Electrical Stimulation for Improving Balance in Diabetes

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1. Introduction and Purpose:

Our long-term goal is to provide a convenient, low-cost therapeutic device and treatment protocol for diabetic patients with high risk of falling. Eventually, we plan for this to be an approach that can be used by patients at home. We will use preliminary data from this study to plan and implement a randomized clinical study in high risk diabetics to evaluate long-term clinical outcomes, specifically a reduction of falls, foot ulcers and amputations in patients that use the electrical stimulation treatment.

This study will be a double-blind randomized clinical trial design consisting of two groups of forty (40) patients with diabetic peripheral neuropathy and some level of postural instability. The study consists of a 12 weeks treatment phase and two weeks of retention. Subjects will be asked to wear a comfortable electrical stimulation device (SENSUS™ Pain Management System, Neurometrix, Inc., Waltham, MA) during night time on daily basis for duration of 8 hours. The proposed dosage regiment was used in our preliminary studies and no related adverse event was reported while a significant improvement in skin perfusion was observed. The objective of this proposed study is threefold:

Aim1: To compare postural control in subjects assigned to use the active Electrical Stimulation (intervention group) and subjects assigned to non-functional stimulator (sham group). Balance will be assessed for both groups at baseline and at monthly intervals. Study hypotheses are:

H1: Electrical Stimulation will improve postural coordination and helps to reduce body sway during standing in the treatment group compared to the sham group as well as compared to the baseline.
H2: Electrical Stimulation will improve gait, gait initiation, and gait inter-cycle variability compared to the sham group as well as compared to the baseline.

Aim2: To compare changes in skin perfusion in patients treated with Electrical Stimulation compared to sham therapy.

H3: Electrical Stimulation will improve dorsal and plantar perfusion compared to the control group and compared to baseline.

Aim3: To evaluate changes in quality of life in high risk diabetes who received Electrical Stimulation compared to sham therapy.

H4: Plantar stimulation will improve subject quality of life in the intervention group assessed using SF36.

H5: Plantar stimulation will improve spontaneous daily physical activity. More specifically, the duration of walking and standing as well as activity organization (i.e. day-to-day activity fluctuation) will be improved.

H6: The risk and fear of falling during activity of daily life will be improved.

2. Background:

This project builds on the results from our previous studies and is designed to translate basic science findings into protocols and methods of therapeutic value. In the following the most relevant studies to the purpose of this project have been summarized:

Study 1: A novel body worn sensor technology for assessing postural control and postural compensation strategy:

Human body motion is traditionally captured using standard optic, magnetic or sonic technologies (Najafi, Aminian et al. 2003; Aminian and Najafi 2004). However, in recent years, body- wearable sensor technology based on electro-mechanical sensors has provided a new avenue for accurately detecting and monitoring body motion and physical activity of an individual under free conditions (Aminian and Najafi 2004; Zijlstra and Aminian 2007; Najafi, Helbostad et al. 2009; Najafi, Horn et al. 2010; Najafi, Miller et al. 2010). In particular, combinations of multiple accelerometers and angular-rate sensors (gyroscopes) show a promising design for a hybrid kinematic sensor module for measuring the 3D kinematics of different body segments (Najafi 2003; Zijlstra and Aminian 2007).

Body-wearable sensors offer the key advantages of low cost and use in all environments—since they don't require installation of any particular infrastructure. These benefits are important in developing a suitable tool for clinical applications, as they enable physicians to (1) improve the evaluation of patient gait and postural control; and (2) help patients care for themselves. Body-worn sensors incorporated with high-speed data acquisition system enable the measurement and recording of 3D body segment motion with sample frequencies much higher than is possible with camera-based systems. The high sample frequency is essential to creating an altered dynamic environment to evaluate the postural response against alteration. In addition, a real-time processing is highly beneficial to the creation a bio-feedback signal from body segment motion or COM for both rehabilitation and evaluation of gait and postural control mechanisms. (Najafi 2003; Aminian and Najafi 2004).

In a recent study, our bioengineer collaborator in the USA, has designed and validated a biosensor technology named BalanSens™. (Najafi, Horn et al. 2010) This system is based on widely-available kinematic sensors (i.e. accelerometer, gyroscope and magnetometer). The system measures ankle and hip motion in three dimensions (3D)-figure 1. We have also integrated the resulting data into a two- link biomechanical model of the human body for estimating the 2D sway of the center of mass (COM) in anterior-posterior (AP) and medial-lateral (ML) directions (Fig. 2). To evaluate the best postural strategy for maintaining balance, a reciprocal compensatory index (RCI) was defined which quantifies how the movement around hip could compensate the movement around ankle for reducing the variation of COM. (Najafi, Horn et al. 2010; Najafi and Wrobel 2010). RCI values near zero represent a good postural control strategy (i.e. negative correlation between hip and ankle movements), RCI values more than one represent inappropriate postural control strategy (i.e. positive correlation between hip and ankle movements leading to increase the variation of COM and ankle, and hip in real time using a two-link biomechanical model of a human body.

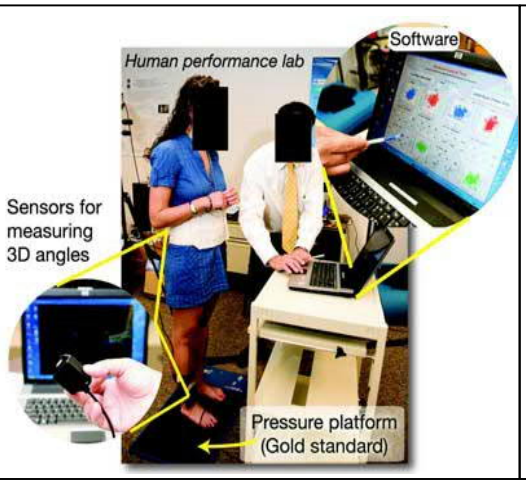


Figure 1 **–Assessing Balance:** two sensors were attached, one to the subject's lower back and one to the shin. These sensors allow measuring three-dimensional angles of ankle and hip joints. Software was developed to estimate the trajectory of COM

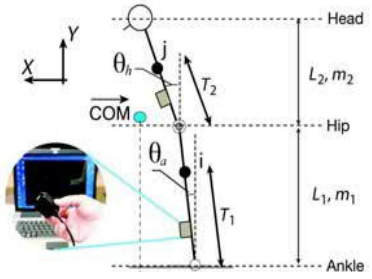


Figure 2 – Two-link biomechanical model of human body for estimating COM trajectory

