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The Impact of Intraneural Facilitation Therapy on Diabetic Peripheral Neuropathy

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School of Allied Health Professions
in conjunction with the
Faculty of Graduate Studies

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The Impact of Intraneural Facilitation Therapy on Diabetic Peripheral Neuropathy

by

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A Dissertation submitted in partial satisfaction of
the requirements for the degree
Doctor of Philosophy in Physical Therapy

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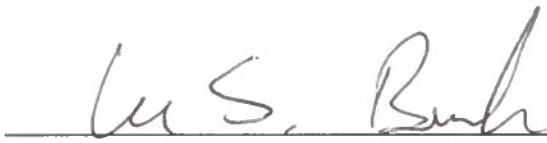
October 2021

Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.



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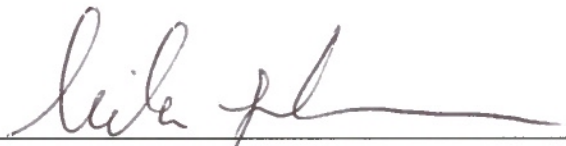

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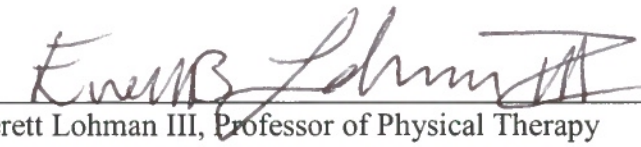

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DEDICATION

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ABBREVIATIONS

INF	Intraneural Facilitation
DPN	Diabetic Peripheral Neuropathy
PN	Peripheral Neuropathy
T2DM	Diabetes Mellitus Type 2
T1DM	Diabetes Mellitus Type 1
NTC	Neuropathic Therapy Center
LLU	Loma Linda University
LOS	Limits of Stability
SOT	Sensory Organization Test
DM	Diabetes Mellitus
QOL	Quality of Life
AGEs	Advanced Glycosylated End Products
RAGE	Receptor for AGE
AR	Aldose Reductase
ROS	Reactive Oxygen Species
PT	Physical Therapist
RCT	Randomized Control Trial
QOL-DN	Quality of Life- Diabetic Neuropathy
SOT	Sensory Organization Test
LOS	Limits of Stability
RT	Reaction Time
EPE	Endpoint Excursion

MXE	Maximum Excursion
DCL	Directional Control
COG	COG
SWM	Semmes-Weinstein Monofilaments
PQAS	Pain Quality Assessment Scale
SDG	Start Date Group
IRB	Institutional Review Board
NTC	Neuropathic Therapy Center
PI	Pulsatility Index
AP	Anterograde Pulsatility Index
RP	Retrograde Pulsatility Index
PSV	Peak Systolic Volume
APSV	Anterograde Peak Systolic Volume
RPSV	Retrograde Peak Systolic Volume
VF	Volume Flow
AV	Anterograde Volume Flow
RV	Retrograde Volume Flow

ABSTRACT OF THE DISSERTATION

The Impact of Intraneural Facilitation Therapy on Diabetic Peripheral Neuropathy
by

Kyan Sahba

Doctor of Philosophy, Graduate Program in Physical Therapy
Loma Linda University, August 2021
Dr. Lee S. Berk, Chairperson

Background: Intraneural facilitation (INF) has shown clinical success, and significant improvements have been found in a recent pilot study. This study aims to investigate further these effects on DMT2 subjects suffering from DPN.

Objective: The purpose of this study is to explore the effects of INF on subjects suffering from DPN impacting blood flow, sensation, balance, gait, pain, and quality of life.

Methods: Twenty-eight subjects between 50-75 years old with T2DM and below ankle moderate-severe DPN, were randomly assigned into two groups (N=17 INF, N=11 sham). All blinded subjects went through 9 therapy visits, and blinded assessing physical therapists completed pre/post-testing measurements consisting of; Pain Quality Assessment Scale, Semmes-Weinstein Monofilaments, NeuroCom SMART Balance Master, QOL- DN, Zeno Walkway, and ultrasound.

Results: There were only two significant differences between each group statistically, for unpleasant pain and protective sensation ($p < 0.05$). There were significant changes within the INF group over time, for 8 PQAS pain qualities, and in 2 pain domains ($p < 0.05$); sham group showed decreases in 2 pain qualities ($p < 0.05$). No significant differences seen between groups for gait velocity and stride length. Only the INF group showed within group improvement in static balance composite equilibrium score over

time ($p < 0.05$) in SOT. For LOS, significant differences between groups were seen in forward (FW) direction for movement velocity (MVL) and in right (RT) direction for reaction time (ReT) ($p < 0.05$). Within the INF group there was improvement for total QOL-DN score, and subcategories; physical functioning/large fiber and symptoms; the sham group showed improvement in subcategory physical functioning/large fiber ($p < 0.05$). With the sonography assessment, there was no difference between each group statistically, however, there were changes within the experimental group with time

Conclusions: Our findings indicate Intraneural Facilitation improved static balance measures within INF group and protective sensation and unpleasant pain quality between groups. Within INF group changes for ultrasound outcomes were encouraging yet further research is needed to elucidate the value of assessing macrovascular regulation using repeated single site sonography assessment. Therefore, applying INF might help benefit those dealing with diabetic peripheral neuropathy.

CHAPTER ONE

INTRODUCTION AND REVIEW OF LITERATURE

Understanding Diabetes

If the body finds itself in a condition in which it has raised levels of glucose and cannot produce a hormone called insulin, it does not have enough insulin, or it cannot use insulin effectively, then the body will develop a chronic condition known as diabetes mellitus (DM) (Cho, Shaw et al. 2018). Insulin is produced by the pancreas and is a hormone used to transport glucose from the bloodstream into the body's cells for conversion to energy. The hallmark of diabetes is hyperglycemia (high levels of glucose), which happens because of the body's lack of insulin or the inability of cells to respond to insulin (Cho, Shaw et al. 2018). There are three main types of diabetes, type 1, type 2, and gestational diabetes (Cho, Shaw et al. 2018). Less common forms are monogenetic and secondary DM (Cho, Shaw et al. 2018). Diabetes mellitus type 1 (T1DM) occurs when the body is unable to produce sufficient insulin for the body (Cho, Shaw et al. 2018). For people with T1DM to survive, they require daily insulin treatment, regular glucose monitoring, and a healthy lifestyle to delay or avoid diabetic complications (Cho, Shaw et al. 2018). Diabetes Mellitus type 2 (T2DM) is an inadequate production of insulin and an inability of the body's ability to respond to insulin (Cho, Shaw et al. 2018). The primary treatment for T2DM is lifestyle modification in diet, exercise, smoking cessation, and body weight maintenance (Cho, Shaw et al. 2018). If this first line of defense does not work, then oral medications begin for hyperglycemia management, and if this fails, then insulin injections are prescribed (Cho, Shaw et al. 2018). Unfortunately, T2DM detection usually occurs when complications arise, such as a foot ulcer, vision

change, renal failure, or infection (Cho, Shaw et al. 2018). T2DM accounts for 90% of all diabetic cases and will be the focus group for this study (Cho, Shaw et al. 2018).

Global Epidemiology of Diabetes

DM is a chronic disease with a global prevalence increasing over recent decades (Cho, Shaw et al. 2018). The World Health Organization (WHO) estimated that 108 million people were living with diabetes mellitus (DM). In 2015, that estimate increased to 415 million people and is still rising now (Cho, Shaw et al. 2018).

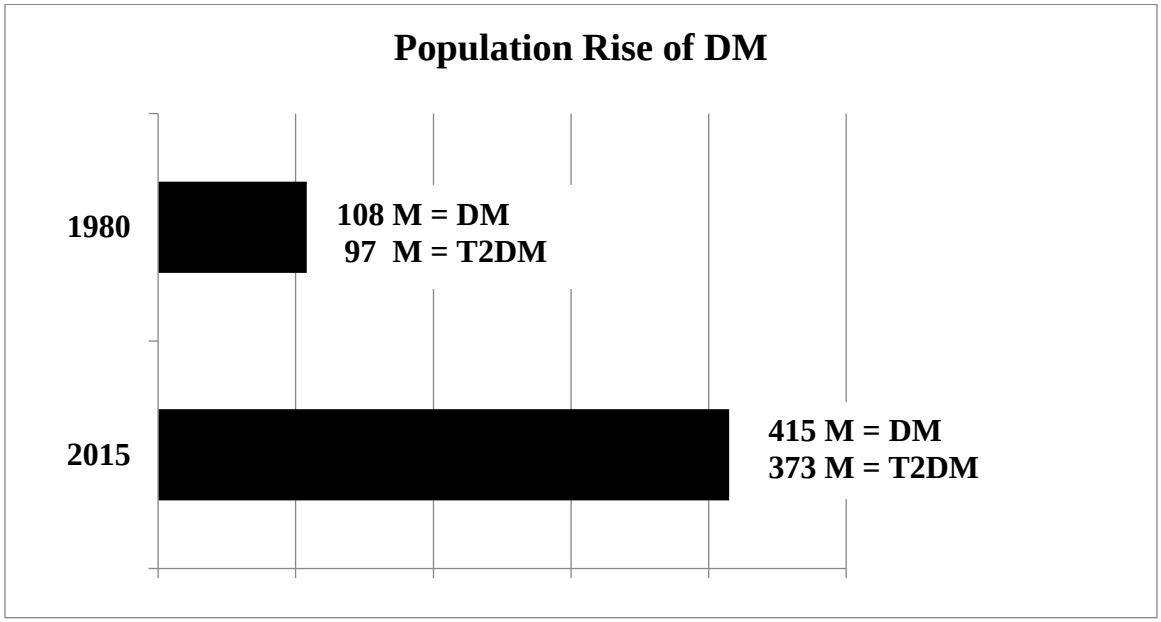

Figure 1. The Population Rise of Diabetes

This increase also means that these individuals have a higher risk of obtaining secondary complications that lead to decreased quality of life (QOL), high medical costs, and increased mortality (Boulton, Vinik et al. 2005, Cho, Shaw et al. 2018, Hicks and Selvin 2019). Microvascular damage is the most common complication associated with T2DM

leading to Diabetic peripheral neuropathy (DPN) and has a lifetime prevalence of 50% in these individuals (Brown, Pribesh et al. 2017, Cho, Shaw et al. 2018). DPN is a primary risk factor for foot ulcers from loss of sensation, retinopathy leading to blindness, chronic kidney disease from nephropathy, fractures from falls and loss of balance, muscle atrophy in lower extremities, inability to perform daily functions, poor QOL, non-traumatic amputations, and traumatic brain injury (Boulton, Vinik et al. 2005, Flerx and Hall 2015, Brown, Pribesh et al. 2017, Valencia and Florez 2017). Apart from having to deal with DM complications, there are also significant costs related to the treatment of these DM complications (Boulton, Vinik et al. 2005, Asif 2014, Chatchawan, Narkto et al. 2018, Hicks and Selvin 2019). The global healthcare expenditure in 2017 for people aged between 20-79 years was estimated at 727 billion dollars (Cho, Shaw et al. 2018).

Peripheral Neuropathy: Diabetic Complication

DPN is the most common long-term complication of T2DM, affecting 50% of this population; it affects the nerve endings in feet, hands, or other regions of the body after an individual has experienced frequent or prolonged durations of hyperglycemia (Boucek 2006, Cade 2008, Van Acker, Bouhassira et al. 2009, Ahn and Song 2012, Brown, Pribesh et al. 2017). It is also responsible for the most diabetic-related hospitalizations (Boucek 2006). Small or large peripheral nerve fibers could be involved. Small fiber neuropathy is associated with pain, ulcers, and autonomic symptoms, while large fiber neuropathy is associated with paresthesia, sensory loss, and muscle weakness (Magrinelli, Briani et al. 2015, American Diabetes 2019). DPN can lead to reduced balance and gait parameters, thus classifying these individuals at high risk for falls (Ahn

and Song 2012). Those with DPN have also been found to have sensory impairments identified as increases in ankle inversion and eversion proprioceptive thresholds (Van den Bosch, Gilsing et al. 1995). These individuals can also develop increased sway during gait, and this decreased balance can result in decreased QOL (Ahn and Song 2012). Overall, when compared to healthy individuals, those with DPN have reduced proprioception, lower extremity sensation, and ankle strength making them more receptive to falls (Tofthagen, Visovsky et al. 2012). Unfortunately, early detection of DPN is rare due to the nature of its presentation, which is asymptomatic or developing silently over time (Brown, Pribesh et al. 2017).

Pathophysiology of Diabetic Peripheral Neuropathy

Diabetes is one of the most common etiology factors for peripheral neuropathy (Head 2006). To start, peripheral nerves are covered by perineurium, of which only several transperineurial arterioles can penetrate through to the endoneurium (Yagihashi, Mizukami et al. 2011). The vascular supply to peripheral nerves is typically sparse, making these nerves more susceptible to ischemia (Yagihashi, Mizukami et al. 2011). The morphological characteristics for DN in the nerve are both demyelination and axonal degeneration of myelinated fibers, degeneration with the regeneration of unmyelinated fibers, and endoneurial microangiopathy (Boucek 2006, Yagihashi, Mizukami et al. 2011).

A prolonged hyperglycemic state can lead to DPN development by hyperactivity of polypol pathway, increased reactions of advanced glycosylated end products (AGEs), and receptor for AGE (RAGE) reactions, increased reactive oxygen species (ROS), and

protein kinase C activation (Boucek 2006, Yagihashi, Mizukami et al. 2011). These metabolic aberrations can produce pro-inflammatory reactions, leading to increased cytokines and macrophages and decreased neurotrophins, all of which promote neuropathy development (Yagihashi, Mizukami et al. 2011). These hyperglycemic induced irregular metabolic mechanisms can also affect endoneurial microvessels and neural tissues through activating poly-ADP-ribose polymerase (PARP), altering protein kinase C (PKC), increasing mitogen-activated protein kinase (MAPK) and activation nuclear factor-kB, all of which leads to peripheral neuropathy (Yagihashi, Mizukami et al. 2011). This hyperglycemic state not only affects the nerve cells, but it also damages nerve repair mechanisms; by decreasing nerve growth factor, microangiopathy with endoneurial hypoxia, increased oxidative stress with overproduction of harmful ROS, defects in macrophage function (Boucek 2006, Head 2006).

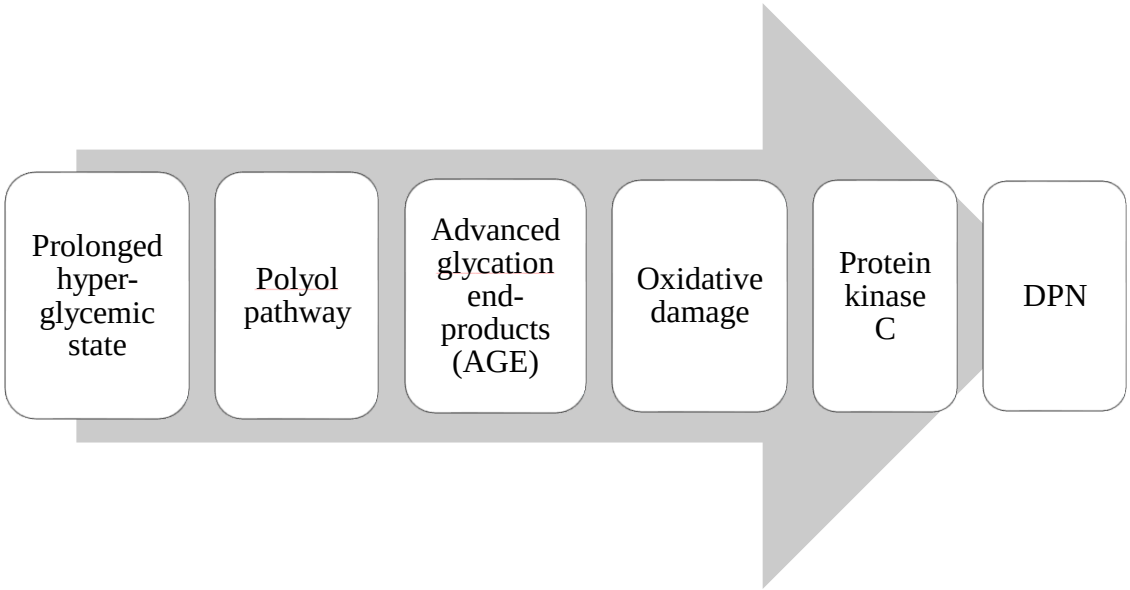

Figure 2. Pathophysiology of Diabetic Peripheral Neuropathy via hyperglycemia

Polyol accumulation is regulated by aldose reductase (AR). The polyol theory remains elusive but is best explained with the osmotic theory, in which increased polyol leads to intracellular hyperosmolarity by the accumulation of impermeable sorbitol cytoplasm, which expands the cell and leads to cell lysis (Yagihashi, Mizukami et al. 2011). The increase in sorbitol also causes a reduction of glutathione and nitric oxide from overconsumption of nicotinamide adenine dinucleotide phosphate (Yagihashi, Mizukami et al. 2011). This osmotic theory mostly explains the genesis of cataracts (Yagihashi, Mizukami et al. 2011). AR inhibitors have been used in many clinical trials to reverse the polyol accumulation, and while they confirm the critical role of AR in diabetic neuropathy, it does not entirely account for neuropathy development (Yagihashi, Mizukami et al. 2011).

