95% Confidence Interval		P
						Lower	Upper	
Mid-patellar Tendon	73.4±31.0	94.3±27.1	-20.9	-2.2	0.3	-40.0	-1.7	0.03*
Tibial Tuberosity	63.9±31.0	78.6±26.5	-14.7	-1.6	0.3	-33.7	4.2	0.12
Midshaft of the Tibia	54.2±29.0	70.5±27.4	-16.3	-1.8	0.3	-34.8	2.3	0.08
Medial Tibial Flare	48.5±27.9	69.5±29.4	-21.0	-2.3	0.4	-39.8	-2.2	0.03*
Fibular Head	47.2±23.3	60.8±22.6	-13.5	-1.8	0.3	-28.7	1.6	0.08
Distal End of the Tibia	39.9±23.5	57.1±25.5	-17.2	-2.2	0.3	-33.3	-1.1	0.04*
Distal End of the Fibula	35.2±25.5	47.9±25.9	-12.7	-1.5	0.2	-29.6	4.2	0.14
Distal End of the Residual Limb	20.5±24.2	33.0±26.3	-12.5	-1.5	0.2	-29.2	4.1	0.13
Midshank of the Fibula	34.3±24.3	45.7±27.4	-11.3	-1.4	0.2	-28.4	5.7	0.18
Anterolateral of Tibia	38.5±22.2	51.7±25.2	-13.2	-1.7	0.3	-28.8	2.5	0.10
Anteromedial of Tibia	42.5±24.2	54.3±25.0	-11.8	-1.5	0.2	-28.0	4.4	0.15
Lateral Side of Popliteus Muscle	44.9±30.0	61.5±28.5	-16.7	-1.8	0.3	-35.9	2.6	0.09

Notes:

r⁺: Effect size; *: difference is statistically significant (*p*<0.05).

Table 3. The values (Mean±SD) of pressure pain threshold (PPT) and pressure tolerance (PT) during two trials and overall pain value for each participant

Participant	PPT (Ncm ⁻²)			PT (Ncm ⁻²)		
	Trial 1	Trial 2	Overall	Trial 1	Trial 2	Overall
1	32.6±11.6	32.3±12.0	32.5±11.8	47.3±25.3	49.9±22.7	48.6±24.0
2	34.1±16.9	34.3±16.6	34.2±16.8	42.9±18.1	43.8±17.1	43.4±17.6
3	20.6±4.3	20.6±4.1	20.6±4.2	30.8±8.2	31.8±7.2	31.3±7.7
4	32.4±12.1	31.9±11.7	32.1±11.9	44.3±17.0	45.6±15.6	45.0±16.3
5	26.0±7.5	26.3±7.7	26.1±7.6	38.3±8.4	39.7±7.9	39.0±8.1
6	37.8±18.9	38.0±19.3	37.9±19.1	49.9±23.9	50.1±22.8	50.0±23.4
7	41.1±20.2	48.3±32.3	44.7±26.3	70.0±33.4	72.4±30.1	71.2±31.8
8	22.5±7.9	23.2±8.5	22.9±8.2	31.3±14.0	31.6±13.6	31.5±13.8
9	61.3±29.1	64.6±28.9	63.0±29.0	82.3±27.1	82.4±26.5	82.4±26.8
10	45.5±18.7	45.3±18.5	45.4±18.6	66.8±21.3	65.2±20.1	66.0±20.7
11	69.2±20.3	69.0±19.1	69.1±19.7	97.3±16.8	101.0±18.8	99.1±17.8
12	87.4±29.9	86.4±30.7	86.9±30.3	93.0±23.0	93.4±21.6	93.2±22.3
13	33.3±17.7	32.6±17.7	33.0±17.7	49.0±27.8	47.7±25.8	48.4±26.8
14	31.8±18.0	33.2±17.6	32.5±17.8	52.8±25.6	48.3±26.7	50.5±26.1
15	30.1±12.8	30.4±12.3	30.2±12.6	55.3±19.1	56.2±17.7	55.7±18.4
16	48.2±33.4	48.6±33.0	48.4±33.2	61.4±31.0	61.4±30.0	61.4±30.5
17	45.6±25.8	45.3±27.9	45.4±26.8	58.8±26.5	59.5±24.9	59.2±25.7
18	105.0±27.2	105.2±30.7	105.1±28.9	111.5±8.8	111.5±8.4	111.5±8.6
19	50.8±19.1	48.6±17.7	49.7±18.4	60.0±17.4	60.6±17.5	60.3±17.5
Mean±SD	45.0±22.1	45.5±22.1	45.2±22.1	60.2±22.3	60.6±22.5	60.4±22.4

Table 4. Variability of pressure pain threshold (PPT) and pressure tolerance (PT) at algometry sites (Part A) and among participants (Part B)

Part A: Classification of algometry sites based on their variability (Note: sites under each class have no significant difference with each other, however there is significant difference ($p<0.05$) between classes)																			
PPT (Ncm ⁻²)				PT (Ncm ⁻²)															
Class 1	Class 2	Class 3	Class 4	Class 1	Class 2	Class 3	Class 4												
8				8															
9	9			9	9														
7	7			7	7														
10	10	10		10	10	10													
6	6	6		11	11	11													
11	11	11		6	6	6													
12	12	12		5	5	5													
5	5	5	5		12	12													
4	4	4	4		4	4	4												
	3	3	3		3	3	3												
		2	2			2	2												
			1				1												
1) Mid-patellar Tendon; 2) Tibial Tuberosity; 3) Midshaft of the Tibia; 4) Medial Tibial Flare; 5) Fibular Head; 6) Distal End of the Tibia; 7) Distal End of the Fibula; 8) Distal End of the Residual Limb; 9) Midshank of the Fibula; 10) Anterolateral of Tibia; 11) Anteromedial of Tibia; 12) Lateral Side of Popliteus Muscle.																			
Part B: Mean rank of participants																			
Assessm ent Type	Participant Number																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
PPT (Ncm ⁻²)	12	17.5	1.5	11	5.5	19.5	24	3.5	31.5	23.5	33.5	35.5	15	12	7.5	27.5	23.5	37.5	29
PT (Ncm ⁻²)	13.5	7.5	2.5	9.5	5.5	16	29.5	2.5	31.5	27.5	35.5	33.5	13	15.5	19.5	25.5	21.5	37.5	23.5