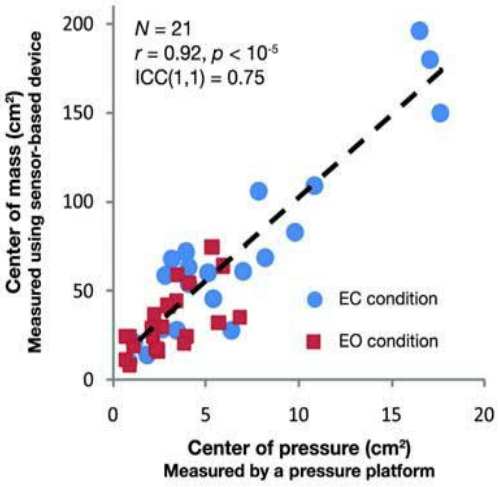
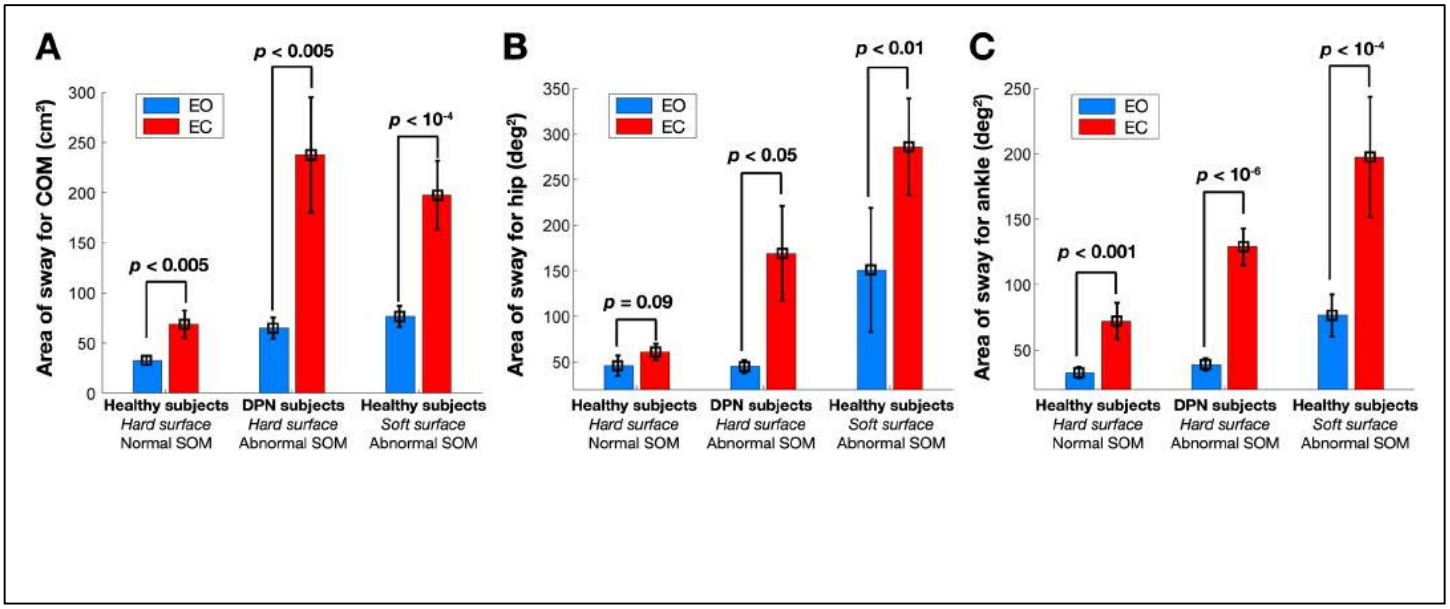


Figure 3 – the validation results compared to force-platform

The validity and reliability of the suggested system were examined by several measurements. (Najafi, Horn et al. 2010) First, the COM estimated using BalanSens was compared with COP measured using a standard pressure platform in 21 healthy subjects. Results suggested a relatively high correlation (r=0.92) between two measurements during both eyes-open and eyes-closed conditions. Interestingly, measuring COM seems to be more than 12 times more sensitive than measuring COP (i.e. 12 times higher range of sway for COM compared to range of sway for COP, see Fig 3). We also examined the sensitivity of the device for screening balance deterioration by comparing the output of the system among several conditions where both visual and somatosensory feedback was altered. Results demonstrated that this system is highly sensitive to detect balance alterations due to challenges in visual (eyes-closed condition) and somatosensory feedback (standing on a soft surface). (Najafi, Wu et al. 2009; Najafi, Horn et al. 2010) Finally, the clinical validity of the system was assessed by comparing balance control of healthy subjects with a group of 17 diabetic patients suffering from lack of somatosensory feedback. (Najafi, Horn et al. 2010) Results demonstrated that DPN patients exhibit significantly greater COM sway than healthy subjects for both EO and EC conditions ($p<0.005$) –Figure 4. The difference becomes highly pronounced while eyes are closed ($197\pm44cm^2$ vs. $68\pm56cm^2$). Furthermore, the results showed that postural compensatory strategy assessed using RCI is significantly better in healthy subjects compared to DPN subjects for both EO and EC conditions as well as in both medial-lateral and anterior-posterior directions ($p<0.05$). Interestingly, alteration in somatosensory feedback in healthy subjects via asking them to stand on a soft surface resulted in diminished RCI values that were similar to those seen in the DPN subjects ($p>0.05$). These results suggest that a low cost technology based on inertial sensors similar to those sensors used in new generation of *iPhone*® can provide accurate

information about patient's balance without using an elaborate gait lab infrastructure. This strategy also appears to be more sensitive and responsive as the changes are approximately 12 times larger than using traditional center of pressure techniques. This degree of discrimination could detect clinically subtle yet meaningful changes in a patient's balance.

Figure 4: The area of sway for **(A)** COM, **(B)** hip joint, and **(C)** ankle joint for healthy subjects while standing on a hard surface (healthy SOM feedback), DPN subjects (distorted SOM feedback), and healthy subjects while standing on a soft surface (distorted SOM feedback)



Study 2 & 3: The benefit of the electrical stimulation device on wound healing:

In a preliminary study, we have employed electrical stimulation on six patients, three men and three women, with an average age of 57.1 ± 9.3 years, all with type II diabetes of a mean 14.7 ± 5.9 years' duration. All wounds evaluated were plantar, five beneath the first metatarsal head, one beneath the fifth metatarsal head, with a mean area of 5.1 ± 1.1 cm^2. All wounds were grade 1A (non- infected, full thickness skin not involving tendon, capsule, or bone) using the University of Texas wound grading system. These wounds were present for a mean 77.3 ± 55.1 days prior to institution of electrical stimulation. All healed uneventfully in a mean 4.1 ± 2.3 weeks. There were no known complications to electrical stimulation during the period of review. The wound healing rate was between 33% and 50% faster than previously reported studies using similar patient populations.(Mueller, Diamond et al. 1989; Armstrong, Lavery et al. 1996).

In a subsequent study(Peters, Lavery et al. 2001), we explored the benefit of pulse-galvanic electric stimulation as an adjunct to healing diabetic foot ulcers. This study was designed as a 12-week, double-blind, randomized, placebo-controlled clinical trial. Forty patients with diabetic foot ulcers consecutively sampled (Table I). Twenty patients each assigned to treatment and placebo groups. We used the Micro-Z™ stimulator (see Section 4, Fig 11), that delivers current via a microcomputer to a Dacron-mesh silver nylon stocking to provide nocturnal electric stimulation to patients randomly assigned to the treatment group. The total program was designed to run at night for an 8-hour period. The placebo group used identical functioning units that delivered no current. Both the treatment and placebo group received traditional wound

care consisting of debridement, topical hydrogel, and off-loading with removable cast walkers. Patients were followed for 12 weeks or until healing, whichever occurred first. Outcomes included the proportion of patients with complete wound healing in 12 weeks, the rate of wound healing, and complications such as infection or need for amputation. Sixty-five percent of the patients healed in the group treated with stimulation, whereas 35% healed with placebo (*P*= .058). After stratification by compliance (Fig 5), a significant difference was identified among compliant patients in the treatment group (71% healed), noncompliant patients in the treatment group (50% healed), compliant patients in the placebo group (39% healed), and noncompliant patients in the placebo group (29% healed, linear-by-linear association =4.32, *p*= .038). There was no significant difference in compliance between the 2 groups. We believe these preliminary data are very promising and warrant further study.