In diabetic nerves, every component of nerve tissues can be excessively glycated (Yagihashi, Mizukami et al. 2011). Nerve tissues, fibers, and endothelial cells of vasa nervosum all express the receptor for AGE (RAGE). When AGE binds to RAGE, an oxidative stress reaction is created through the activation of NADPH oxidase (Yagihashi, Mizukami et al. 2011). As translocation and transcription occur to activate genes for cell death or survival, both microangiopathic processes and neural dysfunction begin resulting in pain or nerve conduction delay (Yagihashi, Mizukami et al. 2011).

Nitro-oxidative stress, in conjunction with a hyperglycemic state, created poly ADP-ribose polymerase (PARP) activation. PARP activation can result in cellular death and dysfunction (Yagihashi, Mizukami et al. 2011).

Current Diabetic Peripheral Neuropathy Treatments

The current treatment for DPN consists of both pharmacological and non-pharmacological agents (Bril, England et al. 2011). The pharmacological agents consist of; anticonvulsants, antidepressants, opioids, antioxidants, aldose reductase inhibitors, topical medications (capsaicin cream), to name a few (Bril, England et al. 2011). Each of these will be discussed in Levels; Level A has strong evidence, Level B has moderate evidence, and Level U has insufficient evidence (Bril, England et al. 2011). Pregabalin, an anticonvulsant, has sufficient evidence in lessening pain and improving QOL in patients with DPN and is considered a clinically appropriate treatment (Bril, England et al. 2011). Pregabalin is currently the only Level A treatment for peripheral neuropathy at this time (Bril, England et al. 2011). Gabapentin and sodium valproate, at Level B, should also be considered in treating DPN (Bril, England et al. 2011). Anticonvulsants: oxcarbazepine, lamotrigine, and lacosamide show level B evidence and should not be considered for DPN treatment (Bril, England et al. 2011). Antidepressants; Amitriptyline, venlafaxine, and duloxetine show Level B evidence in treatment for DPN (Bril, England et al. 2011). Opioids: dextromethorphan, oxycodone, and tramadol, and capsaicin are treatments with Level B evidence that should be considered for treatment and are possibly affective in DPN related pain (Bril, England et al. 2011). Antioxidants such as α-lipoic acid have insufficient evidence in their effectiveness for DPN symptoms, leaving them in Level U (Bril, England et al. 2011). On a molecular level, pharmacological therapies may not be sufficient in reversing or slowing down DPN, only modest benefits have been shown to slow its progression, and it is mostly ineffective in reducing pain (Finnerup, Sindrup et al. 2010). In those individuals dealing with painful DPN, the

recommended course of treatment is pharmacological (Boulton, Vinik et al. 2005, Pop-Busui, Boulton et al. 2017, American Diabetes 2019, Hicks and Selvin 2019).

Also used are non-pharmacological modalities: infrared therapy, shoe magnets, transcutaneous electrical stimulation, to name a few (Bril, England et al. 2011). Currently, the only non-pharmacological treatment showing evidence in treating peripheral neuropathy is transcutaneous electrical stimulation, at Level B (Bril, England et al. 2011). It is found to possibly be effective in reducing pain in DPN as well as improving QOL (Bril, England et al. 2011). However, low-intensity laser treatment, Reiki therapy, and electromagnetic therapy have moderate evidence supporting that they should not be considered for the treatment of DPN patients (Bril, England et al. 2011). In comparison, the treatment for DPN at this time rests solely on pharmacological medication, which may have harmful side effects, and costly modalities to lessen pain and improve QOL by decreasing pain (Bril, England et al. 2011).

Both pharmacological and non-pharmacological agents only address the patient's pain felt and do not address their numbness (Bril, England et al. 2011). In conclusion, each of these treatments has limited evidence, but the degree of effectiveness can be minor, side effects can be intolerable, physical function improvement is limited, and there are high costs involved in treatment (Bril, England et al. 2011).

Physical Therapy Intervention: Diabetes Mellitus

Treatment for DM is a multi-provider plan, and preventions of many of the complications from DM are done by blood glucose control(Cho, Shaw et al. 2018). Physical therapists (PTs) currently assist patients with diabetes by treating the symptoms

of micro/macro vascular-related comorbidities (Cade 2008). Many of these patients presenting to the physical therapy clinic with DM are currently experiencing pain, decreased in function, decreased endurance, loss of ankle reflexes, numbness, paresthesia, extreme sensitivity to touch, insensitivity to pain or temperature, sharp pain, decreased coordination, muscle weakness and decreased balance (Cade 2008, Ites, Anderson et al. 2011, Chapman, Meyer et al. 2017). Evidence proposes that DM patients have less muscular strength than those without T2DM (Hatef, Bahrpeyma et al. 2014). Physical therapy treatments for these patients primarily deal with DPN symptoms to improve their QOL in areas of function (Ites, Anderson et al. 2011, Cho, Shaw et al. 2018).

PT's can assist DM patients by prescribing an exercise program which helps reduce hyperglycemia, insulin resistance, dyslipidemia, and hypertension; these reductions improve the vascular issues occurring with T2DM (Cade 2008, Hameed, Manzar et al. 2012). A study by Hameed et al., found progressive resistance training of five resistive exercises at 65% of 1 repetition maximum and progression had improved muscle strength after only four weeks (Hameed, Manzar et al. 2012). This finding was further supported by a study done by Ibanez et al., in which patients with DM completed progressive resistance training at 50-80% repetition maximum for four weeks and gained significant muscle strength (Ibanez, Izquierdo et al. 2005). Tokmakidis et al., combined the effect of resistance exercise at 60% of 1 repetition maximum, and aerobic exercise of walking/jogging on a treadmill for 75 minutes 2x weekly, which resulted in better glycemic control, improved endurance and muscle strength (Tokmakidis, Zois et al. 2004). Exercises can also improve numerous metabolic factors that affect microvascular

function, indirectly protecting against peripheral nerve damage (Singleton, Smith et al. 2015).

Physical Therapy Intervention: Peripheral Neuropathy

We have discussed how those with DM are treated, but what about those same individuals with T2DM in conjunction with DPN? Physical therapists need to treat not only the above-mentioned potential complications but also added problems that arise when a patient also suffers from PN. These added DPN problems lead to decreased motility due to increased neuropathic pain, which in turn contributes to decreased endurance, strength, and poorly managed glycemic index (Flerx and Hall 2015). The sensory and motor impairments that occur from DPN also lead to impaired gait and balance (Allet, Armand et al. 2010). In a 4-yearlong study by Balducci et al., found that those with DM without DPN who participated in an aerobic exercise program showed improved nerve conduction velocity and vibration threshold and were less likely to develop DPN when compared to those not in an exercise program (Balducci, Iacobellis et al. 2006). However, this study was concluded to lack high-quality evidence to effectively evaluate the effect of exercise on DPN (Kluding, Pasnoor et al. 2012). A study by Kluding et al., came out with a pilot study examining DPN subjects for ten weeks on a supervised aerobic and resistive exercise program, they concluded at the end of 10 weeks improvements in measures of pain, neuropathic symptoms, and cutaneous fiber branching (Kluding, Pasnoor et al. 2012). In a pilot study by Flerx et. al., a physical therapy balance program was implemented in conjunction with monochromatic infrared energy therapy, and results showed an increase in both balance and protective sensation in the feet (Flerx

and Hall 2015). A randomized control trial (RCT) study by Dixit et. al., concluded that aerobic exercise aids in halting, or disrupting the progression diabetic peripheral neuropathy, as evidenced by finding a significant difference in nerve conduction velocity in both peroneal and sural nerves when compared pre and post aerobic (Dixit, Maiya et al. 2014). Other current PT treatments to treat those with DPN are vibrating insoles, lower extremity specific strengthening exercises, and use of assistive devices, which all show good statistical evidence in improving balance (Richardson, Sandman et al. 2001, Priplata, Niemi et al. 2003, Ashton 2011, Ites, Anderson et al. 2011).

Recently, an article by Alshahrani has introduced a new treatment for DPN with a new technique known as Intraneural Facilitation (INF). They found INF to significantly aide in reducing DPN symptoms as observed in the modified Total Neuropathy Scale and the sensory organization test of NeuroCom and movement velocity portion of the limits of stability test in the NeuroCom (Alshahrani, Bussell et al. 2016). In this study, there were also improvements in the reaction time, directional control, endpoint excursion and maximum excursion of the limits of stability test and also improvements in the activities-specific balance confidence scale, but not significant possibly due to the small sample size and no control or sham group was used in this study (Alshahrani, Bussell et al. 2016).

The Rationale for Diabetic Peripheral Neuropathy Research

DPN has only recently been recognized as a significant determinant of the early decline in functional mobility, leading to the physical frailty in people with diabetes (Bittel, Bittel et al. 2015, Kluding, Bareiss et al. 2017). Currently, the most frequently

stated known treatments for DPN are glycemic control, foot care, and pain management (Boulton, Vinik et al. 2005, American Diabetes 2019, Hicks and Selvin 2019). In 2019 by the American Diabetes Association states that the treatment in dealing with neuropathic pain states, "No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions" (American Diabetes 2019). This is alarming because not only are the pharmacological costs in DPN treatment rising, but also, while there are many studies on these drugs, there is a lack of how long it is needed to take them (Peltier, Goutman et al. 2014). Painful DPN is widely undertreated, and under-recognized, while there are many drug studies, there is a need for more studies to look at QOL, pain, and side effects need to be researched (Peltier, Goutman et al. 2014, American Diabetes 2019). The cost in the pharmacological treatment itself leads to the question, is there a cheaper non-pharmacological treatment to assist in painful DPN?

The American Diabetes Association states that regular aerobic exercise might prevent or delay peripheral neuropathy progression in T2DM (Colberg, Sigal et al. 2016). Aerobic exercise and physical activity are acknowledged as assisting in glycemic control for those with T2DM (Colberg, Sigal et al. 2016). Exercise training has also been shown to improve metabolic dysregulation and promote nerve regeneration and function (Colberg, Sigal et al. 2010, Kluding, Bareiss et al. 2017). Exercise has many potential advantages for individuals dealing with DPN, and PTs play an essential role in implementing the ADA guidelines for activity and monitoring and prescribing a safe and effective exercise regime (Kluding, Bareiss et al. 2017). While there is good statistical evidence showing improved balance, a systematic review by Ites et. al., found a lack of

high-quality studies, and a need for more RCTs in investigating the effectiveness of physical therapy interventions and balance in DPN individuals (Ites, Anderson et al. 2011).

While cost is one reason to look at other treatments to aide in those dealing with DPN, another deciding factor is the numerous research articles dealing with the neuropathic symptoms, and not the mechanism of neuropathy itself. All treatments of DPN for physical therapists are regarding function and non-pharmacologic pain management; thus far, we have been unable to address the underlining problem of DPN.

Purpose

The need for this study presented itself as an opportunity to provide an RCT and investigate not only the symptomatic response of neuropathy, but also blood flow, quality of life, balance, skin temperature, protective sensation, and pain in DPN using a new PT intervention. This graduate student research study explores the modulatory effects of INF in T2DM subjects with moderate-severe DPN.

Hypothesis

1. Intraneural Facilitation will improve quality of life, by improving pain and protective sensation in subjects diagnosed with T2DM with moderate-severe DPN.
2. Intraneural Facilitation will improve the quality of life through functional mobility in subjects with T2DM and moderate-severe DPN.
3. Intraneural Facilitation will increase blood flow and pulsatility in the distal posterior tibial artery in subjects with T2DM with moderate-severe DPN.

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CHAPTER TWO

TREATING PERIPHERAL NEUROPATHY IN INDIVIDUALS WITH TYPE II DIABETES WITH INTRANEURAL FACILITATION: A SINGLE BLIND RANDOMIZED CONTROL TRIAL

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Abstract

Objective: To evaluate the effectiveness of a manual physical therapy technique known as intraneural facilitation (INF) on individuals with diabetes type II (T2DM) with below ankle moderate to severe diabetic peripheral neuropathy (DPN).

Research Design and Methods: This was a single-blind, randomized clinical trial. Thirty individuals with T2DM and DPN were randomly assigned to two treatment groups: INF or sham. Twenty-eight patients completed the study. The Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire, Pain Quality Assessment Questionnaire (PQAS), Zeno Walkway, NeuroCom SMART Balance Master: Limits of Stability (LOS) and Sensory Organization Test (SOT), and Semmes-Weinstein Monofilament (SWM) measurements were taken before and after 3-week treatment sessions. The sham treatment consisted of subjects believing they received anodyne monochromatic infrared photoenergy.

Results: A significant decrease within the INF group was seen for 8 PQAS pain qualities, and for 2 pain domains ($p < 0.05$); sham therapy showed decreases in 2 pain qualities ($p < 0.05$). Between groups, there was a significant difference seen only in unpleasant pain ($p < 0.05$). No significant differences seen between groups for gait velocity and stride length. Only the INF group showed within group improvement in static balance composite equilibrium score over time ($p < 0.05$) in SOT. For LOS, significant differences between groups were seen in forward (FW) direction for movement velocity (MVL) and in right (RT) direction for reaction time (ReT) ($p < 0.05$). Within the INF group there was improvement for total QOL-DN score, and subcategories; physical functioning/large fiber and symptoms; the sham group showed improvement in

subcategory physical functioning/large fiber ($p < 0.05$). Also, protective sensation was significantly improved ($p < 0.05$) within the INF group and between groups.

Conclusions: Intraneural Facilitation improved static balance measures within INF group and protective sensation and unpleasant pain quality between groups.

Keywords: Intraneural facilitation, diabetic peripheral neuropathy

Introduction

In 2017 the International Diabetes Federation estimated 651.1 million adults between the ages of 65-99 years to have diabetes mellitus (DM), with 90-95% suffering from type 2 DM (T2DM) (Cho, Shaw et al. 2018). Over 50% of patients with T2DM suffer from diabetic peripheral neuropathy (DPN) (Iqbal, Azmi et al. 2018, Selvarajah, Kar et al. 2019). The annual cost of patients with DM and DPN is $30,000 annually, this expense quadruples if the DPN symptoms are severe and painful (Sadosky, Mardekian et al. 2015). Additionally, DPN complications can negatively affect the patients quality of life (QOL) (Gregg, Beckles et al. 2000, Boulton, Malik et al. 2004), with impaired balance (Gregg, Beckles et al. 2000, Alshahrani, Bussell et al. 2016, Selvarajah, Kar et al. 2019), altered gait (Gregg, Beckles et al. 2000, Morrison, Colberg et al. 2014, Selvarajah, Kar et al. 2019) and increased pain (Davies, Brophy et al. 2006, Hartemann, Attal et al. 2011, Selvarajah, Kar et al. 2019).

Current Treatment for DPN consists of 1) glycemic control, 2) foot care, and 3) pain management (Hicks and Selvin 2019). The American Diabetes Association recommends medication utilization for the relief of painful DPN (Javed, Petropoulos et al. 2015, Pop-Busui, Boulton et al. 2017). Despite ongoing progressive research, only modest benefits from pharmacology have been shown to slow disease progression and reduce pain associated with DPN (Finnerup, Sindrup et al. 2010). Non-pharmacologic modalities such as: infrared therapy, shoe magnets, Reiki therapy, exercise, acupuncture, transcutaneous electrical nerve stimulation, spinal cord stimulation, and biofeedback behavioral therapy, have attempted to reverse the debilitating effects on nerves' axons and improve neural circulation with T2DM (Bril, England et al. 2011). Unfortunately, the

American Academy of Neurology (AAN) does not assign “A” level evidence to the aforementioned interventions.

With no clear treatment that reverses nerve damage due to T2DM, a manual therapy approach has been suggested to improve neurovascular circulation in ischemic neurovascular capillary beds of patients with T2DM; Intraneural Facilitation (INF) is a manual therapy approach that “aims to bias blood flow into the neural fascicle, improve the endoneurial capillary circulation, and reverse intrafascicular ischemia” (Alshahrani, Bussell et al. 2016). This study hypothesizes that INF will decrease perceived pain, and improve balance, ambulation, QOL, and protective sensation in those with moderate to severe DPN with a posited mechanism of neurovascular revascularization.

Research Design and Methods

Recruitment and Subject Criteria

Recruitment activities included distributing flyers in the Loma Linda Community, referrals from medical doctors at the Loma Linda University Medical Center, Loma Linda Diabetes Treatment Center, emails to school staff, and word of mouth. Participants were screened using IRB-approved telephone recruitment methods for all interested participants in which inclusion and exclusion criteria were reviewed along with details of the study.

