EXAMINING NEUROMUSCULAR ADAPTATION IN FOOT AND ANKLE INJURIES USING ULTRASOUND IMAGING

A Dissertation

Presented to

The Faculty of the Curry School of Education

University of Virginia

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

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by

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May 2020

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APPROVAL OF THE DISSERTATION

This dissertation, "Examining Neuromuscular Adaptation in Foot and Ankle Injuries using Ultrasound Imaging", has been approved by the Graduate Faculty of the Curry School of Education in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Acknowledgements

I would start with thanking my advisor and committee chair, Susan Saliba, PhD, PT, ATC for her incessant support, mentorship, and motivation during my time as a graduate student at the University of Virginia. Thank you, Sue, for your trust and conviction in me. I really appreciate for what you have done in the last four years. I would also like to thank my other dissertation committee members, Jay Hertel PhD, ATC, FACSM, Joseph Hart, PhD, ATC, FACSM, and Joseph Park, MD for their guidance and support towards my project. I would especially like to thank Jay for his availability, for his alacrity to answer my many questions, his invaluable advice on statistics and study design, and his great teaching style that made hard concepts much easier to understand. Jay, thank you for being so generous and for teaching me sound scientific methods during my PhD. Joe, thank you for your availability, for your outstanding research questions, you always provided me food for thought and refined my ideas. Dr. Park, thank you for giving me your time in your busy schedule, and providing me good discussion points for my projects. I am fortunate to be a mentee of renowned scientists in sports medicine and rehabilitation. I can`t thank my committee enough for teaching me good science.

Andrea Baellow, thank you for your assistance with my dissertation, your willingness to help whenever needed, and great feedback during all my projects and presentations. Thank you for being such a trustworthy team member to whom I could always rely on. Rachel Rolfe, thank you for your assistance, support, and help during this project, and also for being such a great friend. Thank you, Stephanie, for your help with diabetic section of this dissertation. Thank you to all the undergraduate students who helped during my dissertation and with other projects I did in the EASIL. Thank you to all the faculty at EASIL and previous and current PhD students who helped in any way during the last four years of my PhD.

Thank you to Curry School of Education and Human Development for awarding me IDEAS grant for funding this study and supporting my research. My journey academic journey in the United States started because of Fulbright Scholarship. Thank you to State Department of the United States and United States Education Foundation of Pakistan for awarding me Fulbright Scholarship for my masters and giving me the chance to come to the US and explore the great avenues of research and scholarship which ultimately lead to my PhD. Thank you for giving me a prestigious tag of Fulbright Scholar that I take pride in and cherish. Thank you to International Student Office at UVA for recognizing me with graduate leadership excellence graduate award.

I would also like to thank all my friends who have always supported me throughout my lifetime. I am fortunate to have those friends who prayed for me, listened along the way, and provided immense support during tough time.

Finally, to those who are the cornerstone on which I built my life, my Ami (mother) and Baba (father), who selflessly devoted their lives to build the life of their children. Whatever I write or state about the affection and blessings of my parents on me, I severely understate. Thank you to my siblings who always lifted me up and encouraged me every step of the way.

I may have forgotten several people. Thanks to everyone whom I have forgotten to thank. Thank you for all the incredible help and support I received.

Abstract

Background: The plantar intrinsic foot muscles are comprised of four layers of muscles that originate and insert on the planter surface of the feet. Intrinsic Foot Muscles (IFM) form an integral part of the foot. IFM form the base of support, provide attenuation of the forces, and play a critical role in locomotion by providing the necessary propulsive forces. IFM dysfunction can result in neuromuscular deficits that can affect balance, locomotion, sensory input on the planter surface of the feet and may result in functional limitations. Nevertheless, the body of knowledge pertaining to IFMs structure and function is still limited and primarily that is because of lack of valid tools and methods that can be used to assess these muscles where the weakness is suspected. Lately, ultrasound imaging (US) has been shown to be a mainstay for understanding the size, quality and function of these muscles in both non-weight bearing and weight bearing positions. However, we don`t know how these muscles change over the period of time in foot and ankle dysfunctions such as Chronic Ankle Instability (CAI), Patellofemoral Pain Syndrome (PFP), Diabetes Mellitus, 1st Metatarsophalangeal Joint (1st MTPJ) Arthrodesis etc. especially in the functional weight-bearing position. Previous literature using MRI has shown significant decreases in the muscle volume in IFM of patients with CAI. Similar to IFM, there are significant losses found in the muscle size in peroneal muscle group in CAI. However, to date, there are no studies that have examined the changes or gains in the muscle quality and size in IFM and peroneal muscle groups in patients with CAI. The IFM studied in this dissertation are Abductor Hallucis (AbH) and Flexor Digitorum Brevis (FDB).

Purpose: The purpose of Manuscript 1 (M1) was to compare the differences in IFM morphology and tissue quality in patients with CAI, PFP, 1st MTPJ arthrodesis, diabetes, and healthy individuals in weight-bearing functional position. The primary purpose of Manuscript 2 (M2) was to determine IFM size and quality changes using US imaging following impairment-based rehabilitation incorporating IFM exercises in patients with CAI. Peroneal size and quality changes using US imaging following impairment-based rehabilitation in patients with CAI were assessed in Manuscript 3 (M3).

Methods: M1) A case-control study consisting of 119 participants (PFP=35, CAI=29, Diabetes=9, 1st MTPJ arthrodesis=9, Healthy=38) was performed to assess IFM size muscle size and quality across the spectrum in these pathologies in both non-weight-bearing and functional weight-bearing positions. **M2 & M3)** A pre-post prospective case-series study of 26 physical active individuals with CAI was performed to assess the improvement and gains in IFM size and quality **(M2)**, and peroneal muscle size and quality **(M3)** after a 4-weeks of impairment-based rehabilitation program.

Results: M1) There were statistically significant difference ($P<0.05$) in the CSA of the AbH between all pathology groups when compared to healthy. Post-hoc analysis revealed that it was significantly lower ($P<0.01$) in every group compared to healthy except 1st MTPJ arthrodesis group. Similarly, significant differences ($P<0.01$) were found in the CSA of FDB between groups compared to the healthy group and post-hoc analysis revealed group differences in each group except PFP and 1st MTPJ groups. For echogenicity analysis, significant differences ($P<0.05$) were found between groups for both AbH and FDB. The post-hoc analysis revealed

significantly (P<0.05) higher echogenicity in CAI and 1st MTP groups for AbH, and significantly higher (P<0.05) echogenicity in CAI, 1st MTP and PFP for FDB. Large effect sizes were found in both CSA and echogenicity measures when compared to healthy except PFP group for which small to moderate effect sizes were found. **M2)** A significant (P<0.01) increase was observed after rehabilitation for the normalized CSA with the increase in size of AbH and FDB in both seated and bipedal standing position. There were significant improvements (P<0.05) in CSA observed in the untrained limb for AbH and FDB in the bipedal standing position with moderate to strong effect sizes. However, no significant improvements were seen in the CSA of AbH (P=0.24) and FDB (P=0.19)) in the seated position. There was no significant change seen in the echogenicity measures for both AbH (P=0.26) and FDB(P=0.052) muscles. **M3)** A significant increase was observed after rehabilitation for the normalize CSA with the increase in size in the peroneal muscle group in lying (pre: 3.44 ± 0.99cm^2 , post: 3.72 ± 0.98 cm^2, P<0.01) as well as bipedal (pre:3.46 ± 1.05cm^2, post: 4.31 ± 0.98cm^2, P<0.01). There was a significant increase in the CSA on the untrained side as well in both lying (pre:3.34 ± 0.92cm^2, post:3.63 ± 1.01cm^2, P=0.01) and bipedal (pre:3.59 ± 1.02cm^2, post:4.00 ± 1.21cm^2, P<0.01). There was a significant decrease in echogenicity measures (pre:70.2 ± 9.91, post:65.7 ± 8.68, P=0.001) in the trained limb post-rehabilitation. There was no significant difference in echogenicity in the untrained limb. **Conclusion:** This is the first study to collectively analyze multiple clinical groups with suspected IFMs weakness in functional position for both muscle size and quality. We found significant changes in the muscle CSA and tissue quality in the pathological groups compared to a healthy group. These results suggest that clinicians should evaluate lower extremity injured patients to establish the need for rehabilitation of the IFM muscles in an effort to improve foot and ankle function in these populations. The rehabilitation program was administered in the CAI group to address the weakness found in the first manuscript. Normalized CSA of the IFMs increased in both sitting and standing position for the trained leg. However, the CSA of the IFMs increased only in the functional position for the untrained leg. The muscle quality measures did not change for the IFMs before and after rehabilitation which may be need a longer rehabilitation program to produce positive effects. For **M3)** Normalized CSA of the peroneal muscle group increased in both lying and standing position for the trained leg. However, the CSA of the IFMs increased only in the functional position for the untrained leg. There was a significant increase in the muscle quality as well. Therefore, we observed that there are faster changes in muscle quality in the peroneal muscle group when compared to the IFM and that may be because of different muscle physiology or a because of rehabilitation program that involves more gross motor patterns requiring less motor learning. Over all, the impairment-based rehabilitation was effective in restoring muscle size in IFM, and muscle size and quality in peroneal muscle groups. Rehabilitation programs are recommended for other clinical groups where deficits were observed in this study.

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Comparison of Intrinsic Foot Muscles Function in Patients with Different Lower Extremity Conditions

Abstract

Context: The role of intrinsic foot muscles (IFM), also known as foot core, is essential in providing stable base of support and integrity to the foot skeleton. IFM dysfunction is proposed to cause alterations in the function of foot and has been linked to lower extremity injuries especially foot and ankle pathologies. However, the link of IFM weakness and dysfunction has yet to be explored in lower extremity disorder such as Chronic Ankle Instability (CAI), Patellofemoral Pain (PFP), 1st Metatarsophalangeal joint (1st MTPJ) arthrodesis and in patients with diabetes, as compared to their healthy counterparts. **Objective:** To compare the differences in IFM morphology and tissue quality in patients with CAI, PFP, 1st MTPJ arthrodesis, diabetes, and healthy individuals. **Design:** Cross-sectional study. **Setting:** University laboratory. **Patients or Other Participants:** One hundred and nineteen individuals participated in this study that included 35 PFP (age:20.46 ± 3.79 years; 26F, 9M; Height=170.80±11.91 cm; Weight=73.28±26.58 kg), 25 CAI (Age=21. ± 3.36yrs; 21F, 8M; Height=169.97 ± 10.31 cm; Weight=70.31 ± 13.71 kgs), 9 with 1st MTPJ arthrodesis (Age= 57.56±9.07 yrs; 6F, 3M; Height= 163.2±11.03 cm;Weight = 81.33±13.32 kg), 9 with Diabetes (Age=24.02 ± 8.97 yrs; 13M. 25F; Height=169.7 ± 8.92 cm; Weight= 65.02 ± 12.06 kgs), and 38 healthy (Age=24.02 ± 8.97 yrs; 13M. 25F; Height=169.7 ± 8.92 cm; Weight= 65.02 ± 12.06 kgs) participants. **Main Outcome Measures:** Ultrasound imaging (USI) cross-sectional (CSA) representing muscle size and echogenicity representing muscle quality were measured for Abductor Hallucis (AbH) and Flexor Digitorum Brevis (FDB). All size measures were normalized to body mass. Analysis of Covariance (ANCOVA) was run between groups with age and sex as covariates to determine group differences. **Results:** There were statistically significant difference ($P<0.05$) in the CSA of

the AbH between all pathology groups when compared to healthy. Post-hoc analysis revealed that it was significantly lower ($P<0.01$) in every group compared to healthy except 1st MTPJ arthrodesis group. Similarly, significant differences ($P<0.01$) were found in the CSA of FDB between groups compared to the healthy group and post-hoc analysis revealed group differences in each group except PFP and 1st MTPJ groups. For echogenicity analysis, significant differences ($P<0.05$) were found between groups for both AbH and FDB. The post-hoc analysis revealed significantly ($P<0.05$) higher echogenicity in CAI and 1st MTP groups for AbH, and significantly higher ($P<0.05$) echogenicity in CAI, 1st MTP and PFP for FDB. Large effect sizes were found in both CSA and echogenicity measures when compared to healthy except PFP group for which small to moderate effect sizes were found. **Conclusion:** This is the first study to collectively analyze multiple clinical groups with suspected IFMs weakness in functional position for both muscle size and quality. We found significant changes in the muscle CSA and tissue quality in the pathological groups compared to a healthy group. These results suggest that clinicians should evaluate lower extremity injured patients to establish the need for rehabilitation of the IFM muscles in an effort to improve foot and ankle function in these populations.

Introduction

Similar to lumbopelvic complex, foot skeleton is also supported by local and global stabilizers that comprise the "foot core".[1] Intrinsic foot muscles (IFM) are one of the principal stabilizers of the medal longitudinal arch and are essential to passive, active and neural subsystems forming core musculature of the foot.[1] They serve to stabilize the foot segments while maintaining postural control,[1,2] dissipate forces during loading,[1,3] and generate propulsive forces needed for locomotion.[1,3] Many of the plantar IFM attach proximally to the calcaneus and distally to the toes and are capable of resisting flattening of the longitudinal arch when contracted. Weakness of IFM may result in inability of the arches to sustain load and hence more pressure on plantar fascia causing plantar fasciitis or other foot pathologies like osteoarthritis of the MTP joints and metatarsalgia.[4] They also provide similar resistance to dorsiflexion of metatarsophalangeal joints that has been provided by the plantar fascia in the windlass mechanism when there is increase dorsiflexion moment.[1] Kelly et al.[5], found that many of the IFMs have a role in flexing the midfoot joints when stimulated electrically and they contract isometrically when walking following the heel lift.[5] It was also reported that IFM stretch actively during the first half of the stance during running, storing energy that is released when the muscles shorten during the second half of the stance phase helping in maintaining healthy gait and locomotion.[6]

IFM weakness often causes problems in balance, increase in navicular drop, decrease in strength and biomechanical abnormalities which eventually result in limitation of activity, and negatively affect patient function,[1,4,7] therefore, focus on improving assessment of IFM is paramount. The complex articulation of foot and ankle, and multi-articulated planter foot

musculature makes it difficult to assess these muscles.[8] Perhaps, not having a reliable method of assessment is one of the reasons that there is still disparity found in the orthopedics and sports medicine literature while understanding the role and function of these muscles. From a clinical perspective, there are no tests that reliably examine strength of the IFMs, yet treatments are often focused on the assumed weakness in the foot. Intrinsic foot muscle test (IFMT) and toe dynamometry are commonly employed for measuring IFM strength.[9,10] However, IFMT involves qualitative assessment of the IFM strength and there is a dearth of evidence on its reliability and validity. Hand-held dynamometry[10] is shown to be a reliable measure with an excellent interrater (ICC=0.82-0.88) and intrarater (ICC=0.77-0.94) reliability but it is very hard to differentiate the activity of IFM from the extrinsic flexors in toe flexion.[10] Soysa et al.[11] conducted a review of intrinsic foot muscle strength measures and concluded there is no widely accepted method of directly measuring intrinsic foot muscle strength especially in clinical settings.

MRI can be used as a reliable measure to assess the morphology of the IFMs but MRI is neither prevalent nor cost-effective.[8] Previous literature has validated ultrasound (US) imaging with MRI and has shown to have a good correlation.[12] US imaging has shown to be the only reliable method that can be used to directly visualize these muscles and differentiate them from extrinsic muscle activity.[13,14] US imaging has also been found to be accurate in determining muscle quality by measuring muscle degeneration through echogenicity.[15-17] In addition, US imaging has found to be reliable in weight-bearing position that is the functional position of the IFM.[18] Battaglia et al.[19] and Smith et al.[18] recommended that IFM should be tested in the weight-bearing position to get a better representation of IFM assessment.

It is proposed that IFM weakness may be associated with foot and ankle problems such as patellofemoral pain (PFP), chronic ankle instability (CAI), and 1st metatarsophalangeal joint (1st

MTPJ) arthrodesis, and systematic conditions such as diabetes mellitus.[13,17] CAI has shown to be associated with damage to tibial nerve that is directly supplying IFM and may result in their weakness.[20] Whereas, one of the factors associated with PFP is decrease in navicular drop resulting in compensatory increase in the internal rotation and that can be linked to IFM weakness as well.[21] 1st MTPJ arthrodesis results in the reproduction of symptoms such as metatarsalgia and lateral toes osteoarthritis that can also occur because of the weakness of IFM. [22,23] and patients with diabetes mellitus have shown to have significant atrophy with MRI imaging but the functional assessment of IFM in diabetic patients is yet to be explored.[24] Overall, all the clinical conditions studied in this manuscript have share some common problems such as balance deficits or greater navicular drop and IFM dysfunction may be the underlying cause of the same deficits in different populations. Assessment and rehabilitation are challenging for these injuries, therefore a mutual technique for improved assessment, through a visual method (i.e. US imaging) would be of great significance for clinicians. A shared modifiable problem of foot core weakness may be present in these groups and identifying weakness of IFM on a spectrum may be helpful for clinicians to devise rehabilitation strategies specific to each group. Therefore, the primary objective of this study was to gain deeper understanding of IFM dysfunction by assessing muscle size and quality using US imaging in patients with CAI, PFP, 1st MTPJ arthrodesis and diabetes as compared to healthy groups. We hypothesized that healthy participants would have a greater muscle size and better muscle quality than the injured groups, with people with diabetes displaying lowest IFM size and quality of all groups.

Methods

We performed a cross-sectional study using a sample of convenience in which the independent variables were injury group (CAI, PFP, 1st MTP arthrodesis, diabetes and healthy)

and position (non-weight bearing and weight-bearing)), and the dependent variables were IFM size (cross sectional area of two IFMs) and quality (echogenicity of three IFMs). The muscles imaged in this study were Abductor Hallucis (AbH) and Flexor Digitorum Brevis (FDB). Institutional review board approval was granted and written consent was obtained before the start of the data collection.

Participants

One hundred and nineteen total subjects participated in this study. The groups characteristics along with demographics are briefly mentioned below.

Chronic Ankle Instability:

Twenty-nine participants (Age=21. ± 3.36yrs; 21F, 8M; Height=169.97 ± 10.31 cm; Weight=70.31 ± 13.71 kgs) with the history of CAI participated. Inclusion criteria was based on the recommendations of the International Ankle Consortium.[25] Concisely, participants with CAI had a history of at least 1 significant ankle sprain at least 1 year prior to study enrollment, decrease in self-reported function (Foot and Ankle Ability Measure (FAAM) Sport ≤ 85% and experiencing repetitive bouts of instability or "giving away" with a score on Identification of Functional Ability (IdFAI) >10. Participants with CAI that were included in this study had a FAAM-sport score of 68.35 ± 15.44% and a score of 21.76 ± 4.18 on IdFAI.

Exclusion criteria was any history of lower extremity fracture or surgery, ankle sprain within past 6 weeks, conditions known to affect gait, pregnancy, and currently receiving physical therapy.

Patellofemoral Pain:

Thirty-five participants (Age:20.46 ± 3.79 years; 26F, 9M; Height=170.80±11.91 cm; Weight=73.28±26.58 kg) with the history of PFP participated. PFP participants had similar inclusion criteria as is described previously in literature.[26] Briefly, inclusion criteria included insidious onset of symptoms unrelated to a traumatic event, pain lasting for more than three months, and the presence of peri- or retro- patellar knee pain during at least two of the following activities: stair ascent or descent, running, kneeling, squatting, prolonged jumping, isometric quadricep contraction or palpation of the medial and/or lateral facet of the patella. Participants with PFP should have scores 85 or less on Anterior Knee Pain Scale (AKPS) and greater than 3 out of 10 points on visual analogue scale (VAS) for worst pain over the last 72 hours prior to being tested. An athletic trainer with 3 years of clinical experience assessed all participants with PFP for inclusion. Participants were excluded if they reported a history of internal derangement such as rupture to any of the ligaments in knee or meniscal injury, ligamentous instability, other sources of anterior knee pain or neurological involvement/cognitive involvement.

1st Metatarsophalangeal joint arthrodesis:

Nine participants with unilateral 1st MTPJ arthrodesis (Months from surgery=29.1±17.5; Age= 57.56±9.07 yrs; 6F, 3M; Height= 163.2±11.03 cm;Weight = 81.33±13.32 kg) participated in this study. Inclusion criteria included: have had unilateral arthrodesis procedure to the 1st MTPJ, have had surgery at least 6 months prior to data collection, be over the age of 18 years, have no history of any other lower extremity injury/surgery in the past 6 months, be able to walk for at least 10 minutes, and had not been diagnosed with Diabetes Mellitus, Multiple Sclerosis, or Parkinson's disease. Potential subjects were recruited from a university health system orthopedic foot and ankle clinic staffed by three surgeons.

Diabetes:

Nine participants with the history of diabetes (Age= 34.9 ± 12.8 yrs; 5F, 4M; Height= 169.2 ± 11.5 cm; Weight= 76.0 ± 20.1 kgs; Time since diagnosis: 11.6 ± 9 yrs; 8 type 1, 2 type 2) Participated in this study. Inclusion criteria comrpised of history of diabetes mellitus type 1 or type 2, age between 18 to 70 years, both men and women, independent walking ability for at least 10 minutes, any partial ulcertation should be healed for at least six momths, should not have any partial or total foot amputation, and should not be receiving any physical therapy intervention at the time of testing. Exclusion criteria included presence of any active plantar ulcers, diagnosis of a nuerological disorder, dimentia or inability to give consistent information, receiving any physical therapy intervention at the time of participation in the study.

Healthy:

Thirty-eight healthy participants (Age=24.02 ± 8.97 yrs; 13M. 25F; Height=169.7 ± 8.92 cm; Weight= 65.02 ± 12.06 kgs) participated in this study. "Healthy" was defined as no previous lower extremity surgery, no history of ankle sprains, no lower extremity injury, in the 6 months prior to enrollment, and no known neurological impairments or the diagnosis of diabetes.

Instruments

USI was performed using a Siemens Acuson Freestyle US system with a wireless 8-Mhz linear transducer (Siemens, Mountain View, CA). The images were then measured using ImageJ version 1.50f (National Institutes of Health, Bethesda, MD) loaded onto a HP windows laptop. US scanned all images at the depth of 3.5 cm.

Procedures

Participants reported to the lab and eligibility criteria for the respective group was determined based on the aforementioned inclusion criteria. Following enrollment based on the

inclusion criteria, demographic information (age, body mass, height, duration of pain, injury history) was collected. Afterwards, US imaging was conducted by a licensed physical therapist with 5 years of clinical experience.

Ultrasound Measures:

A customized step (Figure 1-1) was created by investigators in the lab with an aperture of 14cm to take IFMs images in closed chain position, sitting and standing. The US imaging was performed in bilateral standing position which is a functional position. The probe location proven to be reliable and valid was used.[13,14,27] Briefly, AbH was traced by placing the probe along a line perpendicular at the anterior aspect of the medial malleolus for CSA.[13,14,27] The CSA of FDB was identified by scanning the probe perpendicular to a line from the calcaneus to the third toe. [13,14,27] The US transducer compression was kept to a minimum to ensure no distortion in muscle size. Gel was used as a media to conduct US imaging.

Data Processing and Statistical Analysis

The CSA images, in cm^2 were measured by marking the internal circumference of the fascial border of each muscle. Measured US images are shown in (Figure 1-1) for AbH in the sitting position are provided as an example. Similar methods were used to measure FDB in bipedal standing position.

Once all the measurements were taken, average of three single measurements were calculated for each measurement type for each participant. Averages of CSA (cm^2) were then normalized to body mass (kg) to make comparisons between the groups. Grey scale analysis was conducted to calculate the mean grey area of the CSA of each image for both AbH and FDB which gave the echogenicity values.[28]

Statistical Analysis:

A sample of convenience was used for this study. Statistical analysis was conducted using IBM Statistics (v26.0, SPSS, Inc. Chicago, IL, USA). Skewness, kurtosis, and normality of variance proved normally distributed data for the dependent variables. CSA and echogenicity outcome measures were analyzed using an analysis of covariance (ANCOVA) with age and gender as the model covariates for comparison between the groups. Simple contrast post-hoc analysis was used to make comparisons between the clinical groups with healthy group. The a priori level of significance was set at $p \leq 0.05$. Mean differences with 95% confidence interval were calculated, as well as Cohen's *d* effect sizes to determine magnitude of difference in pre-post measures were assessed. Effect sizes were interpreted as follows: <0.2 trivial; 0.2 to 0.4 small; 0.5-0.7 moderate; ≥ 0.8 large.[29]

Results

Dependent variables were normally distributed based off skewness, kurtosis, and normal variance as assessed by Shapiro-Wilk test ($p>0.05$). There was a statistically significant difference ($P<0.01$) in the CSA of AbH between the groups when compared to the healthy group while controlling for age and sex as covariates (Figure 1-3). Post-hoc analysis using simple contrasts revealed that CSA was significantly lower in the Diabetic ($P<0.01$), CAI ($P<0.01$) and PFP ($P<0.01$) groups when compared to healthy group (Table 1-1). However, there was no statistically significant difference ($P=0.14$) in the size of 1st MTP group when compared to healthy group. Large effect sizes noted for all group differences (Figure 1-2). Similarly, significant differences ($P<0.01$) were found in the CSA of FDB between groups compared to the healthy group when controlling for age and sex as covariates. Post-hoc analysis using simple contrasts revealed that CSA of FDB was significantly decreased in the Diabetes ($P<0.01$), and

CAI (P<0.01) groups as compared to healthy group. However, no differences were found in 1st MTPJ arthrodesis group (P=0.06) and PFP group (P=0.71) when compared to healthy. Large effect sizes were found for all group differences except PFP (Figure 1-2)

A significant group difference was found in the echogenicity measures between the groups when compared to healthy for both AbH (P=0.044) and FDB (P=0.001) (Figure 1-3 and Table 1-1). *Post-hoc* analysis using simple contrast for AbH showed that there were significant differences in 1st MTPJ arthrodesis (P=0.023), CAI (P=0.025) and no significant difference in PFP (P=0.145) and the Diabetes group (P=0.07) when compared to the healthy group. Post-hoc analysis using simple contrast for FDB revealed that there were significant differences in 1st MTPJ arthrodesis (P=0.030), CAI (P<0.01), PFP (P=0.008) and no difference (P=0.06) in the diabetic group when compared to healthy. Large effect sizes were observed for all group differences except PFP (Figure 1-2).

Discussion

This is the first study that comprehensively examines the CSA and muscle quality of IFM different pathological groups where IFMs weakness is suspected. This was an effort to understand the spectrum of IFM weakness through CSA and muscle quality in different selected foot and ankle pathologies when compared to healthy group. Our results from this study delineate the importance of IFMs assessment that may be missing from the routine clinical assessments in the foot and ankle research and clinical settings. We found significantly lower muscle CSA of AbH muscle in all the clinical groups except 1st MTP when compared with healthy with moderate to large effect sizes. We also found group differences with lower muscle CSA of FDB in CAI and Diabetes group but not in 1st MTP and PFP groups and large effect sizes were found in all groups except PFP (Figure 1-2 and Figure 1-3). We also discovered that

there were distinct differences in muscle quality for both AbH and FDB when compared to the clinical groups (Figure 1-2). There were large effect sizes found for significant differences for all clinical groups except PFP which exhibited moderate effect sizes (Figure 1-2 and Figure 1-3).

The IFMs are the local stabilizers of the complex foot skeleton. These muscles are characterized by production of smaller torques when compared to the extrinsic muscles yet providing necessary stability for the global movers to function.[1] Whether it be balancing, or walking, IFMs act to stabilize the arch and provide stability.[1,5] Dysfunction of the IFMs can result in disruption of function at the foot and ankle complex; and abnormal movements follows such as excessive pronation at foot followed by greater frontal plane excursion at knee resulting in variety of foot related problems.[30,31] However, the importance of IFMs remained unacknowledged with no mention of IFMs strengthening or rehabilitation in the clinical evidence and guidelines in managing foot and ankle problems especially in rehabilitation.[1] One reason can be inability of clinical researchers to identify the weakness of IFMs because of difficult assessment.[11] However, with the advances in US imaging and its ability to assess these muscles in functional positions with high reliability provides an opportunity for clinicians and researchers to identify the levels of weakness of these muscles in variety of foot and ankle clinical groups.[18,19] This study intended to identify the scope of muscular changes on US imaging corroborating the severity of the disease and underscores the importance of developing strengthening program that will help these patients in improving their foot and ankle function (Figure 1-3). Supporting our hypothesis, we identified differences in size and quality differences of variety of magnitude in different clinical groups when compared to healthy (Figure 1-2). We speculate that the differences in magnitude of size and quality may represent severity of effect of

the conditions examined in this study on the foot and ankle complex. We will subsequently discuss each group independently.

Chronic Ankle Instability

Ankle sprains are the most common orthopedics injuries.[32] An ankle sprain injury is defined as when one or more of the ligaments supporting the talocrural joint are damaged.[33] When the strain on the ligaments exceeds its tensile strength, it results in an injury.[33] The annual health care cost of ankle sprains is $2 billion per year in the United States.[32] Individuals who suffer from ankle sprain often have difficulty in attaining the pre-injury functional level and suffer from recurrent ankle sprains.[34] Moreover, 40 % of the people with ankle sprain go on developing CAI within the first 12 months of sustaining first ankle sprain.[35] CAI is an umbrella term that includes mechanical and functional instability, along with residual symptoms including pain and giving away in the ankle after a lateral ankle sprain.[36]

We found significant decreases in muscle CSA of AbH and FDB in CAI group when compared to healthy. In addition, we also discovered significant increases in echogenicity representing poorer muscle quality in CAI group. One reason of that could be tibial nerve injury.[20] Tibial nerve injury has been previously reported in patients with CAI which supplies the planter intrinsic foot muscles.[20] Previously, it has been shown that tibial nerve block can result in the complete loss of function.[37] It is possible that the atrophy and muscle quality changes observed in patients with CAI are because of tibial nerve injury.

Fraser et al.[29] reported impairments in foot function in individuals with CAI. They found that there were impairments in physiological and accessory motion of the foot and also reported significant decreases in the strength of lesser toe and hallux strength.[29] Loss of motion and lower

strength measures may be because of IFMs weakness. Concurring our results, significant atrophy in IFMs has been reported previously using MRI.[38] However, it was a small sample size of 5 patients and imaging was performed in lying position which is a non-weight bearing position.[38] We had a relatively bigger sample size of 29 participants with CAI and 38 healthy participants in this study and large effect size of d=1.50 and d=1.40 were found for AbH, and FDB, respectively which underlines the magnitude of atrophy present in patients with CAI. Moreover, we also examined quality of tissue which also revealed poorer quality in both AbH and FDB with an effect size of d=0.68 and d=1.08, respectively. This study furthers the evidence regarding the loss of muscle quality and size in IFMs in patients with CAI and proposes a potential reasoning of underlining causes foot impairments in patients with CAI that Fraser et al.[29] noted in their study. This establishes a need of regularly assessing IFMs in clinic while managing patients with CAI, and new intervention strategies should be developed that address these deficits. Certain exercises have been suggested for incorporating in the rehabilitation program to address IFMs weakness.[39] Further studies need to be conducted to understand the impact of these exercises on IFMs muscle size and quality.

Patellofemoral pain group

Patellofemoral pain (PFP) is a common musculoskeletal condition that is characterized by insidious onset of pain localized to the anterior retropatellar and/or peripatellar region of the knee associated with activities involving lower limb loading.[40] The onset of symptoms can be slow or acutely develop, with a worsening of pain with lower limb loading (e.g., squatting, jumping, running, etc.).[41,42] Foot or arch dysfunction has been reported in PFP population and is mostly managed by placing orthotics in the shoes of these individuals.[43] In a recent systematic review, foot evaluation is recommended in people with PFP to better design intervention

strategies.[43] However, it is hard for clinicians to identify the structures in the feet where they can intervene because foot and ankle complex is less studied in the PFP population.

In this study, we aimed to examine the size and quality of IFMs that are the major stabilizers of the arches of the foot, and provide a stable base for the global movers.[1,3] Arch collapse during dynamic activities has shown to be associated with PFP, however the characteristics of major eccentric stabilizers of the arch, the IFMs, has not been studied in this population. Although, we did not find differences in CSA of FDB, significant decreases in AbH CSA and poorer muscle quality of IFMs was noted when compared to healthy groups (Figure 1-3). The decrease in size and quality of IFM, specifically AbH, in weight-bearing functional position may indicate problems in the stabilization of the medial longitudinal arch (MLA) during functional activities. The AbH runs its course right underneath the MLA of the foot, and it is associated with controlling the deformation of medial longitudinal arch during gait.[44] Most of the individuals in the PFP group were young active individuals and are likely to be doing most of their daily living activities in functional weight-bearing positions. Attaining closed chain functional position with weak or dysfunctional major stabilizers of the MLA may result in arch collapse in functional activities that is associated with increase in frontal plan project angle at knee and PFP.[31]

Moreover, IFM weakness is directly associated with collapse of MLA.[30] This is a first study to identify weakness in IFMs in patients with PFP. It will be interesting to administer a rehabilitation program that incorporates IFM and follow them to understand the effect of these exercises on foot and ankle characteristics of group with PFP. 4-weeks of IFMs training has been found to decrease navicular drop and improve balance.[45] It would not be unreasonable to suggest

that addressing AbH weakness in patients with PFP may help increase the stability of their base of base of support which may improve lower extremity kinematics during daily living tasks.

1st MTPJ Arthrodesis

Arthrodesis or the fusion of the 1st MTPJ is performed in individuals who suffer from severe OA to relieve pain and improve quality of life. [22,46] Approximately, 80 % of the patients are satisfied with the outcomes of surgery related to pain relief. [22] However, 20% of the patients remain unsatisfied with the outcome of surgery for the reasons not very well-known. [22] It has been shown that lack of motion in the 1st MTPJ after arthrodesis results in compensation by lateral toes for restoring foot function, resulting in more loading on lateral toes that may cause arthritis of lateral MTP and IP joints and may also cause metatarsalgia.[22,23] Interestingly, the problems in foot seen after 1st MTPJ arthrodesis are similar to what are seen after IFM weakness such as metatarsalgia.[30] We think that there may be IFMs weakness developed post-surgically in these patients that may contribute in development of these problems. Supporting our hypothesis, we found decrease in CSA and very poor muscle quality in these patients. Although, statistical significance was not found in 1st MTP group for AbH and FDB, quite large effect sizes for both AbH (d= 1.60) and FDB (d=2.20) were noted when compared to healthy patients. Moreover, the echogenicity analysis showed extremely poor muscle quality with a huge effect of d= 2.47 and d=3.21, AbH and FDB, respectively. This provides a potential reasoning to some of the possible complications seen in the foot skeleton after surgery in patients with 1st MTPJ arthrodesis. This also distinctly delineates the need of establishing post-surgical rehabilitation in these patients. Addition of this post-surgical group in this study enhances the understanding of clinicians and researchers in understanding pathology in the IFMs on a spectrum in comparison with chronic

problems in relatively young people such as CAI and PFP or a systematic disease such as diabetes.

Diabetes group

The Diabetes group fell on the most extreme side of the spectrum on US imaging among the groups examined in this study (Figure 1-3). There was significant atrophy found in AbH (d=2.20) and FDB (=2.80) CSA of diabetic patients along with poorer muscle quality observed with large effect sizes. We also observed poorer muscle quality for AbH (d=1.15) and FDB (d=1.34) in IFMs of diabetic patients. Our results are similar to the findings regarding IFMs in the diabetic patients reported previously using MRI and US imaging.[47] Adding a group with diabetic patients validates our findings in relation to other groups as multiple reports in the past have highlighted significant losses in IFMs in diabetic patients.[24,47] In addition, lower CSA in the functional position in these patients may show that there is lesser activation of these muscles while weight bearing which may further cause foot and ankle problems in this group because lack of cushioning and poorer shock absorption at the foot.[24] In addition, IFM CSA is associated with balance, and appropriate gait mechanics.[24] Weakness of IFM can lead to increase in planter pressure which consequently may yield to the development of plantar ulceration.[24,48] In addition, we also found poor muscle quality in this group which has not been previously studied.[49] Poor muscle quality is associated with increasing intramuscular adipose and fatty tissue which subsequently is correlated with poor muscle strength and functional limitations.[50-52]

Foot and ankle problems are big issue that are associated with diabetic neuropathy.[53] The risk of patients with diabetic ulcer is 2.5 times higher at 5 years when compared to the patient who has diabetes without foot ulcer.[53] It has been also reported previously that up to 20 % of the people with diabetic ulcer require amputation.[54] There are number of factors associated with the

diabetic peripheral neuropathy and negative impact on the diabetic foot health. One primary association is deterioration of the soft tissue on the planter surface of the foot including the atrophy of the intrinsic foot muscles.[24] Nevertheless, there is no study in the literature that has investigated the effect of IFMs rehabilitation in diabetic group. Assessing IFM in the functional position may provide us information about activation, beyond the size of these muscles. This, in turn, may help researchers to design optimal rehabilitation interventions that can result in increased activation of these muscles in the weight-bearing that is a function position of the foot.

Limitations

There were certain limitations to this study and of those was the choice of only assessing planter intrinsic foot muscles and no dorsal IFMs. However, ultrasound imaging of plantar IFMs is reliable in weight-bearing functional positions.[13,27] Future studies should investigate dorsal intrinsic foot muscles to get a more comprehensive picture of what is happening in the foot in those with foot injury compared to healthy individuals. We assessed all groups in weight-bearing bipedal stance. However, in future efforts may be made to test these muscles in a more dynamic position.

Conclusion

This is the first study to collectively analyze multiple clinical groups with suspected IFMs weakness in functional position on a spectrum of common denominator, the IFMs CSA and tissue quality. We found significant changes in the muscle CSA and tissue quality in the groups with suspected IFMs atrophy comparing them with healthy group. We found that diabetic group was the most severely effected in terms of CSA changes and 1st MTP arthrodesis group had the poorest muscle quality. Large effects sizes were also found in group with CAI. However,

in PFP group in AbH had larger effect sizes when compared with the healthy group. Conclusively, IFM dysfunction is a common source across all the studied pathologies in this manuscript. One important message in this paper is that IFM therapy may benefits patient groups who may have similar consequences and functional impairments. Although, the functional implications of IFM dysfunction was not studied in this project but there is certainly evidence in literature to support a relationship IFM function and lower extremity health. The IFM assessment is commonly missed in clinic when making lower extremity diagnoses. We recommend that practicing physical therapist and athletic trainers should be aware of these IFM deficits in patients with various chronic pathologies.

References:

1. McKeon PO, Hertel J, Bramble D, Davis I. The foot core system: a new paradigm for understanding intrinsic foot muscle function. *Br J Sports Med.* 2015;49(5):290-290.

2. Lynn SK, Padilla RA, Tsang KK. Differences in static-and dynamic-balance task performance after 4 weeks of intrinsic-foot-muscle training: the short-foot exercise versus the towel-curl exercise. *Journal of sport rehabilitation.* 2012;21(4):327-333.

3. Zelik KE, La Scaleia V, Ivanenko YP, Lacquaniti F. Coordination of intrinsic and extrinsic foot muscles during walking. *European journal of applied physiology.* 2015;115(4):691-701.

4. Jaffri AH, Hertel J, Saliba S. Ultrasound examination of intrinsic foot muscles in patients with 1st metatarsophalangeal joint arthrodesis. *The Foot.* 2019;41:79-84.

5. Kelly L, Lichtwark G, Cresswell A. Dynamic function of the plantar intrinsic foot muscles during walking and running. *Journal of Science and Medicine in Sport.* 2013;16:e4.

6. Holowka NB, Lieberman DE. Rethinking the evolution of the human foot: insights from experimental research. *Journal of Experimental Biology.* 2018;221(17):jeb174425.

7. McKeon PO, Fourchet F. Freeing the foot: integrating the foot core system into rehabilitation for lower extremity injuries. *Clinics in sports medicine.* 2015;34(2):347-361.

8. Feger MA, Snell S, Handsfield GG, et al. Diminished foot and ankle muscle volumes in young adults with chronic ankle instability. *Orthopaedic journal of sports medicine.* 2016;4(6):2325967116653719.

9. Jam B. Evaluation and retraining of the intrinsic foot muscles for pain syndromes related to abnormal control of pronation. *Advanced Physical Therapy Education Institute.* 2006.

10. Spink MJ, Fotoohabadi MR, Menz HB. Foot and ankle strength assessment using hand-held dynamometry: reliability and age-related differences. *Gerontology.* 2010;56(6):525-532.

11. Soysa A, Hiller C, Refshauge K, Burns J. Importance and challenges of measuring intrinsic foot muscle strength. *Journal of foot and ankle research.* 2012;5(1):29.

12. Bemben MG. Use of diagnostic ultrasound for assessing muscle size. *Journal of Strength and Conditioning Research.* 2002;16(1):103-108.

13. Angin S, Crofts G, Mickle KJ, Nester CJ. Ultrasound evaluation of foot muscles and plantar fascia in pes planus. *Gait & posture.* 2014;40(1):48-52.

14. Crofts G, Angin S, Mickle KJ, Hill S, Nester C. Reliability of ultrasound for measurement of selected foot structures. *Gait & posture.* 2014;39(1):35-39.

15. Pillen S, van Alfen N. Skeletal muscle ultrasound. *Neurological research.* 2011;33(10):1016-1024.

16. Pillen S. Skeletal muscle ultrasound. *European Journal of Translational Myology.* 2010;20(4):145-156.

17. Unger CL, Wooden MJ. Effect of foot intrinsic muscle strength training on jump performance. / Effet d ' un entrainement de force des muscles intrinseques du pied sur la performance au saut. *Journal of Strength & Conditioning Research (Allen Press Publishing Services Inc).* 2000;14(4):373-378.

18. Smith A, Hides JA, Hodges PW, Collins NJ. Intrinsic foot muscle size can be measured reliably in weight bearing using ultrasound imaging. *Gait & posture.* 2019;68:369-374.

19. Battaglia PJ, Mattox R, Winchester B, Kettner NW. Non-Weight-Bearing and Weight-Bearing Ultrasonography of Select Foot Muscles in Young, Asymptomatic Participants: A Descriptive and Reliability Study. *Journal of Manipulative and Physiological Therapeutics.* 2016;39(9):655-661.

20. Nitz AJ, Dobner JJ, Kersey D. Nerve injury and grades II and III ankle sprains. *The American journal of sports medicine.* 1985;13(3):177-182.

21. McPoil TG, Warren M, Vicenzino B, Cornwall MW. Variations in foot posture and mobility between individuals with patellofemoral pain and those in a control group. *Journal of the American Podiatric Medical Association.* 2011;101(4):289-296.

22. Stevens J, Meijer K, Bijnens W, et al. Gait analysis of foot compensation after arthrodesis of the first metatarsophalangeal joint. *Foot & ankle international.* 2017;38(2):181-191.

23. Oloff LM, Traynor C, Vartivarian SR. Joint Salvage Techniques for Stage III/IV Hallux Rigidus. *The Role of Osteotomy in the Correction of Congenital and Acquired Disorders of the Skeleton*: InTech; 2012.

24. Bus SA, Yang QX, Wang JH, Smith MB, Wunderlich R, Cavanagh PR. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study. *Diabetes care.* 2002;25(8):1444-1450.

25. Gribble PA, Delahunt E, Bleakley C, et al. Selection criteria for patients with chronic ankle instability in controlled research: a position statement of the International Ankle Consortium. JOSPT, Inc. JOSPT, 1033 North Fairfax Street, Suite 304, Alexandria, VA …; 2013.

26. Nakagawa T, Serrão F, Maciel C, Powers C. Hip and knee kinematics are associated with pain and self-reported functional status in males and females with patellofemoral pain. *International journal of sports medicine.* 2013;34(11):997-1002.

27. Battaglia PJ, Mattox R, Winchester B, Kettner NW. Non–weight-bearing and weight-bearing ultrasonography of select foot muscles in young, asymptomatic participants: a descriptive and reliability study. *Journal of manipulative and physiological therapeutics.* 2016;39(9):655-661.

28. Whittaker JL, Teyhen DS, Elliott JM, et al. Rehabilitative ultrasound imaging: understanding the technology and its applications. *journal of orthopaedic & sports physical therapy.* 2007;37(8):434-449.

29. Fraser JJ, Koldenhoven RM, Jaffri AH, et al. Foot impairments contribute to functional limitation in individuals with ankle sprain and chronic ankle instability. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2018:1-11.

30. Headlee DL, Leonard JL, Hart JM, Ingersoll CD, Hertel J. Fatigue of the plantar intrinsic foot muscles increases navicular drop. *Journal of Electromyography and Kinesiology.* 2008;18(3):420-425.

31. Wyndow N, Collins NJ, Vicenzino B, Tucker K, Crossley KM. Foot and ankle characteristics and dynamic knee valgus in individuals with patellofemoral osteoarthritis. *Journal of foot and ankle research.* 2018;11(1):65.

32. Mckay GD, Goldie P, Payne WR, Oakes B. Ankle injuries in basketball: injury rate and risk factors. *British journal of sports medicine.* 2001;35(2):103-108.

33. Hertel J. Functional anatomy, pathomechanics, and pathophysiology of lateral ankle instability. *Journal of athletic training.* 2002;37(4):364.

34. Hertel J. Sensorimotor deficits with ankle sprains and chronic ankle instability. *Clinics in sports medicine.* 2008;27(3):353-370.

35. Doherty C, Bleakley C, Hertel J, Caulfield B, Ryan J, Delahunt E. Recovery from a first-time lateral ankle sprain and the predictors of chronic ankle instability: a prospective cohort analysis. *The American journal of sports medicine.* 2016;44(4):995-1003.

36. Delahunt E, Coughlan GF, Caulfield B, Nightingale EJ, Lin C, Hiller CE. Inclusion criteria when investigating insufficiencies in chronic ankle instability. *Med Sci Sports Exerc.* 2010;42(11):2106-2121.

37. Fiolkowski P, Brunt D, Bishop M, Woo R, Horodyski M. Intrinsic pedal musculature support of the medial longitudinal arch: an electromyography study. *The Journal of foot and ankle surgery.* 2003;42(6):327-333.

38. Feger MA, Snell S, Handsfield GG, et al. Diminished Foot and Ankle Muscle Volumes in Young Adults With Chronic Ankle Instability. *Orthopaedic Journal of Sports Medicine.* 2016;4(6).

39. Fraser JJ, Hertel J. Effects of a 4-Week Intrinsic Foot Muscle Exercise Program on Motor Function: A Preliminary Randomized Control Trial. *J Sport Rehabil.* 2019;28(4):339-349.

40. PROTOCOL S. Ferber R, Farr L, Kendall KD. *Patellofemoral Pain Syndrome: Proximal, Distal, and Local Factors An International Research Retreat.* 2010;40(3):39.

41. Kannus P, Niittymäki S. Which factors predict outcome in the nonoperative treatment of patellofemoral pain syndrome? A prospective follow-up study. *Medicine & Science in Sports & Exercise.* 1994.

42. Sandow M, Goodfellow J. The natural history of anterior knee pain in adolescents. *The Journal of bone and joint surgery British volume.* 1985;67(1):36-38.

43. Collins NJ, Barton CJ, Van Middelkoop M, et al. 2018 Consensus statement on exercise therapy and physical interventions (orthoses, taping and manual therapy) to treat patellofemoral pain: recommendations from the 5th International Patellofemoral Pain Research Retreat, Gold Coast, Australia, 2017. *British journal of sports medicine.* 2018;52(18):1170-1178.

44. Kelly L, Cresswell A, Racinais S, Whiteley R. and Lichtwark, G.(2014). Intrinsic foot muscles have the capacity to control deformation of the longitudinal arch. JR Soc. *Interface.*11:20131188.

45. Mulligan EP, Cook PG. Effect of plantar intrinsic muscle training on medial longitudinal arch morphology and dynamic function. *Manual therapy.* 2013;18(5):425-430.

46. Brodsky JW, Passmore RN, Pollo FE, Shabat S. Functional outcome of arthrodesis of the first metatarsophalangeal joint using parallel screw fixation. *Foot & ankle international.* 2005;26(2):140-146.

47. Severinsen K, Obel A, Jakobsen J, Andersen H. Atrophy of foot muscles in diabetic patients can be detected with ultrasonography. *Diabetes care.* 2007;30(12):3053-3057.

48. Bus SA, Maas M, Michels RP, Levi M. Role of intrinsic muscle atrophy in the etiology of claw toe deformity in diabetic neuropathy may not be as straightforward as widely believed. *Diabetes Care.* 2009;32(6):1063-1067.

49. Taniguchi M, Fukumoto Y, Kobayashi M, et al. Quantity and quality of the lower extremity muscles in women with knee osteoarthritis. *Ultrasound in medicine & biology.* 2015;41(10):2567-2574.

50. Yamada Y, Schoeller DA, Nakamura E, Morimoto T, Kimura M, Oda S. Extracellular water may mask actual muscle atrophy during aging. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences.* 2010;65(5):510-516.

51. Sipilä S, Koskinen SO, Taaffe DR, et al. Determinants of lower- body muscle power in early postmenopausal women. *Journal of the American Geriatrics Society.* 2004;52(6):939-944.

52. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *Journal of applied physiology.* 2001;90(6):2157-2165.

53. Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. *New England Journal of Medicine.* 2017;376(24):2367-2375.

54. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). *The journal of foot and ankle surgery.* 2006;45(5):S1-S66.

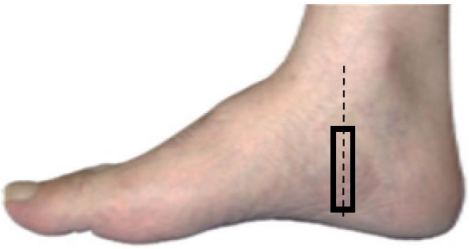
Table 1-1. Ultrasound Measure Values (Mean ± Standard Deviation)

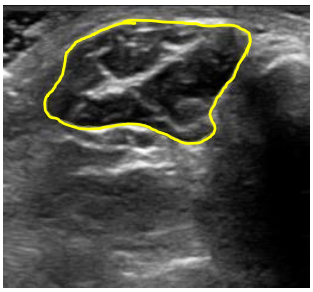
N=26	Groups	Pre-rehab
AbH cross-sectional area (cm^2/kg)	PFP*	.028 ± .0077
	CAI*	.024 ± .0074
	1st MTP	.023 ± .0071
	Diabetes*	.017 ± .0102
	Healthy	.039 ± .0105
FDB cross-sectional area (cm^2/kg)	PFP	.032 ± .0074
	CAI*	.025 ± .0053
	1st MTP*	.021 ± .0095
	Diabetes*	.018 ± .0081
	Healthy	.032 ± .0052
AbH Echogenicity values	PFP	53.08 ± 13.85
	CAI*	56.03 ± 10.51
	1st MTP*	72.89 ± 9.24
	Diabetes	60.42 ± 20.50
	Healthy	49.59 ± 9.42
FDB Echogenicity values	PFP*	54.54 ± 12.02
	CAI*	59.80 ± 9.75
	1st MTP*	79.84 ± 16.14
	Diabetes	62.18 ± 19.41
	Healthy	49.39 ± 10.30

*Significance difference from healthy group
Alpha level set at $p \leq .05$
CAI= Chronic Ankle Instability; PFP= Patellofemoral pain; 1st MTP= 1st Metatarsophalangeal joint arthrodesis.

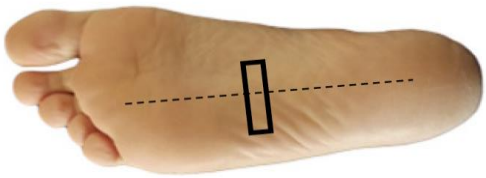
Figure 1-1. Ultrasound Imaging Procedure in Bipedal Standing Position

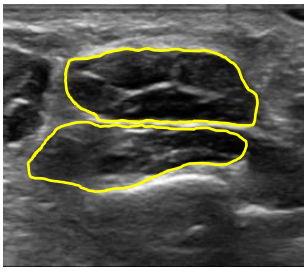
Sitting and bipedal stance on the step to allow access to the medial and plantar side of the foot





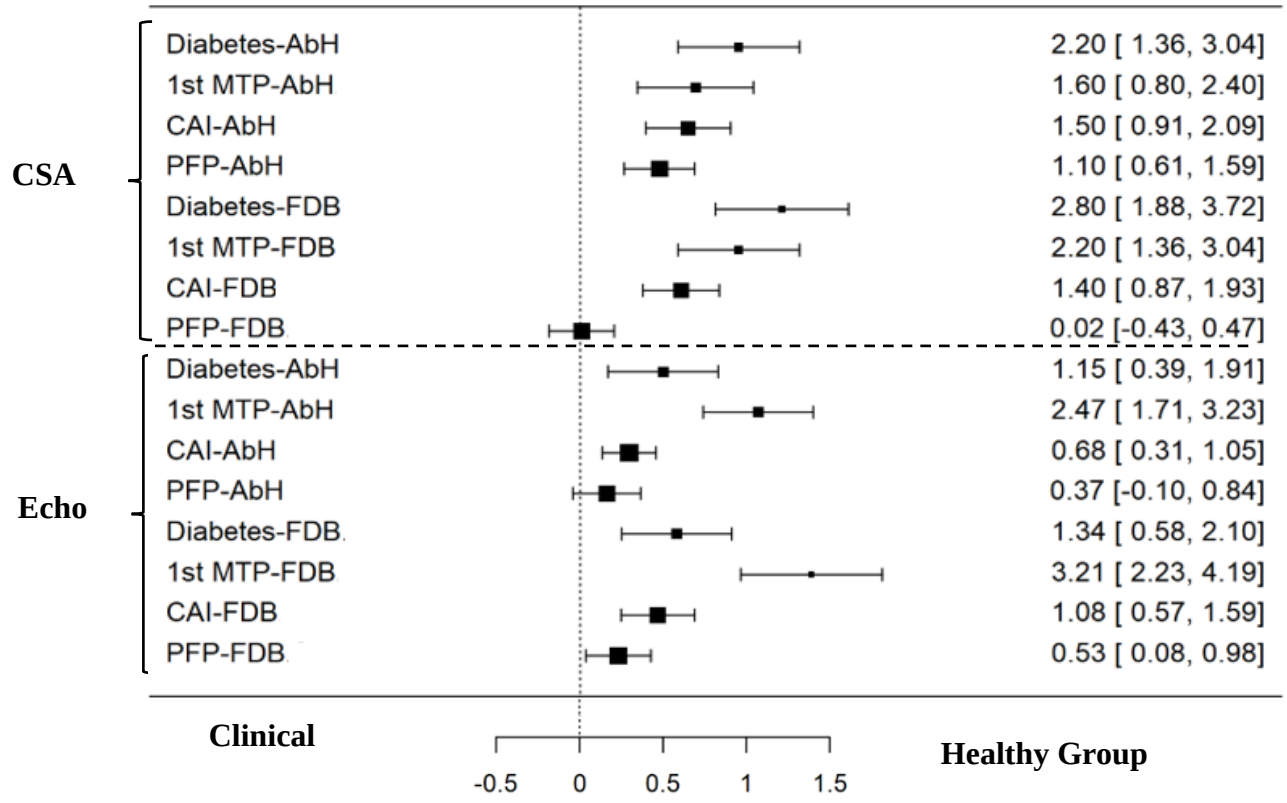
Ultrasound linear transducer placement and cross-sectional area measurement for assessment of the abductor hallucis.





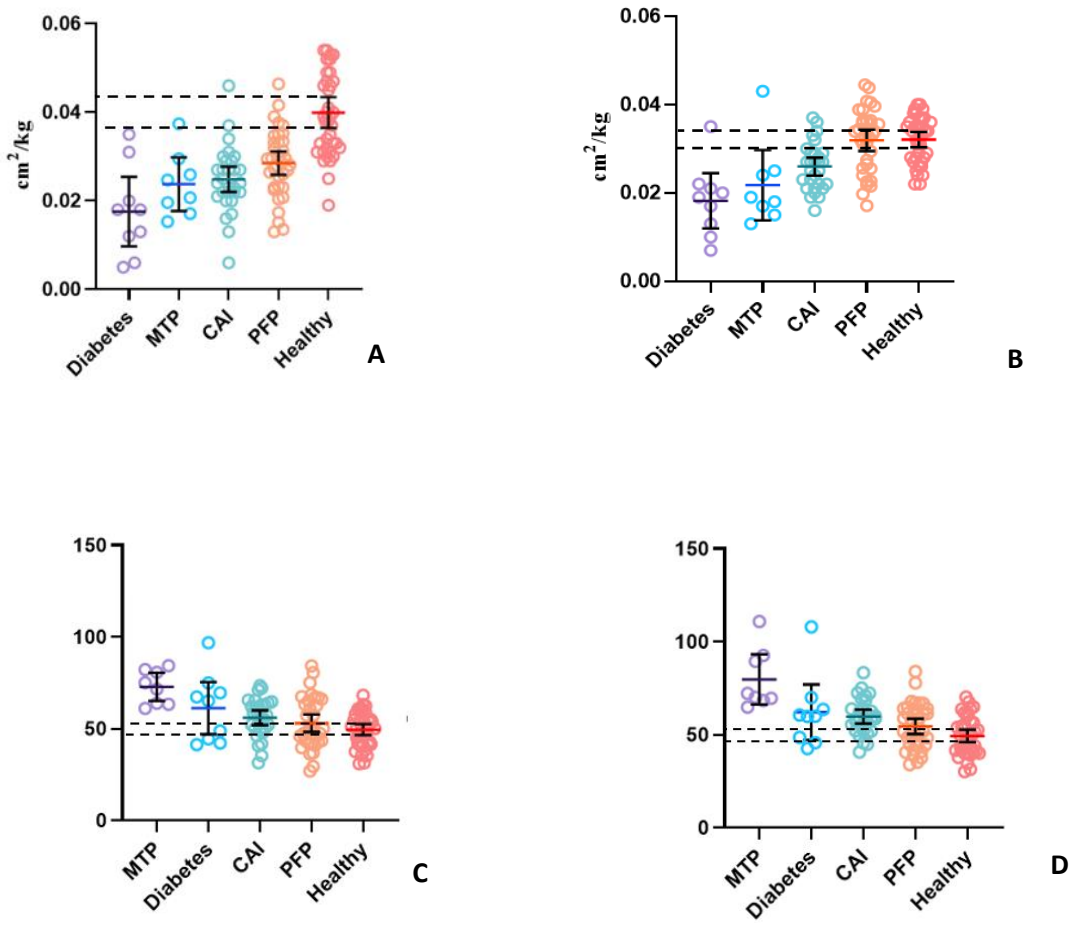
Ultrasound linear transducer placement and cross-sectional area measurement for assessment of the flexor digitorum brevis.

Figure 1-2. Cohen`s *d* Effect Sizes and 95% Confidence Intervals for Intrinsic Foot Muscles Ultrasound Measures



Abbreviations: CSA= Cross-sectional area; Echo= Echogenicity; AbH= Abductor Hallucis; FDB= Flexor Digitorum Brevis; CAI= Chronic Ankle Instability; PFP= Patellofemoral pain; 1st MTP= 1st Metatarsophalangeal joint arthrodesis;

Figure 1-3. Means and 95 % Confidence Intervals for Cross-Sectional Area and Echogenicity Measures in Clinical and Healthy Individuals



A=Cross-sectional area of Abductor Hallucis
B=Cross-sectional area of Flexor Digitorum Brevis
C=Echogenicity measures of Abductor Hallucis
D= Echogenicity measures of Flexor Digitorum Brevis
CAI= Chronic Ankle Instability; PFP= Patellofemoral pain; MTP= 1st Metatarsophalangeal joint arthrodesis

SECTION II: MANUSCRIPT II

Intrinsic Foot Muscle Size and Quality Changes after Impairment-Based Rehabilitation in Patients with Chronic Ankle Instability

Abstract

Context: Intrinsic Foot Muscle (IFMs) are essential to optimal foot function, serving as base of support enduring postural stability, dissipating forces during loading, and generating propulsive forces needed for locomotion. There are large deficits found in IFMs in individuals with chronic ankle instability (CAI) evaluated with MRI, yet the muscles can be visualized with ultrasound (US) imaging which is valid and a cheaper tool to study the muscle size and tissue quality of these muscles. We do not know how these muscle change in terms of their size and quality before and after an impairment-based rehabilitation program. **Objective:** To determine IFMs size and quality changes using US imaging following rehabilitation in patients with CAI. **Design:** Pre-post case series. **Settings:** University Laboratory. **Patients or Other Participants:** 26 patients (age:21.9 ± 3.5 yrs.; 18F, 8M) with CAI completed 8 clinician-supervised rehabilitation sessions over a 4-week period along with home exercises during the days they didn`t complete supervised rehabilitation. **Interventions:** The rehabilitation program was based on individual patient deficits, measures prior to their first treatment session, IFMs strengthening exercises that included short foot exercise, big toe raises, lesser toe raises, and toe spread exercises were incorporated in the lower extremity rehabilitation program. Patients were progression on the aforementioned initial evaluation and individual performance. **Main Outcome Measures:** Prior to the first session and following the final session, US imaging cross-sectional area (CSA) of IFMs during sitting and bilateral standing position were taken both in the leg that was trained and in the untrained leg. The CSA measures were normalized by dividing by participants' body mass in kilograms, and grey scale analysis was performed to measure echogenicity of the image as a surrogate measure of muscle quality. **Results:** A significant ($P<0.01$) increase was observed after rehabilitation for the normalized CSA with the increase in size of AbH and FDB in both seated and bipedal standing position. There were significant improvements ($P<0.05$) in CSA observed

in the untrained limb for AbH and FDB in the bipedal standing position with moderate to strong effect sizes. However, no significant improvements were seen in the CSA of AbH (P=0.24) and FDB (P=0.19)) in the seated position. There was no significant change seen in the echogenicity measures for both AbH (P=0.26) and FDB(P=0.052) muscles. **Conclusion:** Normalized CSA of the IFMs increased in both sitting and standing position for the trained leg. However, the CSA of the IFMs increased only in the functional position for the untrained leg. The muscle quality measures did not change for the IFMs before and after rehabilitation. The IFMs strengthening should be incorporated in the traditional lower extremity rehabilitation programs for patients with CAI. There is a definite increase in size after rehabilitation. However, for muscle quality changes there may be a need of longer rehabilitation programs or a bigger sample size.

