Cover page

Official Title of the study: MUSCLE, JOINT AND MOVEMENT DETERIORATION CONTRIBUTING TO NEUROPATHIC FOREFOOT DEFORMITY

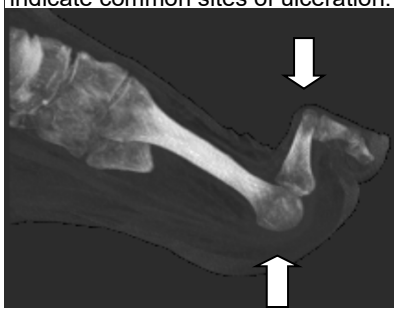
NCT Number: NCT02616263

Date of the document: Title page added on 9/25/2024, Protocol is consistent with what was required for study IRB approval 10/25/2019

3.0 RESEARCH STRATEGY

3.1 Significance

Figure 1. CT image shows MTPJ hyper-extension deformity. Arrows indicate common sites of ulceration.



3.1.1. Metatarsophalangeal joint (MTPJ) hyperextension deformity is an important risk factor for skin breakdown in people with diabetes mellitus (DM) having a prevalence as high as 85% in those with DM and a history of ulcers and amputation.[2] Characteristics of MTPJ deformity are hyperextension of the proximal phalanx on the metatarsal, and prominent metatarsal heads on the bottom of the foot (Fig. 1).[1, 14] Inter-phalangeal joints may be flexed (claw toe) or flexed and extended (hammer toe).[14, 15] Our previous work indicated MTPJ angle is the most important structural variable predicting forefoot peak plantar pressure during walking,[16] and multiple clinical studies have linked the deformity to skin breakdown.[2, 17, 18] 60-70% of the 26 million people with DM in the US have peripheral neuropathy (PN), associated with mild to severe nervous system damage. One in every four patients with DM will develop a foot ulcer[19, 20] and each treatment of a wound infection is estimated to cost approximately $28,000 for the 2 years following diagnosis.[21] Over 80% of the 65,000 diabetes-related amputations performed annually in the US are preceded by a neuropathic ulcer.[3, 4] The Task Force of the Foot Care Interest Group of the American Diabetes Association indicated the "most common triad of causes that interact and ultimately result in ulceration has been identified as neuropathy, deformity, and trauma."[1, 22] Although MTPJ deformity is a common and important acquired neuropathic foot deformity, there is little evidence to guide early detection and treatment to arrest the development and progression of deformity. This study will be the first to examine multiple contributing factors to MTPJ deformity and the potential of a targeted foot specific intervention to de-couple diabetes related mechanisms from MTPJ deformity over 3 years. The results of this study will help identify the primary factors contributing to MTPJ deformity and test an intervention directed at this proposed casual pathway.

3.1.2 Effect of AGEs on lower extremity tissues. Non-enyzmatic advanced glycation end-products (AGEs) are protein-sugar complexes that are formed when proteins or lipids are gylcated and oxidized after contact with glucose.[5] AGEs are thought to be irreversibly created and accumulate in tissues, particularly tissues with low protein turnover such as the extra cellular matrix, connective tissue, skin, and tendons.[5] AGE accumulation increases cross links between the tissues' fibers, making them thicker, stiffer and weaker. The physical properties of the tissue are compromised and are less able to perform their respective function and therefore, more susceptible to injury.[5, 6, 23] AGEs are primary factors in age-related complications affecting the extracellular matrix and connective tissue and their impact is greatly accelerated in people with DM due to the excess glucose in the blood stream and extracellular matrix.[5] The accumulation of AGEs may affect essentially every tissue in the neuropathic foot negatively and it is possible that AGEs are the common denominator in the general deterioration of the diabetic foot.[6] The tissues of particular importance in the development of acquired diabetic foot deformities are the peripheral nerves, muscles, and joints of the lower extremity. (Fig 2)

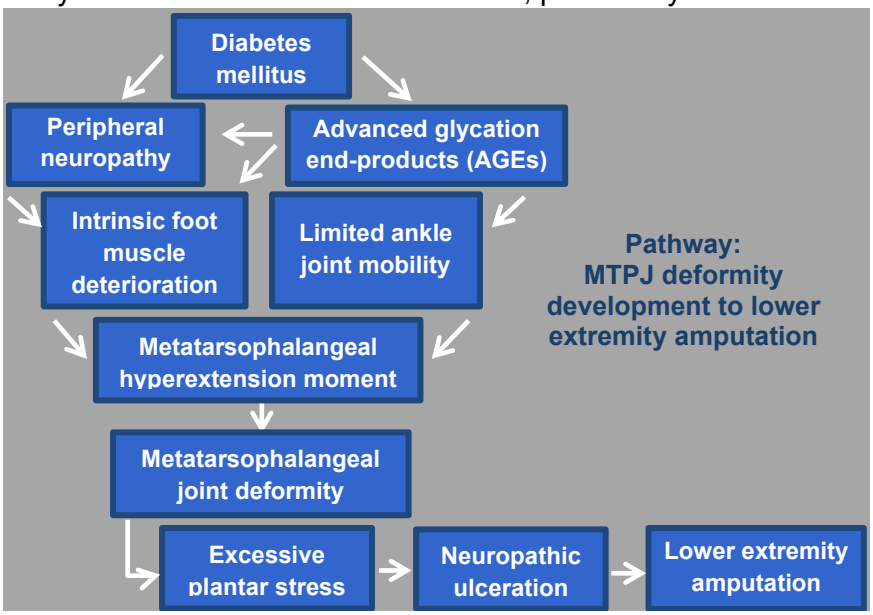


Figure 2. We will investigate the role of metabolic processes (advanced glycation end products), intrinsic foot muscle deterioration, limited joint mobility, and MTPJ hyperextension movement pattern in the presence and progression of MTPJ deformity and the ability to decouple this pathway with a foot specific intervention.

Peripheral neuropathy (PN) has long been identified as a primary risk factor for development of neuropathic plantar ulcers because of the distal deterioration of the sensory, motor, and autonomic nerves to the foot.[3] AGEs are thought to contribute to the development of PN. Meerwaldt et al (2005)[24] and Conway et al (2011)[7] have used skin autofluorescence (as proposed in this project) to identify significant relationships between estimated AGEs in the skin and symptoms of PN. Meerwaldt et al reported that autofluorescence independently explained 55% of the variance in nerve conduction velocity and amplitude ($r=0.74$, $p<0.01$).

Increased AGEs also contribute to increased stiffness and reduced viscoelasticity of muscle[8] and tendon[25] leading to reduced ability to generate muscle force and sarcopenia. We[11, 26, 27] and others[28, 29] have documented the deterioration of lower extremity muscle due to PN, but this proposal will seek to investigate how AGEs may affect muscle through PN and the independent effect from AGEs (see section 3.3.5.).

The link between AGE accumulation, decreased elasticity, increased stiffness, and diabetic limited joint mobility has been established in the upper extremity[30, 31] and hypothesized for the foot,[6, 32] but there has been little research directly linking AGEs and musculoskeletal problems of the foot. We[12]and others[33-36] have documented the relationship between limited joint mobility in the foot and skin breakdown. In particular, limited ankle dorsiflexion motion has been associated with forefoot ulcers and our randomized controlled trial to surgically increase dorsiflexion motion using an Achilles Tendon Lengthening procedure was effective in reducing the rate of ulcer recurrence during the year following the procedure.[37]

John Maynard, a co-author on the Conway et al[7] paper will continue to assist us (see letter of support) in using skin intrinsic fluorescence to estimate the level of skin AGEs. The collagen in skin has low turn-over (15 year),[38] so skin autofluorescence is thought to represent the long-term effects of hyperglycemia and oxidative stress.[24] We hypothesize that the baseline estimate of AGE level in the skin will be a predictor of baseline, 1.5 year, and 3 year MTPJ alignment (Aim 1 Ho1, Aim 3 Ho4).

3.1.3. Intrinsic foot muscle deterioration. Intrinsic foot muscles insert into the proximal phalanx of the toes and are the only muscles able to flex the MTPJ (Fig. 3, #2).[14] The extrinsic long toe extensor muscle, extensor digitorum longus, has its muscle belly in the leg and the tendons attach to the distal phalanges of the toes, resulting in extension at the MTPJ and interphalangeal joints and dorsiflexion of the ankle (Fig. 3, #1). The distal to proximal peripheral neuropathy associated with diabetes results in intrinsic foot muscle deterioration that precedes extrinsic extensor digitorum longus deterioration (Fig. 3, #3).[39-41] The muscle imbalance of weak intrinsic foot muscles in the presence of relatively stronger extrinsic toe extensors, results in a force couple that hyperextends the MTPJ and theoretically contributes to MTPJ deformity.[39]

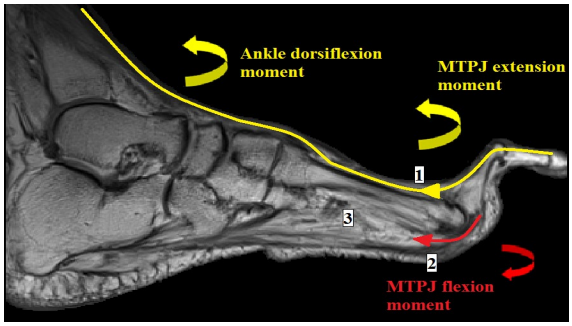


Figure 3. Sagittal MRI slice of DMPN foot with MTPJ hyperextension showing pull from extrinsic long toe extensor tendon (1), diminished pull (2) from atrophied and fat-filled intrinsic foot muscles (3).