Participants were included in the study if they had T2DM, below ankle DPN symptoms (numbness, tingling, burning, sharp pain, increased sensitivity, etc.), moderate to severe DPN as identified by scoring ≥ 10 on the Quality of Life- Diabetic Neuropathy

(QOL-DN) scale, and if they were between the ages of 50-75 years old. Participants were excluded if they had a medical condition suggesting a possible decline in function over the next six months, such as a current regimen of chemotherapy, radiation therapy, or dialysis; if they had any lower extremity amputations or wounds, documented active alcohol or drug misuse; if they have any known health conditions: end-stage renal failure, uncontrolled hypertension, severe dyslipidemia, chronic liver disease, autoimmune disease, advanced chronic obstructive pulmonary disease, and active inflammations; other inflammatory neuropathies including chronic inflammatory demyelinating polyneuropathy, proximal diabetes neuropathy, autonomic neuropathies, or other neuropathies not associated with DM such as B12 deficiency, hypothyroidism, and uremia. Also excluded were those with other severe chronic medical conditions requiring active treatment. Participants were also excluded if they were morbidly obese or if pregnant (self-reported).

Once participants completed the phone recruitment script, an appointment was made to visit the Loma Linda University Physical Therapy Lab to complete the last inclusion criteria, which was to score ≥ 10 on the QOL-DN scale. Participants then signed the IRB consent form, and completed baseline measurements. Once eligible, participants chose either their right or left leg to be treated. Baseline measurements for the Pain Quality Assessment Scale (PQAS), Zeno Walkway, NeuroCom SMART Balance Master computerized dynamic posturography (Limits of Stability and Sensory Organization Test), and Semmes-Weinstein Monofilament (SWM) were completed. The Institutional Review Board (IRB) of Loma Linda University approved all methods and procedures.

Randomization

Once baseline measurements were completed, participants visited the Neuropathic Therapy Center (NTC) for randomization and scheduling. Every participant was asked to choose between two sealed identical envelopes revealing if they were in Group 1 or Group 2. Group 1 (N=17) was the INF group, and participants were given INF treatment. Group 2 (N=11) was the sham group, and participants believed they were given anodyne therapy. After completed treatments, participants returned to the Physical Therapy Lab to complete the same measurements, the tester was blinded to the participants' treatment group.

Outcome Measures

QOL-DN (Quality of Life- Diabetic Neuropathy) Questionnaire

The QOL-DN was used to measure the patient's perception of the effects of diabetic neuropathy, assess neuropathy, and differentiate between autonomic, large, and small fiber neuropathy (Vinik, Hayes et al. 2005). It was developed in the Department of Internal Medicine, Eastern Virginia Medical School, Norfolk, Virginia (Vinik, Hayes et al. 2005). The questionnaire was immediately scored, and subjects classified as having moderate to severe DPN (scoring ≥ 10) were invited to participate. A score range of 2-9 classified the neuropathy as mild, 10-19 as moderate, and greater than or equal to 20 as severe (Vinik, Hayes et al. 2005).

Pain Quality Assessment Scale (PQAS)

The PQAS questionnaire was used to assess distinct pain qualities for 20 pain (quality and spatial) descriptors (Jensen, Gammaitoni et al. 2006). After reading the introduction of the questionnaire, subjects then measured their pain on a numeric scale 0= "no pain" or "no painful sensation" to 10 = "worst imaginable pain sensation" (Jensen, Gammaitoni et al. 2006). There are also three pain quality domains; paroxysmal (which contained the average scores of shooting, sharp, electric, hot, and radiating), superficial (which contained the average scores of itchy, cold, numb, sensitive, and tingling), and deep (which contained the average scores of aching, heavy, dull, cramping, and throbbing) (Victor, Jensen et al. 2008).

Zeno Walkway

The Zeno Walkway (Protokinetics, Havertown, PA) is used to observe the spatiotemporal characteristics of gait in the subjects: velocity and stride length (Lynall, Zukowski et al. 2017). It contains a 16-level pressure-sensing pad, which measures 6.10x1.22 meters in which data is captured using PKMAS and force plate data collected by Vicon Nexus (Vicon Motion Systems, Centennial, CO) (Espley, Brendolise et al. 2009). The Zeno walkway is directly connected to the PKMAS software and analyzed on a computer that can record and store gait output (Vallabhajosula, Humphrey et al. 2019). Participants were instructed to wear their own comfortable walking shoes. The subjects were asked to walk back and forth on the walkway four times.

NeuroCom SMART Balance Master System Computerized Dynamic Posturography

This apparatus is used as a scale for static and dynamic balances developed by the Natus Medical Incorporated, Clackamas, OR (Lininger, Leahy et al. 2018). It consists of two force plates that can move up/down and in an anterior-posterior plane (Lee, Kim et al. 2003). Two tests were administered: Sensory Organization Test (SOT) and limits of stability (LOS).

Sensory Organization Test (SOT). The SOT assesses the subject's visual, somatosensory, and vestibular systems for maintaining upright posture (Harro and Garascia 2018). The standardized test instructions, per NeuroCom protocol, were either "stand quietly with your eyes open" or "stand quietly with your eyes closed," depending on the condition being tested (Harro and Garascia 2019). This test was completed under six different sensory conditions lasting 20 seconds each, and there were three trials of each condition (Emam, Gad et al. 2009). The first three conditions examine static posturography, and the last three conditions examine dynamic posturography (Emam, Gad et al. 2009).

In Condition 1, subjects stand quietly with their eyes open as the force plate measures the subject's sway (McDaniel, Motts et al. 2018). In condition 2, the subject stands quietly with eyes closed, removing their visual aide (McDaniel, Motts et al. 2018). In condition 3, subjects stand quietly with their eyes open as the subject sways on the forward or back on the locked force plate, the surrounding box moves with the subject, now meaning the subject's visual information is saying the subject is not moving, and the proprioceptive information given to the patient is that he or she is moving (McDaniel, Motts et al. 2018). In conditions 4, 5, and 6, the first three conditions are repeated

consecutively, but with the force plate unlocked, this creates a situation in which proprioceptive information is now incorrect because as the patient sways forward or backward, so does the force plate (McDaniel, Motts et al. 2018).

The composite equilibrium score and the balance equilibrium score for each of the six trial conditions were assessed (Alshahrani, Bussell et al. 2016, Pletcher, Williams et al. 2017). The composite equilibrium score is defined as the subjects' anterior/posterior sway during each trial compared with the theoretical sway limit of 12.5 (Alshahrani, Bussell et al. 2016, Harro and Garascia 2019). The composite equilibrium score is calculated by independently taking the average for conditions 1 and 2, and adding this score to scores for all trials in conditions 3, 4, 5, and 6, then dividing that number by the total number of trials (Harro and Garascia 2019). The total score is 100; therefore, those with little AP sway will acquire scores close to 100; scoring a 0 means touching a support surface, shifting feet, or falling (Emam, Gad et al. 2009, Pletcher, Williams et al. 2017).

Limits of Stability (LOS). The LOS test assesses the dynamic balance by measuring the subjects' weight-shifting ability and voluntary limits to stability for eight directional targets set at 100% of theoretical limits of stability for an eight-second hold (Pickerill and Harter 2011, Harro and Garascia 2018). During testing, subjects were asked to lean away from midline towards the direction of one of the eight targets without feet stepping or lifting from standardized foot position (Clark, Rose et al. 1997). The LOS test measures five parameters: reaction time (ReT), movement velocity (MVL), endpoint excursion (EPE), maximum excursion (MXE), and directional control (DC) (Lininger, Leahy et al. 2018). Researchers analyzed these five test parameters for eight

different directions: forward (FW), forward right (FWRT), right (RT), backward right (BWRT), backward (BW), backward left (BWLT), left (LT), and forward left (FWLT).

Semmes-Weinstein Monofilament (SWM) (5.07)

Semmes-Weinstein 5.07/10-gram (CH537, Bailey Duraban Retractable Monofilament 10 gram of pressure, Bailey Instruments Ltd, Manchester, United Kingdom) monofilament (SWM) was used to test the third and fifth distal phalanx. This method was standardized according to generally accepted guidelines (Mueller 1996, Thomson, Potter et al. 2008). The "yes/no" method was used, meaning the patient respond with "yes" each time the subjects sensed the monofilament application. Inability to feel a 5.07 SWM (10 g of pressure) indicates the individual has peripheral neuropathy (McNeely, Boyko et al. 1995).

INF vs. Sham Treatments

INF Treatment. INF is a manual therapy proposed to reduce neuropathy symptoms through revascularizing ischemic peripheral nerves. INF posits to improve the relationship from macrocirculation to microcirculation resulting in an increase of neurovascular pressure that sufficiently overcomes diabetes-induced neural capillary resistance. INF postulates that with a system involving three holds, this is achievable. The first is the facilitation hold, in which the contralateral joint is placed in a maximal loose-pack position (Alshahrani, Bussell et al. 2016). The purported physiologic reason being to stretch the connecting nutrient vessels creating a natural large to small vessel bias and enhanced neurovascular flow. This slight stretch in the contralateral joint is hypothesized to stretch the nerve further than the artery due to the increased elastin in the artery

(Alshahrani, Bussell et al. 2016). The increased neural excursion compared to the artery stretches the coiled nutrient vessel attached between the artery and the nerve. Thus, it is hypothesized that this enlarges the arterial junction's opening, allowing increased blood into the epineurium (Alshahrani, Bussell et al. 2016). Now that pressure has increased, the secondary hold takes place to bias the increased epineurial blood into the transperineurial vessels that bridge the epiperineum and the endoneurial capillaries of the site being treated (Alshahrani, Bussell et al. 2016). Now that the pressure has increased into the open endoneurial capillaries, the goal is to open up ischemic endoneurial capillaries, and this is hypothesized to open by providing the third hold. The third hold is known as the sub hold and encourages blood flow through ischemic endoneurial capillaries that have increased resistance/pressure through the application of Bernoulli's principle. The series of stretches was repeated on affected side for the duration of the allotted time. Trained INF physical therapists provided this therapeutic intervention for those in the INF group for 50-60 minutes.

Sham Treatment. The sham treatment lasted 50-60 minutes and consisted of subjects believing they were receiving infrared light therapy. The anodyne unit was applied to the subject, but the unit was not plugged in (the plug was not visible to the patient). Pads were placed on the subject in the following locations on the affected lower limb: two on the plantar aspect of the foot in a T formation and one pad on the medial and lateral side of the calf. A double-folded towel was wrapped around the subject’s foot at the electrode sites to blind the subjects from the light not emitting from the electrodes due to the anodyne unit not being plugged in.

Data collection

Baseline assessment consisted of baseline demographic data, QOL-DN, PQAS, Zeno walkway, NeuroCom SOT and LOS, and SWM. Post-treatment data assessment consisted of QOL-DN, PQAS, Zeno walkway, NeuroCom SOT and LOS, and SWM, all of which were collected after three weeks of treatment.

Data analysis

Mean ±Standard Deviation was computed for quantitative variables and frequency (percentage) for ordinal variables. Mann-Whitney U test was used to compare INF and sham groups for all variables at baseline. The Wilcoxon's Signed-Ranks Test was used to compare pre- and post-variables.

Data were analyzed using SPSS Statistics Software version 27.0 (SPSS Inc, Chicago, IL, USA). All analyses were performed at an alpha level of .05.

Results

Out of thirty participants satisfying the eligibility criteria, twenty-eight participants completed the study, and were randomly assigned into the INF group (n=17) and sham group (n=13) by picking between two sealed envelopes and completed their treatments. There were seventeen males (mean± SD: 66.55 ± 6.68 years old) and eleven females (mean± SD: 67.29 ± 4.73 years old). The INF group's age (mean± SD: 66.94 ± 5.08 years old), height (mean± SD: 173.47 ± 13.40 cm), and weight (mean± SD: 207.35 ± 52.85 kg) when compared to the sham groups age (mean± SD: 67.09 ± 6.28 years old),

height (mean± SD: 173.18 ± 7.85 cm), and weight (mean± SD: 209.55 ± 39.98 kg) had no significant differences in baseline characteristics (p>0.05).

Monofilament

The results of pre- and post-measurements for the Semmes-Weinstein monofilament tests are shown in Figure 1. Significant findings were seen within the INF group over time for both the third (p<0.001) and fifth (p<0.001) distal phalanx. Also, there was a significant difference between the INF and sham groups (p=0.003) (Figure 1).

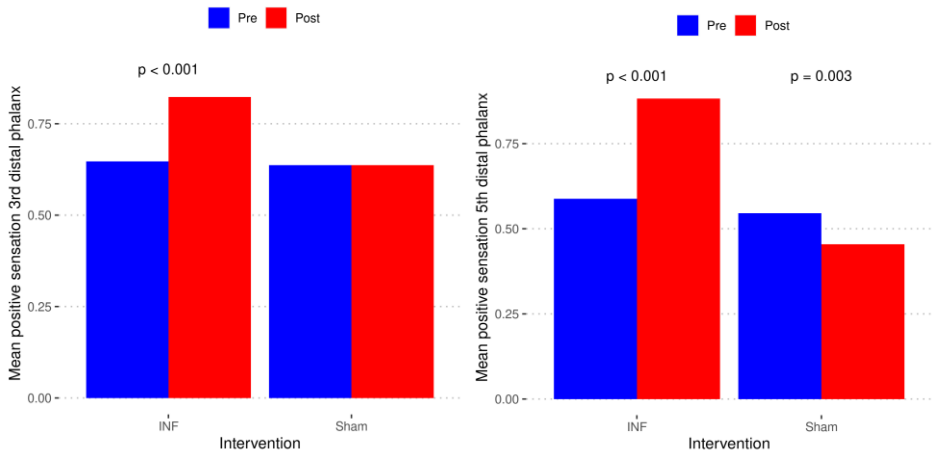

Figure 1. Mean positive responses of third and fifth distal phalanx with 5.07 Semmes-Weinstein Monofilament

PQAS

The Pain Quality Assessment Scale and Sub Categories are shown in table 1.

Table 1. Pain Quality Assessment Scale and Quality of Life Diabetic Neuropathy Questionnaires Pre vs Post for INF and SHAM Groups

QUESTIONAIRES		INF Intervention (n_1=17)			SHAM (n_2=11)			Difference between groups
PQAS		Pre Mean ± SD	Post Mean ± SD	p – value[a]	Pre Mean ± SD	Post Mean ± SD	p – value[a]	p – value[b]
	Shooting	3.59 ± 3.62	2.71 ± 3.10	0.096	4.36 ± 3.61	4.82 ± 3.43	0.833	0.460
	Sharp	5.41 ± 3.00	3.35 ± 2.52	0.019*	5.45 ± 3.30	4.55 ± 3.50	0.311	0.355
	Electrical	3.24 ± 3.33	2.82 ± 3.12	0.644	4.27 ± 3.77	4.55 ± 3.78	0.799	0.756
	Hot	3.88 ± 4.09	2.65 ± 3.26	0.192	3.91 ± 3.67	3.36 ± 2.87	0.574	0.544
	Radiating	2.24 ± 3.49	2.69 ± 3.07	0.394	1.82 ± 3.16	1.91 ± 3.30	1.000	0.715
	Paroxysmal Domain Average	3.67 ±2.83	2.84 ± 2.55	0.268	3.96 ± 2.76	3.83 ±2.81	0.721	0.796
	Itchy	3.00 ± 3.50	3.06 ± 3.25	0.888	3.36 ± 3.78	2.91 ±3.45	0.336	0.664
	Cold	3.71 ± 4.03	2.65 ± 2.52	0.261	4.00 ± 3.35	3.64 ±3.50	0.588	0.297
	Numb	6.82 ± 2.60	4.29 ± 3.44	0.013*	5.91 ± 3.02	4.55 ± 3.42	0.106	0.477
	Sensitive	4.24 ± 3.65	2.94 ± 2.61	0.197	3.82 ± 3.63	3.55 ± 3.01	0.916	0.283
	Tingling	5.71 ± 3.89	4.35 ± 3.20	0.093	6.55 ± 3.53	3.27 ± 2.97	0.014*	0.148
	Superficial Domain Average	4.69 ±2.15	3.46 ± 2.24	0.015*	4.72 ±2.07	3.52 ± 1.95	0.066	0.981
	Aching	3.94 ± 3.68	2.53 ± 3.18	0.192	5.36 ± 2.66	5.55 ± 3.50	0.766	0.306
	Heavy	3.24 ± 3.33	2.00 ± 2.98	0.087	4.18 ± 3.28	4.00 ± 4.00	0.959	0.432
	Dull	4.00 ± 2.62	2.47 ± 2.40	0.034*	4.09 ± 1.70	2.91 ± 2.26	0.032*	0.849
	Cramping	4.53 ± 4.03	2.53 ± 3.66	0.041*	4.00 ± 3.55	3.55 ± 2.77	0.798	0.192
	Throbbing	3.88 ± 3.94	3.13 ± 3.39	0.312	1.91 ± 2.81	2.73 ±3.38	0.400	0.086
	Deep Domain Average	3.93 ± 2.89	2.53 ± 2.53	0.011*	3.91 ± 2.28	3.75 ± 2.66	0.898	0.212
	Intense	5.41 ± 3.16	3.82 ± 3.03	0.039*	6.27 ± 2.65	5.00 ± 3.10	0.089	0.830
	Unpleasant	7.12 ± 2.67	4.18 ± 3.07	0.001*	6.09 ± 2.98	5.73 ± 3.00	0.509	0.013*
	Deep	5.65 ± 3.43	3.71 ± 3.10	0.019*	5.45 ± 3.21	4.73 ± 3.41	0.898	0.331
	Surface	4.41 ±3.28	3.35 ± 3.04	0.107	5.36 ± 3.17	4.55 ± 3.50	0.066	0.336
	Tender	3.00 ± 3.04	2.24 ± 2.86	0.039*	3.45 ± 2.95	3.18 ± 3.51	0.734	0.563
QOL-DN	Total Score	35.6 ±27.5	26.2 ±29.0	0.004*	32.8 ±21.0	28.4 ±23.9	0.061	0.342
	Physical Functioning/Large Fiber	18.0 ±13.9	11.6 ±14.3	0.011*	16.6 ±13.7	14.2 ±13.2	0.049*	0.197
	ADLs	2.8 ±4.9	2.7 ±5.5	0.39	2.36 ±2.6	1.6 ±2.5	0.084	0.922
	Symptoms	10.8 ±6.5	7.7 ±6.1	0.001*	9.6 ±4.6	8.6 ±7.3	0.365	0.168
	Small Fiber	2.9 ±4.2	2.7 ±4.3	0.893	2.5 ±2.2	2.6 ±2.8	0.566	0.904
	Autonomic	1.2 ±1.6	0.7 ±1.0	0.233	1.6 ±1.3	1.1 ±1.2	0.058	0.256