Introduction

Ankle sprains are the most common orthopedics injuries.[1] An ankle sprain injury is defined as when one or more of the ligaments supporting the talocrural joint are damaged.[2] When the strain on the ligaments exceeds its tensile strength, it results in an injury.[2] The annual health care cost of ankle sprains is $2 billion per year in the United States.[3,4] Individuals who suffer from ankle sprain often have difficulty in attaining the pre-injury functional level and suffer from recurrent ankle sprains[5]. Moreover, 40 % of the people with ankle sprain go on developing chronic ankle instability (CAI) within the first 12 months of sustaining first ankle sprain.[6] CAI is an umbrella term that includes mechanical and functional instability, along with residual[7] symptoms including pain and giving away in the ankle after a lateral ankle sprain.[8] Neuromuscular deficits in the lower extremity following ankle sprains are associated with functional instability, one contributing factor to CAI.[1,2,9] In the current literature, emphasis is given to the neuromuscular control, activation, and strengthening of the muscles proximal to the ankle in rehabilitation to improve strength, postural stability and restore normal gait pattern.[10-12] However, recently it has been shown that there are large deficits in intrinsic foot muscle (IFM) volume in CAI group compared to healthy.[13]

The foot skeleton is also supported by local and global stabilizers that comprise the "foot core".[14] IFM are the principal stabilizers of the medal longitudinal arch and are essential to passive, active and neural subsystems forming core musculature of the foot.[14] They serve as a base of support enduring postural stability,[14,15] dissipate forces during loading,[14,16] and generate propulsive forces needed for locomotion.[14,16] IFM weakness often causes problems in balance, increase in navicular drop, decrease in strength and biomechanical abnormalities which eventually result in limitation of activity, and negatively affect patient function,[14,17,18] IFM

atrophy in patients with CAI may result in impairment in foot function while contributing to functional ankle instability in patients with CAI. Fraser et al.[19] reported impairments in foot function in individuals with CAI. They found that there were impairments in physiological and accessory motion of the foot and also reported significant decreases in the strength of lesser toe and hallux strength.[19] One of the potential reasons of IFM weakness in patients with CAI is tibial nerve damage [20], highlighting the need of prolonged rehabilitation for these patients.[20] Although, significant losses in muscle mass have been shown previously in IFM[13], there is not much emphasize give incorporating the IFM training or strengthening in the traditional rehabilitation programs for patients with CAI. Perhaps, addition of IFM training in the rehabilitation programs for CAI can improve the functional outcomes of these patients.

However, the bigger challenge for clinicians and researchers is the assessment of the IFMs. Due to the multiarticular nature of the IFMs it is difficult to assess these muscles. MRI can be used as a reliable measure to assess the morphology of the IFMs but MRI is neither readily available in many clinical settings nor cost-effective.[21] Previous literature has validated ultrasound (US) imaging with MRI and has shown to have a good correlation.[22] US examination of the IFMs has considerably helped researchers and scientists to understand the structure and function of the IFMs that remained a challenge for a long time.[23-25] Moreover, US imaging has shown to be the only reliable method that can be used to directly visualize these muscles and differentiate them from extrinsic muscle activity.[23,24] In addition US imaging can provide measures of muscle CSA of the IFM along with muscle tissue quality providing a more comprehensive assessment of muscle function.[26] To our knowledge, there is no study that has analyzed change in IFM size and quality before and after an impairment-based rehabilitation program using US imaging. Therefore, the objective of this study was to study the changes in

IFM size and quality using US imaging. We hypothesized that there will increase in size and improvement in quality of the IFM in patients with CAI following rehabilitation.

Methods

Study Design

This was a pre-post intervention case-series study part of a larger randomized control trial conducted to assess differences in clinical measures and patient-reported outcomes between a gait training group and a no gait training group, conducted in university settings with two collection time points, at baseline and upon completion of a 4-week, 8 session impairment-based rehabilitation protocol (Koldenhoven May 2019). All participants received impairment-based rehabilitation irrespective of their group allocation with respect to gait training or no gait training. Institutional Review Board approval was obtained prior to initiation of the study and all participants signed informed consent. The muscles imaged in this study were Abductor Hallucis (AbH), and Flexor Digitorum Brevis (FDB), in seated and bipedal standing position.

Participants

Twenty-six participants (age:21.9 ± 3.5 yrs.; 18F, 8M) with the history of CAI were enrolled and completed 8 sessions of supervised rehabilitation. Home exercises including intrinsic foot exercises were also given to participants for the days they didn`t have supervised rehabilitation. Inclusion criteria was based on the recommendations of the International Ankle Consortium. Concisely, participants with CAI had a history of at least 1 significant ankle sprain at least 1 year prior to study enrollment, decrease in self-reported function (Foot and Ankle Ability Measure (FAAM) Sport ≤ 85% and experiencing repetitive bouts of instability or "giving away" with a score on Identification of Functional Ability (IdFAI) >10. Institutional review

board approval was granted and written consent was obtained before the start of the data collection.

Exclusion criteria was any history of lower extremity fracture or surgery, ankle sprain within past 6 weeks, conditions known to affect gait, pregnancy, and currently receiving physical therapy. For the larger randomized control trial investigating the effect of gait training, the participants were randomly divided into two groups, gait training group (n=13) and non-gait training group (n=13). However, in this study, the initial analysis was performed to analyze the differences in CSA and muscle quality dependent measures between the two groups and if no differences found they were pooled together and pre-post changes were examined.

Instruments

US imaging was performed using a Siemens Acuson Freestyle US system with a wireless 8-Mhz linear transducer (Siemens, Mountain View, CA). The images were then measured using ImageJ version 1.50f (National Institutes of Health, Bethesda, MD) loaded onto a HP windows laptop.

Ultrasound Measures:

A customized step (Figure 2-1) was created by investigators in the lab with an aperture of 14cm to take IFMs images in closed chain position, sitting and standing. The US imaging was performed in the sitting as well as in bilateral standing position in a randomized order. The probe location proven to be reliable and valid was used.[23,24,27] Briefly, AbH was traced by placing the probe along a line perpendicular at the anterior aspect of the medial malleolus for CSA. The CSA of FDB was identified by scanning the probe perpendicular to a line from the calcaneus to

the third toe. All the images were collected at baseline, and upon completion of a 4-week, 8 session impairment-based rehabilitation protocol

Impairment-based rehabilitation protocol:

Participants received 4-weeks of impairment-based rehabilitation that included 8 supervised rehabilitation sessions. A physical therapist with 5 years of clinical experience and an athletic trainer with 2 years of clinical experience were involved in the administration of rehabilitation protocol. Similar rehabilitation programs have been administered previously.[10] Broadly, the supervised rehabilitation program focused on individual impairments in range of motion (ROM), balance, strength, and functional activities. In addition, strengthening exercises specifically targeting IFM were also incorporated in the rehabilitation program. Specific details of the impairment-based rehabilitation protocol are provided in appendix C (Table C14).

Briefly, for ROM assessment, the supervising clinician undertook detailed clinical evaluation during the baseline session to understand if there were any arthrokinematics or osteokinematic restrictions. If any restrictions were found, the clinicians administered appropriate joint mobilization ranging from grade 2 to grade 3 on the Maitland scale. Stretching exercises were also performed for foot, ankle and hip muscles. Afterwards, participants performed the IFM exercises that included, short foot exercise, extension of toes 2-5 exercise, great toe extension and toe splaying exercise.[28] For the IFM exercises, participants started in the sitting position, and they were progressed gradually from sitting to bipedal standing, and from bipedal standing to single leg standing while performing the aforementioned exercises. Ankle exercises included heel raises, forefoot raises, 4-2ay manual resistance, D1/D2 PNF patterns, and heel and toe walking. Hip exercises primarily of consisted clamshells with resistance band and birddog exercises. Balance exercises included, reaching tasks, single leg balance training, and

hop to stabilization tasks. Functional exercises included lunges, step and step down the box (30 cm), and jumping drills. Participants were evaluated by the supervising clinician during the baseline visit to determine the appropriate starting point the exercise interventions.

Participants were also provided with home exercise plan (HEP) to do on days when they were not coming to lab for a supervised rehabilitation session (appendix C (Table C14)). The HEP consisted of the above mentioned IFM exercises,[28] single leg balancing, calf stretching, and 4-way ankle exercises using a resistance band. Participants reported the number of days they completed the HEP in between the supervised rehabilitation session at the beginning of each session. Compliance was calculated as a percentage of days the participants completed the HEP divided by the number of days between the impairment-based sessions. The rehabilitation was provided only on one leg that was self-identified by participants as worst, and no impairment based rehabilitation was given on the contralateral limb.

Data Processing:

The CSA images, in cm^2 were measured by marking the internal circumference of the fascial border of each muscle. Measured US images are shown in (Figure 2-1) for AbH in the sitting position are provided as an example. Similar methods were used to measure FDB in sitting as well as standing position.

Once all the measurements were taken, average of three single measurements were calculated for each measurement type of each position and image view for each participant. Grey scale analysis was conducted to calculate the mean grey area of the CSA of each image for both AbH and FDB which gave the echogenicity values.[29]

Statistical Analysis:

Statistical analysis was conducted using IBM Statistics (v26.0, SPSS, Inc. Chicago, IL, USA). Skewness, kurtosis, and normality of variance proved normally distributed data for the dependent variables. Initially, independent t-tests were used to examine differences in CSA and muscle quality in IFMs between the gait training (n=13) and non-gait training group (n=13). If no differences found, the groups were pooled together (n=26) and were examined for pre to post rehabilitation changes in CSA and muscle quality in IFMs. Paired t-tests were used to observe the time effect in both non-weight bearing and weight-bearing position for IFMs cross-sectional area (cm^2) in both trained and untrained leg. Paired t-test was also used to observe changes in echogenicity of IFMs before and after rehabilitation. Mean differences with 95% confidence interval were calculated, as well as Cohen's *d* effect sizes to determine magnitude of difference in pre-post measures were assessed. Effect sizes were interpreted as follows: <0.2 trivial; 0.2 to 0.4 small; 0.5-0.7 moderate; ≥ 0.8 large.[19]

Results

Dependent variables were normally distributed based off skewness, kurtosis, and normal variance as assessed by Levene's test ($p>0.05$). The demographic information for the 26 participants with CAI who participated in the study (Age: 21.9 ± 3.5 years, height: 171 ± 10.25 cm, mass: 71.15 ± 14.23 kgs, 18 females and 8 males), including subjective outcomes following rehabilitation in IdFAI and FAAM scores in outlined in Table (2-1).

We did not find any significant differences ($P>0.05$) in the change scores between the gait training or the non-gait training group for muscle size or quality measures in both AbH and FDB. Significant increase was observed in CSA size in both sitting ($P<0.01$) as well standing position ($P<0.01$) for FDB and AbH in non-weight bearing in sitting as well as weight-bearing in

standing position after the 4-week rehabilitation program in the trained leg. (Table 2-2). However, no change was observed in echogenicity analysis in AbH (P=0.26) and FDB (P=0.052) post-intervention (Table 2-2). There was no significant improvement in size muscles seen in the non-weight bearing position for the untrained leg. However, significant improvements were observed in the weight-bearing position for the untrained leg for AbH (P=0.01) and FDB (P=0.005). Over all compliance for the HEP was 80.2%

Discussion

Supporting our hypothesis there were significant gains in the muscle size for both AbH and FDB post rehabilitation in the leg that was trained for both sitting and standing position. However, greater effect sizes were observed in the standing position as compared to the seated position (Figure 2-2). There were no gains in AbH and FDB seen in the sitting position for the untrained leg however, significant gains were seen in the standing position for untrained leg. Contrary to our hypothesis, we did not observe significant changes in the muscle quality for any of the muscles with trivial to small effect sizes for AbH (d=0.18) and FDB (d=0.36), respectively. Although, there were no significant decrease observed for the echogenicity measures for muscle quality, the incorporation of muscle quality measures of stabilizers of foot, the IFMs, allows for a more comprehensive way to examine foot core. This is a novel assessment of the IFM size changes post-rehabilitation that may provide beneficial insight to clinicians and researchers involved in the treatment and rehabilitation of muscle function in patients with CAI.

This is the first study that comprehensively examines the effect of impairment-based rehabilitation program that incorporated IFMs exercises in both non-weight-bearing and weight-bearing position using US imaging. The literature regarding the structure and function of IFMs is somewhat limited but is evolving. Traditionally, it was thought that IFMs are small muscles with

limited function, and the ability to clinically discern strength is difficult. However, it has been shown that IFMs are even bigger than some extrinsic leg muscles.[30] Total IFMs volume (113.3 cm^3) was greater than flexor hallucis longus (74.0 cm^3), flexor digitorum longus (18.7cm^3) and Tibialus posterior (104.2 cm^3) substantiating their functional importance.[30] Nevertheless, because of the multi-articular nature of the IFMs, their assessment remained a challenge for a long time. [23-25] US imaging provides an avenue to comprehensively understand the changes in muscle by assessing muscle size through CSA in both non-weight bearing and weight bearing position and muscle quality through echogenicity.[27,31] Currently, US imaging provides us an optimal avenue to understand and study the function of IFMs as their clinical assessment through any other means remains questionable.[27,31]

Previously, there are IFMs volume deficits reported in patients.[13] Concurring previous research we also significant losses in the muscle size in patients with CAI in our first manuscript of the series of manuscripts of this dissertation. In addition, we also found significantly poor muscle quality in patients with CAI when compared to the healthy controls in the first manuscript of this dissertation manuscripts series. Therefore, we wanted to find if these deficits in quality and size of the IFM in patients with CAI can be addressed by exercises that activate IFM[28] over the rehabilitation period of 4 weeks. Improvement in IFM function is associated with better neuromuscular control, and provide a more stable base of support, which consequently improves the functional outcomes such as balance.[32] Muscle cross-sectional area has been used as a measure of muscle strength and has been directly correlated with the strength of the muscle.[33] Previous literature has shown that greater CSA of the IFMs is associated with improved balance.[34] Zhang et al.[34] showed that there was a negative correlation between the IFM size and the COM sway. There have been proprioception deficits[17] reported in the patients with

CAI and IFM strengthening may help patients with CAI in regaining balance. IFMs also get activated during gait cycle.[35] Kelly et al.[35] reported that there was a continuous change in the EMG activity and lengthening and shortening of these muscles during both walking and running emphasizing the importance of IFMs in daily locomotion. Previously, significant decreases in the accessory motion of tarsal-metatarsal joints and poor strength have been reported in patients with CAI that may create unstable base of support furthering disability in postural control.[19] Improvements in the CSA which is determinant of strength[33] can improve control in the foot skeleton and may improve balance control in patients with CAI.

We also observed significant improvement in the CSA of IFMs in the untrained leg of the patients with CAI. However, these changes were only seen in the weight-bearing position based on which it appears that weight-bearing position is more sensitive to detecting changes in the CSA of IFMs especially in the patients with CAI. Smith et al.[31] and Battaglia et al.[27] also recommended weight-bearing position, a functional position for IFMs, for testing and found high reliability for CSA measures of IFMs. However, to our knowledge, this is the first study that has investigated IFMs CSA changes in their functional position in patients with CAI. We found that even for the trained limb where the significant differences were found in both sitting as well as standing positions the effect sizes were moderate to large in the functional position when compared to the trivial to moderate effect sizes found in the sitting position. Kelly et al. [36] demonstrated that activation of the IFMs increased when the load was applying on the longitudinal arch.[36] Although, we did not directly measure activation of the IFMs, the exaggerated effect sizes found in the weight-bearing position for both limbs can be attributed to increase in activation of the IFMs which delineates the functional importance of these muscles in weight-bearing activities.

It is intriguing to note that there were changes observed in IFM activation in the limb that did not go through 4-weeks of rehabilitation because of a certain increase in muscle size seen from non-weight bearing to weight bearing position. This phenomenon has been reported in literature previously that primarily states that there is a spillover of training effect on the contralateral side when the exercise is performed on the unilateral side.[37] Primarily, this is because of increase motor neuron outputs rather than muscular adaptations (e.g. hypertrophy or increase in muscle fiber length). There can be spillover from the CNS to the contralateral side or may be transfer effects from cortical, subcortical or spinal levels.[37] Perhaps, this is the reason that improvements are more conspicuous in the weight-bearing position (Figure 2-2). There is a possibility that there are changes in the pattern of neural activity related to motor drive and modifications in neural circuit involved in planning run in parallel to the side that is trained because of the synchronization of motor patterns.[37]

Interestingly, we did not find differences in muscle quality after 4-weeks of impairment-based rehabilitation in IFMs with trivial to small effect sizes (Figure 2-2). Although, we did not find significant differences in the echogenicity measures of IFM, the trend shows ((AbH (P=0.26, d=0.18) and FDB (P= 0.052, d=0.36)) that there was decrease in echogenicity indicating improvement in muscle quality. We propose that perhaps we need to implement longer rehabilitation programs to observe muscle quality changes in the IFMs or larger sample size. Muscle quality changes have been reported after 6 weeks of rehabilitation in the bigger muscles such as vastus lateralis.[38] However, we theorize that IFMs are smaller muscles and patients are usually unaccustomed to the exercises that target IFMs because of which the initial few weeks may be just focused on motor learning and gaining neuromuscular adaptations. Some participants have difficulty performing these exercises without curling their toes which

ultimately differentially activates extrinsic foot muscles instead of IFMs. Exercises for bigger muscle groups are more gross movements and are easy to perform, whereas exercises for activation of IFMs are discrete and require fine motor skills which may need more time to develop than gross movements. The difficulty in motor performance may have led participants to take more time to learn IFMs than they might need to learn for some of the other muscle groups such as quadriceps, peroneal etc. We may have observed larger effects of these exercises after 6 or 8 weeks of rehabilitation program. Furthermore, tibial nerve injury has been reported previously in patients with CAI which is the primary nerve supply of the planter IFMs.[20] The damage may also be a reason of slow progressive change in the muscle quality over 4-weeks of rehabilitation.[20]

Limitations:

This study was not without limitations and the lack of improvement in muscle quality of IFMs may have been attributed to the length of the rehabilitation program. Even though, the CSA improved during the 8 sessions over 4-weeks, quality changes may take longer period of time to see a meaningful increase. Although, the improvements in IFMs CSA have been post-rehabilitation after 4-weeks of intervention, we don`t know if these gains in CSA persist over the longer period of time. Future studies should implement longer rehabilitation programs that may result in the changes muscle quality of IFMs. Moreover, participants need to be followed up for longer period of time to study the sustainability of the improvements detected right after a rehabilitation program.

Conclusion:

This is the first study that evaluated the changes in IFMs CSA and quality measures before and after an impairment-based rehabilitation program that incorporated exercises specific to training IFMs. We identified moderate to large post-rehabilitation gains in the IFMs CSA especially when they were tested in functional position in the trained limb. There were significant improvements observed in the functional position even in the untrained limb. Although, there were no statistically significant improvements seen in muscle quality after rehabilitation, a trend towards muscle quality improvement was observed. Four weeks of impairment-based rehabilitation program with the IFMs exercises is effective in increasing IFM CSA. However, there is a need of longer IFMs exercise programs to gain significant improvements in muscle quality or we need to have a larger sample size to detect differences in muscle quality.

Reference:

1. Mckay GD, Goldie P, Payne WR, Oakes B. Ankle injuries in basketball: injury rate and risk factors. *British journal of sports medicine.* 2001;35(2):103-108.

2. Hertel J. Functional anatomy, pathomechanics, and pathophysiology of lateral ankle instability. *Journal of athletic training.* 2002;37(4):364.

3. Curtis CK, Laudner KG, McLoda TA, McCaw ST. The role of shoe design in ankle sprain rates among collegiate basketball players. *Journal of athletic training.* 2008;43(3):230-233.

4. Kannus P, Renstrom P. Treatment for acute tears of the lateral ligaments of the ankle. *J Bone Joint Surg Am.* 1991;73(2):305-312.

5. Hertel J. Sensorimotor deficits with ankle sprains and chronic ankle instability. *Clinics in sports medicine.* 2008;27(3):353-370.

6. Doherty C, Bleakley C, Hertel J, Caulfield B, Ryan J, Delahunt E. Recovery from a first-time lateral ankle sprain and the predictors of chronic ankle instability: a prospective cohort analysis. *The American journal of sports medicine.* 2016;44(4):995-1003.

7. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index. *Clinical biomechanics.* 2006;21(1):89-98.

8. Delahunt E, Coughlan GF, Caulfield B, Nightingale EJ, Lin C, Hiller CE. Inclusion criteria when investigating insufficiencies in chronic ankle instability. *Med Sci Sports Exerc.* 2010;42(11):2106-2121.

9. Jaffri AH, Newman TM, Smith BI, et al. Dynamic Leap and Balance Test: Ability to Discriminate Balance Deficits in Individuals With Chronic Ankle Instability. *Journal of sport rehabilitation.* 2019;1(aop):1-8.

10. Donovan L, Hart JM, Saliba S, et al. Effects of ankle destabilization devices and rehabilitation on gait biomechanics in chronic ankle instability patients: A randomized controlled trial. *Physical Therapy in Sport.* 2016;21:46-56.

11. Hale SA, Hertel J, Olmsted-Kramer LC. The effect of a 4-week comprehensive rehabilitation program on postural control and lower extremity function in individuals with chronic ankle instability. *Journal of orthopaedic & sports physical therapy.* 2007;37(6):303-311.

12. Kidgell DJ, Horvath DM, Jackson BM, Seymour PJ. Effect of six weeks of dura disc and mini-trampoline balance training on postural sway in athletes with functional ankle instability. *Journal of strength and conditioning research.* 2007;21(2):466.

13. Feger MA, Snell S, Handsfield GG, et al. Diminished Foot and Ankle Muscle Volumes in Young Adults With Chronic Ankle Instability. *Orthopaedic Journal of Sports Medicine.* 2016;4(6).

14. McKeon PO, Hertel J, Bramble D, Davis I. The foot core system: a new paradigm for understanding intrinsic foot muscle function. *Br J Sports Med.* 2015;49(5):290-290.

15. Lynn SK, Padilla RA, Tsang KK. Differences in static-and dynamic-balance task performance after 4 weeks of intrinsic-foot-muscle training: the short-foot exercise versus the towel-curl exercise. *Journal of sport rehabilitation.* 2012;21(4):327-333.

16. Zelik KE, La Scaleia V, Ivanenko YP, Lacquaniti F. Coordination of intrinsic and extrinsic foot muscles during walking. *European journal of applied physiology.* 2015;115(4):691-701.

17. Jaffri AH, Hertel J, Saliba S. Ultrasound examination of intrinsic foot muscles in patients with 1st metatarsophalangeal joint arthrodesis. *The Foot.* 2019;41:79-84.

18. McKeon PO, Fourchet F. Freeing the foot: integrating the foot core system into rehabilitation for lower extremity injuries. *Clinics in sports medicine.* 2015;34(2):347-361.

19. Fraser JJ, Koldenhoven RM, Jaffri AH, et al. Foot impairments contribute to functional limitation in individuals with ankle sprain and chronic ankle instability. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2018:1-11.

20. Jazayeri SS, Didehdar D, Moghtaderi AE. Tibial and peroneal nerve conduction studies in ankle sprain. *Electromyography and clinical neurophysiology.* 2007;47(6):301-304.

21. Feger MA, Snell S, Handsfield GG, et al. Diminished foot and ankle muscle volumes in young adults with chronic ankle instability. *Orthopaedic journal of sports medicine.* 2016;4(6):2325967116653719.

22. Bemben MG. Use of diagnostic ultrasound for assessing muscle size. *Journal of Strength and Conditioning Research.* 2002;16(1):103-108.

23. Crofts G, Angin S, Mickle KJ, Hill S, Nester C. Reliability of ultrasound for measurement of selected foot structures. *Gait & posture.* 2014;39(1):35-39.

24. Angin S, Crofts G, Mickle KJ, Nester CJ. Ultrasound evaluation of foot muscles and plantar fascia in pes planus. *Gait & posture.* 2014;40(1):48-52.

25. Holowka NB, Wallace IJ, Lieberman DE. Foot strength and stiffness are related to footwear use in a comparison of minimally-vs. conventionally-shod populations. *Scientific reports.* 2018;8(1):3679.

26. Taniguchi M, Fukumoto Y, Kobayashi M, et al. Quantity and quality of the lower extremity muscles in women with knee osteoarthritis. *Ultrasound in medicine & biology.* 2015;41(10):2567-2574.

27. Battaglia PJ, Mattox R, Winchester B, Kettner NW. Non–weight-bearing and weight-bearing ultrasonography of select foot muscles in young, asymptomatic participants: a descriptive and reliability study. *Journal of manipulative and physiological therapeutics.* 2016;39(9):655-661.

28. Fraser JJ, Hertel J. Effects of a 4-Week Intrinsic Foot Muscle Exercise Program on Motor Function: A Preliminary Randomized Control Trial. *J Sport Rehabil.* 2019;28(4):339-349.

29. Whittaker JL, Teyhen DS, Elliott JM, et al. Rehabilitative ultrasound imaging: understanding the technology and its applications. *journal of orthopaedic & sports physical therapy.* 2007;37(8):434-449.

30. Chang R, Kent-Braun JA, Hamill J. Use of MRI for volume estimation of tibialis posterior and plantar intrinsic foot muscles in healthy and chronic plantar fasciitis limbs. *Clinical Biomechanics.* 2012;27(5):500-505.

31. Smith A, Hides JA, Hodges PW, Collins NJ. Intrinsic foot muscle size can be measured reliably in weight bearing using ultrasound imaging. *Gait & posture.* 2019;68:369-374.

32. McKeon PO, Hertel J, Bramble D, Davis I. The foot core system: a new paradigm for understanding intrinsic foot muscle function. *British journal of sports medicine.* 2015;49(5):290.

33. Maughan R, Watson JS, Weir J. Strength and cross- sectional area of human skeletal muscle. *The Journal of physiology.* 1983;338(1):37-49.

34. Zhang X, Schütte KH, Vanwanseele B. Foot muscle morphology is related to center of pressure sway and control mechanisms during single-leg standing. *Gait & posture.* 2017;57:52-56.

35. Kelly L, Lichtwark G, Cresswell A. Dynamic function of the plantar intrinsic foot muscles during walking and running. *Journal of Science and Medicine in Sport.* 2013;16:e4.

36. Kelly LA, Cresswell AG, Racinais S, Whiteley R, Lichtwark G. Intrinsic foot muscles have the capacity to control deformation of the longitudinal arch. *Journal of The Royal Society Interface.* 2014;11(93):20131188.

37. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. *Journal of applied physiology.* 2006;101(5):1514-1522.

38. Scanlon TC, Fragala MS, Stout JR, et al. Muscle architecture and strength: Adaptations to short- term resistance training in older adults. *Muscle & nerve.* 2014;49(4):584-592.

Table 2-1. Patient Demographics (Mean ± Standard Deviation)

	Pre-rehab	Post-rehab
Sex	18 female,8 male	
Age (years)	21.88 ± 3.45	
Height (cm)	171.11 ± 10.248	
Mass (kg)	71.156 ± 14.238	
FAAM-ADL (%)	87.9 ± 8.53	94.87 ± 4.59*
FAAM-Sport (%)	67.307 ± 15.801	83.241 ± 10.77*
IdFAI	21.69 ± 3.99	19.807 ± 3.88
TSK	34.46 ± 5.52	32.53 ± 5.55*
IPAQ	4916 ± 2965.14	4965 ± 2265.44
GROC		4.807 ± 1.65

Abbreviations: rehab= rehabilitation; FAAM-ADL= Foot and ankle ability measure-activity of daily living; FAAM-sport= Foot and ankle ability measure-sport; IdFAI= Identification of functional ankle instability; TSK= Tampa scale of kinesiophobia; IPAQ= International physical activity questionnaire; GROC= Global rating of change.
*Significant difference from pre-rehabilitation measure
Alpha level set at $p \leq .05$

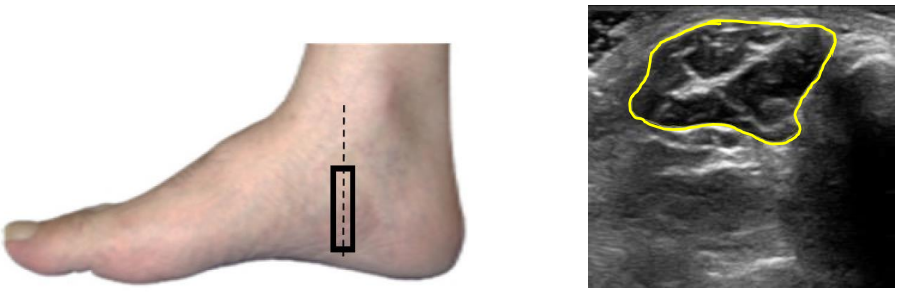
Table 2-2. Ultrasound Measure Values (Mean ± Standard Deviation)

N=26	Position	Pre-rehab	Post-rehab
AbH cross-sectional area (cm^2)-trained limb	Sitting	1.78 ± 0.53	1.98 ± 0.62
	Standing	1.71 ± 0.54	2.71 ± 0.68
AbH cross-sectional area (cm^2)-untrained limb	Sitting	1.80 ± 0.56	1.86 ± 0.63
	Standing	1.71 ± 0.54	2.17 ± 0.68
FDB cross-sectional area (cm^2)-trained limb	Sitting	1.86 ± 0.40	2.07 ± 0.44
	Standing	1.82 ± 0.50	2.12 ± 0.44
FDB cross-sectional area (cm^2)-untrained limb	Sitting	1.98 ± 0.59	2.03 ± 0.57
	Standing	1.99 ± 0.51	2.16 ± 0.49
AbH echogenicity values		55.9 ± 10.18	53.97 ± 11.24
FDB echogenicity values		60.56 ± 9.43	57.31 ± 8.41

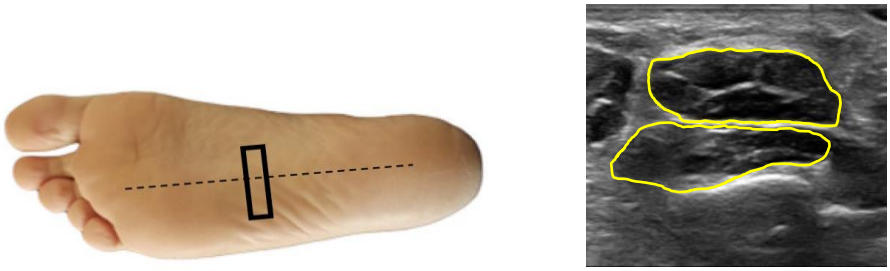
Abbreviations: rehab=rehabilitation
*Significance difference from pre-rehabilitation measures
Alpha level set at $p \leq .05$

Figure 2-1. Ultrasound Imaging Procedure in Sitting and Bipedal Standing Position.

Sitting and bipedal stance on the step to allow access to the medial and plantar side of the foot

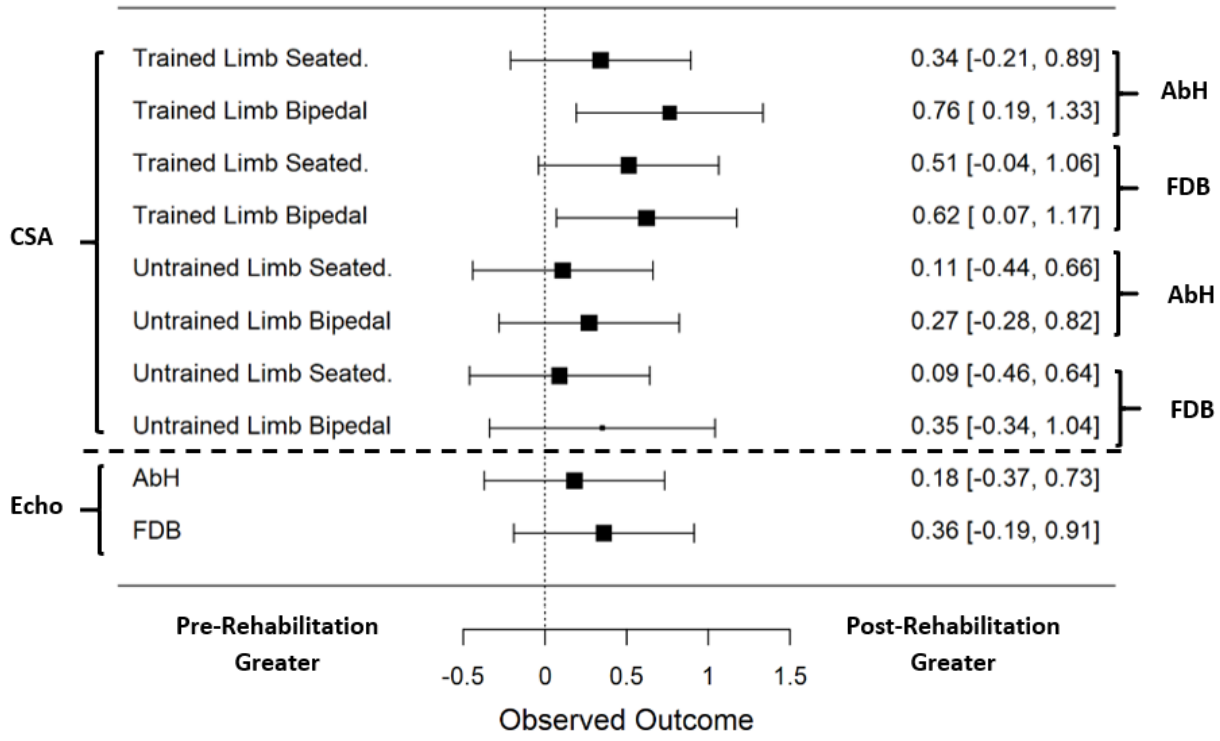


Ultrasound linear transducer placement and cross-sectional area measurement for assessment of the abductor hallucis.



Ultrasound linear transducer placement and cross-sectional area measurement for assessment of the flexor digitorum brevis.

Figure 2-2. Cohen`s *d* Effect Sizes and 95% Confidence Intervals for Intrinsic Foot Muscles Ultrasound Measures



Abbreviations: CSA= Cross-sectional area; Echo= Echogenicity; AbH= Abductor Hallucis; FDB= Flexor Digitorum Brevis

SECTION II: MANUSCRIPT III

Peroneal Muscle Size and Quality Changes after Impairment-Based Rehabilitation in Patients with Chronic Ankle Instability

Abstract

Context: Peroneal dysfunction is associated with impairments in postural control in patients with chronic ankle instability (CAI). Decrease in the cross-sectional area (CSA) of peroneal muscle group has been reported in individuals with CAI. Nevertheless, to our knowledge, no study has evaluated the changes in the peroneal size and tissue quality after impairment-based rehabilitation. **Objective:** To determine peroneal size and quality changes using US imaging following impairment-based rehabilitation in patients with CAI. **Design:** Pre-post case series. **Settings:** University Laboratory. **Patients or Other Participants:** 26 patients (age:21.9 ± 3.5 yrs.; 18F, 8M) with CAI completed 8 clinician-supervised rehabilitation sessions over a 4-week period along with home exercises during the days they didn`t complete supervised rehabilitation. **Interventions:** The rehabilitation program was based on individual patient deficits, measures prior to their first treatment session. Four-way ankle strengthening program that includes strengthening peroneal muscles was included in this the rehabilitation protocol both in supervised rehabilitation and home exercise program given to participants. **Main Outcome Measures:** Prior to the first session and following the final session, US imaging cross-sectional area (CSA) of peroneal muscles during lying and bilateral standing position were taken both in the leg that was trained and in the untrained leg. The CSA measures were normalized by dividing by participants body mass in kilograms, and grey scale analysis was done to measure echogenicity of the image as a surrogate measure of muscle quality. **Results:** A significant increase was observed after rehabilitation for the normalize CSA with the increase in size in the peroneal muscle group in lying (pre: 3.44 ± 0.99cm^2 , post: 3.72 ± 0.98 cm^2, P<0.01) as well as bipedal (pre:3.46 ± 1.05cm^2, post: 4.31 ± 0.98cm^2, P<0.01). There was a significant increase in the CSA on the untrained side as well in both lying (pre:3.34 ± 0.92cm^2, post:3.63 ± 1.01cm^2, P=0.01) and bipedal (pre:3.59 ± 1.02cm^2, post:4.00 ± 1.21cm^2, P<0.01). There was a significant

decrease in echogenicity measures (pre:70.2 ± 9.91, post:65.7 ± 8.68, P=0.001) in the trained limb post-rehabilitation. There was no significant difference in echogenicity in the untrained limb. **Conclusion:** Normalized CSA of the peroneal muscle group increased in both lying and standing position for the trained leg. However, the CSA of the IFMs increased only in the functional position for the untrained leg. There was a certain cross-over effect observed. The muscle quality measures changed for the peroneal muscles before and after rehabilitation. Impairment-based rehabilitation resulted in significant improvement in both size and quality of peroneal muscle group in 4-weeks.

Introduction

Lateral ankle sprains (LAS) are the most orthopedic injury with an annual health care cost of $4.2 billion.[1,2] Many who suffer an ankle sprain do not take it as a substantial injury and avoid seeking formal medical care.[3] This is perhaps a reason that the re-injury rate of ankle sprain is as high as 73%, with a history of previous LAS being a most important risk factor for incurring another sprain injury.[4] Consequently, after an initial ankle sprain, 40% of the individuals eventually end up developing chronic ankle instability (CAI).[5] CAI is characterized as a feeling of instability accompanied by repetitive bouts of giving away with self-reported decrease in function, and recurrent ankle sprains. Commonly seen deficits in individuals with CAI are decreased range of motion, poor postural control, lower strength and dysfunctional neuromuscular control.[5-8] LAS often result from an inversion and plantar flexion mechanism.[1,2] The peroneal muscles constitute the major muscular stability against the inversion movement, and provide antagonizing forces to the sudden inversion thrust movement. [9] Weakness of the peroneal muscles is thought to be a risk factor for ankle sprains.[10] There is often pain and tenderness found in peroneus longus muscle after LAS.

Peroneal dysfunction is also associated with impairment in postural control in subjects with CAI.[11] Decreased reaction times have been reported in peroneal muscle group in CAI group.[12] It is also believed that the impairment in peroneal muscles indirectly may be caused by atherogenic muscle inhibition.[13] Simon and Docherty[9] found that people with CAI had significantly slower NCV in the superficial peroneal nerve that supplies the peroneal muscles seen both at popliteal site and the fibular site. The slowness in NCV of the superficial peroneal nerve may also be a reason of chronic symptoms of giving away and instability in CAI. Furthermore, peroneal strength deficits in the participants with CAI have been reported

previously.[14] Cho et al.[14] reported that that patients with CAI had a peroneal weakness of about 39 % when compared with their contralateral healthy side. Similar findings were reported in another study, where they reported eversion strength deficits of 0.46 N-m/kg when compared to the healthy group. Interestingly they did not find any differences in the EMG measures between healthy subjects and subjects with CAI. These conflicting findings in the EMG studies of the peroneal muscle group can be attributed to the limitations of EMG when measuring muscular activity.[15,16] Although EMG has been traditionally used, it has certain flaws associated that include cross talk from the surrounding muscles, electromechanical delays, and irritation or discomfort (fine-wire EMG).[15,16] In addition, the clinical applicability of this modality is also limited with very few practicing clinicians have access to or are trained in using or analyzing EMG data for clinical decision making.[15,16]

Ultrasound (US) imaging provides an opportunity study to investigate a number of facets of muscle function such as muscle size and quality.[17,18] It is a non-invasive technique used provides a visual advantage over EMG measurements.[17,18] It also gives clinicians and researchers an opportunity to understand muscle function in number of ways such as muscle size through cross-sectional area (CSA) or muscle quality through echogenicity analysis of the images.[18,19] Muscle size and the tissue quality are both considered as an independent measures of muscle strength and function.[20] In addition, US imaging can also be used to assess the activation ratios.[21] The activation ratios can provide insightful information regarding the activation of the muscle in weight-bearing functional positions, and inability to contract peroneal muscles in weight-bearing positions may reveal risk factors for instability. Lobo et al.[22] found significant differences in the CSA of the peroneal muscles between LAS and the healthy group where the peroneal muscle mass was significantly smaller than that of the healthy group. We know that there are deficits

found in peroneal strength and CSA in patients with CAI when compared with healthy controls.[22] However, to our knowledge, there is no study that has analyzed the change in peroneal muscle size and quality before and after an impairment-based rehabilitation program using US imaging. Therefore, the objective of this study was to study the changes in peroneal size and quality using US imaging. We hypothesized that there will increase in size and improvement in quality of the peroneal muscles in patients with CAI following rehabilitation.

Methods

Study Design

This was a pre-post intervention case-series study which was a part of larger randomized control trial conducted to assess differences in clinical measures and patient-reported outcomes between a gait training group and a no gait training group, conducted in university settings with two collection time points, at baseline and upon completion of a 4-week, 8 session impairment-based rehabilitation protocol (Koldenhoven May 2019). All participants received impairment-based rehabilitation irrespective of their group allocation with respect to gait training or no gait training. Institutional Review Board approval was obtained prior to initiation of the study and all participants signed informed consent.

Participants

Twenty-six participants (age:21.9 ± 3.5 yrs.; 18F, 8M) with the history of CAI were enrolled and completed 12 sessions of rehabilitation. Inclusion criteria was based on the recommendations of the International Ankle Consortium. Concisely, participants with CAI had a history of at least 1 significant ankle sprain at least 1 year prior to study enrollment, decrease in

self-reported function (Foot and Ankle Ability Measure (FAAM) Sport ≥ 85% and experiencing repetitive bouts of instability or "giving away" with a score on Identification of Functional Ability (IdFAI) >10.

Exclusion criteria was any history of lower extremity fracture or surgery, ankle sprain within past 6 weeks, conditions known to affect gait, pregnancy, and currently receiving physical therapy. For the larger randomized control trial investigating the effect of gait training, the participants were randomly divided into two groups, gait training group (n=13) and non-gait training group (n=13). However, in this study, the initial analysis was performed to analyze the differences in CSA and muscle quality dependent measures between the two groups and if no differences found they were pooled together and pre-post changes were examined.

Instruments

US imaging was performed using a Siemens Acuson Freestyle US system with a wireless 8-Mhz linear transducer (Siemens, Mountain View, CA). The images were then measured using ImageJ version 1.50f (National Institutes of Health, Bethesda, MD) loaded onto a HP windows laptop.

Ultrasound measurements.

A customized step (Figure 3-1) was created by investigators for the patients to stand in bipedal stance. The US imaging was first performed in the sitting position and in bilateral standing position. The probe location used n this study has been previously proven to be reliable and valid.[23,24] Briefly, the probe was placed at 50% of the fibular length. All the images were collected at baseline, and upon completion of a 4-week, 8 session impairment-based rehabilitation protocol. Gel was applied over the probe and on the imaging site before taking

images. Peroneus longus and brevis both were imaged together in this study in lying as well as bipedal stance.

Impairment-based rehabilitation protocol:

Participants received 4-weeks of impairment-based rehabilitation that included 8 supervised rehabilitation sessions. A physical therapist with 5 years of clinical experience and an athletic trainer with 2 years of clinical experience were involved in the administration of rehabilitation protocol. Similar rehabilitation programs have been administered previously.[25] Broadly, the supervised rehabilitation program focused on individual impairments in range of motion, balance, strength, and functional activities. In addition, strengthening exercises specifically targeting IFM were also incorporated in the rehabilitation program. Specific details of the impairment-based rehabilitation protocol are provided in appendix C (Table C14).

Briefly, for ROM assessment, the supervising clinician undertook detailed clinical evaluation during the baseline session to understand if there were any arthrokinematics or osteokinematic restrictions. If any restrictions were found, the clinicians administered appropriate joint mobilization ranging from grade 2 to grade 3 on the Maitland scale. Stretching exercises were also performed for foot, ankle and hip muscles. Afterwards, participants performed the IFM exercises that included, short foot exercise, extension of toes 2-5 exercise, great toe extension and toe splaying exercise.[26] For the IFM exercises, participants started in the sitting position, and they were progressed gradually from sitting to bipedal standing, and from bipedal standing to single leg standing while performing the aforementioned exercises. Ankle exercises included heel raises, forefoot raises, 4-2way manual resistance, D1/D2 PNF patterns, and heel and toe walking. Hip exercises primarily of consisted clamshells with resistance band and birddog exercises. Balance exercises included, reaching tasks, single leg balance training,

and hop to stabilization tasks. Functional exercises included lunges, step and step down the box (30 cm), and jumping drills. Participants were evaluated by the supervising clinician during the baseline visit to determine the appropriate starting point the exercise interventions.

Participants were also provided with home exercise plan (HEP) to do on days when they were not coming to lab for a supervised rehabilitation session (appendix C). The HEP consisted of the above mentioned IFM exercises,[26] single leg balancing, calf stretching, and 4-way ankle exercises using a resistance band. Participants reported the number of days they completed the HEP in between the supervised rehabilitation session at the beginning of each session. Compliance was calculated as a percentage of days the participants completed the HEP divided by the number of days between the impairment-based sessions. The rehabilitation was provided only on one leg that was self-identified by participants as worst, and no impairment-based rehabilitation was given on the contralateral limb.

Data Processing and Statistical Analysis

Cross-sectional area measurement

Muscle CSA was obtained by measuring in centimeters square inside the fascial border of the CSA demarcation of the peroneal muscle group. ImageJ software (National Institute of Health, Bethesda, MD) was used for all image measurement. Once all images were measured, the three CSA measured obtained for each position were averaged for both limbs.

Statistical analysis

Statistical analysis was conducted using IBM Statistics (v26.0, SPSS, Inc. Chicago, IL, USA). Skewness, kurtosis, and normality of variance proved normally distributed data for the dependent variables**.** Initially, independent t-test was used to examine differences in CSA and muscle quality in peroneal muscle group between the gait training (n=13) and non-gait training

group (n=13). If no differences found, the groups were pooled together (n=26) and were examined for pre to post rehabilitation changes in CSA and muscle quality in peroneal muscle group. Paired t-test was used to observe the differences in both non-weight bearing and weight-bearing position for peroneal muscle group cross-sectional area (cm^2) in both trained and untrained leg. Paired t-test was also used to observe the changes after rehabilitation in echogenicity of peroneal muscles. Mean differences with 95% confidence interval were calculated, as well as Cohen's *d* effect sizes to determine magnitude of difference in pre-post measures were assessed.

Results

Dependent variables were normally distributed based off skewness, kurtosis, and normal variance as assessed by Levene's test >0.05. The demographic information for the 26 participants with CAI who participated in the study (Age: 21.9 ± 3.5 years, height: 171 ± 10.25 cm, mass: 71.15 ± 14.23 kgs, 18 females and 8 males), including subjective outcomes following rehabilitation in IdFAI and FAAM scores in outlined in Table (3-1). There were no significant differences (P>0.05) observed in the gait training vs non-gait training groups in mean change scores of CSA, or muscle quality in peroneal muscle group. Significant gain (P<0.01) was observed in CSA size in both sitting as well standing position for peroneal muscles in non-weight bearing as well as weight-bearing standing position after the 4-week rehabilitation program in the trained leg. (Table 3-2). There were significant improvements seen in the both non-weight bearing (P=0.01) as well as weight-bearing (P <0.01) positions. Significant decrease (P=0.01) in echogenicity were found in the trained leg, however, no change (P=0.15) was detected in the untrained leg. Moderate to large effect sizes were found for the weight-bearing

position when compared to the non-weight bearing position which showed smaller effect size (Figure 3-2). Over all compliance for the HEP was 80.2%.

Discussion

Supporting our hypothesis, we found significant increase in CSA of peroneal muscle group in after impairment-based rehabilitation in both non-weight bearing (sitting) and weight-bearing (bipedal stance) position in the trained limb. There was also significant improvement found in the muscle quality after rehabilitation that was shown by significant decrease in the echogenicity measures in the trained limb. Interestingly, we also found significant improvements in the untrained leg in terms of CSA size in both lying and bipedal stance. However, the effect sizes were lower than that of the trained limbs (Figure 3-2). We did not find significant differences in the echogenicity measures in the untrained limb.

To our knowledge, this is the first study that uses US imaging to understand the changes in size and muscle quality of peroneal muscle group after 4-weeks of impairment-based rehabilitation in patients with CAI in the trained limb. There are multiple reports of decrease in strength, lower activation, and smaller CSA of peroneal muscles in patients with CAI.[9,11,14,22] This study adds a valuable insight to the literature by understanding the effects of rehabilitation on the CSA and muscle quality of peroneal muscles after rehabilitation. We found a CSA of mean± SD (3.44 ± 0.98 cm^2) that is similar to what has been reported by Angin et al.[23] in participants with pes planus (3.26 ± 0.80 cm^2) who had weak peroneal muscles in lying position. There was an increase in 9.67% in the CSA of peroneal muscles (3.72 ± 0.98 cm^2) after rehabilitation in patients with CAI. We also examined these muscles in the weight bearing bipedal stance position that had greater CSA (3.46 ± 1.05 cm^2) at baseline than lying position. Interestingly, we also found that there was greater change of 29% in CSA of the peroneal

muscles in bipedal standing position when compared to the changes in the lying position. It was also corroborated by the moderate to large effect sizes found in the weight-bearing position (Figure 3-2). These results are indicative of superiority of weight-bearing positions that essentially is a functional position for peroneal muscles in detecting changes over the course of rehabilitation. Based on our findings, we will recommend using weight-bearing functional position for testing peroneal muscles.

Significant gains in peroneal CSA in patients with CAI in our study is in line with previously research. Increase in the CSA has been attributed to number of changes taking place during exercise in muscles.[27] It has also been shown that molecular changes start happening in the muscle within hours or even minutes of exercise and fiber hypertrophy has been found within 4 weeks of training.[28] Some of the most conspicuous changes are adaptations in the CSA of the muscle. There is an increase in the size and increase in the number of the myofibrils of the muscle fibers. The satellite cells are activated during the early stages of training; their increase in number and later fusion with the existing fibers apparently is involved in the hypertrophic responses of the muscles to the resistance training.[27] There are certain other changes that take place in response to the resistance training and purportedly there is an increase in the number of muscle cells, change in fiber type, muscle architecture, myofilament density and the structure of tendons and connective tissue.[27] Sayennes et al.[28] showed that there was considerable hypotrophy (3.2% to 5.2 %) seen in quadriceps muscles only after 20 days of 5 weeks training. We have found similar findings in our study where there was an increase of 9.67% in CSA after 30 days of rehabilitation in purely non-weight-bearing position. However, for weight-bearing loaded position in the trained leg we had greater increase of 29% in the CSA which implies that there were activation gains obtained because of rehabilitation or it may be because of smaller size of

peroneal muscles when compared to quadriceps which insinuates that subtle changes may register as high percentage differences especially in the weight-bearing position . It is generally believed that initial strength gains are because of neural adaptations and greater neural drive and hypertrophy follows this increased activation.[28] It has been previously reported that there is an increase in neural drive during within few weeks of strength exercises. [28]

The greater activation in the weight-bearing position after rehabilitation shows neuromuscular gains because of rehabilitation. Greater effect sizes were seen in the weight-bearing position after rehabilitation. Hodges et al.[29] showed that looking at the muscular architectural the activity of the muscle is best examined during low levels of contraction (20 or 30 % of the MVCs), relatively smaller changes in the muscle activity are associated with larger changes in the muscular architecture.[29] Therefore, it can be said that US measures are able to detect muscle activity through architectural changes at lower intensity when compared to MVC.[29] This supports the results we are finding here in this study where there is greater activation during the functional position (Figure 3-2) found in the peroneal muscles in the post rehabilitation measures. The greater improvements in the weight-bearing position may reveal improvement in the ability of the peroneal muscles to control in the functional position which is important for patients with CAI as peroneal muscle group is a major antagonist to the sudden inversion movements associated with recurrent instability.

In addition to muscle CSA, we also studied muscle tissue quality in this study using grey-scale echogenicity analysis. We found a significantly lower echogenicity scores post-rehabilitation which indicate better muscle quality.[20] Therefore, it is essential to study muscle quality characteristics using ultrasonography images along with muscle size. Differences in echogenicity have been found in the past between injured and healthy groups.[20] Furthermore,

changes in echogenicity have been observed after short term rehabilitation programs. There was decrease in echogenicity of vastus lateralis after 6 weeks of resistance training in older adults.[30] However, it was not known if peroneal muscle quality can improve in patients with CAI after 4-weeks of rehabilitation. Concurring previous data, our study showed improvements in muscle quality measures post-rehabilitation in patients with CAI.

Apart from the improvements seen in US characteristics of peroneal muscles on the trained side, we also observed significant improvement in CSA on the untrained side. We observed 9% gain in peroneal muscle CSA in non-weight bearing and 11.7% gain in bipedal stance. The gain in lying position was similar to the trained side, however, the gain in the functional position was only 40% of the gains in the functional position on the trained side. Similar findings of gains around 50 % and 40 % on the contralateral side have been reported previously.[31] It is possible that there are adaptations running in parallel to the neural mechanisms on the contralateral side similar to the mechanisms on the unilateral side because of the synchronization of the motor patterns.[31] There can be spill over from the CNS to the contralateral side or may be transfer effects from cortical, subcortical or spinal levels.[31]

Limitations:

Although, we tried to capture peroneal muscles in the weight-bearing functional position, it was still not captured in dynamic activities. It will be better representation of peroneal muscle function to measure their CSA changes and activation during a more dynamic task such as walking. Additionally, even though 4-weeks of impairment-based rehabilitation showed significant improvements in size, quality and neuromuscular activation at post-treatment, the long-term benefits of the rehabilitation program are unknown. We do not know if the improvements in muscle function seen at 4 weeks are sustainable over a longer period of time.

Lastly, we studied a convenience sample of participants as part of a larger investigation. Future studies should follow up patients with CAI at 6-months and 1 year after impairment to analyze the sustainability of these improvements seen at 4-weeks. Moreover, researchers may need to develop techniques to assess these muscles using US imaging in a more dynamic pattern such as walking.

Conclusion:

An 8 session, 4-week impairment-based rehabilitation showed a significant increase in the CSA, and muscle quality of the peroneal muscles in patients with CAI. There were greater effect sizes and percentage changes observed in weight-bearing functional position than non-weight bearing position. Non-trained limb also showed significant improvement in muscle size, however, no changes were observed in muscle quality.

References:

1. Curtis CK, Laudner KG, McLoda TA, McCaw ST. The role of shoe design in ankle sprain rates among collegiate basketball players. *Journal of athletic training.* 2008;43(3):230-233.

2. Kannus P, Renstrom P. Treatment for acute tears of the lateral ligaments of the ankle. *J Bone Joint Surg Am.* 1991;73(2):305-312.

3. Waterman BR, Owens BD, Davey S, Zacchilli MA, Belmont Jr PJ. The epidemiology of ankle sprains in the United States. *JBJS.* 2010;92(13):2279-2284.

4. Mckay GD, Goldie P, Payne WR, Oakes B. Ankle injuries in basketball: injury rate and risk factors. *British journal of sports medicine.* 2001;35(2):103-108.

5. Delahunt E, Monaghan K, Caulfield B. Altered neuromuscular control and ankle joint kinematics during walking in subjects with functional instability of the ankle joint. *The American journal of sports medicine.* 2006;34(12):1970-1976.

6. Fraser JJ, Koldenhoven RM, Jaffri AH, et al. Foot impairments contribute to functional limitation in individuals with ankle sprain and chronic ankle instability. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2018:1-11.

7. Sauer LD, Beazell J, Hertel J. Considering the Intrinsic Foot Musculature in Evaluation and Rehabilitation for Lower Extremity Injuries. *Athletic Training & Sports Health Care: The Journal for the Practicing Clinician.* 2011;3(1):43-47.

8. Jaffri AH, Newman TM, Smith BI, et al. Dynamic Leap and Balance Test: Ability to Discriminate Balance Deficits in Individuals With Chronic Ankle Instability. *Journal of sport rehabilitation.* 2019;1(aop):1-8.

9. Simon J, Docherty C. Slower nerve conduction velocity in individuals with functional ankle instability. *International journal of sports medicine.* 2014;35(09):731-736.
10. Mansfield PJ, Neumann DA. *Essentials of kinesiology for the physical therapist assistant.* Elsevier Health Sciences; 2018.

11. Bellew JW, Frilot CF, Busch SC, Lamothe TV, Ozane CJ. Facilitating activation of the peroneus longus: electromyographic analysis of exercises consistent with biomechanical function. *The Journal of Strength & Conditioning Research.* 2010;24(2):442-446.

12. Lynch SA, Eklund U, Gottlieb D, Renstrom PA, Beynnon B. Electromyographic latency changes in the ankle musculature during inversion moments. *The American journal of sports medicine.* 1996;24(3):362-369.

13. Kim K-M, Ingersoll CD, Hertel J. Altered postural modulation of Hoffmann reflex in the soleus and fibularis longus associated with chronic ankle instability. *Journal of Electromyography and Kinesiology.* 2012;22(6):997-1002.

14. Cho B-K, Park J-K, Choi S-M, SooHoo NF. The Effect of Peroneal Muscle Strength on Functional Outcomes After the Modified Broström Procedure for Chronic Ankle Instability. *Foot & ankle international.* 2018;39(1):105-112.

15. De Luca CJ. The use of surface electromyography in biomechanics. *Journal of applied biomechanics.* 1997;13(2):135-163.

16. Bolek JE. Electrical concepts in the surface electromyographic signal. *Applied psychophysiology and biofeedback.* 2010;35(2):171-175.

17. Delaney S, Worsley P, Warner M, Taylor M, Stokes M. Assessing contractile ability of the quadriceps muscle using ultrasound imaging. *Muscle & nerve.* 2010;42(4):530-538.

18. Worsley PR, Kitsell F, Samuel D, Stokes M. Validity of measuring distal vastus medialis muscle using rehabilitative ultrasound imaging versus magnetic resonance imaging. *Manual therapy.* 2014;19(3):259-263.

19. Sakai S, Urabe Y, Morikawa M, et al. Quantity and quality of the peroneus longus assessed using ultrasonography in leg with chronic ankle instability. *Journal of physical therapy science.* 2018;30(12):1396-1400.

20. Taniguchi M, Fukumoto Y, Kobayashi M, et al. Quantity and quality of the lower extremity muscles in women with knee osteoarthritis. *Ultrasound in medicine & biology.* 2015;41(10):2567-2574.

21. Mangum LC, Henderson K, Murray KP, Saliba SA. Ultrasound Assessment of the Transverse Abdominis During Functional Movement. *Journal of Ultrasound in Medicine.* 2018;37(5):1225-1231.

22. Lobo CC, Morales CR, Sanz DR, Corbalán IS, Marín AG, López DL. Ultrasonography comparison of peroneus muscle cross-sectional area in subjects with or without lateral ankle sprains. *Journal of manipulative and physiological therapeutics.* 2016;39(9):635-644.

23. Angin S, Crofts G, Mickle KJ, Nester CJ. Ultrasound evaluation of foot muscles and plantar fascia in pes planus. *Gait & posture.* 2014;40(1):48-52.

24. Crofts G, Angin S, Mickle KJ, Hill S, Nester C. Reliability of ultrasound for measurement of selected foot structures. *Gait & posture.* 2014;39(1):35-39.

25. Donovan L, Hart JM, Saliba S, et al. Effects of ankle destabilization devices and rehabilitation on gait biomechanics in chronic ankle instability patients: A randomized controlled trial. *Physical Therapy in Sport.* 2016;21:46-56.

26. Fraser JJ, Hertel J. Effects of a 4-Week Intrinsic Foot Muscle Exercise Program on Motor Function: A Preliminary Randomized Control Trial. *J Sport Rehabil.* 2019;28(4):339-349.

27. Folland JP, Williams AG. Morphological and neurological contributions to increased strength. *Sports medicine.* 2007;37(2):145-168.

28. Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *Journal of applied physiology.* 2007.

29. Hodges P, Pengel L, Herbert R, Gandevia S. Measurement of muscle contraction with ultrasound imaging. *Muscle & nerve.* 2003;27(6):682-692.

30. Scanlon TC, Fragala MS, Stout JR, et al. Muscle architecture and strength: Adaptations to short- term resistance training in older adults. *Muscle & nerve.* 2014;49(4):584-592.

31. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. *Journal of applied physiology.* 2006;101(5):1514-1522.

Table 3-1. Patient Demographics (Mean ± Standard Deviation)

	Pre-rehab	Post-rehab
Sex	18 female,8 male	
Age (years)	21.88 ± 3.45	
Height (cm)	171.11 ± 10.248	
Mass (kg)	71.156 ± 14.238	
FAAM-ADL (%)	87.9 ± 8.53	94.87 ± 4.59*
FAAM-Sport (%)	67.307 ± 15.801	83.241 ± 10.77*
IdFAI	21.69 ± 3.99	19.807 ± 3.88
TSK	34.46 ± 5.52	32.53 ± 5.55*
IPAQ	4916 ± 2965.14	4965 ± 2265.44
GROC		4.807 ± 1.65

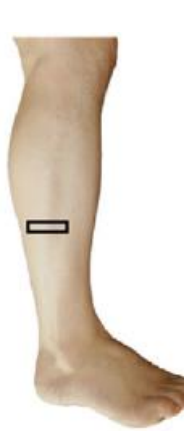
Abbreviations: rehab= rehabilitation; FAAM-ADL= Foot and ankle ability measure-activity of daily living; FAAM-sport= Foot and ankle ability measure-sport; IdFAI= Identification of functional ankle instability; TSK= Tampa scale of kinesiophobia; IPAQ= International physical activity questionnaire; GROC= Global rating of change.
*Significant difference from pre-rehabilitation measure
Alpha level set at $p \leq .05$

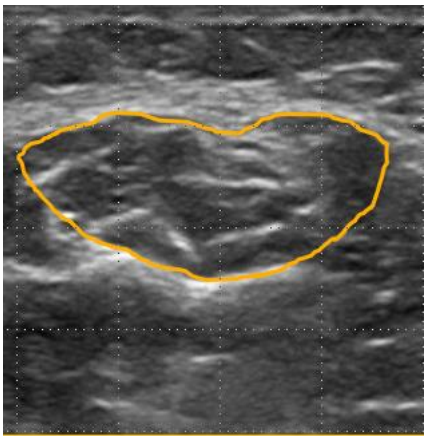
Table 3-2. Ultrasound Measure Values (Mean ± Standard Deviation)

N=26	Position	Pre-rehab	Post-rehab
Cross-sectional area (cm^2)-trained limb	Sitting*	3.44 ± 0.99	3.72 ± 0.98
	Standing*	3.46 ± 1.05	4.31 ± 0.98
Cross-sectional area (cm^2)-untrained limb	Sitting*	3.34 ± 0.92	3.63 ± 1.01
	Standing*	3.59 ± 1.02	4.00 ± 1.21
Echogenicity values-trained limb*		70.2 ± 9.91	65.7 ± 8.68
Echogenicity values-untrained limb		69.80 ± 8.15	68.27 ± 8.04

Abbreviations: rehab=rehabilitation
*Significance difference from pre-rehabilitation measures
Alpha level set at $p \leq .05$

Figure 3-1. Ultrasound Imaging Procedure in Sitting and Bipedal Standing Position

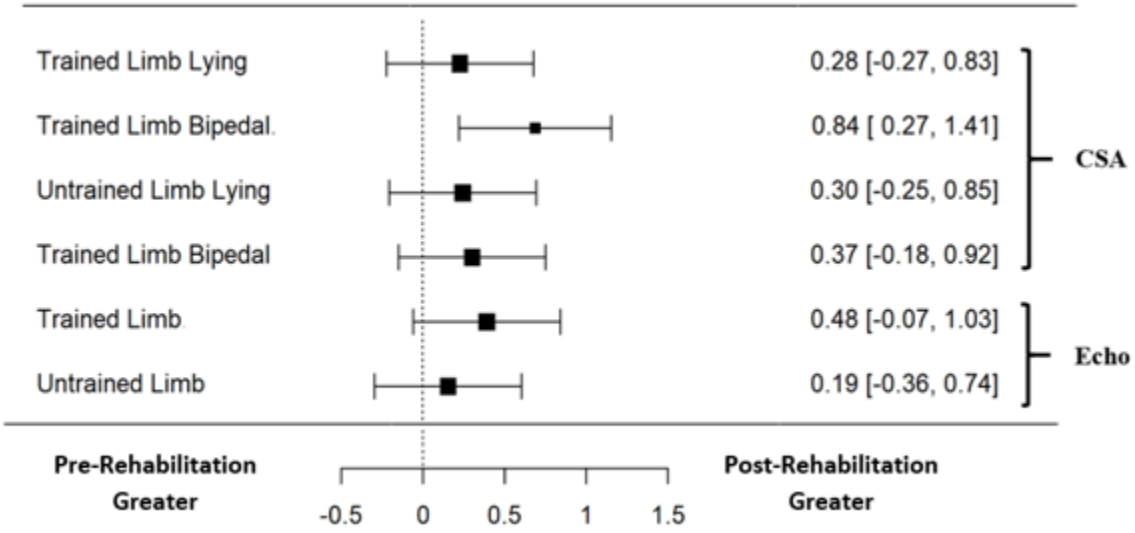




Ultrasound linear transducer placement and cross-sectional area measurement for assessment of peroneal muscles.