We and others have found that people with DMPN indeed have severe deterioration of their intrinsic foot muscles, with a reduction in muscle up to 70%.[10, 11, 26, 28, 29, 41, 42] (Fig. 4) We have recently developed a reliable (ICC>0.95), valid (r^2>.97, RMSE<5%), and nimble quantitative magnetic resonance imaging (MRI) measure of not only intrinsic foot muscle volume but also fat volume.[26] The tool can be used to measure specific slices or can accurately measure the entirety of the intrinsic foot muscle compartment. In our recent publication,[11] we compared lean muscle and fat volumes from the talonavicular to the tarsometatarsal joints of participants with DMPN without severe forefoot deformity (n=23) and controls (n=12). The DMPN group had less lean muscle tissue (18.2 ± 11.0 vs. 31.6 ± 12.8 cm^3, p<0.01) and more fat in the intrinsic foot muscle compartment (17.9 ± 10.5 vs. 9.3 ± 3.8 cm^3, p<0.01). Although many others have measured and reported muscle atrophy,[10, 28, 29, 41, 42] our work and methods are novel in the ability to accurately measure multi-slice volumes of both muscle and fat.

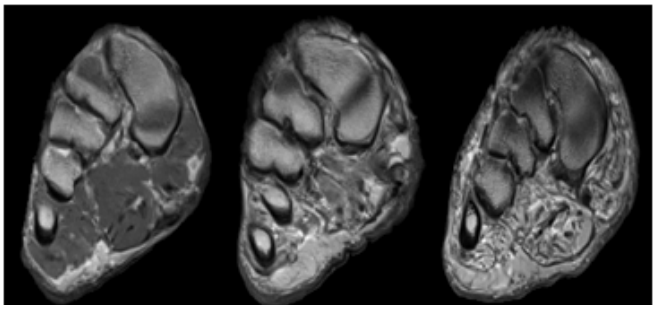


Figure 4. Coronal MRI through the midfoot of a control (left) and 2 participants with DMPN (center, right). Those with DMPN had decreased muscle volume (dark) and increased fat volume (bright) in the intrinsic foot muscle compartment.

The use of our very precise measurement methods will provide a critical component in the study of the role of muscle atrophy in the development and progression of MTPJ hyperextension deformity. In our work described above, using our quantitative methods in one of the larger reported samples of participants with DMPN, we found a significant correlation between intrinsic foot muscle deterioration and the second MTPJ alignment (r = -0.51, p=0.013). This correlation increased to r= -0.81 (p<0.01) when atrophy was severe, marked by intrinsic foot fat volume exceeding muscle volume (n=12). Ledoux et al had similar findings using computed tomography scans. Only study participants with DMPN and deformity had a reduction in intrinsic foot muscle volume compared to those without PN and/or without deformity.[43] In contrast, using less precise measurement methods (one slice of the forefoot and smaller sample sizes), Bus et al (2002 and 2009) found no relationship between intrinsic muscle volume and

deformity. The ability to measure accurately both muscle and fat, in a large sample of participants with DMPN will assist in clarifying the role of intrinsic foot muscle deterioration in MTPJ deformity development and progression.[10, 28] Additionally, we believe that intrinsic muscle atrophy alone will not result in MTPJ deformity but must be combined with limited ankle joint mobility and a repetitive MTPJ hyperextension movement pattern for MTPJ deformity to develop and progress.

3.1.4. MTPJ hyperextension movement pattern. A new and innovative aspect of this proposal is that we will test the hypothesis that loss of intrinsic foot muscle volume must be coupled with an MTPJ hyperextension movement pattern to cause MTPJ deformity. (Aim 1 Ho1, Aim 3 Ho4) We operationally **define a MTPJ hyperextension movement pattern as a substantial increase in MTPJ extension with active ankle joint dorsiflexion** (Figs. 3, 10, & 11)**.** Results of this study will help to define the magnitude of a "substantial increase", but preliminary data in section 3.3.4.4 suggests this value to be 10°. We believe the MTPJ hyperextension movement pattern is the result of increased reliance on the extensor digitorum longus to assist in dorsiflexing the stiff ankle joint during daily activities and a reduction in intrinsic muscle strength to resist MTPJ extension (i.e., sit to stand, Fig. 10).[13, 44, 45] Repetition of this movement pattern may lead to MTPJ deformity. Supporting that hypothesis, we have found that MTPJ hyperextension deformity was strongly correlated with limited ankle dorsiflexion range of motion (r=0.69 to 0.80) in people without DM.[13] Limited ankle dorsiflexion range of motion is a common impairment in individuals with DMPN,[12, 36] likely caused by an accumulation of AGES and thickening of the Achilles tendon.[23] We hypothesize, and will test in this proposal, that maximum ankle joint dorsiflexion and MTPJ extension during sit-to/from-stand, will predict MTPJ alignment at baseline, 1.5, and 3 years. (Aim 1 Ho1, Aim 3 Ho4)

3.1.5. Foot Specific Intervention. The relevance and significance of this proposal is enhanced by our integrative study design that includes a foot specific intervention. We hypothesize that the intervention, targeted at the key downstream residuals of diabetes (leg and foot muscle deterioration, limited ankle joint dorsiflexion, and MTPJ hyperextension movement pattern) can decouple disease driven mechanisms from MTPJ hyperextension deformity development and progression. The intervention is a progressive, home based exercise program aimed to increase ankle and foot plantarflexion muscle strength, increase ankle dorsiflexion and toe flexion range of motion, and to retrain individuals to dorsiflex the ankle while keeping the toes in a neutral position (see sec 3.3.5 and appendix A). A trained physical therapist with experience working with older adults with diabetes and foot specific complications will monitor and progress the exercise program assuring participant safety and maximizing exercise benefit.

There has been very little work on the ability of exercise interventions to improve leg and foot muscle strength, ankle dorsiflexion, or foot function in those with diabetes and peripheral neuropathy. In our recent published randomized controlled trial, participants with DMPN performed a progressive walking program that also included select exercises to improve balance, flexibility, and ankle muscle strength. Using this more comprehensive but less focused intervention program, we demonstrated that participants could significantly increase distance walked in 6 minutes and, important for this proposal, ankle dorsiflexion ROM and Foot and Ankle Ability Measure (self-report of foot function) (4.1°, 95% CI = 1.7 to 6.5°; 10.7 points, 95% CI=1.8 to 19.5 points, respectively).[23, 46] Toe flexion strength gains, up to 36%, have been reported in older people who completed a targeted exercise program[47] and healthy adults had improved strength and function on high level tasks (vertical jump and 50 meter dash) after completing a toe strengthening program.[48] We recognize the possibility that neuropathic muscle may have a limited ability to respond to an exercise stimulus. This challenge and the lack of research in this important area make this a proposal that will have exciting and relevant outcomes that will advance our knowledge and understanding of diabetes related complications, their plasticity, and guide treatment decisions.

The **shoulder specific control intervention** is another novel and creative component of our proposal. This control intervention will be useful to participants, will not contaminate the foot specific intervention outcomes, and likely will have stand-alone scientific merit. Our previous and current work investigating shoulder dysfunction in individuals with DM found that 63% of people attending an outpatient Diabetes Center reported shoulder pain or disability and almost all had limited joint mobility that may be a precursor to more severe problems.[49-51] Shoulder, foot and ankle pathology and may have some of the same contributing factors (i.e., increased AGEs, muscle weakness, decreased movement) in people with DM.[5, 6, 8, 23, 25, 30, 31] Thus, a shoulder specific intervention will provide an excellent control for the foot specific intervention and meet a need of many of our participants. In addition, the outcome data measured at 6 months, 1.5 and 3 years will provide useful long-term follow-up data that will complement our currently funded, short-term R21 (Grant #: DK100793, Clinical Trials.gov: https://clinicaltrials.gov/ct2/show/NCT02162212) to inform patient care and guide future research in the understudied area of upper extremity disabilities associated with DM.

Summary of significance: The cost and burden of care for foot disease in people with DM is staggering. One in four of the 26 million people with DM will develop skin breakdown[19] and the treatment for each wound infection is estimated to cost approximately $28,000 over the 2 years following diagnosis.[21] As many as 85% of those with a history of skin breakdown or amputation have forefoot deformity.[2] **This proposal focuses on the significant questions of "what are the causes and predictors of acquired forefoot deformity in people with DMPN and can a foot specific intervention make a difference in the short and long term outcomes?"** Previous investigators[28, 40] have not been able to determine why some people with DMPN develop this deformity and others do not, likely because important factors associated with MTPJ deformity development and progression were not studied. For the first time, we will investigate an innovative and comprehensive set of potentially modifiable causal factors leading to MTPJ deformity, provide an intervention to assess how modifiable the factors are and follow progression over a 3 year time period. A successful foot specific intervention would immediately and easily translate into clinical practice at a very nominal cost to the health care system. For patients with diabetes, a non-invasive intervention that halts or slows the cascade of events leading to amputation would yield improved function and reduced disability. In addition to understanding better the causes of MTPJ deformity, the results of this project will have important implications for understanding other severe and disabling neuropathic foot deformities such as Charcot neuroarthropathy.