*p-values <0.05
[a]p-value within groups
[b]p-value between groups

There was a significant decrease in pain within the INF group over time in sharp (p=0.019), numb (p=0.013), dull (p=0.034), cramping (p=0.041), tender (p=0.039), intense (p=0.039) unpleasant (p=0.001), and deep (p=0.019). Significant decreases were also seen in superficial (p=0.015) and deep (p=0.011) subcategories over time for the INF group. There was a significant decrease in tingling (p=.014) and dull (p=0.032), for the sham group and no significant findings for any domains (Table 1). Also, there was a significant decrease in unpleasant pain quality (p=0.013) between groups.

Zeno Gait

The results of pre- and post-measurements for Zeno Gait Changes are shown in table 2.

Table 2. Changes in Spatiotemporal Parameters of Gait - Pre vs. Post Treatment

	Gait Velocity (m/sec)				Stride Length (cm)				Stride Width (cm)			
Groups	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	***p-value*[b]**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	***p-value*[b]**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	***p-value*[b]**
INF	107.5 ±16.3	118.2 ±20.8	0.005 *	0.107	61.1 ±6.6	65.2 ±9.5	0.007 *	0.156	7 ±4.4	7.7 ±5.2	0.74	0.652
SHAM	91.4 ±31.7	103.4 ±31.4	0.014 *		52.4 ±16.1	56.8 ±14.9	0.007 *		10.4 ±6.9	10.0 ±5.5	0.206	

*p-values <0.05
[a]p-value within groups
[b]p-value between groups
Abbreviations: Int, intervention; SD, standard deviation, INF, intraneural facilitation; m, meter; cm, centimeter.

There were significant increases in mean gait velocity (p=.005) and stride length (p=.007) over time for the INF group. There were also significant increases in mean gait velocity (p=.014) and stride length (p=.007) over time for the sham group. No significant differences were seen between groups.

SOT and LOS of NeuroCom

The results of the pre- and post-measurements for the SOT are shown in Table 3.

Table 3. Sensory Organization Test: Static and Dynamic Balance Changes - Pre vs. Post Treatment

	INF Intervention (n_1=17)			**SHAM (n_2=11)**			**Difference between groups**
SOT Conditions	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	***p-value*[b]**
Condition 1	93.1 ±1.6	93.5 ±1.3	0.368	91.9 ±2.7	90.6 ±5.3	0.398	0.180
Condition 2	86.1 ±4.7	87.7 ±5.0	0.113	86.1 ±7.7	86.2 ±6.6	0.689	0.249
Condition 3	84.9 ±8.3	88.5 ±4.1	0.056	84.0 ±6.2	85.3 ±5.5	0.398	0.510
Condition 4	82.7 ±13.0	85.7 ±9.2	0.210	73.1 ±17.3	72.3 ±23.8	0.248	0.495
Condition 5	56.7 ±20.5	59.9 ±23.1	0.507	48.5 ±24.9	53.0 ±27.3	0.123	0.760
Condition 6	53.2 ±19.8	61.2 ±18.2	0.093	41.9 ±28.4	51.2 ±28.7	0.477	0.655
Composite[1]	71.9 ±9.7	77.0 ±8.7	0.040*	65.5 ±13.0	70.0 ±15.2	0.139	0.832
Somatosensory[2]	0.9 ±0.1	0.9 ±0.1	0.287	0.9 ±0.1	1.0 ±0.0	0.790	0.832
Visual[3]	0.9 ±0.1	0.9 ±0.1	0.332	0.8 ±0.2	0.8 ±0.3	0.110	0.165
Vestibular[4]	0.6 ±0.2	0.6 ±0.2	0.653	0.5 ±0.3	0.6 ±0.3	0.051	0.410
Preference[5]	1.0 ±0.1	1.0 ±0.3	0.492	0.9 ±0.1	1.0 ±0.1	0.859	0.981

*p-values <0.05
[a]p-value within groups
[b]p-value between groups
[1]Composite score is the summation of all conditions.
[2]Somatosensory system score is the condition comparison of condition 2 to condition 1.
[3]Visual system score is the condition comparison of condition 4 to condition 1.
[4]Vestibular system score is the condition comparison of condition 5 to condition 1.
[5]Preference score is the condition comparison of conditions (3+6) to conditions (2+6).

There was a significant increase in the mean composite score (p=0.040) over time for the INF group. However, no significant changes between groups.

Pre- and post-measurements for the limits of stability test are shown in Table 4.

Table 4. Limits of Stability Changes - Pre vs. Post Treatment

Variables		Reaction Time (ReT) (s)			Movement Velocity (MVL) (deg/s)			Endpoint Excursion (EPE) (%)			Maximal Excursion (MXE) (%)			Directional Control (DCL) (%)		
Directions	**Groups**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	***p-value*[a]**
FW	INF	1.4 ±0.8	1.4 ±0.6	0.938	2.7 ±1.7	2.5 ±1.1	0.623	39.3 ±13.6	45.5 ±15.0	0.218	59.4 ±12.8	59.7 ±12.6	0.887	76.7 ±20.9	78.9 ±14.4	0.906
	SHAM	1.6 ±0.8	1.2 ±0.5	0.109	3.1 ±1.9	2.0 ±1.2	0.074	35.3 ±13.3	28.6 ±11.3	0.139	52.1 ±18.3	52.6 ±16.6	0.964	86.2 ±5.8	77.8 ±12.9	0.068
FWRT	INF	1.4 ±0.8	1.4 ±0.5	0.959	2.9 ±1.1	3.2 ±1.4	0.000*	75.4 ±13.5	55.7 ±18.5	0.587	69.6 ±12.7	70.0 ±15.0	0.669	75.7 ±14.5	71.1 ±18.4	0.224
	SHAM	1.6 ±0.9	1.4 ±1.2	0.278	2.8 ±1.3	2.3 ±1.3	0.102	49.9 ±23.9	52.9 ±21.8	0.959	65.5 ±16.1	65.5 ±19.0	0.831	67.2 ±18.0	72.3 ±19.6	0.507
RT	INF	1.0 ±0.5	1.2 ±0.4	0.237	2.9 ±1.2	3.1 ±1.4	0.569	58.4 ±16.5	58.4 ±23.8	0.679	72.8 ±14.3	74.4 ±16.1	0.477	85.1 ±7.0	83.9 ±10.7	0.776
	SHAM	1.3 ±0.5	0.7 ±0.4	0.005*	3.1 ±1.8	2.9 ±1.4	0.350	56.2 ±18.4	62.0 ±17.5	0.635	71.0 ±13.0	75.2 ±11.2	0.284	85.7 ±7.2	85.8 ±7.10	0.959
BWRT	INF	1.3 ±0.7	1.2 ±0.4	0.487	2.7 ±1.2	2.2 ±0.8	0.205	39.2 ±14.1	52.5 ±20.9	0.018*	58.4 ± 22.6	68.4 ±21.4	0.046*	44.9 ±30.3	54.6 ±25.6	0.076
	SHAM	1.1 ±0.5	1.0 ±0.4	0.638	2.3 ±1.1	2.4 ±1.3	1.000	44.6 ±19.3	48.6 ±17.9	0.533	67.6 ±11.9	70.8 ±22.7	0.533	54.2 ±31.4	50.1 ±31.7	0.689
BW	INF	0.8 ±0.5	0.9 ±0.6	0.644	2.1 ±1.7	2.7 ±1.2	0.026*	36.4 ±14.7	42.1 ±17.5	0.332	59.3 ±19.1	60.4 ±21.6	0.687	60.2 ±29.8	58.4 ±25.8	0.407
	SHAM	0.9 ±0.6	0.8 ±0.5	0.577	1.9 ±1.5	2.2 ±1.6	0.755	37.3 ±12.6	37.8 ±14.3	0.721	53.8 ±20.3	64.0 ±24.4	0.141	61.9 ±30.7	68.1 ±17.5	0.563
BWLT	INF	1.0 ±0.6	1.1 ±0.5	0.660	2.6 ±0.6	2.9 ±1.3	0.712	46.5 ±21.1	50.2 ±13.1	0.477	71.8 ±20.1	76.3 ±18.3	0.356	51.0 ± 27.7	60.7 ±17.8	0.083
	SHAM	1.2 ±0.4	1.3 ±0.6	0.413	2.5 ±1.8	2.7 ±1.3	0.441	50.1 ±20.2	50.0 ±21.5	0.953	67.9 ±17.0	65.6 ±18.2	0.533	48.9 ±27.1	49.8 ±23.8	0.577
LT	INF	1.0 ±0.5	1.1 ±0.4	0.758	3.1 ±1.3	3.6 ±1.6	0.016*	66.8 ±21.4	69.8 ±17.1	0.518	80.4 ±14.2	83.7 ±14.0	0.148	86.2 ±7.4	85.9 ±8.50	0.678
	SHAM	1.1 ±0.3	0.8 ±0.6	0.206	3.0 ±1.5	3.4 ±1.9	0.358	60.7 ±23.0	71.6 ±13.2	0.053	73.4 ±15.3	78.9 ±11.2	0.197	84.1 ±7.7	85.6 ±8.00	0.398
FWLT	INF	1.0 ±0.4	1.0 ±0.4	1.000	2.9 ±1.1	3.5 ±1.3	0.070	94.6 ±147.9	64.2 ±21.3	0.530	74.5 ±15.1	75.3 ±14.5	0.047*	73.9 ±9.3	70.2 ±14.1	0.379
	SHAM	0.9 ±0.4	0.8 ±0.4	0.700	2.5 ±1.4	4.2 ±2.8	0.011*	55.0 ±23.5	52.5 ±20.8	0.859	64.5 ±18.9	65.8 ±16.5	0.029*	72.6 ±11.8	77.8 ±8.60	0.262

*p-values <0.05

[a]p-value within groups

Abbreviations: BW, backward; BWLT, backward left; BWRT, backward right; DCL, directional control; EPE, endpoint excursion; FWD, forward; FWLT, forward left; FWRT, forward right; LT, left; MVL, movement velocity; MXE, maximum excursion; ReT, reaction time; RT, right.

Significant increases within the INF group were in the FWRT direction for MVL (p=0.000), BW direction for MVL (p=0.026), BWRT direction for EPE (p=0.018) and MXE (p=0.046) and FWLT direction for MXE (p=0.047). For the sham group, there was a significant decrease in the RT direction for ReT (p=0.005) and significant increases for FWLT direction for MVL (p=0.011) and MXE (p=0.029). Significant differences between groups were seen in the FW direction for MVL (p=0.034) and in the RT direction for ReT (p=0.006).

QOL-DN

QOL for diabetic neuropathy test is shown in Table 1. There was a significant decrease within the INF group in the total score (p=0.004), physical functioning/large fiber (p=0.011), and symptoms (p=0.001). There was also a significant decrease in physical functioning/large fiber (p=0.049) within the sham group. No significant differences between groups.

Discussion

The analysis showed no significant differences in baseline demographic characteristics of either group, confirming the random assignment of study participants into INF and sham groups.

The current study suggests a manual therapy intervention and its effects related to pain symptoms in DPN. This study showed significant improvement over time in the INF group for pain quality factors found in small nerve fiber symptoms described in the superficial domain and the deep pain domain of the PQAS. DPN affecting the small

nerve fibers involves multiple symptoms, including burning, shooting, prickling, cramping, numbness, heat sensation loss, allodynia, and itching pain (Hoeijmakers, Faber et al. 2012, Sasaki, Kawamura et al. 2020). This could suggest that INF affected small nerve fibers on a pathophysiological level by possibly increasing the nerve myelinated fiber density, which is decreased in small fiber neuropathy. Between groups there was significance seen for the pain quality, unpleasant pain. Unpleasant sensation in the feet is extremely important to individuals with DPN; in an article by Davies et al., in 2006 they found that those with painful DPN rated the unpleasant category of pain in the neuropathic pain scale as one of the highest (Davies, Brophy et al. 2006). The significant "reduction of pain symptoms observed in both treatment and sham groups is consistent with the concept that the formation of a "sustained partnership" between the health care provider and the patient can have direct therapeutic benefits (Gillespie, Gillespie et al. 2007).

There is little information on treatments that can improve patients' with DM gait parameters and decrease their fall risk (Allet, Armand et al. 2010). The importance of improving gait velocity means the decreased risk of falls in those with DPN (Kang, Zhou et al. 2020). The INF and sham group showed improvements in gait velocity and stride length, with no significant differences seen between groups (Table 2). The improvement in gait velocity and stride length post-intervention for those with DPN is also seen in an article by Morrison et al., which studied exercise as an intervention for those with T2DM with and without DPN, but no sham group used (Morrison, Colberg et al. 2014). When comparing starting means for gait velocity and stride length in the Morrison et al. article

with ours, we notice our means were higher, suggesting our subjects were higher functioning and possibly creating a ceiling effect.

A fair amount of research provides insight into decreased balance in individuals with DPN versus without DPN (Gregg, Beckles et al. 2000, Ites, Anderson et al. 2011, Brown, Handsaker et al. 2015, Timar, Timar et al. 2016, Kluding, Bareiss et al. 2017, Selvarajah, Kar et al. 2019); however, fewer research articles are utilizing the NeuroCom for SOT. In a study by Emam et al., SOT static balance was significantly lower in neuropathic experiencing patients than non-neuropathic experiencing patients, with no significant difference seen in dynamic balance (Emam, Gad et al. 2009). This is expected because a decline in somatosensory function, along with damage to the peripheral nervous system, is referred to as peripheral neuropathy for individuals with DM (Xu, Zhang et al. 2016, Szok, Tajti et al. 2019). In 2016, Alshahrani et al. observed the relation between subjects' with DPN pre- and post-INF treatments and found significant improvement in static balance with SOT; however, their study lacked a control or comparative sham group. This is similar to the findings in the current study in which the static balance composite score was significantly increased within the INF group (Table 3). However, the composite score did not make the minimal detectable change (MDC), which needed a change of greater than 8 points (Wrisley, Stephens et al. 2007).

No significant changes were observed between the INF or Sham group. This could be because the average mean composite score pre-intervention in this study (71.9 ±9.7) was a lot higher than the pre-intervention means in Alshahrani et al.'s study (53.77 ±21.81), suggesting the current study participants had less balance deficiencies than Alshahrani et al. study.

There is also limited research utilizing NeuroCom LOS with subjects with DPN. The only comparison article available is Alshahrani et al. which reported improved MVL dynamic balance with LOS on the NeuroCom (Alshahrani, Bussell et al. 2016). Between groups, there was a significant difference in MVL for FW direction in favor of INF and ReT in RT direction in favor of sham. The MVL result is similar to the Alshahrani et al. study in which MVL was also significant. However, in the current study with a comparative sham group, the dynamic balance was improved in the INF group over the sham group. MVL had three directional improvements over time in INF as well suggesting the INF manual therapy approach affects the speed of the subject to change their COG and reach their target without losing balance. The ReT improvement in sham over INF was also found between groups. We did not anticipate this result, but only one direction was seen significantly improved over time in the sham group. Authors believe further research in LOS with an increased sample size will help us understand the relationship between INF and LOS.