A: represent the non-weight bearing lying position that was used for imaging peroneal muscles in the non-weight bearing position
B: represents the weight-bearing bipedal position that was used for imaging peroneal muscles in the weight bearing position

Figure 3-2. Cohen`s *d* Effect Sizes and 95% Confidence Intervals for Peroneal Muscles Ultrasound Measures



Abbreviations: CSA= Cross-sectional area; Echo= Echogenicity

SECTION III: APPENDICES

APPENDIX A

The Problem

Statement of the Problem

Intrinsic Foot Muscles (IFM) form an integral part of the foot. IFM form the base of support, provide attenuation of the forces, and play a critical role in locomotion by providing the necessary propulsive forces. IFM maintain the longitudinal arch of the foot and help in holding its springy nature that is necessary in saving energy needed to walk and run. Kinetic energy is converted in to elastic energy in the first half of the stance and then it is brough back as an elastic recoil in the second half making mammals walk and run. IFM dysfunction can result in neuromuscular deficits that can affect balance, locomotion, sensory input on the planter surface of the feet and may result in functional limitations. However, the body of knowledge pertaining to IFMs structure and function is still limited. Moreover, an important problem that has perturbed clinicians and researchers is the lack of assessment tools for the IFM because of their multi-articular nature. It is challenging to differentiate IFM from extrinsic muscles in foot and ankle function. IFMT is one test that is purported to assess IFM function, however, the validity of this test has not been established. To date, there are no clinical tests or assessment methods that can be used in clinic to assess IFM in patients where IFM weakness is suspected. One way to objectively assess IFM is by using ultrasound imaging. Ultrasound imaging can be used to analyze the size and quality of the IFM. Previous research has focused on assessing the IFM in non-weight bearing however, the functional position of the IFM is weight bearing and provide a more natural and closer depiction of IFM function.

In addition, we don`t know how these muscles change over the period of time in foot and ankle dysfunctions such as Chronic Ankle Instability, Patellofemoral Pain Syndrome, Diabetes Mellitus, 1st Metatarsophalangeal Joint Arthrodesis etc. especially in the functional weight-bearing position. There is also a need to understand the functional impairments that are present because of the IFM dysfunction. There are no studies in the literature that have focused on identifying functional deficits in IFM in diverse set of pathologies where IFM weakness is suspected ranging from systematic problems such as diabetes, chronic musculoskeletal dysfunctions such as Chronic Ankle Instability and Patellofemoral Pain Syndrome, and post-surgical conditions such as 1st Metatarsophalangeal Joint Arthrodesis. It is of great clinical significance that IFM may be assessed in variety of foot and ankle dysfunctions to delineate the changes in this group of muscles in a spectrum which will help clinicians to design appropriate rehabilitation interventions.

Previous literature using MRI has shown significant decreases in the muscle volume in IFM of patients with Chronic Ankle Instability (CAI). However, there are no studies that have addressing these deficits by incorporating IFM targeted interventions in the rehabilitation programs that are traditionally focused on muscle groups proximal to ankle. A rehabilitation program incorporating a component focusing on improvement of strength and activation of the IFM may be beneficial to patients with CAI and create a more stable base of support during functional activities. Toe yoga that include short foot exercise (SFE) are purported to activate IFM. It is imperative to add these exercises in the rehabilitation programs targeting patients with CAI. It is also of great clinical importance to objectively assess the size and quality of these muscles using ultrasound imaging to identify any potential gains in the muscle morphology due to these rehabilitation interventions.

Another group of muscles that are commonly affected in the CAI are peroneal. Previous literature has shown significant decreases in strength and muscle mass in peroneal group of muscles in patients with CAI. Peroneal weakness can further increase the instability of the ankle joint as it forms the primary lateral muscular wall of the ankle and resists the inversion forces that cause trauma to the lateral ligament complex of ankle joints. There are deficits in strength, size and quality of the peroneal muscles previously reported in patients with CAI. However, there are no studies that have specifically looked at changes in the size and quality of these muscles post-rehabilitation.

Research Questions

1. Are there any morphological changes present in terms of size and quality of IFM between different groups with foot and ankle dysfunction and healthy controls in both weight-bearing and non-weight-bearing positions?
2. Are there any changes in activation of the IFM from non-weight bearing to weight bearing positions among different pathologies and healthy controls?
3. Are there any changes in the IFM size and quality after four weeks of impairment base rehabilitation incorporating IFM in patients with CAI?
4. Are there any changes in the Peroneal muscle group size and quality after four weeks of impairment base rehabilitation in patients with CAI?

Experimental Hypothesis

1. There will be smaller size and poorer muscle quality in pathological groups when compared with the matched healthy group.
2. The activation from non-weight bearing to weight bearing position would be lesser in the pathological group when compared with the healthy group

3. There will be improvement in quality and increase in size of the IFM after four weeks of impairment base rehabilitation in patients with CAI
4. There will be improvement in quality and increase in size of the peroneal group of muscles after four week of impairment base rehabilitation in patients with CAI

Assumptions

- Ultrasound unit will provide high resolution images representative of underlying anatomy that muscle cross-sectional area, thickness, and quality is measurable.
- Participants will be honest when answering all questions related to inclusion and exclusion criteria
- Participants will perform with best effort on balance and functional tasks
- Supervising clinician is progressing appropriately for each individual participant
- Participants will give their best effort during the rehabilitation
- Measurement tools will accurately collect the data
- Participants will not be receiving clinical care or rehabilitation in another location during time of the study.

Delimitations

- Participants will be between ages of 18 and 70
- Participants have not had another (other than the included ones for a particular group) lower extremity injury in the past 6 months or a history of lower extremity surgery.
- Participants do not have any illness or disability known to affect gait or balance.
- Participants will be recruited from the university and the surrounding community

Limitations

- Ability to sustain contraction during the short foot exercise may not capture the true thickest point during contraction.
- Anatomical variance between participants
    - Quadratus plantae may be incorporated in the Flexor Digitorum Brevis in some participants
- There not a long-term follow-up period for the study to evaluate the influence of the rehabilitation program on the self-reported and functional outcomes at set time points upon the completion of the study.
- We did not evaluate the recurrent ankle sprains in the impairment-based rehabilitation section of this dissertation to make a conclusion about whether impairment-based rehabilitation was preventative.

Operational Definitions

Short Foot Exercise (SFE): A maneuver that involves flexion of the metatarsophalangeal joints while keeping the interphalangeal joints extended making the foot shorter

Ultrasound Imaging (USI): Imaging technique using ultrasound to visualize structures within the body, including muscles, neurovascular structures and organs

Muscle size: Oblique or cross-sectional measure of the muscle with in the facial borders

Muscle quality: grey scale analysis of the image that reflects on the integrity of the muscle tissue

Activation ratio (AR): muscle size during a contraction divided by that same muscle`s size at rest

Functional activation ratio (FAR): activation ratio with muscle size during a functional or weight-bearing position divided by the rested muscle size at non-weight bearing or sitting position

Impairment-based rehabilitation: rehabilitation based on an initial baselines collection of range of motion, strength, functional task movement efficiency that is progressed based on individual gains

Disability: diminished capacity following injury

Patellofemoral pain (PFP): peri or retropatellar pain with an insidious onset that causes a change in activity

Chronic ankle instability (CAI): A consequence of ankle sprain that is characterized by functional instability and decrease in strength, changes in balance and gait pattern

1st metatarsophalangeal joint arthrodesis (1st MTP arthrodesis): A condition where big toe is fixed surgically after osteoarthritis of the big toe.

Significance of the study

Understanding the connection of a distal disintegration contributing to proximal pathology is a growing interest in sports medicine and orthopedics literature. Identifying the dysfunction in specific muscle group allows clinicians to develop target interventions. Moreover, developing valid muscle assessment tools is of integral help to clinicians for better assessing the problem and intervening appropriately. IFM assessment remains a long-standing

challenge to clinicians. Efforts towards devising better clinical assessment methods for these muscles can of great clinical significance to clinicians working in orthopedics and sports medicine settings. Moreover, recognition of a potential spectrum of commonality at distal small musculature such as IFM for multiple chronic musculoskeletal conditions, CAI, PFP, Diabetes and 1st MTP arthrodesis, would highlight an area that clinicians should include an intervention across these pathologies. In addition, insight into how individuals with CAI change their IFM activity following an impairment-based rehabilitation with incorporated IFM exercises that includes an individualized progression can be of great importance for clinicians.

Appendix B

Literature Review

Section 1: Intrinsic Foot Muscles

1.1 Anatomy and evolutionary perspective of Intrinsic Foot Muscles:

Intrinsic foot muscles (IFM) differ from extrinsic foot muscles that have their origins in the leg and the long tendons cross the ankle joint complex.[1] However, IFM originate within the foot and insert in the foot.[1] There are two categories of IFM, dorsal intrinsic muscles and planter intrinsic muscles.[1] When we talk about IFM, we refer to planter intrinsic muscles as they have a very important role in maintaining the integrity of arches of the foot and in optimizing foot function during every day activities.[1] IFM are considered to be important local stabilizers for the foot and contribute to lower extremity function by working in synergy with the extrinsic global stabilizers.[2] The plantar intrinsic foot muscles are organized into four layers.[1] The most superficial layer is deep to the plantar aponeurosis and includes the abductor hallucis (AH), flexor digitorum brevis (FDB), and the abductor digiti minimi.[1] The second layer consists of the quadratus plantae (QP) and the lumbricals. The third layer consists of the adductor hallucis transverse, adductor hallucis oblique, flexor hallucis brevis, and flexor digiti minimi brevis.[1] The deepest layer consists of the three plantar interossei.

The intrinsic foot muscles are active during walking.[3-5] However, it is unknown whether these muscles act concentrically or eccentrically.[6] Mann and Inman suggested that the role of the intrinsic foot muscles is stabilization of the foot during propulsion.[3] The role of the intrinsic foot muscles in the support of the medial longitudinal arch has been investigated in both standing[3-5] and walking.[3-5] An EMG study revealed a small amount of activity in the abductor hallucis,

flexor digitorum brevis, and the quadratus plantae muscles during relaxed standing with a significant increase in activity with increased postural demands.[7]

The implications of intrinsic foot muscle weakness has been linked to the development of pes cavus in Charcot-Marie-Tooth disease, lesser toe deformities, hallux valgus, and heel pain.[8] One theory suggests that intrinsic foot muscle atrophy causes dorsiflexion of the MTP joints due to the unopposed pull of the extensors of the toe. Dorsiflexion at the MTP joints elevates the longitudinal arch, ultimately leading to Charcot-Marie-Tooth disease and toe deformities.[9,10]

1.2 Evolution of longitudinal arches of the foot:

Spring in the foot is helpful in saving energy needed to walk and run. Kinetic energy and potential energy is converted in to elastic energy in the first half of the stance and then it is brought as elastic recoil in the second half of the stance making mammals run in a way as if rubber ball is bouncing along.[11] Tendons of the muscles of leg have shown to possess these properties and so does the arches of the foot.[11] Although, mammals and humans both have plantigrade walking (bringing the whole foot down instead of unguligrade (using only digits) there are some primary differences between human and apes (the closest ancestry to humans in evolutionary standpoint) in terms of the structure of their feet. Humans have longitudinal arches but the feet in apes are devoid of any arches.[12]

Longitudinal arches of the foot also help in the forward propulsion during walking and running by stiffening the mid foot joints (joints between calcaneus and metatarsals) (the same mechanism of storing elastic energy and then releasing it in the form of forward propulsive force).[12]

1.3 What constitutes longitudinal arch?

"Longitudinal arch is defined by the bones of midfoot, which are held in place by ligaments, muscles and most superficially, the plantar aponeurosis, a sheet of connective tissue."[12] Planter fascia (aponeurosis) has one attachment on the calcaneal tubercle and the other one on the bases of proximal phalanges and on tissue structures under metatarsal heads. Because of the above-mentioned attachment of the plantar aponeurosis dorsiflexion moment at the MTP joints are converted in to linear forces that make planter aponeurosis taut, starting windlass mechanism of the foot. This tension pulls the longitudinal arch together stiffening midstance during the push-off. However, the windlass mechanism is not present in chimpanzee with their midfoot maintaining contact with the ground during push off (called midfoot break)[12]

1.4 Windlass and intrinsic foot muscles:

Many of the plantar IFM attach proximally to the calcaneus and distally to the toes and are capable of resisting compression of the longitudinal arch when contracted, similar to resistance provided by the planter fascia (weakening of these muscles may result in inability of the arches to sustain load and hence more pressure on plantar fascia causing plantar fasciitis or other foot pathologies like osteoarthritis of the MTP joints or IP joints and metatarsalgia.[13] They also provide similar resistance to dorsiflexion that has been provided by the plantar fascia in the windlass mechanism when there is increase dorsiflexion moment.[14] Kelly et al. 2014, 15 found that many of the IFMs have role in flexing the midfoot joints when stimulated electrically and they contract isometrically when walking following the heel lift.[15] These findings show us that foot stiffness is enhanced by the contraction of the IFMs, which help to oppose the high dorsiflexion moment that has been created at the midfoot joints during push off.

It was initially thought that there is no windlass mechanism present in the apes as there is no longitudinal arch and hence no stiffness of the midfoot rather midfoot break during walking.

Recently, it was shown in a study that planter pressure distribution during bipedal walking in humans and some chimpanzee species (bonobos and orangutan) and some of the great apes were overlapping suggesting that there is middle foot joint stiffening going on in these species.[12] The only potential explanation behind this stiffness (essentially windlass mechanism in apes (that`s surprising without any arch)) is perhaps the activation of the IFMs, which have the same attachments in apes and humans. There is no EMG/US data yet that can show activation but this provides the only explanation to the midfoot stiffening. This shows that great apes also have ability to transform the foot into moderately stiff lever.

Kelly et al. 2015 reported that IFMs stretch actively during the first half of the stance during running, storing energy that could be released when they become short during the second half of the stance phase. Energy is probably stored in the central tendons, extracellular matrix surrounding the fibers and titin molecules of their myofilaments. Elastic energy storage is dependent on the presence of longitudinal arches and great apes perhaps cannot store energy because of lack of the longitudinal arch.[12]

1.5 Longitudinal arch and IFMs:

There is a shortening of the Longitudinal arch of the human foot during mid to late stance through flexion and adduction of the metatarsals in combination of the supination of the rear foot. These changes result in the stiffening of the foot and make it a rigid level, allowing ankle plantar flexor torque to be efficiently transmitted to the ground. Recent studies have proposed that in addition to the planter fascia, IFM also play an integral role in stiffening of the foot and the propulsion.[16]

There is lack of clarity in scientific literature regarding the function of the IFM during stance and gait. There is a disparity that is present in the mechanical action of these muscles gained through EMG studies when compared with what is written in anatomy text books (essentially just describe them as the accessory flexors of the toes).[16] In an experiment by Kelly et al.[16] the loading on the longitudinal Arch was increased gradually up to 150 % of the body weight and it resulted in the increased activation of the IFMs up to 125 % of the body weight after which it plateaued and there was no further increased. This data shows that IFM can contribute in maintaining the arch height during normal loadings such as walking during everyday living activities. The EMG data showed that there is a certain change in activation with load on the IFMs.[16] The interesting finding was that the relationship between the foot loading and IFMs activation was not linear especially at the lower loads. At the lower loads although there was change in the length of the IFMs however, there was no electrical activity registered on the EMG showing that change in length at lower loads didn`t initiate stretch reflex. In addition, the IFMs activity plateaued at a very high load (>125%). It was also reported that the electrical stimulation of the IFMs that crossed their natural activity resulted in stiffening of the longitudinal arches while loaded and has a potential to resist arch deformation seen at higher loads.

Section 2.How to assess intrinsic foot muscles:

The complex articulation of foot and ankle, and multi-articulated planter foot musculature makes it difficult to assess these muscles.[17] There are various attempts made in literature to appropriately assess the IFM. We will try to make an exhaustive comparison benefits and draw backs of different methodologies currently available to assess IFM.

2.1 Direct clinical measurements

From a clinical perspective, there are no tests that reliably examine strength of the IFMs, yet treatments are often focused on the assumed weakness in the foot. Intrinsic foot muscle test (IFMT) and toe dynamometry are commonly employed for measuring IFMs strength.[18,19] However, IFMT is the qualitative assessment of the IFMs strength and there is a dearth of evidence on its reliability and validity. Hand-held dynamometry[19] is shown to be a reliable measure with an excellent interrater (ICC=0.82-0.88) and intrarater (ICC=0.77-0.94) reliability but it is very hard to differentiate the activity of IFM from the extrinsic flexors in toe flexion.[19] It is proposed that hand-held dynamometry can form a good assessment tool if the IFM are assessed with passively holding the ankle in maximum plantarflexion because that ensures that extrinsic toe flexors are less likely to influence the measurement as the extrinsic muscles would go in active insufficiency and would be less likely to generate forces.[19] However, to test this hypothesis we have to validate the force measures from dynamometry against the more objective measures of muscle strength and function such as ultrasound (US) Imaging or magnetic resonance imaging (MRI). Soysa et al.[8] conducted a review of intrinsic foot muscle strength measures and concluded there is no widely accepted method of directly measuring intrinsic foot muscle strength especially in clinical settings.

2.2 Surrogate assessment methods:

Indirect methods of assessment utilizing surrogate measures of muscle size and quality can be used to assess the strength and function of the IFM. Indirect methods used to analyze muscle function include MRI, computerized tomography (CT), ultrasonography (US), electromyography (EMG) and muscle biopsies.

MRI can be used in assessing muscle function as it can analyze the total muscle volume by identifying the cross-sectional area of the muscle.[19] Anderson et al.[19] used MRI to assess IFM

volume in patients with diabetes and found that there was significant atrophy in patients who had the history of diabetes. In addition, a recent advancement such as dynamic MRI can be used to attain images while participants perform an activity.[20] Nevertheless, currently dynamic MRI has only been used to assess the kinematic characteristics of the foot such as the axis of rotation of the talocrural joint and subtalar joints.[20] Furthermore, the dynamic MRI has only been used in closed units so far and participants remain in the supine position. Therefore, images are not representative of the functional position of the feet which is weight-bearing.[20] Also, MRI is an expensive assessment method which is out of reach of many patients especially in the rehabilitation settings where it may be need to be performed prospectively over the length of the rehabilitation programs to assess muscles. It also needs to be ordered by physician rendering it inaccessible for the rehabilitation professional such as athletic trainers, or physical therapists. Henceforth, MRI may not be an optimal tool to assess the IFM in the rehabilitation settings.

Another indirect modality that can be used for assessment of IFM is CT scans.[21] CT scans have been used in the past to estimate muscle size and differentiate muscles from bones.[21,22] Previous research has shown that it was difficult to demarcate the borders of IFM using CT as an assessment method.[23] In addition, CT scans are also an expensive diagnostic test and requires physicians referral which makes it utility limited in clinical rehabilitation settings. Its exposure on regular basis can also expose patients to the harmful ionizing radiations.[21] Ultrasound imaging has come out as a reliable, easy to use, inexpensive and objective methods of muscle assessment. There is also an effort among clinicians and researchers to assess IFM through ultrasound imaging. We discuss in detail in the next section regarding the utility of ultrasound when studying muscles.

Section 3 Assessment using Ultrasound Imaging

3.1 Superiority of US over other assessment techniques of muscles:

US are basically mechanical sound waves produced longitudinally to acquire an image.[21] Because of clinical utility over other methods for studying musculature (CT, MRI, biopsy, EMG) US is a suitable measure for studying muscles.[24] US is also a cheaper modality when it comes to muscular assessment if compared with the assessment methods such as MRI, CT scans or biopsies. [24] It is a non-invasive widely available method to study muscle structure.[24] Moreover, because of its dynamic and portable nature it is easy to use and it is becoming a common modality to be used in clinical settings as well. It also has a potential to be a feedback tool. Scanlon et al.[25] reported that US is even superior to DEXA in detecting changes in CSA. Moreover, US is also considered to be superior measure muscle strength and function than dynamometrical measurements. Because force generation can be affected by number of factors such as hand placement, pain, motivation of subject etc. Force production can be affected in people suffering from chronic musculoskeletal injuries by number of factors that can be pain, fear avoidance, instability, kinesophobia. However, there is no change as such in the measurement technique of US imaging because of deleterious effect of a chronic musculoskeletal injury for e.g. Tanugachi et al.[26] used ultrasound measures to study physiology of the muscles because force production in Knee OA can be affected by pain. Therefore, the assessment of the morphological changes in the quadricep using a method of measurement that is not affected by pain or any outside factors is preferable.

US provides an exceptional solution for studying IFM. It can be used to measure the size and quality of IFM and can play a vital role in understanding these muscles. US has been previously used to reliably analyze the morphology and dimensional properties of IFM including cross-sectional area[27-29] and muscle thickness[27-29]. However, these assessments were done in the

non-weight bearing positions which are not functional position of the IFM and may not be true representative of muscle function. Battaglia et al.[30] and Smith et al.[31] performed US imaging of IFM in the weigh-bearing positions for the healthy participants and found the measurements to be highly reliable. The functional assessment of IFM in different injured groups has yet to be performed.

3.2 Ultrasound Anatomy of Muscle:

There are two views used. In the transverse plane, that is perpendicular to the long axis of the muscle we get a speckled appearance (reflection of perimysium connective tissue sheaths) of a muscle showing it`s cross-sectional area and covered by fascia.[32] In the longitudinal plane (along the long axis of the muscle), we see the fascicular architecture of the muscles becoming visible. It shows us linear, pinnate or triangular structures on the ultrasound image.[32] There is a distinct boundary around these muscles because the epimysium is a very reflective structure.[32]

B-mode is commonly used in studying muscle morphology in US imaging.[33] B-mode images give information from the entire length of transducer and are made up of visible dots or pixels of varying degree of brightness that actually depict the location and density of the structures encountered by the beam. Each pixel`s brightness depends on the strength of echo, which is dependent upon the location and strength of the structure generating this echo. The position of the pixel is determined by the direction of the US wave entering the tissue. There is relatively large field of view with b-mode and it can easily show us the positional relationship of several structures (for example the contraction of the muscle). Hence, b-mode US is believed to enhance clinical understanding by providing useful feedback about the behavior of the muscle during therapeutic intervention.[33]

B-mode has also been validated against the MRI.[33] It has also been found to be moderately accurate in determining the quality of tissue (infiltration of the fatty tissue) in the shoulder muscles when compared against the MRI.[33] Lately, the role of b-mode ultrasound is established in measuring muscular degeneration through echogenicity. Muscular degeneration is characterized as decrease in water and increase in fat and fibrous tissue. It results in greater echogenicity of the images and loss of demarcation lines and pennate patterns.[33] Using grey scale analysis (through image j) It is possible to detect neuromuscular deficits with 90 % percent predictive ability.[32,34] Basically, this analysis involves calculating the mean grey area, the mean gray value of the selected region (proven to be reliable with hand held tool of image j) can be calculated through histogram. Which really means that that with quantitative grey scale analysis the entire image is brought back to one value, elucidating that how black, grey or white the muscle in the picture is. The system settings are very important in this analysis so the researchers need to make sure that all the system settings such as gain, TGC, compression focus are all constant/same for all the pictures taken including the device should be same as well for all images.[32] Quantification of echo intensity has added great value in daily clinical practice.[32] This method has previously differentiated pathological muscular tissue from normal with great accuracy and sensitivity. Because of its ability to detect muscle quality US is suggested to be a great tool to diagnose neuromuscular disorders.[32] Another benefit of measuring echo intensity is that it is less user dependent and more objective.[32]

Taniguchi et al.[26] also took muscle quality in addition, to muscle size to understand the physiology of muscles in patients with knee osteoarthritis. In addition to the loss of muscle size, changes in the quality of muscular tissue, infiltration of fats (adipose tissue) are associated with poor muscle strength and functional limitations.[35-37] Muscle quality is assessed through

echogenicity or echo intensity. Enhanced echo-intensity is associated with increasing intramuscular adipose and fibrous tissue.[26] It has also been reported that muscle size and quality both independently effect muscle strength.[26] Therefore, it is essential to identify the muscle quality characteristics using ultrasonography images. There are number of studies that have used muscle quality verification with the quadriceps muscles in Knee osteoarthiritis.[26] However, nothing has been looked below the limbs and especially the intrinsic foot muscle. It will be interesting to investigate if there is any relationship between the strength measures and echo-intensity of the small muscles such as IFM. Strength measures in these muscles should be strongly negatively correlated with the echo intensity. Taniguchi et al.[26], found significantly higher muscle echo-intensity in severe OA groups than healthy groups. Echo-intensity directly associates with the fibrous and fatty tissue, and greater echogenic image of the muscle tissue is correlated with muscular weakness due to reduction of actual contractile tissue. Extracellular water may increase with the decrease in the number of muscle cells that forms the contractile tissue. And extracellular has been reported to not be associated with strength.[35] Moreover, greater echogenicity of the muscle tissue is also associated with relative decrease in the contractile tissue because of increase in ratio of fat and fibrous tissue, without even losing the size of the muscle.[26] This assertion is supported by the fact that there is age-related decrease in cell mass with a relative increase in the extracellular portion.[26,35]

Changes in echogenicity have been observed after short term rehabilitation. It was reported that there was decrease in EI after 6 weeks of rehabilitation training for Vastus Lateralis.[25] They concluded that 6 weeks of resistance training was affective in changing muscle quality and size in older adults.[25] Although, there is a lot of evidence that establishes that muscle hypertrophy can occur during the early stages of rehabilitation, Damas et al.[38] proposed that the

hypertrophy seen after 3-4 weeks of training may be, at least in part, is because of muscular edema or damage from the unaccustomed exercises. [38,39] Jenkin et al.[40] showed that echo-intensity decreased at 3 week (-3.8 %) and 6 (-6.8%) of the baseline of the resistance training program.[39] However, we don`t know if there is any changes in muscles post-exercise in the rehabilitation of the foot and ankle dysfunction.

US measures of muscular architecture have been compared with EMG activity. Hodges et al.[41] showed that looking at the muscular architectural the activity of the muscle is best examined during low levels of contraction (20 or 30 % of the MVCs), relatively smaller changes in the muscle activity are associated with larger changes in the muscular architecture.[41] Therefore, it can be said that Ultrasound measures are able to detect muscle activity through architectural changes at lower intensity when compared to MVC. [41]

Activation ratio is developed to mimic the normalizing strategy that uses resting state (relaxed muscle) in the denominator and allows us to better understand the muscle function. The functional activation ratio mentioned here is similar to what is used for EMGs activation-processing method. This mechanism normalizes the activity of the muscle (during a functional task, like SFE) to the quiet stance.[42] Similarly, functional activation ratio (FAR) can be used to compare the changes in muscle activity from the resting state to the functional state.

Ratio: Thickness/CSA (unipedal/bipedal stance)

Thickness/CSA (sitting position)

FAR in this dissertation will be calculated for unipedal and bipedal stance when compared for both peroneal and the intrinsic foot muscles. The functional activation ratio uses size measures (thickness/CSA) during functional task as the numerator of the ratio and divides

the thickness by a resting/quiet stance measure comparable to the starting position for the respective task.[42]

The FAR is a method that can be used to identify individuals that are not able to activate the muscles in the functional position. The inability to contract these muscles in the functional positions may reveal risk factor for the chronic foot injuries. Because of the prevalence of the foot pain/sprain in the society, and its recurrence, assessing muscle activity in variety of ways is the natural next step. Quantifying muscles activity provides clinicians an opportunity for advanced biofeedback and training as patient progresses. Doing FAR clinicians would be able to know in which functional positions patients are unable to activate their muscles and same positions and views can be used to provide feedback to patients and train them to improve their functional daily life and sports activity status.

Section 4. Foot and Ankle Dysfunctions and Intrinsic Foot Muscles

4.1 Chronic Ankle Instability:

Ankle sprains are the most common orthopedics injuries.[43] An ankle sprain injury is defined as when one or more of the ligaments supporting the talocrural joint are damaged.[44] When the strain on the ligaments exceeds its tensile strength, it results in an injury.[44] The annual health care cost of ankle sprains is $2 billion per year in the United States.[43] Individuals who suffer from ankle sprain often have difficulty in attaining the pre-injury functional level and suffer from recurrent ankle sprains[45]. Moreover, 40 % of the people with ankle sprain go on developing chronic ankle instability (CAI) within the first 12 months of sustaining first ankle sprain.[46] CAI is an umbrella term that includes mechanical and functional instability, along with residual symptoms including pain and giving away in the ankle after a lateral ankle sprain.[47]

Feger et al.[48] identified large deficits in the volume of the intrinsic foot muscles in patients with CAI. It has been shown previously that lateral ankle sprain result in damage to the tibial and peroneal nerve.[49] Tibial nerve is the major supply of planter intrinsic muscle of the feet. The damage of tibial nerves can result in the weakness of the IFM and the need of prolonged rehabilitation.[50] Although, significant losses in muscle mass have been shown previously in IFM, there is not much emphasize give incorporating the IFM training or strengthening in the traditional rehabilitation programs for patients with CAI. Perhaps, addition of IFM training in the rehabilitation programs for CAI can improve the functional outcomes of these patients.

4.2 Patellofemoral Pain Syndrome:

Patellofemoral pain (PFP) is a common musculoskeletal condition that is characterized by insidious onset of pain localized to the anterior retropatellar and/or peripatellar region of the knee associated with activities involving lower limb loading.[51] The onset of symptoms can be slow or acutely develop, with a worsening of pain with lower limb loading (e.g., squatting, jumping, running, etc.).[52,53]A pronated foot posture has been noted in some individuals with PFP. [54,55] Foot pronation has been linked to faulty movements at the knee in other lower extremity injury groups, yet there is not a comprehensive understanding factors are causing this foot posture. It has been shown that FMM measures is greater in people with Patellofemoral osteoarthritis and with patellofemoral pain.[54] The direct relationship between the foot and ankle characteristics is still not very clear, however, greater FMM is associated with greater FPPA (frontal plane projection angle) which is basically increase in dynamic knee valgus. [54] Foot orthoses are given to the people with increased FMM which aim to support the mid foot is given and are shown to help these subjects with great foot mobility.[54,55]

Relationship between the foot pronation and PFP is well established.[55,56] Pronation of the foot results in the compensatory increase in the internal rotation of the lower extremity increasing the quadricep angle that causes lateral patellar tracking.[55] AHI only takes in to account the sagittal movement of the navicular. However, there is also a mediolateral movement of the navicular (navicular drop) that also needs to be assessed. McPoil et al.[55] described the foot mobility magnitude, which is a composite measure of sagittal and mediolateral mobility of the midfoot.[55]

IFM weakness has also been associated with pronated foot.[57] It will insightful to find out if there is a weakness in the IFM in patients with PFP when compared to the healthy group.

4.3 Diabetes:

Foot and ankle problems are big issue that are associated with diabetic neuropathy.[58] The risk of patients with diabetic ulcer is 2.5 times higher at 5 years when compared to the patient who has diabetes without foot ulcer.[58] It has been also reported previously that up to 20 % of the people with diabetic ulcer require amputation.[59] There are number of factors associated with the diabetic peripheral neuropathy and negative impact on the diabetic foot health.

One primary association is deterioration of the soft tissue on the planter surface of the foot including the atrophy of the intrinsic foot muscles.[60] IFM have a role in shock absorption at the foot. [60] In addition, they are associated with balance, and appropriate gait mechanics.[60] Weakness of IFM can lead to increase in planter pressure which consequently may yield to the development of plantar ulceration.[60,61] IFM weakness can also result in metatarsalgia and IP joint arthritis because of increase in the planter pressure. [60,61]

Recently, Ultrasound is used to investigate the integrity of the IFM.[60] Moreover, US imaging has shown to be the only reliable method that can be used to directly visualize these muscles and differentiate them from extrinsic muscle activity.[62,63] In diabetes foot literature, IFM are assessed in the non-weight bearing position which is not the functional position of for the activation of IFM. Assessing IFM in the functional position may provide us information about activation, beyond the size of these muscles. This, in turn, may help researchers to design optimal rehabilitation interventions that can result in increased activation of these muscles in the weight-bearing that is a function position of the foot. In one part of this dissertation, we intend to examine the IFM in the functional position in diabetic patients. One aim of our project is to analyze IFM across a spectrum of different dysfunctions that can affect their structure and function. One of our groups in this dissertation is diabetic group patients.

4.4 1st metatarsophalangeal (MTP) arthrodesis:

Pain and disability associated with the toe region makes up 14 % of the non-traumatic, and 21% of the traumatic consultations in the primary care setting. [64] Hallux plays an integral role in the locomotion, and is mostly involved in the toe-off phase of gait. [65] The integrity of 1st Metatarsophalangeal Joint (1st MTPJ) can be compromised because of bony malalignment, hallux valgus, hallux rigidus, ultimately leading to osteoarthritis (OA) of the 1st MTPJ. [66,67] Potential causes of the OA of the 1st MTPJ include overuse, trauma, prior surgeries, deformation, difference in the length of the first metatarsals. [66,67] OA of the 1st MTPJ results in chronic pain, and negatively affects the quality of life of patients. [66] Arthrodesis or the fusion of the 1st MTPJ is performed in individuals who suffer from severe OA to relieve pain and improve quality of life. [66,67]

Approximately 80 % of the patients are satisfied with the outcomes of surgery related to

pain relief. [66] However, 20% of the patients remain unsatisfied with the outcome of surgery for the reasons not very well-known. [66] It has been shown that lack of motion in the 1st MTPJ after arthrodesis results in compensation from lateral toes for restoring foot function, resulting in more loading on lateral toes. [66] One fourth of body`s weight is supported by 1st MTPJ but when 1st MTPJ becomes fixed, the weight shifts to interphalangeal joint and lateral MTP joints[66,68]. This may result in arthritis of other toes and IP joints. [66,68] The load shift after the arthrodesis of the 1st MTPJ potentially results in arthritis of other distal joints of foot and metatarsalgia. Stevens et al.[66] reported that the hindfoot and forefoot were compensating for loss of motion in the 1st MTPJ, while lateral metatarsals were loaded more than fixed hallux during normal gait pattern. Gaudin et al.[69] reported 158 cases of revision 1st MTPJ arthrodesis, 11 % of these revisions were because of IP joint disorders developed because of first surgery, 11 % because of metatarsalgia, 8 % because of malunion and 14 % because of non-union.

Interestingly, the insult to the bones and joints of the foot seen after 1st MTPJ arthrodesis are similar to what are seen when there is weakness of the intrinsic foot muscles (IFMs), which causes greater forces on the skeleton of the foot causing foot skeleton problems such as metatarsalgia and arthritis in foot joints. [70] It is also possible that there are changes in the morphology and function of the foot muscles especially IFMs after surgery because of lack of motion or loss of function of 1st MTPJ as many of IFMs insert at 1st MTPJ. Inability of the foot muscles to compensate for lack of motion or weight bearing by the 1st MTPJ may also be adding more pressure on foot skeleton and advancing the foot problems post-surgery in the patients who have poorer surgical outcomes. IFM activation results in smaller ground reaction forces and greater shock absorption during gait and hence less pressure on the foot skeleton. [71]

However, the bigger challenge for clinicians and researchers is the assessment of the IFMs. Due to the multiarticular nature of the IFMs it is difficult to assess these muscles. MRI can be used as a reliable measure to assess the morphology of the IFMs but MRI is neither prevalent nor cost-effective. [17] Previous literature has validated ultrasound (US) imaging with MRI and has shown to have a good correlation. [72] Moreover, US imaging has shown to be the only reliable method that can be used to directly visualize these muscles and differentiate them from extrinsic muscle activity. [62,63] To our knowledge, there is no study that has assessed the IFMs after 1st MTPJ arthrodesis. Therefore, one of the aims of this study are to assess the changes in the morphology and structure IFMs after 1st MTP arthrodesis using US imaging. It will be of great interest to see the morphological changes in this group patients in comparison with other musculoskeletal injuries such as Diabetes, PFP, CAI, and heathy group.

Section 5 Intrinsic foot muscles intervention and its effects

Evidence of Intrinsic Foot Muscle Training in Improving Foot Function: A Systematic Review and Meta-analysis

Abstract

Background:

Intrinsic Foot Muscle (IFM) weakness has been linked to a number of foot and ankle pathologies. There are some strength training protocols developed for improving IFM strength and function. However, there is an absence of evidence-based measures of foot function that can serve as a surrogate measure to the benefits of IFM strength training immediately post-intervention or at longer follow-ups. The aim of this review was to critically assess the literature focused on strength training of the intrinsic foot muscles, and resulting improvements in foot function.

Methods:

A search of electronic databases PubMed, CINHAL, Web of Science, and SPORT Discus was completed between January 2000 to June 2019. Interventional studies, randomized control trials (RCTs) or pre/post interventional studies with at least two weeks of intervention programs administered were included in this review. The PEDro scale was used to assess the methodological quality of included studies with two independent reviewers rating each study.

Studies with a PEDro score greater than 4/10 were included in this review. Outcome variables of interest were broadly divided in to five broad categories of foot posture, balance, strength, patient-reported outcomes (PROs) and sensory function and motor performance. Separate random effects meta-analysis was performed for outcomes that were at least reported by two studies.

Results:

Based on inclusion criteria, 9 studies were included to evaluate strength training of the IFM on foot function in clinical and healthy samples. Pooled effect size (ES) estimates reflect that IFM strength training improved navicular drop (ES range:0.22,0.93), balance (ES range =0.09,2.60), and strength (ES range=0.51,1.58) while the control groups pooled ES ranges crossed zero for these outcomes. For PROs of pain and disability, no superiority of IFM strength training was seen in reducing pain, however, IFM exercises were superior in decreasing disability (ES range=0.65,1.5) while control intervention pooled effect for disability crossed zero. We could not perform meta-analysis for sensory function and motor performance as there was only study reporting each outcome, however these results supported the use of IFM strength training.

Conclusion:

There were improvements observed in the strength, balance, navicular drop, and in sensory function and motor performance of the foot after IFM rehabilitation. IFM strength training had no superiority in reducing pain when compared to control, however, patients reported decreases in disability. IFM strength training is helpful for patients in improving foot and ankle function.

1. Introduction:

The human foot is made up of complex articulations and is integral to human locomotion.[73] It provides support to the human body while generating necessary forces that help us perform dynamic activities.[73] During walking, the feet support the weight of the body and continuously adjust to the surface, assist in force dissipation, and act as a propulsive lever.[73] Any disruption in foot function can jeopardize the function of structures up the kinetic chain.[73] A deeper understanding of normal foot function is essential for clinicians to effectively manage any foot dysfunction.

Similar to the lumbopelvic complex, the foot skeleton is also supported by local and global stabilizers that comprise the "foot core".[14] Intrinsic foot muscles (IFM) are the principal

stabilizers of the medal longitudinal arch and are essential to passive, active, and neural subsystems forming core musculature of the foot.[14] They serve as a base of support during postural stability[14,74], help dissipate forces during loading,[14,75] and generate propulsive forces needed for locomotion.[14,75] IFM weakness is associated with number of musculoskeletal pathologies including plantar fasciitis, pes planus, patellofemoral pain (PFP), and chronic ankle instability (CAI), 1st metatarsophalangeal (MTP) joint arthrodesis,[13,17,57,76] and systemic conditions such as diabetes mellitus.[60,77] IFM weakness often causes problems in balance, increased navicular drop, decreased strength, and biomechanical abnormalities which eventually result in limitation of activity and negatively affect patient function.[13,14,78]

IFM strengthening has been recommended for the treatment of different foot and ankle conditions such as CAI, 1st MTP joint arthrodesis, PFP, pes planus and plantar fasciitis.[17,79] It is thought that incorporating IFM exercises into lower extremity injury rehabilitation protocols can improve functional outcomes such as balance, strength, sensory function and motor performance, and subjective measures of pain and disability in clinical groups.[14,78] However, the evidence that IFM exercises improve functional outcomes has not been studied extensively.[78] Therefore, the aim of this review is to critically and holistically evaluate the effect of IFM strengthening on the functional outcomes. The evaluation and synthesis of current evidence associated with IFM strength training has implications for assessment, diagnosis, targeted therapies, and avenues of future research in the treatment of foot and ankle injuries.

2. Methodology:

2.1 Search Strategy:

A health sciences librarian assisted in the development of a systematic search of electronic data bases (PubMed, CINHAL, SPORT Discus and Web of Science) and manual searches of references lists were performed between May 30, 2019 to June 30, 2019 to identify potentially relevant articles. The following search strategy was used:

Table B-1. Search Strategy used

Search Term	Limiters
1. (((((((intrinsic foot muscles) OR intrinsic foot musculature) OR intrinsic foot flexor) OR intrinsic planter muscles) OR intrinsic plantar muscles)) AND 2. (((((((Strength) OR strengthening) OR training) OR therapy) OR "Toe Yoga") OR "Short Foot Exercise") OR "Short Foot Exercises")) AND (((((((Function) OR "foot function") OR "motor performance") OR foot) OR "dynamic balance") OR "balance") OR "static balance") OR "postural control" OR "functional status" OR "motor function").	• Full text English articles • Published in peer-reviewed journals • Published between January 2000 and June 2019

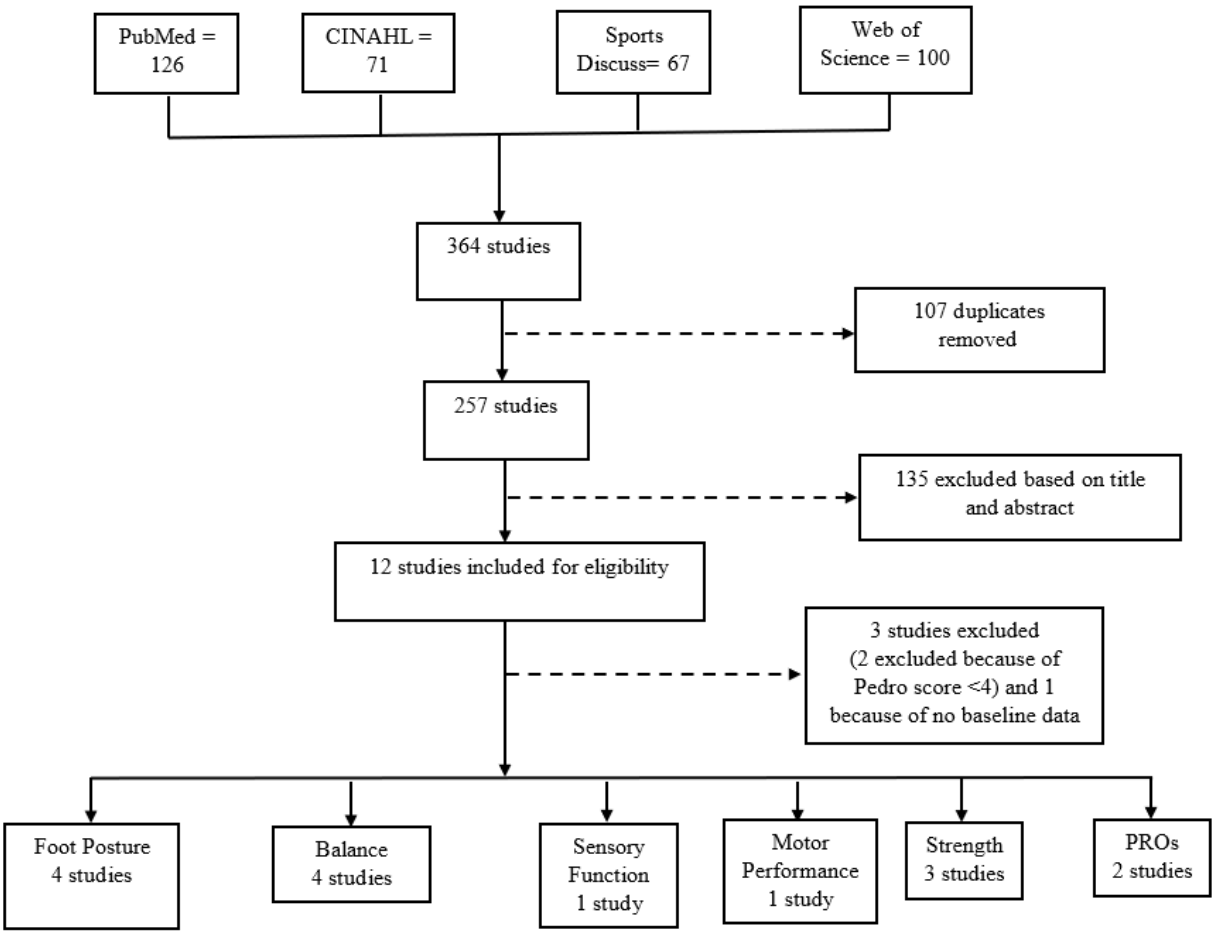
A single researcher completed the database search, screening of the literature and data extraction.

2.2 Study selection criteria:

The screening of the literature began with the removal of duplicate articles. The remaining articles were then screened based on title and abstract based on the following criteria.

1. Research specific to IFM
2. Intervention studies either pre/post design or randomized control trials with at least 2 weeks of IFM training administered.
3. At least one desired functional outcome of interest (see Figure 1)

Figure B-1. Study Selection Process and Search Results with Outcome Measure of Concern.



2.3 Assessment of methodological quality:

Methodological quality of the included studies was assessed using PEDro scale, a 10 item assessment instrument, with a score of 10 representative of highest quality and 0 representative of lowest.[80] Two examiners independently scored the selected articles, with any disagreement resolved by reaching consensus after discussion. Any study with a PEDro score of less than 4 was excluded. Details of methodological quality assessment are provided in Table 2.

Table B-2. Pedro Scoring for Studies Included in Analysis.

	Unger (2000)[81]	Lee (2019)[82]	Hashimoto (2014)[83]	Fraser (2019)[79]	Kamonseki (2015)[84]	Saikia (2015)[85]	Unver (2019)[86]	Jung (2011)[87]	Mulligan (2013)[88]	Lynn (2012)
Eligibility criteria?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Random allocation?	N	Y	N	Y	Y	Y	N	Y	N	N
Allocation concealed	N	N	N	Y	Y	Y	N	Y	N	N
Groups similar?	N	Y	N	Y	Y	Y	Y	Y	N	N
Subject blinding?	N	N	N	N	N	N	N	N	N	N
Therapist blinding?	N	N	N	N	N	N	N	N	Y	Y
Assessor blinding?	N	Y	N	Y	Y	N	Y	Y	Y	Y
85 % subjects completed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Allocation maintained or intention to treat?	Y	Y	Y	Y	Y	N	N	Y	Y	Y
9. Between groups statistical comparisons?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1. Point and variability measures reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
PEDro score	4	7	4	8	8	6	5	8	6	6

2.4 Data extraction:

Study design, population, experimental and comparison interventions, pre and post intervention time points, sample sizes, sets, repetitions and progression of the interventions, and main findings for the desired functional outcomes were extracted for every reported time point in the included studies (Table 3). Means, standard deviations and p-values for the outcomes of interest are detailed in Table 4.

Table B-3. Summary of the Ten Studies Included in this Study.

Author (Year) Study Design	Sample Population	Inclusion Criteria	Groups/Intervention	Outcomes measures	Results
Unger and Wooden (2000)[81] Pre/Post	Adults (n=15; 6 women/9 men) healthy subjects	• Healthy adults	• Subjects completed 3 training sessions per week for 6 weeks using Archxerciser. Sessions were completed 24-72 hours apart based on individual convenience. Subjects were instructed not to change their life-style in any way in forms of activity level or training (strengthening or stretching).	• Toe flexion Strength (kg)	• There was a significant increase in the toe strength, vertical jump and horizontal jump height in test leg when compared to control leg.
Lee et al. (2019)[82] RCT	Adults with ankle sprains (n= 30; 15 women/15 men)	• History of first ankle sprain more than 1 year prior to trial • A score of less than 24 on Cumberland Ankle Instability Tool (CAIT) • No incidence of ankle sprain within	• Interventional group (n=15) performed Short Foot Exercise (SFE). SFE was performed in 4 sets of five minutes each. 20 to 25 minutes a day. It was performed three times a week for eight weeks. • Control group (n=15)	• Dynamic Balance (cm) • Somatosensory function (μm)	• Significant benefit of SFE over PSE was observed for somatosensory function. • Significant improvements in the dynamic balance were noted in SFE group when compared to the PSE group.

		6 weeks of the start of trial • Experienced at least 2 more ankle sprains in the past 2 months.	Proprioceptive Sensory Exercise (PSE) with same intensity, time and frequency per week for eight weeks.		
Hashimoto and Sakuraba (2014)[83] Pre/Post	Adults (n=12; 12 men)	• Healthy adults	• Intrinsic foot muscles exercise was performed for 200 repetitions, once per day, three times per week with a 3-kg load that was use using scale with a maximum capacity of 10 kg. • Training was conducted over 8 weeks	• Intrinsic foot flexor muscle strength (kg) • Arch drop (cm)	• Significant improvement was seen in intrinsic foot flexor strength, and significant decrease in arch drop.
Fraser and Hertel (2019)[79] RCT	Adults (n=24; 12 women; 12 men)	• Healthy, recreationally active individuals. • Recreationally active was defined as at least 20 min. per day, at least 3 times a week.	• Intervention group (n=12) received intrinsic foot muscle exercises • Control group received no intervention	• Motor function (4 points ordinal scale) • Perceived rating of difficulty (5 points Likert scale)	• Significant improvement in motor function in the intervention group • Significant improvement in the perceived level of difficulty in the intervention group

Kamonseki et al. (2015)[84] RCT	Adults (n=83; 66 women;17 men), 20-60 years of age, with a diagnosis of plantar fasciitis	• Pain on the plantar face of the heel • Insidious pain onset • Pain that was accentuated after long periods of upright activities or after rest, such as the first step in the morning • A reduction in pain following light activities	• There were three intervention groups, stretching alone exercise group (SAEG), foot exercise group (FEG), foot and hip exercise group (FHEG). • The total intervention period was 8 weeks. • SAEG only performed stretching, FEG performed same stretching plus strengthening exercises for foot. FHEG performed same exercises plus the exercises for abductors and lateral rotators of hip.	• Dynamic balance (cm) • Pain and quality of life measures taken from FOAS.	• Significant improvements were seen in each group for all the outcomes measures • There was no significant group-by-time interaction.
Unver et al. (2019)[86] RCT	Adults (n=41; 25 women;16 men)	• Age 18-25 years of age • Bilateral pes planus according to navicular drop (ND) and foot posture index (FPI).	• Short foot exercise group (SFEG) and control group (CG). • SFEG performed short-foot exercise for 6 weeks • CG did not receive any intervention.	• ND (mm) • FPI (scale from -2 to +2) • Pain and disability from FFI.	• Significant reduction pain, disability, FPI and ND in the SFEG. No change was observed in the CG. • There was significant increase in the force on the lateral midfoot in the SFEG group. No change was seen in the CG

Jung et al. (2011)[87] RCT	Adults (n=28) with bilateral pes planus	• Resting calcaneal stance position (RCSP) with 4-degree eversion or more • navicular drop (ND) greater than 13 mm	• Subjects were randomly assigned to foot orthosis (FO) group or Foot orthosis short foot (FOSF) group for a 8 weeks intervention. • Both groups wore orthosis but the subjects in the FOSF group also performed SFE. Three sets of 5 reps were performed daily for each foot.	• Toe flexor strength (kgf)	• Significant improvement in strength in both groups. The mean change in the FOSF group was greater than FO group.
Mulligan and Cook (2013)[88] Pre/Post	Adults (n=21; 18 women; 3 men)	• Healthy participants without any sign of foot pain, history of patellofemoral pain, plantar fasciitis, anterior or posterior tibial dysfunction or evidence of neurological disease within the past 6 months that would affect motor function.	• Short foot exercise (SFE) training for 4-weeks was provided to participants. • Each subject performed unsupervised SFE for 5 seconds each up to three minutes every day for four weeks at home. • Exercise was progressed from sitting to standing position.	• ND (cm) • IFMT (ordinal grading 1-3) • Dynamic balance (cm)	• Significant decrease in ND was found in these subjects at 4 weeks and 8 weeks compared to baseline • Significant improvement of IFM grading was observed post-rehab • There were significant improvement in the reach distances found from baseline in the SEBT at both 4 week and 8 week timepoints.

Lynn et al. (2012)[74] RCT	Adults (n=30; 15 women; 15 men)	• Healthy participants with no history of major lower limb pathology or balance impairments.	• Participants were assigned randomly to 1 of the 3 groups, a short foot exercise (SFE) group, a towel-curl exercise (TCE) group, or a control group. • Participants in both SFE and TCE groups were instructed to perform 100 repetitions of their prescribed exercise on a daily basis for 4 weeks. • In first and second week, participants performed these exercises in the sitting position, and in third and fourth weeks, participants performed these exercises in standing position.	• ND (mm) • Static Balance (COP movement in mm) • Dynamic Balance (cm)	• No significant differences were found in static balance for any of the groups • No significant changes in the ND were seen in either of the groups • Significant improvement in the dynamic balance were seen in the two exercise groups, and the SFE improved more than that of TCE group.

Pre= Pre-intervention, Post= post-intervention, RCT= Randomize Control Trials, PDQ= pain and disability questionnaire, FFI= foot function index, FOAS= foot and ankle outcome score, FPI= foot postural index, ND=navicular drop, NDT= navicular drop test, IFMT= Intrinsic Foot Muscle Test, mm=millimeters, cm= centimeters, kg=kilograms, kgf= kilogram force, COP= center of pressure

2.5 Study Characteristics:

There were six RCTs [74,79,82,84-87] and three repeated measures pre/post [81,83,88] included in this review. All the studies had at least two weeks of the IFM training administered. Most of the

studies included short foot exercise (SFE) as part of their intervention; eight [74,79,82,84,87,88] out of ten studies had SFE included in their intervention programs. SFE includes doming of the arch of the foot while trying maintain the toes planted on the ground.[79,88] Fraser et al.[79] also included hallux extension, lesser toe extension, and toe spread out exercises in their protocol. Kamonseki et al.[84] utilized toe curl exercises along with SFE for IFM training. In addition to SFE, Jung et al.[87] utilized foot orthosis in their intervention program for comparison with the orthosis only group. Two studies[81,83] did not incorporate SFE in their intervention protocol but rather had toe flexion exercises, and an arch exercise device to strengthen IFM, respectively.

There were 328 total participants in the included. There were healthy (n=96) as well as clinical groups (n=232) (history of ankle instability, pes planus, plantar fasciitis) involved in terms of study population (Table 3).

2.6 Measures of treatment effect:

We used Cohen's *d* effect sizes (ES) with associated 95% confidence interval (CI) to perform statistical analysis.[89] Cohen`s *d* effect sizes and effect size standard errors using a pooled standard deviation between baseline and post-intervention measures were calculated to determine the magnitude of difference between the two points because of IFM training given. Forest plots were used to illustrate ES and 95% CI between the baseline and post-treatment data for pre-post interventional studies and RCTs. ES were interpreted using the scheme recommended by Cohen[89]: <0.2 as trivial; 0.2-0.49 as small, 0.5-0.79 as moderate, and > 0.8 as large. When 95% CI of the ES point estimates of the treatment effect did not cross zero, it was interpreted as conclusively advantageous. The data used for calculating ES using following data: sample sizes, means, and standard deviations, both at baseline and post-treatment, for all studies (both pre-post interventional studies and RCTs) (Table 3 and Table 4). For RCTs, baseline and

post-treatment data points were used for both treatment group and control group and were plotted together for the outcomes of interest.

Table B-4. Descriptive Point Estimate Statistics for Selected Outcome Measure of the Included Studies.

Author (Year) **Study Design**	**Outcomes measures**	**Experimental group** **M(SD)** **(post)**	**Control group** **M(SD)** **(pre)**
Unger and Wooden (2000)[81] Pre/Post	• Toe Strength (kg)	• 1.81(1.41)	• -0.64 (1.93)
Lee et al (2019)[82] RCT	• Dynamic Balance (cm) • Somatosensory function (μm)	Dynamic Balance • B =4.27(1.58) P=2.15(0.85) Somatosensory function • B=4.29(0.98) P=2.50(0.79)	Dynamic Balance • B=3.62(1.36) P=2.57(0.99) Somatosensory function • B=3.73 (1.14) P=2.87(1.24)
Hashimoto and Sakuraba (2014)[83] Pre/Post	• Intrinsic foot muscle strength (kg) • Arch drop (cm)	Intrinsic foot muscle strength • 9.4(5.11) Arch drop • 18.7(1.33)	Intrinsic foot muscle strength • 14.2(2.83) Arch drop • 18.1(1.80)
Fraser and Hertel (2019)[79] RCT	• Motor function (4 points ordinal scale)	• B= 1.9(0.5) P=2.6(0.5)	• B=2.0(0.6) P=2.0(0.7)
Kamonseki et al. (2015)[84] RCT	• Dynamic balance (cm) • Pain and quality of life measures taken from FAOS	Dynamic Balance • B=73.7(19) P=77.7(18) Pain • B=56.3(17) P=73.9(16) Quality of life • B=34.2(22) P=50.9(25)	Dynamic Balance • B=76.5(24) P=82.7(24) Pain • B=56.9(17) P=71.2(22) Quality of life • B=29.2(21) P=52.2(23)
Unver et al. (2019)[86] RCT	• ND (mm) • FPI (scale from -2 to +2)	ND • B=16.47(5.45) P=10.85(5.92) FPI • B=8.95(1.46) P=7.33(2.15) Pain	ND • B=17.25(5.31) P=16.90(5.90) FPI • B=8.40(1.95) P=8.50(2.03) Pain

	• Pain and disability from FFI.	• B=12.23(11.96) P=7.85(8.78) Disability • B=7.80(6.91) P=3.95(4.52)	• B=7.20(10.34) P=5.00(6.31) Disability • B=4.05(7.52) P=3.55(5.73)
Jung et al. (2011)[87] RCT	• Toe flexor strength (kgf)	• B=6.35(2.98) P=8.14(3.17) md= 1.78(1.21-2.35)	• B=6.38(3.53) P=7.26(3.24) md=0.88(0.50-1.25)
Mulligan and Cook, (2013)[88] Pre/Post	• ND (cm) • IFMT (ordinal grading 1-3) • Dynamic balance (cm)	ND • 12.7(6.0) IFMT • 2 (IFMT) Dynamic Balance • 57.8(7.4)	ND • 10.5(5.7) IFMT • 3 (IFMT) Dynamic Balance • 61.6(6.6)
Lynn et al. (2012)[74] RCT	• ND (mm) • Static Balance (COP displacement in mm) • Dynamic Balance (cm)	ND • B=45.9(3.4) P=44.6(2.5) Static Balance • B=37.9(3.5) P=39.7(3.1) Dynamic Balance • B=52.4(4.5) P=43.1(5.1)	ND • B=42.8(5.4) P=42.5(4.3) Static Balance • B=38.6(3.4) P=38.6(5.1) Dynamic Balance • B=47.8(7.8) P=48.1(5.5)

Pre= pre-intervention, Post= post-intervention, RCT= randomize control trials, M= means, SD= standard deviation, B= baseline point measures, P= post-treatment point measures, ADLs= activities of daily living, FOAS= foot and ankle outcome score, SAEG= stretching alone exercise group, FEG= foot exercise group, FEHG= foot and hip exercise group, ADL-FEHG= activity of daily livings score in foot and hip exercise group, ADL-SAEG= activity of daily livings score in stretching alone group, ADL-FEG= activity of daily livings score in foot exercise group, ND=navicular drop, PRO= patient-reported outcomes, FPI= foot posture index, md= mean difference, SB=static balance, DB=dynamic balance, PDQ= pain and disability, NDT= navicular drop test

2.7 Assessment of Heterogeneity:

If at least two studies reported on the same outcome measure, meta-analysis was deemed possible. We were able to perform meta-analysis on the outcomes of strength, balance, navicular drop and patient-reported outcomes of pain and disability.

Heterogeneity among the studies selected were analyzed using I^2 and Q test statistics as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[90] *I^2 statistic* was interpreted using the following guideline : 0-40 %= heterogeneity might not be important; 30-60%= moderate heterogeneity; 50-90 %= substantial heterogeneity; 75-100 %= considerable heterogeneity.[90] We used JASP software (JASP Team 2019, v0.9.2, University of Amsterdam) to perform meta-analysis when more than one study investigated the same outcome of interest.