Table I: Characteristics of Patients Who Received Placebo and Electric Stimulation

	PLACEBO GROUP	TREATMENT GROUP
History of diabetes (years)	17.0 ±	16.4 ± 11.6
Ulcer duration (months)	5.5 ±	5.0 ± 6.4
Age (years)	59.9 ±	54.4 ± 12.4
Gender	16 male, 4 female	18 male, 2 female
Glycosylated Hemoglobin (%)	9.5 ± 2.4	9.2 ± 2.1
Peak Plantar Pressure ($Ncm^{\angle}$)	81.5 ±	91.1 ± 15.7
Transcutaneous Oxygen	43.4 ±	47.1 ± 13.0
Semmes-Weinstien Monofilament	1.9 ± 2.4	3.2 ±
Vibratory Perception Threshold (volts)	41.5 ±	38.5 ±
Percentage with neuropathy	100%	100%
Compliance per week (hours)	27.9	30.2 ± 11.9

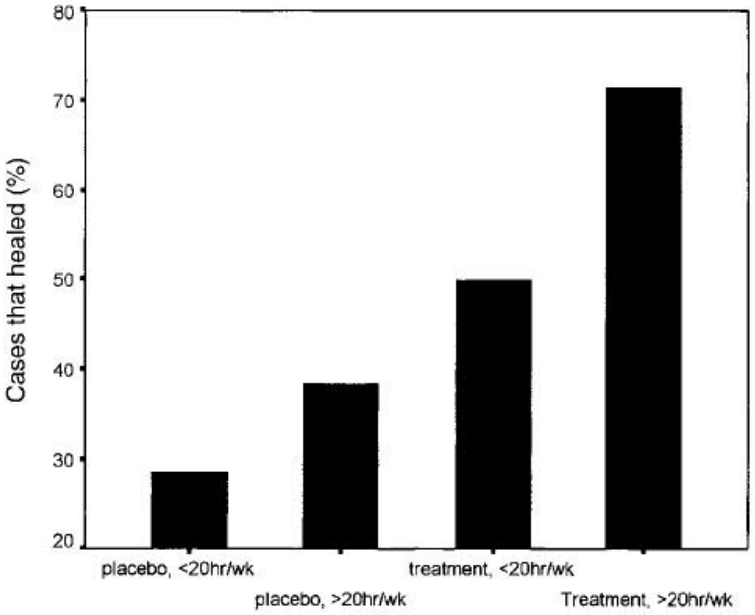
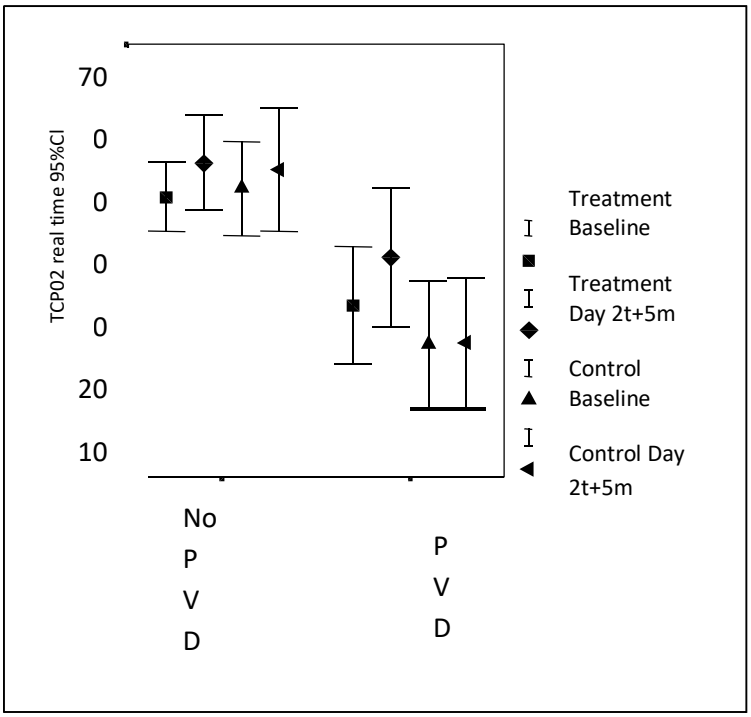


Figure 5: Results of electric stimulation on wound healing, stratified by compliance. Patients who used electric stimulation for 20 hours or more a week were more likely to heal than those who used the devices less than 20 hours a week or patients who used the placebo device: (X^2 for trend=4.35, p=.037).

Study 4: Electrical stimulation and increased perfusion:

The purpose of this study (Peters, Armstrong et al. 1998) was to evaluate the effect of galvanic electrical stimulation on vascular perfusion in diabetic patients. Nineteen subjects with diabetes were enrolled. Eleven subjects (57.9%) were diagnosed with impaired peripheral perfusion based upon their initial transcutaneous oximetry values (< 40 mm Hg). The subjects were studied over a 2-day period. On the 1st day, one foot was electrically stimulated for four 60-minute periods by an external electrical stimulation device (Micro- Z™ stimulator, Fig 11). Vascular perfusion of both feet was assessed before and after the sessions of electrical stimulation. On the 2nd day, no electrical stimulation was applied and noninvasive vascular measurements were repeated. For the 1st hour, transcutaneous oxygen pressure was measured continuously during stimulation at the lateral aspect of the leg. Subsequently, perfusion between the periods of stimulation was measured on the dorsum of the foot with both transcutaneous oximetry and laser Doppler flowmetry after each stimulation period. In the group with impaired peripheral perfusion, a significant rise in tissue oxygenation as compared to the control measurements was measured during the first 5 minutes of stimulation ($p < .040$, Fig 6). For those without vascular disease ($TcpO2 > 40$ mm Hg) however, there was not a significant increase compared to baseline ($p = .280$). After the periods of stimulation, the stimulated feet did not show any higher perfusion levels than the control feet. Patterns in perfusion during the day, as measured by laser Doppler flowmetry, were similar in the tested feet and in the controls. These data suggest that external sub-sensory electrical stimulation induces a transient rise in skin perfusion in persons with diabetes and impaired peripheral perfusion.

Figure 6: Average changes in transcutaneous oxygen pressure after usage of plantar stimulation.



Study 5: Postural control improvement post recovery loss of mechanical sensitivity using a novel Plantar Stimulation technology- A Double-Blinded, Randomized Study.

Many patients with diabetic peripheral neuropathy (DPN) experience a marked loss of mechanical sensitivity, a condition that puts them at risk for the formation of dangerous skin ulcers and postural instability. The purpose of this pilot research (Najafi, Crews et al. 2011) was to test whether a specific form of subcutaneous electrical stimulation improves postural control in patients suffering from DPN.