One explanation of the minimal significant findings is that the LOS test focuses on the motor response; the interventions provided in the current study did not address motor system response. Future studies would benefit from looking at INF in conjunction with specific exercises improving motor control.

In the current study, significant improvements were observed in the INF group pre vs. post for the total QOL-DN neuropathy score, physical functioning/large fiber category, and symptoms category (Table 1). The symptom category of the QOL-DN questionnaire involved: numbness, tingling, electric shocks, unusual sensations, superficial pain, deep pain, weakness, and allodynia. These symptoms are also indicative

of both small and large fiber nerve involvement. The large fiber pathophysiology involving more axonal neuropathy, suggesting possible changes are happening at the axon. The sham group had a significant improvement in physical functioning/large fiber (Table 1). There were no significant differences between groups seen, possibly due to our unequal sample size.

Diminished sensation in individuals with DPN can lead to diabetic ulcers and non-traumatic amputations (Frykberg, Lavery et al. 1998). The use of the 5.07 SWM with 10-grams of pressure is an essential tool used to diagnose loss of protective sensation and assess an amputation risk (Pop-Busui, Boulton et al. 2017). This is important due to the rising health care costs associated with T2DM (Vinik, Park et al. 2000, Gordois, Scuffham et al. 2003, Sadosky, Mardekian et al. 2015). There are typically 65,000 amputations a year in the United States alone, one every 10 minutes, and neuropathy is the contributing factor in 87% of these cases (Vinik, Park et al. 2000). This 10-grams of pressure is important in the 5.07 SWM because it "assesses the integrity of the Merkel touch domes and Meissner's corpuscles and their associated large diameter fibers" (Feng, Schlosser et al. 2009). This is also similar to the current study's QOL-DN questionnaire findings, where the large fiber subcategory significantly improved within INF (Table 1). The INF group showed significant improvement in protective sensation after INF treatments in tested areas (Figure 1). INF results were more significant than the sham group, suggesting that INF could be a contributing factor in reducing amputations and ulcers related to individuals with DPN.

The results of the present study showed a strong placebo effect. This was anticipated as we had mimicked the anodyne sham comparative group in a study by

Lavery et al., in which a large placebo effect was also seen (Lavery, Murdoch et al. 2008).

The current study aimed to provide an alternative manual therapy physical therapy approach to assist in combating and improving DPN symptoms in those with T2DM and hopefully bringing down healthcare-related DPN costs in those where aerobic exercise may not be safe or feasible.

Study Limitations

Limitations to the current study was the small and uneven sample size not allowing for significant findings between groups nor ruling out a possible placebo effect in some cases. Improvement in the pre-screening process utilizing subjects with a diagnosed balance and gait issues would allow for less ceiling effect and more room to see possible post-intervention improvement. Moreover, our study did not measure long-term effects. Authors recommend additional research to include a larger and equal sample size with balance deficits in conjunction with DPN.

Conclusion

This is a new manual therapy approach in physical therapy to address DPN symptoms. This study showed that Intraneural Facilitation (INF) improved within group composite static balance measure and between group protective sensation and unpleasant pain quality in subjects with diabetic peripheral neuropathy. Further studies with increased and equal sample size per group are needed to determine further benefits of this intervention.

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Competing Interests

Dr. Mark Bussell is inventor on several patent applications filed by the Loma Linda University Medical Center which covers the subject matter of Intraneural Facilitation presented in this paper.

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CHAPTER THREE

A MICROCIRCULATORY RESPONSE FROM INTRANEURAL FACILITATION ON DIABETIC PERIPHERAL NEUROPATHY: A RANDOMIZED CONTROL TRIAL

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Abstract

Background/Purpose: To assess the variability of anterograde and retrograde pulsatility, peak systolic volume, and volume flow in patients with type II diabetic peripheral neuropathy receiving Intraneural Facilitation (INF) or sham intervention over 5 weeks.

Method: A single-blind, randomized, sham-controlled clinical trial was performed. Thirty individuals with DPN received Intraneural Facilitation (INF) or sham anodyne treatment with 28 patients completing the 5-week study, 17 in INF cohort and 11 in sham. Ultrasound assessment using Phillips Affinity 50 was taken during the course of this study for both groups with anterograde pulsatility index (AP), retrograde pulsatility index (RP), anterograde peak systolic velocity (APSV), retrograde peak systolic velocity (RPSV), anterograde volume flow (AV) and retrograde volume flow (RV) at the distal posterior artery on the treated extremity at baseline and after week 1, week 2, and week 3 of treatments. A within and between-group statistical analysis was performed.

Results: There was no difference between each group statistically, however, there were changes within the experimental group with time. Within and between groups statistical analysis was performed.

Conclusion: Within INF group changes were encouraging yet further research is needed to elucidate the value of assessing macrovascular regulation using repeated single site sonography assessment.

Keywords: intraneural facilitation, diabetic peripheral neuropathy

Introduction

Diabetes is diagnosed in 34.2 million Americans, approximately 10.5% of the United States' population (Dhatariya, Corsino et al. 2000). By 2060 adults with diabetes is projected to triple (Lin, Thompson et al. 2018). Diabetes is considered an emerging pandemic with 415 million people having the disease worldwide (Papatheodorou, Banach et al. 2018). Those with type two diabetes mellitus (T2DM) are characterized by chronic hyperglycemia resulting from insulin resistance which can lead to many complications both microvascular (including neuropathy, retinopathy, and nephropathy) and macrovascular complications (including heart attack, stroke, and other cardiac comorbidities) (Cade 2008, DeFronzo, Ferrannini et al. 2015, Ghardashi Afousi, Izadi et al. 2018). Diabetic peripheral neuropathy (DPN) is the most common complication with 8.5% occurring in diagnosed youth and lifetime prevalence of 50% (Juster-Switlyk and Smith 2016, Jaiswal, Divers et al. 2017). However, 50% of DPN may be unrecognized (Pop-Busui, Boulton et al. 2017).

DPN symptoms and side-effects include numbness, tingling, sharp and intractable pain (Kaur, Pandhi et al. 2011, Schreiber, Nones et al. 2015, Bodman and Varacallo 2021). Individuals with painful DPN report both a mental and physical impact profoundly altering their quality of life (QOL) (Van Acker, Bouhassira et al. 2009). Sensation impairment, muscle weakness, and impaired function are often present (Bansal, Kalita et al. 2006, Ylitalo, Herman et al. 2013). Complications from DPN result in more hospitalizations than any other diabetic complication (Kaur, Pandhi et al. 2011).

These DPN impairments occur from the peripheral vascular and axonal degeneration associated with DPN (Head 2006). Profound microvascular changes occur

with capillary basement membrane thickening in endoneurial capillaries, reduced capillary length, irregular capillary distribution, pericyte loss, transperineurial constriction and endothelial mitochondrial loss (Hill and Williams 2004, Beltramo and Porta 2013, Hsu, Liao et al. 2016, Richner, Ferreira et al. 2018). A study using nailfold videocapillaroscopy evaluated microcirculation in patients with T2DM and found a positive correlation in the number of microvascular complications and DPN (Hsu, Liao et al. 2016). As a consequence of resultant ischemia, oxygen deprivation impairs neural potassium channels performance and local metabolic waste uptake is impaired leading to reduced neural performance with enhanced nerve trunk hyperalgesia (Jiang, Sigworth et al. 1994).

There is an inverse relationship between endothelial function and elevated retrograde shear rate in those with T2DM (Gibbs, Dobrosielski et al. 2011, Ghardashi Afousi, Izadi et al. 2018). It has been found that low-volume high-intensity interval training in patients with T2DM can increase flow-mediated dilation and outward arterial remodeling as a result of increased nitric oxide production, as resulted by increasing anterograde sear and decreasing retrograde shear and oscillatory index (Ghardashi Afousi, Izadi et al. 2018).

Diabetic nerve inflammation is not limited to the periphery, but is universal with vagal nerve axonal damage identified post-mortem (Guo, McLeod et al. 1987). Diabetic cardiac autonomic neuropathy (CAN) involves vagal nerve and sympathetic nerve dysregulation with overt symptoms including orthostatic hypotension, tachycardia, decreased heart rate variability, exercise intolerance, and abnormal blood pressure regulation (Pop-Busui 2010). Cardiac autonomic neuropathy is a significant, yet

overlooked symptom of diabetes (Vinik and Ziegler 2007). While diagnosed DPN CAN symptomatology is clear, evidence suggest subtle autonomic vascular dysregulation occurs with DPN resulting in inconsistent vascular pressure to the vasa nervorum from the microcirculation (Amenta, Mione et al. 1983, Barrett, Liu et al. 2017).

Currently physical therapists assist individuals with T2DM with micro/macrovascular changes through evaluation and treatment of movement and functional disorders, which in return improves quality of life (Cade 2008). Interventions physical therapists mainly provide to assist in their treatment is exercise (Cade 2008). In a pilot study, physical therapists used a novel manual therapy technique to assist in treating DPN symptoms, this manual therapy treatment is called Intraneural Facilitation (INF) (Alshahrani, Bussell et al. 2016). INF has been shown to improve balance and mTNS scores in patients with DPN diagnosis (Alshahrani, Bussell et al. 2016). While this manual intervention therapy is thought to enhance vasa nervorum microcirculation, it is unknown the impact of this therapy or other interventions has on reducing variability of DPN macrovascular circulation. Sympathetic damage occurs in diabetic neuropathy and there are sympathomimetic agents to help reverse these functional disturbances (Watkins and Edmonds 1983). However, there is still a need for more non pharmacological interventions to aide in treating DPN.

This study aims to assess potential changes in macrovascular variability in response to an intervention which is thought to enhance sensation and reduce painful DPN. The study is novel in attempting to show a link between macrovascular dysregulation and microvascular ischemia through microvascular treatment and

macrovascular evaluation over time. The authors are not aware of a similar study at the time of writing this article.

The null hypothesis is, there will be no difference in ultrasound measurement of the distal posterior tibial artery between patients who have DPN and receive Intraneural Facilitation experimentally and patients who receive a sham intervention. Measurements evaluated will include anterograde pulsatility, retrograde pulsatility, anterograde volume flow and retrograde volume flow.

Research Design and Methods

Recruitment, Subject Criteria, and Randomization

Subjects were recruited by distributing flyers in the Loma Linda Community, referrals from medical doctors at the Loma Linda University Medical Center, Loma Linda Diabetes Treatment Center, and through emails to school staff, faculty, and word of mouth. The Institutional Review Board (IRB) of Loma Linda University approved all methods and procedures, and all subjects signed the informed consent before beginning their measurements and therapy. Thirty middle-aged male and female adults medically diagnosed with T2DM with DPN below ankle level were recruited. Phone recruitment and screening were completed with IRB-approved telephone recruitment for all interested subjects in which inclusion and exclusion criteria were reviewed along with details of the study.

Subjects were included in the study if they had T2DM, below ankle DPN symptoms (numbness, tingling, burning, sharp pain, increased sensitivity, etc.), moderate

to severe DPN as identified by scoring ≥ 10 on the Quality of Life- Diabetic Neuropathy (QOL-DN) scale, and if they are between the ages of 50-75 years old. Subjects were excluded if they had a medical condition suggesting a possible decline in function over the next 6 months such as; a current regimen of chemotherapy, radiation therapy, or dialysis, any lower extremity amputations or wounds, documented active alcohol and/or drug misuse, known health conditions: end stage renal failure, uncontrolled hypertension, severe dyslipidemia, chronic liver disease, autoimmune disease, advanced chronic obstructive pulmonary disease and active inflammations, patients with other inflammatory neuropathies including; chronic inflammatory demyelinating polyneuropathy, proximal diabetes neuropathy, and autonomic neuropathies, patients with other neuropathies not associated with DM such as B12 deficiency, hypothyroidism, and uremia, other severe chronic medical conditions requiring active treatment, morbidly obese, and if pregnant (self-reported).

Once subjects completed the phone recruitment script, subjects attended a session at Loma Linda University, School of Allied Health, Department of Physical Therapy Department, Ortho-Science Research Lab to complete the last inclusion criteria, which was to score ≥ 10 on the QOL-DN scale, and sign IRB consent form. Once subjects completed this initial visit, subjects went to the Neuropathic Therapy Center (NTC) for randomization and scheduling therapy. Every subject was asked to choose between two sealed identical envelopes in a basket, within the envelope revealed if they were in Group 1 or Group 2. Group 1 (N=17) was the INF group and was given INF treatment. Group 2 (N=11) was the sham group and was given anodyne therapy.

Upon first treatment a blinded physical therapist provided ultrasound to the posterior tibial artery of the subject prior to treatment. Ultrasound was completed before first treatment, and after the 3rd treatment (the first week), after the 6th treatment (second week), and after the 9th treatment (3rd and final week). Treatment physical therapists were not blinded and were different then the accessing blinded physical therapists.

Environment

All subjects completed initial measurements initial measurements and post treatment reveal of their group at the Loma Linda University, School of Allied Health, Department of Physical Therapy Department, Ortho-Science Research Lab. All lights were kept on, temperature was kept the same, and no music was played. All subjects completed testing in the same manner. All subjects completed their ultrasound and therapy treatments at the same facility, located at the Neuropathic Therapy Center. All lights were kept on, temperature was kept the same, the same music channel was played, and all subjects were treated in the same private treatment room.

Outcome Measures

Philips Affiniti 50

We utilized the Phillips Affiniti 50 diagnostic ultrasound unit to measure pulsatility, and blood volume for wave form analysis (Philips, Anvover, MA). There is no reliability and validity for this instrument as of yet. Ultrasound was taken at the distal posterior tibialis artery of the symptomatic foot, at 1 inch proximal to the medial malleolus.

Measurements of anterograde pulsatility index (AP), retrograde pulsatility index (RP), anterograde peak systolic velocity (APSV), retrograde peak systolic velocity (RPSV), anterograde volume flow (AV) and retrograde volume flow (RV) were assessed with the ultrasound. This analysis took 10 minutes to complete.

Active INF vs. SHAM Anodyne Treatments

INF- Intraneural Facilitation

INF aims to use the body's own nervous system to bias blood flow to closed endoneurial capillaries. In order to do this INF utilizes three manual holds. The first is the facilitation hold, in which the contralateral joint is placed in a maximal loose-pack position to pressurize the nervous system and bias circulation from the artery into the epineurium (Alshahrani, Bussell et al. 2016). This slight stretch in the contralateral joint is hypothesized to stretch the nerve further than the artery, due to the increased amount of elastin found in the artery (Alshahrani, Bussell et al. 2016). The increased neural excursion in comparison to the artery stretches the coiled nutrient vessel attached between the artery and the nerve, thus it is hypothesized that this enlarges the opening of the arterial junction allowing increased blood into the epineurium (Alshahrani, Bussell et al. 2016). Now that we have increased this pressure, we begin the secondary hold to bias the increased epineurial blood into the transperineurial vessels that bridge the epiperineum and the endoneurial capillaries of the site being treated (Alshahrani, Bussell et al. 2016). Now that the pressure has increased into the open endoneurial capillaries, the goal is to open up ischemic endoneurial capillaries and this is hypothesized to open by providing the third hold. The third hold is known as the sub hold and encourages blood

flow through ischemic endoneurial capillaries that have increased resistance/pressure through the application of Bernoulli's principle. This therapy was provided by a trained INF physical therapist for those in the active treatment group for 50-60 minutes at the Neuropathic Therapy Center.

SHAM Anodyne Therapy

A physical therapist performed the sham anodyne therapy at the same site as the INF therapy location, at the Neuropathic Therapy Center. The sham treatment lasted 50-60 minutes and consisted of using an anodyne unit for application of near-infrared light therapy. The unit was not switched on, but the pads were placed on the subject and the subject was be blinded to the unit being on. The anodyne therapy pads were placed in the following locations on the affected lower limb: two on the plantar aspect of the foot in a T formation and one pad on the medial and lateral side of the calf. A double-folded towel was wrapped around the subject's foot at the electrode sites to blind the subjects from the light not emitting from the electrodes, due to the anodyne unit being off.

Data collection

Baseline demographics was gathered a week prior to treatments. Ultrasound data was collected prior to the 1st (Baseline), and after the 3rd, (Week 1), 6th (Week 2), and 9th (Week 3) treatment visits.

Data analysis

Mean and standard deviation were computed for quantitative variables and frequency (percentage) for ordinal variables. The Wilcoxon's Signed-Ranks Test was used to compare pre- and post- variables in both groups. A Linear mixed effects model (repeated measure) was used to examine the screening from baseline to week 3. Data were analyzed using R software, R Core Team (2020). All analyses were performed at an alpha level of .05.