2.8 Outcome variables:

Outcome variables were divided in to five broad categories, foot posture, strength, balance, patient-reported outcomes, and sensory function and motor performance. Foot posture included the measures of arch height index, and foot posture index. Balance measures included dynamic balance, and strength measures included force dynamometry. Patient-reported outcomes included pain and disability. Changes in sensory function (vibratory sense) and motor performance because of IFM were also reported by two studies separately.[79,82] The outcomes were reported but meta-analysis was not performed on these outcomes. Details of each studies reported functional outcomes are given in Table 4.

3. Results:

The first search resulted in 364 studies. After removing duplicates, 257 were left and then 135 more were excluded based on irrelevant titles and screening of abstracts. A further 3 articles were removed. [85,91,92] Two articles[91,92] were removed because PEDro score lower than 4. Saikia et al.[85] was removed because they did not report any baseline data. Based on inclusion criteria, ten studies were included to evaluate the outcomes of IFM training on foot function (Table 2). Out of the ten studies included, four studies reported significant decrease in navicular drop as a

result of IFM training (Figure 2).[74,83,86,88] Three out of four studies that used balance as an outcome reported significant improvement (Figure 3).[74,82,84,88] Three studies reported significant improvement in strength[81,83,87] outcomes (Figure 4), and two significant improvement in patient-reported outcomes (PROs)[84,86] (Figure 5). Meta-analyses could not be performed on the outcomes of sensory function and motor performance because one study each reported improvements in motor performance and sensory function after training.[79,82]

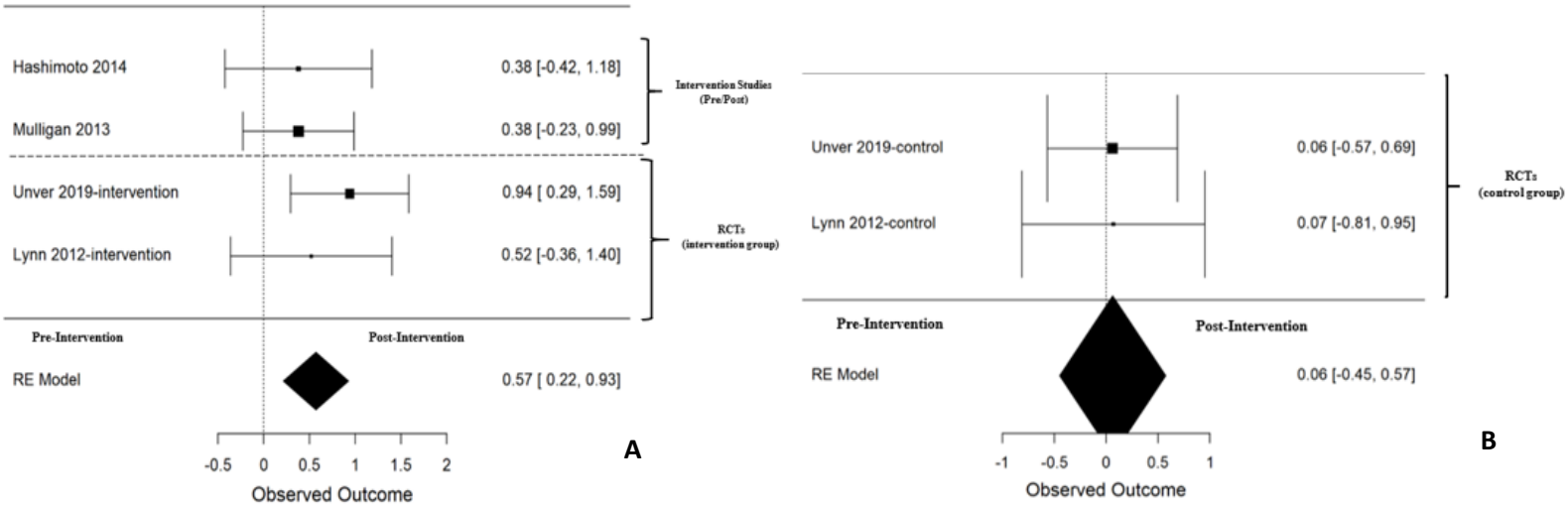
3.1 Foot Posture:

Four studies reported measures of foot posture that primarily involved measuring the decrease in navicular drop. [74,83,86,88] Out of these four studies, two were pre and post intervention studies and three were randomized control trials. Hashimoto et al.[83] used Burkeman foot print to measure arch height. Mulligan et al.[88] used digital caliper (Neiko 01407A, Neiko Tools USA) to measure the arch height index, and navicular drop. The difference between seated and standing navicular position was considered as the navicular drop. Similarly, Unver et al.[86] measured navicular height difference between the sitting and the standing position with a relaxed foot in millimeters. They also took foot posture index (FPI). Effect Sizes (ES) point estimates with associated 95% Confidence Intervals (CI) for Pre to Post intervention studies and for RCTs to compare the treatment effect on navicular drop are illustrated in Figure 2. Meta-analysis was performed only on the arch height measures as they were reported by all the studies whereas FPI was reported only by Unver et al[86]. Meta-analyses of the effect sizes were performed separately for intervention and control groups. The meta-analyses for the intervention groups reflected that there was significantly less drop in arch height ($p<0.01$, pooled ES= 0.57 [0.22,0.93], $I^2=0\%$) after IFMs training program (Figure 2A). However, for the control groups there was no difference in the arch height ($p=0.808$, pooled ES=0.06 [-0.45,0.57], $I^2=0\%$) between pre and

post measures (Figure 2B). The trend favors to support the IFM training for decreasing the navicular drop. Unver et al.[86] also reported FPI where the intervention group showed a greater decrease in foot pronation (ES=0.75 [0.12,1.38]) after 4-weeks of intervention as compared to the control group (ES=0.05 [-0.58,0.68]).

Figure B-2. Effect sizes and 95% CIs of decrease in navicular drop measures comparing the post-treatment measures with baseline for both interventional studies (Pre/Post) and RCTs.

2A= Decrease in navicular drop for intervention groups
2B= Decrease in navicular drop for control groups



3.2 Balance:

Four out of ten included studies reported balance as an outcome measure.[74,82,84,88] Of these studies, Lynn et al.[74] reported both static and dynamic balance changes whereas, all other studies reported changes in dynamic balance measurements. Lee et al.[82] used postural stability program using Biodex software (Biodex 950-302 Biodex, Inc., USA) that measures longitudinal

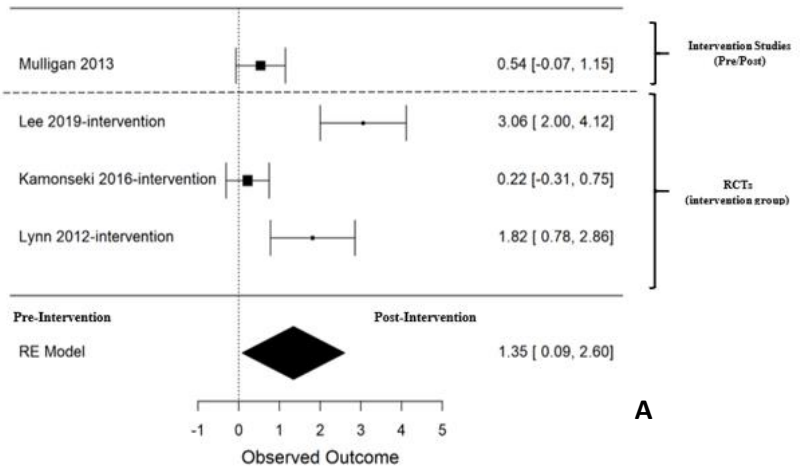
and lateral motions of the body as dependent measures of balance. Kamonseki et al.[84], Mulligan et al.[88], and Lynn et al.[74] used the Star Excursion Balance Test (SEBT) to measure changes in dynamic balance. Lynn et al.[74] also measured static balance by having participants stand on their one foot for 30 seconds on a force plate measuring their center of pressure (COP). The details of the subject characteristics, treatment given, and assessment time points are summarized in Table 3 and Table 4. ES point estimates and 95% CI for comparison pre to post intervention are given in Figure 3. Mulligan et al.[88] was a pre-post intervention study whereas, the other three studies were RCTs. Meta-analyses of the effect sizes were performed separately for intervention and control groups for dynamic balance. The meta-analyses for the intervention groups revealed that there was significant improvement in balance (p=0.03, pooled ES= 1.35 [0.09,2.60], I^2=91.06%) after IFMs training program (Figure 3A). However, there was no significant improvement in balance found (p=0.11, pooled ES=0.45 [-0.11,1.011], I^2=45.61%] (Figure 3B). Overall, the trend of ES point estimates for dynamic balance appears to favor groups treated with IFM exercises. Individually, we observe that where most of the studies in the intervention group had moderate to large effect sizes in balance improvement after intervention, Kamonseki et al.[84] did not show any preferential improvement in balance in intervention group compared with control group which was stretching only group (Figure 3A). The control group in Lee et al.[82] had a large effect size perhaps because it was also an exercise group with Proprioceptive Sensory Exercise (PSE) (Figure 3B) . However, the intervention group that was Short Foot Exericse (SFE) group had comparatively bigger effect size than the PSE group after intervention demonstrating the superiority of SFE over PSE in improving dynamic balance (Figure 3A).

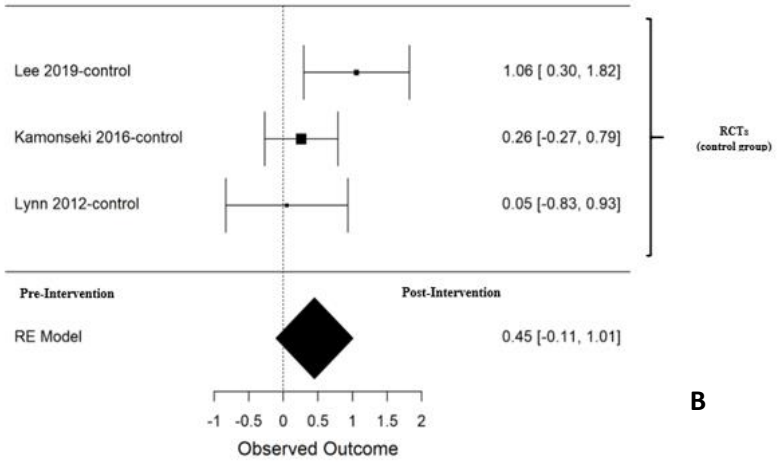
We could not perform meta-analyses for static balance as only one study reported it.[74] However, the greater magnitude improvement was observed in static balance (ES=0.58 [-0.32-

1.48] in IFM intervention group when compared to the control (ES=0.00 [-0.90,0.90) which again demonstrated positive effects of IFM exercise on static balance.

Figure B-3. Effect sizes and 95% CIs of decrease in balance measures comparing the post-treatment measures with baseline for both interventional studies (Pre/Post) and RCTs.

3A= Dynamic balance outcome scores for intervention groups
3B= Dynamic balance outcome scores for control groups



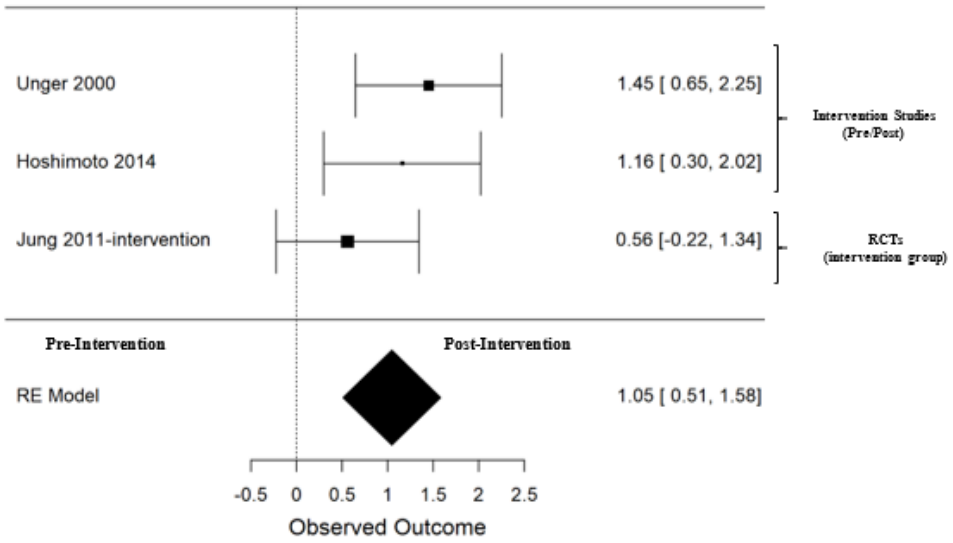


3.3 Strength:

Three studies reported strength measures (dynamometric measurements) as an outcome.[81,83,87] Of these, two are pre/post intervention studies and one is RCT. The details of the subject characteristics, treatment administered, and assessment time points are summarized in Table 3. ES point estimates and 95% CI for comparisons of the strength measures are illustrated in Figure 4. The meta-analyses for the intervention groups revealed that there was a significant increase in strength ($p<0.01$, pooled ES= 1.05 [0.51,1.58], $I^2=22.83\%$) after IFMs training program (Figure 4). We could not perform meta-analyses on the control groups as there was only one study[87] that was RCT and had control group in it. However the individual assessment of the

control group in Jung et al.[87] revealed a smaller magnitude difference (ES=0.22 [-0.54,0.98]) when compared to the intervention group (ES=0.56 [-0.22,1.34]). There was a trend of improvement in dynamometric strength measurements in all the three studies with moderate to large effect size.

Figure B-4. Effect sizes and 95% CIs of increase in strength measures (dynamometric) comparing the post-treatment measures with baseline for both interventional studies (Pre/Post) and RCTs.



3.4 Sensory function and motor performance:

Fraser and Hertel[79] reported motor performance and Lee et al.[82] reported sensory function as an outcome after IFM exercise training. Both of these studied were RCTs. Fraser and Hertel[79], used Clinician-assessed motor performance (4-point scale: 0= does not initiate movement and 3=performs exercise in standard pattern) to assess improvement in motor performance. Lee et al.[82] measured vibration using a Neurosensory Analyzer-II (Vibratory Sensory Analyzer-II, MEDOC, Inc., Ramat, Israel) as an outcome measure. The details of the subject characteristics, treatment administered, and assessment time points are summarized in Table 3. We could not perform meta-analyses on this data as there was only one study for each outcome of interest.

However, the individual assessment of the magnitude change in Lee et al.[82] revealed that there was a greater improvement in sensory function in the intervention group with a strong effect (ES=2.27 [1.35,3.19]) when compared to the control group (ES=0.69 [-0.05,1.43]). Similarly, for Fraser and Hertel[79] greater improvement in the motor performance was observed in the intervention group (ES=1.40 [0.77,2.03]) when compared to the control group (ES=0.00 [-0.63,0.63]).

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3.5 PROs:

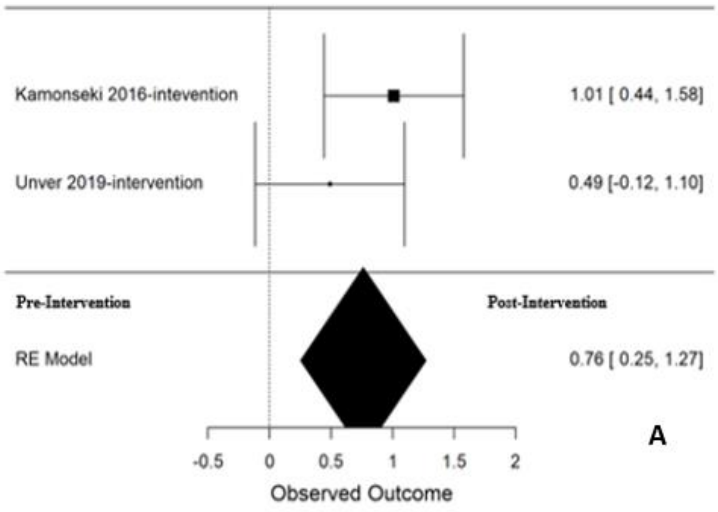
Pain and Disability were the outcomes of interest among PROs. Two RCTs reported pain and disability as an outcome in the PROs.[84-86] Kamonseki et al.[84] reported quality of life and activity of daily living using Foot and Ankle Outcome Score (FAOS). Increase in score indicated improvement in the pain and disability. Unver et al.[86] used pain and disability subscales (both include 9 items) of the Foot Function Index. Pain scale was used to measure the level of foot pain in different situations, and disability scale assessed difficulty because of foot problems in performing daily living activities. Every item was rated using a visual analogue scale. Decrease in score highlighted improvement in pain and disability. The details of the subject characteristics, treatment administered, and assessment time points are summarized in Table 3. ES point estimates and 95% CI for comparisons of the PROs of pain and disability are given in Figure 5. The meta-analyses of the intervention group revealed that there was a significant improvement in pain ($p<0.01$, pooled ES= 0.76 [0.25,1.27], $I^2=33.3\%$) after IFMs training program (Figure 5A). Interestingly, the meta-analyses of the control group for pain also demonstrated significant improvement in pain ($p<0.01$, pooled ES=0.57 [0.15,0.98], $I^2=0\%$) after IFMs training programs

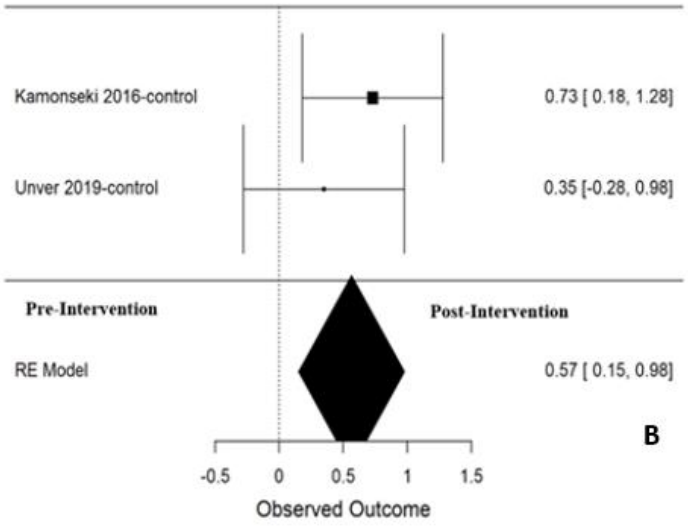
(Figure 5B). No preferential effect of IFM interventions were seen over other or no intervention for improvement of pain (Figure 5A and 5B).

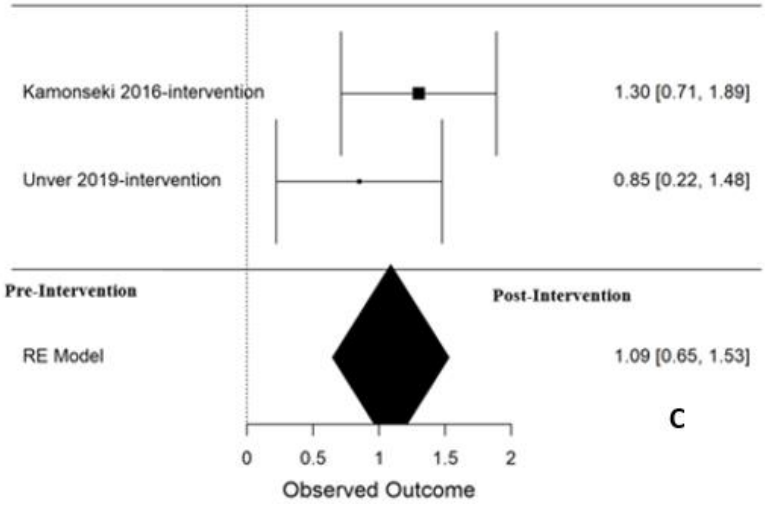
For disability, the meta-analysis of the pre to post measures showed significant improvement ($p<0.001$, pooled ES=1.09 [0.65,1.53], I^2= 4.98%) because of IFMs intervention (Figure 5C). However, the meta-analysis revealed that there was no significant improvement ($p=0.154$, pooled= 0.38 [-0.14,0.89], I^2= 39.38%) in disability in control group (Figure 5D).

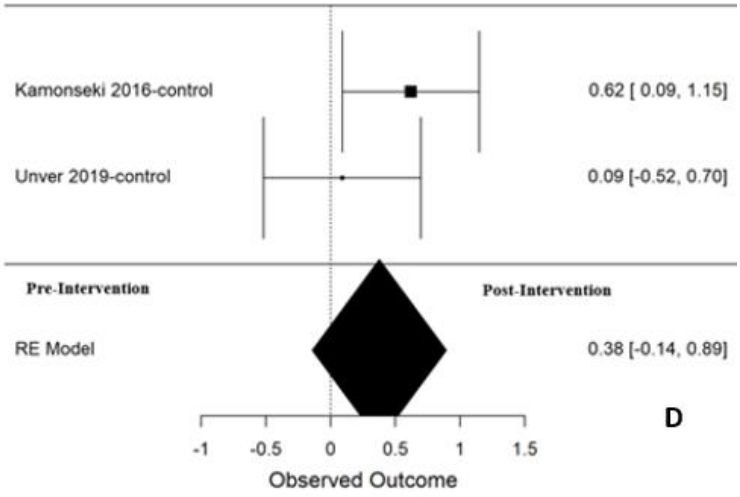
Figure B-5. Effect sizes and 95% CIs of improvement in patient-reported outcomes comparing the post-treatment measures with baseline for RCTs (both treatment and the control group).

5A= Pain outcome scores for intervention groups
5B= Pain outcome scores for the control groups
5C= Disability outcomes scores for the intervention groups
5D= Disability outcomes scores for the control group









4. Discussion:

Mckeon et al.[78] highlighted the significance of IFM training in the rehabilitation of the lower extremity injuries for improving functional outcomes. However, they identified the need of finding and developing the therapeutic interventions that can best activate IFM.[78] The body of literature regarding the function of IFM and the benefits of strengthening IFM is still nascent and is in the developing phase.[14,78] There is also a debate regarding which functional outcomes can

be improved by rehabilitating IFM in lower extremity injuries.[14,78] Mckeon et al.[14,78] recommended using objective measures such as navicular drop, balance, strength and balance assessment along with patient-reported outcomes such as pain to establish the efficacy of interventions specifically targeting IFMs. In this review and meta-analysis an effort has been made to systematically and holistically study the effects of IFM exercises on both objective and subjective patient outcomes. Significant improvements were observed because of IFMs interventions in most of the objective functional outcomes and PROs studied in this review. Superiority of IFMs interventions were also seen when compared to the control groups except pain where we did not observe any preferential improvement because of IFM intervention. These meta-analyses provide clinicians an opportunity to assess IFM and choose IFM exercise interventions that are most effective for their patients' care.

Groups which received IFM exercise intervention generally had significantly greater improvement in strength, balance, sensorimotor function, navicular drop and PROs. In the interventional studies and the treatment group for the RCTs, the ES favored the implementation of IFM exercises (Figures 2A,3A,4A,5A,5C). There is a definite merit in incorporating IFM exercises in the broad lower extremity rehabilitation programs because of the vast improvements seen in objective as well as subjective functional outcomes. A total of ten studies were included in this review and meta-analysis that compared the effectiveness of IFM exercises at two different timepoints (pre and post) and by making comparisons with controls.

4.1 Short Foot Exercise:

The most commonly employed IFM exercise in these studies was the SFE. SFE appears to be the most effective and commonly used treatment intervention for strengthening IFM and improving both subjective and objective outcomes. SFE is a maneuver that involves contraction

of midfoot moving the metatarsal heads posteriorly toward calcaneus without flexing the toes.[88] This maneuver results targets activations of the IFM and increase the medial longitudinal arch height.[88] SFE is thought to selectively activate IFM without activating extrinsic foot muscles. In this review and meta-analysis, it was used isolated or integrated with other treatment interventions and was proven to be superior to control groups. Significant improvements were seen in dynamic measures of postural control when SFE was used as a treatment intervention. Lee et al.[82] reported significant improvements in dynamic balance for the SFE group when compared with the Proprioceptive Sensory Exercise group. They also observed significant preferential improvement with large effect size of 2.27 in the vibratory sense in feet after intervention whereas the effect size of the control group was moderate 0.69. Similarly, Lynn et al.[74] noted the superiority of SFE in improving balance when compared with the towel exercise group or the control group. Mulligan et al.[88] showed improvements in dynamic balance at 4 weeks after SFE training which were sustained even after 8 weeks when compared to the baseline. Unver et al.[86] also demonstrated the benefit of using SFE for 6 weeks in patients with the history of pes planus when they compared it with a control group that did not receive any treatment. There were strong effect sizes shown for the decrease in pain, disability, and improvement in navicular drop in the group that received SFE when compared with control (Figure 2A,5A,5B). Jung et al.[87] studied IFM strength as an outcome in two groups of adults with bilateral pes planus. One group had foot orthosis used as treatment and the other also did SFE in conjunction with foot orthosis and they found that the mean changes in strength were higher in group that had SFE in the treatment plan (Figure 4).

Kamonseki et al.[84] also used SFE in conjunction with other foot exercises such as toe curl exercises when compared to stretching only group and found that dynamic balance

improved in all the groups. However, the individual analysis of the study revealed that foot exercise group could not demonstrate its superiority to the stretching only group rather the effect sizes were small for both groups (Figure 3A). It appears that SFE when used in isolation was more effective than when used with other forms of IFM exercises such as towel curl exercises.[74,84] Towel curl exercises perhaps activate long flexors tendons instead of IFM. Due to their insertion on the distal phalanx the extrinsic muscles of the foot get activated when there is curling of the toes.[11] For the same reason, we think that SFE is a better maneuver to use as a treatment intervention for rehabilitating IFM than other forms of IFM rehabilitation exercises that are utilized. In the pre to post interventional studies where SFE was used certain improvements were seen after 4-6 weeks of interventions in the outcomes of interest. Over all, there was a strong evidence in a significant decrease of navicular drop, increase in IFM strength, enhancing sensory function and motor performance and improvement in patient reported outcomes in the groups that had SFE as a treatment intervention.

4.2 Clinical Groups

This review and meta-analysis involve the effect of IFM exercises in both healthy and clinical populations. This further substantiates the use of these exercises in variety of patients of foot and ankle problems. Some of the clinical groups included this review are pes planus, Chronic Ankle Instability (CAI), and planter fasciitis.[82,84-87]

4.2.1 Pes Planus

Pes planus is a condition with lower medial longitudinal and alters the load distribution in the lower extremity causing excessive stresses in the foot, ankle and knee joints, and compensatory increased internal rotation at the hip joint.[86] Pes Planus is associated with number

of lower limb pathologies such as hallux valgus, planter fasciitis, tarsal tunnel syndrome, ACL injuries, and patellofemoral pain.[86] Significant reduction in navicular drop, pain and disability in pes planus group with intrinsic foot muscle exercises when compared to the control group.[86] Similarly, the superiority of IFM exercises over standard physiotherapy (included active movements and isometrics) was reported in decreasing navicular drop and pain in long standing workers who were tested positive for navicular drop.[85] Another study found that the group that also had IFM exercises as treatment in addition to foot orthosis had greater improvements in strength than that of the group that only had foot orthosis.[87] Overall, there was a strong evidence for administering IFM exercises as treatment for pes planus.

4.2.2 Planter Fasciitis:

Kamonseki et al.[84] studied the effects of foot exercises in the patients with plantar fasciitis comparing them with the group that received stretching only exercises. Planter fasciitis is characterized by pain on the planter surface of the heel.[84] They found that both groups improved in in dynamic balance, and subjective function of pain and disability. There was no group by time significant interaction present. One reason of not finding any differences between the groups could be because many exercises were used together at the same time that means lesser focus and time on the SFE that has shown to be a better intervention than other exercises such as towel curls in activating IFM.[74]

4.2.3 Chronic Ankle Instability:

Lee et al.[82] tested SFE in CAI that is a condition associated with decrease in function especially postural control due to recurrent ankle sprains.[93] Lee et al.[82] found that there were significant improvements in dynamic balance and sensory function in individuals that received

SFE when compared with the group that received proprioceptive sensory exercise. There were very large effect sizes observed for both dynamic balance and sensory function for intervention group when compared to control. It has been shown previously that lateral ankle sprain results in damage to the tibial nerve that can cause the weakness of IFM group and may also result in the decrease in sensory feedback on the plantar surface of the foot.[49] There have been large deficits in the IFM group identified previously in CAI patients.[17] However, there is less emphasis given to the IFM training when rehabilitating CAI patients. There is a need of more studies to further understand the efficacy of IFM exercises in CAI patients.

4.2.4 Healthy groups:

Studies that tested IFM exercises in healthy subjects found merit in their use in improving functional outcomes such as navicular drop, balance, strength and subjective function.[79,81,83,88] These results of these studies are important and promising in determining the effects of the IFM exercises and finding the best possible interventions that can be beneficial for the foot and ankle health. The literature regarding IFM function, deficits and treatment is still developing and these review and meta-analysis can be of critical importance for clinical-decision making while treating lower extremity injuries.

4.3 Limitations

There were certain limitations found in this analysis. There was greater heterogeneity found for intervention group for the dynamic balance outcome which is greater variance in the effect sizes between different studies where Kamonseki et al.[84] showed trivial effect size (ES=0.22) and Lynn et al.[74] (ES=1.82) and Lee et al.[82] (ES=3.06) showed very large effect sizes. Moreover, to increase the external validity of the IFM exercises they still need to be tested in

variety of clinical populations. We found positive results of administering IFM exercises for clinical groups such as pes planus, planter fasciitis, and CAI. However, we still don`t know if these exercises can work for other clinical groups where IFM atrophy or deficits are reported especially in the older group of patients such as diabetic patients[60,77] or patients with the history of 1st MTP joint arthrodesis.[13]

5. Conclusion:

In conclusion, this is the first review that systematically looks at the effects of IFM on functional outcomes. Based on the ten studies investigated emphasize the importance of IFM exercises in improving foot and ankle function. There are certain benefits of using IFM exercises in rehabilitation of lower extremity in improving balance, strength, somatosensory function and in decreasing navicular drop, pain and disability. This review also shows that SFE is perhaps the most beneficial exercise treatment that can be used in addressing the deficits of IFM. Based on the low risk and great benefits of improved self-reported and clinically measures functional outcomes such as balance, strength, pain and disability, it is recommended that IFM exercises should be used in isolation or integrated in the comprehensive rehabilitation program, including stretching and exercise, in the treatment of foot and ankle injuries.

Section 6 Peroneal muscles

6.1 Peroneal muscles and CAI:

Weakness of the fibularis muscles is thought to be a risk factor for ankle sprains.[94] There is often pain and tenderness found in peroneus longus muscle after lateral ankle sprain (LAS). Moreover,

peroneal injuries are sometimes misdiagnosed as LAS because of the similar clinical presentation.[95] Peroneal tendon injury may be associated with CAI.

Peroneal dysfunction is associated with impairment in postural control in subjects with CAI.[96] Restoration of ankle stability after the rehabilitation program was considered an integral for successful outcomes.[97] Peroneal strength deficits in the participants with CAI have been reported previously.[98] Cho et al.[98] reported that that patients with CAI had a peroneal weakness of about 39 % when compared with their contralateral healthy side.

Impairments in neuromuscular recruitment patterns of peroneal muscles have also been shown in the past. Decreased reaction times have been reported in peroneal muscle group in CAI group.[99] It is also believed that the impairment in peroneal muscles indirectly may be caused by atherogenic muscle inhibition.[100] Peroneal tendons can also be directly damaged in ankle sprains because of split lesion during sprain or after development of CAI.[101] Conclusively, the peroneal dysfunction is considered to be one of the contributing factors to the development of the chronic ankle instability.

If we enumerate the reasons of peroneal weakness in CAI. They are following

- Atherogenic muscle inhibition (indirect)
- Peroneal lesion during sprain or after because of chronically instable ankles
- It can also be because of disuse atrophy if CAI subjects are intentionally avoiding movements that can stress the ankle joint.

In another study by Donnelly et al.[102] it was found that there are eversion strength deficits between the CAI and healthy subjects.. However, they didn`t find any differences in healthy vs CAI for surface EMG measures for Peroneal muscles. They did find that there are similar

motor unit recruitments between healthy and CAI subjects, however, still CAI subjects are unable to produce more force. We think that may US imaging is more useful in this group of patients, in terms of looking at muscle fibers length and the CSA which can tell us about the muscular adaptations. The changes in muscle morphology or size can explain these changes in force measures found when there were no significant changes in the EMG measures.

In addition, given that there is a difference in the function of peroneal muscles between weight bearing and non-weight bearing positions Donnelly et al.[102] recommended tested these muscles in the weight bearing position. There is some conflicting evidence as well regarding the strength of peroneal in the ankle instability. Kaminski et al. [103] did a study and couldn`t find any strength differences between the CAI and the healthy subjects. They didn`t find any difference in concentric , eccentric or isometric strength in the peroneal of the CAI group when compared with healthy group.[103] Conclusively, there are changes reported in the peroneal function in the CAI group. However, we don`t know if there are changes in function in this group of muscles after rehabilitation. Moreover, there is a conflicting evidence regarding the activation of peroneal group of muscles using EMG. This study is also intended to look at the differential changes in the peroneal muscle group in patients with CAI after 4-weeks of impairment-based rehabilitation in both resting and functional positions that has not been studied before using US imaging.

6.2 Studying peroneal muscles using US imaging:

Lobo et al.[104] found significant differences in the CSA of the peroneal muscles between LAS and the healthy group where the peroneal muscle mass was significantly smaller than that of the healthy group. However, it has been suggested in the past that muscle size alone is enough for assessing muscle tissue as the CSA can be overestimated because of accumulation of adipose

tissue.[105] where the muscle might not be able to produce a lot of force because of decrease in number of cells and increase in the adipose tissue. A recent study came out that assessed the quality of the peroneal muscles in the CAI subjects.[105] The greater amount of adipose tissue in the muscle, results in the greater brightness in the image because of the difference in the acoustic impedance of muscle adipose tissue. And the echo-intensity of the muscle is correlated with muscle strength and the adipose tissue. Sakai et al. [105] found that there was greater echogenicity in the peroneal muscles in the CAI subjects as compared to the non-CAI side. They didn`t find any difference in the CSA of the peroneal muscles, the reason for that is that it is shown that orthopedic conditions cause decline in muscle quality than muscle quantity. [105] It is possible that reflex inhibition and decrease muscle activity after sprain could contribute to the accumulation of adipose tissue within the muscle. Rehabilitation (resistance training improves muscle quality and quantity) and we wanted to see If there is a change in the size and quality of peroneal post-rehabilitation. [105]

Abdeen et al.[106] did not find any difference in the peroneal sizes between the healthy, coper and the CAI group. Although they didn`t find any difference in the size of these muscles we don`t know if there are differences in the neuromuscular control. These muscles were tested in the resting state where the muscles are not activated. Therefore, it is possible that the size was not different but the difference in control and activation can exist between the two groups.

Stabilizing reflexes from the superficial and deep peroneal nerves as well as static ligaments on the lateral side of the ankle provides stability. [107] Approximately 85 % of all the sprains are the lateral ankle sprain.[107] There are number of studies that have shown that there is delayed response of peroneal during inversion perturbation. However, number of studies have found conflicting results.[107] Simon and Docherty,[107] found that people with CAI had significantly

slower NCV in the superficial peroneal nerve that supplies the peroneal muscles seen both at popliteal site and the fibular site. This slowness in NCV of the superficial peroneal nerve may also be a reason of FAI. The slower NCVs are may be due to mild to moderate traction lesion because of repetitive bouts of instability. Stretching peripheral nerve beyond its limit can have acute and long-term consequences. It will be interesting for researchers and clinicians to examine the activation of peroneal in functional positions such as double leg standing or single leg standing when compared with the resting position.

6.2 Testing peroneal muscles in weight-bearing position:

As recommended by Donnelly et al.[102] in the weight-bearing positions may be a better way to test peroneal muscles using ultrasonography. There is a difference in function in the weight-bearing position for peroneal for e.g. in the open chain peroneal are only acting concentrically and moving the foot in eversion.

However, in weight-bearing peroneus longus depresses the head of first metatarsal due to strong pull on its insertion. Maintains the transverse arch of the foot due to how it crosses the foot. Steadies the leg on the foot by drawing it on the lateral leg, and stops it from collapsing medially. The primary source of lateral stability by the musculotendinous structure is provided by peroneals.[96] There is a difference in the function of peroneal (especially peroneus longus) between the non-weight bearing and the weight bearing positions. During the weight-bearing peroneus longus stabilizes the first ray especially in the stance phase.[96] This functional activation of the peroneal longus muscle may not be seen in the non-weight bearing positions missing out important information.

It has been shown in the literature that there is difference in the activation of peroneus longus in weight bearing conditions. The reasoning for that can be.

1. Stabilizing the forefoot on the weight bearing condition (you have both single leg and double leg weight bearing for your Ultrasound study) during dynamic activities.[96]
2. it is also possible that tactile stimulation is also facilitating the functional activation of the peroneal muscles that is not possible in the non-weight bearing condition.[96]

Section 7 Neuromuscular and morphological changes after rehabilitation:

7.1 Primary morphological changes:

There are number of changes that take place following resistance training. Some of the most conspicuous changes are adaptations in the cross-sectional area (CSA) of the muscle. There is an increase in the size and increase in the number of the myofibrils of the muscle fibers. Supposedly, satellite cells are activated during the early stages of training; their increase in number and later fusion with the existing fibers apparently is involved in the hypertrophic responses of the muscles to the resistance training. There are certain other changes that take place in response to the resistance training and purportedly there is an increase in the number of muscle cells, change in fiber type, muscle architecture, myofilament density and the structure of tendons and connective tissue.[108]

It is generally believed that initial strength gains are because of neural adaptations and greater neural drive and hypertrophy follows this increased activation later on.[109] It has been previously reported that there is an increase in neural drive during within few weeks of strength exercise[109] However, it has also been shown that molecular changes start happening in the muscle within

hours or even minutes of exercise and fiber hypertrophy has been found within 4 weeks of training.[109]

Sayennes et al.[109] showed that there was considerable hypotrophy (3.2 to 5.2 %) seen in quadricep muscles only after 20 days of 5 weeks training. They also documented that there was an increase of 0.2 % per day in the first 20 days. Strength increased by 38 % and quadricep CSA increased by 7 %. This shows that major increase in strength was because of neural factors (increase recruitment). [109] There was an increase in pennation angle and fascicle length also seen in this study. This suggests that there was addition of sarcomeres both in series and in parallel.[109] A significant increase in fiber length (2 %) was seen before any increase in pennation angles and CSA. All these changes were seen just at 3 weeks of resistance training.[109] Conclusively, There are certain changes that take place because of resistance training in the muscular architecture, primarily muscle hypertrophy is achieved by remodeling the contractile tissue that can be examined macroscopically by looking at the fiber length, pennation angles, and muscle thickness.[110]

7.2 Neurological changes:

Neurological changes include learning and coordination. There is also changes in contralateral limb even though training might be unilateral. There is adaptation in activation of muscles (measured through EMGs), increased in firing frequencies etc. (potentially because of increase in motor unit recruitment). [108]

Sage mentions that muscle is the engine generating force while neural network is the controller of that engine.[111] Moreover, he also mentions that there are certain types of neural adaptations

that can take place after rehabilitation or strength training of the muscles. Following two neural adaptations are more noticeable.

Training can result in the recruitment of more motor units or the recruitment of higher threshold motor units. It has also been suggested that it is very important to recruit these high threshold motor units because they contain large number of muscle fibers. For instance, it has been reported that triceps brachii only contains 5 % of the high threshold motor units (type 2b) but even this small number contains 20 % of the total muscle fibers. These motor fibers are usually activated in the contracted state. [111] In this dissertation, we also will try to understand the functional activation of the IFM and peroneal by taking resting and contracted values, from non-functional position to the functional positional testing.

The second way to increase the activation of the muscle is through increasing the firing rate of these motor units. Change in the firing rate of the motor unit can vary its force output over about 10-fold range, known as force-frequency relationship.[111]

Increase in motor unit firing rates and recruitment of more motor units (specifically higher threshold motor units) together is called motor unit activation[111]

7.3 Contralateral training effect:

This phenomenon has been reported in literature previously that primarily states that there is a spillover of training effect on the contralateral side when the exercise is performed on the unilateral side. It has been reported in the literature that there is an increase in the strength on the contralateral untrained side of at least 50 % to the trained side or 8% of the initial strength.[112] PRIMARILY, this is because of increase motor neuron outputs rather than muscular adaptations

(e.g. hypertrophy or increase in muscle fiber length). There can be spill over from the CNS to the contralateral side or may be transfer effects from cortical, subcortical or spinal levels.

In addition, there are some studies that reported some muscle activity on the contralateral side, however, that was very small. There was also no change in the CSA seen on the contralateral side. This evidence actually suggests that muscular adaptations on the contralateral side are unlikely, however, minor adaptations cannot be ruled out. However, if we believe that changes in contralateral strength is not because of muscular adaptations then there must be neurological triggers for that emanating from CNS. There is possibility that there are changes in the pattern of neural activity related to motor drive and modifications in neural circuit involved in motor planning and execution. It's possible that there are adaptations running in parallel to the neural mechanisms on the contralateral side similar to the mechanisms on the unilateral side because of the synchronization of the motor patterns. [112]

7.4 CSA and Muscle Thickness relationship:

It has been previously reported that there is a strong correlation between the thickness of the quadricep muscle to the CSA (r=0.91) determined by the MRI.[113] It is hard to measure CSA by US in the bigger muscles this study ran correlations between CSA by MRI and thickness by US and it was found that thickness can be used to measure muscle size. In the same study, it was shown that there was a decrease in muscle size (2.1-4.4 %) after the bed rest.

It has also been shown that B-mode US measures of muscle size and fat are most reliable when taken by the same person.[114] B-mode ultrasound is a better technological advancement that gives a two-dimensional image of both fat and muscle thicknesses.[114] In addition, images should be normalized to mass when doing group comparisons as it has been shown in the literature that

CSA area is effected by differences in mass.[104] However, there is no influence of height on muscle CSA and therefore, it is not necessary to normalize the CSA of the muscle to height.[104]

APPENDIX C: ADDITIONAL METHODS

Table C-1. University of Virginia Institutional Review Board Approved Application and Protocol (M1)

RESEARCH APPLICATION

Investigators Experience

INSTRUCTIONS:
Provide a brief description of the investigators experience in working with this population in the clinical and research arena.
If this study will be done in a foreign country, add their experience working within the foreign country.

Answer/Response:

Dr. Susan Saliba, PhD, M.P.T., ATC

Dr. Saliba is a certified athletic trainer and physical therapist with over 20 years of clinical experience. She has been the primary investigator for numerous studies through the University of Virginia's IRB-HSR, with a strong research interest therapeutic modalities, interventions and applications administered to improve physical performance.

Study Coordinator – Abbis H.Jaffri, PT.,MS

Mr. Jaffri is a graduate assistant in the PhD program in Sports Medicine at the University of Virginia. Mr. Jaffri's research focus is in area of chronic ankle instability and the relationship to lower extremity biomechanics and balance. Mr. Jaffri has participated in and conducted descriptive and outcome studies while completing thesis requirements at the University of Virginia.

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The protocol will abide by the ethical standards of The Belmont Report
5. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.

6. That no personnel will have access to subjects in this protocol or their information until they have completed the human subject research protection on-line training through CITI and the IRB-HSR has been notified.
7. That all personnel working on this protocol will follow all Policies and Procedures of:
   - the UVA Human Research Protection Program (HRPP SOPS)
   - the IRB-HSR http://www.virginia.edu/vprgs/irb/
   - the School of Medicine Clinical Trials Office: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm.
   - and any additional UVA requirements for conducting research.
8. I will ensure that all those personnel delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
9. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
10. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
11. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
12. That all subjects will give informed consent unless the requirement has been specifically waived by the IRB.
13. That unless written consent has been waived by the IRB all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
14. They will establish and maintain an open line of communication with research subjects within their responsibility.
15. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
16. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
17. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
18. That any serious deviation from the protocol will be reported promptly to the Board in writing.
19. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
20. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
21. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
22. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI leaves UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
23. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.

24. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept according to UVA Records Management policies.
25. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
26. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

IF THE IRB-HSR WILL BE THE IRB OF RECORD FOR MULTIPLE SITES IN A MULTISITE TRIAL, THE UVA PI AGREES TO CARRY OUT THE FOLLOWING RESPONSIBILITIES:

1. Ensure all UVa personnel designated as Conflict of Interest Investigators complete Reviewing IRB's financial interest disclosure requirements unless the UVa personnel will adhere to the UVa conflict of interest policies that are compliant with DHHS requirements.
2. Promptly provide the Principal Investigator at each site with:
    a. Current approved protocol and consent documents;
    b. Approved modifications, amendments or changes to research protocols; and
    c. Approval of continuing reviews and reviews of unanticipated problems;
3. Notify the Principal Investigator at each site of standards and guidelines for reporting any post approval events such as adverse events, subject injuries, unanticipated problems, and protocol violations. Collect reports from Principal Investigator at each site of any unanticipated problems, deviations, suspensions and terminations, non-compliance, subject complaints, and submit such reports to Reviewing IRB per reporting requirements.
4. Notify the Principal Investigator at each site promptly of any unanticipated problems involving risks to subjects or others as determined by the Reviewing IRB.
5. Collect required information from the Principal Investigator at each site necessary for completing continuing review submissions.
6. Notify the Principal Investigator at each site promptly about any lapses of approval. Forward to the IRB of Record any request from the Principal Investigator of a site for continuation of a specific research subject on a protocol during a lapsed period of approval.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

INSTRUCTIONS:
The Principal Investigator signature is ONLY required if this is a new protocol, a 5 year update or a modification changing the Principal Investigator.

Department Chair or Designee

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.
4. He/she is not the Principal Investigator or a sub investigator on this protocol.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

INSTRUCTIONS:
The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
If the Department Chair fills one of these rolls on this protocol, the Department Chair's supervisor must sign here.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator.

Brief Summary/Abstract

INSTRUCTIONS:
Provide a very brief summary or abstract of this study (500 words or less). Include the purpose or hypothesis, a brief description of the experiment, and plans for data analysis. DO NOT Reference the sponsors protocol here.
If you plan to deviate from the Sponsor's protocol in any way, such as not doing certain sub-studies, include a description of those deviations in this summary.
For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no sponsors/common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/procedures/data points.

Answer/Response:

A. Brief Summary: Patients with the history of foot and ankle pathologies will be recruited to participate in this descriptive laboratory study for data collection. This study will help us in understanding the underlying causes of these pathologies. We will do Ultrasound imaging of foot musculature and will collect some subjective outcome data. Data collection will require only 1 visit of 45 to 60 minutes
B. Purpose: The purpose of this study is to learn more about the foot and ankle pathologies to help clinicans identify the underlying causes. This study will also help clinicans in designing their rehabilitation protocols when rehabbing patients who have history of foot/ankle surgery or pathologies. The global goal is improve care of patients and outcomes following surgery, thereby improving quality of life.
C. Hypothesis: Comparisons between objective and subjective measures will be made. We will expect that tehre will be differences in the foot muscle cross-sectional area (CSA) and thickness measures between different individuals with history of different foot/ankle pathologies.
D. Data Analysis: We will use independent sample t-test to compare CSA and thickness measures between patients.

Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

*The UVa HIPAA covered entity includes the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory, the Exercise Physiology Laboratory and the UVA Center for Survey Research.

1. **How do you plan to identify potential subjects?**

- To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
- If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.
- Check the methods you plan to utilize:

a.____ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).
If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) please see option b below.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

b____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.
If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) you are required to submit your request to the CDR. The CDR staff will work with the EDW to obtain the data you need.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

--a volunteer approved by the School of Medicine

The information from which you are obtaining potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

IRB# _____

If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797

c. ____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT
Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

d. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

DHHS: NA
HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

e. __X__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: NA

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

IRB# of registry/ database: _____

DHHS & HIPAA: NA

g. ____ Other: Specify Answer/Response:

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Answer/Response:

2. How will potential subjects be <u>contacted?</u>

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods below you plan to utilize:

a. ____Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

<u>Note:</u> Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

<u>DHHS/HIPAA:</u> Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

<u>IMPORTANT:</u>
Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by

individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- a UVa student working in the UVa HIPAA Covered Entity*
- a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
- --a volunteer approved by the School of Medicine

b.____Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
a UVa student working in the UVa HIPAA Covered Entity*
a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:

- Your name
- Who you are: physician, nurse etc. at the University of Virginia.
- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information use one of the following as an option for response.
    - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN: Your doctor, Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.
    - We obtained your information from your medical records at UVa.
    - Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.
- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c.____Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
HIPAA: Allowed under Health Care Operations.

d.___X_ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

DO NOT UNCHECK THIS BOX EVEN IF YOU DO NOT INTEND TO USE THIS RECRUITMENT METHOD AT THIS TIME.
The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

When entering a classroom to recruit students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non- participating students the option of leaving the classroom, thereby alleviating pressure to participate.

DHHS: Study team requests a Waiver of Consent to contact potential subjects.

HIPPA: NA

3. **Will any information be obtained from a potential subject during "prescreening"?**

Pre-screening for IRB purposes is the term used to describe activities PRIOR to obtaining Informed Consent and may not include any research procedures.

The activities may involve pre-screening of potential subjects over the telephone or in person is generally performed to determine their initial eligibility for, and, interest in a study and is a common strategy in the recruitment process.
Questions appropriate for pre-screening address the specific inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multiple times.

It is NOT appropriate at this point in the process (i.e. prior to obtaining informed consent/enrollment) to gather information that is not directly related to assessing eligibility and suitability (e.g. obtaining complete medical histories, obtaining blood specimens for lab tests).

An additional telephone script is not required, for this pre-screening process, in addition to any scripts required under Recruitment question # 2.

Answer/Response:
No

IF YES, submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.
NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

IF YES,
DHHS: study team requests a Waiver of Documentation of Consent for Pre-screening questions.

HIPPA:
HIPAA does not apply if:
--no PHI is collected or
--if PHI is collected from a potential subject by an individual from a department that is not part of the HIPAA covered entity.

HIPAA does apply if the collection occurs by individuals* who work in a department that is part of the HIPAA covered entity.

In this case the collection will be covered under Health Care Operations/

These individuals are those that meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

IF YES, Will any of the questions involve health information?
Answer/Response:

IF YES, will you collect HIPAA identifiers with the health information?
Answer/Response:

IF YES, which HIPAA identifiers will be recorded?
Answer/Response:

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner?
Answer/Response:

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?**

For example: come to the first visit fasting, stop taking medications that may be an exclusion criteria, change diet. As this is still part of pre-screening one is not allowed to gather information that is not directly related to inclusion/exclusion criteria or other issues of suitability (e.g. is person able to come to UVa for multiple visits)

NOTE:
Only those members of the study team with a DEA# (license to prescribe drugs) are allowed to determine if a potential subject may be asked/informed to stop taking a drug which is an exclusion criteria.
It is recommended that the potential subject notify their health care provider if they plan to stop a prescription drug.

Answer/Response:
No
►**IF YES, explain in detail what you will ask them to do**.
Answer/Response:

Tips to Study Team
You must document their verbal consent in the study records.
If a subject is asked to stop taking a drug, document the date and name of the person on the study team giving the verbal order to stop medications (again- must be a person with a DEA#).

DHHS: Study team requests the use of Verbal Consent (Waiver of Documentation of Consent) for minimal risk screening procedures.

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity this is covered under Health Care Operations
If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity consenting is covered under Health Care Operations.

If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

Describe the setting for the consent process.
If the study is of a sensitive nature and/or includes a reference to a medical condition how will you protect the privacy of the potential subject when they are approached to participate?
Who will discuss the study with the potential subject?
Where will the consenting process take place?
How will you assess subject understanding?
How much time will pass between obtaining written consent and initiation of study procedures?
See Protocol Examples: Consenting Process for examples of how to answer this question.
If recruiting minors, specify how parental /guardian consent will be obtained prior to approaching the minor.

Answer/Response:

The consenting process will take place in the Exercise and Sport Injury Lab (EASIL) in Memorial Gymnasium in a quiet and private area. Subjects will be given a consent form and be asked to read through it in its entirety and be given as much time as necessary. If there is concern that the potential subject may not be able to read, the potential subject will be asked to read the first sentence of the consent form to determine if they are capable of reading. Depending on the response they will either be offered the opportunity to read the consent form or have the consent form read to them.

Subjects will be given the opportunity to ask questions and have all questions answered by a member of the research team prior to signing the consent form. A member of the research team will summarize the consent form and procedure verbally to ensure that the individual understands the protocol process. If the subject agrees to participate the

person obtaining consent and the subject will sign the form and subjects will be given a copy of the signed consent form.

6. Will subjects sign a consent form for any part of the study?

Answer/Response:

Consent will be signed for the entire study.

7. Will the study procedures be started the same day the subject is recruited for the study?

Answer/Response:

No, but they will start the same day they sign the consent.

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

Answer/Response:

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.

Answer/Response:

8. Is there the potential to recruit a vulnerable population? (e.g. economically or educationally disadvantaged subjects, or other vulnerable subjects such as students , employees, investigator is health care provider of potential subject, pregnant women, children or prisoners?

INSTRUCTIONS: If you will be recruiting patients from the UVa Health System, you must answer this question YES as the UVa Health System cares for patients who are economically disadvantaged.

Answer/Response:

Yes

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?

Check all applicable options:

_X___ Consent will be obtained by the CRC rather than the Investigator

__X__ Subjects will be assured that their relationship with their UVA health care providers non-participation in the study will not be affected if they decide not to participate

__X__ Subjects will be given all the time needed to make their decision, and will not be pressured for a quick decision. They will be encouraged to seek advice from friends and family before signing consent.

____ Employees will be reassured that their decision will not affect their job or benefits.

__X__ Students will be reassured that their decision will not affect their status as a student or their grades.

____ If minors are enrolled, parental permission will be obtained prior to explaining the study to a minor and the minor's assent will be obtained prior to initiation of study procedures.

____ all subjects, especially those who are educationally disadvantaged will be asked open ended questions to confirm that they understand the study.

___ Other Explain:

9. Do you need to perform a "dry run" of any procedure outlined in this protocol?

A "dry run" is a procedure done to validate the system used to obtain results. It requires a human "subject" however the results of the dry run are used for system validation and not for the actual research. A common example a "dry run" is the validation or qualification MRI scans required by sponsor to ensure the MRI at UVa is able to perform the study-required scans.

- **If you are doing a sponsored study that involves an MRI for research, you are encouraged to say YES to this question**
- If YES, complete and submit a Consent for a Dry Run Procedure
- A template for a Consent for Dry-Run MRI is located under FORMS on the IRB Website
- IF YES, answer the following questions.

Answer/Response:

No

9a. List the "dry run" procedure(s) that must be performed.

Answer/Response:

9b. How many "subjects" will be recruited for "dry run" procedures?

These "subjects" should NOT be counted with your total enrollment figures.

Answer/Response:

9c. Describe the recruitment procedures for those participating in the "dry run".

Answer/Response:

9d. Will those participating in the "dry run" be compensated?

IF YES, add the "dry run compensation" as a line item to the payment section of this protocol.

Answer/Response:

9e. Who will pay for the cost of the "dry run" procedure(s)?

Answer/Response:

10. Is the study regulated by the Department of Defense (DoD)?

Answer/Response:

No

If YES, do you confirm the following protections will be in place for military research participants to minimize undue influence?

Answer/Response:

- Officers are not permitted to influence the decision of their subordinates.
- Officers and senior non-commissioned officers may not be present at the time of recruitment.
- Officers and senior non-commissioned officers have a separate opportunity to participate.
- When recruitment involves a percentage of a unit, an independent ombudsman is present.

If YES, do you also confirm that the following procedures will be in place to require limitations on dual compensation?

Answer/Response:

- Prohibit an individual from receiving pay of compensation for research during duty hours.
- An individual may be compensated for research if the participant is involved in the research when not on duty.
- Federal employees while on duty and non- federal persons may be compensated for blood draws for research up to $50 for each blood draw.
- Non-federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

11. **Non-Monetary Retention Incentives**

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the study team will submit a description and approximate retail value of the item to the IRB.

Study Procedures- Biomedical Research

1. Where will the study procedures be done?

Check One:

____ UVA medical center facilities (In patient or outpatient)

_X___ UVA but not medical center facilities: LIST specific location Answer/Response:

Exercise and Sport Injury lab.

____ Other: List specific location Answer/Response:

2. If the study involves medical risk and study procedures will be done outside of the UVa Medical Center what is your plan to protect the subjects in case of a medical emergency?

__*X*__ *NA*

Check all applicable options:

_____ MD, RN, onsite during procedures

_____ Individual trained in CPR on site during procedures

_____ AED and Individual trained to use it onsite

_____ Call 911

_____ Other: Describe Answer/Response:

3. List the procedures, in bullet form, that will be done for <u>RESEARCH PURPOSES</u> as stipulated in this protocol.

INSTRUCTIONS:
Examples: blood tests, EKG, x-rays, surveys, administration of investigational drug/device, randomization to one of two approved drugs
Do NOT list those procedures which are being ordered for clinical standard of care.
If ALL procedures are being done for the research study, simply write: ALL

Answer/Response:

Patient reported outcomes measures

Ultrasound imaging.

4. Do you confirm that, except for blood draws through a peripheral site, that all invasive procedures will be performed by a licensed health care provider under the supervision of an MD?

Answer/Response:

N/A

5. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study?

Answer/Response:

No

IF YES, will the data/specimens be used in this study without a new consent from the original donor?

Answer/Response:

IF YES, explain how the proposed use is consistent with the use planned in this study and submit a copy of the consent form used to collect the data/specimens.

INSTRUCTIONS: If you are unable to locate the consent form, you must request a Waiver of Consent. Consult with IRB staff to determine additional sections to be added to this protocol.

Answer/Response:

6. Will any of the procedures listed in item # 3 have the potential to identify an incidental finding? This includes ALL procedures, assessments and evaluations that are being done for <u>RESEARCH PURPOSES</u> that may or may not be considered investigational.

Examples: MRI/CT/PET/CXR shows possible tumor, Blood collected and analyzed using an investigational assay, Blood tests show possibility of leukemia, Surveys which reveal depression/ suicidal tendencies.

Answer/Response:

No

►IF YES, check one of the following two options:

_____The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. **There exists the potential for the discovery of clinically significant incidental findings.**

- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- If an incidental finding is serious and emergent (e.g. subject answers questionnaires implying they may be suicidal/mass on x-ray), the study team will inform the subject and contact the subject's health care provider.
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

____This examination(s) utilizes non-standard/investigational, technique, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

7. Do any of the procedures listed above, under question # 3, utilize any imaging procedures for <u>RESEARCH PURPOSES</u>?

Examples: ultrasound, CT scans/ x-rays etc.

Answer/Response:

Yes

IF YES, list procedures:

Answer/Response:

►IF YES, check one of the following two options:

__**X**___This imaging research examination utilizes the same imaging techniques, equipment, scanning sequences that would be used if the subject were to have the imaging performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

►If checked, answer the following:

Will the images be read by a licensed radiologist and the reading placed in the subject's medical record?

Answer/Response:

No

►IF NO: The PI takes full responsibility for the identification of incidental findings:

- The PI will have all incidental findings reviewed by a radiologist who will advise the PI regarding clinical significance.
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided t**o t**he subject with instructions to either show the letter to their PC or if the subject has **no** PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic.

_____This imaging research examination utilizes non-standard/investigational imaging modality, techniques, equipment, scanning sequences, etc. It is impossible to determine the significance of such images, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

8. Will your study involve measures used to screen or assess for depression and/or suicidality <u>for research purposes? No</u>

NOTE: Answer this question YES if any of the following apply:

1) *The protocol has a research purpose to study suicide, suicidal ideation, depression or trauma*
2) *The protocol has a research purpose to study traumatic life events that may evoke powerful emotion or induce mood changes in participants;*

3) *The protocol includes **assessments** or tools (e.g. Surveys, exams, questionnaires, etc.) that can be used to screen or identify **depression (C-SSRS/BID/SCID, questions related to mood, etc.) and/or suicidal ideation** (thoughts of suicide, either active or passive), plan (the means or mechanism) or intent (the expressed desire and willingness to act on the plan).*

a. Which research staff members will be available to provide appropriate referral for further care or intervention if the study tools indicate this need?
Answer by position with study (e.g. PI, sub investigator etc. Do not include names in answer.
Answer/Response:

b. Include specific guidelines for intervention or further assessment based on tools and rating scales used in this study (i.e. based on score of xxx or response of X, subject will be assessed further by the PI for suicide risk or referred urgently to an ED, crisis center, or clinic immediately).
Answer/Response:

c. Describe a plan to link participants to psychological help if needed and include written materials listing those resources as an attachment to the protocol. State how imminent risk of harm will be handled. (i.e. may include a list of local psychiatry/psychotherapy providers at UVA)
Answer/Response:

d. If your subjects will be patients at UVA Medical Center, confirm you plan to adhere to **Medical Center Policy 0140 Judicial Treatment Order and 0197 Suicide Risk Assessment and Prevention.**
Answer/Response:

e. Will subjects, who discontinue or are withdrawn secondary to suicidal ideations/depression prior to study completion, be asked to come to the site for an early withdrawal visit as soon as possible?
Answer/Response:

If No, provide outline of plan for follow-up or indicate if follow up is not required.

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?
Answer/Response:
There is no benefit to individual participants. The information from this study will also help clinicians understand surgical outcomes for the global purpose of improving quality of life

following orthopaedic surgery/injury as well as help optimize patient care in regard to the rehabilitative process.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

INSTRUCTIONS: Analyze the risk-benefit ratio and justify your answer.
Analyze the risk- benefit of interventions offering potential health benefit separately from those done solely to answer a research question or generate generalizable knowledge. Clarify risk-benefit for direct benefit to individual participant versus benefit to society.

Answer/Response:

The risk to the subject who participates in this study is minimal, including fatigue, whereas the benefit to this patient population and society in general is great. Although the initial benefits to each subject are minimal, uncovering a better understanding of how an injury and/ or surgery affect lower extremity function will inherently aid the clinician and researcher in developing better rehabilitative processes, with the global goal of improving quality of life. Therefore, the risk-benefit ratio is acceptable.

Data and Safety Monitoring Plan

This study has been deemed minimal risk. Because this study poses minimal risk to the subject, **adverse events will only be collected or recorded if a causal relationship to the study intervention is suspected.** If any adverse event is considered serious and unexpected, the event must be reported to the IRB-HSR within 7 days from the time the study team receives knowledge of the event.