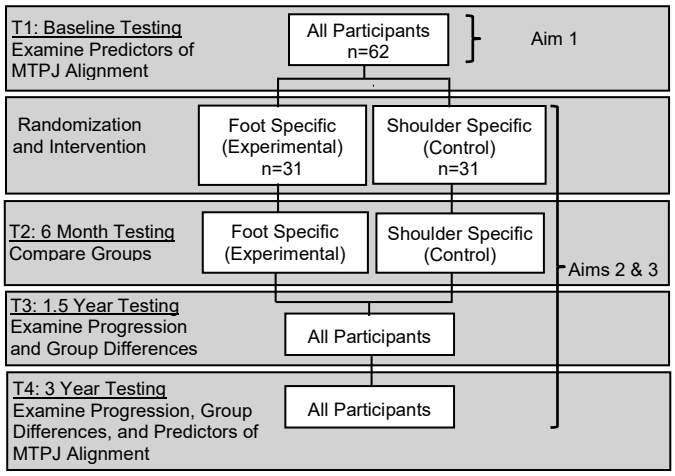
3.2 Innovation

This proposal is particularly innovative in its 1) comprehensive examination of the physiological, behavioral and mechanical/musculoskeletal contributions to MTPJ deformity development, 2) inclusion of an intervention program focused on key contributing factors and 3) examination of MTPJ progression and factors that predict progression over a 3 year time period. The project uses innovative and quantitative measures of metabolic function (AGEs),[7] intrinsic foot muscle deterioration,[26] and 3D ankle and foot intersegmental joint motion during functional activities,[52] which have only recently been developed and validated, to address the aims of this proposal. There is growing evidence that AGEs contribute to the deterioration of a variety of tissues in the diabetic foot.[6] Most of this work, however, has been at the cellular or tissue level with little investigation at the human level, especially in regard to the muscle and joint changes in the diabetic foot. No studies have been conducted on the spectrum of tissues we propose. The SCOUT device allows us to estimate AGE levels in the skin, non-invasively,[7] and relate those levels to important impairments in nerve, muscle, and joint mobility. Others have investigated intrinsic foot muscle atrophy,[28, 29, 42] but we have recently developed reliable and valid quantitative measures of lean muscle and fat volumes in these small and important muscles of the foot.[26] We also have quantitative 3D kinematic measures of intersegmental foot motion during walking and a dorsiflexion task to characterize and define a MTPJ hyperextension movement pattern.[53, 54]

3.3. Approach

3.3.1. Research Design. This research design is illustrated in Fig 5. Aim 1 will use a cross-sectional design to determine baseline relationships between AGE level, intrinsic foot muscle volume, ankle joint mobility, MTPJ movement patterns and MTPJ extension alignment at baseline. Aim 2 is a clinical stu dy with the foot specific intervention focused on improving foot and ankle strength, mobility, and function. The control group will receive a meaningful, comparable, but distinct intervention targeted at improving shoulder mobility, a common limitation in those with DMPN. All participants will repeat testing at 6 months, 1.5 years, and 3 years. Aim 3 will determine the key variables that predict progression of MTPJ extension deformity at 1.5 and 3 years. Intervention status will be entered as a potential predictor variable to examine the ability of a foot specific intervention to impact deformity progression.

Figure 5: Research Design



Sixty-two participants with DMPN (defined below) and a wide range of MTPJ extension angle will be recruited and followed for 3 years. We will recruit a wide range of MTPJ extension angles to have broad variance in the magnitude and presentation of this deformity so we can understand better the primary factors with which it is associated. We will not break participants into groups based on amount/severity of MTPJ hyperextension allowing us to maintain the continuous nature of important predictors and dependent variables, and hence, increase power of our repeated measures research design.[55, 56] Only participants with DMPN will

be recruited (vs. otherwise healthy people with MTPJ deformity) so we can focus on the muscle and limited joint mobility problems unique to DMPN. Measures will be taken at baseline, as described below in Table 1, and then all participants will be randomized into a foot specific or a shoulder specific intervention group. Participants will receive 6 intervention visits and a home program. Physical therapist directed interventions will occur during the first 4 months of study participation (3 visits in the first month, and then 1 per month for 3 months). Participants will be instructed, and encouraged by phone call follow up, to continue the home program for the duration of study enrollment. The research coordinator will call participants every 3 months to determine any change in medical status (i.e., skin breakdown, medical emergency), assess adherence with the home program and to keep them "connected" to the study. Participant testing will be repeated at 6 months, 1.5 years, and 3.0 years so that impact of treatment and predictors of change in deformity can be examined. Although we consider this clinical study preliminary, testers will be blinded to group assignment, treatments will take place in a different location than the assessments, and CONSORT guidelines will be followed.

Sample size determination.
Aim 1: A power analysis was conducted based on Hsieh et al's[57] sample size calculation for logistic and linear regression. 62 participants with DMPN are needed to detect a significant correlation of .44 between the predictor (intrinsic foot muscle volume) and the dependent variable (baseline MTPJ alignment) after adjusting for the other variables (AGE level, maximum ankle dorsiflexion, and maximum MTP extension during ankle dorsiflexion tasks), assuming all the predictors account for 37% of baseline MTPJ alignment. We are confident we will achieve these values for aim 1 since our preliminary data showed a higher correlation (r=0.60).

Aim 2: The power analysis for the pilot clinical study is based on a two-sample t-test. We anticipate an effect size of mean ankle joint dorsiflexion range of motion at 6 months, between the foot and shoulder specific intervention groups, of 4 ± 5°.[46] A sample of 52 (26 in each group) will be able to detect this effect size. Our targeted sample size 62 is conservative for this aim considering very low attrition rate at 6 month.

Aim 3: There is little existing evidence documenting the progression of diabetic foot deformity and we acknowledge that our work proposed in aim 3 is novel and exploratory. Aim 3 Ho3 is powered based on anticipated mean progression of MTPJ alignment 4° every 1.5 years after baseline in 50% people with DMPN assuming a standard deviation of 7.6° with a two-sided paired t-test. We assumed a much more conservative correlation of 0.6 between MTPJ alignment at baseline and 1.5 years later. Our preliminary data documented a progression in midfoot angle deterioration (Meary's angle) that worsened from -15.1 (14.3)° to -22.8 (14.2)° over 2 years in a group of subjects with a history of midfoot deformity, a correlation between measurement time points of 0.81.[58] Assuming a 20% attrition of the recruited sample, results in a required sample size of 62.

3.3.2. Subject recruitment will occur primarily from the Recruitment Enhancement Core of the Institute of Clinical And Translational Sciences here in the medical center. Several data bases are available to help recruit (e.g., Research Participant Registry through Volunteers for Health, and patient databases of the Applied Biomechanics and Human Biodynamics Laboratories). These resources have sufficient numbers of potential participants to help us achieve our goal. Potential participants will be mailed the consent prior to their first visit to allow them to carefully review the information and formulate questions regarding the study requirements. The requirements, risks and benefits of participation will be explained and all questions the potential participant may have will be answered. If willing to enroll in the study, written informed consent will be obtained. The potential participants will be screened and included if they meet the following inclusion and exclusion criteria:

Inclusion criteria: Subjects must have Type 2 DM and diabetic PN. The presence of PN will be determined by 1) inability to sense a 5.07 Semmes-Weinstein monofilament on at least one location on the plantar foot, 2) a vibration perception threshold on the plantar great toe greater than 25 V as measured by a biothesiometer, AND 3) an examination score on the Michigan Neuropathy Screening Instrument >2. As part of the screening process and to ensure a wide range of MTPJ deformity, we will estimate magnitude of MTPJ deformity using a goniometer and our previously published methods[59] to recruit 1/3 of subjects in each of the following 3 categories of MTPJ severity; <30°, 30-50°, and >50°.[13, 60]

Exclusion criteria: PN with causal factor other than DM (i.e., alcoholic, chemo toxic, lumbar radiculopathy); dialysis; severe arterial disease (ABI < 0.9 or > 1.3)[1]; rigid MTPJ deformity; metal implants or pace makers which would interfere with MRI data collection; unable to physically complete testing for the study; lower extremity amputations including multiple toes; acute shoulder pain or disability that would prevent participation in shoulder specific intervention (i.e. severe shoulder pain >6/10, rotator cuff tear, upper extremity surgery, thoracic outlet syndrome); pregnant; weight greater than 180 kg (MRI table limitations); presence of a neuropathic ulcer; or age greater than 75 (to minimize extreme age related changes on muscle or joint).

The age exclusion will not be applied for the walking study. Also, MRI compatibility characteristics (e.g., metal implants or pacemakers, pregnant, weight) and shoulder problems will not be applied for the walking study. For the participants in the walking study, people who have neurological disorders (e.g., Parkinson's disease, stroke, multiple sclerosis) that may change walking behavior and use the assistive device when walking will be excluded.

		Baseline (T1)		1- 15 Weeks	6 Month (T2)		7-17 Months	Year 1.5 (T3)		19-35 Months	Year 3 (T4)	
	Time (min)	Visit 1	Visit 2		Visit 1	Visit 2		Visit 1	Visit 2		Visit 1	Visit 2
Informed Consent	15	√										
Clinical Intake Data	30	√			√			√			√	
Instrumented Measures												
Skin Fluorescence	10	√									√	
Magnetic Resonance	30		√			√						√
Computed Tomography	15		√			√			√			√
Kinematic Assessment	90	√			√			√			√	
Clinical Measures												
Foot and Shoulder Questionnaires	20	√			√			√			√	
Neuropathy Assessment	30	√						√			√	
Vascular Assessment	15	√						√			√	
Joint Mobility Assessment	15	√			√			√			√	
Weight Bearing Foot X-ray	15		√									√
Routine Serum Chemistry (hsCRP, HbA1c)	10		√						√			√
Intervention	~30			√ (x8)								
Phone Contact (1 call every 3 months)	5						√ (x3)			√ (x5)		
Total (minutes)		**225**	**70**	**240**	**155**	**45**	**15**	**200**	**25**	**25**	**200**	**70**

Table 1. List and burden of tests

3.3.3. Testing Burden. The tests listed in Table 1 and described below will be conducted in 2 visits over 2 days, for a total of five hours, to minimize testing burden and to allow tests to be grouped by site. All tests for visit 1 will be conducted in the Movement Science Research Center. CT and MR imaging and blood work will be conducted during visit 2 either in the East Building or in the Center for Clinical Imaging Research. All testing sites have ample parking and are easily accessible to participants. All interventions will occur in the Movement Science Research Center.

For participants who are completing a follow-up visit, the walking study will take approximately 30 additional minutes. For participants who are not participating in the study "Muscle, Joint and Movement Deterioration Changes in Diabetes", the walking study will last 2 hours, 1 visit.

3.3.4. Measurement Methods: The investigative team has experience and a publication history in all tests and measures to be used in this project. All testers will be blinded to intervention status. Methods and preliminary data for all testing are described below.