Results

Out of forty-five participants screened, thirty subjects satisfied the eligibility criteria, agreed to participate, were randomly assigned into the INF group (n=17) and sham group (n=13) by picking between two sealed envelopes and completed their treatments (Figure 1).

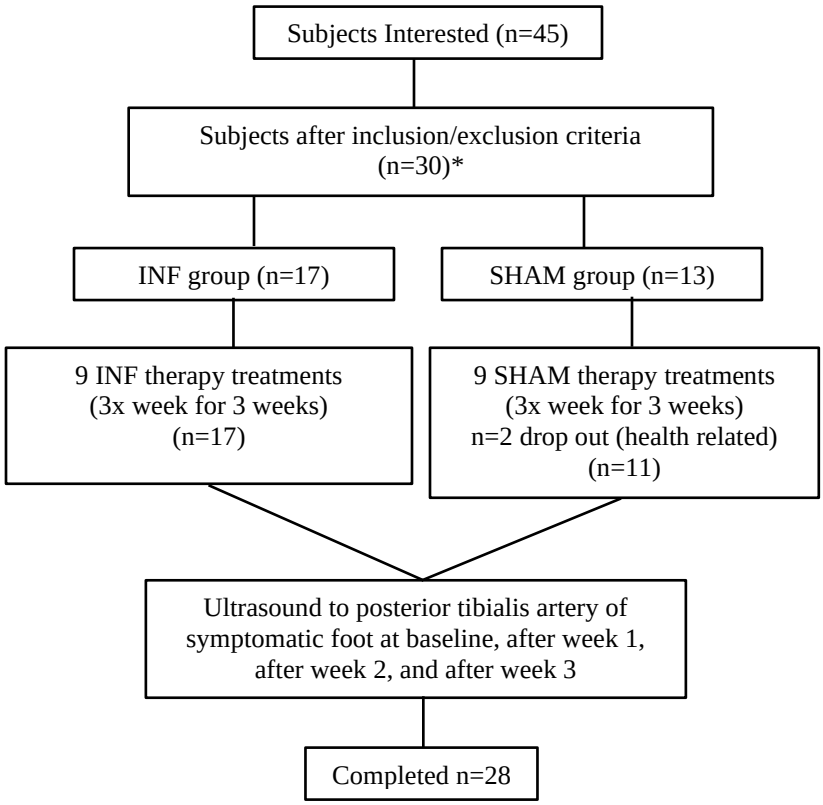

Figure 1. Subject Screening and Completion (n=45)
*Every subject had a chance to draw Group 1 or Group 2 therapy (INF or sham therapy)

The analysis showed no significant differences in baseline demographic characteristics of either group, except for gender (Table 1).

Table 1. Subject Characteristics

	INF (n=17) Mean±SD (Min,Max)	**SHAM (n=11) Mean±SD (Min,Max)**	***p – value*[a]**
Age (years)	66.94 ± 5.08 (60.00,75.00)	67.09 ± 6.28 (54.00,73.00)	0.945
Height (cm)	173.47 ± 13.40 (152.40,195.58)	173.18 ± 7.85 (160.02,182.88)	0.944
Weight (kg)	207.35 ± 52.85 (130.00,284.00)	209.55 ± 39.98 (157.00,262.00)	0.908
Gender			0.000
Female	7 (41.2)	4 (36.4)	
Male	10 (58.8)	7 (63.6)	

[a]p-value within groups

Two dropouts occurred in the sham group due to health issues. Thus, only twenty-eight participants completed the study (Figure 1).

Pulsatility Index

Anterograde PI was compared over time and there was no significant difference seen between INF and SHAM. Also, there was no significant change over time for both groups (Figure 2A).

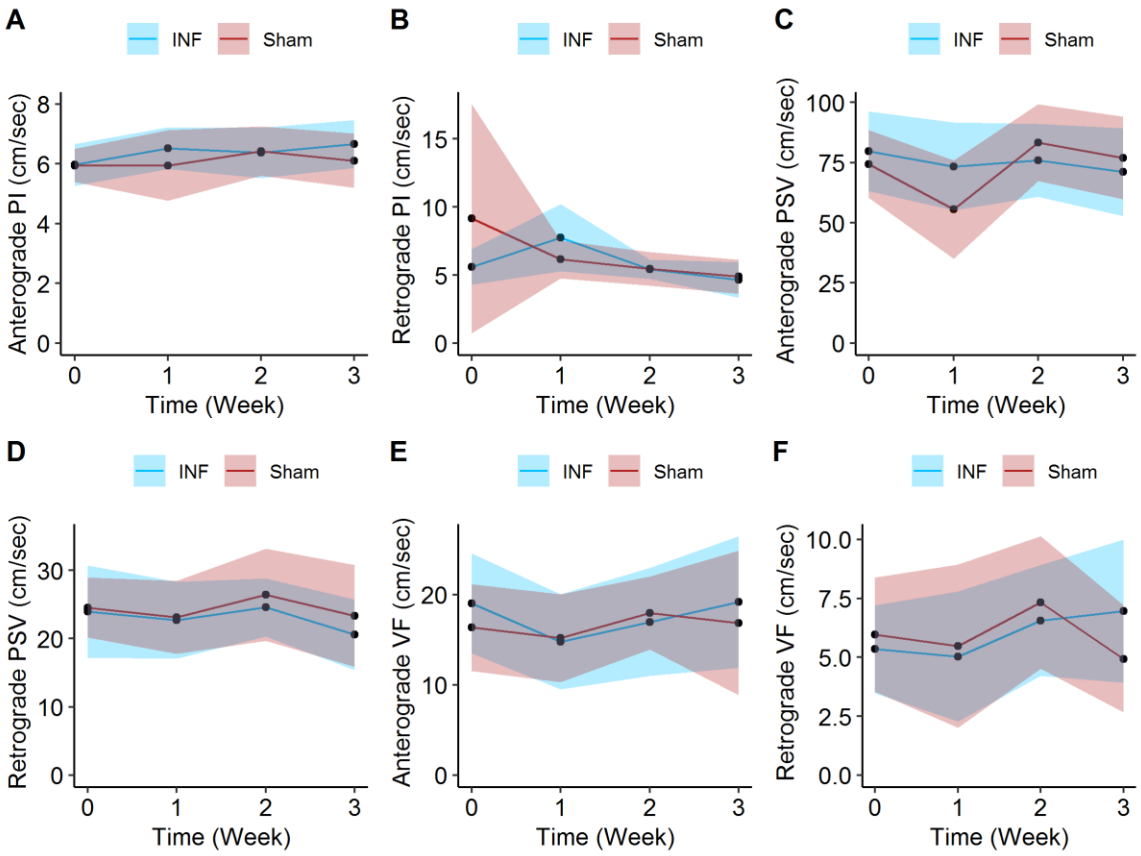

Figure 2. Linear mixed-effects plot for INF vs. SHAM Over Time
Abbreviations: PI, pulsatility index; PSV, peak systolic velocity; VF, volume flow

However, there was a significant difference from week 1 and week 3 compared to baseline (p=0.015, p=0.017) (Table 2).

Table 2. Pulsatility Index, Peak Systolic Volume and Volume Flow Over Time; INF vs. SHAM & Comparison of Ultrasound Outcomes from Week (1-3) to Baseline

Variables	Intervention (n=17)			SHAM (n=11)		
	Mean ± SD	Mean Difference	p- value	Mean ± SD	Mean Difference	p- value
PI Anterograde Week 0	5.97 ± 1.47			5.95 ± 0.94		
Week 1	6.53 ± 1.48	0.56	0.015	5.95 ± 1.81	0.00	0.859
Week 2	6.37 ± 1.78	0.40	0.136	6.43 ± 1.26	0.48	0.859
Week 3	6.66 ± 1.64	0.69	0.017	6.11 ± 1.46	0.16	0.799
PI Retrograde Week 0	5.60 ± 2.76			9.15 ± 14.22		
Week 1	7.75 ± 5.20	2.15	0.196	6.16 ± 2.13	-2.99	0.441
Week 2	5.42 ± 1.42	-0.18	0.326	5.46 ± 1.88	-3.69	0.722
Week 3	4.66 ± 2.67	-0.94	0.156	4.88 ± 2.03	-4.27	0.575
PSV Anterograde Week 0	79.69 ± 34.9			74.35 ± 23.80		
Week 1	73.41 ± 38.47	-6.28	0.013	55.51 ± 31.23	-18.84	0.109
Week 2	75.86 ± 31.88	-3.83	0.507	83.35 ± 24.35	9.00	0.515
Week 3	71.06 ± 37.11	-8.63	0.234	76.93 ± 26.36	2.58	0.594
PSV Retrograde Week 0	23.94 ± 14.18			24.55 ± 7.47		
Week 1	22.72 ± 11.85	-1.23	0.501	23.11 ± 8.16	-1.44	0.235
Week 2	24.85 ± 8.68	0.91	0.410	26.43 ± 10.36	1.88	0.594
Week 3	20.58 ± 10.54	-3.36	0.155	23.32 ± 11.39	-1.23	0.314
VF Anterograde Week 0	19.02 ± 11.63			16.36 ± 8.14		
Week 1	14.75 ± 11.07	-4.27	0.055	15.17 ± 7.43	-1.19	0.594
Week 2	16.97 ± 12.59	-2.05	0.603	17.97 ± 6.20	1.61	0.767
Week 3	19.19 ± 14.86	0.17	0.313	16.87 ± 12.91	0.51	0.646
VF Retrograde Week 0	5.35 ± 3.93			5.97 ± 4.11		
Week 1	5.03 ± 5.81	-0.32	0.278	5.48 ± 5.30	-0.49	0.441
Week 2	6.56 ± 4.79	1.21	0.501	7.33 ± 4.30	1.36	0.374
Week 3	6.97 ± 6.20	1.62	0.156	4.93 ± 3.67	-1.04	0.285

[a]p-value within groups. Abbreviations: PI, pulsatility index; PSV, peak systolic velocity; VF, volume flow; Week 0: before 1st treatment; Week 1: after 3rd treatment; Week 2: after 6th treatment; Week 3: after 9th; Mean difference: Week1, 2 & 3 compared to baseline. Paired t-test.

Retrograde PI was compared over time with no significant difference seen between INF and SHAM. Also, no significant change over time for both groups (Figure

2B). No significance was seen when the baseline of RP was compared to week 1, 2, or 3 for the INF or sham groups.

Peak Systolic Volume

Anterograde PSV was compared over time and there was no significant difference seen between INF and SHAM. However, there was significant change over time (p=0.032) (Figure 2C) (Table 3).

Table 3. Ultrasound Variables Compared Between Groups, Over Time, and Interaction

	Anterograde PI p- value	Anterograde PI p- value	Anterograde PSV p- value	Retrograde PSV p- value	Retrograde PSV p- value	Retrograde VF p- value
Intervention	0.4590	0.6383	0.6582	0.7222	0.8747	0.9029
Time	0.3344	0.1864	0.0319	0.1781	0.5494	0.4692
Time*Intervention	0.3720	0.2986	0.2176	0.7519	0.6498	0.2878

p-value = <0.05. Abbreviations: PI, pulsatility index; PSV, peak systolic velocity; VF, volume flow

In addition, there was a significance change seen in APSV in the INF group when baseline was compared to week 1 (p=0.013), but not when compared to week 2, or 3 (Table 2).

Retrograde PSV was compared over time with no significant difference seen between INF and SHAM. Also, no significant change over time for both groups (Figure 2D). No significance was seen when the baseline of RP was compared to week 1, 2, or 3 for the INF or sham groups (Table 2).

Volume Flow

Anterograde VF was compared over time and there was no significant difference seen between INF and SHAM. Also, there was no significant change over time for both groups (Figure 2E). No significance was seen when the baseline of RP was compared to week 1, 2, or 3 for the INF or sham groups (Table 2).

Retrograde VF was compared over time with no significant difference seen between INF and SHAM. Also, no significant change over time for both groups (Figure 2F). No significance was seen when the baseline of RP was compared to week 1, 2, or 3 for the INF or sham groups (Table 2).

Discussion

There is limited research on utilization of ultrasound parameters (pulsatility index, peak systolic volume and volume flow) to assess the after-effects of a manual therapy intervention. This article attempts to observe the relationship of this physical therapy intervention on blood flow. In an article by Ishii et. al., blood flow was analyzed in ocular ischemic syndrome before and after carotid artery stenting; findings showed that RPSV was an indicator of stenosis (Ishii, Hayashi et al. 2016). Furthermore, all patients with RV in the ophthalmic artery changed to AV post carotid artery stenting, also those with RV in the ophthalmic artery prior to stenting showed poorer visual outcomes (Ishii, Hayashi et al. 2016). Applying this to the current study, we would hope to see anterograde values increase and retrograde values decrease. No retrograde significance was found in PI, PSV, or VF. AP in the INF group was increased when compared to baseline at week 1 and week 3, alluding to possible improved microcirculation at posterior tibial artery.

APSV decreased significantly in INF group after one week of treatments when compared to baseline but not when compared to week 2, or 3. This could suggest possible beginning shock changes occurring to the circulatory system. The trend seen in the INF and sham group with APSV was however fluctuating, implying that the frequency of treatments was possibly too low to show significance over time.

No changes were seen in volume flow with this study. The authors believe this is preliminary work in investigating changes to the microcirculatory system using INF in patients with DPN. We suggest that additional research should be considered with our study limitations of small sample size and disproportionate group sizes rendering between group analysis inconclusive.

Study Limitations

A larger and equal sample size in both groups should be utilized in the future studies. Furthermore, increased duration of treatment time and post follow-ups comparison would be helpful in discerning long-term effects.

Conclusion

Within INF group changes were encouraging yet further research is needed to elucidate the value of assessing macrovascular regulation using repeated single site sonography assessment.

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Competing Interests

Dr. Mark Bussell is inventor on several patent applications filed by the Loma Linda University Medical Center which covers the subject matter of Intraneural Facilitation presented in this paper.

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CHAPTER FOUR

DISCUSSION

Diabetic peripheral neuropathy impact on those with T2DM is expected to dramatically increase over the years and one of its complications, DPN, is one of the costliest symptoms (Bril, England et al. 2011). Neuropathic symptoms from T2DN are mostly treated pharmacologically (Bril, England et al. 2011). Due to the rising diagnosis of T2DM and subsequently the rising cost expenditure on caring for T2DM, this study investigated Intraneural Facilitation as a possible treatment to aide in reversing DPN symptoms.

First, we hypothesized that Intraneural facilitation would improve quality of life, by improving pain and protective sensation in subjects diagnosed with T2DM with moderate-severe DPN. Significant difference between INF and sham group was found for only one category in the PQAS questionnaire, unpleasant pain. Protective sensation for the third and fifth distal phalanx was significantly improved within the INF and between the INF and sham groups. Signifying that INF improved protective sensation in those individuals with DPN. The magnitude of this finding eludes that INF has the ability to improve protective sensation which when decreased can lead ulcers and over time amputations (Frykberg, Lavery et al. 1998, Pop-Busui, Boulton et al. 2017).

We also hypothesized that Intraneural Facilitation would improve the quality of life through functional mobility in subjects with T2DM and moderate-severe DPN. There were no significant differences seen between groups for gait, and both groups actually significantly improved. In the area of balance, only the INF group showed a difference over time for composite static balance measure. Also, for QOL, both groups saw

significant improvements in physical functioning/large fiber symptoms over time. INF also showed total QOL score to be significantly improved overtime, but there was no difference between groups. In conclusion there were marked improvements over time in both groups with no significant changes between groups.

Lastly, we hypothesized that Intraneural Facilitation would increase blood flow and pulsatility in the distal posterior tibial artery in subjects diagnosed with T2DM with moderate-severe DPN. Significant differences were seen in anterograde increase in AP in week 1 and week 3 when compared to baseline and decrease in APSV in week 1 when compared to baseline. While some INF group changes were observed over time, further research is needed to reveal the value of assessing macrovascular regulation using repeated single site sonography assessment. Furthermore, an increased sample size would further assist in examining INF's effects on circulation in those with DPN.

The most noticeable finding in this study was the significant improvement in protective sensation in individuals with T2DM and DPN. This finding is highlighted because it is a rare finding. To date, according to the researchers' literature review, there are only two other studies who found improved protective sensation with the 5.07 SWM using monochromatic near-infrared energy (MIRE) treatments (Leonard, Farooqi et al. 2004, Flerx and Hall 2015). This is the first manual therapy treatment that can be used to aide in improving protective sensation.

While this study has begun showing promising results, more research in each of these areas are encouraged. Future research should focus on increasing and equaling the sample size in both groups and increasing treatment sessions to further explore the effects of INF on individuals with T2DM and DPN.