1. Definitions

1.1 How will you define adverse events (AE)?

Do not change this answer

An adverse event will be considered any undesirable sign, symptom or medical condition considered **related to the intervention**. Medical condition/diseases present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

1.2 How will you define an unanticipated problem?

Do not change this answer

An unanticipated problem is any issue that involves increased risk(s) to participants or others. This means issues or problems that cause the subject or others to be placed at greater risk than previously identified, even if the subject or others do not incur actual harm. For example if a subject's

confidentiality is compromised resulting in serious negative social, legal or economic ramifications, an unanticipated problem would need to be reported. (e.g. serious loss of social status, loss of job, interpersonal conflict.)

1.3 What are the definitions of a protocol deviation and/or noncompliance?

Do not change this answer

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol deviations may be major or minor.

Noncompliance can be a protocol deviation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations**.** Noncompliance may be minor or sporadic, or it may be serious or continuing.

Additional Information: see the IRB-HSR website at
Protocol Deviations, Non-compliance and Protocol Exceptions

2. What risks are expected due to the intervention in this protocol?

INSTRUCTIONS:

- The risks should be consistent with those in the consent form (if applicable), although they should be written in technical terms in the protocol and in lay terminology in the consent form.
- List the most serious or most frequent risk first
- Delete last two rows if no additional risks added.
- Add additional rows to the table below if needed.

Expected Risks related to study participation	**Pick One**
There is a small risk that breaches of privacy and/or confidentiality might occur. The risk of violation of subject privacy and confidentiality is minimal due to the requirements of the privacy plan in this protocol.	Occurs rarely
• Fatigue	Occurs rarely
• Muscle Soreness	Occurs rarely
• Falling, injury to joint or muscle	Occurs rarely

3. When will recording and reporting of unanticipated problems/adverse events begin?

___X__After subject signs consent

_____After subject begins study intervention

_____Other Specify Answer/Response:

4. When will the recording/reporting of unanticipated problems/adverse events end?

__X___Subject completes participation in the protocol

_____End of intervention

_____30 days post intervention

_____Subject completes intervention and follow up period of protocol

_____Other: Specify Answer/Response:

5. What is your plan for safety monitoring?

Do not change this answer

Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will be performed by the PI and IRB-HSR through continuation review at least annually.

6. What is your plan for reporting a Unanticipated Problem, Protocol Deviations or Data Breach?

Do not change this answer

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance (*The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.)*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form
Data Breach* of Protected Health Information	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Police: phone- (434) 924-7166

*A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

Privacy Plan

The following procedures must be followed.

- The data will be secured per the Data Security Plan of this protocol.
- Only investigators for this study and clinicians caring for the patient will have access to data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa University Data Protection Standards will be followed.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's Highly Sensitive Data Protection Standard for Individual-Use Electronic Devices or Media Additional requirements may be found in the University's Security of Network-Connected Devices Standard. If identifiable data is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- Data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Standard.
- Data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Standard .
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards (UDPS 3.0).
- Data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

If you have a question or concerns about the required security standards contact InfoSec at *it-security@virginia.edu*

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-data that reveals an individual's health condition and/or history of health services use.
Protected Data (PHI) a type of Highly Sensitive Data, is data combined with a HIPAA identifier
Identifiable Data under HIPAA regulations is considered to be *Highly Sensitive Data at UVa.*

A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data* at UVa. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.

Highly Sensitive Data **(Identifiable Health Info per HIPAA)**	**Moderately Sensitive Data** **(Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know.
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with InfoSec or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center:	
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately

Highly Sensitive Data (Identifiable Health Info per HIPAA)	Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with InfoSec or Health System Web Development Office: 434-243-6702 University Side: IT-Security@virginia.edu Health System: Web Development Center: Contract must include required security measures.	
May be stored in UVA's Qualtrics portal for Highly Sensitive Data (HSD) May NOT be stored in places like UVaBox, UVaCollab or QuestionPro May also NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.	May be stored in places like UVaBox, UVaCollab, UVA's Qualtrics portal for Moderately Sensitive Data May NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*
***The UVa HIPAA covered entity includes the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory, the Exercise Physiology Laboratory and the UVA Center for Survey Research.*

Legal/Regulatory/Ethical Considerations

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at
http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/924-2620) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the UVa Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/924-2620), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

Informed Consent

Unless waived by the IRB, subjects will be fully informed of the:

- purpose of the study,
- reasonably anticipated benefits,
- potential risks or discomfort participation in the study may entail,
- and any alternative treatments.

They will also be informed that their

- consent is voluntary and that they may withdraw their consent to participate at any time, and
- (if applicable) choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The consent documents used to obtain informed consent of the subject must be approved by the IRB prior to use. Any written materials (consent/ short form) will be provided to the potential subject in a language they can read understand. The subjects will be given sufficient time to read the consent form and have the opportunity to ask questions.. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and

provide their consent voluntarily will be enrolled. After this explanation and before entry into the study, consent should be appropriately recorded. Subjects will be given a copy of the signed consent/ short form.

Institutional Review Board (IRB)

No subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment.
Any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

PROTOCOL

Background

27. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under "What will be done in this protocol?"
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.
- If this is a FIVE YEAR UPDATE make sure the information throughout the protocol includes the most current information.

Answer/Response:

Foot intrinsic muscles are considered to be important local stabilizers for the foot and lower extremity function that work in synergy with the extrinsic global stabilizers.[3] However, because of the complex articulation of foot and ankle and multi-articulated planter foot musculature it is difficult to do assessment of these muscles. [2] Feger et al.[2] did a study using Magnetic Resonance Imaging (MRI) to look

at the extrinsic and intrinsic musculature of foot and ankle. They found a significant decrease in the volume of the adductor hallicus obliques and flexor hallucis brevis in CAI subjects when compared with the control.[2] However, MRI is neither prevalent nor an economical avenue for the assessment of intrinsic foot muscles. Moreover, we think that intrinsic muscles of the foot are best activated in their functional position that is the weight bearing position. It is also difficult to functionally assess intrinsic foot muscles with the use of MRI. Battaglia et al. [1] used ultrasound for the functional assessment of the intrinsic foot muscles. The found an excellent intratester and intertester (ICC>0.75) reliability of Cross Section Area (CSA) measurements of intrinsic foot muscles in both non-weight bearing and weight bearing positions.

Ultrasound assessment is more economical and feasible for functional assessment of the intrinsic foot muscles. There have been no previously reported studies that have looked at the weight-bearing CSA of foot intrinsic which is a natural functional position of these muscles. This study will help in understanding the intrinsic foot muscles morphology in a number of foot and ankle pathologies. This study would also help in highlighting the importance of intrinsic foot muscles activation during the rehabilitation programs after foot or ankle pathology and/or surgery .

Objectives/Hypothesis

INSTRUCTIONS:
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

Answer/Response:

Aim 1: Is there a difference in morphology (CSA and thickness measures) of intrinsic foot muscles between different foot and ankle pathologies.
Hypothesis 1: We will expect to see differences in morphology (CSA and thickness measures of intrinsic foot muscles between different foot and ankle pathologies
Aim2: Is there a difference between weight bearing and non-weight bearing assessments of intrinsic foot muscles
Hypothesis 1: We will expect to see differences in the intrinsic foot assessment when comparing weight bearing position to the non-weight bearing.

Study Design: Biomedical

1. Will controls be used?

Answer/Response:

No

►IF YES, explain the kind of controls to be used.

Answer/Response:

7. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question. (http://www.virginia.edu/vpr/irb/learningshots/Writing_protocol_June09/player.html

Answer/Response:
Descriptive Laboratory study

8. Does the study involve a placebo?

Answer/Response:
No
►IF YES, provide a justification for the use of a placebo
Answer/Response:

Human Participants

Ages: __18-60__
Sex: __male and female__

Race: **__any__**

Subjects- see below

INSTRUCTIONS: **For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.**

1. Provide target # of subjects (at all sites) needed to complete protocol.

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Answer/Response:
100 foot/ankle/lower limb injury subjects.

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

Answer/Response:

We don`t expect any drop out

3. How many subjects will be enrolled at all sites?

INSTRUCTIONS: **This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.**

Answer/Response:
100

4. How many subjects will sign a consent form under this UVa protocol?

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Answer/Response:
100

Inclusion/Exclusion Criteria

INSTRUCTIONS:

5. The inclusion and exclusion criteria should be written in bullet format.
6. *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .
7. If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
8. If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
9. The stop date must be prior to the version date of this protocol.
10. *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

Answer/Response:

1) 18 to 60 years of age.

2) History of any lower limb or foot and ankle surgical procedure (e.g. Achilles tendon surgery, turf toe, big toe arthrodesis, LAS surgery, ACL-reconstruction or any other relative foot and ankle surgical reconstruction.)
3) History of any lower limb or chronic foot and ankle pathology (e.g. Chronic Ankle Instability (CAI), Planter fasciitis, Pes Planus, Pes Caves or any other relevant foot and ankle pathology)

2. List the criteria for exclusion

Answer/Response:

1) Subjects with implanted biomedical devices (active or inactive implants) including device leads, deep brain stimulators, cochlear implants and vagus nerve stimulator
2) History of skull fracture
3) Open wound on lower limb or foot or ankle (contraindication to ultrasound)
4) Unable to provide consent
5) Pregnant (self-reported)

3. List any restrictions on use of other drugs or treatments.

Answer/Response:

N/A

Statistical Considerations

6. Is stratification/randomization involved?

Answer/Response:

No

►IF YES, describe the stratification/ randomization scheme.

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

Answer/Response:

►**IF YES, who will generate the randomization scheme?**

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
_____ Other: Specify Answer/Response:

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints
--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

Answer/Response:
Independent sample t-test will be used to compare thickness and cross-sectional area measures of intrinsic foot muscles between different types of foot pathologies.

3. Provide a justification for the sample size used in this protocol.

Include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response:
This is a novel project and there is nothing in the literature that has been reported on the functional assessment of intrinsic foot muscles with Ultrasound. We will be taking a sample of convenience for this project. We are expecting to have (N=100) subjects for this study.

4. What is your plan for primary variable analysis?

Include a sketch of the analysis to assess primary study objectives.

Answer/Response:
Thickness and cross-sectional area measures of intrinsic foot muscles will be compared between different types of foot and ankle pathologies using independent t-test.

5. What is your plan for secondary variable analysis?

Include the following:
--A sketch of the analysis to assess secondary study objectives.
--For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response:

Independent sample t-test will also be used to see the differences in IFM CSA and thickness between the weight bearing and non-weight bearing positions.

6. Have you been working with a statistician in designing this protocol?

Answer/Response:

No

IF YES, what is their name?

Answer/Response:

7. Will data from multiple sites be combined during analysis?

Answer/Response: No

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?

Answer/Response:

IF YES, will randomization be done at each site or among sites?

Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?

Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Answer/Response:

7(d). Is there a common protocol used in all sites?

Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?

INSTRUCTIONS:
This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.
This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified. Describe and justify any control and experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

Special note for studies with waiver of consent/waiver of documentation of consent:
Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

Answer/Response:
This study will constitute of only one visit by the subjects. Subjects will report to Exercise and Sport Injury Laboratory (EASIL) for this study.
Informed consent will be obtained.

- Demographics:
  The following demographics will be collected: sex, age, height, weight, leg length, foot postural index (FPI) and occupation
- Patient Reported Outcomes (PROs):
  All PROs employed in this study are commonly used clinical measures of pain and function and will be completed once.
  1. International Physical Activity Questionnaire (IPAQ)- self-report of physical activity over the course of a typical week

2. Foot and Ankle Ability Measure (FAAM)-a region-specific outcome questionnaire requires subjects to assess their perceived ability in both activities of daily living and sports.

3. American Orthopedic Foot and Ankle Society Score (AOFAS): is a self-reported instrument used for measuring the outcome of treatment in patients who sustained a complex ankle or hindfoot injury.

4. Fear-Avoidance Beliefs Questionnaire (FABQ) - A questionnaire that measures the avoidance of physical activity because of pain.

5. Tampa Scale of Kinesiophobia-A questionnaire that measures the avoidance of physical activity because of pain

6. Tegner activity scale- self-report of physical activity over the course of a typical week

- Balance Measures:
  Pressure Mat (Teckscan) will be used to take balance measures of the subjects. Participants will stand on the pressure mat on the for 10 seconds with their eyes closed and their arms wrapped around their chest. Three trials will be taken on each of their limbs.
- Ultrasound Imaging Assessment:
  Ultrasound imaging will be used to measure the CSA and thickness of foot muscles using a Siemens Acuson Freestyle ultrasound unit (Siemens, Mountain View, CA). Ultrasound imaging will be performed in weight bearing (bilateral double limb stance and single limb stance with hand support) and non-weight bearing positions (lying and sitting). Ultrasound images will be repeated on both feet.

- **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
Instructions: Answer NA if this study does not involve a study treatment.

Answer/Response:

N/A

Bibliography

INSTRUCTIONS: Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

1. Battaglia PJ, Mattox R, Winchester B, Kettner NW. Non–Weight-Bearing and Weight-Bearing Ultrasonography of Select Foot Muscles in Young, Asymptomatic Participants: A Descriptive and Reliability Study. *Journal of manipulative and physiological therapeutics*. 2016;39:655-661.

2. Feger MA, Snell S, Handsfield GG, et al. Diminished Foot and Ankle Muscle Volumes in Young Adults With Chronic Ankle Instability. *Orthopaedic journal of sports medicine*. 2016;4:2325967116653719.

3. McKeon PO, Hertel J, Bramble D, Davis I. The foot core system: a new paradigm for understanding intrinsic foot muscle function. *Br J Sports Med*. 2014;bjsports-2013-092690.

Table C-2. University Of Virginia IRB Approved Consent Form IRB-HSR (M1)

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

Principal Investigator:	Susan Saliba, Ph.D, M.P.T., ATC Department of Kinesiology PO Box 400407 Charlottesville, VA 22908 (P) 434-243-4033 (E) saf8u@virginia.edu

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

Who is funding this study?

This study is not receiving any funding.

Why is this research being done?

The purpose of this study is to evaluate the foot muscles in people who have had foot or ankle surgery or who have conditions of the foot or ankles. This will help clinicians in identifying any size or thickness differences in the foot muscles and in better understanding the underlying causes of the foot/ankle conditions. It will also help clinicians in developing more targeted rehabilitation protocols.

You are being asked to be in this study because you have the history of ankle/foot surgery or injury.

Up to 100 people will be in this study at UVA.

What will happen if you are in the study?

This study is a one-time visit at the UVA Exercise and Sport Injury Laboratory. All procedures are being done for research purposes.

CONSENT and SCREENING (will take about 5-10 minutes):

If you have a history of foot or ankle injuries in the past or have had foot/ankle surgery history, you will be eligible to participate in this study. In addition, you will be asked some questions regarding the date/time/severity of your injury history or surgery.

IRB-HSR Approval Date:02APR2018
IRB-HSR Expiration Date:14MAR2019

Once it is determined that you are eligible then you will be able to participate in the study. The procedures in this study are being done for research purposes only.

STUDY PROCEDURES

Questionnaires (5-10 minutes):

You will complete a series of questionnaires. These will ask about:

- Questions about your general health as it relates to your ankle injury
- Questions about your current physical activity level
- Questions about your foot/ankle function
- Questions about how you feel when you move

Ultrasound Imaging (20 to 30 minutes):

Ultrasound imaging will be used to measure the thickness of foot muscles using a Siemens Acuson Freestyle ultrasound unit (Siemens, Mountain View, CA). Ultrasound imaging will be performed during weight bearing positions such as normal standing (double limb stance) and then single limb stance with hand support, and during non-weight bearing positions such as lying and sitting. Ultrasound images will be repeated on both feet.

Balance Testing (5 min):

You will be asked to do the following:

1) 3 times on your **left leg**, with your **eyes open**.
2) 3 times on your **right leg**, with your **eyes open**.
3) 3 times on your **left leg**, with your **eyes closed**.
4) 3 times on your **right leg**, with your **eyes closed**.

Force Measures (2 min):

You will be asked to bend your small toe and your big toe. The force made by your toes will be measured by a hand-held meter (dynamometer).

What are your responsibilities in the study?

You have certain responsibilities to help ensure your safety.

These responsibilities are listed below:

- You must come to each study visit.
- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.

How long will this study take?

Your participation in this study will require 1 visit that will last around approximately 45 to 60 minutes.

If you want to know about the results before the study is done:

The purpose of the study is NOT to diagnose any disease or abnormality you may have. If any test results are concerning, your study leader will let you know. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results.

What are the risks of being in this study?

Risks and side effects related to the include:

Likely

- You may experience muscle soreness or fatigue
- You may experience a slight discomfort in the joints of lower limb

Less Likely

- There is a slight chance of losing your balance in the weight-bearing position. If you experience a loss of balance and fall, you may experience an injury to your joint or muscle.

Could you be helped by being in this study?

You will not benefit from being in this study. However, the information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

The only choice is not to be in this study. If you are a patient at UVa your usual care will not be affected if you decide not to participate in this study. If you are an employee of UVa your job will not be affected if you decide not to participate in this study. If you are a student at UVa, your grades will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?

You will not get any money for being in this study.

Will being in this study cost you any money?

All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study visit and for any parking costs.

What if you are hurt in this study?

If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) You become injured and can no longer participate in the study
b) The principal investigator closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to verbally indicate that you are no longer interested in participating in the study to a member of the study team. If you do withdraw, a note will be placed in your file indicating that you withdrew from the study.

How will your personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Susan Saliba
Department of Kinesiology
PO Box 400407
Charlottesville, VA 22908
Telephone: (434)243-4033

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908
Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Signature of Impartial Witness

If this consent form is read to the subject because the subject is blind or illiterate, an impartial witness not affiliated with the research or study doctor must be present for the consenting process and sign the following statement. The subject may place an X on the Participant Signature line above.

I agree the information in this informed consent form was presented orally in my presence to the **identified individual(s)** who has had the opportunity to ask any questions he/she had about the study. I also agree that the **identified individual(s)** freely gave their informed consent to participate in this trial.

Please indicate with check box the identified individual(s):

☐ Subject

IMPARTIAL WITNESS (SIGNATURE)	IMPARTIAL WITNESS (PRINT)	DATE

Table C-3. University of Virginia Institutional Review Board Approved Application and Protocol (M1)

RESEARCH APPLICATION

Investigators Experience

INSTRUCTIONS:
Provide a brief description of the investigators experience in working with this population in the clinical and research arena.
If this study will be done in a foreign country, add their experience working within the foreign country.

Answer/Response:

Dr. Susan Saliba, PhD, M.P.T., ATC

Dr. Saliba is a certified athletic trainer and physical therapist with over 20 years of clinical experience. She has been the primary investigator for numerous studies through the University of Virginia's IRB-HSR, with a strong research interest therapeutic modalities, interventions and applications administered to improve physical performance.

Study Coordinator – Abbis H.Jaffri, PT.,MS

Mr. Jaffri is a graduate assistant in the PhD program in Sports Medicine at the University of Virginia. Mr. Jaffri's research focus is in area of chronic ankle instability and the relationship to lower extremity biomechanics and balance. Mr. Jaffri has participated in and conducted descriptive and outcome studies while completing thesis requirements at the University of Virginia.

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

28. I am not currently debarred by the US FDA from involvement in clinical research studies.
29. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
30. That if this study involves any funding or resources from an outside source or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
31. The protocol will abide by the ethical standards of The Belmont Report
32. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
33. That no personnel will have access to subjects in this protocol or their information until they have completed the human subject research protection on-line training through CITI and the IRB-HSR has been notified.
34. That all personnel working on this protocol will follow all Policies and Procedures of:

- the UVA Human Research Protection Program (HRPP SOPS)
- the IRB-HSR http://www.virginia.edu/vprgs/irb/
- the School of Medicine Clinical Trials Office: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm.
- and any additional UVA requirements for conducting research.

35. I will ensure that all those personnel delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
36. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
37. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
38. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
39. That all subjects will give informed consent unless the requirement has been specifically waived by the IRB.
40. That unless written consent has been waived by the IRB all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
41. They will establish and maintain an open line of communication with research subjects within their responsibility.
42. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
43. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
44. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
45. That any serious deviation from the protocol will be reported promptly to the Board in writing.
46. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
47. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
48. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
49. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI leaves UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
50. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
51. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept according to UVA Records Management policies.
52. No data/specimens may be taken from UVa without a signed Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are

considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.

53. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

IF THE IRB-HSR WILL BE THE IRB OF RECORD FOR MULTIPLE SITES IN A MULTISITE TRIAL, THE UVA PI AGREES TO CARRY OUT THE FOLLOWING RESPONSIBILITIES:

9. Ensure all UVa personnel designated as Conflict of Interest Investigators complete Reviewing IRB's financial interest disclosure requirements unless the UVa personnel will adhere to the UVa conflict of interest policies that are compliant with DHHS requirements.
10. Promptly provide the Principal Investigator at each site with:
    a. Current approved protocol and consent documents;
    b. Approved modifications, amendments or changes to research protocols; and
    c. Approval of continuing reviews and reviews of unanticipated problems;
11. Notify the Principal Investigator at each site of standards and guidelines for reporting any post approval events such as adverse events, subject injuries, unanticipated problems, and protocol violations. Collect reports from Principal Investigator at each site of any unanticipated problems, deviations, suspensions and terminations, non-compliance, subject complaints, and submit such reports to Reviewing IRB per reporting requirements.
12. Notify the Principal Investigator at each site promptly of any unanticipated problems involving risks to subjects or others as determined by the Reviewing IRB.
13. Collect required information from the Principal Investigator at each site necessary for completing continuing review submissions.
14. Notify the Principal Investigator at each site promptly about any lapses of approval. Forward to the IRB of Record any request from the Principal Investigator of a site for continuation of a specific research subject on a protocol during a lapsed period of approval.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

INSTRUCTIONS:
The Principal Investigator signature is ONLY required if this is a new protocol, a 5 year update or a modification changing the Principal Investigator.

Department Chair or Designee

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

11. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
12. That the Principal Investigator is qualified to perform this study.
13. That the protocol is scientifically relevant and sound.
14. He/she is not the Principal Investigator or a sub investigator on this protocol.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

INSTRUCTIONS:
The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
If the Department Chair fills one of these rolls on this protocol, the Department Chair's supervisor must sign here.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator.

Brief Summary/Abstract

Answer/Response:

A. Brief Summary: Patients with the history of diabetes along with healthy controls will be recruited to participate in this descriptive laboratory study for data collection. This study will help us in understanding the changes in the morphology of the muscles in diabetic group. We will do ultrasound imaging of the foot musculature and will also collect NIRS data to examine foot function. Participants will also perform an exercise of foot to activate foot muscles and this investigation will be used to determine if this exercise maneuver can activate the muscles of the foot in the diabetic patients
B. Purpose: The purpose of this study is to learn more about foot and ankle health/function in the diabetic group. This study will also help clinicians to design rehabilitation protocols when rehabbing patients who have history of diabetes. The global goal is to improve care of patients with diabetes, thus improving their quality of life.
C. Hypothesis: We will expect that there will be a difference in the morphology of foot muscles between the healthy and the diabetic group. Also, we will expect that there will be increase in the activation of the foot muscles with short foot exercise.
D. Data Analysis: We will use independent sample t-test to compare muscles morphology and perfusion changes between feet of diabetic patients and healthy controls.

Sponsor

INSTRUCTIONS:

7. If you have internal funding from your department to conduct this study list the department as the sponsor.
8. If you have external funding, list names of companies, institutes, foundations with which you have a grant or a contract to conduct this study.

Example: This study is funded via a contract with the University of New York, which has a grant from the NIH to conduct this study.

- **Explain the sponsorship for this study.**

Answer/Response:

N/A

Support Source

INSTRUCTIONS:

The support source is any source outside of UVA providing support such as supplies/drug/device's or financial assistance. The entity should NOT be considered a Support Source if they are taking on the responsibilities of a sponsor such as monitoring, safety

oversight or data analysis. Do not enter a company/ organization as a supply source unless the support has been secured. The IRB-HSR must be notified and the consent form revised if a support source changes. (Example-the NIH or an investigator-initiated study in which the pharmaceutical company is providing drug free of charge.)

1 .Describe what will be provided and by whom.

Answer/Response:

N/A

Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.
*The UVa HIPAA covered entity includes the UVa Health System including the School of Medicine& the School of Nursing, the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.
PHI may also be shared without tracking disclosures with the following groups as agreements are already in place: VP Office of Research, Nutrition Services (Morrison's) and the UVA Center for Survey Research.

h. How do you plan to <u>identify</u> potential subjects?

- To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
- If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.
- Check the methods you plan to utilize:

a.__X__ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).
<u>If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) please see option b below.</u>

<u>DHHS:</u>
<u>Pre 2018 Common Rule:</u> Study team requests Waiver of Consent to identify prospective subjects.
<u>2018 Common Rule:</u> Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

b____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.
If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) you are required to submit your request to the CDR. The CDR staff will work with the EDW to obtain the data you need.

DHHS:
Pre 2018 Common Rule: Study team requests Waiver of Consent to identify prospective subjects.
2018 Common Rule: Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

The information from which you are obtaining potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

IRB# _____

If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797

- __X__ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

DHHS:
Pre 2018 Common Rule: Study team requests Waiver of Consent to identify prospective subjects.
2018 Common Rule: Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT
Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

- __X__ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

DHHS: NA
HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

- __X__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: NA

- _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

IRB# of registry/ database: _____

DHHS & HIPAA: NA

- ____ Other: Specify Answer/Response:

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Answer/Response: Yes, the PHI (name, phone #, and email) will be given to the EASIL lab for direct contact of potential subjects for recruitment purposes.

i. How will potential subjects be <u>contacted?</u>

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods below you plan to utilize:

a. __X__ Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

<u>Note:</u> Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

<u>Pre 2018 Common Rule:</u>
<u>DHHS/HIPAA:</u> Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

<u>2018 Common Rule:</u>
<u>DHHS:</u>
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
<u>HIPAA:</u> Study team requests a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

f. a UVa student working in the UVa HIPAA Covered Entity*
g. a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

h. a volunteer approved by the School of Medicine

b.____Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

Pre 2018 Common Rule:
DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

2018 Common Rule:
DHHS:
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
HIPAA: Study team requests a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
a UVa student working in the UVa HIPAA Covered Entity*
a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:

- Your name
- Who you are: physician, nurse etc. at the University of Virginia.

- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information use one of the following as an option for response.

  - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN: Your doctor, Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.
  - We obtained your information from your medical records at UVa.
  - Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.

- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c.__X__Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

Pre 2018 Common Rule:
DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPAA: Allowed under Health Care Operations.

2018 Common Rule:
DHHS:
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
HIPAA: Allowed under Health Care Operations.

d.___X_ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

DO NOT UNCHECK THIS BOX EVEN IF YOU DO NOT INTEND TO USE THIS RECRUITMENT METHOD AT THIS TIME.
The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

- ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

When entering a classroom to recruit students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non- participating students the option of leaving the classroom, thereby alleviating pressure to participate.

Pre 2018 Common Rule:
DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPAA: NA

2018 Common Rule:
DHHS:
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
HIPAA: NA

3. Will any information be obtained from a potential subject during "prescreening"?

Pre-screening for IRB purposes is the term used to describe activities PRIOR to obtaining Informed Consent and may not include any research procedures.

The activities may involve pre-screening of potential subjects over the telephone or in person to determine their initial eligibility for, and, interest in a study and is a common strategy in the recruitment process.

Questions appropriate for pre-screening address the specific inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multiple times.

It is NOT appropriate at this point in the process (i.e. prior to obtaining informed consent/enrollment) to gather information that is not directly related to assessing eligibility and suitability (e.g. obtaining complete medical histories, obtaining blood specimens for lab tests).

An additional telephone script is not required, for this pre-screening process, in addition to any scripts required under Recruitment question # 2.

Answer/Response: Yes

IF YES, submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.
NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

IF YES,
DHHS:

Pre 2018 Common Rule: Study team requests a Waiver of Documentation of Consent for Pre-screening questions.

2018 Common Rule: No waiver of documentation of consent required per 45CFR46.116 (g).

45CFR46.116(g) an IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subjects legally authorized representative if either of the following conditions are met:

- *The investigator will obtain information through oral or written communication with the prospective subject or LAR or*
- *The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.*

HIPPA:
HIPAA does not apply if:
--no PHI is collected or

--if PHI is collected from a potential subject by an individual from a department that is not part of the HIPAA covered entity.

HIPAA does apply if the collection occurs by individuals* who work in a department that is part of the HIPAA covered entity.

In this case the collection will be covered under Health Care Operations/

These individuals are those that meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

IF YES, Will any of the questions involve health information?
Answer/Response: Yes

IF YES, will you collect HIPAA identifiers with the health information?
Answer/Response: No

IF YES, which HIPAA identifiers will be recorded?
Answer/Response:

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner?
Answer/Response:

j. Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?

For example: come to the first visit fasting, stop taking medications that may be an exclusion criteria, change diet. As this is still part of pre-screening one is not allowed to gather information that is not directly related to inclusion/exclusion criteria or other issues of suitability (e.g. is person able to come to UVa for multiple visits)

NOTE:
Only those members of the study team with a DEA# (license to prescribe drugs) are allowed to determine if a potential subject may be asked/informed to stop taking a drug which is an exclusion criteria.
It is recommended that the potential subject notify their health care provider if they plan to stop a prescription drug.

Answer/Response:
No
►**IF YES, explain in detail what you will ask them to do**.
Answer/Response:

Tips to Study Team
You must document their verbal consent in the study records.
If a subject is asked to stop taking a drug, document the date and name of the person on the study team giving the verbal order to stop medications (again- must be a person with a DEA#).

DHHS: Study team requests the use of Verbal Consent (Waiver of Documentation of Consent) for minimal risk screening procedures.

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity this is covered under Health Care Operations
If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

k. How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity consenting is covered under Health Care Operations.

If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

Describe the setting for the consent process.
If the study is of a sensitive nature and/or includes a reference to a medical condition how will you protect the privacy of the potential subject when they are approached to participate?
Who will discuss the study with the potential subject?
Where will the consenting process take place?
How will you assess subject understanding?
How much time will pass between obtaining written consent and initiation of study procedures?
See Protocol Examples: Consenting Process for examples of how to answer this question.
If recruiting minors, specify how parental /guardian consent will be obtained prior to approaching the minor.

Answer/Response:

The consenting process will take place in the Exercise and Sport Injury Lab (EASIL) in Memorial Gymnasium in a quiet and private area. Subjects will be given a consent form and be asked to read through it in its entirety and be given as much time as necessary. If there is concern that the potential subject may not be able to read, the potential subject will be asked to read the first sentence of the consent form to determine if they are

capable of reading. Depending on the response they will either be offered the opportunity to read the consent form or have the consent form read to them.

Subjects will be given the opportunity to ask questions and have all questions answered by a member of the research team prior to signing the consent form. A member of the research team will summarize the consent form and procedure verbally to ensure that the individual understands the protocol process. If the subject agrees to participate the person obtaining consent and the subject will sign the form and subjects will be given a copy of the signed consent form.

6. Will subjects sign a consent form for any part of the study?

Answer/Response:

Consent will be signed for the entire study.

7. Will the study procedures be started the same day the subject is recruited for the study?

Answer/Response:

No, but they will start the same day they sign the consent.

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

Answer/Response:

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.

Answer/Response:

8. Is there the potential to recruit a vulnerable population? (e.g. economically or educationally disadvantaged subjects, or other vulnerable subjects such as students , employees, investigator is health care provider of potential subject, pregnant women, children or prisoners?

INSTRUCTIONS: If you will be recruiting patients from the UVa Health System, you must answer this question YES as the UVa Health System cares for patients who are economically disadvantaged.

Answer/Response:

Yes

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?

Check all applicable options:

__X__ Consent will be obtained by the CRC rather than the Investigator

_X___ Subjects will be assured that their relationship with their UVA health care providers will not be affected if they decide not to participate

__X__ Subjects will be given all the time needed to make their decision, and will not be pressured for a quick decision. They will be encouraged to seek advice from friends and family before signing consent.

___X_ Employees will be reassured that their decision will not affect their job or benefits.

___X_ Students will be reassured that their decision will not affect their status as a student or their grades.

____ If minors are enrolled, parental permission will be obtained prior to explaining the study to a minor and the minor's assent will be obtained prior to initiation of study procedures.

____ all subjects, especially those who are educationally disadvantaged will be asked open ended questions to confirm that they understand the study.

___ Other Explain:

9. Do you need to perform a "dry run" of any procedure outlined in this protocol?

A "dry run" is a procedure done to validate the system used to obtain results. It requires a human "subject" however the results of the dry run are used for system validation and not for the actual research. A common example a "dry run" is the validation or qualification MRI scans required by sponsor to ensure the MRI at UVa is able to perform the study-required scans.

- **If you are doing a sponsored study that involves an MRI for research, you are encouraged to say YES to this question**
- If YES, complete and submit a Consent for a Dry Run Procedure
- A template for a Consent for Dry-Run MRI is located under FORMS on the IRB Website
- IF YES, answer the following questions.

Answer/Response:

No

9a. List the "dry run" procedure(s) that must be performed.

Answer/Response:

9b. How many "subjects" will be recruited for "dry run" procedures?

These "subjects" should NOT be counted with your total enrollment figures.

Answer/Response:

9c. Describe the recruitment procedures for those participating in the "dry run".
Answer/Response:

9d. Will those participating in the "dry run" be compensated?

IF YES, add the "dry run compensation" as a line item to the payment section of this protocol.

Answer/Response:

9e. Who will pay for the cost of the "dry run" procedure(s)?
Answer/Response:

10. Is the study regulated by the Department of Defense (DoD)?
Answer/Response:
No

If YES, do you confirm the following protections will be in place for military research participants to minimize undue influence?
Answer/Response:

- Officers are not permitted to influence the decision of their subordinates.
- Officers and senior non-commissioned officers may not be present at the time of recruitment.
- Officers and senior non-commissioned officers have a separate opportunity to participate.
- When recruitment involves a percentage of a unit, an independent ombudsman is present.

If YES, do you also confirm that the following procedures will be in place to require limitations on dual compensation?
Answer/Response:

i. Prohibit an individual from receiving pay of compensation for research during duty hours.
ii. An individual may be compensated for research if the participant is involved in the research when not on duty.
iii. Federal employees while on duty and non- federal persons may be compensated for blood draws for research up to $50 for each blood draw.
iv. Non-federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according

to local prevailing rates and the nature of the research.

11. **Non-Monetary Retention Incentives**
If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the study team will submit a description and approximate retail value of the item to the IRB.

Study Procedures- Biomedical Research

1. Where will the study procedures be done?

Check One:

____ UVA medical center facilities (In patient or outpatient)

__X__ UVA but not medical center facilities: LIST specific location Answer/Response:

Exercise and Sport Injury Lab (EASIL)

____ Other: List specific location Answer/Response:

2. If the study involves medical risk and study procedures will be done outside of the UVa Medical Center what is your plan to protect the subjects in case of a medical emergency?

_*X*___ *NA*

Check all applicable options:

_____ MD, RN, onsite during procedures

_____ Individual trained in CPR on site during procedures

_____ AED and Individual trained to use it onsite

_____ Call 911

_____ Other: Describe Answer/Response:

3. List the procedures, in bullet form, that will be done for <u>RESEARCH PURPOSES</u> as stipulated in this protocol.

INSTRUCTIONS:
Examples: blood tests, EKG, x-rays, surveys, administration of investigational drug/device, randomization to one of two approved drugs
Do NOT list those procedures which are being ordered for clinical standard of care.
If ALL procedures are being done for the research study, simply write: ALL

Answer/Response:

- Ultrasound imaging
- Nears infrared spectroscopy (NIRS) measurements
- Balance assessment

4. Do you confirm that, except for blood draws through a peripheral site, that all invasive procedures will be performed by a licensed health care provider under the supervision of an MD?

Answer/Response:

N/A

5. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study?

Answer/Response: No

IF YES, will the data/specimens be used in this study without a new consent from the original donor?

Answer/Response:

IF YES, explain how the proposed use is consistent with the use planned in this study and submit a copy of the consent form used to collect the data/specimens.

INSTRUCTIONS: If you are unable to locate the consent form, you must request a Waiver of Consent. Consult with IRB staff to determine additional sections to be added to this protocol.

Answer/Response:

6. Will any of the procedures listed in item # 3 have the potential to identify an incidental finding?

Answer/Response: No

INSTRUCTIONS: This includes ALL procedures, assessments and evaluations that are being done for RESEARCH PURPOSES that may or may not be considered investigational.
Examples: MRI/CT/PET/CXR shows possible tumor, Blood collected and analyzed using an investigational assay and results show possibility of leukemia

►IF YES, check one of the following two options and list the applicable procedures, assessments or evaluations below.

_____The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care.
Procedures, assessments, evaluations: _____

There exists the potential for the discovery of clinically significant incidental findings.

f. The PI takes full responsibility for the identification of incidental findings:
g. The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
h. If an incidental finding is serious and emergent (e.g. mass on x-ray), the study team will inform the subject and contact the subject's health care provider.
i. If applicable a follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

____This examination(s) utilizes non-standard/investigational, technique, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

Procedures, assessments, evaluations: _____

7. Do any of the procedures listed above, under question # 3, utilize any imaging procedures for RESEARCH PURPOSES?

Examples: ultrasound, CT scans/ x-rays etc.

Answer/Response:

Yes

►IF YES, check one of the following two options:

__**X**___This imaging research examination utilizes the same imaging techniques, equipment, scanning sequences that would be used, if the subject were to have the imaging performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

►If checked, answer the following:

L**ist procedures:**

Answer/Response: Ultrasound

Will the images be read by a licensed radiologist and the reading placed in the subject's medical record?

Answer/Response: No

►IF NO: The PI takes full responsibility for the identification of incidental findings:

2 The PI will have all incidental findings reviewed by a radiologist who will advise the PI regarding clinical significance.

3 The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**

4 A follow-up letter describing the finding should be provided t**o t**he subject with instructions to either show the letter to their PC or if the subject has **no** PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic.

_____This imaging research examination utilizes non-standard/investigational imaging modality, techniques, equipment, scanning sequences, etc. It is impossible to determine the significance of such images, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

L**ist procedures:**

Answer/Response:

8. Will your study involve measures used to screen or assess for depression and/or suicidality for research purposes? NO

NOTE: Answer this question YES and answer the questions below if any of the following apply:

- *The protocol has a research purpose to study suicide, suicidal ideation, depression or trauma*
- *The protocol has a research purpose to study traumatic life events that may evoke powerful emotion or induce mood changes in participants;*
- *The protocol includes **assessments** or tools (e.g. Surveys, exams, questionnaires, etc.) that can be used to screen or identify **depression (C-SSRS/BID/SCID, questions related to mood, etc.) and/or suicidal ideation** (thoughts of suicide, either active or passive), plan (the means or mechanism) or intent (the expressed desire and willingness to act on the plan).*

    - Which research staff members will be qualified and available to provide a referral for further care or intervention if the subject's responses indicate this need?
      Answer by position with study (e.g. PI, sub investigator etc. Do not include names in answer.
      Answer/Response:

    - Include specific guidelines for intervention or further assessment based on tools and rating scales used in this study. Include information regarding how soon information from a subject will be reviewed. *(e.g. Questionnaire(s) will be reviewed the same day they are administered/submitted. Based on score of xxx or response of X, subject will be assessed further by the PI for suicide risk or referred urgently to an ED, crisis center, or clinic immediately).*
      Answer/Response:

REMINDER: If your subjects will be patients at UVA Medical Center, you must adhere to **Medical Center Policy 0140 Judicial Treatment Order and 0197 Suicide Risk Assessment and Prevention.**

9. Will any data from this study be submitted to or held for inspection by the FDA?

NOTE: Publication is not equivalent to submission of data to the FDA.

Answer/Response: No

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

Answer/Response: There is no benefit to individual participants. The information from this study will help clinicians to increase their understanding of the foot and ankle function in diabetic patients for the global purpose of improving quality of life following orthopedic surgery/injury as well as help optimize patient care in regard to the rehabilitative process.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

INSTRUCTIONS: Analyze the risk-benefit ratio and justify your answer.
Analyze the risk- benefit of interventions offering potential health benefit separately from those done solely to answer a research question or generate generalizable knowledge. Clarify risk-benefit for direct benefit to individual participant versus benefit to society.

Answer/Response:

The risk to the subject who participates in this study is minimal, including fatigue, whereas the benefit to this patient population and society in general is great. Although the initial benefits to each subject are minimal, uncovering a better understanding of diabetes effects foot function will inherently aid the clinician and researcher in developing better rehabilitative processes, with the global goal of improving quality of life. Therefore, the risk-benefit ratio is acceptable.

Payment

INSTRUCTIONS:

What is the difference between compensation and reimbursement?

A reimbursement is used when the subject is paid back for travel expenses such as mileage, lodging, food while traveling. Receipts or mileage must be submitted for a reimbursement.

Compensation is "payment" for things such as time, discomfort, inconvenience.
Total possible compensation should reflect the true value of the total possible dollar amount per participant for one year involvement in the study whether it be cash, check, gift card, goods, etc. or a combination of these items.

Retention "Gifts"- gifts may be given to a subject periodically during the study to remind them they are in the study. Sponsors may provide such items as water bottles, birthday cards etc. to the subject. NOTE: Cash or gift cards are NOT allowed as retention items.

1. Are subjects being reimbursed for travel expenses ?

INSTRUCTIONS:

1. If subject will NOT submit receipts for actual expenses (e.g. hotel, food, you MUST answer this NO.
2. If subjects will have mileage/distance traveled, calculated and confirmed *via Mapquest for example, this questions should be answered YES

3. Reimbursements must be paid with Oracle Expenditure types found under the Travel Heading.
4. For instructions on how to process a reimbursement please see "Goods and Services Procurement Guide" at http://www.procurement.virginia.edu/main/. You may also call the Procurement Help Desk at 924-4212.
5. The money will not be reportable to the IRS as income, but will be withheld if the subject owes money to the state.

Answer/Response: No

►IF YES, explain rate/ amount/ upper limits of reimbursements.
Answer/Response:

►IF YES, Do you confirm you are aware of the following procedures to follow for reimbursements?

INSTRUCTIONS
- Subject will submit receipts for actual expenses (e.g. hotel, food)
- Reimbursements must be paid with Oracle Expenditure types found under the Travel Heading.
- For instructions on how to process a reimbursement see "Goods and Services Procurement Guide" at http://www.procurement.virginia.edu/main/. You may also call the Procurement Help Desk at 924-4212. The money will not be reportable to the IRS as income, but will be withheld if the subject owes money to the state.
- Reimbursements may not be done with gift cards

Answer/Response:

2. Are subjects compensated for being in this study?
Answer/Response: Yes

►IF YES, answer the following questions (2a-2d).

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?
Answer/Response: $20

2b. Explain compensation to be given.
Answer/Response: Amazon gift cards will be given to participants at the completion of the study.

2c. Is payment pro-rated?

e.g. some compensation is given even if subjects do not complete the entire study

Answer/Response: No

If No, explain why payment cannot be pro-rated.
Answer/Response: It cannot be pro-rated because it`s only one visit.

2d. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa?

INSTRUCTIONS
Examples of when to say no:

- Researcher is using their own personal funds to compensate participants.
- Compensation is coming from a UVa Foundation and therefore not subject to UVA financial policies and procedures.

Examples of when to say yes:

- Sponsor, via a grant or contract, sends money to OSP/ SOM Grants and Contracts office to cover cost of compensation to be given to subjects. Subjects are then paid via Oracle system
- UVA researcher purchases gift cards for distribution to subjects and there is NO outside sponsor.
- Sponsor purchases gift cards/ debit cards and sends to UVa for study team to distribute to the subjects.

Answer/Response: Gift cards will be provided

▶IF YES, answer the following questions [2d(i)-2d(ii)].

2d(i). How will the researcher compensate the subjects?

_____ Check issued to participant via UVA Oracle or State system

_____ Petty cash account*

*Per UVa Policy petty cash payments are limited to a maximum of $100 per payment and $599 per calendar year per individual.

__X___ Gift card/Debit Card

_____ Other type of compensation:
Specify Answer/Response:

2d(ii). Which category/ categories best describes the process of compensation?

Choose one of the following 3 options

_____ All compensation will be made via check issued to participant via UVA Oracle or State system
The preferred method

_____ Compensation will include an alternative method (petty cash, gift card, other) and tax information will be collected, securely stored, and submitted electronically to Procurement Services as required.

►If this box is checked and an alternate method will be used, justify why you are unable to issue checks through the UVa Oracle or state system.

Guidance to answer this question.
See question: When is it justifiable to provide compensation using an alternative method of payment while still collecting tax information?

Answer/Response:

IMPORTANT: If you check this box you will be required to submit the subjects' name, Social Security number, full address and amount of payment to Procurement at the end of each calendar year. The Office of the VP for Research will send you instructions on this procedure at a later date.

If the sponsor is providing the gift card/debit card and sending to UVA study team for distribution, please include the statement "SPONSOR REQUEST" under the request for justification.

___X__ Compensation will include an alternative method (petty cash, gift card, other) and tax information cannot be collected. Total possible compensation per participant for participating in the research study over one year is limited to <=$50.

INSTRUCTIONS: If the subject will receive <$50/year in this study check this option and insert the following answer to both questions below. Subjects will be compensated $50 or less per year for this protocol and subjects may hesitate to enroll in the study if it requires they share their Social Security number for such a small amount of money.

►If an alternate method will be used justify why you are unable to issue checks through the UVa Oracle or state system:

Guidance to answer this question.
See question: When is it justifiable to provide compensation using an alternative method of payment while still collecting tax information?

Answer/Response: Subjects will be compensated for $50 or less per year for this protocol and subjects may hesitate to enroll in the study if it requires, they share their social security number for such a small amount of money.

►If you are unable to collect the tax information justify why it cannot be collected.

Answer/Response: Subjects will be compensated for $50 or less per year for this protocol and subjects may hesitate to enroll in the study if it requires, they share their social security number for such a small amount of money.

Guidance to answer this question.
See question: When is it justifiable to provide compensation if the tax information cannot be collected?

Data and Safety Monitoring Plan

This study has been deemed minimal risk. Because this study poses minimal risk to the subject, **adverse events will only be collected or recorded if a causal relationship to the study intervention is suspected.** If any adverse event is considered serious and unexpected, the event must be reported to the IRB-HSR within 7 days from the time the study team receives knowledge of the event.

DELETE SECTION 1 BELOW IF THERE IS A PROTOCOL THAT ALREADY INCLUDES THESE DEFINITIONS.

1. Definitions

- **How will you define adverse events (AE)?**

Do not change this answer

An adverse event will be considered any undesirable sign, symptom or medical condition considered **related to the intervention**. Medical condition/diseases

present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

- **How will you define an unanticipated problem?**

Do not change this answer

An unanticipated problem is any issue that involves increased risk(s) to participants or others. This means issues or problems that cause the subject or others to be placed at greater risk than previously identified, even if the subject or others do not incur actual harm. For example if a subject's confidentiality is compromised resulting in serious negative social, legal or economic ramifications, an unanticipated problem would need to be reported. (e.g. serious loss of social status, loss of job, interpersonal conflict.)

1.3 What are the definitions of a protocol deviation and/or noncompliance?

Do not change this answer

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol deviations may be major or minor.

Noncompliance can be a protocol deviation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations**.** Noncompliance may be minor or sporadic, or it may be serious or continuing.

Additional Information: see the IRB-HSR website at
Protocol Deviations, Non-compliance and Protocol Exceptions

2. What risks are expected due to the intervention in this protocol?

INSTRUCTIONS:

- The risks should be consistent with those in the consent form (if applicable), although they should be written in technical terms in the protocol and in lay terminology in the consent form.
- List the most serious or most frequent risk first
- Delete last two rows if no additional risks added.
- Add additional rows to the table below if needed.

Expected Risks related to study participation	**Pick One**

There is a small risk that breaches of privacy and/or confidentiality might occur. The risk of violation of subject privacy and confidentiality is minimal due to the requirements of the privacy plan in this protocol.	Occurs rarely
• Fatigue	Occurs rarely
• Muscle Soreness	Occurs rarely

3. When will recording and reporting of unanticipated problems/adverse events begin?

__X___After subject signs consent

_____After subject begins study intervention

_____Other Specify Answer/Response:

4. When will the recording/reporting of unanticipated problems/adverse events end?

__X___Subject completes participation in the protocol

_____End of intervention

_____30 days post intervention

_____Subject completes intervention and follow up period of protocol

_____Other: Specify Answer/Response:

5. What is your plan for safety monitoring?

Do not change this answer

Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will be performed by the PI and IRB-HSR through continuation review at least annually.

6. What is your plan for reporting a Unanticipated Problem, Protocol Deviations or Data Breach?

Do not change this answer

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance (*The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.)*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form
Data Breach* of Protected Health Information	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, https://security.virginia.edu/report-information-security-incident Police: phone- (434) 924-7166

*A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

Privacy Plan

The following procedures must be followed.

- The data will be secured per the Data Security Plan of this protocol.
- Only investigators for this study and clinicians caring for the patient will have access to data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa University Data Protection Standards will be followed.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's Highly Sensitive Data Protection Standard for Individual-Use Electronic Devices or Media Additional requirements may be found in the University's Security of Network-Connected Devices Standard. If identifiable data is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- Data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Standard.
- Data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Standard .
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards (UDPS 3.0).
- Data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

If you have a question or concerns about the required security standards contact InfoSec at it-security@virginia.edu

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-data that reveals an individual's health condition and/or history of health services use.
Protected Data (PHI) a type of Highly Sensitive Data, is data combined with a HIPAA identifier
Identifiable Data under HIPAA regulations is considered to be *Highly Sensitive Data at UVa.*

A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data* at UVa. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.

Highly Sensitive Data **(Identifiable Health Info per HIPAA)**	**Moderately Sensitive Data** **(Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know.
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data **(Identifiable Health Info per HIPAA)**	**Moderately Sensitive Data** **(Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with InfoSec or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center:	
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately

Highly Sensitive Data (Identifiable Health Info per HIPAA)	Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with InfoSec or Health System Web Development Office: 434-243-6702 University Side: IT-Security@virginia.edu Health System: Web Development Center: Contract must include required security measures.	
May be stored in UVA's Qualtrics portal for Highly Sensitive Data (HSD) May NOT be stored in places like UVaBox, UVaCollab or QuestionPro May also NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.	May be stored in places like UVaBox, UVaCollab, UVA's Qualtrics portal for Moderately Sensitive Data May NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*
***The UVa HIPAA covered entity includes the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory, the Exercise Physiology Laboratory and the UVA Center for Survey Research.*

Legal/Regulatory/Ethical Considerations

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners

may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at
http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/924-2620) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the UVa Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/924-2620), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

Informed Consent

Unless waived by the IRB, subjects will be fully informed of the:

- purpose of the study,
- reasonably anticipated benefits,
- potential risks or discomfort participation in the study may entail,
- and any alternative treatments.

They will also be informed that their

- consent is voluntary and that they may withdraw their consent to participate at any time, and
- (if applicable) choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The consent documents used to obtain informed consent of the subject must be approved by the IRB prior to use. Any written materials (consent/ short form) will be provided to the potential subject in a language they can read understand. The subjects will be given sufficient time to read the consent form and have the opportunity to ask questions.. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. After this explanation and before entry into the study, consent should be appropriately recorded. Subjects will be given a copy of the signed consent/ short form.

Institutional Review Board (IRB)

No subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment.
Any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

PROTOCOL

Background

54. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under “What will be done in this protocol?”
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.

- If this is a FIVE YEAR UPDATE make sure the information throughout the protocol includes the most current information.

Answer/Response:

Foot and ankle problems are big issue that are associated with diabetic neuropathy. [1] The risk of patients with diabetic ulcer is 2.5 times higher at 5 years when compared to the patient who has diabetes without foot ulcer.[1] It has been also reported previously that up to 20 % of the people with diabetic ulcer require amputation.[2] There are number of factors associated with the diabetic peripheral neuropathy and negative impact on the diabetic foot health.

One primary association is deterioration of the soft tissue on the planter surface of the foot including the atrophy of the intrinsic foot muscles.[3] Intrinsic foot muscles have a role in shock absorption at the foot. [3] In addition, they are associated with balance, and appropriate gait mechanics.[3] Weakness of Intrinsic foot muscles can lead to increase in planter pressure which consequently may yield to the development of plantar ulceration.[3,4] Intrinsic foot muscle weakness can also result in metatarsalgia and IP joint arthritis because of increase in the planter pressure. [3,4]

Recently, Ultrasound is used to investigate the integrity of the intrinsic foot muscles.[3] Moreover, US imaging has shown to be the only reliable method that can be used to directly visualize these muscles and differentiate them from extrinsic muscle activity.[5,6] In diabetes foot literature, intrinsic foot muscles are assessed in the non-weight bearing position which is not the functional position of for the activation of intrinsic foot muscles. Assessing intrinsic foot muscles in the functional position may provide us information about activation, beyond the size of these muscles. This, in turn, may help researchers to design optimal rehabilitation interventions that can result in increase activation of these muscles in the weight-bearing that is a function position of the foot. In this study, we intend to examine the intrinsic foot muscles in the functional position. Moreover, we will also assess the changes in the plantar blood flow in these patients during short foot exercise[7] , a maneuver used to activate intrinsic foot muscles, using nears infrared spectroscopy (NIRS). NIRS is a non-invasive device that used infrared light to measure the blood flow measurement.

Objectives/Hypothesis

INSTRUCTIONS:
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

Answer/Response:

Aim 1: To assess if there is a difference in morphology (CSA and thickness measures) of foot muscles between diabetic patients and healthy control in both non-weight bearing and weight bearing positions
Hypothesis 1: We will expect to see a difference in morphology (CSA and thickness measures) of foot muscles between diabetes and health control in both non-weight bearing and weight bearing positions
Aim 2: To compare planter perfusion in the foot during the short foot exercise between the diabetic and the healthy group.
Hypothesis 2: We will expect greater perfusion in the healthy group when compared to the diabetic group

Study Design: Biomedical

1. Will controls be used?

Answer/Response:

Yes

►**IF YES, explain the kind of controls to be used.**

Answer/Response:

Yes, those without Diabetes of matched age

15. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question. (http://www.virginia.edu/vpr/irb/learningshots/Writing_protocol_June09/player.html

Answer/Response:

Case-Control design

16. Does the study involve a placebo?

Answer/Response:

No

►**IF YES, provide a justification for the use of a placebo**

Answer/Response:

Human Participants

Ages: _18-70___

Sex: _male and female __

Race: **_any___**

Subjects- see below

INSTRUCTIONS: **For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.**

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Answer/Response: 30 (15 diabetes and 15 healthy)

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

Answer/Response:
5 %, approximately 1 per group

3. **How many subjects will be enrolled at all sites?**

INSTRUCTIONS: **This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.**

Answer/Response:
16 diabetes and 16 healthy

4. How many subjects will sign a consent form under this UVa protocol?

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Answer/Response:
all

Inclusion/Exclusion Criteria

INSTRUCTIONS:

15. The inclusion and exclusion criteria should be written in bullet format.
16. *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .
17. If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
18. If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
19. The stop date must be prior to the version date of this protocol.
20. *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

Answer/Response:

Diabetic Patients:

- Either gender
- Adults up to 70 years
- Diabetes Mellitus type 1 or 2 diagnosed.
- Independent walking ability for at least 10 m
- Any plantar ulceration should be healed for at least six months
- Not having any partial or total foot amputation
- Not receiving any physical therapy intervention

Healthy:

- Either gender
- Adults up to 70 years
- No history of diabetes or any lower limb neuropathy
- Not having any partial or total foot amputation
- Not receiving any physical therapy intervention

2. List the criteria for exclusion

Answer/Response:

Diabetic Patients:

- Presence of an active plantar ulcer
- Diagnosis of neurological diseases
- Dementia or inability to give consent and consistent information
- Receiving any physiotherapy during the intervention period

Healthy:

- Presence of an active plantar ulcer
- Diagnosis of neurological diseases
- Dementia or inability to give consent and consistent information
- Receiving any physiotherapy during the intervention period

3. List any restrictions on use of other drugs or treatments.

INSTRUCTIONS: List only those drugs or treatments that are prohibited while on study, not those listed as an exclusion criteria.

Answer/Response:
No Restriction

Statistical Considerations

9. Is stratification/randomization involved?

Answer/Response:
No

►IF YES, describe the stratification/ randomization scheme.

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

Answer/Response:

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
_____ Other: Specify Answer/Response:

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints
--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

Answer/Response:

Independent samples t-tests will be done at each different time points to analyze the difference in the morphology and perfusion between the healthy and the Diabetic group. Significance level will be set at a priori $P<.05$. We will also calculate 95% CI for each measure.

3. Provide a justification for the sample size used in this protocol.

Include sample size calculations or statistical power estimation. If not applicable, please provide explanation.
Also include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response:

This is a novel project, and there is nothing in literature that has reported on the functional assessment of foot muscles in diabetic patients. We will be taking a sample of convenience for this project. We are expecting to have (N=32) subjects for this study.

4. What is your plan for primary variable analysis?

Include primary outcome(s)/predictor variable(s), statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.

Answer/Response:

Muscle morphology measures (Cross-sectional area, and muscle thickness) measures will be compared between different types of foot and ankle pathologies using independent t-test.

5. What is your plan for secondary variable analysis?

Include the following:

--Secondary outcome(s)/predictor variables, statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.
--For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response:
Perfusion measures will be compared between different types of foot and ankle pathologies using independent t-test.

6. Have you been working with a statistician in designing this protocol?

Consultation with a professional statistician is highly recommended to ensure good science of the study and facilitate the review process.

Answer/Response: No

IF YES, what is their name?
Answer/Response:

7. Will data from multiple sites be combined during analysis?
Answer/Response:

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?

Answer/Response:

IF YES, will randomization be done at each site or among sites?
Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?
Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Answer/Response:

7(d). Is there a common protocol used in all sites?

Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?

INSTRUCTIONS:

This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.
This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified. Describe and justify any control and experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

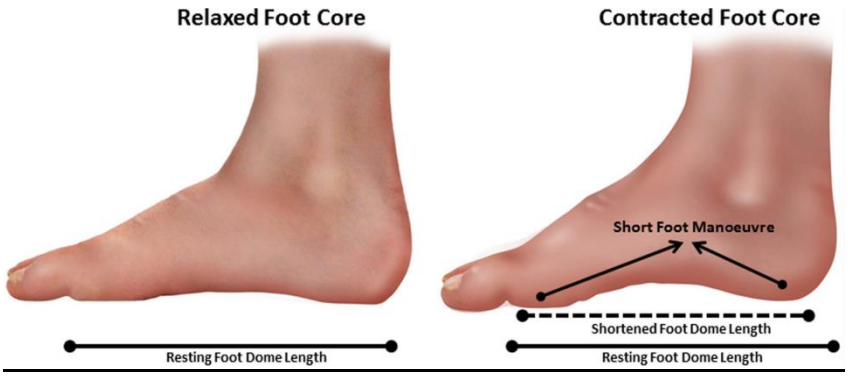
Special note for studies with waiver of consent/waiver of documentation of consent:
Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

Answer/Response:

This study will constitute of only one visit by the subjects. Subjects will report to Exercise and Sport Injury Laboratory (EASIL) for this study.
Informed consent will be obtained.

- Demographics:
  The following demographics will be collected: sex, age, height, weight, leg length, foot postural index (FPI), occupation and patient-reported outcomes (PROs) will be collected including Michigan Neuropathy Screening Instrument, Tegner activity level Scale, Tampa Scale-11, Foot and Ankle Ability Measure (FAAM) sports subscale, and the FAAM activities of daily living subscale.
- Testing Procedure:
  - Patients will come to the EASIL and rest for 10 minutes.
  - Baselines measurements will be taken
    - Ultrasound measurements of the foot muscles, NIRS measurements, balance and toe strength measurements, and Semmes Weinstein sensory test on the bottom of the foot
  - After baselines testing, half of the participants will perform short foot exercise for 15 reps * 5 sets. Short foot exercise is basically contracting the arch of the foot (Figure 1). The other half will do 5 min. of walking exercise in the mem gym.

Figure 1:



- Ultrasound measures of foot muscles and NIRS measurements will be taken.
- Participants will crossover, the participants who performed exercises first will do walking now, and the participants who walked first will do short foot exercises (15 reps * 5 sets).
- Ultrasound measures of foot muscles and NIRS measurements will be taken for the last time.
- All these steps will be performed on one limb.

The whole study duration will be around 60 to 90 minutes.

- **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
Instructions: Answer NA if this study does not involve a study treatment.

Answer/Response:

N/A

Bibliography

INSTRUCTIONS: Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

1. Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. *New England Journal of Medicine.* 2017;376(24):2367-2375.

2. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). *The journal of foot and ankle surgery.* 2006;45(5):S1-S66.

3. Bus SA, Yang QX, Wang JH, Smith MB, Wunderlich R, Cavanagh PR. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study. *Diabetes care.* 2002;25(8):1444-1450.

4. Bus SA, Maas M, Michels RP, Levi M. Role of intrinsic muscle atrophy in the etiology of claw toe deformity in diabetic neuropathy may not be as straightforward as widely believed. *Diabetes Care.* 2009;32(6):1063-1067.

5. Angin S, Crofts G, Mickle KJ, Nester CJ. Ultrasound evaluation of foot muscles and plantar fascia in pes planus. *Gait & posture.* 2014;40(1):48-52.

6. Crofts G, Angin S, Mickle KJ, Hill S, Nester C. Reliability of ultrasound for measurement of selected foot structures. *Gait & posture.* 2014;39(1):35-39.

7. Mulligan EP, Cook PG. Effect of plantar intrinsic muscle training on medial longitudinal arch morphology and dynamic function. *Manual therapy.* 2013;18(5):425-430.

Table C4-. University of Virginia IRB Approved Consent Form IRB-HSR (M1)

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a copy of this form.

Who is funding this study?

This study is funded through Curry School of Education, University of Virginia.

Key Information About This Research Study

Principal Investigator:	Susan Saliba, Ph.D, M.P.T., ATC Department of Kinesiology PO Box 400407 Charlottesville, VA, 22908 P: 434-243-4033

You are being asked to take part in a research study. You do not have to take part in this study. You should only agree to take part in this study after reading this consent form and discussing it with the study team. You may also discuss this with your family, friends, health care providers or others before you make a decision.

What problem is this study trying to solve?