Fifty subjects with type 1 or type 2 diabetes and mild to moderate peripheral sensory neuropathy (insensate to 10 gram monofilament at 1-3 of the following locations: hallux, 1st metatarsal head, 3rd metatarsal head, and 5th metatarsal head) were enrolled. The study consisted of a six week treatment phase with five treatments per week followed by 26 weeks of follow-up. Subjects were randomized in to either sham or active stimulation. Both groups soaked their feet for five 30-minute sessions per week in identical stimulator baths named WaveRx® (Fig. 7) that were connected to electrical stimulators. The active group received continuous stimulation in the bath during the soaking sessions, while the active group's stimulators were non-functional and provided no stimulation. Patients were instructed at the initiation of each treatment to gradually increase the stimulator's power to 40% or until the patient felt a comfortable tingling sensation. If the device was active it would deliver 120 Hz pulsed current waveforms up to a maximum of 50 miliamperes. Postural control was assessed in a sub-sample of thirteen subjects at baseline and every two weeks during the treatment phase as well as in 3 and 6 months later. Postural control was quantified by measuring the area of center of mass sway (COM) using the body worn sensor technology explained in the preliminary study #1 (Fig 8).

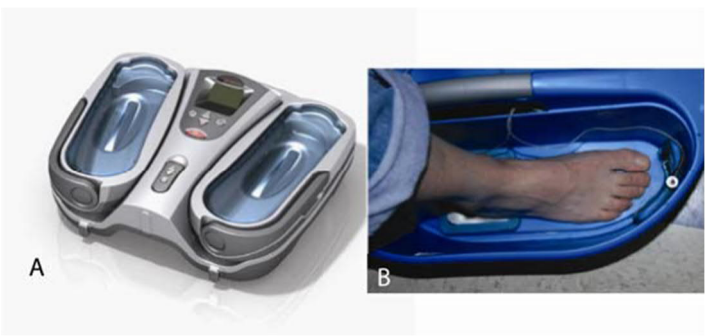


Figure 7: WaveRx Electrical Stimulation System

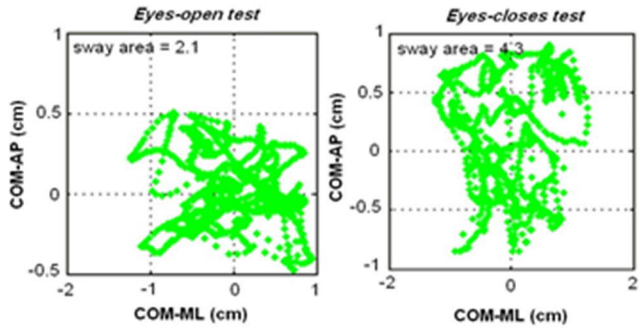


Figure 8: Balance was quantified by measuring the area of Sway for COM

A significant improvement in postural control was observed in the active group (ANOVA, $p<0.05$)- Fig 9. The area of COM sway was significant reduced on average 36% on treatment week two.

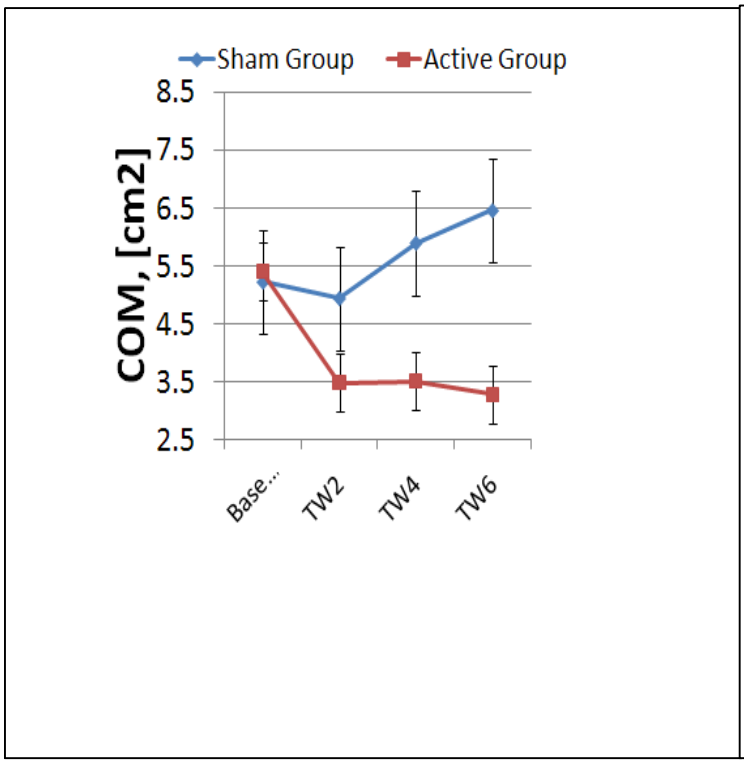


Figure 9 Aqueous treatment of DPN using stimulator plantar stimulation technology significantly improved postural control in Active group compared to baseline as well as sham group.

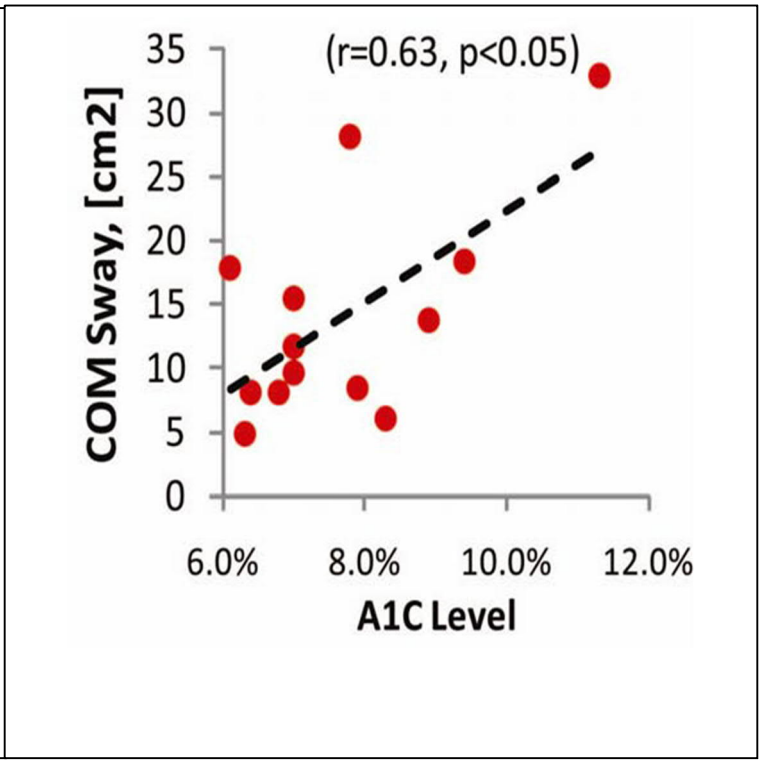


Figure 10 Patients with poor hyperglycemia control (higher A1C level) has weaker postural control

3. Concise Summary of Project:

This is a double-blind randomized clinical trial. Both patients and the study coordinator who collects data with the subject will be blinded to electrical stimulation application. The Study Physicians (PI/Sub-!) will evaluate and monitor study subjects. The Physicians (PI/Sub-I) will not be blinded to the treatment the subject receives and determine the status of active treatment versus sham treatment. This documentation will be only in the PI/Sub-I possession. The manufacturer of the units will be asked to not inform which patient received which unit. Each unit will be coded with a unique identification number, and the manufacturer units revealed their status, placebo or electric stimulation, only at the end of data collection for the last patient. Subsequently, the investigators could match the status of the identification numbers with the corresponding units to start analyzing the data. Patients that receive an activated electrical stimulation unit will receive a standard dose of
50 volts as described above.