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APPENDIX A

LOMA LINDA UNIVERSITY
School of Allied Health Professions

INFORMED CONSENT

TITLE: THE EFFECT OF INTRANEURAL FACILITATION THERAPY ON DIABETIC PATIENTS WITH PERIPHERAL NEUROPATHY

PRINCIPAL INVESTIGATOR: Lee S. Berk, DrPH, MPH, FACSM, CHES, CLS

Key Information for You to Consider

- **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate or discontinue participation.
- **Purpose**. The purpose of this research is to explore the effects of Intraneural facilitation (INF, which is a series of positional changes and stretches completed while lying on a therapeutic table) in Diabetes Mellitus Type 2 (DMT2) subjects with moderate – severe diabetic peripheral neuropathy (DPN). We want to observe improvements in blood flow in the foot, pain, sensation, and quality of life.
- **Duration.** It is expected that your participation will last 5 weeks. First week will be: visit 0 (baseline measurement) 120 minutes, then weeks two through four will consist of 60 minute long visits. Visit 10 will be on week 5 (final measurement) lasting 120 minutes.
- **Procedures and Activities.** You will be asked to participate for 5 weeks in total. First week will be only one visit in which baseline measurements are taken (60 minutes). The baseline measurements are; Pain Quality Assessment Scale, Semmes-Weinstein Monofilaments, Neuropen, NeuroCom SMART Balance Master, Quality of Life- Diabetic Neuropathy Scale (QOL- DN), Zeno Walkway, and Skin Temperature. Then weeks 2-4 will consist of therapy visits 1-9, 3 times per week on Monday, Wednesday and Friday with a one day break in between (60 minutes). During visit 1, 3, 6, and 9 your therapy visit will be coupled with an ultrasound to assess blood flow in your foot. The final week, in week 5 there will be a final measurement (60 minutes) of the same 7 measurements completed in the first week at baseline. There is an optional baseline measurement, the Neurovascular Index, that will require an additional visit (60 minutes each) on the first and last week of the study.
- **Risks.** Some of the foreseeable risks or discomforts of your participation include possible breach of confidentiality, risk of falling, uncomfortable with answering questions, and/or uncomfortable positioning during therapy.
- **Benefits**. Some of the benefits that may be expected include improvements in diabetic peripheral neuropathy symptoms below the ankle, improved balance, blood circulation in your foot, improved gait speed, sensation, quality of life, and decreased pain.
- **Alternatives.** Participation is voluntary and the only alternative is to not participate.

A Seventh-day Adventist Organization
LOMA LINDA UNIVERSITY | School of Allied Health Professions
24951 N Circle Drive, Nichol Hall, Room A118, Loma Linda, CA 92350
phone (909) 558-4000 • *fax* (909) 558-0302 • alliedhealth.llu.edu/research

WHY IS THIS STUDY BEING DONE?

The purpose of this graduate student research is to explore effects of INF (which is a series of positional changes and stretches completed while lying on a therapeutic table) in diabetes mellitus type 2 (DMT2) subjects with moderate – severe diabetic peripheral neuropathy (DPN). We want to explore a possible therapeutic option to better your quality of life.

You are invited to be in this study because you have below ankle DPN with DMT2, you are aged between 50-80 years, you have no other known underlying disease and you have a QOL-DN score ≥10. You do not have a medical condition that suggested possible decline in function over the next 6 months such as; a current chemotherapy treatment, radiation therapy, or dialysis. You do not have any lower extremity amputations or wounds. You do not have any documented active alcohol and/or drug misuse, any known health conditions: end stage renal failure, uncontrolled high blood pressure, severe dyslipidemia, chronic liver disease, autoimmune disease, advanced chronic obstructive pulmonary disease and active inflammations. You do not have inflammatory neuropathies including chronic inflammatory demyelinating polyneuropathy (CIDP), proximal diabetes neuropathy, and autonomic neuropathies. You do not have other types of neuropathies not associated with DM such as B12 deficiency, underactive thyroid gland, and urine in your blood. You do not have severe chronic medical condition requiring active treatment. You are not morbidly obese, and/or are pregnant.

Approximately 48 subjects will participate at LLU.

HOW WILL I BE INVOLVED?

Participation in this study involves the following:

Visit 0

- Quality of Life- Diabetic Neuropathy Scale (QOL- DN) to confirm score ≥10 to classify you as at least moderate symptoms associated with DPN.
- Baseline Measurements; Pain Quality Assessment Scale to evaluate quality of pain, Semmes-Weinstein Monofilaments to assess and sensation loss, Neuropen to assess reduced sensation to sharpness/pain in small nerve fibers, NeuroCom SMART Balance Master to assess balance, Zeno Walkway to assess your walking speed and step length, and skin laser thermometer to assess your skin temperature. Randomization into the INF treatment, or the light therapy treatment, you will not know if you are receiving the SHAM treatment. The INF group will involve a series of positioning and stretches while you lay on a therapeutic table. The light therapy group will be receiving light therapy while lying on a therapeutic table.

Visit 1-9

- Ultrasound given before therapy on visit 1, and after therapy for visits 3, 6, and 9 to obtain information on blood flow.
- Then therapy will be provided for the group you have been randomized in to.

Visit 10

- You will do the same testing as Visit 1

Optional – Additional 2 Visits (1st visit between visit 0 and visit 1, and the 2nd after visit 10)

- *Neurovascular Index to assess blood flow through ultrasound on arteries in upper and lower extremities. Each visit lasting 60 minutes.*

WHAT ARE THE REASONABLY FORESEEABLE RISKS OR DISCOMFORTS I MIGHT HAVE?

This study poses no greater risk to you than what you routinely encounter in day-to-day life. Participating in this study will involve the following risks: possible breach of confidentiality, risk of falling (addressed by researcher standing next to patient during walking and balance testing), uncomfortable with answering questions (you do not have to answer a question if you do not want to), uncomfortable positioning during therapy (you will be able to tell researcher if you are uncomfortable and therapy will adjust or discontinue).

All records and research materials that identify you will be held confidential. Any published document resulting from this study will not disclose your identity without your permission. Information identifying you will only be available to the study personnel.

Information will be kept on a USB drive and in a locked file cabinet, all information on a computer will be password protected, and all written files and paperwork will be kept in a locked file.

WILL THERE BE ANY BENEFIT TO ME OR OTHERS?

Although you may not personally benefit from this study, your participation may help practitioners' better identify/provide insights into treating DPN symptoms (numbness, tingling, burning, sharp pain, increased sensitivity, etc.).

WHAT ARE MY RIGHTS AS A SUBJECT?

Your participation in this study is entirely voluntary. You may refuse to participate or withdraw once the study has started. Your decision whether or not to participate or terminate at any time will not affect your future care with the researchers. You do not give up any legal rights by participating in this study.

If at any time you feel uncomfortable, you may refuse to answer questions.

WHAT COSTS ARE INVOLVED?

There is no cost to you for participating in this study.

WILL I BE PAID TO PARTICIPATE IN THIS STUDY?

You will be paid $100 for completing this study in full. If you wish to participate in optional testing procedures, you will receive an additional $50. In order to receive such payments, you may be asked to provide your home address.

If you are not eligible for the study by scoring ≤ 10 on the Quality of Life- Diabetic Neuropathy Scale (QOL- DN), you will be thanked for your time and given a $5 gift card for travel reimbursement.

WHO DO I CALL IF I AM INJURED AS A RESULT OF BEING IN THIS STUDY?

If you feel you have been injured by taking part in this study, consult with a physician or call 911 if the situation is a medical emergency. No funds have been set aside nor any plans made to compensate you for time lost for work, disability, pain or other discomforts resulting from your participation in this research.

WHO DO I CALL IF I HAVE QUESTIONS?

Call 909-558-4647 or e-mail patientrelations@llu.edu for information and assistance with complaints or concerns about your rights in this study.

SUBJECT'S STATEMENT OF CONSENT

- I have read the contents of the consent form and have listened to the verbal explanation given by the investigator.
- My questions concerning this study have been answered to my satisfaction.

WHO DO I CALL IF I HAVE QUESTIONS?

Call 909-558-4647 or e-mail patientrelations@llu.edu for information and assistance with complaints or concerns about your rights in this study.

SUBJECT'S STATEMENT OF CONSENT

- I have read the contents of the consent form and have listened to the verbal explanation given by the investigator.
- My questions concerning this study have been answered to my satisfaction.
- Signing this consent document does not waive my rights nor does it release the investigators, institution or sponsors from their responsibilities.
- I may call Lee Berk during routine office hours at (909) 558-0302 if I have additional questions or concerns.
- I hereby give voluntary consent to participate in this study.

I understand I will be given a copy of this consent form after signing it.

Signature of Subject _____ Printed Name of Subject _____

Date _____

Please also indicate your consent for the optional procedures by initialing the appropriate statement:

_____ I **agree to** participate in ***Neurovascular Index*** measurements that will be performed during two additional study visits

_____ I **do not agree** to participate in *Neurovascular Index* measurements, and will only attend the normal amount of 10 study visits.

INVESTIGATOR'S STATEMENT

I have reviewed the contents of this consent form with the person signing above. I have explained potential risks and benefits of the study.

Signature of Investigator _____ Printed Name of Investigator _____

Date _____

- Signing this consent document does not waive my rights nor does it release the investigators, institution or sponsors from their responsibilities.
- I may call Lee Berk during routine office hours at (909) 558-0302 if I have additional questions or concerns.

- I hereby give voluntary consent to participate in this study.

I understand I will be given a copy of this consent form after signing it.

Signature of Subject	Printed Name of Subject

Date

Please also indicate your consent for the optional procedures by initialing the appropriate statement:

_____ I **agree to** participate in ***Neurovascular Index*** measurements that will be performed during two additional study visits

_____I **do not agree** to participate in *Neurovascular Index* measurements, and will only attend the normal amount of 10 study visits.

INVESTIGATOR'S STATEMENT

I have reviewed the contents of this consent form with the person signing above. I have explained potential risks and benefits of the study.

Signature of Investigator	Printed Name of Investigator

Date

APPENDIX B

Volunteers Needed for Diabetic Peripheral Neuropathy Study

Looking for volunteers with moderate-severe below ankle neuropathy symptoms for a graduate student research study: "The Effect of Intraneural Facilitation Therapy on Diabetic Patients with Peripheral Neuropathy".

Are you diagnosed with diabetic peripheral neuropathy and deal with numbness, tingling, burning, sharp pain and/or increased sensitivity in your feet?

Who Do We Need:

- Individuals between 50-80 years old with Type II Diabetes and moderate-severe diabetic peripheral neuropathy below ankles.
- Subjects will be excluded if you have:
  - Medical conditions that suggest possible decline in function over the next six months such as: a current regimen of chemotherapy, radiation therapy or dialysis, any lower extremity amputations or wounds
  - Any documented active alcohol and/or drug misuse
  - End stage renal failure, uncontrolled hypertension, severe dyslipidemia, chronic liver disease, autoimmune disease, advanced chronic obstructive pulmonary disease and active inflammations
  - Inflammatory neuropathies including: chronic inflammatory demyelinating polyneuropathy, proximal diabetes neuropathy, and autonomic neuropathies
  - If you have other types of neuropathies not associated with diabetes, such as B12 deficiency, hypothyroidism and uremia
  - Any severe chronic medical condition requiring active treatment
  - If you are morbidly obese, and/or are pregnant

Where: Loma Linda University and Loma Linda University Health Neuropathic Therapy Center.

Length: Your participation will be required in total for five weeks. During the first and last week, only one visit is required for baseline measurement; the second, third and fourth weeks you will be required to participate in three visits per week, for three weeks consecutively. Each visit lasts approximately 60 minutes. There are two additional visits during the first and last week, each 60 minutes, which are optional.

What: This is a physical therapy study where participants will be receiving a series of positions and stretches, or light therapy. All participants finishing the study will receive a $100 gift card. You may be eligible to receive an additional $50, if you choose to complete optional testing.

Principal Investigator: Lee S. Berk, DrPH, MPH, FACSM, CHES, CLS
Sponsor: Loma Linda University School of Allied Health Professions
For Further Information Contact: Graduate Student Investigator Kyan Sahba, PT, DPT, PhDc at **714-235-0087** or **ksahba@llu.edu**.

LOMA LINDA UNIVERSITY HEALTH

Many Strengths. One Mission.

APPENDIX C

Recruitment Script

"The Effect of Intraneural Facilitation Therapy on Diabetic Patients with Peripheral Neuropathy"

- Hello, my name is Kyan Sahba, from Loma Linda University. I am a doctoral candidate from the physical therapy department. May I please have your name?
- We are working on a graduate student research study about the effect of a new physical therapy procedure called Intraneural Facilitation to treat diabetic peripheral neuropathy in diabetes mellitus type 2.
- Would it be convenient for me to talk to you about this study right now?
- Your participation during this conversation is entirely voluntary.
- The purpose of this study is to explore the effects of Intraneural facilitation (INF) in Diabetes Mellitus Type 2 (DMT2) subjects with below ankle moderate – severe diabetic peripheral neuropathy (DPN).
- We want to observe improvements in blood flow and pulsatility in distal posterior tibial artery, quality of pain and protective sensation, and quality of life.
- Your information will only be seen by researchers at Loma Linda University. We will make sure that the information we collect from you is kept private and will be used only for the research study we are discussing.
- If you decide to participate in this study, you will need to visit Loma Linda University to enroll in the study and for further screening.
- The inclusion criteria are:
    - You have DMT2 and moderate- severe DPN with no other known underlying disease
    - Below ankle DPN symptoms (numbness, tingling, burning, sharp pain, increased sensitivity, etc.)
    - ≥10 on Quality of Life- Diabetic Neuropathy Scale (QOL- DN)
    - Between age 50-75 years
- The exclusion criteria are:
    - Patients with a medical condition that suggested possible decline in function over the next 6 months such as; a current regimen of chemotherapy, radiation therapy, or dialysis
    - Any lower extremity amputations or wounds
    - Documented active alcohol and/or drug misuse
    - Known health conditions: end stage renal failure, uncontrolled hypertension, severe dyslipidemia, chronic liver disease, autoimmune disease, Advanced chronic obstructive pulmonary disease and active inflammations
    - DM patients with inflammatory neuropathies including chronic inflammatory demyelinating polyneuropathy (CIDP), proximal diabetes neuropathy, and autonomic neuropathies
    - Patients with other types of neuropathies not associated with DM such as B12 deficiency, hypothyroidism, and uremia
    - Other severe chronic medical condition requiring active treatment
    - Morbidly Obese patients
    - Pregnancy (self reported)
- You will be paid $100 upon completion for your participation in this study in full
- If you wish to participate in optional testing procedures, you will receive an additional $50.

Loma Linda University Health
Institutional Review Board
Approved 10/8/2019
IRB# 5190128

Draft OSR 2/24/04

- Your participation will be required in total for 5 weeks, first and last week, only one visit is required for measurements, the 2nd, 3rd, and 4th week you will be required to participate in 3 visits per week, for 3 weeks. Each visit lasts approximately 60 minutes. There are 2 additional visits during the first and last week, each 60 minutes that are optional.
- After the study is completed, it will be disclosed whether or not you were in the SHAM group.
- Some of the foreseeable risks or discomforts of your participation include possible breach of confidentiality, risk of falling, uncomfortable with answering questions, and/or uncomfortable positioning during therapy. However, measures will be taken in order to minimize such risks.
- Possible benefits are improvements in diabetic peripheral neuropathy symptoms below the ankle, improved balance, blood flow and pulsatility in distal posterior tibial artery, improved gait speed, sensation quality of life, and decreased pain.
- Do you have any questions?
- You can contact the principal investigator Lee Berk, office (909) 558-0302, or email him at Lberk@llu.edu if you have questions about this study.
- Participation is voluntary. Your decision whether or not to participate or to terminate at any time will not affect your care.
- Would you like to participate in this study?
- Please understand you are not officially enrolled until you come to Loma Linda University for the study and sign a consent form.
- Thank you for your time.

APPENDIX D

Quality of Life Questionnaire (QOL-DN)

Diabetic Neuropathy Version

Name: _____ **Date:** _____

Subject #: _____ **Visit:** _____

Date of Birth: _____ **Gender:** ❑ Male ❑ Female

Race: ❑ White ❑ Black ❑ Hispanic
❑ Native American[1] ❑ Asian / Pacific Area[2] ❑ Other: _____

[1] Native American includes American Indian, Eskimo, and Aleut
[2] Pacific Area Embraces Polynesian (including Hawaiian and Samoan), Micronesian (including Guamanian), and Melanesian

Do you have diabetes? ❑ Yes ❑ No

Do you have neuropathy (nerve damage)? ❑ Yes ❑ No

Do you have any known medical condition that causes pain or weakness? ❑ Yes ❑ No
-- If yes, what condition: _____

How long have you had any symptoms of neuropathy? _____Years _____Months

Are the symptoms the same on the right as on the left? ..... ❑ Yes ❑ No…which is worse? ❑ Left ❑ Right
…only one side? ❑ Left ❑ Right

Are the symptoms usually worse at night? ..... ❑ Yes ❑ No

How many medications or other treatments have you used for any of these symptoms (both in the past and presently)? Please write the number on the line. _____

Have you ever been told that you have neuropathy? ..... ❑ Yes ❑ No

Have you ever had ulcer(s) on your feet?..... ❑ Yes ❑ No

Have you ever had gangrene? ..... ❑ Yes ❑ No

Have you had any toes (or fingers) amputated?..... ❑ Yes ❑ No

In the past 4 weeks, have you had a problem with involuntary urinating when laughing or coughing?
❑ Yes ❑ No

(MALES ONLY) In the past 4 weeks, have you had a problem with obtaining or maintaining erections?
❑ Yes ❑ No

(FEMALES ONLY) In the past 4 weeks, have you had a problem with vaginal dryness during intercourse?
❑ Yes ❑ No

Part I: Symptoms

Have you had any of the following symptoms in the past 4 weeks? Please Check all that apply.