3.3.4.1. Skin intrinsic fluorescence (SIF) will be our estimate of Advanced Glycation End Products (AGEs) collected from the SCOUT DS device *(*VeraLight, Albuquerque, NM). The SCOUT DS device measures the fluorescent signal of the AGEs in the dermal collagen (Fig. 6).[7, 9] This measure gives an aggregate estimate of AGE accumulation because the half-life of dermal collagen is approximately 15 years.[38] Because of this slow turnover of dermal collagen, skin fluorescence will be measured at baseline only. Each scan time is 2 minutes, non-invasive, does not require fasting, and uses low intensity UV light to measure SIF. Participants will be seated with their arm positioned on the SCOUT skin fluorescence spectrometer and 2 trials of data will be collected from the left volar forearm skin using previously established methods.[7] Based on previous studies, SIF will be excited with an LED centered at 405 nm and detected over the emission range of 441–482 nm.[7, 61] The skin reflectance will be measured over the excitation and emission regions to compensate for absorbance caused by melanin and hemoglobin.[7] The intrinsic fluorescence correction equations will be used as described previously using the same correction factor. The SIF Intra-participant and inter-day Hoorn coefficient of variation were 4.0% and

Figure 6. SCOUT DS Device

6.9%.[62, 63] John Maynard, previously Vice President of Technology at VeraLight, the company that developed and manufactured our SCOUT device, has conducted previous studies using the technology[7, 61, 63, 64] and is serving as a consultant on this project to help analyze and interpret data (see letter of support).

Preliminary data: We recruited 19 participants with DMPN (mean age 59 ± 9 years) who met the identical inclusion and exclusion criteria proposed in this project. We collected SIF and the Michigan Neuropathy Screening Instrument (MNSI) score, a reliable and valid measure of severity of neuropathy.[65, 66] MNSI scores were positively correlated with SIF values (r =0.62, p<0.01), indicating more severe PN is associated with increased AGE accumulation in the dermal collagen. *(*SIF = 24.1 ± 4.5 arbitrary units; MNSI examination scores = 5.6 ± 1.9, where >2 indicates PN). This proposal will explore the relationship of AGE levels to deformity severity and progression.

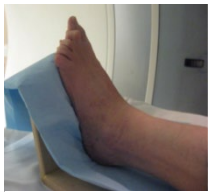


Figure 7. Position during CT scan

3.3.4.2. Spiral CT Scanning for MTPJ Deformity and Joint Positions: The purposes of using spiral CT scans for this project are to measure: 1) MTPJ alignment over the 3 year follow up period, 2) measure precisely maximum ankle joint dorsiflexion, and 3) maximum MTPJ active flexion in resting position. CT scans and measurements will be taken in 3 positions. At Visit 4 an additional CT scan will be taken of the foot not followed as part of the study for a comparison.

1) Resting position - the calf and foot are placed on a positioning device to standardize ankle position in resting position of 30º plantar flexion (approximate mid position of physiological ankle range of motion from 10º dorsiflexion to 50º plantar flexion, see Fig.7).[13, 59] The measure of MTPJ angle in resting position will serve as our primary outcome measure defining the amount of MTPJ hyperextension. MTPJ alignment will be defined as the angle between the phalanx and the extension of the bisector of the metatarsal. A larger angle will indicated less deformity.[13, 67] (Aims 1-3, Fig. 8).
2) Maximum active ankle dorsiflexion - The study participant will be instructed to maximally dorsiflex their ankle joint. Maximum active ankle dorsiflexion and concurrent MTPJ angle will provide the measure of ankle mobility for Aims 1 &2 and an indicator of MTPJ hyperextension movement pattern for Aims 1-3. (Fig. 8b)
3) Maximum active MTPJ flexion – The study participant will be instructed to maximally flex their MTPJ with their foot supported in the positioning device. Maximum active MTPJ flexion is an exploratory outcome measure that should improve with the foot specific intervention through increasing MTPJ joint mobility and intrinsic muscle strength. (Fig. 8c)

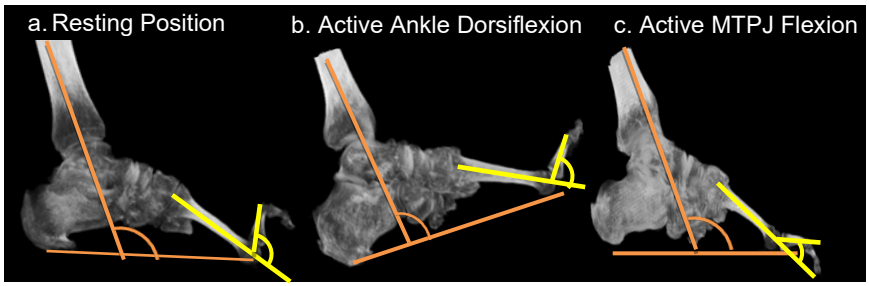


Figure 8. CT positions for measuring MTPJ and ankle angles. MTPJ alignment is the angle between the phalanx and the extension of the bisector of the metatarsal. A larger MTPJ angle indicates less deformity.

Participants will be positioned supine on the CT scanner table using our previously published reliable and precise methods to measure MTPJ angles.[54, 59, 67-69] Briefly, we use a multi-slice Siemens Sensation 64 CT scanner (Siemens Medical Systems, Inc., Iselin, NJ) that allows a spatial isotropic resolution of 0.6 millimeters (mm) for a clear detailed visualization with a rapid acquisition time (gantry rotation speed of 0.5 seconds). The following CT parameters will be used to acquire the scans: 0.5 second rotation time, 64 x 0.6 mm collimation, 220 mAs, 120 kVp, a pitch of one, and a 512 x 512 matrix. The lower one third of the leg and the entire foot are scanned. Acquisition time will depend slightly on the size of the subject's foot but generally is less than 2 minutes of x-ray tube time for all 3 scanning positions. The CT projection data sets will be reconstructed with a resolution of approximately 0.6 x 0.6 x 0.6 mm^3. The CT data will be de-identified, archived on DVDs using DICOM format, and processed in the Electronic Radiology Laboratory. The SCT data will be converted from DICOM format to an Analyze software file format[54] (ANALYZE Software, Biomedical Resource Mayo Clinic, Rochester, MN). As Illustrated in Figure 8, the following angles will be measured for all three scans: (1) MTPJ angle: 180º minus the angle between the phalanx and metatarsal for all five metatarsals and (2) Ankle joint position: tibia and a line drawn between the bottom of the calcaneus and the second metatarsal head.[54]

Preliminary Data: We recruited 19 participants with DMPN (mean age 59 ± 9 years) who met the identical inclusion and exclusion criteria proposed in this project. MTPJ alignment in resting will be reported in combination with the intrinsic muscle volumes in section 3.3.4.3, Fig 9. During the maximum active ankle joint dorsiflexion task, MTPJ angle was negatively correlated with maximum ankle joint dorsiflexion (Spearman's rho r = -.58, p<.01). This finding supports the hypothesis that the MTPJ deformity is

associated with limited ankle joint mobility. This proposal will examine the role of limited ankle joint mobility in MTPJ deformity development and progression and the ability of a foot specific intervention to improve ankle dorsiflexion range of motion.

3.3.4.3. Intrinsic Foot Muscle Volume: We have developed a reliable, valid, and quantitative volumetric analysis of the intrinsic foot muscles using Magnetic Resonance Imaging (MRI) to identify how these muscles contribute to weakness and the development and progression of foot deformity.[26, 60] Lean muscle and fat volumes are tissue within the muscular compartment. We believe the ability to measure fat volume is a particularly novel component of our measurement tool as intermuscular fat is associated with insulin resistance and metabolic impairments and may provide insight into function and deformity not previously explored.[60, 70, 71]

Coronal plane MR images using published methods[26] (Fig. 4) will be collected using a Siemens Magnetom Trio 3T scanner (Siemens Medical Systems, Malvern, PA). The scans are T1 weighted for best adipose and muscle tissue discrimination, with the following parameters: spin echo pulse sequence, TR/TE = 700/11 msec, field of view = 120 mm, bandwidth = 244 Hz/pixel, 65 slices, thickness = 3.5 mm, transverse orientation, signal averages = 1, flip angle = 128°, matrix = 320 × 320, echo train length = 4, and pixel size 0.375 x 0.375 mm. The subjects lay supine with the target foot perpendicular to the table in a head coil for an acquisition time of 10 minutes. The primary region of interest is from the talonavicular joint (midfoot) through 50% of the 2nd metatarsal but data are collected on the entire foot.

Preliminary data: Intrinsic foot muscle and fat volumes were measured from the talonavicular joint through 50% of the 2nd metatarsal in the 19 participants with DMPN described above. The average muscle volume was 64.5 ± 24.6 cm^3 and total fat volume was 32.7 ± 15.5 cm^3. Less MTPJ deformity (greater MTPJ angle) was positively correlated with greater total muscle volume (r = .60, p< .01, Fig. 9). Total fat volume was not significantly associated with MTPJ angle (r = -.32, p=.18) in this preliminary investigation. These data support the hypothesis that a decline in intrinsic muscle volume is associated with MTPJ deformity but does not completely explain the magnitude of the deformity. This proposal will expand on our preliminary work by recruiting a larger sample, following participants over 3 years, examining the contribution of multiple potential contributors (AGE level, MTPJ hyperextension movement pattern, and limited ankle joint mobility) to MTPJ alignment, and exploring the ability of a foot specific intervention to de-couple diabetes related mechanisms from MTPJ deformity.

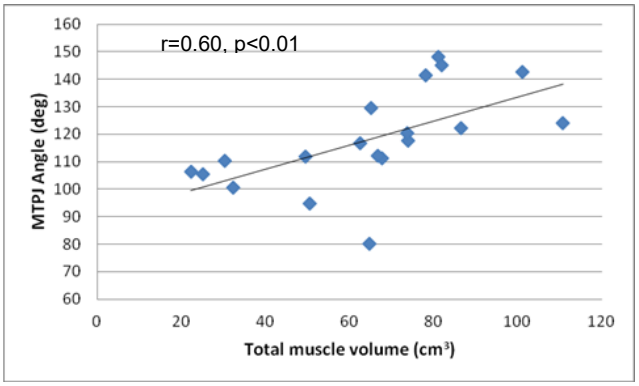


Figure 9. Better MTPJ alignment (increasing values) is correlated with greater intrinsic muscle volume.