Figure 11

SENSUS™ Pain Management System

Since most patients that participate in this project will have moderate to severe peripheral

sensory neuropathy, they will not be able to “feel” if they are receiving electrical stimulation. Placebo controls will have an electrical stimulation unit programmed not to provide any electrical current. However, all the other lights and programming indicators will be functional. Both active and inactive electrical stimulation units will be programmed to download the period that they are used on a weekly basis in order to verify that the units are used for the prescribed time period. A sealed randomization schedule envelope will be held at the coordinating center (UT Southwestern). Except in a medical emergency, subjects will remain blinded with regard to group assignment until crossover opportunity or such time that all source documentation is complete, e.g., transcription into the CRFs has been completed, CRFs have been signed by the Principal Investigator, and the database has been closed.

We will enroll a cohort of 80 diabetes (type II) patients with peripheral neuropathy (see section 6 for sample size justification). The diagnosis of diabetes mellitus will be based on World Health Organization criteria.(World-Health-Organization 1999). The inclusion and exclusion criteria are described in table III. The clinical assessments are described in table IV. The investigator will discuss the study design, duration, and its risks with potential subjects asked to participate. We will then provide the participant with a consent form to read at their leisure. The investigator will be available to answer questions or provide more explanation as requested by potential participants and their family.

Subjects will be recruited from two clinical centers: 1) Wound and Diabetic Foot center at the Hamad Medical Corporation (HMC-Doha-Qatar) under supervision of Dr Talal (contact-LPI) and 2) the University of Texas Southwestern Medical Center (UT Southwestern), Dallas, Texas under supervision of Prof. Lavery (Lead-PI).

4. Study Procedures:

There will be a total of five study visits required for each patient. There will be one scheduled visit for baseline evaluation and four additional visits at 2 weeks, 4 weeks, 6 weeks during treatment and 8 weeks (2 weeks post stopping the treatment). The baseline visit will involve completion of a standardized intake form, which will include pertinent demographics such as age, height, weight, education level, occupation, and comorbidities of the study patient (see Table IV). Several clinical assessments will be performed at baseline as well as at each study visit to evaluate severity of neuropathy and skin perfusion as described in the table IV.

5. Sub-Study Procedures:

N/A

Table IV: Clinical Assessments

Baseline	**Medical History:** This will include: duration and type of diabetes, type of diabetes medication (insulin, oral, combination therapy, diet), previous history of foot ulcers, previous history of falls, amputation (toe, foot), lower extremity bypass, lower extremity angioplasty, Coronary artery bypass surgery, cardiac angioplasty, arthritis, liver disease, osteoporosis, malignancy, and bone tumors. We will use the Kaplan co-morbidity index to record disease severity. We will use the New York Heart Association criteria to classify congestive heart failure, and the National Kidney Foundation Disease Outcomes Quality Initiative Clinical Practice Guidelines for chronic kidney disease to stage kidney disease. We will document all prescription and over-the-counter medications. We will measure height and weight to determine body mass index (BMI). We will record prescription and over-the-counter medications.
Baseline	**Social Factors**: We will evaluate the following factors: marital status, years of education, type of work, tobacco history (pack years, current smoker, current use of chewing tobacco, previous smoker, no tobacco history), drug history (current, previous history, no drug history), education, occupation, and alcohol history. **Foot questionnaire and foot exam**
Baseline Questionnaires	**Screening Test for frailty assessment:** Fried Frailty Criteria: Weight loss >10 pounds in preceding year; Grip strength; Low levels of physical activity; 15 foot walk time; Exhaustion[13] *** Screening for cognitive problem: Folstein Mini-Mental State Exam** score [15] *** Foot questionnaire and foot exam** *** Barthel ADL Index** *** Depression Assessment** *** Fear of Falling Scale** *** Mobility Tiredness Scale** *** Pain Assessment Scale** *** SF-12 (at baseline and 6 week time points)**

Baseline & each 2- week follow-up (week 2, week 4, week 6, and week 8) **± 2 day visit window for each protocol related visit starting at Week 2.**	**Peripheral Neuropathy**: We will evaluate Vibration Perception Threshold (VPT) Testing to evaluate large fiber neuropathy We will also use Semmes-Weinstein monofilaments, and the Modified Neuropathy Disability Score. (Armstrong and Lawrence 1998) We will assess light touch and pressure sensation at nine sites on each foot using 4, 10, 26, and 60 Semmes-Weinstein gram monofilaments. (Diamond, Mueller et al. 1989) The Modified Neuropathy Disability Score is a scored clinical examination that includes Achilles deep tendon reflex, pressure, vibration sensation and temperature sensation in both feet. (Abbott, Carrington et al. 2002; Caselli, Spallone et al. 2006). **Pain:** Visual Analogue Scale **Gait test:** 8 sensors will be attached to the legs and lower back using comfortable straps and will be asked to walk 20 meters on a flat surface, two times. A third 20 meter walk will be performed with an additional distractive cognitive task (counting -1). The 4th test will be fast walking. Walking performance (e.g., speed, cadence, and stability) and spatio-temporal parameters of gait (e.g., velocity, stride time, gait inter-cycle variability, double support, and gait initiation) will be measured. **Balance test:** The BalanSens^{TM} kinematic sensor will be attached to the legs and lower back and will be used to measure the variation of subject's center of mass measured by the Romberg protocol including double stance, semi-tandem, and full-tandem tests. Patients will be asked to stand straight, feet together, hands crossed for 30 seconds, 20 seconds, and 15 seconds respectively for double stance test, semi-tandem, and full tandem tests with eyes open and closed.
Baseline and 6 weeks follow-up	**Activity Monitoring:** Spontaneous daily physical activity will be monitored in home environment for 2 days using PAMSys^{TM} **Removal log:** participants will be asked to note the time off, time on, and reason for removal if the PAMSys^{TM} is removed during the 2 day collection period. Refer to Activity Monitoring Log for times of use and removal. **Quality of life questionnaire:** SF12 will be administered.
Other assessment	**Fall log:** participant will receive a log and agree to call the study overseer in the event of a fall during the 4 weeks study period. **Other patient information:** if it was available patients record including medical history, neurological exam results, and physical examination may be gathered from patient record after authorization of the subject (see form T504a). In addition, subject photograph or video during experiment may be taken after subject's authorization.