This study is trying to find out if there is a difference in activation of the foot muscles between diabetics and healthy participants. We also intend to investigate in this study if there is an increase in blood circulation because of the Short Foot Exercise (SFE). SFE is a maneuver that has been shown activate foot muscles in certain patient populations. Overall, the results of this study is intended to improve foot health in diabetic patients.

You are being asked to take part in this study because either you have diabetes or you are a healthy subject without diabetes.

Why would you want to take part in this study?
You will not be helped by being in this study, but the information gained by doing this study may help others in the future.

Why would you NOT want to take part in this study?
You might not want to take part in this study because it will require about an hour of your time.

What will I have to do if I take part in this study?
Full details of all the procedures are found later in this form.
If you take part in this study you will:
Visit Exercise and Sport Injury (EASIL) lab in the department of Kinesiology at the University of Virginia for only 1 visit. The visit duration will be 60 to 90 minutes.

What will happen if you are in the study?

If you agree to be in this study, you will sign this consent form before any study related procedures take place.

STUDY PROCEDURES

- Demographics: (5 min)
  The following demographics will be collected: sex, age, height, weight, leg length, foot postural index (FPI), occupation.
  You will be asked to complete some questionnaires. The questions are about your foot and ankle health and function.
- Testing Procedure: (55 to 90 min)
  - Patients will come to the EASIL and rest for 10 minutes.
  - The following measurements will be taken:
    - We are going to assess foot muscle size, blood circulation and sensation on the bottom of the foot and balance and toe strength.
      - Muscle size will be examined using ultrasound imaging on your foot and ankle in the sitting and the standing position. Ultrasound is an imaging method that uses high-frequency sound waves to produce images of structures within your body. The ultrasound is non-invasive and is done using an ultrasound device outside your body.
      - We will assess blood flow on the bottom and top of your foot while standing using nears infrared spectroscopy (NIRS). NIRS is a non-invasive device taped to your foot to measure the amount of oxygen in your blood and blood flow.

- We will also perform sensory testing using small filaments on your foot. The small filaments are touched to the bottom of your foot to measure sensation.

- After baselines testing, half of the participants will perform a short foot exercise for 15 repetitions 5 times. The other half will do 5 min. of walking exercise in the gym.
- Ultrasound measures of foot muscles and NIRS measurements will be taken once again.
- Participants will crossover, the participants who performed exercises first will do walking now, and the participants who walked first will do short foot exercises (15 reps * 5 sets).
- Ultrasound measures of foot muscles and NIRS measurements will be taken for the last time.
- All these steps described above will be performed on one foot.

WHAT ARE YOUR RESPONSIBILITIES IN THE STUDY?
You have certain responsibilities to help ensure your safety.

These responsibilities are listed below:

- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.

How long will this study take?

Your participation in this study will require 1 visit, that will last from 60-95 minutes.

If you want to know about the results before the study is done:

The purpose of the test is NOT to diagnose any disease or abnormality you may have. Because the test is investigational there is no way for the study leader to understand if the results are "normal" or "abnormal". However, if any test results are concerning, your study leader will let you know. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you may ask for more information about the study results.

What are the risks of being in this study?

Risks and side effects related to the foot *exercise* include:

Likely

- You may experience muscle soreness after the isometric exercise.

Less Likely

- You may experience a slight discomfort in the joints of foot after the isometric exercise.

Could you be helped by being in this study?

You will not benefit from being in this study. However, the information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

The only choice is not to be in this study. If you are a patient at UVa your usual care will not be affected if you decide not to participate in this study. If you are an employee of UVa your job will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?

You will be paid up to a maximum of $20 in Amazon gift cards for finishing this study.

You will receive the gift card at the completion of study procedures during your visit to EASIL.

Will being in this study cost you any money?

All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study assessment and for any parking costs.

What if you are hurt in this study?

If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader of this study can take you out of the study. Some of the reasons for doing so may include

a) You become injured and can no longer participate in the study

b) The principal investigator closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to verbally indicate that you are no longer interested in participating in the study to a member of the study team. If you do withdraw, a note will be placed in your file indicating that you withdrew from the study.

How will your personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

Information obtained from you during this study will not be used in future research.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

Please contact the Principal Investigator listed earlier in this form to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Susan Saliba
<Human services, Curry School of Education PO BOX 400407>
Telephone:(434)243-4033

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483, Charlottesville, Virginia 22908, Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Table C-5. University of Virginia Institutional Review Board Approved Application and Protocol (M1, M2 and M3)

RESEARCH APPLICATION

Investigators Experience

INSTRUCTIONS:
Provide a brief description of the investigators experience in working with this population in the clinical and research arena.
If this study will be done in a foreign country, add their experience working within the foreign country.

Answer/Response:

PI - Jay Hertel is a Joe Gieck Professor in Sports Medicine. He is a renowned ankle researcher and has contributed to consensus and position statements in this area.
Investigator – Rachel Koldenhoven is a doctoral student in Sports Medicine in the Curry School of Education. She has 4 years of research experience in musculoskeletal injuries.
Sub-investigator - Mark Abel is a professor in the Medical School and has much experience in pediatric orthopaedic conditions affecting the musculoskeletal system. He will be serving as a faculty member on this project.
Sub-investigator – Joseph Hart is a professor in Sports Medicine and has many years of research experience related to anterior cruciate ligament reconstruction and other musculoskeletal conditions. He will be serving as a faculty mentor on this project.
Sub-investigator – Susan Saliba is a professor in Sports Medicine and has many years of research experience related musculoskeletal conditions and various treatment approaches to these conditions. She will be serving as a faculty mentor on this project.
Sub-investigators– Andrea Baellow, Stephan Bodkin, Mihyang Chang, Revay Corbett, Alexandra DeJong, Nicholas Erdman, Abbis Jaffri, and Samuel Walton are all current doctoral students in Sports Medicine in the Curry School of Education. All investigators have at least 1 year or more of related research experience in Sports Medicine.

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

55. I am not currently debarred by the US FDA from involvement in clinical research studies.
56. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
57. That if this study involves any funding or resources from an outside source or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
58. The protocol will abide by the ethical standards of The Belmont Report
59. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB

including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.

60. That no personnel will have access to subjects in this protocol or their information until they have completed the human subject research protection on-line training through CITI and the IRB-HSR has been notified.
61. That all personnel working on this protocol will follow all Policies and Procedures of:
    - the UVA Human Research Protection Program (HRPP SOPS)
    - the IRB-HSR http://www.virginia.edu/vprgs/irb/
    - the School of Medicine Clinical Trials Office: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm.
    - and any additional UVA requirements for conducting research.
62. I will ensure that all those personnel delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
63. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
64. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
65. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
66. That all subjects will give informed consent unless the requirement has been specifically waived by the IRB.
67. That unless written consent has been waived by the IRB all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
68. They will establish and maintain an open line of communication with research subjects within their responsibility.
69. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
70. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
71. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
72. That any serious deviation from the protocol will be reported promptly to the Board in writing.
73. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
74. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
75. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
76. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI leaves UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.

77. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
78. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept according to UVA Records Management policies.
79. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
80. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

IF THE IRB-HSR WILL BE THE IRB OF RECORD FOR MULTIPLE SITES IN A MULTISITE TRIAL, THE UVA PI AGREES TO CARRY OUT THE FOLLOWING RESPONSIBILITIES:

17. Ensure all UVa personnel designated as Conflict of Interest Investigators complete Reviewing IRB's financial interest disclosure requirements unless the UVa personnel will adhere to the UVa conflict of interest policies that are compliant with DHHS requirements.
18. Promptly provide the Principal Investigator at each site with:
    a. Current approved protocol and consent documents;
    b. Approved modifications, amendments or changes to research protocols; and
    c. Approval of continuing reviews and reviews of unanticipated problems;
19. Notify the Principal Investigator at each site of standards and guidelines for reporting any post approval events such as adverse events, subject injuries, unanticipated problems, and protocol violations. Collect reports from Principal Investigator at each site of any unanticipated problems, deviations, suspensions and terminations, non-compliance, subject complaints, and submit such reports to Reviewing IRB per reporting requirements.
20. Notify the Principal Investigator at each site promptly of any unanticipated problems involving risks to subjects or others as determined by the Reviewing IRB.
21. Collect required information from the Principal Investigator at each site necessary for completing continuing review submissions.
22. Notify the Principal Investigator at each site promptly about any lapses of approval. Forward to the IRB of Record any request from the Principal Investigator of a site for continuation of a specific research subject on a protocol during a lapsed period of approval.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

INSTRUCTIONS:
The Principal Investigator signature is ONLY required if this is a new protocol, a 5 year update or a modification changing the Principal Investigator.

Department Chair or Designee

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

21. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
22. That the Principal Investigator is qualified to perform this study.
23. That the protocol is scientifically relevant and sound.
24. He/she is not the Principal Investigator or a sub investigator on this protocol.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

INSTRUCTIONS:
The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
If the Department Chair fills one of these rolls on this protocol, the Department Chair's supervisor must sign here.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator.

Brief Summary/Abstract

INSTRUCTIONS:
Provide a very brief summary or abstract of this study (500 words or less). Include the purpose or hypothesis, a brief description of the experiment, and plans for data analysis. DO NOT Reference the sponsors protocol here.
If you plan to deviate from the Sponsor's protocol in any way, such as not doing certain sub-studies, include a description of those deviations in this summary.
For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no sponsors/common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/procedures/data points.

Answer/Response: Individuals with chronic ankle instability (CAI) have demonstrated altered gait patterns. Gait training may be necessary to address these alterations as protocols focusing solely on strength or balance have not been shown to impact walking gait. Biofeedback about the foot position during walking may help improve gait biomechanics. Our purpose is to determine whether a 4-week rehabilitation program that includes biofeedback has beneficial effects on self-reported function and ankle gait kinematics compared to rehabilitation alone in people with CAI. The design is a single-blinded randomized controlled trial. Participants will complete baseline self-reported function questionnaires and walking gait trials and then be randomized to complete 4- weeks of supervised rehabilitation with or without audiovisual biofeedback. Follow up emails will ask for participant information about ankle health and to complete questionnaires about their ankle for 6 months and 12 months after completing rehabilitation. Separate mixed-model ANOVAs and Tukey post-hoc tests with *a priori* significance level of $P \leq 0.05$ will be used to identify differences in self-reported function, strength, range of motion, and balance. For the kinematic and kinetic measures, group means and standard deviations for each condition will be calculated across the entire gait cycle. Then we will use statistical parametric mapping (SPM) ANOVAs to compare differences between the groups.

In addition, we will compare gait biomechanics between people with CAI and ankle sprain copers (history of only one sprain with no residual symptoms). Coper participants will be matched to CAI participants and will complete baseline self-reported function, strength, and balance measures.

Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

*The UVa HIPAA covered entity includes the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory, the Exercise Physiology Laboratory and the UVA Center for Survey Research.

10. How do you plan to <u>identify</u> potential subjects?

- To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
- If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.
- Check the methods you plan to utilize:

a.____ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).
<u>If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) please see option b below.</u>

<u>DHHS:</u> Study team requests Waiver of Consent to identify potential subjects.

<u>HIPAA:</u> Allowed under Preparatory to Research if PHI to be accessed.

<u>IMPORTANT</u>

Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

--a volunteer approved by the School of Medicine

b____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.
<u>If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) you are required to submit your request to the CDR. The CDR staff will work with the EDW to obtain the data you need.</u>

<u>DHHS:</u> Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

--a volunteer approved by the School of Medicine

The information from which you are obtaining potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

IRB# _____

If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797

l. ____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT
Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

--a volunteer approved by the School of Medicine

m. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

DHHS: NA
HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

n. __X__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: NA

o. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

IRB# of registry/ database: _____

DHHS & HIPAA: NA

p. ____ Other: Specify Answer/Response:

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Answer/Response:

11. How will potential subjects be contacted?

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods below you plan to utilize:

a. ____ Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care

providers of patients. Information will not be collected from psychotherapy notes.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- a UVa student working in the UVa HIPAA Covered Entity*
- a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
- --a volunteer approved by the School of Medicine

b.____Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

a UVa student working in the UVa HIPAA Covered Entity*

a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:

- Your name
- Who you are: physician, nurse etc. at the University of Virginia.
- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information use one of the following as an option for response.
  - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN: Your doctor,

Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.
- We obtained your information from your medical records at UVa.
- Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.

- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c.____Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.

See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
HIPAA: Allowed under Health Care Operations.

d.___X_ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

DO NOT UNCHECK THIS BOX EVEN IF YOU DO NOT INTEND TO USE THIS RECRUITMENT METHOD AT THIS TIME.
The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

i. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted

directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

When entering a classroom to recruit students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non- participating students the option of leaving the classroom, thereby alleviating pressure to participate.

DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPPA: NA

12. **Will any additional information be obtained from a potential subject during "prescreening"?**

Pre-screening for IRB purposes is the term used to describe activities PRIOR to obtaining Informed Consent and may not include any research procedures.

The activities may involve pre-screening of potential subjects over the telephone or in person is generally performed to determine their initial eligibility for, and, interest in a study and is a common strategy in the recruitment process.
Questions appropriate for pre-screening address the specific inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multiple times.
It is not appropriate at this point in the process (i.e. prior to obtaining informed consent/enrollment) to gather information that is not directly related to assessing eligibility and suitability (e.g. obtaining complete medical histories, obtaining blood specimens for lab tests).
An additional telephone script is not required, for this pre-screening process, in addition to any scripts required under Recruitment question # 2.

Answer/Response:
Yes. People will be asked screening questions via an email link to a Qualtrics Survey to see if they qualify for more in-depth screening. Those who do, will be asked to come in for consent and the remainder of the screen assessment questionnaires.

IF YES, submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.
NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

IF YES,
DHHS: study team requests a Waiver of Documentation of Consent for Pre-screening questions.

HIPPA:
HIPAA does not apply if:

--no PHI is collected or

--if PHI is collected from a potential subject by an individual from a department that is not part of the HIPAA covered entity.

HIPAA does apply if the collection occurs by individuals* who work in a department that is part of the HIPAA covered entity.

In this case the collection will be covered under Health Care Operations/

These individuals are those that meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

--a volunteer approved by the School of Medicine

IF YES, Will any of the questions involve health information?
Answer/Response:
Yes

IF YES, will you collect HIPAA identifiers with the health information?
Answer/Response:
No

IF YES, which HIPAA identifiers will be recorded?
Answer/Response: N/A

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner?
Answer/Response: N/A

13. Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?

For example: come to the first visit fasting, stop taking medications that may be an exclusion criteria, change diet. As this is still part of pre-screening one is not allowed to gather

information that is not directly related to inclusion/exclusion criteria or other issues of suitability (e.g. is person able to come to UVa for multiple visits)

NOTE:
Only those members of the study team with a DEA# (license to prescribe drugs) are allowed to determine if a potential subject may be asked/informed to stop taking a drug which is an exclusion criteria.
It is recommended that the potential subject notify their health care provider if they plan to stop a prescription drug.

Answer/Response:
No

►**IF YES, explain in detail what you will ask them to do**.

Answer/Response:
N/A

Tips to Study Team
You must document their verbal consent in the study records.
If a subject is asked to stop taking a drug, document the date and name of the person on the study team giving the verbal order to stop medications (again- must be a person with a DEA#).

DHHS: Study team requests the use of Verbal Consent (Waiver of Documentation of Consent) for minimal risk screening procedures.

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity this is covered under Health Care Operations
If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

14. How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity consenting is covered under Health Care Operations.

If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

Describe the setting for the consent process.

If the study is of a sensitive nature and/or includes a reference to a medical condition how will you protect the privacy of the potential subject when they are approached to participate?
Who will discuss the study with the potential subject?
Where will the consenting process take place?
How will you assess subject understanding?

How much time will pass between obtaining written consent and initiation of study procedures?
See Protocol Examples: Consenting Process for examples of how to answer this question.

If recruiting minors, specify how parental /guardian consent will be obtained prior to approaching the minor.

Answer/Response:
Potential participants will be given information about the study and have the informed consent available for review. The researcher who will be screening the participant will discuss the study and answer any questions they may have prior to participation. The participants will be given as much time as needed to review the documentation and make a decision prior to participating in any screening visit or data collection. We will assess subject understanding by asking if they have any questions or concerns in regards to the study. Once consented, participants can participate in the screening/baseline visit immediately or schedule for a later date based on their availability. No minors will be recruited for this study.

6. Will subjects sign a consent form for any part of the study?

Answer/Response:
Yes. All subjects will sign a consent form prior to participation.

7. Will the study procedures be started the same day the subject is recruited for the study?

Answer/Response:
Yes, if the patient is available and ready for participation. If they do not have time, they may schedule a time based on their availability to return for the baseline visit.

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

Answer/Response:
Subjects may schedule a return time if needed.

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.

Answer/Response:
Subjects may schedule a return time if needed.

8. Is there the potential to recruit a vulnerable population? (e.g. economically or educationally disadvantaged subjects, or other vulnerable subjects such as students , employees, investigator is health care provider of potential subject, pregnant women, children or prisoners?

INSTRUCTIONS: If you will be recruiting patients from the UVa Health System, you must answer this question YES as the UVa Health System cares for patients who are economically disadvantaged.

Answer/Response: Yes. We will be recruiting from the surrounding university area which could include students or employees of the university. We will not be recruiting pregnant women, children, or prisoners.

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?

Check all applicable options:

____ Consent will be obtained by the CRC rather than the Investigator

__X__ Subjects will be assured that their relationship with their UVA health care providers non-participation in the study will not be affected if they decide not to participate

__X__ Subjects will be given all the time needed to make their decision, and will not be pressured for a quick decision. They will be encouraged to seek advice from friends and family before signing consent.

__X__ Employees will be reassured that their decision will not affect their job or benefits.

___X_ Students will be reassured that their decision will not affect their status as a student or their grades.

__N/A__ If minors are enrolled, parental permission will be obtained prior to explaining the study to a minor and the minor's assent will be obtained prior to initiation of study procedures.

__X__ all subjects, especially those who are educationally disadvantaged will be asked open ended questions to confirm that they understand the study.

___ Other Explain:

9. Do you need to perform a "dry run" of any procedure outlined in this protocol?

A "dry run" is a procedure done to validate the system used to obtain results. It requires a human "subject" however the results of the dry run are used for system validation and not for the actual research. A common example a "dry run" is the validation or qualification MRI scans required by sponsor to ensure the MRI at UVa is able to perform the study-required scans.

- **If you are doing a sponsored study that involves an MRI for research, you are encouraged to say YES to this question**
- If YES, complete and submit a Consent for a Dry Run Procedure
- A template for a Consent for Dry-Run MRI is located under FORMS on the IRB Website
- IF YES, answer the following questions.

Answer/Response:

No.

9a. List the "dry run" procedure(s) that must be performed.

Answer/Response:

9b. How many "subjects" will be recruited for "dry run" procedures?

These "subjects" should NOT be counted with your total enrollment figures.

Answer/Response:

9c. Describe the recruitment procedures for those participating in the "dry run".

Answer/Response:

9d. Will those participating in the "dry run" be compensated?

IF YES, add the "dry run compensation" as a line item to the payment section of this protocol.

Answer/Response:

9e. Who will pay for the cost of the "dry run" procedure(s)?

Answer/Response:

10. Is the study regulated by the Department of Defense (DoD)?

Answer/Response:

No

If YES, do you confirm the following protections will be in place for military research participants to minimize undue influence?

Answer/Response:

- Officers are not permitted to influence the decision of their subordinates.
- Officers and senior non-commissioned officers may not be present at the

time of recruitment.

- Officers and senior non-commissioned officers have a separate opportunity to participate.
- When recruitment involves a percentage of a unit, an independent ombudsman is present.

If YES, do you also confirm that the following procedures will be in place to require limitations on dual compensation?
Answer/Response:

- Prohibit an individual from receiving pay of compensation for research during duty hours.
- An individual may be compensated for research if the participant is involved in the research when not on duty.
- Federal employees while on duty and non- federal persons may be compensated for blood draws for research up to $50 for each blood draw.
- Non-federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

11. **Non-Monetary Retention Incentives**
If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the study team will submit a description and approximate retail value of the item to the IRB.

Study Procedures- Biomedical Research

1. Where will the study procedures be done?

Check One:

____ UVA medical center facilities (In patient or outpatient)
__X__ UVA but not medical center facilities: LIST specific location Answer/Response:
Memorial Gymnasium
____ Other: List specific location Answer/Response:

2. If the study involves medical risk and study procedures will be done outside of the UVa Medical Center what is your plan to protect the subjects in case of a medical emergency?

__*X*__ *NA*

Check all applicable options:

_____ MD, RN, onsite during procedures
_____ Individual trained in CPR on site during procedures

_____ AED and Individual trained to use it onsite
_____ Call 911
_____ Other: Describe Answer/Response:

3. List the procedures, in bullet form, that will be done for RESEARCH PURPOSES as stipulated in this protocol.

INSTRUCTIONS:
Examples: blood tests, EKG, x-rays, surveys, administration of investigational drug/device, randomization to one of two approved drugs
Do NOT list those procedures which are being ordered for clinical standard of care.
If ALL procedures are being done for the research study, simply write: ALL

Answer/Response:
All of the project will be done for research purposes.

4. Do you confirm that, except for blood draws through a peripheral site, that all invasive procedures will be performed by a licensed health care provider under the supervision of an MD?
Answer/Response:
N/A

5. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study?
Answer/Response:
No.

IF YES, will the data/specimens be used in this study without a new consent from the original donor?
Answer/Response:

IF YES, explain how the proposed use is consistent with the use planned in this study and submit a copy of the consent form used to collect the data/specimens.

INSTRUCTIONS: If you are unable to locate the consent form, you must request a Waiver of Consent. Consult with IRB staff to determine additional sections to be added to this protocol.

Answer/Response:

6. Will any of the procedures listed in item # 3 have the potential to identify an incidental finding? This includes ALL procedures, assessments and evaluations that are being done for RESEARCH PURPOSES that may or may not be considered investigational.

Examples: MRI/CT/PET/CXR shows possible tumor, Blood collected and analyzed using an investigational assay, Blood tests show possibility of leukemia, Surveys which reveal depression/ suicidal tendencies.

Answer/Response:
No.

►IF YES, check one of the following two options:

_____The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. **There exists the potential for the discovery of clinically significant incidental findings.**

- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- If an incidental finding is serious and emergent (e.g. subject answers questionnaires implying they may be suicidal/mass on x-ray), the study team will inform the subject and contact the subject's health care provider.
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

____This examination(s) utilizes non-standard/investigational, technique, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

7. Do any of the procedures listed above, under question # 3, utilize any imaging procedures for <u>RESEARCH PURPOSES</u>?

Examples: ultrasound, CT scans/ x-rays etc.

Answer/Response: Yes. Ultrasound images of the foot muscles.

IF YES, list procedures:
Answer/Response:

►IF YES, check one of the following two options:

___**x**__This imaging research examination utilizes the same imaging techniques, equipment, scanning sequences that would be used if the subject were to have the imaging performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

►If checked, answer the following:

Will the images be read by a licensed radiologist and the reading placed in the subject's medical record?

Answer/Response: No. Ultrasound imaging for foot muscles does not require a licensed radiologist to read them. We measure the images for research comparisons only.

►IF NO: The PI takes full responsibility for the identification of incidental findings:

- The PI will have all incidental findings reviewed by a radiologist who will advise the PI regarding clinical significance.
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided t**o t**he subject with instructions to either show the letter to their PC or if the subject has **no** PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic.

___X__ This imaging research examination utilizes non-standard/investigational imaging modality, techniques, equipment, scanning sequences, etc. It is impossible to determine the significance of such images, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

8. Will your study involve measures used to screen or assess for depression and/or suicidality for research purposes? No

NOTE: Answer this question YES if any of the following apply:

4) *The protocol has a research purpose to study suicide, suicidal ideation, depression or trauma*
5) *The protocol has a research purpose to study traumatic life events that may evoke powerful emotion or induce mood changes in participants;*
6) *The protocol includes **assessments** or tools (e.g. Surveys, exams, questionnaires, etc.) that can be used to screen or identify **depression (C-SSRS/BID/SCID, questions related to mood, etc.) and/or suicidal ideation** (thoughts of suicide, either active or passive), plan (the means or mechanism) or intent (the expressed desire and willingness to act on the plan).*

j. Which research staff members will be available to provide appropriate referral for further care or intervention if the study tools indicate this need?
Answer by position with study (e.g. PI, sub investigator etc. Do not include names in answer.
Answer/Response:

k. Include specific guidelines for intervention or further assessment based on tools and rating scales used in this study (i.e. based on score of xxx or response of X, subject will be assessed further by the PI for suicide risk or referred urgently to an ED, crisis center, or clinic immediately).
Answer/Response:

l. Describe a plan to link participants to psychological help if needed and include written materials listing those resources as an attachment to the protocol. State how imminent risk of harm will be handled. (i.e. may include a list of local psychiatry/psychotherapy providers at UVA)
Answer/Response:

m. If your subjects will be patients at UVA Medical Center, confirm you plan to adhere to **Medical Center Policy 0140 Judicial Treatment Order and 0197 Suicide Risk Assessment and Prevention.**
Answer/Response:

n. Will subjects, who discontinue or are withdrawn secondary to suicidal ideations/depression prior to study completion, be asked to come to the site for an early withdrawal visit as soon as possible?
Answer/Response:

If No, provide outline of plan for follow-up or indicate if follow up is not required.

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

Answer/Response:

The benefits of using impairment based rehabilitation have been shown previously to:

1. Improve self-reported function
2. Increase range of motion at the ankle joint
3. Improve balance
4. Increase ankle strength

The CAI participants may experience all of these improvements as a benefit for participating in this study. Additionally, society may benefit if the gait training protocol shows to improve gait mechanics. This information will benefit other researchers as well as clinicians who treat individuals with CAI.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

INSTRUCTIONS: Analyze the risk-benefit ratio and justify your answer.
Analyze the risk- benefit of interventions offering potential health benefit separately from those done solely to answer a research question or generate generalizable knowledge. Clarify risk-benefit for direct benefit to individual participant versus benefit to society.

Answer/Response: Yes. Risks are minimal and there is a potential for individual and societal benefit.

Payment

INSTRUCTIONS:

What is the difference between compensation and reimbursement?

A reimbursement is used when the subject is paid back for travel expenses such as mileage, lodging, food while traveling. Receipts or mileage must be submitted for a reimbursement.

Compensation is "payment" for things such as time, discomfort, inconvenience.
Total possible compensation should reflect the true value of the total possible dollar amount per participant for one year involvement in the study whether it be cash, check, gift card, goods, etc. or a combination of these items.

Retention "Gifts"- gifts may be given to a subject periodically during the study to remind them they are in the study. Sponsors may provide such items as water bottles, birthday cards etc. to the subject. NOTE: Cash or gift cards are NOT allowed as retention items.

1. Are subjects being reimbursed for travel expenses ?

INSTRUCTIONS:

5 If subject will NOT submit receipts for actual expenses (e.g. hotel, food, you MUST answer this NO.
6 If subjects will have mileage/distance traveled, calculated and confirmed *via Mapquest for example, this questions should be answered YES
7 Reimbursements must be paid with Oracle Expenditure types found under the Travel Heading.
8 For instructions on how to process a reimbursement please see "Goods and Services Procurement Guide" at http://www.procurement.virginia.edu/main/. You may also call the Procurement Help Desk at 924-4212.
9 The money will not be reportable to the IRS as income, but will be withheld if the subject owes money to the state.

Answer/Response: No

►IF YES, explain rate/ amount/ upper limits of reimbursements.
Answer/Response:

►IF YES, Do you confirm you are aware of the following procedures to follow for reimbursements?

INSTRUCTIONS

- Subject will submit receipts for actual expenses (e.g. hotel, food)
- Reimbursements must be paid with Oracle Expenditure types found under the Travel Heading.

- For instructions on how to process a reimbursement see "Goods and Services Procurement Guide" at http://www.procurement.virginia.edu/main/. You may also call the Procurement Help Desk at 924-4212. The money will not be reportable to the IRS as income, but will be withheld if the subject owes money to the state.
- Reimbursements may not be done with gift cards

Answer/Response:

2. Are subjects compensated for being in this study?

Answer/Response: Yes

►IF YES, answer the following questions (2a-2d).

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?

Answer/Response: CAI subjects- $100. Coper subjects - $20.

2b. Explain compensation to be given.

Answer/Response: CAI participants who complete all study visits will receive $100 compensation for their time. $30 will be given at the initial visit due to the increased time commitment during the enrollment. $70 will be given after the subject completes the study.

Coper participants who complete the second study visit will receive $20 as compensation for their time.

2c. Is payment pro-rated?

e.g. some compensation is given even if subjects do not complete the entire study

Answer/Response:

CAI subjects- Yes

Coper subjects - No

If No, explain why payment cannot be pro-rated.

Answer/Response: The initial visit for coper subjects lasts about 10 minutes or less. They can participate on the same day if they choose. They will be compensated for their increased time requirement associated with the second visit which lasts about an hour. Visit 1 and 2 are about 1 week apart (if needed).

2d. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa?

INSTRUCTIONS

Examples of when to say no:

- Researcher is using their own personal funds to compensate participants.

- Compensation is coming from a UVa Foundation and therefore not subject to UVA financial policies and procedures.

Examples of when to say yes:

6. Sponsor, via a grant or contract, sends money to OSP/ SOM Grants and Contracts office to cover cost of compensation to be given to subjects. Subjects are then paid via Oracle system
7. UVA researcher purchases gift cards for distribution to subjects and there is NO outside sponsor.
8. Sponsor purchases gift cards/ debit cards and sends to UVa for study team to distribute to the subjects.

Answer/Response: Yes.

►IF YES, answer the following questions [2d(i)-2d(ii)].

2d(i). How will the researcher compensate the subjects?

_X____ Check issued to participant via UVA Oracle or State system

_____ Petty cash account*

*Per UVa Policy petty cash payments are limited to a maximum of $100 per payment and $599 per calendar year per individual.

_____ Gift card/Debit Card

_____ Other type of compensation:
Specify Answer/Response:

2d(ii). Which category/ categories best describes the process of compensation?

Choose one of the following 3 options

___X__ All compensation will be made via check issued to participant via UVA Oracle or State system
The preferred method

_____ Compensation will include an alternative method (petty cash, gift card, other) and tax information will be collected, securely stored, and submitted electronically to Procurement Services as required.

►If this box is checked and an alternate method will be used, justify why you are unable to issue checks through the UVa Oracle or state system.

Guidance to answer this question.

See question: When is it justifiable to provide compensation using an alternative method of payment while still collecting tax information?

Answer/Response:

IMPORTANT: If you check this box you will be required to submit the subjects' name, Social Security number, full address and amount of payment to Procurement at the end of each calendar year. The Office of the VP for Research will send you instructions on this procedure at a later date.

If the sponsor is providing the gift card/debit card and sending to UVA study team for distribution, please include the statement "SPONSOR REQUEST" under the request for justification.

_____ Compensation will include an alternative method (petty cash, gift card, other) and tax information cannot be collected. Total possible compensation per participant for participating in the research study over one year is limited to <=$50.

INSTRUCTIONS: If the subject will receive <$50/year in this study check this option and insert the following answer to both questions below. Subjects will be compensated $50 or less per year for this protocol and subjects may hesitate to enroll in the study if it requires they share their Social Security number for such a small amount of money.

►If an alternate method will be used justify why you are unable to issue checks through the UVa Oracle or state system:

Guidance to answer this question.
See question: When is it justifiable to provide compensation using an alternative method of payment while still collecting tax information?

Answer/Response:

►If you are unable to collect the tax information justify why it cannot be collected.

Answer/Response:

Guidance to answer this question.
See question: When is it justifiable to provide compensation if the tax information cannot be collected?

Data and Safety Monitoring Plan

This study has been deemed minimal risk. Because this study poses minimal risk to the subject, **adverse events will only be collected or recorded if a causal relationship to the study intervention is suspected.** If any adverse event is considered serious and unexpected, the event must be reported to the IRB-HSR within 7 days from the time the study team receives knowledge of the event.

1. Definitions

- **How will you define adverse events (AE)?**

Do not change this answer

An adverse event will be considered any undesirable sign, symptom or medical condition considered **related to the intervention**. Medical condition/diseases present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

- **How will you define an unanticipated problem?**

Do not change this answer

An unanticipated problem is any issue that involves increased risk(s) to participants or others. This means issues or problems that cause the subject or others to be placed at greater risk than previously identified, even if the subject or others do not incur actual harm. For example if a subject's confidentiality is compromised resulting in serious negative social, legal or economic ramifications, an unanticipated problem would need to be reported. (e.g. serious loss of social status, loss of job, interpersonal conflict.)

1.3 What are the definitions of a protocol deviation and/or noncompliance?

Do not change this answer

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol deviations may be major or minor.

Noncompliance can be a protocol deviation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations**.** Noncompliance may be minor or sporadic, or it may be serious or continuing.

Additional Information: see the IRB-HSR website at
Protocol Deviations, Non-compliance and Protocol Exceptions

2. What risks are expected due to the intervention in this protocol?

INSTRUCTIONS:

- The risks should be consistent with those in the consent form (if applicable), although they should be written in technical terms in the protocol and in lay terminology in the consent form.
- List the most serious or most frequent risk first
- Delete last two rows if no additional risks added.
- Add additional rows to the table below if needed.

Expected Risks related to study participation	**Pick One**
There is a small risk that breaches of privacy and/or confidentiality might occur. The risk of violation of subject privacy and confidentiality is minimal due to the requirements of the privacy plan in this protocol.	Occurs rarely
▪ Tripping or falling during: walking or jogging on treadmill, or balance exercises	Occurs rarely
▪ Mild muscle soreness from exercise or rehabilitation	Occurs frequently
▪ Ankle sprain due to participation	Occurs rarely

There is a minimal risk of a subject falling while completing the balancing tasks or walking on the treadmill. An investigator will be close enough during the balance tasks to stop a person from falling if they lose their balance. Subjects will be instructed to put their opposite leg down and grasp a stable surface if they feel that they may lose their balance. There is a railing to grab on to on the treadmill if they feel uncomfortable. The speed can be adjusted or the treadmill can be immediately stopped if

needed. During all tasks, a certified Athletic Trainer or Physical Therapist will be present. All exercises during the rehabilitation sessions are considered usual care and will be monitored by a Certified Athletic Trainer or Physical Therapist who is an expert at rehabilitation.

3. When will recording and reporting of unanticipated problems/adverse events begin?

_____After subject signs consent

__X___After subject begins study intervention

_____Other Specify Answer/Response:

4. When will the recording/reporting of unanticipated problems/adverse events end?

_____Subject completes participation in the protocol

_____End of intervention

_____30 days post intervention

___X__Subject completes intervention and follow up period of protocol

_____Other: Specify Answer/Response:

5. What is your plan for safety monitoring?

Do not change this answer

Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will be performed by the PI and IRB-HSR through continuation review at least annually.

6. What is your plan for reporting a Unanticipated Problem, Protocol Deviations or Data Breach?

Do not change this answer

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance (*The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.)*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form
Data Breach* of Protected Health Information	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Police: phone- (434) 924-7166

*A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

Privacy Plan

The following procedures must be followed.

- The data will be secured per the Data Security Plan of this protocol.
- Only investigators for this study and clinicians caring for the patient will have access to data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa University Data Protection Standards will be followed.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's Highly Sensitive Data Protection Standard for Individual-Use Electronic Devices or Media Additional requirements may be found in the University's Security of Network-Connected Devices Standard. If identifiable data is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.

- Data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Standard.
- Data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Standard .
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards (UDPS 3.0).
- Data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

If you have a question or concerns about the required security standards contact InfoSec at *it-security@virginia.edu*

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-data that reveals an individual's health condition and/or history of health services use.
Protected Data (PHI) a type of Highly Sensitive Data, is data combined with a HIPAA identifier
Identifiable Data under HIPAA regulations is considered to be *Highly Sensitive Data at UVa.*

A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data* at UVa. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.

Highly Sensitive Data **(Identifiable Health Info per HIPAA)**	**Moderately Sensitive Data** **(Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know.
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data **(Identifiable Health Info per HIPAA)**	**Moderately Sensitive Data** **(Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with InfoSec or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center:	
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately

Highly Sensitive Data (Identifiable Health Info per HIPAA)	Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with InfoSec or Health System Web Development Office: 434-243-6702 University Side: IT-Security@virginia.edu Health System: Web Development Center: Contract must include required security measures.	
May be stored in UVA's Qualtrics portal for Highly Sensitive Data (HSD) May NOT be stored in places like UVaBox, UVaCollab or QuestionPro May also NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.	May be stored in places like UVaBox, UVaCollab, UVA's Qualtrics portal for Moderately Sensitive Data May NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*
***The UVa HIPAA covered entity includes the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory, the Exercise Physiology Laboratory and the UVA Center for Survey Research.*

Legal/Regulatory/Ethical Considerations

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners

may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at
http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/924-2620) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the UVa Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/924-2620), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

Informed Consent

Unless waived by the IRB, subjects will be fully informed of the:

- purpose of the study,
- reasonably anticipated benefits,
- potential risks or discomfort participation in the study may entail,
- and any alternative treatments.

They will also be informed that their

- consent is voluntary and that they may withdraw their consent to participate at any time, and
- (if applicable) choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The consent documents used to obtain informed consent of the subject must be approved by the IRB prior to use. Any written materials (consent/ short form) will be provided to the potential subject in a language they can read understand. The subjects will be given sufficient time to read the consent form and have the opportunity to ask questions.. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. After this explanation and before entry into the study, consent should be appropriately recorded. Subjects will be given a copy of the signed consent/ short form.

Institutional Review Board (IRB)

No subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment.
Any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

PROTOCOL

Background

81. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under “What will be done in this protocol?”
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.

- If this is a FIVE YEAR UPDATE make sure the information throughout the protocol includes the most current information.

Answer/Response:

Lateral ankle sprains are a common musculoskeletal injury in athletic populations as well as the general public. Following an initial lateral ankle sprain (LAS), many individuals do not seek care from a medical professional. Lack of care could contribute to the decreased neuromuscular function, poor postural control, and altered gait patterns seen in individuals with a history of LAS.[1,3] Lack of treatment may also result in long-term consequences such as decreased physical activity across the lifespan, decreased quality of life, and an earlier onset of ankle osteoarthritis. Following an initial LAS, 40% of individuals develop chronic ankle instability (CAI).[5] This condition involves feelings of instability or "giving way, decreased self-reported function, and recurrent sprains. Deficits in individuals with CAI have been linked to range of motion, sensorimotor control, proprioception, postural control, and strength.[9] Research studies commonly target only one area in their rehabilitation protocols. Focusing treatment in only one of the areas of where deficits lie may not actually improve the patient's condition overall. Impairment-based rehabilitation uses an "asses, treat, re-assess" approach to target deficits and has previously shown to improve patient reported outcomes associated with CAI.[7,8] ***Thus, taking a global treatment approach using impairment-based rehabilitation to intervene where deficits are observed is essential.*** During walking gait, CAI patients demonstrate alterations in neuromuscular control, plantar pressure, kinematics, and spatial-temporal measures. Over time this may represent a larger problem as walking is the primary form of locomotion and is a common daily activity.

During walking, individuals with CAI may be at risk for subsequent ankle sprains due to position of the foot and ankle during terminal swing and at initial contact (IC) leading into the loading response.[1] Several factors may contribute to the compromised foot position during gait including altered distal and proximal muscle function, laxity of the lateral ankle ligaments, and decreased proprioception.[10] ***Individuals with CAI have been shown to be 6-7º more inverted prior to IC during walking.***[3] ***When the ankle is inverted during the swing phase, it is in an open packed position which may leave the joint susceptible to inversion ankle injuries.*** This inverted foot position may also translate to the more lateral pressures under the foot in those with CAI during gait.[10] ***Gait retraining has been suggested as a way to address ankle alterations with hopes to reduce the risks of recurrent ankle sprains.***[4,10,14]

Individuals take approximately 1,000 steps per limb per mile during walking. Over the course of several miles the total number of steps taken increases rapidly. As walking is a relatively simple task, it may be helpful to address deficits in this area for individuals with CAI. Traditionally, gait deficits have been targeted with strength or balance training but these interventions have not been successful at correcting gait mechanics.[11] Likewise, Davis and Futrell note that ***strength training without neuromuscular reeducation rarely translates to changes in movement patterns***.[2]

Weinstein previously defined motor learning as "a set of internal processes associated with practice or experience leading to a relatively permanent change in the capability for responding.[13] These processes are thought to be "complex central nervous system phenomena whereby sensory and motor information is organized and integrated." More clinically applicable interventions have also used simple forms of feedback such as holding a mirror in front of a treadmill or using audio cues. ***It has become apparent that in order to change gait mechanics, we need to perform specific gait training.***

With the advancements in technology, it is now possible to provide real-time visual feedback to participants through computer monitors or projector screens that reflect the motion of the subject. A study by Noehren et al.[12] looked at the effects of real-time gait retraining on hip kinematics in patients with patellofemoral pain and found that pain and function in participants were improved following gait retraining. The participants completed 8 sessions over 2 weeks and walked on a treadmill while their hip adduction angle of the involved limb was displayed on a monitor throughout the stance phase. They were given instruction to keep their superimposed hip angle within the shaded area (indicating $\pm$1SD of mean of healthy individuals). They used intermittent feedback which has been shown to have better long-term effects than subjects who receive continuous immediate feedback.[12] During the first 4 sessions participants received 100% continuous immediate feedback and then had faded feedback for the remaining sessions (Figure 2).[12] Runners were able to decrease their hip adduction, internal rotation, and contralateral pelvic drop following the retraining and were able to maintain changes at the 1-month follow up visit.[12]

Gait training with the use of feedback has not been extensively studied in individuals with CAI. Only one published study has used audio cues to provide feedback during walking gait.[6] Auditory biofeedback devices were worn in the shoes to alert participants when too much force was placed on the sensor which was placed under the lateral aspect of the foot while surface electromyography and plantar pressure were simultaneously recorded. Participants were instructed to walk in a way that would not trigger the audible cue. When walking in the auditory feedback condition, the participants demonstrated large and significant decreases in peak pressure and pressure time integral in the lateral midfoot and forefoot and increases in the hallux.[6] Donovan et al. [6] speculated that this shift in pressure may be due increased amplitudes of the peroneus longus and medial gastrocnemius muscles.

For individuals with CAI, it may be beneficial to provide visual feedback in addition to impairment based rehabilitation to teach safer ankle positioning around IC. When the foot contacts the ground in an increasingly inverted position, an ankle sprain could potentially occur. Therefore, addressing the position of the ankle at IC could be beneficial in adapting less risky motor patterns ultimately reducing the risk of subsequent ankle sprains.

Objectives/Hypothesis

INSTRUCTIONS:

If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

Answer/Response:

Specific Aim #1: To assess differences in walking gait biomechanics between individuals with CAI and lateral ankle sprain copers at preferred, fast, and standardized walking speeds.

Hypothesis#1: Individuals with CAI will have more inverted foot position throughout the gait cycle. Inversion changes will be greater at faster walking speeds.

Specific Aim#2: To assess if impairment-based rehabilitation with visual feedback gait training is more effective than rehabilitation without gait training at improving the ankle inversion angle at IC during walking in CAI patients.

Hypothesis#2: Impairment-based rehabilitation utilizing visual biofeedback gait training will lead to a more everted rearfoot angle at IC compared to rehabilitation without gait training in CAI patients.

Specific Aim#3: To assess if impairment-based rehabilitation with visual feedback gait training is more effective than rehabilitation without gait training at improving patient-reported outcomes in CAI patients.

Hypothesis#3: Impairment-based rehabilitation utilizing visual biofeedback gait training will lead to greater improvements in patient-reported outcomes compared to rehabilitation without gait training in CAI patients.

Specific Aim #4: To assess if impairment-based rehabilitation with visual feedback gait training is more effective than rehabilitation without gait training for intrinsic foot muscle strength, cross section (CSA), and foot morphology in CAI patients.

Hypothesis#4: Impairment-based rehabilitation utilizing visual biofeedback gait training will lead to greater improvements in strength, CSA and thickness measures of foot intrinsic muscles compared to rehabilitation without gait training in CAI patients.

Specific Aim #5: To assess if impairment-based rehabilitation with visual feedback gait training is more effective than rehabilitation without gait training at maintaining improvements at 6 and 12 months after study completion.

Hypothesis#5: Impairment-based rehabilitation utilizing visual biofeedback gait training will lead to greater improvements in patient-reported outcomes compared to rehabilitation without gait training in CAI patients at the 6 and 12 month follow up (via email).

Specific Aim #6: To assess if impairment-based rehabilitation with visual feedback gait training affects gluteal muscle activation during standardized, self-selected, and fast walking gait for gluteus medius and maximus activity ratios and preferential activation ratios through ultrasound imaging.

Hypothesis #6: Impairment-based rehabilitation with visual feedback during gait training will lead to increased gluteus maximus and medius activity ratios, and increased preferential activation of the gluteus medius muscle during stance phases of gait compared to rehabilitation without gait training in CAI patients, and will present more similarly to the coper group.

Study Design: Biomedical

1. Will controls be used?

Answer/Response:

Yes

►**IF YES, explain the kind of controls to be used.**

Answer/Response:

Lateral ankle sprain copers (history of 1 sprain) will serve as a control for the baseline visit.

For aims 2-4, a control group of CAI participants will be used

23. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question. (http://www.virginia.edu/vpr/irb/learningshots/Writing_protocol_June09/player.html

Answer/Response:

Aim 1: descriptive laboratory

Aims 2-4: single blinded randomized controlled trial

24. Does the study involve a placebo?

Answer/Response:

No

►**IF YES, provide a justification for the use of a placebo**

Answer/Response:

Human Participants

Ages: __18-30__

Sex: _Any___

Race: **_Any___**

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Answer/Response: 80
Aim 1: 20 total
Aims 2-4: 60 total

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

Answer/Response:
Up to 15% attrition rate has been accounted for in the sample size calculation of all aims. Screen failure/dropouts/withdrawal rates are not expected to be high, but we estimate for up to 20 total.

3. **How many subjects will be enrolled at all sites?**

INSTRUCTIONS: This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.

Answer/Response: **100 total**

Aim 1: 20 total
Aims 2-4: 60 total
Dropouts/withdrawals/screen fail: 20

4. How many subjects will sign a consent form under this UVa protocol?

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Answer/Response:
Up to 100

Inclusion/Exclusion Criteria

INSTRUCTIONS:

25. The inclusion and exclusion criteria should be written in bullet format.
26. *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .
27. If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
28. If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
29. The stop date must be prior to the version date of this protocol.
30. *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

Answer/Response:

Coper

1) ≥1 Ankle Sprain (>12 months prior)
2) Physically active (>1.5 hr/week)
3) Either
   - ➢ Scores ≤ 10 on Identification of Functional Ankle Instability (IdFAI)

   OR
   - ➢ (a) Answers "no" to question "Do you frequently roll your ankle or feel like it gives way?" AND (b) Answers "never" or "Once a year" for the following questions: "During activities of daily life how often does your ankle feel unstable?", "During sport or recreational activity how often does your ankle feel unstable?"
4) 99 Foot and Ankle Ability Measure (FAAM) Activities of Daily Living (ADL)
5) 97 FAAM Sport

CAI

1) ≥1 Ankle Sprain (>12 months prior)
2) Physically active (>1.5 hr/week)
3) 10 on Identification of Functional Ankle Instability (IdFAI)
4) ≤ 90 Foot and Ankle Ability Measure (FAAM) Activities of Daily Living (ADL)

5) ≤ 85 FAAM Sport

2. List the criteria for exclusion

Answer/Response:

Coper & CAI

1) -Hx of LE fracture
2) -Hx of LE surgery
3) -Hx of ankle sprain within last 6 weeks
4) -Participating in physical therapy for ankle
5) -Multiple Sclerosis
6) -Marfan's Syndrome
7) -Lumbosacral Radiculopathy
8) -Ehlers-Danlos Syndrome
9) -Diabetes Mellitus

-Pregnant (self-reported)

-Unable to provide informed consent

3. List any restrictions on use of other drugs or treatments.

Answer/Response: none

Statistical Considerations

15. Is stratification/randomization involved?

Answer/Response:

Yes

►**IF YES, describe the stratification/ randomization scheme.**

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

Answer/Response:
Participants will be randomly assigned to either the control or experimental group by random number generator after baseline testing has been completed via sealed envelope. The randomization will be completed following the baseline testing. The investigator who supervises the rehabilitation program will be blinded to group assignment. Only a third party disinterested individual will complete the randomization and have access to the randomization scheme.

►**IF YES, who will generate the randomization scheme?**

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
__X___ Other*:* Specify Answer/Response: A UVA faculty member will generate the randomization scheme prior to any participant enrollments. A disinterested third party member will have access to the scheme and reveal to the clinician performing the intervention part of the study.

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints
--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

Answer/Response:
Aims 1 & 2: For the dependent variables degrees of inversion-eversion and dorsiflexion-plantar flexion motion during gait, group means will be calculated across all 100 points of the gait cycle. Statistical parametric mapping (SPM) repeated measures ANOVAs will be used to compare group differences and post-hoc 1-dimentional SPM t-tests will be used when $p<0.05$. For Aim 1,

a 2x3 (group by speed) SPM ANOVA will be used. For aim 2, a 2x2 (group by time) SPM ANOVA will be used.

Aims 3-5: For primary dependent variables (FAAM-ADL and Sport measures, intrinsic foot strength, CSA, and foot morphology) and secondary dependent variables (ankle ROM, strength, and balance) a 2x2 mixed model ANOVA will be conducted. The between factor will be group (control and experimental) and the within factor with repeated measures will be time (pre, post). Tukey's post hoc tests will be used to identify specific significant differences in the presence of significant interactions or main effects. For secondary dependent variables (strength and balance) a 2x1 mixed model ANOVA will be conducted. The between factor will be group (CAI patients and Coper participants) and the within factor with repeated measures will be time (baseline). Tukey's post hoc tests will be used to identify specific significant differences in the presence of significant interactions or main effects. The level of significance will be set a priori at $P \leq 0.05$ for all analyses. Cohen's d effect size and associated 95% CIs will also be calculated. Effect sizes will be interpreted as 0.80 was large, 0.50 to 0.79 as moderate, 0.49 to 0.20 as small and <0.20 as trivial. Data will be analyzed using Statistical Package for Social Sciences (SPSS) Version 20.0 (SPSS, Inc, Chicago, IL).

3. Provide a justification for the sample size used in this protocol.

Include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response:

Aim 1:
An a priori sample size estimate was performed based on previously published data[4] estimating a group difference of 2º for ankle inversion/eversion at toe-off between CAI and coper participants during walking. The variability was approximately 2º. To find statistically significant differences at an alpha level (Type I error) of 0.05 and power (1−β) of 0.8, with an 15% of data lost due to attrition, we will collect up to 20 subjects per group. Note that 20 CAI participants from aims 2-4 will be matched to the copers.

Aims 2-5:
An a priori sample size estimate was performed based on previously published data[3] estimating a group difference of 3.5º for ankle inversion/eversion at IC between control and functional ankle instability participants during walking. Assuming a variability of approximately 4.6º, we estimated that 25 subjects per group would be needed to find statistically significant differences at an alpha level (Type I error) of 0.05 and power (1−β) of 0.8. We estimate up to 15% of data will be lost due to attrition and will collect up to 30 subjects per group. Therefore, we will enroll up to 60 participants in this study.

4. What is your plan for primary variable analysis?

Include a sketch of the analysis to assess primary study objectives.

Answer/Response:
We will do SPM ANOVAs to determine any significant differences in gait biomechanics.

We will do an analysis of variance to determine any significant differences in self-reported function measures between the control and experimental group.

5. What is your plan for secondary variable analysis?

Include the following: --A sketch of the analysis to assess secondary study objectives. --For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response:
We will do an analysis of variance to determine any significant differences in strength, ROM, and balance measures between the control and experimental group.

6. Have you been working with a statistician in designing this protocol?
Answer/Response:
No

IF YES, what is their name?
Answer/Response:

7. Will data from multiple sites be combined during analysis?
Answer/Response:

INSTRUCTIONS: IF YES, answer the following questions

No

7(a). Does the study involve randomization?

Answer/Response:

IF YES, will randomization be done at each site or among sites?
Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?
Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Answer/Response:

7(d). Is there a common protocol used in all sites?

Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?

INSTRUCTIONS:
This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.
This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified. Describe and justify any control and experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

Special note for studies with waiver of consent/waiver of documentation of consent:
Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

Answer/Response:
Interested participants will sign consent and the following will be completed for screening purposes: Foot and Ankle Ability Measure (FAAM-ADL and Sport), and Identification of foot and ankle instability (IdFAI).

Each CAI subject will complete two testing sessions (1 pre and 1 post intervention) and a 4- week rehabilitation program (with or without biofeedback intervention). Each coper subject will complete only the self-reported function forms and the first testing session (can be completed on same day if participant prefers).

The first testing session (following enrollment/screening) will consist of an evaluation of walking gait including gluteal muscle imaging, an evaluation of jumping, foot alignment, intrinsic foot muscle imaging, range of motion, laxity, strength, and balance. After the first testing session, the CAI subjects only will return to the lab to start the 4-week rehabilitation protocol a minimum of 7 days later. At this time each subject will be randomly assigned to the experimental group or control group via random number generator by a non-affiliated third party. Both the control group and experimental group will complete a 4-week supervised rehabilitation protocol that will encompass traditional exercises to improve range of motion, strength, balance, and functional activities. The experimental group will differ from the control group by receiving biofeedback about their ankle position during walking. The rehabilitation sessions will be supervised by a Certified Athletic Trainer and/or Physical Therapist. After 4 weeks, each group will be asked to return to the lab to complete the 2nd testing day. At this time, both groups will fill out self-reported function questionnaires and have their walking gait with gluteal muscle imaging, jumping gait, foot alignment, intrinsic foot muscles, range of motion, laxity, strength and balance re-evaluated. The 2nd session will be completed by the same investigator as the 1st testing session

Session 1

Self-reported Function: Questionnaires will be administered to each subject. This will be completed on the first visit after informed consent has been received and will be completed again on the second visit after 4 weeks.

1. International Physical Activity Questionnaire (IPAQ)- self-report of physical activity over the course of a typical week and the time spent doing activity.

2. Foot and Ankle Ability Measure (FAAM) Activities of daily living and FAAM sport subscale - region-specific outcome questionnaires that requires subjects to assess their perceived ability in both activities of daily living and sports.

3. Identification of foot and ankle instability (IdFAI)- A questionnaire that provides specific information about their ankle instability

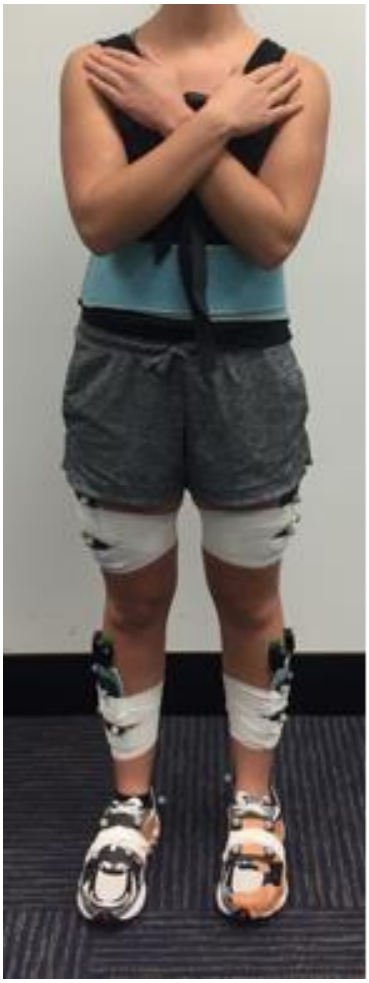
4. Tampa Scale of Kinesiophobia (TSK) – a questionnaire that provides information about fear of movement patterns (avoidance or altered movements)

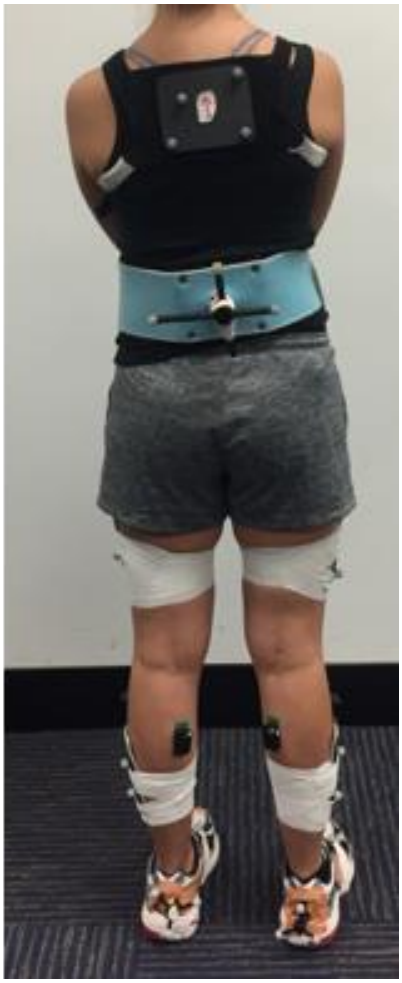
5. Visual analog scale (VAS) – assessment of ankle pain

6. Global Rating of Change – provides information about how participant feels after completing study compared to before the study

7. Patient Specific Functional Scale – used to quantify activity limitation and measure functional outcome for patients with any orthopaedic condition

1. **Walking/Jumping Gait Analysis:** Participants will wear standard laboratory shoes (Brooks) during motion analysis. Three-dimensional joint kinematics of the ankle will be measured using the Vicon motion analysis system controlled by Motion Monitor software. A forceplate embedded in the treadmill will be used to collect ground reaction forces for determination of initial contact and terminal stance during walking trials. A total of 10 clusters of markers (38 markers) will be placed on the upper back, lower back, lateral mid-thigh, lateral mid-shank, posterior calcaneus, and the foot. Electromygraphy (EMG) of lower extremity musculature (medial gastrocnemius, fibularis longus, anterior tibialis, and gluteus medius) will also be collected synchronously using wireless surface EMG electrodes. Additionally, subjects will wear an ultrasound transducer housed in a custom foam block and belt on the hip of their affected, and control-matched, limb. Participant setup can be seen in image below. An example of the ultrasound setup is included in a separate image below. Once sensor set-up is complete, the participant will be instructed to walk on the treadmill at their preferred walking speed (PWS) for 5 minutes. Once the subject is familiar with the treadmill and has completed the 5-minute warm-up, we will collect 60 seconds of walking at the PWS, a fast (120% of PWS), and standardized (3.0mph) walking speeds. After walking trials, we will collect 60 seconds of jogging at the preferred jogging speed (PJS), a fast (120% of PJS), and standardized (6.0mph) walking speeds. At this time, the ultrasound transducer will be removed. Then the subjects will complete 15 jump landing tasks. Subjects will stand on a 30 cm box place half their height away from the force plate. They will be instructed to jump forward off the box and land on the force plate. Once they land, they will be asked to jump straight into the air as high as they can.





2. **Foot alignment:** Each participant will have their foot alignment evaluated using the Jaktool arch height index. Participants will be required to sit then stand facing forward while the investigator measures these alignments. A visual inspection of the foot (foot posture index) will be done with participants facing forward and then backward. These tests are widely used in assessing people with lower extremity pathologies.

3. **Range of motion:** We will collect three measurements of the posterior glide test, seated straight leg dorsiflexion, seated straight leg plantarflexion, seated inversion, seated eversion, and weight bearing dorsiflexion. We will also analyze hip flexion, extension, abduction and adduction.

4. **Laxity:** We will assess laxity by doing 3 measures of the anterior drawer test, internal rotation test, and talar tilt test. All tests for laxity are commonly used in the clinical setting.

5. **Strength:** Ankle dorsiflexion, plantar flexion, inversion, eversion, plantar flexion, eversion, and hip flexion, extension, and abduction will be measured using a hand-held dynamometer (Microfet2). Three 5-second maximum voluntary isometric contraction (MVIC) trials will be completed for each motion.

6. **Balance Testing**: Each subject will complete the Star excursion balance test (SEBT), and static

balance testing

a. Star Excursion balance test- The tester will first measure the subject's leg length. The test requires subjects to balance on one foot and reach with the opposite foot as far as they can along a tape measure on the floor then return to standing on both feet. They will reach in three different directions (4, 8, and 12 o'clock) for three trials each direction for a total of nine repetitions on the tested foot. Fifteen seconds of rest is given between repetitions. The tester measures the total distance reached (cm) of each repetition. This test will be completed for both legs.

b. Static balance test- Subjects will stand on a force plate (Accusway Plus) with both feet together and their hands on their hips. They will be instructed to raise the leg not being tested off the ground to 90 degrees of flexion. At this point, they will be instructed to balance on one leg while maintaining their hands on their hips for 10 seconds. This will be completed for 3 trials with their eyes open and then three trials with their eyes closed. Both legs will be tested. The investigator will stand close to the subject for each trial to prevent the subject from falling.

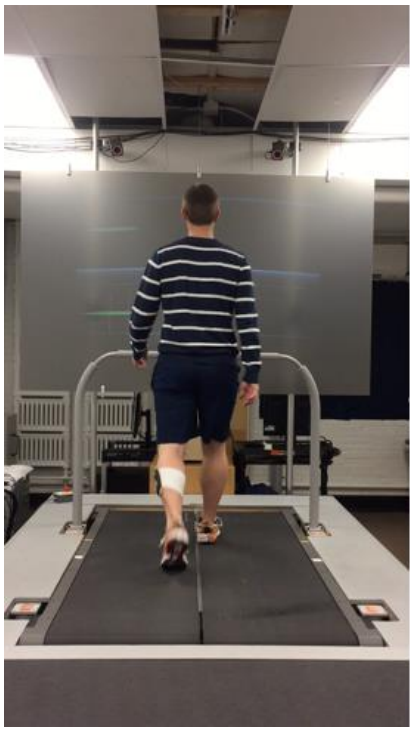
7. **Ultrasound Imaging (Seimens Accuson Freestyle):** Water-soluble ultrasound gel will be placed on the bottom of the foot. The ultrasound probe will be placed on the skin over the gelled area. This will display underlying muscles on ultrasound computer screen.