3.3.4.4. Foot and ankle motion function using 3D motion analysis: The primary purpose of 3D motion analysis is to measure the MTPJ hyperextension movement pattern observed during dorsiflexion tasks. During our pilot work for this proposal we had 19 participants, described above, complete numerous movement tasks thought to elicit the MTPJ hyperextension movement pattern including: sit-to-stand, walking at a self-selected speed, ankle dorsiflexion and toe flexion tasks with the knee flexed and extended, and a sitting foot arch elevation task. The sit-to-stand and knee extension ankle dorsiflexion tasks were the most capable of clearly differentiating those with the greatest deformity from those with the least deformity and will be included in this proposal. In addition, our previous work indicates that measuring forefoot plantarflexion motion relative to the hindfoot during a single leg heel rise task is a foot specific challenge capable of identifying those with poor foot intrinsic foot muscle quality in those with DMPN and so this task will also be included.[53](Aims 1-3)

This study uses fifty 10 mm, reflective markers to define 5 segments on each leg: shank, hindfoot, forefoot, second metatarsal, and second toe proximal phalanx. Bilateral kinematic data will be collected using an 8 camera 3D motion capture system (Vicon, Los Angeles, CA, USA) and methods from Dr. Hastings recent publications.[52, 53] All data will be processed and analyzed using Vicon Nexus, Visual3D (C-motion, Inc., Rockville, MD), and MatLab (Mathworks, Natick, MA) software, using established and published methods.[52] The participants will perform the following tasks:

1) Sit-to/from-stand task: 3 trials of coming from sit-to-stand and stand-to-sit. This is a weight-bearing task requiring recruitment of the ankle dorsiflexors to control the tibia. We hypothesize MTPJ excursion from sit-to/from-stand will predict MTPJ alignment at baseline, 1.5, and 3 years (Aims 1 & 3) and MTPJ excursion will be reduced after the foot specific intervention (Aim 2).

2) Ankle Dorsiflexion/Plantarflexion Task: 5 trials of seated full ankle dorsiflexion and plantarflexion with the knee in full extension. We predict dorsiflexion will be decreased and MTPJ excursion increased in those with MTPJ deformity (Aim 1) and that dorsiflexion will increase and MTPJ excursion will decrease after the foot specific intervention (Aim 2).
3) Unilateral heel rise task: 10 trials of unilateral heel rise (both right and left). The unilateral heel rise task provides an indicator of foot function, especially intrinsic muscle force production to plantarflex the forefoot on the hindfoot while lifting 100% of body weight. We hypothesize that the amount of forefoot relative to hindfoot plantarflexion during heel rise will be associated with intrinsic muscle volume and improve with the foot specific intervention.
4) Walking task: 5 trials of self-selected pace will be collected on a small subset of individuals. Participants may agree to participate in additional walking trials at various speeds and time.

Preliminary Data. Our study team, led by Dr. Hastings, developed and published work investigating the intersegmental foot motions of people with DMPN and medial column deformity and those that received a tendon transfer surgery to correct foot drop.[52, 53] We will be using the same intersegmental foot model for this project and have added segments for the second metatarsal and proximal phalanx of the second toe to capture 2nd MTPJ motion during our selected tasks.

Sit-to/from-stand task: MTPJ extension excursion during sit-to/from-stand was significantly correlated with MTPJ alignment (r=.48, p<.02) in our 19 pilot participants. To visualize the difference in the movement pattern we graphed the excursion of the 2nd MTPJ during the task for the 5 participants with the largest MTPJ deformity (red) and the 5 participants with the smallest MTPJ deformity (blue). Those with MTPJ deformity had greater MTPJ extension excursion during the sit-to/from-stand components of the task when compared to those without MTPJ deformity. (Fig. 10) These preliminary data provide support for our hypothesis that those with MTPJ deformity have the MTPJ hyperextension movement pattern repeated during daily tasks and our proposal will examine the relationship between this pattern and the progression of MTPJ deformity.

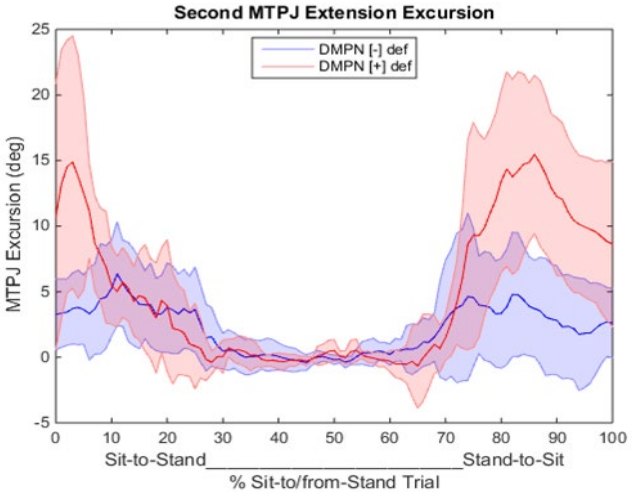


Figure 10: Second MTPJ Extension Excursion during sit-to/from-Stand. The DMPN with MTPJ deformity (red) have more MTPJ extension in both sit-to/from stand compared to DMPN without MTPJ deformity (blue).

Ankle Plantarflexion/Dorsiflexion Task: Ankle and MTPJ motion was measured during active ankle plantarflexion and dorsiflexion in our pilot participants. Maximum ankle dorsiflexion was significantly correlated with MTPJ alignment (r=.40, p=04), where those with deformity showed greater deficits in dorsiflexion. To visualize the difference in the movement pattern, we graphed ankle motion versus simultaneous MTPJ motion (Fig. 11) for the entire task for the 5 participants with the largest MTPJ deformity (red) and the 5 participants with the smallest MTPJ deformity (blue). Those with MTPJ deformity showed deficits in dorsiflexion (positive, x-axis), and extended the MTPJ over a greater range than those without deformity (positive y-axis, ~30 deg vs. ~20 deg). Those with deformity also showed a steeper rise in MTPJ extension as the ankle moved into dorsiflexion (lower bound of motion curve).

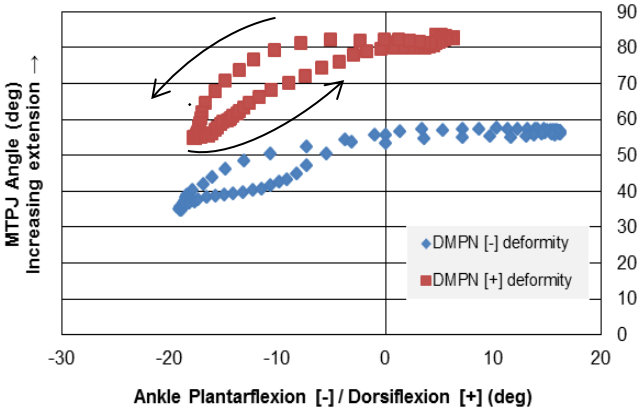


Figure 11. MTPJ angle during ankle plantarflexion and dorsiflexion. Starting at 0° ankle plantarflexion/dorsiflexion, the motion curve moves counter-clockwise as the ankle plantarflexes then dorsiflexes. The DMPN with MTPJ deformity (red) have more MTPJ motion and a steeper increase in MTPJ extension as the ankle moves into dorsiflexion (lower bound of curve).

Unilateral heel rise task: The shank, hindfoot and forefoot motion was measured during unilateral heel rise in 23 individuals with DMPN with and without midfoot deformity and 12 controls. Compared to controls, those with DMPN had less hindfoot relative to shank plantarflexion (controls=20°, DMPN=7-12°; p<.02) and failed to plantarflex their forefoot on their hindfoot during heel rise (controls=13°, DMPN=2-5°; p<.02, Fig. 12). A regression analysis found that intrinsic foot fat volume explained 19% of the variance in forefoot relative to hindfoot plantarflexion excursion. These pilot data support this task as a useful indicator of the intrinsic foot muscle's ability to plantarflex the forefoot relative to the hindfoot.

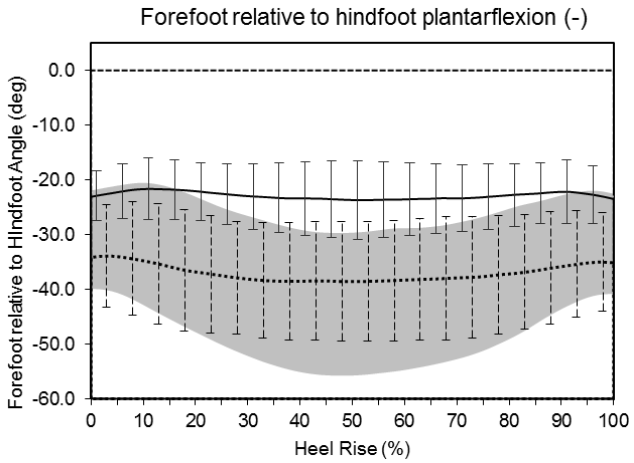


Figure 12: Forefoot relative to hindfoot plantarflexion (-). The mean ± 1 standard deviation are reported for controls (shaded band), DMPN and deformity (solid line), and DMPN without deformity (dotted line). Those with DMPN failed to plantarflex their forefoot relative to their hindfoot

3.3.4.5. Clinical tests and measures. Clinical tests will be completed to characterize the participants and to assess the spectrum of disease, impairment, and other potential contributors. (see description below & Table1)

3.3.4.5.1. Intake Information. Physical examination and medical history will be performed by Dr. Hastings. Demographic information including age, gender, race, weight, shoe size, type and duration of DM and medications will be obtained from the participants or their medical records. Co-morbidities will be determined based on interview, medical history review, and physical examination. Digital photographs of the feet will be collected to correspond to MR and CT images. Since foot type or other foot deformity may influence MTPJ deformity foot[18, 72] type (high, normal, low arch) will be classified using previously established clinical assessment.[18, 73] Standing navicular height, calcaneal eversion, and arch angle will be collected to assist in foot type classifications.[73-75]

3.3.4.5.2. Peripheral neuropathy will be assessed using a 5.07 Semmes-Weinstein monofilaments and a biothesiometer to quantify vibration perception threshold using previously described reliable and valid methods.[76-78] The Michigan Neuropathy Screening Instrument (MNSI) will also be completed to characterize the severity of PN.[66, 79] This is a a lower extremity physical exam that assesses foot deformity, vibration sensation, and ankle reflexes. A composite score ≥2 indicates presence of peripheral neuropathy.[66, 79]

3.3.4.5.3. Vascular status. Ankle brachial index, toe pressures and waveforms will be assessed using Doppler ultrasound (Koven Technology Inc) and established methods.[1] Vascular status will be used to exclude individuals with ankle brachial indexes that indicate severe peripheral vascular disease (ABI < 0.9 or > 1.3).