Baseline & each 2- week follow-up	**Vascular Assessment:** We will assess perfusion of the macro-circulation with arterial Doppler studies and micro-circulation with Skin Perfusion Pressure measurements and transcutaneous oxygen measurements. Ankle Brachial Index (ABI), Toe Pressures and Waveforms (pulse volume recordings) will be measured on both extremities. If the ankle is too painful to perform a Doppler examination, we will get Doppler measurements once the patient is in the operating room and under anesthesia. ABI's have been reported to be reliable measurements for diagnosing peripheral vascular disease. ABI's have a 95% sensitivity in detecting angiographically positive disease in an ABI of less than 0.9. Non-compressible foot vessels will be defined as ABI's >1.30. Peripheral arterial occlusive disease will be defined as an ABI<0.90. Monckeberg's medial calcific sclerosis or calcification of the media of the arteries can limit the effectiveness of using ABI's in persons with diabetes. Therefore, we will use the SensiLase system (Väsamed) to measure Skin Perfusion Pressure (SPP) in mmHg and records PVR waveforms with its laser Doppler sensor and computer-automated cuff. This technique has high sensitivity and high positive and negative predictive value to predict amputation.(Castronuovo, Adera et al. 1997; Yamada, Ohta et al. 2008) In addition we will measure transcutaneous oxygen measurements ar 2 sites on the foot and two sites on the lower leg during the course of therapy.

Specific Aim 1: Our first goal is to compare postural control in subjects assigned to use the active Electrical Stimulation (intervention group) and subjects assigned to non-functional stimulator (sham group). Balance will be assessed for both groups at baseline and at bi-weekly intervals. Static balance and postural compensatory strategy will be assessed using the body worn sensor technology (BalanSens™) explained in the preliminary study #1. The duration of assessment is approximately five minutes. The test includes quiet upright standing for a period of at least 30 seconds under two conditions: eyes-open and eyes-closed. Postural control will be quantified by measuring the range of motion of center of mass (COM) in medial-lateral and anterior-posterior direction. COM is estimated using an innovative and validated technology based on wearable sensors as explained in our preliminary study #1 – Figure 12. The key advantage of this technology is that balance is assessed outside of gait laboratory and directly in our podiatric center. Additionally, it allows measuring directly COM instead of center of pressure (COP). Our recent study suggests that measuring COM is 12 times more sensitive to assess postural instability than COP (Figure 3) (Najafi, Horn et al. 2010).

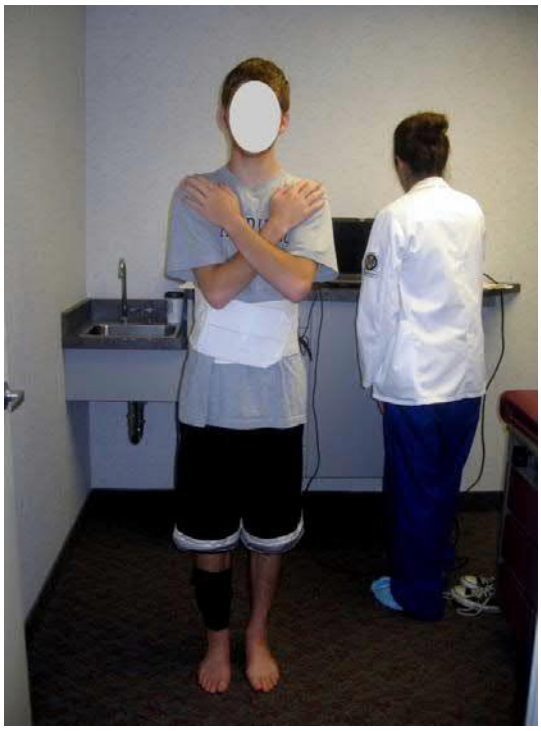


Figure 12: Balance will be assessed according Romberg protocol and will quantified using a validated technology based on body worn sensors

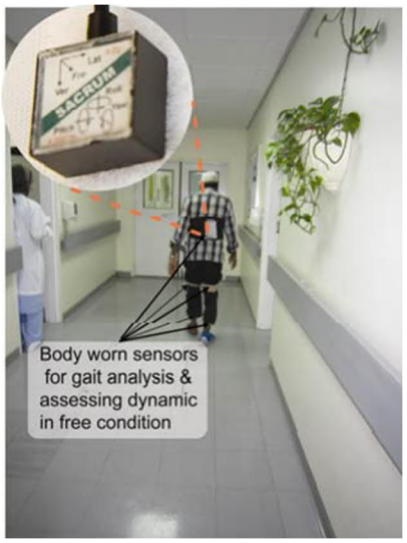


Figure 13: An innovative device based on body worn sensors allows measuring spatio-temporal parameters of gait and gait initiation in free condition including outside of a gaitlab.

To examine postural compensatory strategy, we will use RCI (reciprocal compensatory index) introduced in our previous study-see preliminary study #1(Najafi, Horn et al. 2010). This index represents how the movement around ankle joint is compensated by the reciprocal movement around hip joint to reduce the variation of COM. (Najafi, Horn et al. 2010) By comparing the balance control and postural compensatory strategy between DPN and control group, we will explore whether and how neuropathy may impact balance and during which conditions (e.g. closing eyes). The data is coded so the investigators involved in the data analysis are blind to the subject group (i.e. Sham v. Intervention group). We assumed at baseline there is no significant difference for the static postural control between two groups. But during treatment, balance will be significantly improved in the intervention group while it will be deteriorated or remained the same in the sham group (Hypothesis 1).

For assessing spatio-temporal parameters of gait as well as dynamic balance during walking, we will use an innovative wearable technology developed and validated by Prof. Najafi (PI) and his team in previous studies.(Aminian, Najafi et al. 2002; Aminian and Najafi 2004; Aminian, Trevisan et al. 2004; Lindemann U., Najafi B. et al. 2008; Najafi, Helbostad et al. 2009; Najafi, Crews et al. 2010; Najafi, Miller et al. 2010) This wearable technology comprises miniaturized motion sensors placed on the front of each lower leg and thigh and held in place with elastic Velcro straps, and a lightweight data logger worn on a belt around the person's waist (Fig 13). The sensors attached to lower-limbs are a triaxial gyroscope, triaxial accelerometers, and triaxial magnetometer that allow measuring of three-dimensional rotation of body segment using a quaternion scheme. (Najafi, Horn et al. 2010; Wrobel and Najafi 2010; Wrobel, Edgar et al. 2010 (In Press)) Another sensor attached to the lumbar region permits measuring the range of motion of center of mass (COM) for each gait stride in both the anterior-posterior and medial-lateral directions. (Najafi, Helbostad et al. 2009; Najafi, Miller et al. 2010) Signals from sensors are digitized (16 bit) at a sampling rate of 200 Hz by the light portable data logger and stored for off-line analysis on a Secure Digital (SD) memory card. This configuration allows measuring spatiotemporal parameters of gait, dynamic balance, and kinematics of lower limbs during walking as well as obstacle crossing. The method for calculating spatiotemporal parameters of gait has been described in detail and validated in previous publications.(Aminian, Najafi et al. 2002; Aminian and Najafi 2004; Najafi, Helbostad et al. 2009) To summarize, the gait phases are determined from the precise moments of heel-strike (initial foot contact) and toe-off (terminal foot contact). These moments are extracted from gyroscopes attached to each shank through a local minimal peak detection scheme. (Aminian, Najafi et al. 2002) The key advantage of this technology is the ability to extract gait and balance parameters outside of a gait laboratory and directly our clinical centers. Additionally, it allows extracting enough number of steps which is of key importance to increase the accuracy of gait estimation as well as assessing inter-cycle gait variability. Recent studies suggested that inter-cycle gait variability (or gait unsteadiness) is a sensitive parameter to assess risk of falling.(Dubost, Beauchet et al. 2002; Beauchet, Kressig et al. 2003; Beauchet, Aminian et al. 2005; Dubost, Kressig et al. 2006; Dubost, Annweiler et al. 2008; Beauchet, Annweiler et al. 2009; Beauchet, Annweiler et al. 2009)

For the purpose of gait analysis, subjects will be asked to walk at their habitual speed in a distance of approximately 20 meters while wearing the gait analyzer sensors (Fig 13). The system allows extracting over 30 spatio-temporal parameters of gait including stride velocity, stride length, stride time, stance, double support time, COM in medial-lateral and anterior-posterior, and gait initiation(Najafi, Helbostad et al. 2009; Najafi, Miller et al. 2010). We assumed that the performance of gait and dynamic balance will be improved in the intervention group after treatment compared to baseline and compared to sham group (Hypothesis 2). Additionally, we anticipate that the inter-cycle gait variability and gait initiation will be improved after treatment in the active group compared to

baseline and compared to sham group.