Table 5. The results of correlation assessment between mean of pressure pain threshold (PPT) and pressure tolerance (PT) with clinical and demographic characteristics of participants

Type of Assessment	Statistics Value	Clinical & Demographic Characteristics							
		Quantitative ^a							Nominal ^b
		Age	Weight	Height	BMI	Time after Amputation (y)	Years of Prostheses Use (y)	Daily Prostheses Use (h)	Prostheses Type
PPT	Correlation Coefficient	0.11	0.30	0.06	0.27	-0.06	-0.04	0.52*	0.05
	p	0.66	0.22	0.81	0.27	0.79	0.88	0.02	0.65
PT	Correlation Coefficient	0.13	0.31	0.02	0.31	-0.09	-0.06	0.48*	0.10
	p	0.61	0.20	0.93	0.20	0.72	0.81	0.04	0.45

Notes:

*: Correlation is statistically significant; ^a: Pearson's r; ^b: Partial eta squared value.

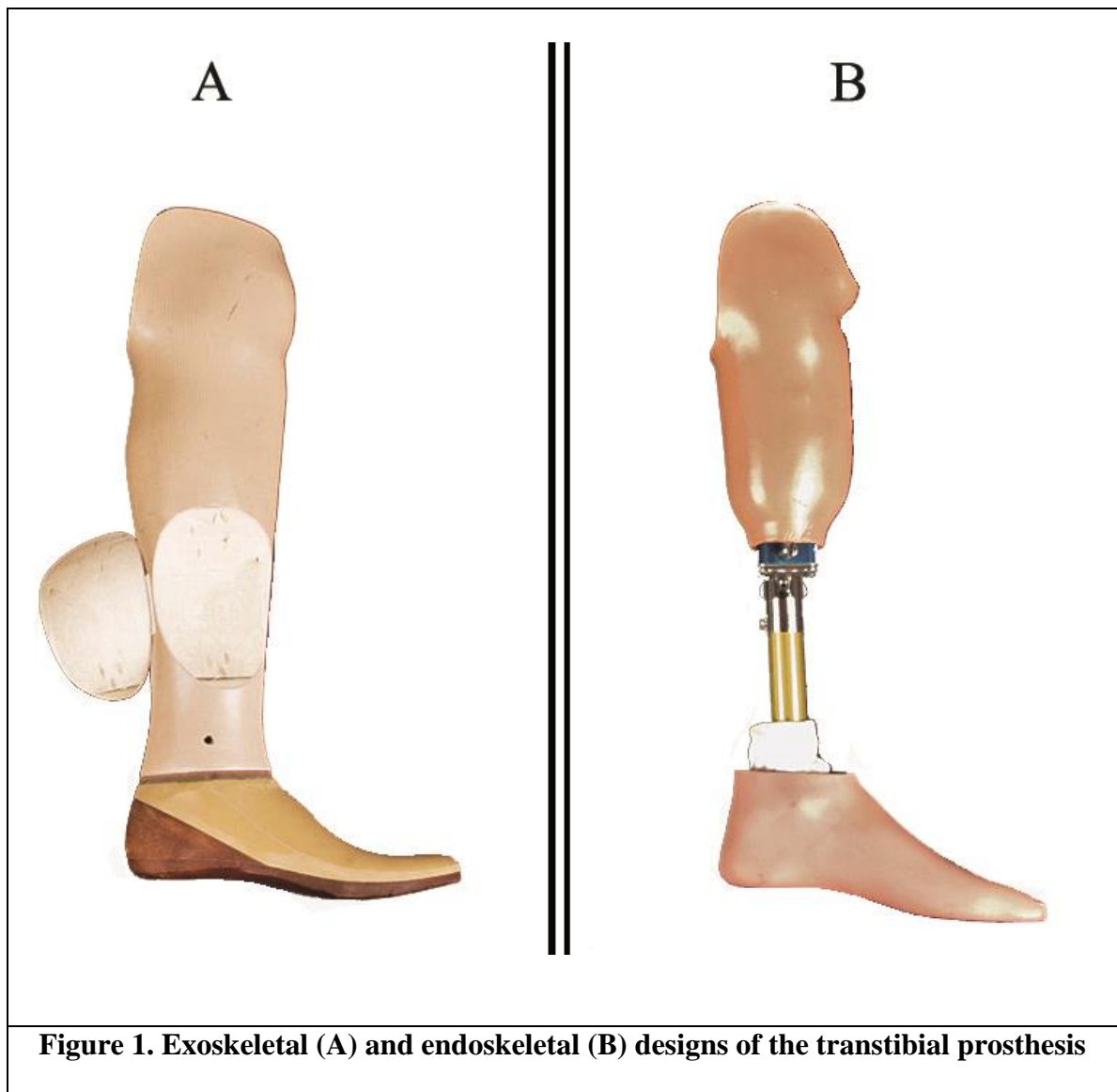




Figure 2. Digital algometer