In the walking study, participants will self-report the peripheral vascular disease or be assessed with the ABI.

3.3.4.5.4. Foot Function Questionnaire. The Foot and Ankle Ability Measure questionnaire will be used to quantify the participants' perception of their ability to complete 21 activities of daily living (e.g., walking on even ground, walking up hills, stepping up and down curbs, home responsibilities, recreational activities). The FAAM is a reliable, responsive, and valid self-report measure of physical function for individuals with a broad range of musculoskeletal disorders of the lower leg, foot, and ankle.[65]

3.3.4.5.5. Shoulder Function Questionnaire. The Shoulder Pain and Disability Index (SPADI) questionnaire is a 13 item questionnaire (5 items for pain and 8 items for disability) that will be used to quantify participant perception of shoulder function. The SPADI will be used for all participants and will provide preliminary data on the ability of the control group shoulder specific intervention to impact shoulder pain and disability. The SPADI is reliable and valid and takes only 5 minutes to administer.[80, 81]

3.3.4.5.6. Joint mobility assessment. Standardized goniometry methods will be used to assess limitations in ankle dorsiflexion / plantarflexion, calcaneal eversion / inversion range of motion,[13, 76] first MTPJ mobility, shoulder flexion and shoulder internal/external rotation. Our previous work found that ankle dorsiflexion and MTPJ angle were negatively correlated for toes 2–4 (r = -0.38 to -0.56) as were calcaneal eversion and MTPJ angle (r = -0.45 to 0.60) in people without DM or PN.[13] We will measure grip strength also.

3.3.4.5.7. Blood glucose level control & inflammatory biomarker. The level of glycated hemoglobin (HbA1c) is a measure of plasma glucose concentration, and an indicator of how well diabetes is controlled in a subject. High

sensitivity C-reactive protein (hsCRP) provides a measure of chronic inflammation. A single blood draw will be taken and analyzed at laboratory services in Barnes-Jewish hospital and used to characterize subjects.

3.3.4.5.8. Screening for other structural factors that might contribute to MTPJ deformity. We recognize that other factors besides those included in this proposal may contribute to the development of acquired MTPJ deformities. The most commonly reported factors are capsular or plantar plate tears at the MTPJ or plantar fascia that is torn or thickened that reduce joint stability and allow MTPJ deformity to develop.[14, 76] For this reason, Dr. Jeffrey Johnson, an Orthopedic Surgeon who regularly diagnoses these structural problems using MR, will review all MR images for evidence of other substantial structural problems (i.e., plantar plate or plantar fascia tear, bunion, hallux valgus) that may contribute to the deformity (see letter of support). These data will be used to help characterize the subject sample and deformities, and interpret the results.

3.3.4.5.9. Weight bearing lateral foot radiograph. The lateral view radiograph will provide a visual reference for the progression of the foot deformity. These data will be used to help characterize the subject samples.

3.3.5 Intervention. Participants will be randomly assigned to receive either a foot specific (experimental) or shoulder specific (control) intervention. The rationale for the **foot specific (experimental) intervention** is described in section 3.1.5 and will consist of a progressive exercise program, outlined in Appendix A. The foot specific program is an adaptation of the exercise program used in our previous randomized controlled trial to increase walking tolerance in people with DMPN and which was found to improve not only walking tolerance, but also ankle dorsiflexion range of motion and Foot and Ankle Ability Measure scores.[46] Other research has shown the ability to improve foot function outcomes in the elderly and others,[47, 48] but to our knowledge, there is no other evidence besides our own randomized controlled trial that has investigated whether an exercise and movement program can improve foot-related outcomes in people with DMPN. Unlike our previous randomized controlled trial that aimed primarily to increase weight-bearing activity, this foot specific intervention will consist of a carefully prescribed progressive home program that will include passive stretching of the ankle and MTPJs, strengthening of the foot intrinsic and ankle plantarflexor muscles, and movement pattern training to reduce toe extension associated with active dorsiflexion movements. (Appendix A) The overall goal is to improve specific muscle strength, joint range of motion and movement patterns to minimize MTPJ deformity.

The **shoulder specific (control) intervention** was selected to control for personal interactions with investigators, provide useful information for common upper extremity musculoskeletal problems in people with DM,[49-51] but not have an effect on foot and ankle outcome measures. This intervention is an adaptation of a current exercise program we are using successfully in our R21 (Grant #: DK100793, Clinical Trials.gov: https://clinicaltrials.gov/ct2/show/NCT02162212) and is described in detail in Appendix B. Participants will be trained in a progressive home exercise program that includes passive and active shoulder movements with the goal to improve the limited shoulder joint mobility, pain, and disability that is often seen in people with DM. Shoulder pathology may have some of the same contributing factors as foot and ankle pathology (i.e., increased AGEs, muscle weakness, decreased movement) in people with DM. [5, 6, 8, 23, 25, 30, 31] Therefore, this intervention will not only provide a control for the foot specific intervention but may also yield important outcomes on the long term effects of a shoulder movement program on shoulder ROM, pain, and disability.

The foot and shoulder specific interventions will be provided by a trained physical therapist that will assess and progress the home program over 8 visits in 5 months (3 visits in the first month, 2 visits in the second month and then 1 per month for 3 months). All participants will be asked to complete the entire home program 5 times/week, 30 minutes per day for the first 4-5 months. Participants will be asked to continue an abbreviated and targeted home program 3 times/week for 15 minutes per session for the remainder of the 3 year study. Participant adherence will be monitored with use of an exercise log. (Appendix C) All interventions will be provided in the Movement Science Research Center. Patient and skin safety concerns will be followed consistent with our recent randomized controlled trial[46] and 30 year history with this population (see biosketches).

3.3.6. Statistical Analyses Descriptive statistics for continuous variables (mean, median, range and standard deviation) will be obtained for the sample. Frequency will be tabulated for categorical variables.

Aim 1: A multiple linear regression analysis will be used to test Aim 1. The primary dependent variable for Aim 1 will be baseline MTPJ alignment. The independent variables (predictors) for Aim 1 will be AGE level, intrinsic foot muscle volume, maximum ankle dorsiflexion, and MTPJ extension excursion during sit to stand. A Pearson correlation matrix will be obtained on all variables to understand better inter correlations. Adjusted R square from the multiple linear regression model will be obtained.

Aim 2: A repeated measures ANOVA analysis will be used to estimate the effect of the intervention by determining the between group changes over time in the primary outcome measures MTPJ extension alignment and the secondary outcome measures of intrinsic muscle volume, ankle joint dorsiflexion range of motion, MTPJ extension excursion during sit-to/from-stand and Foot and Ankle Ability Measure. Contrasts will be used to determine mean differences of interest.

Aim 3 Ho3: MTPJ deformity progression will be calculated as progression every 1.5 years (MTPJ deformity at baseline – MTPJ deformity at 1.5 years and MTPJ deformity at 1.5 years – MTPJ deformity at 3 years). Means and standard deviations for these differences will be obtained and paired t-tests will be performed to test for significant progression every 1.5 years. The proportion of individuals with DMPN and MTPJ deformity progression at 4 degrees or more within 1.5 years will be calculated with 95% confidence interval.

Aim 3 Ho4: MTPJ deformity progression will be assessed as progression at 1.5 and 3 years (MTPJ deformity at baseline – MTPJ deformity at 1.5 years and MTPJ deformity at baseline – MTPJ deformity at 3 years). Analysis of covariance model will be fitted to these two progression variables with intervention status as the major predictor adjusting for baseline measures of AGE level, intrinsic foot muscle volume, MTPJ extension excursion during sit to stand.

All statistical tests will be two-sided with a significance level of 0.05 and performed with SAS 9.4. Careful attention will be paid to ensuring that data satisfy assumptions required of a particular analytic strategy. Thus, paired t-tests will only be accepted as valid if normality assumptions are satisfied. Similarly, we will evaluate regression residuals before we reach conclusions based on linear regression analysis. When required assumptions are violated, we will explore the use of data transformations and potentially, perform some analyses using non-parametric or semi-parametric methods based on the rank of some variables. In the event of multicollinearity with numerous predictors in regression models, highly redundant variables will be eliminated from the analyses, or where possible, composite variables will be formed to capitalize on the higher reliability of combined measures. Sample size limitations and potential multicollinearity may preclude the examination of all predictors in one analysis. To avoid this problem, we will examine the impact of predictors individually or in small, conceptually sensible, subsets.

3.3.7. Proposed Timeline and Plans for Future Studies.

We propose to complete the aims of this project in 5 years with the following milestones:
9/1/2015 – start date; Year 1: Methods and personnel are ready to begin testing immediately. Based on current recruitment methods, we are confident we can recruit and test 4 subjects per month. Therefore, we plan to conduct all baseline testing in the first 16 months of the study; 48 in year 1 and 14 in year 2. Data processing and entry into databases will occur on an on-going basis. Intervention will be initiated immediately after baseline testing has been completed
Year 2: Participant recruitment, baseline testing, intervention and 6 month follow up testing will be completed in year 2. Data analysis for baseline measures and the manuscript related to Aim 1 will be completed by the end of year 2. 1.5 year re-testing will begin on 24 subjects. Data analysis for Aim 2, 6 month data will be analyzed and the related manuscript prepared for publication.
Year 3: Complete 1.5 year re-testing on remaining 38 participants for total of 62 participants. Analyze and summarize all data.
Year 4: Complete 3 year retesting on 48 participants.
Year 5: Complete 3 year retesting on remaining 14 participants and complete all data analysis, submit publications for aim 2 and 3, submit next RO1. We plan to present results at scientific conferences and submit manuscripts throughout years 2-5.