Specific Aim 2: Our second aim is to compare changes in skin perfusion in patients treated with Electrical Stimulation (ESTIM) compared to sham therapy. We anticipate that electrical Stimulation will improve dorsal and plantar perfusion compared to the control group and compared to baseline (Hypothesis 3). As described in the clinical assessment (Table IV), we will assess perfusion of the macro-circulation with arterial Doppler studies and micro-circulation with Skin Perfusion Pressure measurements and transcutaneous oxygen measurements.

Specific Aim 3: Our last aim us to evaluate changes in quality of life in high risk diabetes that receive Electrical Stimulation compared to sham therapy. Our hypotheses and methods of assessment described in the following:

Hypothesis 4: We assume that plantar electrical stimulation will improve subject quality of life in the intervention group. Quality of life will be assessed using SF-12 questionnaire (Melville, Lari et al. 2003) at the baseline visit and at week 6.

Hypothesis 5: We also anticipate that plantar electrical stimulation will improve spontaneous daily physical activity. More specifically, the duration of walking and standing as well as activity organization (i.e. day-to-day activity fluctuation) will be improved. Spontaneous daily physical activity will be assessed using PAMSys™ designed and validated by Prof. Najafi (PI) and his team with collaboration of Biosensics LLC. Participants will wear PAMSys□□ embedded in a lightweight breathable tank top worn under clothing for 2 consecutive days at baseline and each study visit (Fig 14). This device uses a combination of miniaturized kinematic sensors housed in a single portable sensor attached to the chest. It can detect body posture (sitting, standing, and lying), as well as provide an accurate assessment of periods of locomotion (e.g., walking, postural transition). The validity of this approach has been established in 3 separate pilots studies, and by benchmarking the results with independent analysis by an optical motion system.(Najafi, Aminian et al. 2002; Najafi, Aminian et al. 2003; Najafi, Wrobel et al. 2008; Najafi, Crews et al. 2010) These studies demonstrate that the PAMSys™ has an overall sensitivity of 99% for detecting the time of various postural transitions (e.g., sit-to-stand or stand-to-sit) and more than 87% sensitivity and specificity for identifying the transition type. *This fine-grained analysis of human movement represents a tremendous leap in technology over what is presently available.* Thus, this measurement technique will provide unique data, not previously acquired, on actual participation in daily life.

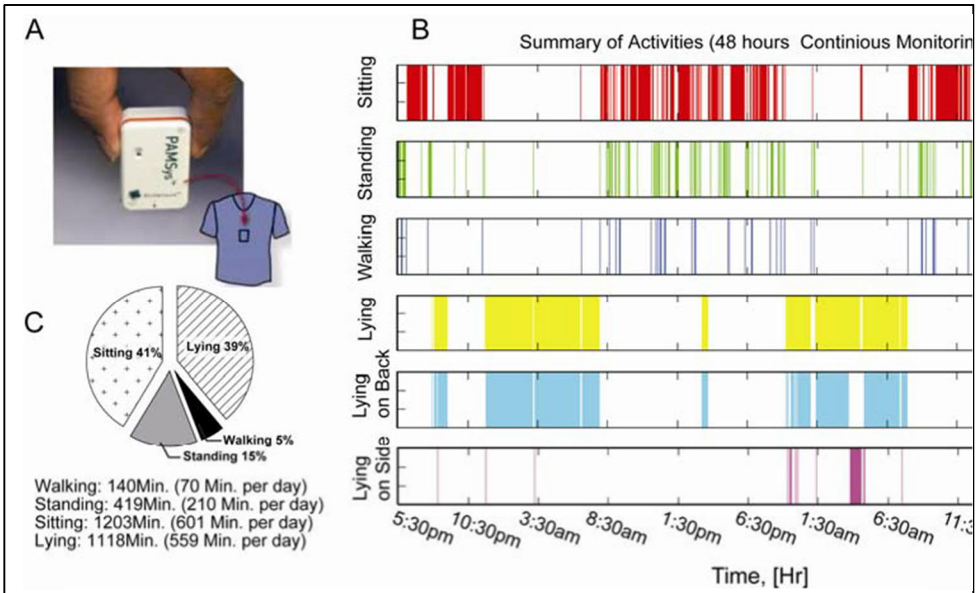


Figure 14- (A) The ambulatory device for measurement of physical activity during everyday life (PAMSys). This device designed to be worn unobtrusively by the subject. (B) Physical activity measured by ambulatory activity monitor for typical subject during 48 hours. (C) Same data reported as the time percentage of each major posture – walking covers a very low portion (3.5%) of the subject's physical activity

Hypothesis 6: Finally, we assumed that risk and fear of falling in the intervention group will be reduced compared to baseline and compared to sham group. To evaluate the fear of falling, we will use Fall Efficacy Scale (FES) questionnaire (Bula, Martin et al. 2006; De Bruin, Najafi et al. 2007). The risk of falling will be assessed using test timed Up&Go (Shumway-Cook, Brauer et al. 2000) as well as the duration required for rising or sitting on a chair as described by Najafi et al.(Najafi, Aminian et al. 2002)

6. Criteria for Inclusion of Subjects:

Inclusion
Men or women (non pregnant) 18 years old or above
Diagnosed for Diabetes Mellitus (type 2)* and *ADA criteria Diabetes (World-Health-Organization*
Evidence of peripheral neuropathy on neurologic examination *Identified by our clinical staff examination and based on the criteria explained in ADA statement (Boulton et al, 2005)*
Agreed to participate in this study and comply with instruction

May have a toe amputation

7. Criteria for Exclusion of Subjects:

Exclusion
Amputation and active ulcers or infection
Cognitive deficits. *MMSE score of 24 or lower*
Unable to stand for more than 5 minutes (including symptomatic orthostatic hypotension or pain)
Any clinically significant orthopedic, muscular, or peripheral vascular disorders that affect
Alcohol or substance abuse within 6 months or major psychiatric disorder.
Significant vision problem *Less than 20/100 vision after correction*
Any other neurological or medical disorders *that may significantly affect balance based on clinical judgment (e.g. CVA, asymmetric*
Refusing or lacking medical decisional capacity to provide informed consent.
Use of medications that is likely to affect cognition or balance (based on physician review) within 14 days

8. Sources of Research Material:

Demographic information (age, gender, ethnicity), medical and social history, results of examinations of the feet, balance testing, responses to questionnaires, use of the electrical stimulation device, adverse events and treatment.