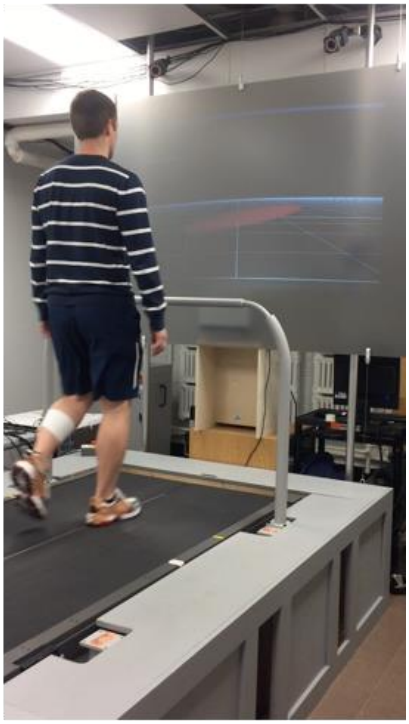
8. **Physical Activity (CAI only):** each CAI participant will receive a Fitbit to wear for the duration of their rehabilitation and return upon completion. The Fitbit will allow us to count the number of steps taken by each participant.

Rehabilitation Protocol (Only the CAI subjects will complete)

Randomization: Prior to starting rehabilitation, subjects will be randomized into either the control group or experimental group via random number generator. This will be completed by a 3rd party individual with no affiliation with this project from our lab.

4-week Rehabilitation: Subjects will return to the lab a minimum 7 days after completing their first test day. Subjects will be asked to complete 8 rehabilitation sessions (2x week) over a 4 week period. Subjects must complete 7 rehabilitation sessions in order to be included in the analysis. The investigator for each of the rehabilitation sessions will be a certified Athletic Trainer (ATC) and/or Physical Therapist (PT) and blinded to intervention group status. A separate ATC or PT not involved in the rehabilitation portion of the project will conduct all walking and jogging after rehabilitation is completed for the visit. Only this clinician will know the status of feedback or no feedback and will not discuss this with the person providing rehabilitation. Each rehabilitation session will last approximately 1 hour. Rehabilitation does not need to be completed by the same ATC or PT, but each ATC/PT will follow a pre-determined progression and record the intensity and duration for each individual session as seen in the data collection sheet. Both groups will complete standard of care rehabilitation that all investigators will have routinely done in clinical practice. Rehabilitation exercises will aim to improve ROM, strength, balance, and neuromuscular control. These methods have been previously employed at the University of Virginia. Lastly, the experimental group will receive feedback during walking about their ankle position. Feedback for the intervention group will be based off of information the computer receives about the foot position when contacting the ground. When the shape is red, the participant is too inverted (bad foot position). When the shape is green, the participant is in a good foot position. See image below for example of





projection for feedback.

Session 2

After completing the 4 weeks of rehabilitation, the CAI subjects will return to our lab within 72 hours later and all outcome measures as described in session one will be completed so that

change scores can be calculated and compared between treatment arms. These measures will be collected by the original investigator.

Follow Up Emails (6- and 12-months post rehab)
After study completion, participants will receive an email at 6 and 12 months. The email will include a link to a Qualtrics survey and will include the following questionnaires: International Physical Activity Questionnaire (IPAQ), Identification of foot and ankle instability (IdFAI), Foot and Ankle Ability Measure (FAAM-ADL & sport subscale), Tampa Scale of Kinesiophobia (TSK), Global Rating of Change (GROC), and VAS for current pain, best pain, and worst pain over past 6-months. We will also ask questions about ankle health.

- **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

  Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
  Instructions: Answer NA if this study does not involve a study treatment.

  Answer/Response:

  NA

(Unapproved Device being used but not evaluated)

INSTRUCTIONS: This section is to provide the IRB with information about the safety of a device that is being USED, but not evaluated in this study for safety and efficacy. The device may have FDA approval and is being used for a non-approved indication OR the device may not have FDA approval [these are typically known as Research Use Only (RUO) Devices]. Again the RUO Device is only being USED and NOT being evaluated for safety and efficacy in this study. The information below will be used by the IRB to make a minimal risk determination regarding this protocol.

1. **List name of device(s) being used in an unapproved manner in this protocol**.

   Per the statute: Federal Food, Drug, and Cosmetic Act Sec 201.h [21USC321]
   DEVICE: (h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
   (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
   (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Answer/Response:
1. Ultrasound Transducer
2. Custom foam block and belt

2. **Do you confirm the device is only being USED and NOT being evaluated in this study?**
   Answer/Response: Yes

3. **Is the device a Research Use Only (RUO) device?**

IF YES, submit the manufactures brochure/information regarding the RUO with other documents at the time of pre-review.
IMPORTANT: The RUO designation is made by the FDA.
The package insert MUST stipulate that this is a RUO device.

Answer/Response: NO

►If the device is a RUO device, do you agree to use the device according to instructions in the manufacturers brochure?
Answer/Response:

►If the device is NOT a RUO device, is the device currently approved for any indication?
Answer/Response:

►If the device is currently approved list the indication:

INSTRUCTIONS: Also submit the Manufacturer's Brochure

Answer/Response:

►If the device is currently approved, do you confirm that results will not be used in clinical care of the subject (e.g. will not be used for diagnosis or treatment?)
Answer/Response:

4. **In how many humans has this device been used previously as it is being used in this study?**
   Answer/Response: None

5. **Describe pertinent human data that is available regarding the safety of this device as you are using it in this protocol.**
   Answer/Response: None available at this time.

6. **If this protocol will be used in children, describe any previous use of this device with children of a similar age range as it is being used in this study.**
   Answer/Response: No

7. **What steps will be taken to minimize risk?**
   Answer/Response: The ultrasound device is non-invasive and will be placed on the participant while they are awake and aware, so the participant will be able to say if the foam block and/or belt is uncomfortable.

8. Would you consider the use of this device to be minimal risk? Why or why not?

Minimal Risk: probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 45CFR46.102

Answer/Response: Yes, the ultrasound device is non-invasive and the foam block and belt will be adjusted to the comfort of the participant.

Bibliography

INSTRUCTIONS: Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

1. Delahunt E, Monaghan K, Caulfield B. Altered Neuromuscular Control and Ankle Joint Kinematics During Walking in Subjects With Functional Instability of the Ankle Joint. *Am J Sports Med*. 2006;34(12):1970-1976.

2. Chinn L, Dicharry J, Hertel J. Ankle kinematics of individuals with chronic ankle instability while walking and jogging on a treadmill in shoes. *Phys Ther Sport*. 2013;14(4):232-239. doi:10.1016/j.ptsp.2012.10.001.

3. Doherty C, Bleakley C, Hertel J, Caulfield B, Ryan J, Delahunt E. Recovery From a First-Time Lateral Ankle Sprain and the Predictors of Chronic Ankle Instability A Prospective Cohort Analysis. *Am J Sports Med*. 2016;44(4):995-1003.

4. Hertel J. Functional anatomy, pathomechanics, and pathophysiology of lateral ankle instability. *J Athl Train*. 2002;37(4):364.

5. Donovan L, Hart JM, Saliba SA, et al. Rehabilitation for Chronic Ankle Instability With or Without Destabilization Devices: A Randomized Controlled Trial. *J Athl Train*. 2016;51(3):233-251. doi:10.4085/1062-6050-51.3.09.

6. Donovan L, Hertel J. A new paradigm for rehabilitation of patients with chronic ankle instability. *Phys Sportsmed*. 2012;40(4):41-51. doi:10.3810/psm.2012.11.1987.

7. Koldenhoven RM, Feger MA, Fraser JJ, Saliba S, Hertel J. Surface electromyography and plantar pressure during walking in young adults with chronic ankle instability. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(4):1060-1070.

8. Yen S-C, Chui KK, Corkery MB, Allen EA, Cloonan CM. Hip-ankle coordination during gait in individuals with chronic ankle instability. *Gait Posture*. 2017;53:193-200. doi:10.1016/j.gaitpost.2017.02.001.

9. Doherty C, Bleakley C, Hertel J, Caulfield B, Ryan J, Delahunt E. Locomotive biomechanics in persons with chronic ankle instability and lateral ankle sprain copers. *J Sci Med Sport*. 2016;19(7):524-530. doi:10.1016/j.jsams.2015.07.010.

10. McKeon PO, Paolini G, Ingersoll CD, et al. Effects of balance training on gait parameters in patients with chronic ankle instability: a randomized controlled trial. *Clin Rehabil*. 2009;23(7):609-621. doi:10.1177/0269215509102954.

11. Davis IS, Futrell E. Gait Retraining: Altering the Fingerprint of Gait. *Phys Med Rehabil Clin N Am*. 2016;27(1):339-355. doi:10.1016/j.pmr.2015.09.002.

12. Winstein C. Knowledge of results and motor learning--implications for physical therapy. *Phys Ther*. 1991;71(2):140-149.

13. Noehren B, Scholz J, Davis I. The effect of real-time gait retraining on hip kinematics, pain and function in subjects with patellofemoral pain syndrome. *Br J Sports Med*. 2011;45(9):691-696. doi:10.1136/bjsm.2009.069112.

14. Donovan L, Feger MA, Hart JM, Saliba S, Park J, Hertel J. Effects of an auditory biofeedback device on plantar pressure in patients with chronic ankle instability. *Gait Posture*. 2016;44:29-36. doi:10.1016/j.gaitpost.2015.10.013.

Table C-6. University of Virginia IRB Approved Consent Form IRB-HSR (M1, M2 and M3)

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

Principal Investigator:	Jay Hertel, PhD, ATC University of Virginia 210 Emmet St South Charlottesville, VA 22904 434-243-8673
Sponsor:	**1)** The Curry School of Education at the University of Virginia **2)** The Mid-Atlantic Athletic Trainers' Association 3) The National Athletic Trainers' Association

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

Who is funding this study?

This study has received grant funding from the Curry School of Education, the Mid-Atlantic Athletic Trainers' Association, and the National Athletic Trainers' Association for participant payments and supplies for study.

Why is this research being done?

The purpose of this study is to see if rehabilitation and receiving information while you are walking, will improve ankle function for people who have chronic ankle instability (CAI). This study will also compare how people with CAI walk compared to people who are copers (people who sprained their ankle and recovered fully).

People with CAI have symptoms from an ankle sprain that last more than one year. The symptoms include feeling like you may roll your ankle, having repeated ankle sprains, or feel like your ankle is loose. This study could help clinicians provide better exercises to help people with CAI and see how they walk differently from people with no ankle instability.

You are being asked to be in the study because you have CAI or are a coper and are physically active (do physical activity for at least 30 minutes per day, three days per week). People with CAI have a history of repetitive ankle sprains, and/or have feelings of ankle "giving way" and prolonged symptoms, and are not seeking therapy or treatment for your ankle condition.

Up to ***100*** people will be in this study at UVA.

What will happen if you are in the study?

If you agree to be in this study, you will sign this consent form before any study related procedures take place. All procedures are done for research purposes and will take place at the UVA Memorial Gymnasium.

SCREENING

Before you can start in the study, there will be a screening period **(Visit 1)**. We will ask you some questions during this time to make sure you are eligible and it is safe for you to participate. These include the following:

Ankle Questionnaires:

82. Questions about your general health as it relates to your ankle injury
83. A questionnaire asking about your current physical activity level
84. Questionnaires asking about your ankle function
85. A questionnaire asking about how you feel when you move

If these items show you are eligible, you will return within **7 days** to begin the study.

STUDY PROCEDURES

Coper study procedures include ONLY screening and baseline visit. CAI study procedures will include screening and multiple visits.

BASELINE STUDY PROCEDURES Visit 2 (will take about 2 hours to complete):

Walking and Jogging Testing:

86. You will have sensors attached to your skin that will passively record how you move and how your muscles turn on during walking and jogging.
87. You will have ultrasound with a belt put on your hip for images of your hip muscles while you are moving
88. With the sensors and ultrasound on, you will walk for up to 15 minutes and jog for up to 5 minutes on a treadmill.

Jumping Testing:

- With the same sensors on, you will jump up to 15 times off a 30cm box
- Without the sensors on, you will do a timed jump test

Foot Alignment:

- You will have your foot alignment measured.
- You will be asked to so sit and to stand upright for visual inspection and measurement.

Range of motion:

- Your ankle and hip motion will be measured 3 times in 4 directions. These motions are: pulling your foot toward yourself, pointing your foot away from yourself, turning your foot inward, turning your foot outward, pulling your leg forward, pushing your leg backward, pushing your leg outward, and pulling your leg inward.

Ankle Laxity:

- You will have tests done that will determine how "loose" your ankles are.

Ankle and Hip Strength:

- You will have your ankle and hip strength tested 3 times in 4 directions. The tester will use a device held in their hand that records how hard you can push using your ankle. These motions are: pulling your foot toward yourself, pointing your foot away from yourself, turning your foot inward, and turning your foot outward, pulling your leg forward, pushing your leg backward, and pushing your leg outward.

Balance Testing

- You will complete 2 different tasks that will determine how well you balance. The tasks are:
    - **Star Excursion balance test**: This test will require you to stand on one leg with your hands on your hips and reach as far as you can with your opposite leg in various directions. You will reach forward, backwards to your left, and backwards to your right. You will be given rest between each reach.
    - **Static Balance Test:** (eyes opened and eyes closed) while standing on a force plate for 10 seconds

Muscle Imaging

- You will have images of your foot muscles taken using ultrasound imaging
- You will be asked to lie on a table and relax while images are taken

This is the end of procedures for coper participants.

CAI Participants will continue with the following procedures:

Physical Activity

- You will be given a FitBit pedometer that will count how many steps you take each day
- You will wear the FitBit for the duration of your rehabilitation and return it when you're done participating

You will be asked to return to the lab within 7 days to begin the 8 rehabilitation sessions.

VISITS 3 TO 10 (REHABILITATION TREATMENT SESSIONS 1 TO 8)
You will be randomly assigned (like the flip of a coin) to 1 of 2 study groups. You have an equal chance of being assigned to any one of the groups (**Group 1** and **Group 2**). You cannot choose to which group you are assigned.

Group 1:
Group will be asked to complete 4 weeks of treatment for their ankle instability. You will be asked to complete 2 sessions per week for a total of 8 sessions. During the treatment you will complete exercises that are considered standard of care. Each session you will complete ankle motion, strength, balance and functional exercises. During the walking, you will get feedback about how you are walking. The feedback will appear on a screen in front of the treadmill.

Group 2:
Group 2 will be asked to complete 4 weeks of treatment that will treat their ankle instability. You will be asked to complete 2 sessions per week for a total of 8 sessions. During the treatment you will complete exercises that are considered standard of care. Each session you will complete ankle motion, strength, balance and functional exercises.

During this study, you will be asked to fill out some questionnaires. These questionnaires ask about:

25. how you are feeling
26. your lifestyle habits
27. daily activities
28. how your ankle instability affects your lifestyle

FOLLOW UP:

VISIT 11 Both groups 1 and 2 will return to the lab approximately 48 to 96 hours after their final rehab session. You will complete the same testing as you did on the first day. This will take no longer than 1.5 hours.

Email follow up
You will be contacted at 6 months and 12 months after you complete the follow-up testing. You will complete the same questionnaires from previous visits and answer questions about your current ankle health.

Study Schedule

	Visit 1 (Screening)	Visit 2 (Baseline)	Visits 3-10 (Rehab)*	Visit 11 (Follow-up)*	Email Follow-up*
Study Week	-1	0	1-4	5	6 and 12 months
Informed Consent	X				
Review study eligibility	X				
Ankle Questionnaires	X			X	X
Walking, jogging, jumping, strength, ROM, balance testing		X	X	X	
Muscle images		X		X	

*CAI participants only

WHAT ARE YOUR RESPONSIBILITIES IN THE STUDY?

You have certain responsibilities to help ensure your safety.

These responsibilities are listed below:

31. You must be completely truthful about your ankle health history.
32. Follow all instructions given.
33. Attend all rehab sessions.
34. You should tell the study investigator or staff about any changes in your health or the way you feel.
35. Answer all of the study-related questions completely.
36. Inform the study investigator or study staff as soon as possible if you have to take any new injuries.

How long will this study take?

Your participation in this study will require ***2 or 11*** of study visits over ***4-5 week*** period of time depending on if you are a CAI or a Coper participant. Each visit will last about **1-1.5** hours. Study visits 2 and 11 will last up to **2** hours. Email follow ups for CAI participants will be sent 6 and 12 months after the follow-up visit and will take about **30 minutes** to complete.

If you want to know about the results before the study is done:

The rehabilitation sessions will use common measure normally used during physical therapy and rehabilitation. If any test results are concerning, your study leader will let you know. In addition, as the research moves forward, your study leader will keep you informed of any new findings about the research itself that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all

the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results.

What are the risks of being in this study?

Risks and side effects related to the intervention and rehabilitation:
Likely

16. Mild soreness of muscles involved with exercises

Rare but serious

17. Tripping or falling during: walking or jogging on treadmill, jumping or balance exercises
18. Ankle sprain due to participation in exercises

Other unexpected risks:
You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?

You may or may not benefit from being in this study. Possible benefits for CAI participants include: decreased symptoms associated with ankle instability and better overall movement from the rehab sessions. In addition, information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment may include the following as determined by your care provider:

- Seeking formal physical therapy for your ankle
- Wearing a brace or ankle tape during normal activity

If you are an employee of UVa your job will not be affected if you decide not to participate in this study. If you are a student at UVa, your grades will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?

If you are a CAI participant, you will be paid $100 for finishing this study by check.

You should get your:

1) first payment of $30 about 4-6 weeks after your initial visit.
2) second payment of $70 4-6 weeks after finishing the study.

If you are a coper participant, you will be paid $20 for finishing this study by check. You should get your payment of $20 about 4-6 weeks after your study visit.

The income may be reported to the IRS as income.

You will not be paid at all if **you** decide not to finish this study. If the study leader says you cannot continue, you will be paid the full amount for the study.

If you owe money to any Virginia state agency, the state can use the money you earn in this study to pay those debts. These state agencies include the UVa Medical Center, VCU Medical Center or a college or university. The money may be withheld to pay back debt for such things as unpaid medical bills, taxes, fines, child support. Even if this happens, the money you earn may be reported to the IRS as taxable income.

Will being in this study cost you any money?

All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study visit and for any parking costs.

What if you are hurt in this study?

If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) Your principal investigatory is concerned about your health
b) Your ankle instability gets worse
c) The side effects of the treatment are too dangerous for you
d) You do not follow your study team's instructions

If you decide to stop being in the study, we will ask you to: ***notify your study team you are no longer willing to participate.***

How will your personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

A description of this clinical trial will be available on *http:// www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

A copy of this consent form will be put in your medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your medical records will be able to find out that you are in this study. This is done so your regular doctors will know what you receive as part of this study. If you have other health problems during the study, they will be able to treat you properly.

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Jay Hertel
University of Virginia
210 Emmet St South
Charlottesville, VA 22904
Telephone: (434)243-8673

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908
Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your

questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Signature of Impartial Witness

If this consent form is read to the subject because the subject is blind or illiterate, an impartial witness not affiliated with the research or study doctor must be present for the consenting process and sign the following statement. The subject may place an X on the Participant Signature line above.

I agree the information in this informed consent form was presented orally in my presence to the **identified individual(s)** who has had the opportunity to ask any questions he/she had about the study. I also agree that the **identified individual(s)** freely gave their informed consent to participate in this trial.

Please indicate with check box the identified individual(s):

☐ Subject

_____	_____	_____
IMPARTIAL WITNESS (SIGNATURE)	IMPARTIAL WITNESS (PRINT)	DATE

Table C-7. Data Collection Sheet

Data Collection Sheet IRB # 20548

Patient ID: _____ Investigators: _____

Date of Collection: _____

Time of Collection: _____

Sex _____

Age _____

Occupation _____

Visit One Performed: Date: _____

Date of Birth: _____ Weight: _____ Height: _____

Date of Surgery: _____ Date of Injury: _____

(use elevator for taking patients up and down the lab)

❖ **Ultrasound Measures**

Both limbs (always start from right)

Order	Position	R CSA	SF	R MT	SF	L CSA	SF	L MT	SF
1	**Seated**	AH 1,2,3	1,2 3	AH 1,2 3	1,2, 3	FHB 1,2, 3	1,2, 3	FHB 1,2 3	1,2 3
		FDB 1,2,3	1,2, 3	FDB 1,2,3	1,2, 3	FDB 1,2,3	1,2, 3	FDB 1,2 3	1,2, 3
		FHB 1,2,3	1,2, 3	FHB 1,2,3	1,2, 3	FHB 1,2,3	1,2, 3	FHB 1,2,3	1,2, 3
2	**Double Leg**	AH 1,2,3	1,2, 3	AH 1,2,3	1,2 3	FHB 1,2,3	1,2, 3	FHB 1,2 3	1,2 3
		FDB 1,2,3	1,2, 3	FDB 1,2,3	1,2, 3	FDB 1,2, 3	1,2, 3	FDB 1,2,3	1,2 3
		FHB 1,2,3	1,2, 3	FHB 1,2,3	1,2, 3	FHB 1,2,3	1,2 3	FHB 1,2,3	1,2 3

Total : 144 Images.

Table C-8. Ultrasound Imaging Collection Procedures

1. Ultrasound System Setup
    a. On Siemens Acuson Freestyle ultrasound unit monitor, press the power button on the left side of the lower panel. (Figure C1)
    b. Once blank scanning screen appears (after startup of system), remove the 8-MHz linear transducer from the holding area on the back of the monitor.
    c. Insert a battery pack into the back of the linear transducer and power on with two fingers pressed simultaneously on the + and – buttons on the transducer. An auditory chiming sound will ring as the transducer powers on.
    d. Check that Bluetooth is operating with a battery indicator on the lower right of the screen with a "P" for probe.

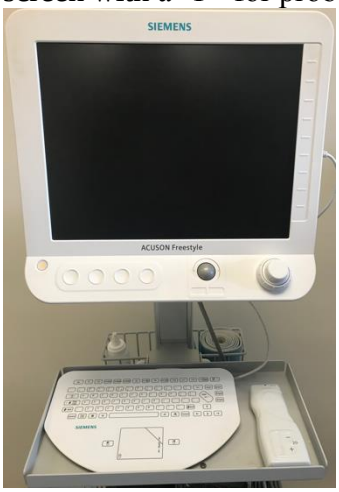


Figure C1. Siemens Acuson Freestyle Ultrasound with linear transducer displayed in bottom right corner next to keyboard.

2. New Participant File Setup
    a. Press "Setup" tab on bottom of screen. (Figure C2)

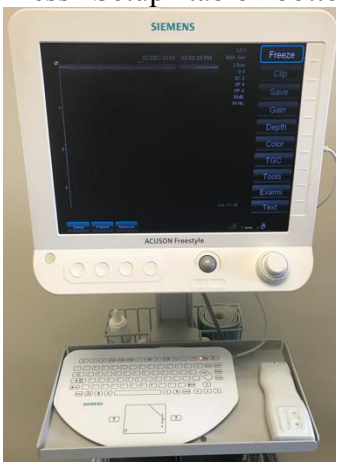


Figure C2. Startup screen of Acuson Freestyle

    b. Press "New Patient Study" on the setup menu. (Figure C3)

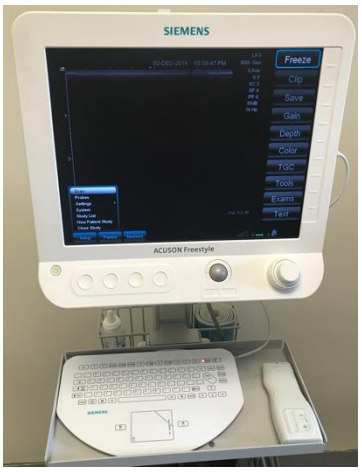


Figure C3. New patient study setup menu

c. Under the last name, type “IRB#_Subject#” and press save. (Figure C4)

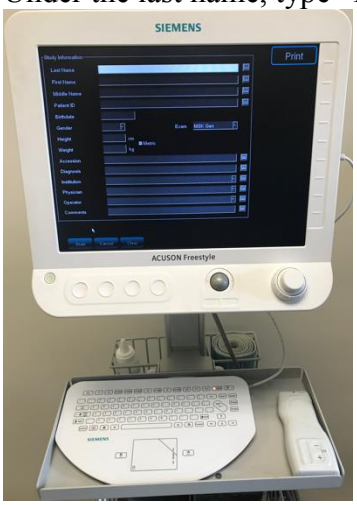


Figure C4. Input screen for Patient ID with IRB# and Subject#

d. Select the “Scan” button and the unit is ready for ultrasound image collection. (Figure C5)

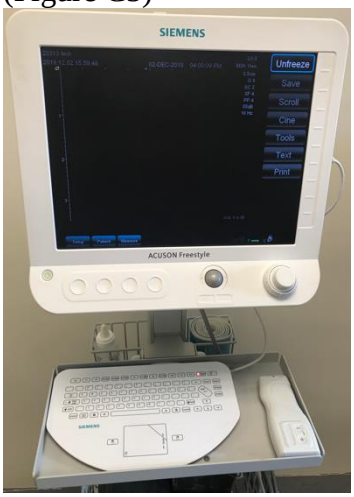


Figure C5. Ready screen for ultrasound image collection

e. Select the “Gain” button and increase gain to 11cm. (Figure C6)

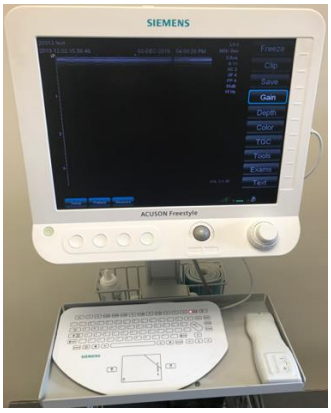


Figure C6. Gain button to increase to 11

f. Ensure that the correctly named file appears in the top left-hand corner of the screen prior to saving the first image.

3. **Bipedal Leg Stance Position**: participants were placed standing with the testing foot on the platform, and the non-testing foot held behind the tested foot for 3 rested and 3 contracted images of each muscle. (Figure C7)

Figure C7. Single leg stance position with ultrasound.

a. The foot was positioned over the opening in the platform
b. Ultrasound gel was placed on the ultrasound transducer
c. Abductor Hallucis
    i. The linear transducer was placed perpendicular to the long axis of the foot at the anterior aspect of the medial malleolus
d. Flexor Digitorum Brevis/Quadratus Plantae
    i. The linear transducer was placed perpendicular to the line from the medial tubercle of the calcaneus to the 3rd toe
e. To save an image, the “Save” button was pressed
f. Once saved, subsequent images could be taken.
g. For contracted images, participants were asked to perform a short foot exercise by contracting their intrinsic foot muscles to increase the arch height and shorten the foot. Image capture and saving occurred while participants held this contraction.

Table C-9. Anterior Knee Pain Scale

Anterior Knee Pain Scale

Subject Number: _____
Date: _____
Knee: L/R

For each question, circle the latest choice (letter), which corresponds to your knee symptoms.

1. Limp
(a) None
(b) Slight or periodical
(c) Constant

2. Support
(a) Full support without pain
(b) Painful
(c) Weight bearing impossible

3. Walking
(a) Unlimited
(b) More than 1 mile
(c) Less than 1 mile
(d) Unable

4. Stairs
(a) No difficulty
(b) Slight pain when descending
(c) Pain both when descending and ascending
(d) Unable

5. Squatting
(a) No difficulty
(b) Repeated squatting painful
(c) Painful each time
(d) Possible with partial weight bearing
(e) Unable

6. Running
(a) No difficulty
(b) Pain after more than 1 mile
(c) Slight pain from start
(d) Severe pain
(e) Unable

7. Jumping
(a) No difficulty
(b) Slight difficulty
(c) Constant pain
(d) Unable

8. Prolonged sitting with the knees flexed
(a) No difficulty
(b) Pain after exercise
(c) Constant pain
(d) Pain forces to extend knees temporarily
(e) Unable

9. Pain
(a) None
(b) Slight and occasional
(c) Interferes with sleep
(d) Occasionally severe
(e) Constant and severe

10. Swelling
(a) None
(b) After severe exertion
(c) After daily activities
(d) Every evening
(e) Constant

11. Abnormal painful kneecap (patellar) movements (subluxations)
(a) None
(b) Occasionally in sports activities
(c) Occasionally in daily activities
(d) At least one documented dislocation
(e) More than two dislocations

12. Atrophy of thigh
(a) None
(b) Slight
(c) Severe

13. Flexion deficiency
(a) None
(b) Slight
(c) Severe

Total Score: _____/100

Table C-10. Tegner Activity Level Scale

TEGNER ACTIVITY LEVEL SCALE

Please indicate in the spaces below the HIGHEST level of activity that you participated in BEFORE YOUR INJURY and the highest level you are able to participate in CURRENTLY.

BEFORE INJURY: Level_____ CURRENT: Level_____

Level 10	**Competitive sports- soccer, football, rugby (national elite)**
Level 9	**Competitive sports- soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball**
Level 8	**Competitive sports- racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing**
Level 7	**Competitive sports- tennis, running, motorcars speedway, handball** **Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running**
Level 6	**Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week**
Level 5	**Work- heavy labor (construction, etc.)** **Competitive sports- cycling, cross-country skiing,** **Recreational sports- jogging on uneven ground at least twice weekly**
Level 4	**Work- moderately heavy labor (e.g. truck driving, etc.)**
Level 3	**Work- light labor (nursing, etc.)**
Level 2	**Work- light labor** **Walking on uneven ground possible, but impossible to back pack or hike**
Level 1	**Work- sedentary (secretarial, etc.)**
Level 0	**Sick leave or disability pension because of knee problems**

Y Tegner and J Lysolm. *Rating Systems in the Evaluation of Knee Ligament Injuries.* Clinical Orthopedics and Related Research. Vol. 198: 43-49, 1985.

SURGICAL HISTORY

Have you had any additional surgeries to your knee other than those performed by Dr. Stone?

Yes / No

If Yes:

What procedure(s) were performed? _____

When was the surgery performed?_____

Who performed the surgery?_____

Table C-11. Foot and Ankle Ability Measure

Foot and Ankle Ability Measure (FAAM)
Activities of Daily Living Subscale

Please Answer **every question** with **one response** that most closely describes your condition within the past week.
If the activity in question is limited by something other than your foot or ankle mark "Not Applicable" (N/A).

	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Standing	☐	☐	☐	☐	☐	☐
Walking on even Ground	☐	☐	☐	☐	☐	☐
Walking on even ground without shoes	☐	☐	☐	☐	☐	☐
Walking up hills	☐	☐	☐	☐	☐	☐
Walking down hills	☐	☐	☐	☐	☐	☐
Going up stairs	☐	☐	☐	☐	☐	☐
Going down stairs	☐	☐	☐	☐	☐	☐
Walking on uneven ground	☐	☐	☐	☐	☐	☐
Stepping up and down curbs	☐	☐	☐	☐	☐	☐
Squatting	☐	☐	☐	☐	☐	☐
Coming up on your toes	☐	☐	☐	☐	☐	☐
Walking initially	☐	☐	☐	☐	☐	☐
Walking 5 minutes or less	☐	☐	☐	☐	☐	☐
Walking approximately 10 minutes	☐	☐	☐	☐	☐	☐
Walking 15 minutes or greater	☐	☐	☐	☐	☐	☐

Foot and Ankle Ability Measure (FAAM)
Activities of Daily Living Subscale
Page 2

Because of your foot and ankle how much difficulty do you have with:

	No Difficulty at all	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Home responsibilities	☐	☐	☐	☐	☐	☐
Activities of daily living	☐	☐	☐	☐	☐	☐
Personal care	☐	☐	☐	☐	☐	☐
Light to moderate work (standing, walking)	☐	☐	☐	☐	☐	☐
Heavy work (push/pulling, climbing, carrying)	☐	☐	☐	☐	☐	☐
Recreational activities	☐	☐	☐	☐	☐	☐

How would you rate your current level of function during you usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities.

___ . 0 %

Martin, R; Irrgang, J; Burdett, R; Conti, S; VanSwearingen, J: Evidence of Validity for the Foot and Ankle Ability Measure. Foot and Ankle International. Vol.26, No.11: 968-983, 2005.

Foot and Ankle Ability Measure (FAAM)
Sports Subscale

Because of your foot and ankle how much difficulty do you have with:

	No Difficulty at all	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Running	☐	☐	☐	☐	☐	☐
Jumping	☐	☐	☐	☐	☐	☐
Landing	☐	☐	☐	☐	☐	☐
Starting and stopping quickly	☐	☐	☐	☐	☐	☐
Cutting/lateral Movements	☐	☐	☐	☐	☐	☐
Ability to perform Activity with your Normal technique	☐	☐	☐	☐	☐	☐
Ability to participate In your desired sport As long as you like	☐	☐	☐	☐	☐	☐

How would you rate your current level of function during your sports related activities from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

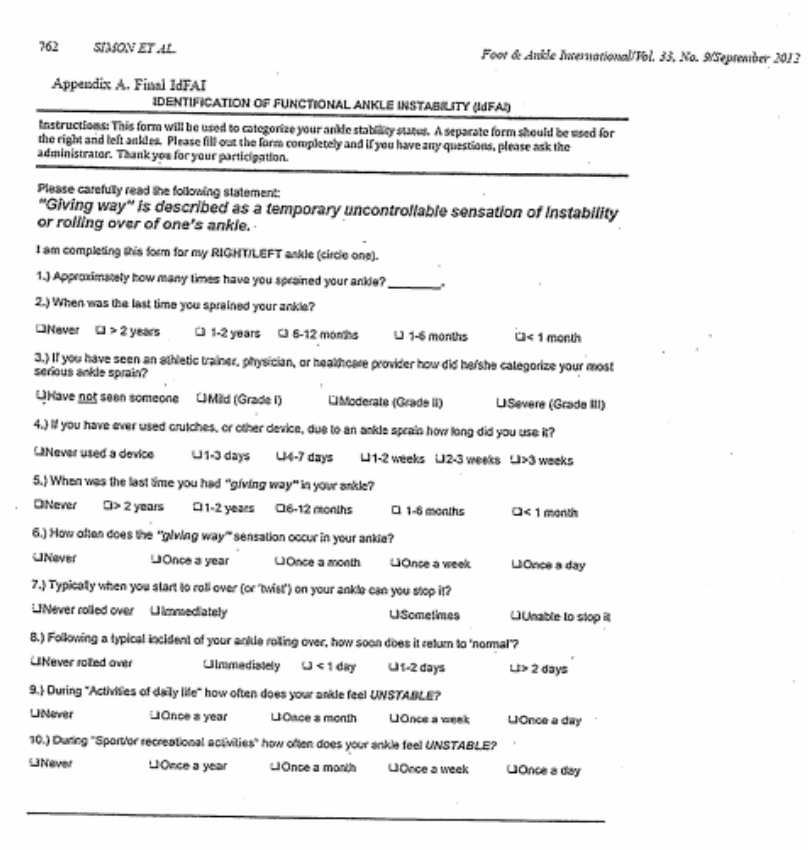
___ . 0%

Overall, how would you rate your current level of function?

☐ Normal ☐ Nearly Normal ☐ Abnormal ☐ Severely Abnormal

Martin, R; Irrgang, J; Burdett, R; Conti, S; VanSwearingen, J: Evidence of Validity for the Foot and Ankle Ability Measure. Foot and Ankle International. Vol.26, No.11: 968-983, 2005.

Table C-12. Identification of Functional Ankle Instability



Appendix A. Final IdFAI

IDENTIFICATION OF FUNCTIONAL ANKLE INSTABILITY (IdFAI)

Instructions: This form will be used to categorize your ankle stability status. A separate form should be used for the right and left ankles. Please fill out the form completely and if you have any questions, please ask the administrator. Thank you for your participation.

Please carefully read the following statement:
"Giving way" is described as a temporary uncontrollable sensation of instability or rolling over of one's ankle.

I am completing this form for my RIGHT/LEFT ankle (circle one).

1.) Approximately how many times have you sprained your ankle? _____.

2.) When was the last time you sprained your ankle?

❑Never ❑ > 2 years ❑ 1-2 years ❑ 6-12 months ❑ 1-6 months ❑< 1 month

3.) If you have seen an athletic trainer, physician, or healthcare provider how did he/she categorize your most serious ankle sprain?

❑Have not seen someone ❑Mild (Grade I) ❑Moderate (Grade II) ❑Severe (Grade III)

4.) If you have ever used crutches, or other device, due to an ankle sprain how long did you use it?

❑Never used a device ❑1-3 days ❑4-7 days ❑1-2 weeks ❑2-3 weeks ❑>3 weeks

5.) When was the last time you had *"giving way"* in your ankle?

❑Never ❑> 2 years ❑1-2 years ❑6-12 months ❑ 1-6 months ❑< 1 month

6.) How often does the *"giving way"* sensation occur in your ankle?

❑Never ❑Once a year ❑Once a month ❑Once a week ❑Once a day

7.) Typically when you start to roll over (or 'twist') on your ankle can you stop it?

❑Never rolled over ❑Immediately ❑Sometimes ❑Unable to stop it

8.) Following a typical incident of your ankle rolling over, how soon does it return to 'normal'?

❑Never rolled over ❑Immediately ❑ < 1 day ❑1-2 days ❑> 2 days

9.) During "Activities of daily life" how often does your ankle feel *UNSTABLE*?

❑Never ❑Once a year ❑Once a month ❑Once a week ❑Once a day

10.) During "Sport/or recreational activities" how often does your ankle feel *UNSTABLE*?

❑Never ❑Once a year ❑Once a month ❑Once a week ❑Once a day

Table C-13. Impairment Based Rehabilitation Sheet

Impairment Based Rehabilitation

Sync & charge Fitbit ☐

Did you forget to wear your Fitbit at all since last session? If so, how long? _____

Home exercise compliance

Did you remember to do your at home exercises? _____

How many days did you complete your home exercises program since last session? _____

Intrinsic Foot Exercises Progression if needed

Exercise	**Reps**	**Duration (minutes)**
Short foot exercise		
1st toe extension		
2-5 toe extension		
Extend & splay		

Range of Motion

Arthrokinematic restrictions? If yes, list joints: _____

Joint Mobilization **Type/Grade**	**Sets**	**Duration (minutes)**	**Grade Mob.**

Stretching exercises: 3x30 seconds each selected

Stretch Position	**Sets**	**Duration (seconds)**
Seated Straight Knee		
Seated Bent Knee		
Standing Straight Knee		
Standing Bent Knee		

Ankle Strength Progression if needed

Exercise (circle appropriate)	**Sets**	**Repetitions**
Double legged/Single legged heel raises		
Double legged/Single legged forefoot raises		
4-way manual resistance		
D1/D2 PNF		
3-way walks		

Hip Strength Progression if needed

Exercise (circle appropriate)	**Sets**	**Repetitions**	**Resistance**

Quadraped: arm extension/leg extension			
Clamshells with theraband			
4-way hip with theraband			
Internal/External rotation on BOSU: No resistance/Theraband			
Band walking			

Balance

Static Balance (circle appropriate phase) **Goal 3x30 seconds**	**Sets**	**Duration (seconds)**
1. Eyes Open Single leg balance		
2. Eyes Open Single leg balance on a foam		
3. Eyes Open Single leg balance on Dynadisc™		
Eyes Closed Progression		
1. Eyes Closed Single leg balance		
2. Eyes Closed Single leg balance on a foam		
3. Eyes Closed Single leg balance on Dynadisc™		

Reach Tasks (circle appropriate phase) **Goal 2x10 each direction**	**Sets**	**Duration (seconds)**
1. Completing the exercise standing on firm surface		

2. Completing the exercise standing on foam surface		
3. Completing the exercise standing on Dynadisc™		

Hop to Stabilization (circle appropriate phase) **Goal is 10 consecutive trials**	**Repetitions Completed**
1. 18-inch hop with arm assistance	
2. 18-inch hop with hands on hips	
3. 27-inch hop with arm assistance	
4. 27-inch hop with hands on hips	
5. 36-inch hop with arm assistance	
6. 36-inch hop with hands on hips	
Hops with foam	
1. 18-inch hop with arm assistance while jumping onto a foam pad	
2. 18-inch hop with hands on hips while jumping onto a foam pad	
3. 27-inch hop with arm assistance while jumping onto a foam pad	
4. 27-inch hop with hands on hips while jumping onto a foam pad	
5. 36-inch hop with arm assistance while jumping onto a foam pad	
6. 36-inch hop with hands on hips while jumping onto a foam pad	

Functional Exercises

Lunges (circle appropriate phase) **Goal is 2x10 each leg**	**Sets**	**Repetitions**

1. Complete lunges on firm surface		
2. Complete lunges with foam beneath stance leg and lunge on top another foam pad		
3. Complete lunges with Dynadisc™ beneath stance leg and lunge on top another Dynadisc™		

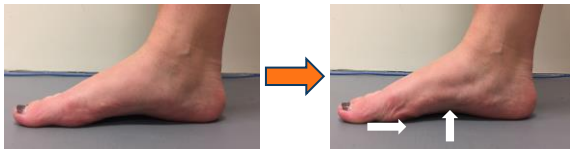
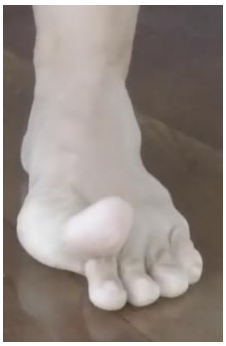
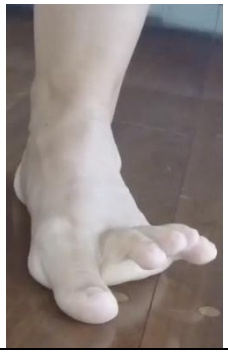
Forward Step-ups and Step-downs (circle appropriate phase) Goal is 3x10	**Sets**	**Repetitions**
1. Step on and off of a box		
2. Step on and off of a box with foam pad		
3. Step on and off of a box with Dynadisc™		

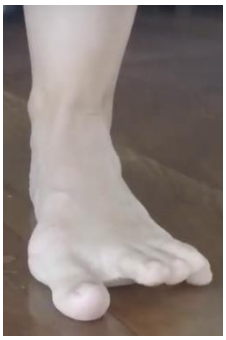
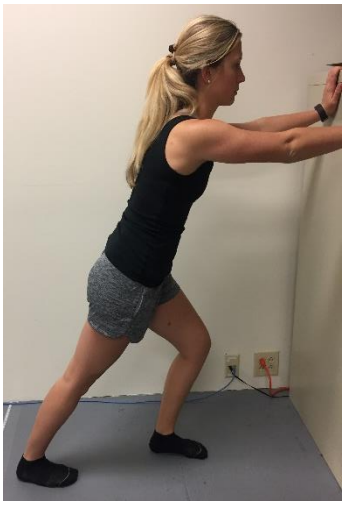
Dot Jumping Drill at 24-inches (circle appropriate phase) **Goal is 3x30 seconds**	**Sets**	**Repetitions**
1. Double legged lateral to medial hops, double legged anterior to posterior jumps, double legged figure 8 jumps		
2. Single legged lateral to medial hops, single legged anterior to posterior jumps, single legged figure 8 jumps		

NOTES:

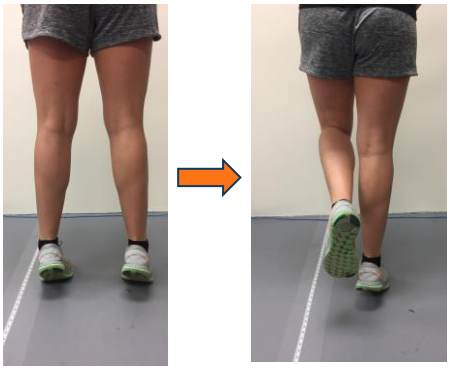
Table C-14. Impairment Based Rehabilitation Exercise Guide

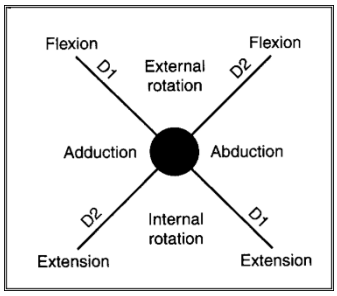
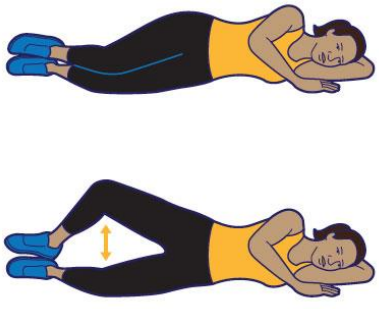
Rehab Guide

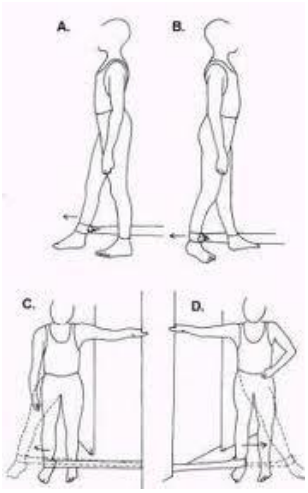
Name	Description	Photo
Intrinsic Foot Muscle Exercises		
Short Foot Exercise	Patient starts in seated or standing position with foot flat on the ground. They are asked to raise their arch up without curling their toes (bring first metatarsal head backward toward calcaneus). Progression: seated, bipedal standing, single limb stance Goal is 50 repetitions	
1st Toe Extension	Patient starts in seated or standing position with foot flat on the ground. They are asked to extend their 1st toe while keeping toes 2-5 on the ground. Progression: seated, bipedal standing, single limb stance Goal is 50 repetitions	
Toes 2-5 Extension	Patient starts in seated or standing position with foot flat on the ground. They are asked to extend their toes 2-5 while keeping 1st toe on the ground. Progression: seated, bipedal standing, single limb stance Goal is 50 repetitions	

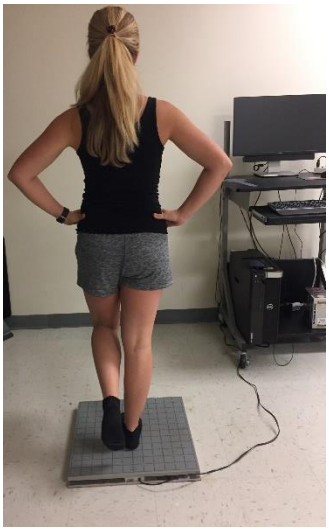
Toe Extension & Splay	Patient starts in seated or standing position with foot flat on the ground. They are asked to extend all toes, then abduct ("splay"), and then slowly lower toes starting with 1 & 5, then 2-4. Progression: seated, bipedal standing, single limb stance Goal is 50 repetitions	
Stretches		
Standing straight knee dorsiflexion	Patient stands, places hands on wall, stretches back leg with knee straight. Goal is 3x30 seconds	
Standing bent knee dorsiflexion	Patient stands, places hands on wall, stretches back leg with knee bent. Goal is 3x30 seconds	

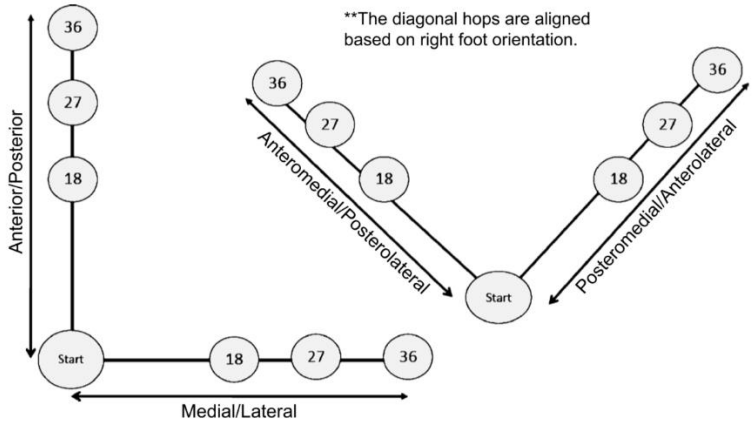
Seated towel stretches	Patient sits with one leg bent and other leg straight, use towel to pull foot into dorsiflexion. Repeat with stretching leg in bent position. Goal is 3x30 seconds	

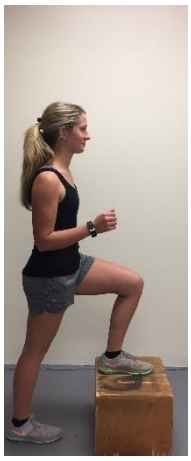
Ankle Exercises		
Double legged/Single legged heel raise	Patient stands on ground with one or both feet and is asked to raise up onto their toes bringing their heel off of the ground. Goal is 3x10. Then progress.	
Double legged/Single legged forefoot raise	Patient stands on ground with one or both feet and is asked to raise up their toes keeping their heel on the ground. Goal is 3x10. Then progress.	
4-way manual resistance	Patient sits with leg straight on the table. Clinician resists them through the full range of motion in the following directions: dorsiflexion, inversion, eversion, plantar flexion Progression: concentric contraction to eccentric contractions	

	Increase resistance if exercise is not challenging enough.	
D1/D2 PNF	Patients will move ankle in diagonal D1 and D2 patterns against manual resistance. Increase resistance if exercise is not challenging enough.	
3-way walks	Patient walks with their feet in 4 positions: on their toes, on their heels, on the "inside" of their foot for 10m lap. Increase reps as needed.	
Hip Exercises		
Quadraped: arm extension/leg extension	Patient starts in position on hands and knees. The patient then simultaneously will extend one arm and the opposite leg. Then they will repeat on the opposite side. Progression: arm/leg only, both arm and leg Proper form is more important than high reps. Goal is 3x10.	
Clamshells with theraband	Patient starts in side-lying position with knees and hips flexed. Ask patient to rotate leg upward then return to start position. Progression: Place the theraband around their mid-thigh, increase resistance (color) Progress when they can complete 3x10.	

4-way hip with theraband	Patient stands on their “healthy” limb and uses ankle sprain limb to perform hip motions. Place appropriate theraband around lower leg. Patient completes the following motions at the hip: flexion, abduction, extension, and adduction. Progression: increase theraband resistance color, have patient stand further from anchor Progress when they can complete 3x10.	
Internal/External rotation on BOSU with theraband	Patient sits on BOSU ball with erect posture. Place the appropriate theraband around the lower leg. Have patient internally and externally rotate the hip. Progression: increase theraband resistance color, have patient sit further from anchor Progress when they can complete 3x10.	

Balance		
Single leg balance	Patient position: stand with 1 on ground, arms crossed in front of their chest, lift the uninvolved limb to about 30º of hip flexion and 45º of knee flexion, and stand as still as possible. Progression eyes: open to closed Progression surface: firm, foam, DynaDisc	

	Progress if patient can complete 3x30 seconds error free.	
Reach tasks (Star Excursion Balance Test)	Patient stands with hands on hips, on the test limb at the edge of the tape measure. The patient reaches as far as they can in the designated direction. Patient is instructed to reach in specific directions. They must control their motion, tap as far as they can, and return to the start position. Pick 3 different directions for each visit. Progression surface: firm, foam, DynaDisc Progress when they can complete 2x10.	
Hop to stabilization	Patients will perform 10 hops in each of 4 directions: medial to lateral, anterior to posterior, anteromedial to posterolateral, and anterolateral to posteromedial. Targets will be placed at a set distance away. Progression: 18 inch, 27 inch, 36 inch. Progression surface: firm, foam, DynaDisc Add reach in opposite direction of hop for increased difficulty. Progress after 10 error-free hops.	

Functional Exercises		
Lunges	Patient will lunge forward and will progress by surface type. Hands will remain on their hips. Errors include taking hands off of hips, lost balance during descent or ascent, unable to reach 90º/90º position, or excessively alter the trunk lean during any phase of the lunge. Progression surface: firm, foam, DynaDisc Progress after 10 error-free lunges.	
Forward step-ups and step-downs (30 cm box)	Step up: patient will stand behind box and step up in forward direction with the involved limb Step down: patient will stand on top of box and step down in forward direction with the involved limb Progression surface: firm, foam, DynaDisc Increase difficulty as needed. Goal is 3x10	  
Lateral step-ups and step-downs (30 cm box)	Step up: patient will stand next to box and step up to the side with the involved limb Step down: patient will stand on top of box and step down to the side with the involved limb Progression surface: firm, foam, DynaDisc Increase difficulty as needed. Goal is 3x10.	

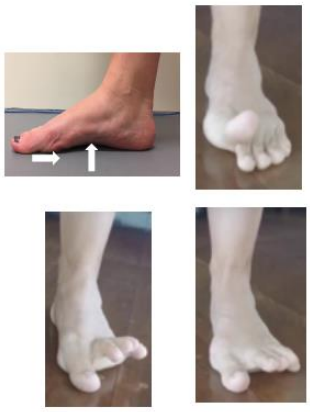
Dot jumping drill	Dots (targets) will be placed apart by 24 inches. Participants will jump from dot to dot as fast as possible while remaining comfortable. Hop directions include: medial to lateral, anterior to posterior, figure of 8 randomized jumps. (Change direction of figure 8 as necessary) Phase 1: double legged jumps Phase 2: single legged jumps Phase 3: progress duration of single legged jumps by 15 seconds after completing 3 successful trials at previous duration Goal is 3x30 seconds comfortably	

Table C-15. Home Exercise Plan

Home exercise program:

Ankle Home Exercise Plan

Intrinsic Foot Exercises
Perform 50 repetitions of each exercise 1x/day



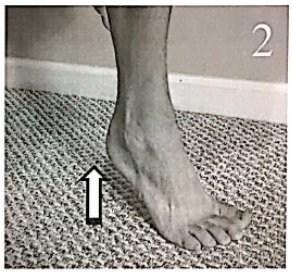
Calf Stretching
With heel in contact with the ground, perform with knee straight for 30 seconds and knee bent for 30 seconds, 3x/day

Balancing
Stand on affected limb, place hands on hips and maintain balance 30 seconds, 3x/day

Resisted toe raises

With a resistance band/tube wrapped around your foot, extend your foot slowly over 2 secs to the end of the motion. Slowly return your foot to starting position over a 4 sec count. Perform 30 times, 3 times a day.

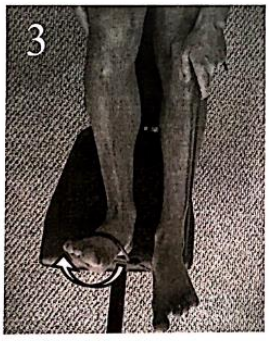
Resisted heel raises

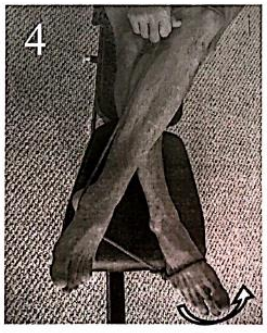


While standing on one foot (and touching a wall for balance), slowly lift your heel over 2 secs to the end of the motion. Slowly return your foot to starting position over a 4 sec count. Perform 30 times, 3 times a day.

Resisted eversion

With a resistance band/tube wrapped around your foot, rotate your foot outboard slowly over 2 secs to the end of the motion. Slowly return your foot to starting position over a 4 sec count. Perform 30 times, 3 times a day.





Resisted inversion

With a resistance band/tube wrapped around your foot, rotate your foot inboard slowly over 2 secs to the end of the motion. Slowly return your foot to starting position over a 4 sec count. Perform 30 times, 3 times a day.

Appendix D

Additional Results

Manuscript 1.

ANCOVA between groups based on age (covariate is age) for Abductor Hallucis size

Tests of Between-Subjects Effects

Dependent Variable: AH_DL_CSA

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.007[a]	6	.001	15.382	.000
Intercept	.003	1	.003	35.619	.000
Age	.000	1	.000	5.026	.027
Sex	4.588E-5	1	4.588E-5	.617	.434
Groups	.006	4	.001	19.318	.000
Error	.008	112	7.431E-5		
Total	.123	119			
Corrected Total	.015	118			

a. R Squared = .452 (Adjusted R Squared = .422)

Parameter Estimates

Dependent Variable: AH_DL_CSA

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Intercept	.044	.005	8.875	.000	.034	.054
Age	.000	.000	-2.242	.027	-.001	-3.158E-5
Sex	.001	.002	.786	.434	-.002	.005
[Groups=1.0]	-.007	.005	-1.455	.149	-.018	.003
[Groups=2.0]	-.019	.003	-5.603	.000	-.026	-.012
[Groups=3.0]	-.016	.002	-7.365	.000	-.020	-.012
[Groups=4.0]	-.012	.002	-5.976	.000	-.016	-.008
[Groups=5.0]	0[a]	.	.	.	.	.

a. This parameter is set to zero because it is redundant.