Given a better understanding of the causes of MTPJ deformities, complimentary studies could be done to determine the muscle, joint, and movement patterns that contribute to catastrophic midfoot deformity caused by Charcot neuroarthropathy. Data collected by this project also will provide a wealth of information for preliminary study data for future grants. The relationship between baseline AGE levels and various anatomical structures (i.e., thickness of tendons or plantar fascia) or clinical measures (i.e., FAAM, strength, or range of motion) besides those listed in Aim 1 will be examined. Measures collected in this project (i.e., AGE levels or intrinsic muscle volume) may be indicators of general deterioration of the diabetic neuropathic foot and be part of future investigations to improve predictions for skin breakdown or amputation. Furthermore, this project will capitalize on a useful, complimentary shoulder-specific control intervention that will allow long-term investigation of multiple factors (AGE level, movement intervention) on the common development of diabetic shoulder limited joint mobility, pain, and disability.[49-51]

3.3.8. Potential Problems. All expertise, equipment and resources are available to accomplish these aims. Preliminary data have been collected on all methods, and we are confident measures can be completed as described. Subject recruitment can be a challenge in human research. We are confident that we will be successful because this research team has been recruiting subjects with DMPN for over 20 years and we have an active database of previous subjects that have provided consent to be contacted for future studies. In addition, Dr. Jeffrey Johnson, an orthopedic surgeon and co-investigator on this project with expertise in the diabetic foot, has an active clinical practice from which to recruit.

Another potential limitation is that other factors besides those included in the specific aims may contribute to the development of acquired MTPJ deformities. For example, foot type[1, 2], other foot deformities (i.e., bunion*),* capsular or plantar plate tears at the MTPJ or plantar fascia that is torn or thickened[28, 40] may reduce joint stability and allow the development of MTPJ deformity. For this reason, Dr. Hastings will provide a clinical evaluation of all subjects to collect data on these variables and Dr. Jeffrey Johnson will review all MR images for evidence of other substantial structural problems (i.e., plantar plate or plantar fascia tear) that may contribute to the deformity as described in sections 3.3.4.4.1 & 3.3.4.4.9.

In summary, the results of this study will have profound implications for helping to understand the causes and a corresponding treatment intervention for acquired neuropathic foot deformities. Understanding and treating the causes of acquired neuropathic foot deformities has great potential to halt or slow the cascade of events leading to amputation, while improving the mobility and minimizing disability in the 26 million people in the US with DM.

Protection of Human Subjects

Risks to Human Subjects

a. Human Subjects Involvement, Characteristics and Design

All methods for the proposed study titled "Muscle, joint and movement deterioration contributing to neuropathic forefoot deformity" have been approved by the Institutional Review Board and Human Research Protection Office (HRPO) of the Washington University School of Medicine and currently are being piloted. Review of the full proposal will occur prior to initiation of data collection or attainment of informed consent.

Subject groups. The proposed research will employ a single-group cross-sectional and longitudinal, repeated measures design composed of individuals with diabetes mellitus, peripheral neuropathy, and a wide range of metatarsalphalangeal joint hyperextension. Participants will be followed for 3 years with testing at baseline, 6 months, 1.5 years, and 3 years. The participants will be recruited primarily from St. Louis city and the surrounding metropolitan area. Age will be limited to less than ≤75 years to minimize extreme age related changes on muscle or joint.

Inclusion/exclusion criteria.

Inclusion Criteria (n=62)

1) Type 2 DM
2) Diabetic peripheral neuropathy (PN): unable to sense a 5.07 Semmes-Weinstein monofilament on at least one location on the plantar foot, a vibration perception threshold greater than 25 V as measured by a biothesiometer, and an examination score on the Michigan Neuropathy Screening Instrument >2.
3) As part of the screening process and to ensure a wide range of MTPJ deformity, we will estimate magnitude of MTPJ deformity using a goniometer to recruit 1/3 of subjects in each of the following 3 categories of MTPJ severity; <30^{o}, 30-50^{o}, and >50^{o}.

Exclusion Criteria

1) PN with causal factor other than DM (i.e., alcoholic, chemo toxic, lumbar radiculopathy);
2) Dialysis
3) Severe arterial disease (ABI < 0.9 or > 1.3)[1]
4) Rigid MTPJ deformity (unable to move > 20 degrees)
5) Metal implants or pace makers which would interfere with MRI data collection
6) Unable to physically complete testing for the study
7) Lower extremity amputations including toes
8) Acute shoulder pain or disability that would prevent participation in shoulder specific intervention (i.e. severe shoulder pain >6/10, rotator cuff tear, upper extremity surgery, thoracic outlet syndrome);
9) Pregnant
10) Weight greater than 180 kg (MRI table limitations)
11) Presence of a neuropathic ulcer (history of ulcer is ok)
12) Age >75 years

Participants will be randomized into a foot specific or a shoulder specific intervention group. Participants will receive 8 intervention visits and a home program. Physical therapist directed interventions will occur during the first 5 months of study participation (3 visits in the first month, 2 visits in the second month and then 1 per month for 3 months), with a home program to be completed independently, 5 times/week-estimated to take 30 minutes to complete. Participants will be instructed, and encouraged by phone call follow up, to continue an abbreviated home program, 3 times/week-estimated to take 15 minutes to complete, for the duration of study enrollment. The research coordinator will call participants every 3 months to determine any change in medical status (i.e., skin breakdown, medical emergency), assess adherence with the home program and to keep them "connected" to the study. Participant testing will be repeated at 6 months, 1.5 years, and 3.0 years so that impact of treatment and predictors of change in deformity can be examined. Although we consider this clinical study preliminary, testers will be blinded to group assignment, treatments will take place in a different location than the assessments, and CONSORT guidelines will be followed.

Sample size.

Aim 1: A power analysis was conducted based on Hsieh et al's[53] sample size calculation for logistic and linear regression. 62 participants with DMPN are needed to detect a significant correlation of .44 between the

predictor (intrinsic foot muscle volume) and the dependent variable (baseline MTPJ alignment) after adjusting for the other variables (AGE level, maximum ankle dorsiflexion, and maximum MTP extension during ankle dorsiflexion tasks), assuming all the predictors account for 37% of baseline MTPJ alignment. We are confident we will achieve these values for aim 1 since our preliminary data showed a higher correlation (r=0.60).
Aim 2: The power analysis for the pilot clinical study is based on a two-sample t-test. We anticipate an effect size of mean ankle joint dorsiflexion range of motion at 6 months, between the foot and shoulder specific intervention groups, of 4 ± 5°.[46] A sample of 52 (26 in each group) will be able to detect this effect size. Our targeted sample size 62 is conservative for this aim considering very low attrition rate at 6 month.
Aim 3: There is little existing evidence documenting the progression of diabetic foot deformity and we acknowledge that our work proposed in aim 3 is novel and exploratory. Aim 3 Ho3 is powered based on anticipated mean progression of MTPJ alignment 4° every 1.5 years after baseline in 50% people with DMPN assuming a standard deviation of 7.6° with a two-sided paired t-test. We assumed a much more conservative correlation of 0.6 between MTPJ alignment at baseline and 1.5 years later. Our preliminary data documented a progression in midfoot angle deterioration (Meary's angle) that worsened from -15.1 (14.3)° to -22.8 (14.2)° over 2 years in a group of subjects with a history of midfoot deformity, a correlation between measurement time points of 0.81.[54] Assuming a 20% attrition of the recruited sample, results in a required sample size of 62.

b. Sources of Materials (see section in bold for additional detail).
The following research materials will be obtained from our human subjects:

1. Medical history and personal information **(3.3.4.5.1.)**
2. Measure skin fluorescence non-invasively using the SCOUT DS device. Three measurements will be taken and a skin intrinsic fluorescence score obtained **(3.3.4.1.)**
3. A MR and CT scan will be performed on one foot **(3.3.4.2. & 3.3.4.3.)**
4. Ankle and MTPJ positions during tasks using 3D Motion Analysis by taping reflective markers on the left and right feet and legs below the knee, where special cameras recognize and track the marker locations. No identifying information is captured by these cameras **(3.3.4.4.)**
5. Foot sensation will be measured using a monofilament, a biothesiometer and the Michigan Neuropathy Screening Instrument **(3.3.4.5.3.)**
6. Lower extremity perfusion will be assessed non-invasively with the Ankle brachial index and toe brachial indexes. **(3.3.4.5.4.)**
7. Foot and shoulder function questionnaire **(3.3.4.5.5. & 3.3.4.5.6.)**
8. Foot, ankle, and shoulder range of motion will be measured using a goniometer **(3.3.4.5.7.)**
9. A blood draw will be performed to determine how well diabetes is under control (HbA1c) and a measure of chronic inflammation will also be taken (hsCRP). **(3.3.4.5.8.)**
10. Digital photographs of the feet will be taken, with no identifying information on them. They will be stored using the subject identification number on a computer secured with a password. Only study personnel will have access to photos **(3.3.4.5.1.)**
11. Weight bearing lateral view foot radiographs will be taken of both feet. The data will be stored with study

		Baseline (T1)		1- 15 Weeks	6 Month (T2)		7-17 Months	Year 1.5 (T3)		19-35 Months	Year 3 (T4)	
	Time (min)	Visit 1	Visit 2		Visit 1	Visit 2		Visit 1	Visit 2		Visit 1	Visit 2
Informed Consent	15	√										
Clinical Intake Data	30	√			√			√			√	
Instrumented Measures												
Skin Fluorescence	10	√									√	
Magnetic Resonance	30		√			√						√
Computed Tomography	15		√			√			√			√
Kinematic Assessment	90	√			√			√			√	
Clinical Measures												
Foot and Shoulder Questionnaires	20	√			√			√			√	
Neuropathy Assessment	30	√						√			√	
Vascular Assessment	15	√						√			√	
Joint Mobility Assessment	15	√			√			√			√	
Weight Bearing Foot X-ray	15		√									√
Routine Serum Chemistry (hsCRP, HbA1c)	10		√						√			√
Intervention	~30			√ (x8)								
Phone Contact (1 call every 3 months)	5						√ (x3)			√ (x5)		
Total (minutes)		225	70	240	155	45	15	200	25	25	200	70

Table 1. List and burden of tests

identification number and no personal health identifiers. Only study personnel will have access to the radiographs **(3.3.4.5.10)**

c. Potential Risks

Likely:

This study will expose you to radiation from the computed tomography (CT) scanning and from the weight bearing lateral view foot radiographs. The amount of radiation from this, when averaged over your entire body, is 22% of the amount of radiation exposure all people in St. Louis receive each year from naturally occurring radiation sources. It is not a big risk when compared with other risks you take every day.