9. Recruitment Methods and Consenting Process:

Subjects will be recruited from the investigator's patient population at the Parkland ASC Clinic and the UTSW Wound Clinic. The Lead Coordinator or another member of the research team will identify potential subjects during a standard care visit and asked if they are interested in participation in this research. Subjects who express interest will be given a copy of the Consent to take home, read and discuss with family/friends. The Lead Coordinator will schedule a Screening Visit.

Subjects will be given ample time to read and consider the Consent and allowed to bring a family member or friend to the screening visit. Alternatives to participation will be presented and discussed.

The subject will also be told that a decision not to participate in the research will not affect his/her treatment relationship with the physician/investigator.

A member of the research team will review the Consent with the subject and answer any questions. If the subject agrees to participate, he/she will sign the Consent and HIPAA Authorization. He/She will receive copies of the signed documents. The consent process will be documented in the source file.

10. Potential Risks:

Study Intervention

In previous clinical research, no risks have been identified with the SENSU (Neurometrix, Inc. ; http://www.sensusrx.com/) That is, no previous subjects have experienced any adverse events (side effects) from wearing thedevice.

Loss of Confidentiality

Any time information is collected; there is a potential risk of loss of confidentiality.

Other Risks

There may possibly be other side effects that are unknown at this time.

11. Subject Safety and Data Monitoring:

The principal investigator will monitor the experience of the subjects at least monthly and the conduct of the protocol, including:

- Study accrual rate
- Experience of study participants
- Study attrition including participant withdrawals/dropouts
- Patterns of AEs and/or unanticipated events
- Patterns of protocol deviations and/or violations
- Changes in risk/benefit

12. Procedures to Maintain Confidentiality:

All study procedures will be conducted in the private treatment areas at UT Southwestern.

For participants who are screened but not eligible for participation in the study, their essential documents will be securely maintained and placed in a locked cabinet with all of the hard copies of the essential documents obtained during this research. For participants who are screened and then enrolled in the study, their essential documents will be filed with the individual's research file. The HIPAA Authorization covers all PHI collected through the course of the participation in the study in addition to that which is covered through the screening process.

Hard copy documents (source files) will be kept in locked cabinets in the locked research office. Electronic data will be stored on a dedicated research drive that is password-protected with access limited to members of the research team. No identified data will leave the campus. Presentations, papers and publications from this research will use only aggregate data and no personally identifiable information.

13. Potential Benefits:

Wearing the Sensus stimulator may improve balance, circulation (blood flow), and quality of life, but this cannot be guaranteed.

We hope the information learned from this study will benefit others with diabetic peripheral neuropathy in the future. Information gained from this research could lead to better treatment.

14. Biostatistics:

Power & Sample Size Estimation: The sample size for the study was designed to achieve 85% power when comparing the change in the actively treated group to the change in the sham treated group, using assumed rates of 50% and 10% improvement, respectively. A two-sided test of results in evaluable subjects (qualified for analyses of efficacy on vibration perception threshold and on structured S-W monofilament testing) will provide the specified power at a 5% significance level. Sample size calculations resulted in a requirement for a total of twenty-seven (27) subjects in each group. The sample size was also estimated using our pilot data in which we explored the benefit of plantar stimulation for improving balance (Study 5). At baseline, the area of sway for center of mass (COM) was 5.23±2.81 cm^2 and 5.41±1.14cm^2 respectively for the sham and intervention groups. After week two of treatment, the area of COM sway was 4.94±3.42cm^2 for the sham and 3.49±1.25 cm^2 for the intervention group. Using the same criteria explained above, to observe a significant improvement in the intervention group receiving active stimulation compared to sham group (with nonfunctional stimulator), twenty seven subjects per group is required. Assuming 10% drop out, therefore, 40 subjects per group (a total of 80 subjects) should be enough for the purpose of this study.

No suitable alternative treatments exist for patients with loss of protective sensation due to diabetic peripheral neuropathy, so a statistically detected difference in improvement between groups may be considered a clinically meaningful result. However, the study was designed to detect a sufficiently large difference to account for an anticipated “placebo effect” in the sham treated group.

Analysis Plan:

P-values of 0.05 or less will be considered statistically significant based on a two-sided test unless otherwise noted. All variables will be tabulated descriptively at each scheduled time point. For each continuous variable, the analyses will include the mean, standard deviation, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages. Each variable will be analyzed using all available data. Baseline variables will be summarized using descriptive statistics. Between-group differences for primary and secondary endpoints will be explored at the time of the last treatment visit (weeks 12) and every two weeks of treatment.
Additionally, the retention of potential benefit will be assessed at the time of follow-up visit following the completion of treatment (two weeks post termination of treatment). The frequency of subjects

with adverse events (AEs) will be tabulated. AEs will also be tabulated by severity and, when appropriate, by relationship to study treatment. The difference in the occurrence of adverse events between the study groups will be compared descriptively.

To determine whether gait, balance, and physical activity variables change significantly across different study visit epochs, within-subject analyses of variance (ANOVA's) will be employed. We assume that plantar electrical stimulation is helpful to improve subjects gait, balance, and physical activity. Then sensor-derived movement variables should change substantially from baseline to the end of the study for the active group with no significant change in placebo group. For example, the range of motion of COM and RCI values should be reduced and gait velocity should be increased.

Next, for all continuous variables, pretreatment scores will be regressed on post-treatment scores to form residualized change scores (e.g. VPT, monofilament test, pain intensity, A1C, etc). Correlations will then be generated among these scores to determine whether changes in sensor-derived movement factors are related appropriately with increases in (clinically assessed) functional capacities and self-report measures of activities, mood, socializing, etc. ANOVA test will be used to examine significant difference between intervention and sham group at baseline for age and BMI as well as the indicated outcomes (e.g. gait, balance, VPT, ABI,. Etc). We assumed there is no significant difference between sham and intervention group at baseline for the indicated variables. The same test will be repeated for the week 12. We assumed that the outcomes of study will be improved in the intervention group compared to the sham group. Paired- sample t-test will be used to examine the retention of the electrical stimulation therapy at two weeks post stopping the therapy compared to week-12. We assumed the benefit of the electrical stimulation therapy will be retained at least for two weeks. Additional analyses will examine the degree to which early-treatment changes in cognitive variables and functional capacity variables (representing functional restoration processes) predict late-treatment changes in moving ability post plantar electrical stimulation therapy. Such analyses will also allows to elucidate the relative contributions fear of falling (assessed using FES score); and/or and range of motion (assessed using body worn sensors) made to bringing about clinically meaningful changes in gait balance control. Moderator effects will also be examined for exploratory purposes. Using gender as an example, mixed design ANOVA's will be conducted to determine whether gait and balance factors change over the course of treatment at different rates or with different patterns for men and women as well as for patients with high or low severity of neuropathy and peripheral vascular disease. We assume those who have higher peripheral vascular problem will receive maximum benefit from electrical stimulation. Additional analyses will test whether changes in gait and balance variables predict changes in clinically important outcome factors (e.g., fear of falling (FES) , quality of life (SF12), adverse events, foot ulcer, etc) depending on gender.