Contrast Results (K Matrix)

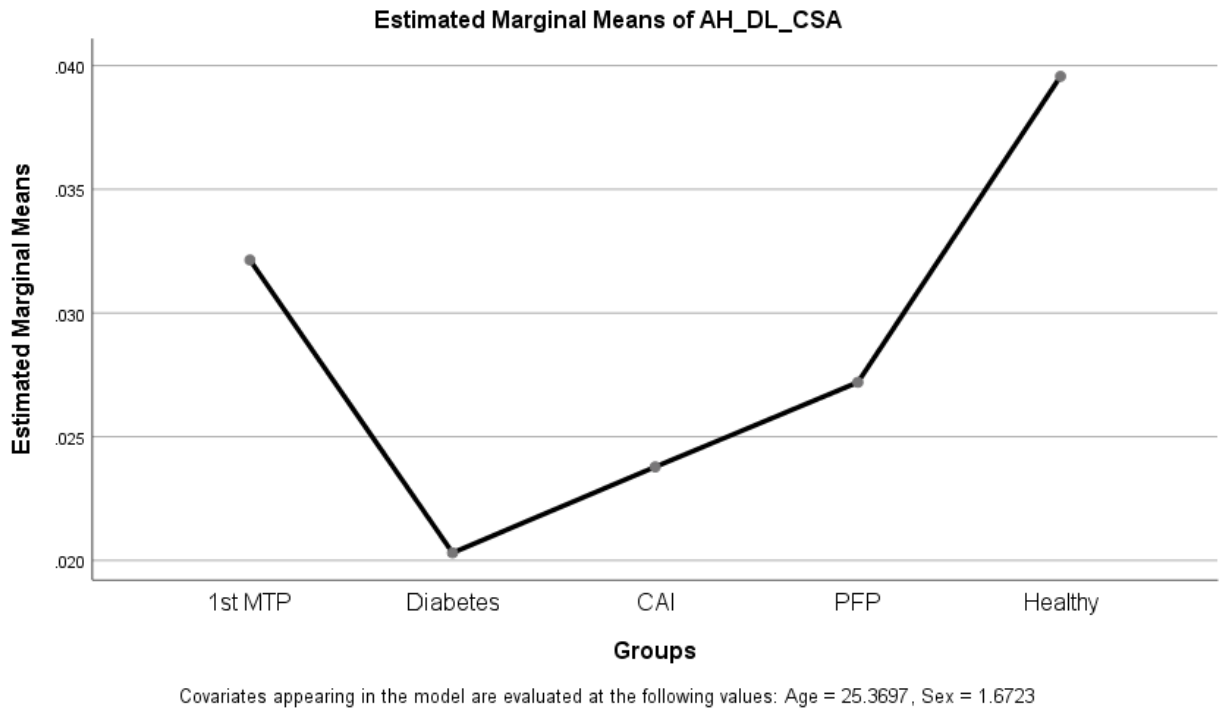
Groups Simple Contrast[a]			Dependent Variable AH_DL_CSA
Level 1 vs. Level 5	Contrast Estimate		-.007
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.007
	Std. Error		.005
	Sig.		.149
	95% Confidence Interval for Difference	Lower Bound	-.018
		Upper Bound	.003
Level 2 vs. Level 5	Contrast Estimate		-.019
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.019
	Std. Error		.003
	Sig.		.000
	95% Confidence Interval for Difference	Lower Bound	-.026
		Upper Bound	-.012
Level 3 vs. Level 5	Contrast Estimate		-.016
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.016
	Std. Error		.002
	Sig.		.000
	95% Confidence Interval for Difference	Lower Bound	-.020
		Upper Bound	-.012
Level 4 vs. Level 5	Contrast Estimate		-.012
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.012
	Std. Error		.002
	Sig.		.000
	95% Confidence Interval for Difference	Lower Bound	-.016
		Upper Bound	-.008

a. Reference category = 5

Descriptive Statistics

Dependent Variable: AH_DL_CSA

Groups	Mean	Std. Deviation	N
1st MTP	.02375	.007106	8
Diabetes	.01756	.010212	9
CAI	.02486	.007477	29
PFP	.02851	.007698	35
Healthy	.03995	.010534	38
Total	.03013	.011343	119



ANCOVA between groups based on age (covariate is age and sex) for Flexor Digistorum size

Descriptive Statistics

Dependent Variable: FDB_DL_CSA

Groups	Mean	Std. Deviation	N

1st MTP	.02175	.009513	8
Diabetes	.01822	.008136	9
CAI	.02597	.005302	29
PFP	.03194	.006941	35
Healthy	.03205	.005276	38
Total	.02880	.007704	119

Tests of Between-Subjects Effects

Dependent Variable: FDB_DL_CSA

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.003[a]	6	.000	10.651	.000
Intercept	.003	1	.003	67.415	.000
Age	5.803E-5	1	5.803E-5	1.458	.230
Sex	.000	1	.000	3.551	.062
Groups	.002	4	.000	10.006	.000
Error	.004	112	3.981E-5		
Total	.106	119			
Corrected Total	.007	118			

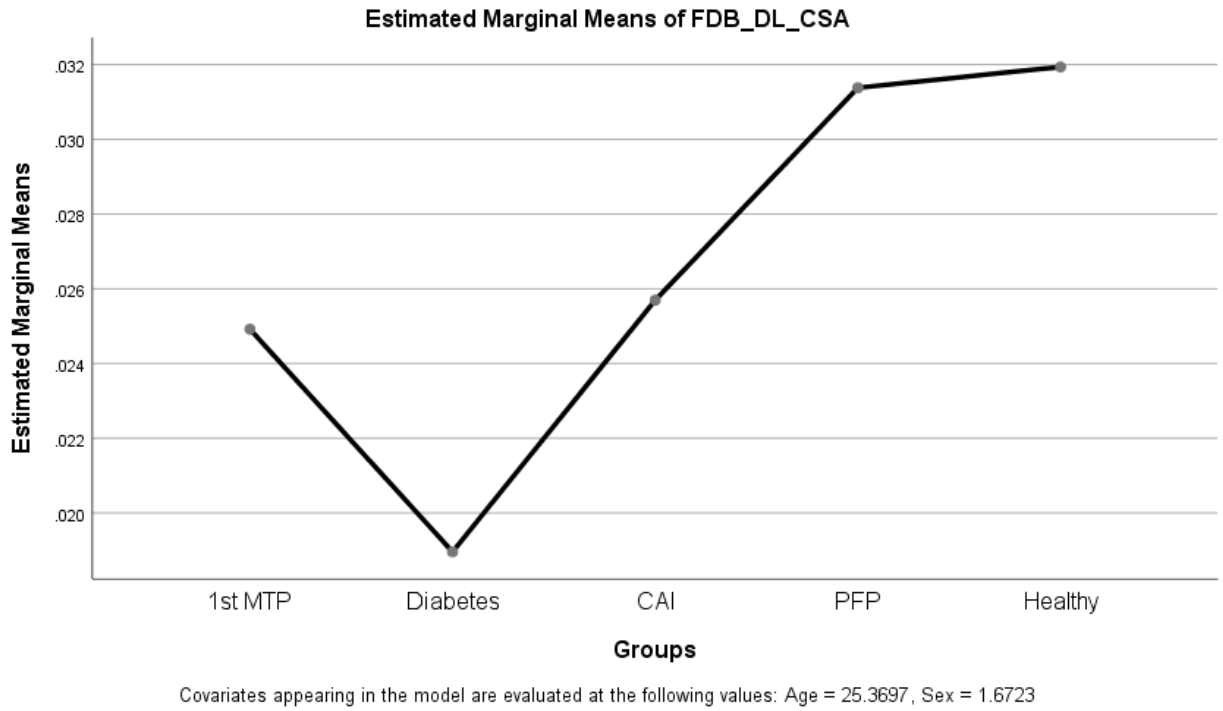
a. R Squared = .363 (Adjusted R Squared = .329)

Contrast Results (K Matrix)

Groups Simple Contrast[a]			Dependent Variable FDB_DL_CSA
Level 1 vs. Level 5	Contrast Estimate		-.007
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.007
	Std. Error		.004
	Sig.		.063
	95% Confidence Interval for Difference	Lower Bound	-.014
		Upper Bound	.000
Level 2 vs. Level 5	Contrast Estimate		-.013
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.013
	Std. Error		.003

	Sig.		.000
	95% Confidence Interval for Difference	Lower Bound	-.018
		Upper Bound	-.008
Level 3 vs. Level 5	Contrast Estimate		-.006
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.006
	Std. Error		.002
	Sig.		.000
	95% Confidence Interval for Difference	Lower Bound	-.009
		Upper Bound	-.003
Level 4 vs. Level 5	Contrast Estimate		-.001
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		-.001
	Std. Error		.002
	Sig.		.713
	95% Confidence Interval for Difference	Lower Bound	-.004
		Upper Bound	.002

a. Reference category = 5



Echogenicity Analysis

Echo Analysis_AbH

Between-Subjects Factors

		Value Label	N
Groups	1.0	1st MTP	8
	2.0	Diabetes	9
	3.0	CAI	29
	4.0	PFP	35
	5.0	Healthy	38

Descriptive Statistics

Dependent Variable: AH_Echo

Groups	Mean	Std. Deviation	N
1st MTP	72.8938	9.24179	8
Diabetes	60.4211	20.50193	9
CAI	56.0359	10.51964	29
PFP	53.0840	13.85342	35
Healthy	49.5976	9.42257	38
Total	54.5767	13.32215	119

Tests of Between-Subjects Effects

Dependent Variable: AH_Echo

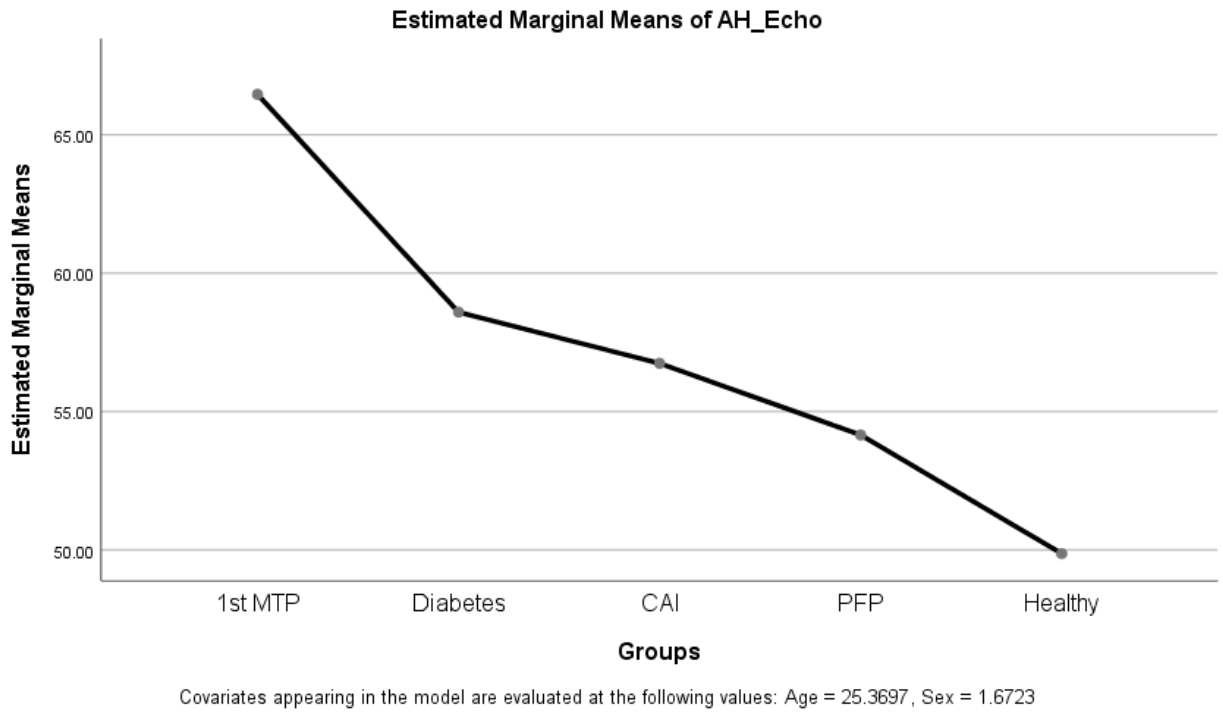
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	4313.747[a]	6	718.958	4.842	.000
Intercept	5785.554	1	5785.554	38.967	.000
Age	228.035	1	228.035	1.536	.218
Sex	63.509	1	63.509	.428	.514
Groups	1506.877	4	376.719	2.537	.044
Error	16628.868	112	148.472		
Total	375398.236	119			
Corrected Total	20942.615	118			

a. R Squared = .206 (Adjusted R Squared = .163)

Contrast Results (K Matrix)

Groups Simple Contrast[a]			Dependent Variable AH_Echo
Level 1 vs. Level 5	Contrast Estimate		16.601
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		16.601
	Std. Error		7.213
	Sig.		.023
	95% Confidence Interval for Difference	Lower Bound	2.310
		Upper Bound	30.893
Level 2 vs. Level 5	Contrast Estimate		8.727
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		8.727
	Std. Error		4.859
	Sig.		.075
	95% Confidence Interval for Difference	Lower Bound	-.900
		Upper Bound	18.354
Level 3 vs. Level 5	Contrast Estimate		6.876
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		6.876
	Std. Error		3.029
	Sig.		.025
	95% Confidence Interval for Difference	Lower Bound	.874
		Upper Bound	12.879
Level 4 vs. Level 5	Contrast Estimate		4.289
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		4.289
	Std. Error		2.925
	Sig.		.145
	95% Confidence Interval for Difference	Lower Bound	-1.506
		Upper Bound	10.084

a. Reference category = 5



Echo Analysis_FDB

Between-Subjects Factors

		Value Label	N
Groups	1.0	1st MTP	8
	2.0	Diabetes	9
	3.0	CAI	29
	4.0	PFP	35
	5.0	Healthy	38

Descriptive Statistics

Dependent Variable: FDB_Echo

Groups	Mean	Std. Deviation	N
1st MTP	79.8438	16.14630	8
Diabetes	62.1867	19.41592	9
CAI	59.8021	9.75936	29
PFP	54.5429	12.02155	35

Healthy	49.3928	10.29974	38
Total	56.4590	14.07196	119

Tests of Between-Subjects Effects

Dependent Variable: FDB_Echo

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	9329.906[a]	6	1554.984	12.408	.000
Intercept	2332.150	1	2332.150	18.609	.000
Age	1329.188	1	1329.188	10.606	.001
Sex	1678.131	1	1678.131	13.390	.000
Groups	2607.700	4	651.925	5.202	.001
Error	14036.472	112	125.326		
Total	402692.437	119			
Corrected Total	23366.378	118			

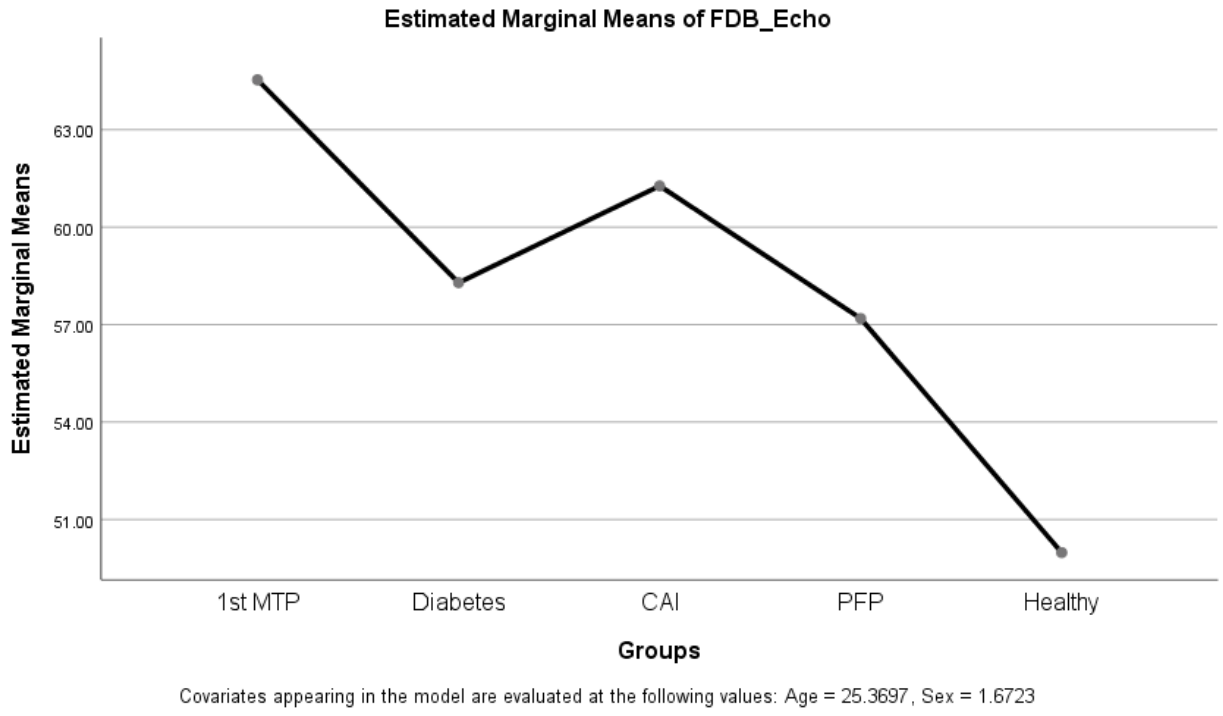
a. R Squared = .399 (Adjusted R Squared = .367)

Contrast Results (K Matrix)

Groups Simple Contrast[a]			Dependent Variable FDB_Echo
Level 1 vs. Level 5	Contrast Estimate		14.553
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		14.553
	Std. Error		6.627
	Sig.		.030
	95% Confidence Interval for Difference	Lower Bound	1.423
		Upper Bound	27.683
Level 2 vs. Level 5	Contrast Estimate		8.309
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		8.309
	Std. Error		4.464
	Sig.		.065
	95% Confidence Interval for Difference	Lower Bound	-.536
		Upper Bound	17.154
Level 3 vs. Level 5	Contrast Estimate		11.288

	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		11.288
	Std. Error		2.783
	Sig.		.000
	95% Confidence Interval for Difference	Lower Bound	5.774
		Upper Bound	16.803
Level 4 vs. Level 5	Contrast Estimate		7.209
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		7.209
	Std. Error		2.687
	Sig.		.008
	95% Confidence Interval for Difference	Lower Bound	1.885
		Upper Bound	12.533

a. Reference category = 5



Combined Echogenecity Analysis:

Between-Subjects Factors

		Value Label	N
Groups	1.0	1st MTP	8
	2.0	Diabetes	9
	3.0	CAI	29
	4.0	PFP	35
	5.0	Healthy	38

Descriptive Statistics

Dependent Variable: Combined_Echo

Groups	Mean	Std. Deviation	N
1st MTP	76.3713	10.07924	8
Diabetes	61.3056	18.60385	9
CAI	57.9217	7.52023	29
PFP	53.8129	10.80570	35
Healthy	49.4958	7.71245	38
Total	55.5188	11.88292	119

Tests of Between-Subjects Effects

Dependent Variable: Combined_Echo

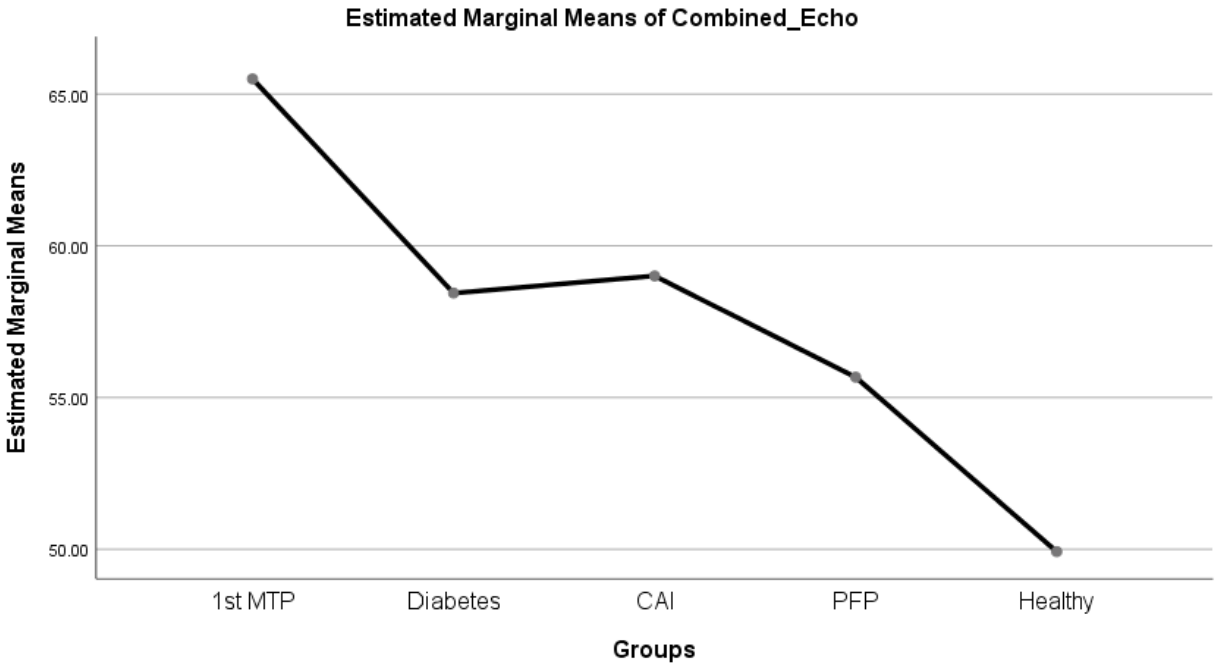
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	6396.041[a]	6	1066.007	11.630	.000
Intercept	3865.744	1	3865.744	42.174	.000
Age	664.847	1	664.847	7.253	.008
Sex	598.740	1	598.740	6.532	.012
Groups	1964.230	4	491.057	5.357	.001
Error	10266.003	112	91.661		
Total	383460.476	119			
Corrected Total	16662.044	118			

a. R Squared = .384 (Adjusted R Squared = .351)

Contrast Results (K Matrix)

Groups Simple Contrast[a]			Dependent Variable Combined_Echo
Level 1 vs. Level 5	Contrast Estimate		15.577
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		15.577
	Std. Error		5.667
	Sig.		.007
	95% Confidence Interval for Difference	Lower Bound	4.348
		Upper Bound	26.806
Level 2 vs. Level 5	Contrast Estimate		8.518
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		8.518
	Std. Error		3.818
	Sig.		.028
	95% Confidence Interval for Difference	Lower Bound	.954
		Upper Bound	16.083
Level 3 vs. Level 5	Contrast Estimate		9.085
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		9.085
	Std. Error		2.380
	Sig.		.000
	95% Confidence Interval for Difference	Lower Bound	4.368
		Upper Bound	13.801
Level 4 vs. Level 5	Contrast Estimate		5.748
	Hypothesized Value		0
	Difference (Estimate - Hypothesized)		5.748
	Std. Error		2.298
	Sig.		.014
	95% Confidence Interval for Difference	Lower Bound	1.195
		Upper Bound	10.301

a. Reference category = 5



Covariates appearing in the model are evaluated at the following values: Age = 25.3697, Sex = 1.6723

Manuscript 2

Position into time points repeated measures ANOVA

Trained Leg

CSA size of Abductor Hallucis.

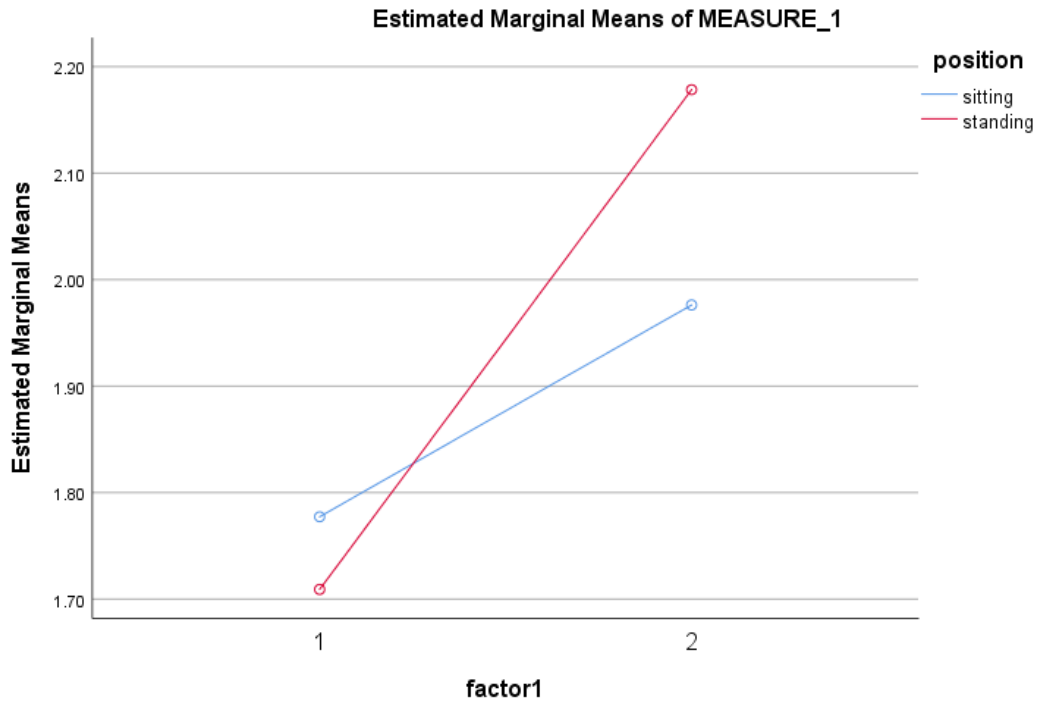
Descriptive Statistics

	position	Mean	Std. Deviation	N
pre_AH_tr	sitting	1.7773	.53515	26
	standing	1.7091	.54198	26
	Total	1.7432	.53438	52
post_AH_tr	sitting	1.9762	.65272	26
	standing	2.1784	.67681	26
	Total	2.0773	.66619	52

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	2.902	1	2.902	42.749	.000	.461
	Greenhouse-Geisser	2.902	1.000	2.902	42.749	.000	.461
	Huynh-Feldt	2.902	1.000	2.902	42.749	.000	.461
	Lower-bound	2.902	1.000	2.902	42.749	.000	.461
factor1 * position	Sphericity Assumed	.475	1	.475	7.005	.011	.123
	Greenhouse-Geisser	.475	1.000	.475	7.005	.011	.123
	Huynh-Feldt	.475	1.000	.475	7.005	.011	.123
	Lower-bound	.475	1.000	.475	7.005	.011	.123
Error(factor1)	Sphericity Assumed	3.394	50	.068			
	Greenhouse-Geisser	3.394	50.000	.068			
	Huynh-Feldt	3.394	50.000	.068			
	Lower-bound	3.394	50.000	.068			



FDB CSA_Trained Leg

Descriptive Statistics

	position	Mean	Std. Deviation	N
pre_FDB_tr	sitting	1.8577	.40801	26
	standing	1.8240	.49266	26
	Total	1.8408	.44819	52
post_FDB_tr	sitting	1.9777	.58817	26
	standing	2.1153	.43996	26
	Total	2.0465	.51893	52

Tests of Within-Subjects Effects

Measure: MEASURE_1

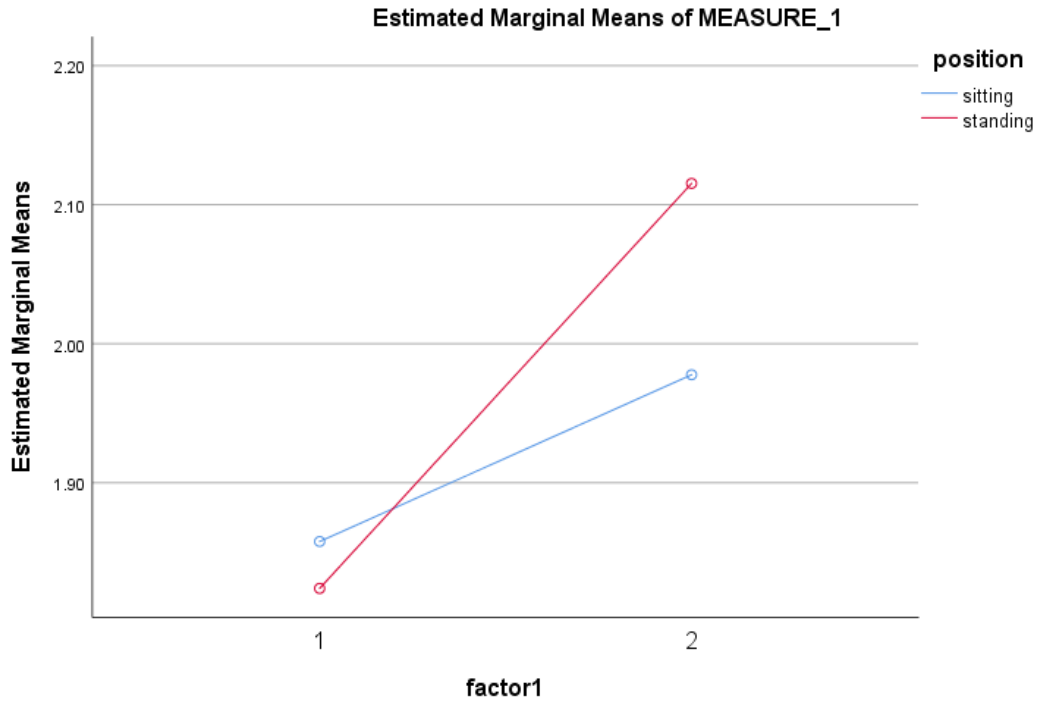
Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial
factor1	Sphericity Assumed	1.100	1	1.100	15.052	.000	
	Greenhouse-Geisser	1.100	1.000	1.100	15.052	.000	
	Huynh-Feldt	1.100	1.000	1.100	15.052	.000	

	Lower-bound	1.100	1.000	1.100	15.052	.000	
factor1 * position	Sphericity Assumed	.191	1	.191	2.611	.112	
	Greenhouse-Geisser	.191	1.000	.191	2.611	.112	
	Huynh-Feldt	.191	1.000	.191	2.611	.112	
	Lower-bound	.191	1.000	.191	2.611	.112	
Error(factor1)	Sphericity Assumed	3.653	50	.073			
	Greenhouse-Geisser	3.653	50.000	.073			
	Huynh-Feldt	3.653	50.000	.073			
	Lower-bound	3.653	50.000	.073			

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	factor1	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta S
factor1	Level 1 vs. Level 2	2.199	1	2.199	15.052	.000	
factor1 * position	Level 1 vs. Level 2	.382	1	.382	2.611	.112	
Error(factor1)	Level 1 vs. Level 2	7.306	50	.146			



Untrained leg:

Abductor Hallucis CSA:

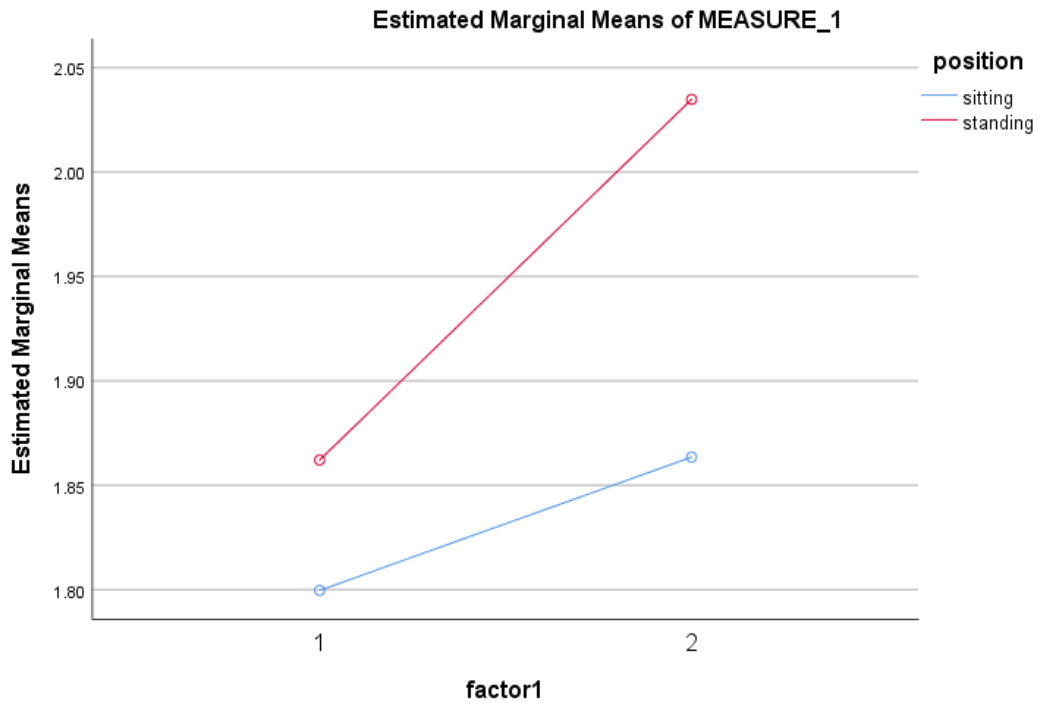
Descriptive Statistics

	position	Mean	Std. Deviation	N
pre_AH_unt	sitting	1.7996	.56464	26
	standing	1.8620	.62850	26
	Total	1.8308	.59238	52
post_AH_unt	sitting	1.8635	.63316	26
	standing	2.0348	.64186	26
	Total	1.9491	.63715	52

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	.364	1	.364	7.639	.008	.133
	Greenhouse-Geisser	.364	1.000	.364	7.639	.008	.133
	Huynh-Feldt	.364	1.000	.364	7.639	.008	.133
	Lower-bound	.364	1.000	.364	7.639	.008	.133
factor1 * position	Sphericity Assumed	.077	1	.077	1.619	.209	.031
	Greenhouse-Geisser	.077	1.000	.077	1.619	.209	.031
	Huynh-Feldt	.077	1.000	.077	1.619	.209	.031
	Lower-bound	.077	1.000	.077	1.619	.209	.031
Error(factor1)	Sphericity Assumed	2.382	50	.048			
	Greenhouse-Geisser	2.382	50.000	.048			
	Huynh-Feldt	2.382	50.000	.048			
	Lower-bound	2.382	50.000	.048			



FDB untrained CSA:

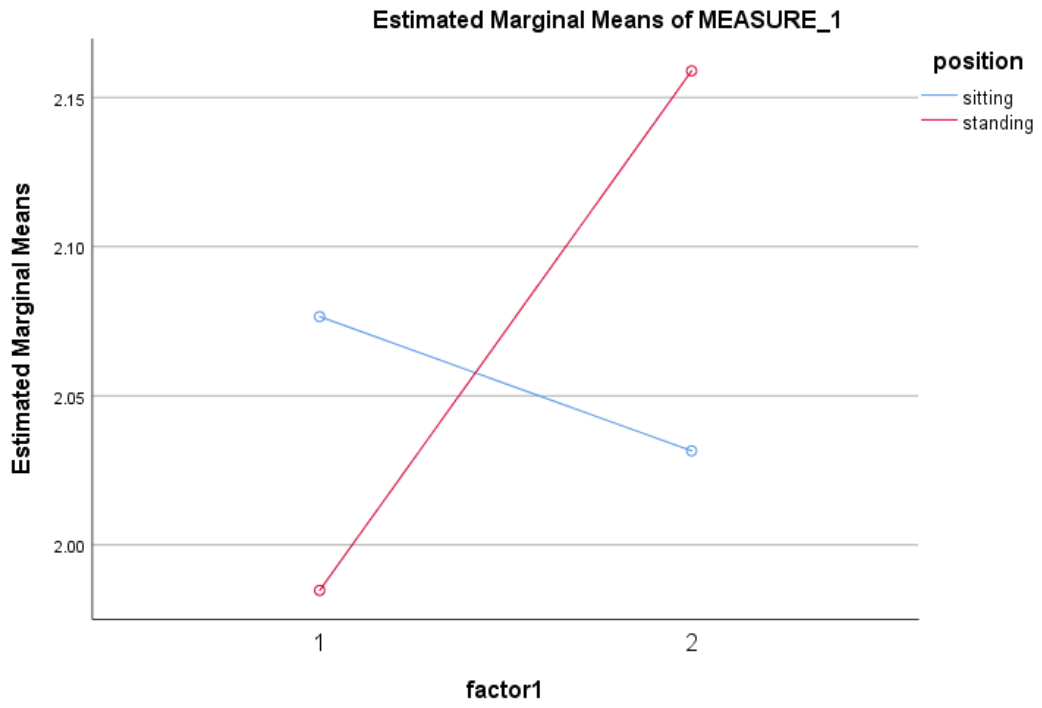
Descriptive Statistics

	position	Mean	Std. Deviation	N
pre_FDB_unt	sitting	2.0765	.43779	26
	standing	1.9848	.51357	26
	Total	2.0307	.47475	52
post_FDB_unt	sitting	2.0315	.56151	26
	standing	2.1589	.48856	26
	Total	2.0952	.52507	52

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial
factor1	Sphericity Assumed	.108	1	.108	1.435	.237	
	Greenhouse-Geisser	.108	1.000	.108	1.435	.237	
	Huynh-Feldt	.108	1.000	.108	1.435	.237	
	Lower-bound	.108	1.000	.108	1.435	.237	
factor1 * position	Sphericity Assumed	.312	1	.312	4.132	.047	
	Greenhouse-Geisser	.312	1.000	.312	4.132	.047	
	Huynh-Feldt	.312	1.000	.312	4.132	.047	
	Lower-bound	.312	1.000	.312	4.132	.047	
Error(factor1)	Sphericity Assumed	3.778	50	.076			
	Greenhouse-Geisser	3.778	50.000	.076			
	Huynh-Feldt	3.778	50.000	.076			
	Lower-bound	3.778	50.000	.076			



Manuscript 3

Trained leg, peroneal CSA and position effect:

ANOVA in trained leg showed that there was a significant interaction between position and time points.

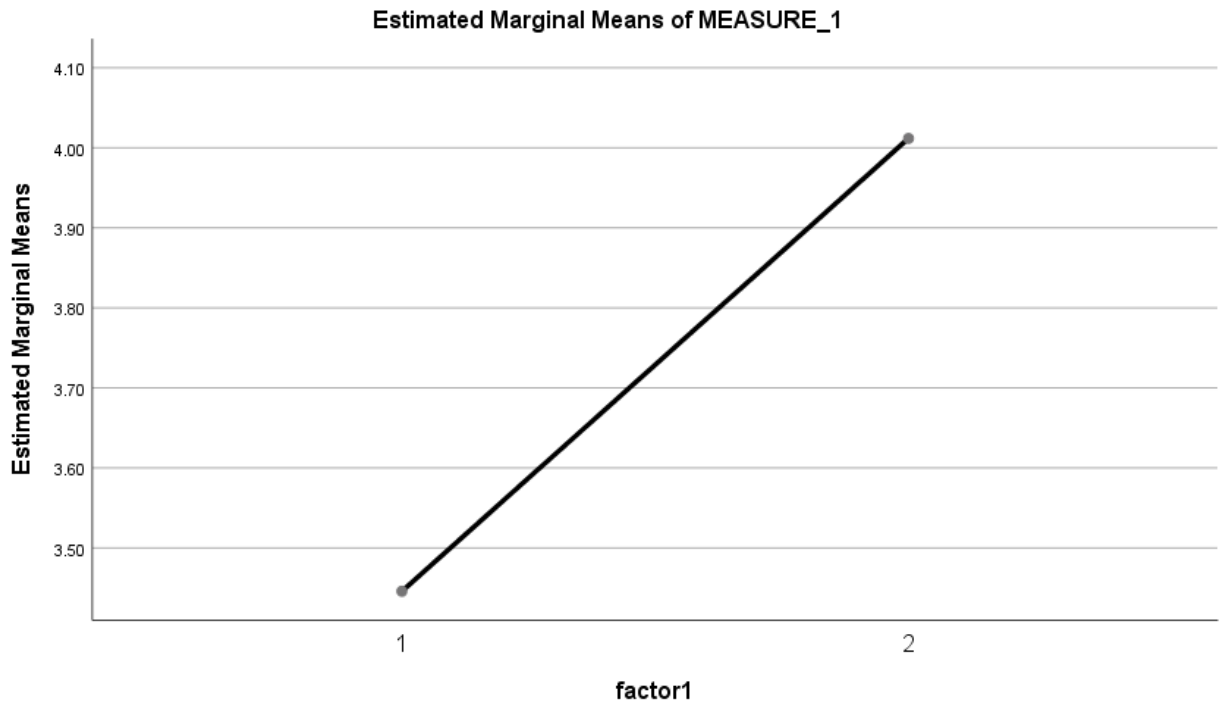
Descriptive Statistics

	position	Mean	Std. Deviation	N
pre_trained	lying	3.4362	.98743	26
	standing	3.4558	1.05874	26
	Total	3.4460	1.01367	52
post_trained	lying	3.7169	.97805	26
	standing	4.3065	.98202	26
	Total	4.0117	1.01501	52

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	8.322	1	8.322	75.082	.000
	Greenhouse-Geisser	8.322	1.000	8.322	75.082	.000
	Huynh-Feldt	8.322	1.000	8.322	75.082	.000
	Lower-bound	8.322	1.000	8.322	75.082	.000
factor1 * position	Sphericity Assumed	2.112	1	2.112	19.052	.000
	Greenhouse-Geisser	2.112	1.000	2.112	19.052	.000
	Huynh-Feldt	2.112	1.000	2.112	19.052	.000
	Lower-bound	2.112	1.000	2.112	19.052	.000
Error(factor1)	Sphericity Assumed	5.542	50	.111		
	Greenhouse-Geisser	5.542	50.000	.111		
	Huynh-Feldt	5.542	50.000	.111		
	Lower-bound	5.542	50.000	.111		



Tests of Within-Subjects Effects

Measure: MEASURE_1

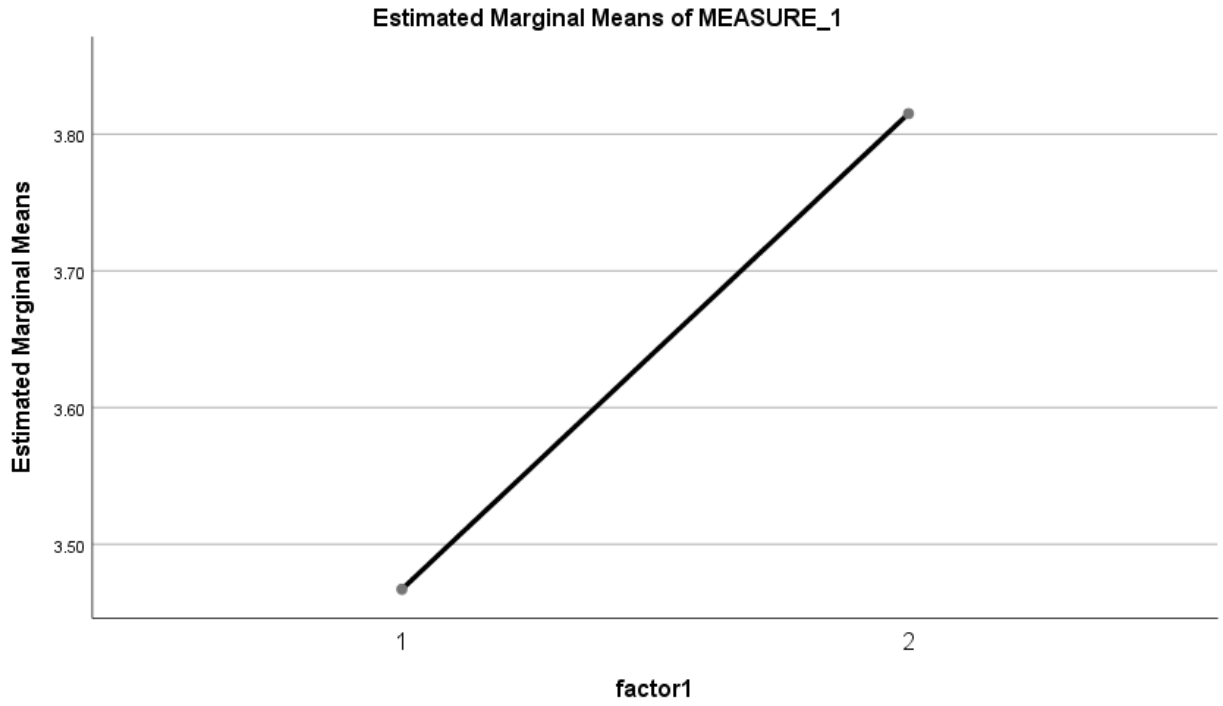
Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	3.147	1	3.147	24.500	.000
	Greenhouse-Geisser	3.147	1.000	3.147	24.500	.000
	Huynh-Feldt	3.147	1.000	3.147	24.500	.000
	Lower-bound	3.147	1.000	3.147	24.500	.000
factor1 * position	Sphericity Assumed	.088	1	.088	.687	.411
	Greenhouse-Geisser	.088	1.000	.088	.687	.411
	Huynh-Feldt	.088	1.000	.088	.687	.411
	Lower-bound	.088	1.000	.088	.687	.411
Error(factor1)	Sphericity Assumed	6.422	50	.128		
	Greenhouse-Geisser	6.422	50.000	.128		
	Huynh-Feldt	6.422	50.000	.128		
	Lower-bound	6.422	50.000	.128		

ANOVA in untrained leg

No interaction was found between the position and time points in the untrained leg. However, there was significant time effect.

Descriptive Statistics

	position	Mean	Std. Deviation	N
pre_untrained	lying	3.3404	.92288	26
	standing	3.5938	1.01942	26
	Total	3.4671	.97123	52
post_untrained	lying	3.6300	1.01058	26
	standing	4.0000	1.21154	26
	Total	3.8150	1.12029	52



Appendix E: Back Matter

Recommendations for Future Research

1. Correlating ultrasound measures with functional assessment methods to best identify the tools or tests that can be used to differentiate the activity of Intrinsic Foot Muscles from the extrinsic muscles

2. Administration of longer rehabilitation programs, greater than 4-weeks of impairment-based rehabilitation, to further understand the changes especially in muscle quality

3. Use of ultrasound imaging to create more discriminative clinical screening of muscle activity to identity impairments in lower extremity muscles and follow prospectively for injury occurrence

4. Use of ultrasound imaging during the impairment-based rehabilitation not only at baseline and final collection, but throughout rehab to understand the point where physiological changes start taking place and to guide the progression of exercises

5. Administration of impairment-based rehabilitation in clinical sub-groups where IFM dysfunction was identified in this dissertation and analyzing if the rehab can address these deficits

6. Understanding the activity of Intrinsic Foot Muscles in the maneuvers that are purported to strengthen these muscles such as short foot exercises etc.

7. Biofeedback program with impairment-based model structure for training of lower limb muscles such as Intrinsic Foot Muscles and peroneal

8. Correlating ultrasound measures with functional improvements such as balance, that can show if the changes in ultrasound measures correspond with parallel functional improvement

Bibliography

1. Kura H, Luo ZP, Kitaoka HB, An KN. Quantitative analysis of the intrinsic muscles of the foot. *The Anatomical Record: An Official Publication of the American Association of Anatomists.* 1997;249(1):143-151.

2. McKeon PO, Hertel J, Bramble D, Davis I. The foot core system: a new paradigm for understanding intrinsic foot muscle function. *Br J Sports Med.* 2014:bjsports-2013-092690.

3. MANN R, INMAN VT. Phasic activity of intrinsic muscles of the foot. *JBJS.* 1964;46(3):469-481.

4. Basmajian JV, Stecko G. The role of muscles in arch support of the foot: an electromyographic study. *JBJS.* 1963;45(6):1184-1190.

5. Chang R, Larsen R, Kent-Braun J, Hamill J. Energetics of the intrinsic foot muscles in plantar fasciitis. *Journal of foot and ankle research.* 2008;1(S1):O1.

6. Rolian C, Lieberman DE, Hamill J, Scott JW, Werbel W. Walking, running and the evolution of short toes in humans. *Journal of Experimental Biology.* 2009;212(5):713-721.

7. Kelly LA, Kuitunen S, Racinais S, Cresswell AG. Recruitment of the plantar intrinsic foot muscles with increasing postural demand. *Clinical biomechanics.* 2012;27(1):46-51.

8. Soysa A, Hiller C, Refshauge K, Burns J. Importance and challenges of measuring intrinsic foot muscle strength. *Journal of foot and ankle research.* 2012;5(1):29.

9. Sabir M, Lyttle D. Pathogenesis of pes cavus in Charcot-Marie-Tooth disease. *Clinical orthopaedics and related research.* 1983(175):173-178.

10. Myerson M, Shereff M. The pathological anatomy of claw and hammer toes. *The Journal of bone and joint surgery American volume.* 1989;71(1):45-49.

11. Ker R, Bennett M, Bibby S, Kester R, Alexander RM. The spring in the arch of the human foot. *Nature.* 1987;325(6100):147-149.

12. Holowka NB, Lieberman DE. Rethinking the evolution of the human foot: insights from experimental research. *Journal of Experimental Biology.* 2018;221(17):jeb174425.

13. Jaffri AH, Hertel J, Saliba S. Ultrasound examination of intrinsic foot muscles in patients with 1st metatarsophalangeal joint arthrodesis. *The Foot.* 2019;41:79-84.

14. McKeon PO, Hertel J, Bramble D, Davis I. The foot core system: a new paradigm for understanding intrinsic foot muscle function. *Br J Sports Med.* 2015;49(5):290-290.

15. Kelly L, Lichtwark G, Cresswell A. Dynamic function of the plantar intrinsic foot muscles during walking and running. *Journal of Science and Medicine in Sport.* 2013;16:e4.

16. Kelly LA, Cresswell AG, Racinais S, Whiteley R, Lichtwark G. Intrinsic foot muscles have the capacity to control deformation of the longitudinal arch. *Journal of The Royal Society Interface.* 2014;11(93):20131188.

17. Feger MA, Snell S, Handsfield GG, et al. Diminished foot and ankle muscle volumes in young adults with chronic ankle instability. *Orthopaedic journal of sports medicine.* 2016;4(6):2325967116653719.

18. Jam B. Evaluation and retraining of the intrinsic foot muscles for pain syndromes related to abnormal control of pronation. *Advanced Physical Therapy Education Institute.* 2006.

19. Spink MJ, Fotoohabadi MR, Menz HB. Foot and ankle strength assessment using hand-held dynamometry: reliability and age-related differences. *Gerontology.* 2010;56(6):525-532.

20. Sheehan FT. The instantaneous helical axis of the subtalar and talocrural joints: a non-invasive in vivo dynamic study. *Journal of foot and ankle research.* 2010;3(1):13.

21. Kuo GP, Carrino JA. Skeletal muscle imaging and inflammatory myopathies. *Current opinion in rheumatology.* 2007;19(6):530-535.

22. Alanen A, Falck B, Kalimo H, Komu M, Sonninen V. Ultrasound, computed tomography and magnetic resonance imaging in myopathies: correlations with electromyography and histopathology. *Acta neurologica scandinavica.* 1994;89(5):336-346.

23. Robertson DD, Mueller MJ, Smith KE, Commean PK, Pilgram T, Johnson JE. Structural changes in the forefoot of individuals with diabetes and a prior plantar ulcer. *JBJS.* 2002;84(8):1395-1404.

24. Smith MMF, Hides JA, Hodges PW, Collins NJ. Intrinsic foot muscle size can be measured reliably in weight bearing using ultrasound imaging. *Gait & posture.* 2019;68:369-374.

25. Scanlon TC, Fragala MS, Stout JR, et al. Muscle architecture and strength: Adaptations to short- term resistance training in older adults. *Muscle & nerve.* 2014;49(4):584-592.

26. Taniguchi M, Fukumoto Y, Kobayashi M, et al. Quantity and quality of the lower extremity muscles in women with knee osteoarthritis. *Ultrasound in medicine & biology.* 2015;41(10):2567-2574.

27. Hing WA, Rome K, Cameron AF. Reliability of measuring abductor hallucis muscle parameters using two different diagnostic ultrasound machines. *Journal of foot and ankle research.* 2009;2(1):33.

28. Mickle KJ, Nester CJ, Crofts G, Steele JR. Reliability of ultrasound to measure morphology of the toe flexor muscles. *Journal of foot and ankle research.* 2013;6(1):12.

29. Angin S, Crofts G, Mickle KJ, Nester CJ. Ultrasound evaluation of foot muscles and plantar fascia in pes planus. *Gait & posture.* 2014;40(1):48-52.

30. Battaglia PJ, Mattox R, Winchester B, Kettner NW. Non-Weight-Bearing and Weight-Bearing Ultrasonography of Select Foot Muscles in Young, Asymptomatic Participants: A Descriptive and Reliability Study. *Journal of Manipulative and Physiological Therapeutics.* 2016;39(9):655-661.

31. Smith A, Hides JA, Hodges PW, Collins NJ. Intrinsic foot muscle size can be measured reliably in weight bearing using ultrasound imaging. *Gait & posture.* 2019;68:369-374.

32. Pillen S. Skeletal muscle ultrasound. *European Journal of Translational Myology.* 2010;20(4):145-156.

33. Whittaker JL, Teyhen DS, Elliott JM, et al. Rehabilitative ultrasound imaging: understanding the technology and its applications. *journal of orthopaedic & sports physical therapy.* 2007;37(8):434-449.

34. Pillen S, van Alfen N. Skeletal muscle ultrasound. *Neurological research.* 2011;33(10):1016-1024.

35. Yamada Y, Schoeller DA, Nakamura E, Morimoto T, Kimura M, Oda S. Extracellular water may mask actual muscle atrophy during aging. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences.* 2010;65(5):510-516.

36. Sipilä S, Koskinen SO, Taaffe DR, et al. Determinants of lower- body muscle power in early postmenopausal women. *Journal of the American Geriatrics Society.* 2004;52(6):939-944.

37. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *Journal of applied physiology.* 2001;90(6):2157-2165.

38. Damas F, Phillips SM, Lixandrão ME, et al. Early resistance training-induced increases in muscle cross-sectional area are concomitant with edema-induced muscle swelling. *European journal of applied physiology.* 2016;116(1):49-56.

39. Jenkins ND. *Neuromuscular adaptations to three and six weeks of high-versus low-load resistance training.* The University of Nebraska-Lincoln; 2016.

40. Jenkins ND, Housh TJ, Buckner SL, et al. Neuromuscular adaptations after 2 and 4 weeks of 80% versus 30% 1 repetition maximum resistance training to failure. *Journal of strength and conditioning research.* 2016;30(8):2174-2185.

41. Hodges P, Pengel L, Herbert R, Gandevia S. Measurement of muscle contraction with ultrasound imaging. *Muscle & nerve.* 2003;27(6):682-692.

42. Mangum LC, Henderson K, Murray KP, Saliba SA. Ultrasound Assessment of the Transverse Abdominis During Functional Movement. *Journal of Ultrasound in Medicine.* 2018;37(5):1225-1231.

43. Mckay GD, Goldie P, Payne WR, Oakes B. Ankle injuries in basketball: injury rate and risk factors. *British journal of sports medicine.* 2001;35(2):103-108.

44. Hertel J. Functional anatomy, pathomechanics, and pathophysiology of lateral ankle instability. *Journal of athletic training.* 2002;37(4):364.

45. Hertel J. Sensorimotor deficits with ankle sprains and chronic ankle instability. *Clinics in sports medicine.* 2008;27(3):353-370.

46. Doherty C, Bleakley C, Hertel J, Caulfield B, Ryan J, Delahunt E. Recovery from a first-time lateral ankle sprain and the predictors of chronic ankle instability: a prospective cohort analysis. *The American journal of sports medicine.* 2016;44(4):995-1003.

47. Delahunt E, Coughlan GF, Caulfield B, Nightingale EJ, Lin C, Hiller CE. Inclusion criteria when investigating insufficiencies in chronic ankle instability. *Med Sci Sports Exerc.* 2010;42(11):2106-2121.

48. Feger MA, Snell S, Handsfield GG, et al. Diminished Foot and Ankle Muscle Volumes in Young Adults With Chronic Ankle Instability. *Orthopaedic Journal of Sports Medicine.* 2016;4(6).

49. Nitz AJ, Dobner JJ, Kersey D. Nerve injury and grades II and III ankle sprains. *The American journal of sports medicine.* 1985;13(3):177-182.

50. Jazayeri SS, Didehdar D, Moghtaderi AE. Tibial and peroneal nerve conduction studies in ankle sprain. *Electromyography and clinical neurophysiology.* 2007;47(6):301-304.

51. PROTOCOL S. Ferber R, Farr L, Kendall KD. *Patellofemoral Pain Syndrome: Proximal, Distal, and Local Factors An International Research Retreat.* 2010;40(3):39.

52. Kannus P, Niittymäki S. Which factors predict outcome in the nonoperative treatment of patellofemoral pain syndrome? A prospective follow-up study. *Medicine & Science in Sports & Exercise.* 1994.

53. Sandow M, Goodfellow J. The natural history of anterior knee pain in adolescents. *The Journal of bone and joint surgery British volume.* 1985;67(1):36-38.

54. Wyndow N, Collins NJ, Vicenzino B, Tucker K, Crossley KM. Foot and ankle characteristics and dynamic knee valgus in individuals with patellofemoral osteoarthritis. *Journal of foot and ankle research.* 2018;11(1):65.

55. McPoil TG, Warren M, Vicenzino B, Cornwall MW. Variations in foot posture and mobility between individuals with patellofemoral pain and those in a control group. *Journal of the American Podiatric Medical Association.* 2011;101(4):289-296.

56. Unver B, Erdem EU, Akbas E. Effects of Short-Foot Exercises on Foot Posture, Pain, Disability and Plantar Pressure in Pes Planus. *J Sport Rehabil.* 2019:1-16.

57. Chang R, Kent-Braun JA, Hamill J. Use of MRI for volume estimation of tibialis posterior and plantar intrinsic foot muscles in healthy and chronic plantar fasciitis limbs. *Clinical Biomechanics.* 2012;27(5):500-505.

58. Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. *New England Journal of Medicine.* 2017;376(24):2367-2375.

59. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). *The journal of foot and ankle surgery.* 2006;45(5):S1-S66.

60. Bus SA, Yang QX, Wang JH, Smith MB, Wunderlich R, Cavanagh PR. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study. *Diabetes care.* 2002;25(8):1444-1450.

61. Bus SA, Maas M, Michels RP, Levi M. Role of intrinsic muscle atrophy in the etiology of claw toe deformity in diabetic neuropathy may not be as straightforward as widely believed. *Diabetes Care.* 2009;32(6):1063-1067.

62. Angin S, Crofts G, Mickle KJ, Nester CJ. Ultrasound evaluation of foot muscles and plantar fascia in pes planus. *Gait & posture.* 2014;40(1):48-52.

63. Crofts G, Angin S, Mickle KJ, Hill S, Nester C. Reliability of ultrasound for measurement of selected foot structures. *Gait & posture.* 2014;39(1):35-39.

64. Menz HB, Jordan KP, Roddy E, Croft PR. Characteristics of primary care consultations for musculoskeletal foot and ankle problems in the UK. *Rheumatology.* 2010;49(7):1391-1398.

65. Houglum PA, Bertoti DB. *Brunnstrom's clinical kinesiology.* FA Davis; 2011.

66. Stevens J, Meijer K, Bijnens W, et al. Gait analysis of foot compensation after arthrodesis of the first metatarsophalangeal joint. *Foot & ankle international.* 2017;38(2):181-191.

67. Brodsky JW, Passmore RN, Pollo FE, Shabat S. Functional outcome of arthrodesis of the first metatarsophalangeal joint using parallel screw fixation. *Foot & ankle international.* 2005;26(2):140-146.

68. Oloff LM, Traynor C, Vartivarian SR. Joint Salvage Techniques for Stage III/IV Hallux Rigidus. *The Role of Osteotomy in the Correction of Congenital and Acquired Disorders of the Skeleton*: InTech; 2012.

69. Gaudin G, Coillard J-Y, Augoyard M, et al. Incidence and outcomes of revision surgery after first metatarsophalangeal joint arthrodesis: Multicenter study of 158 cases. *Orthopaedics & Traumatology: Surgery & Research.* 2018.

70. Headlee DL, Leonard JL, Hart JM, Ingersoll CD, Hertel J. Fatigue of the plantar intrinsic foot muscles increases navicular drop. *Journal of Electromyography and Kinesiology.* 2008;18(3):420-425.

71. Okamura K, Kanai S, Hasegawa M, Otsuka A, Oki S. The effect of additional activation of the plantar intrinsic foot muscles on foot dynamics during gait. *The Foot.* 2018;34:1-5.

72. Bemben MG. Use of diagnostic ultrasound for assessing muscle size. *Journal of Strength and Conditioning Research.* 2002;16(1):103-108.

73. Donatelli R. *The biomechanics of the foot and ankle.* FA Davis Company; 1996.

74. Lynn SK, Padilla RA, Tsang KK. Differences in static-and dynamic-balance task performance after 4 weeks of intrinsic-foot-muscle training: the short-foot exercise versus the towel-curl exercise. *Journal of sport rehabilitation.* 2012;21(4):327-333.

75. Zelik KE, La Scaleia V, Ivanenko YP, Lacquaniti F. Coordination of intrinsic and extrinsic foot muscles during walking. *European journal of applied physiology.* 2015;115(4):691-701.

76. Garth JR WP, Miller ST. Evaluation of claw toe deformity, weakness of the foot intrinsics, and posteromedial shin pain. *The American journal of sports medicine.* 1989;17(6):821-827.

77. Andersen H, Gjerstad MD, Jakobsen J. Atrophy of foot muscles: a measure of diabetic neuropathy. *Diabetes care.* 2004;27(10):2382-2385.

78. McKeon PO, Fourchet F. Freeing the foot: integrating the foot core system into rehabilitation for lower extremity injuries. *Clinics in sports medicine.* 2015;34(2):347-361.

79. Fraser JJ, Hertel J. Effects of a 4-week intrinsic foot muscle exercise program on motor function: a preliminary randomized control trial. *Journal of sport rehabilitation.* 2019;28(4):339-349.

80. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Physical therapy.* 2003;83(8):713-721.

81. UNGER CL, WOODEN MJ. Effect of foot intrinsic muscle strength training on jump performance. *The Journal of Strength & Conditioning Research.* 2000;14(4):373-378.

82. Lee E, Cho J, Lee S. Short-foot exercise promotes quantitative somatosensory function in ankle instability: a randomized controlled trial. *Medical science monitor: international medical journal of experimental and clinical research.* 2019;25:618.

83. Hashimoto T, Sakuraba K. Strength training for the intrinsic flexor muscles of the foot: effects on muscle strength, the foot arch, and dynamic parameters before and after the training. *Journal of physical therapy science.* 2014;26(3):373-376.

84. Kamonseki DH, Gonçalves GA, Liu CY, Júnior IL. Effect of stretching with and without muscle strengthening exercises for the foot and hip in patients with plantar fasciitis: a randomized controlled single-blind clinical trial. *Manual therapy.* 2016;23:76-82.

85. Saikia P, Dutta A, Bhattacharya U, Boruah K. Effectiveness of Intrinsic Muscle Strengthening with Orthosis Over Conventional Physiotherapy with Orthosis for Navicular Drop in Prolong Standing Workers. *INTERNATIONAL JOURNAL OF PHYSIOTHERAPY.* 2015;2(4):610-618.

86. Unver B, Erdem EU, Akbas E. Effects of Short-Foot Exercises on Foot Posture, Pain, Disability and Plantar Pressure in Pes Planus. *Journal of sport rehabilitation.* 2019:1-16.

87. Jung D-Y, Koh E-K, Kwon O-Y. Effect of foot orthoses and short-foot exercise on the cross-sectional area of the abductor hallucis muscle in subjects with pes planus: a randomized controlled trial 1. *Journal of back and musculoskeletal rehabilitation.* 2011;24(4):225-231.

88. Mulligan EP, Cook PG. Effect of plantar intrinsic muscle training on medial longitudinal arch morphology and dynamic function. *Manual therapy.* 2013;18(5):425-430.

89. Cohen J, Cohen P, West SG, Aiken LS. *Applied multiple regression/correlation analysis for the behavioral sciences.* Routledge; 2013.

90. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions.* Vol 4: John Wiley & Sons; 2011.

91. Ebrecht F, Sichting F. Does neuromuscular electrostimulation have the potential to increase intrinsic foot muscle strength? *The Foot.* 2018;35:56-62.

92. Tudpor K, Traithip W. Fall Prevention by Short-Foot Exercise in Diabetic Patients. *Indian Journal of Physiotherapy & Occupational Therapy.* 2019;13(2).

93. Jaffri AH, Newman TM, Smith BI, et al. Dynamic Leap and Balance Test: Ability to Discriminate Balance Deficits in Individuals With Chronic Ankle Instability. *Journal of Sport Rehabilitation.* 2020;29(3):263-270.

94. Mansfield PJ, Neumann DA. *Essentials of kinesiology for the physical therapist assistant.* Elsevier Health Sciences; 2018.

95. Yammine K, Fathi Y. Ankle "sprains" during sport activities with normal radiographs: incidence of associated bone and tendon injuries on MRI findings and its clinical impact. *The Foot.* 2011;21(4):176-178.

96. Bellew JW, Frilot CF, Busch SC, Lamothe TV, Ozane CJ. Facilitating activation of the peroneus longus: electromyographic analysis of exercises consistent with biomechanical function. *The Journal of Strength & Conditioning Research.* 2010;24(2):442-446.

97. DiGiovanni CW, Brodsky A. Current concepts: lateral ankle instability. *Foot & ankle international.* 2006;27(10):854-866.

98. Cho B-K, Park J-K, Choi S-M, SooHoo NF. The Effect of Peroneal Muscle Strength on Functional Outcomes After the Modified Broström Procedure for Chronic Ankle Instability. *Foot & ankle international.* 2018;39(1):105-112.

99. Lynch SA, Eklund U, Gottlieb D, Renstrom PA, Beynnon B. Electromyographic latency changes in the ankle musculature during inversion moments. *The American journal of sports medicine.* 1996;24(3):362-369.

100. Kim K-M, Ingersoll CD, Hertel J. Altered postural modulation of Hoffmann reflex in the soleus and fibularis longus associated with chronic ankle instability. *Journal of Electromyography and Kinesiology.* 2012;22(6):997-1002.

101. Bonnin M, Tavernier T, Bouysset M. Split lesions of the peroneus brevis tendon in chronic ankle laxity. *The American journal of sports medicine.* 1997;25(5):699-703.

102. Donnelly L, Donovan L, Hart JM, Hertel J. Eversion strength and surface electromyography measures with and without chronic ankle instability measured in 2 positions. *Foot & ankle international.* 2017;38(7):769-778.

103. Kaminski TW, Perrin DH, Gansneder BM. Eversion strength analysis of uninjured and functionally unstable ankles. *Journal of athletic training.* 1999;34(3):239.

104. Lobo CC, Morales CR, Sanz DR, Corbalán IS, Marín AG, López DL. Ultrasonography comparison of peroneus muscle cross-sectional area in subjects with or without lateral ankle sprains. *Journal of manipulative and physiological therapeutics.* 2016;39(9):635-644.

105. Sakai S, Urabe Y, Morikawa M, et al. Quantity and quality of the peroneus longus assessed using ultrasonography in leg with chronic ankle instability. *Journal of physical therapy science.* 2018;30(12):1396-1400.

106. Abdeen R, Comfort P, Starbuck C, Nester C. Ultrasound characteristics of foot and ankle structures in healthy, coper, and chronically unstable ankles. *Journal of Ultrasound in Medicine.* 2018.

107. Simon J, Docherty C. Slower nerve conduction velocity in individuals with functional ankle instability. *International journal of sports medicine.* 2014;35(09):731-736.

108. Folland JP, Williams AG. Morphological and neurological contributions to increased strength. *Sports medicine.* 2007;37(2):145-168.

109. Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *Journal of applied physiology.* 2007.

110. Franchi MV, Atherton PJ, Maganaris CN, Narici MV. Fascicle length does increase in response to longitudinal resistance training and in a contraction-mode specific manner. *Springerplus.* 2016;5(1):94.

111. Sale DG. Neural adaptation to resistance training. *Medicine and science in sports and exercise.* 1988;20(5 Suppl):S135-145.

112. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. *Journal of applied physiology.* 2006;101(5):1514-1522.

113. Abe T, Kawakami Y, Suzuki Y, Gunji A, Fukunaga T. Effects of 20 days bed rest on muscle morphology. *Journal of gravitational physiology: a journal of the International Society for Gravitational Physiology.* 1997;4(1):S10-14.

114. Ishida Y, Carroll J, Pollock M, Graves J, Leggett S. Reliability of B- mode ultrasound for the measurement of body fat and muscle thickness. *American journal of human biology.* 1992;4(4):511-520.