Calculation of radiation:

15 x 3 = 45 millirem of radiation/visit

The study has 4 visits over 3 years (Baseline, 6 months, 1.5 years, and 3 years)

Over the 3 year study a participant receives 4 x 45 = 180 millirem of radiation

Visit 4 has one additional CT of other foot: 15 millirem of radiation

Total CT radiation= 195 miliirem of radiation

Radiographs: 2 radiographs at Visit 1 and Visit 4. 0.17 millirem/radiograph x 4= 0.68

Total CT + Radiograph radiation=195.68.

Less likely:

You may experience muscle soreness or pain due to increased activity from the intervention, but this will be minimized by introducing new exercises in a gentle and progressive manner.

Blood draw – may experience discomfort, bruising, and/or bleeding at the site of needle insertion from blood drawing. Occasionally some people experience dizziness or feel faint.

SCOUT DS - If you have a lot of hair on the underside of your forearm, a small area (about the size of a post-it note) will be shaved with a disposable safety razor and shaving cream before being tested with the SCOUT DS. There is a slight risk of receiving a cut from the use of a safety razor and minor skin irritation.

MRI – might have difficulty getting on and off the MRI scanner table. We will minimize this potential for injury by helping the participant get on and off the scanner table.

Rare:

MRI – It is unlikely, but the participant may become uncomfortable from maintaining the position of the foot while being scanned. The participant may experience temporary muscle cramps in legs or feet during or after the scan. To minimize this risk, we will use soft rolls and comfortable leg and foot positions and teach how to stretch the leg and foot muscles and tendons to prevent cramping and being uncomfortable during the scans. If the participant becomes claustrophobic in tight spaces, they might experience anxiety while in the MR scanner.

SCOUT DS - The measurement of skin fluorescence by the SCOUT DS, using UV exposure from the instrument, is less than that routinely encountered from exposure to sunlight for two minutes. Nonetheless, there is a known risk to using the SCOUT DS device. Since some of the light shone on the skin is at the same wavelength as sunlight, there is a small risk of skin irritation. One case of skin irritation out of ~12,000 participants has occurred in prior studies with SCOUT DS and that subject had a prior sun allergy (photosensitivity). The skin reaction was controlled by topical ointment. If the skin is known to be very sensitive light, this measure will not be collected.

Blood draw – There is a rare risk of infection with the needle insertion from the blood draw.

Videotape – There is a possibility of skin sensitivity to adhesive markers placed on the feet during the videotaping for 3D kinematics. The participant may develop a mild skin irritation at the site of the marker placement. The irritation should not last more than two days.

Questionnaires – There may be discomfort in answering items on the questionnaires. If any particular question makes the participant uncomfortable, they may discuss its importance and the need to answer it with the

specially trained interviewer. The participant may choose not to answer any questions and this will not have an effect on their medical care.

If the participant wears or has electronic medical devices implanted such as a pacemaker, they will be excluded from the study. If the participant has a drug pump, they will be asked to tell the study doctors and research staff. Due to the magnets that make the MRI work, they can pose a risk to health and interrupt the functioning of the electronic devices. Participants will be asked to refrain from wearing and having metals or anything that can interfere with the magnetic field in the exam room (i.e. jewelry, credit cards, removable dental work, eyeglasses, etc.). There are no known biological hazards to humans being exposed to magnetic fields of the strength used in MRI

There is a possibility of minor discomfort resulting from the removal of the passive reflective markers, which are affixed to the skin using double-sided removable tape.

Participation in this study may cause all or some of the side effects listed above. In addition, there is always the risk of developing previously unknown side effects.

Adequacy of Protection Against Risks

a. Recruitment and Informed Consent.

Subject Recruitment will occur primarily from the Recruitment Enhancement Core (http://icts.wustl.edu/icts-researchers/icts-cores/find-services/by-core-name/recruitment-enhancement-core) of the Institute of Clinical And Translational Sciences at Washington University School of Medicine. Several data bases are available to help recruit (Research Participant Registry through Volunteers for Health, and patient databases of the Applied Biomechanics and Human Biodynamics Laboratories). These resources have sufficient numbers of potential participants to help us achieve our goal. Potential participants will be mailed the consent prior to their first visit to allow them to carefully review the information and formulate questions regarding the study requirements. The requirements, risks and benefits of participation will be explained and all questions the potential participant may have will be answered. If willing to enroll in the study, written informed consent will be obtained. The subject can discuss the study with family/friends before deciding on participation. If volunteers agree to participation, we will then obtain informed consent.

Informed Consent. The informed consent form will be signed when the participant comes to the laboratory for their visit. The consent form provides information about the purpose of the study, what the participant will be asked to do during the study, the risks and benefits of participating, and their rights as a research participant. Additional information will be given about their health information confidentiality and protection, as well as their right to withdraw or discontinue their participation in the study at any time for any reason.

b. Protections Against Risk

For the telephone screening, if a potential subject is not eligible or not interested, we ask their permission to keep the information they have given us on file. If they do not allow us to keep their information, we will shred their information immediately. The research record is stored in a secured location that only the research team has access to.

We will keep the participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of the participants' participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- People who use the registry
- Primary care physician if a medical condition that needs urgent attention is discovered
- Hospital or University representatives, to complete Hospital or University responsibilities
- Information about participation in this study may be documented in health care records and be available to health care providers who are not part of the research team.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants).

To help protect confidentiality, we will ensure that only members of the research team will be allowed in the room for the consent process and the testing area. If we write a report or article about this study or share the study data set with others, we will do so in such a way that participants cannot be directly identified. Only members of the research team will have access to the information, and the research coordinator will provide, to the subject, any information in their file upon request.

Protected Health Information (PHI) is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, the subject must give the research team permission to use and disclose (share) their PHI for the study as explained in the consent form. The research team will follow state and federal laws and may share health information with the agencies and people listed in the informed consent document.

The research team will only use and share information as talked about in the informed consent form. When possible, the research team will make sure information cannot be linked (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form.
All imaging will be performed by trained technologists. All testing and intervention will be performed with a trained physical therapist present. Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) will be stored in a locked cabinet in a locked office (Movement Science Research Center, B110, 4444 Forest Park Ave., St. Louis, MO 63108).
Electronic records (computer files, electronic databases, etc.) will be de-identified and stored on a secure network drive via a computer that is password and firewall protected. The de-identified information will be backed-up periodically on DVDs. The folders on the backed up data will be encrypted. These DVDs will be stored in locked cabinets in a locked laboratory (Movement Science Research Center, B110, 4444 Forest Park Ave., St. Louis, MO 63108). The master list linking the subject ID to PHI will be stored on a separate file that will be password protected. This file will be saved on a secure drive via password and firewall protected computer.
Biologic samples (blood draws) will be transported directly to laboratory services Barnes-Jewish hospital in closed test tubes and sealed bags. The tubes will be labeled with the subject's study identification number, date of birth, and date of blood draw. The BJH laboratory will destroy any remaining sample not needed for analysis. No blood will be stored as a part of the research proposal.

Potential Benefits of the Proposed Research to Human Subjects and Others
Participants may benefit from the intervention provided as part of study enrollment. Indirectly, the participants will benefit from the knowledge gained from this study, as detailed below. Participants may also receive education and instruction in proper foot care if necessary. For example, we routinely examine the foot closely and provide participants instructions on how to identify and prevent skin lesions or breakdown consistent with current American Diabetes Association guidelines (Boulton AJ, et al, 2008).

Importance of Knowledge to be Gained
The relationship between intrinsic foot muscle deterioration, movement and the progression of metatarsophalangeal joint deformity is not well understood. Results from this investigation will improve our understanding of the mechanism behind the development of structural deformity in the diabetic, neuropathic foot, and its associated functional deficits. These results will inform the use of conservative treatment options that may assist in slowing or preventing deformity development and progression that results in reducing the risk of neuropathic plantar ulceration and lower extremity amputation. These benefits greatly outweigh the small level of risk associated with participation in this project.

Data and Safety Monitoring Plan
To ensure the safety of research participants, Drs. Hastings and Mueller will be responsible for continuous and close monitoring of data collection safety and confidentiality. This will be accomplished by ensuring standard methods of data collection that maximize participant safety and minimize potential risks. In addition all identifying information and health identification data collected as part of research project will be kept in a locked cabinet (separate from the data file), separate from the data file, that can be accessed only by authorized lab personnel. The participants will be assigned a number upon entering the study. The number will be used for all data analysis and presentation. All serious adverse events (SAEs) will be reported to the IRB: a) death – immediately; b) life-threatening within 7 calendar days; c) all other SAEs within 10 working days using *my*IRB Reportable Event Form. Should there be a serious adverse event that occurs that increases the risks to

the participants, the study will be stopped, an investigation will be conducted, and a findings report will be generated before the study is resumed. A data safety monitoring committee will be formed and include Drs. Mary Hastings, Michael Mueller, Jeffrey Johnson, and Todd Cade, our committee member outside the project. Dr. Hastings will formally review all data (maintaining a blinded status) with the data safety monitoring committee every December, starting in 2017, to further ensure participant safety and timely publication of results. Dr. Mueller will provide unblinded oversight to assure treatment data and participant safety is maintained.

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