	Feet	Legs	Hands	Arms	None
1. Numbness	❑	❑	❑	❑	❑
2. Tingling, Pins and Needles	❑	❑	❑	❑	❑
3. Electric Shocks	❑	❑	❑	❑	❑
4. Other Unusual Sensations	❑	❑	❑	❑	❑
5. Superficial Pain	❑	❑	❑	❑	❑
6. Deep Pain	❑	❑	❑	❑	❑
7. Weakness	❑	❑	❑	❑	❑

Part II: Activities of Daily Life

Answer these questions according to the following scale:	Not a problem 0	Very mild problem 1	Mild problem 2	Moderate problem 3	Severe problem 4
8. In the past 4 weeks, has pain kept you awake or woken you at night?	❑	❑	❑	❑	❑
9. In the past 4 weeks, has the touch of bed sheets, clothes, or wearing shoes bothered you?	❑	❑	❑	❑	❑
10. In the past 4 weeks, have you burned or injured yourself and been unable to feel it?	❑	❑	❑	❑	❑
11. In the past 4 weeks, have any symptoms kept you from doing your usual activities during the day?	❑	❑	❑	❑	❑
12. In the past 4 weeks, have you had difficulty doing fine movements with your fingers, like buttoning your clothes, turning pages in a book, picking up coins from a table?	❑	❑	❑	❑	❑
13. In the past 4 weeks, have you felt unsteady on your feet when you walk?	❑	❑	❑	❑	❑
14. In the past 4 weeks, have you had any problem getting out of a chair without pushing with your hands?	❑	❑	❑	❑	❑
15. In the past 4 weeks, have you had a problem walking down stairs?	❑	❑	❑	❑	❑
16. In the past 4 weeks, have you been unable to feel your feet when walking?	❑	❑	❑	❑	❑
17. In the past 4 weeks, have you been unable to tell hot from cold water **with your hands**?	❑	❑	❑	❑	❑
18. In the past 4 weeks, have you been unable to tell hot from cold water **with your feet**?	❑	❑	❑	❑	❑
19. In the past 4 weeks, have you had a problem with vomiting, particularly after meals (but not due to flu or other illness)?	❑	❑	❑	❑	❑
20. In the past 4 weeks, have you had a problem with diarrhea and/or loss of bowel control?	❑	❑	❑	❑	❑
21. In the past 4 weeks, have you had a problem with fainting or dizziness when you stand?	❑	❑	❑	❑	❑

In the past 4 weeks, how much difficulty have you had performing the following activities:

	Not at all	A little	Somewhat	Moderately	Severely
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
22. Bathing/Showering?	❑	❑	❑	❑	❑
23. Dressing?	❑	❑	❑	❑	❑
24. Walking?	❑	❑	❑	❑	❑
25. Getting on or off the toilet?	❑	❑	❑	❑	❑
26. Using eating utensils?	❑	❑	❑	❑	❑

	Not at all	A little	Somewhat	Moderately	Severely
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
In the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical or emotional health?					
27. Cut down on the amount of time you spent on work or other activities?	❑	❑	❑	❑	❑
28. Accomplished less than you would like?	❑	❑	❑	❑	❑
29. Were limited in the kind of work or other activities you could perform?	❑	❑	❑	❑	❑
30. Had difficulty performing the work/other activities (it took extra effort)?	❑	❑	❑	❑	❑

31. In general, would you say your health now is:

Excellent	Very Good	Good	Fair	Poor
❑	❑	❑	❑	❑

32. Compared with 3 months ago, how would you rate your health in general now?

Much Better	Somewhat Better	About the Same	Somewhat Worse	Much Worse
❑	❑	❑	❑	❑

	Not at all	A little	Somewhat	Moderately	Severely
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
33. In the past 4 weeks, to what extent has your physical health interfered with your normal social activities with family, friends, neighbors, or groups?	❑	❑	❑	❑	❑
34. In the past 4 weeks, how much did **pain** interfere with your normal work (including work both outside the home and housework)?	❑	❑	❑	❑	❑
35. In the past 4 weeks, how much did **weakness or shakiness** interfere with your normal work (including work both outside the home and housework)?	❑	❑	❑	❑	❑

APPENDIX E

Manual and Scoring Algorithm for QOL-DN

1) Description:

The QOL-DN is a self-administered questionnaire, designed to capture and quantify the impact of diabetic neuropathy on the quality of life of individual patients with diabetic neuropathy. Fourteen of the items are of a health-related, biographical nature and are not scored. These are on the front page, and they are not numbered nor scored. The remaining 35 scored questions are numbered items that comprise the entire scale, and they are arranged thematically so that the wording of the questions and the type of response is grouped together. However, the content and topic of each individual question concerns particular functions or symptoms that are related to the following themes:

- Total Quality of Life Score
- Physical Functioning/Large Fiber Neuropathy
- Activities of Daily Living (ADLs)
- Symptoms
- Small Fiber Neuropathy
- Autonomic Neuropathy

These scales and the administration of the questionnaire are described in detail below. In general, items 1-7 (Part I) are a simple inventory of symptoms of neuropathy. The presence of the symptom is checked in whichever box applies, and an absence of a symptom is checked under "none." Positive responses are scored as 1; and negative responses, as 0. Items 8-35 (Part II) pertain to Activities of Daily Life, and most of these are scaled on a 5-point Likert scale ranging from 0 ("Not a problem") to 4 ("Severe problem"). However, Questions 31 and 32 are scored differently. In Question 31, "Good", the middle item, is scored as O. "Very Good" is scored as –1, Excellent" is scored as –2. "Fair is scored as 1, and "Poor" is scored as 2. In Question 32, "About the Same", the middle item, is scored as 0. "Somewhat better" is scored as –1, "Much better" is scored as -2. "Somewhat worse" is scored as 1, and "Much worse" is scored as 2.

A final important point of the overall instrument is that the patient/subject is instructed to rate most items **over the last 4 weeks**, so responses should be interpreted as cumulative over that time period - not merely an inventory of the patient's status at the moment of filling out the questionnaire.

2) Administering the questionnaire:

Administering the questionnaire to the patient or experimental subject is very straightforward: the patient simply fills out the paper form. It is important that the patient is in a quiet area, free of undue distractions, and patients are encouraged to answer the questions themselves (i.e. spouses and significant others should not fill out the questionnaire or influence the patient's responses). *These are subjective patient responses.* The responses are coded and scored when they are entered into the appropriate

database, and the algorithm is supplied below. All questions should be answered. The gender-specific sexual functions questions located on the biographical page should obviously be answered according to gender. It is not recommended to compare responses on this questionnaire directly to the patient's medical history or any other sources of similar information such as other pain questionnaires, etc.

3) Data Accumulation:

De-identified data are accumulated in database format (e.g. MS Excel 2000) and entered by a HIPAA certified research assistant. The original hard copies of the responses are retained as source documents in the patient/subject's medical record. The database is secured by password access to authorized users only. The structure is that of a single table containing all fields for a single questionnaire.

4) Sub-scales and Scoring Algorithm:

The scales listed above were determined based on an exploratory factor analysis, so the questions have loaded into their respective domains. All symptoms (1-7) are scored as either a 1 or a 0, indicating a presence or absence of the symptom. With the exception of Questions 31, and 32, the other items are scored according to the 5-point Likert Scale (0-4, "No Problem" to "Severe Problem"). In Question 31, "Good", the middle item, is scored as O. "Very Good" is scored as –1, Excellent" is scored as –2. "Fair is scored as 1, and "Poor" is scored as 2. In Question 32, "About the Same", the middle item, is scored as 0. "Somewhat better" is scored as –1, "Much better" is scored as -2. "Somewhat worse" is scored as 1, and "Much worse" is scored as 2.

The Total QOL and five domains should be summed as follows:

- Total QOL $\Sigma(1\text{-}7, 8\text{-}35)$
- Physical Functioning/Large Fiber $\Sigma(8, 11, 13\text{-}15, 24, 27\text{-}35)$
- Activities of Daily Living (ADLs) $\Sigma(12, 22, 23, 25, 26)$
- Symptoms $\Sigma(1\text{-}7, 9)$
- Small Fiber $\Sigma(10, 16, 17, 18)$
- Autonomic $\Sigma(19, 20, 21)$

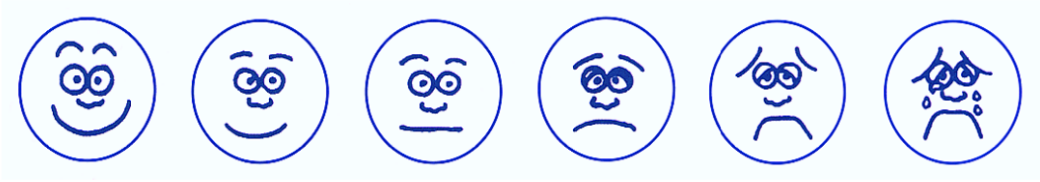
These scales and subscales are calculated without weighting of any kind, and reported as the integer sum of the listed questionnaire items.

THOMSON
PROFESSIONAL
POSTGRADUATE SERVICES

Pain Assessment Scales

The National Initiative on Pain Control™ (NIPC™) has provided these diagnostic tools to assist you in assessing the severity and quality of pain experienced by your patients. We suggest that you produce multiple photocopies so that you may obtain written feedback to place in the patient's history file.

Wong-Baker FACES Pain Rating Scale

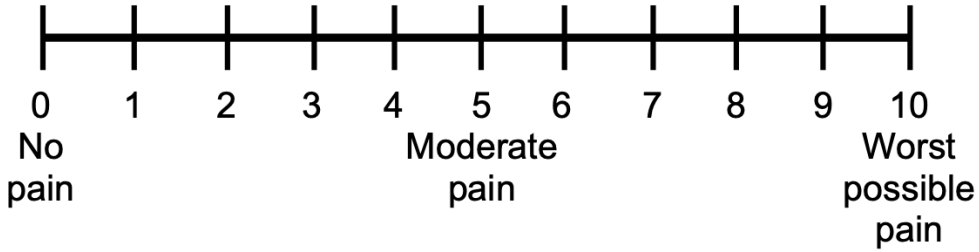


Explain to the person that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can image, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling.

Rating scale is recommended for persons age 3 years and older.

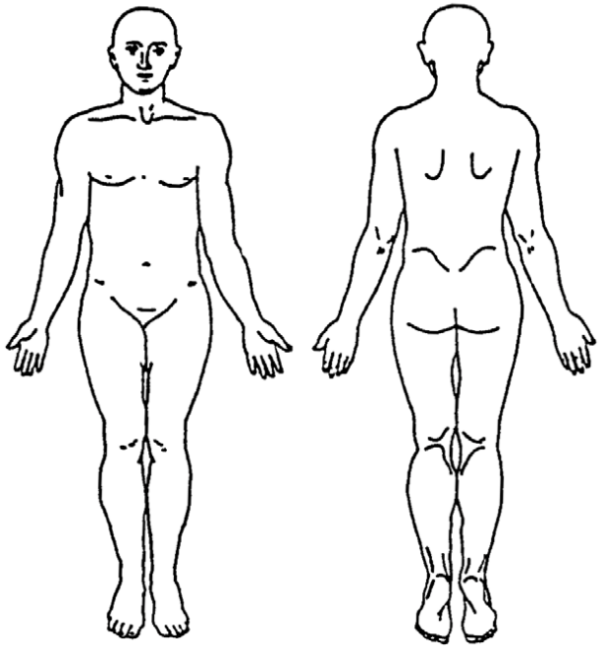
Brief word instructions: Point to each face using the words to describe the pain intensity. Ask the child to choose face that best describes own pain and record the appropriate number.

0–10 Numeric Pain Rating Scale



Where is Your Pain?

Please mark, on the drawings below, the areas where you feel pain. Write “E” if external or “I” if internal near the areas which you mark. Write “EI” if both external and internal.



PAIN QUALITY ASSESSMENT SCALE© (PQAS©)

Instructions: There are different aspects and types of pain that patients experience and that we are interested in measuring. Pain can feel sharp, hot, cold, dull, and achy. Some pains may feel like they are very superficial (at skin-level), or they may feel like they are from deep inside your body. Pain can be described as unpleasant and also can have different time qualities.

The Pain Quality Assessment Scale helps us measure these and other different aspects of your pain. For one patient, a pain might feel extremely hot and burning, but not at all dull, while another patient may not experience any burning pain, but feel like their pain is very dull and achy. Therefore, we expect you to rate very high on some of the scales below and very low on others.

Please use the 20 rating scales below to rate how much of each different pain quality and type you may or may not have felt *OVER THE PAST WEEK, ON AVERAGE.*

1. Please use the scale below to tell us how **intense** your pain has been over the past week, on average.

No pain	0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain has felt over the past week. Words used to describe sharp feelings include "like a knife," "like a spike," or "piercing."

Not sharp	0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10	The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain has felt over the past week. Words used to describe very hot pain include "burning" and "on fire."

Not hot	0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10	The most **hot** sensation imaginable ("burning")

4. Please use the scale below to tell us how **dull** your pain has felt over the past week.

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most **dull** sensation imaginable

5. Please use the scale below to tell us how **cold** your pain has felt over the past week. Words used to describe very cold pain include "like ice" and "freezing."

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** *your skin has been to light touch or clothing rubbing* against it over the past week. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **tender** *your pain is when something has pressed against it* over the past week. Another word used to describe tender pain is "like a bruise."

Not tender	0	1	2	3	4	5	6	7	8	9	10	The most **tender** sensation imaginable ("like a bruise")

8. Please use the scale below to tell us how **itchy** your pain has felt over the past week. Words used to describe itchy pain include "like poison ivy" and "like a mosquito bite."

Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most **itchy** sensation imaginable ("like poison ivy")

9. Please use the scale below to tell us how much your pain has felt like it has been **shooting** over the past week. Another word used to describe shooting pain is "zapping."

Not shooting	0	1	2	3	4	5	6	7	8	9	10	The most **shooting** sensation imaginable ("zapping")

10. Please use the scale below to tell us how **numb** your pain has felt over the past week. A phrase that can be used to describe numb pain is "like it is asleep."

Not numb	0	1	2	3	4	5	6	7	8	9	10	The most **numb** sensation imaginable ("asleep")

11. Please use the scale below to tell us how much your pain sensations have felt **electrical** over the past week. Words used to describe electrical pain include "shocks," "lightning," and "sparking."

Not electrical	0	1	2	3	4	5	6	7	8	9	10	The most **electrical** sensation imaginable ("shocks")

12. Please use the scale below to tell us how **tingling** your pain has felt over the past week. Words used to describe tingling pain include "like pins and needles" and "prickling."

Not tingling	0	1	2	3	4	5	6	7	8	9	10	The most **tingling** sensation imaginable ("pins and needles")

13. Please use the scale below to tell us how **cramping** your pain has felt over the past week. Words used to describe cramping pain include "squeezing" and "tight."

Not cramping	0	1	2	3	4	5	6	7	8	9	10	The most **cramping** sensation imaginable ("squeezing")

14. Please use the scale below to tell us how **radiating** your pain has felt over the past week. Another word used to describe radiating pain is "spreading."

Not radiating	0	1	2	3	4	5	6	7	8	9	10	The most **radiating** sensation imaginable ("spreading")

15. Please use the scale below to tell us how **throbbing** your pain has felt over the past week. Another word used to describe throbbing pain is "pounding."

Not throbbing	0	1	2	3	4	5	6	7	8	9	10	The most **throbbing** sensation imaginable ("pounding")

16. Please use the scale below to tell us how **aching** your pain has felt over the past week. Another word used to describe aching pain is "like a toothache."

Not aching | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **aching** sensation imaginable ("like a toothache")

17. Please use the scale below to tell us how **heavy** your pain has felt over the past week. Other words used to describe heavy pain are "pressure" and "weighted down."

Not heavy | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **heavy** sensation imaginable ("weighted down")

18. Now that you have told us the different types of pain sensations you have felt, we want you to tell us overall how **unpleasant** your pain has been to you over the past week. Words used to describe very unpleasant pain include "annoying," "bothersome," "miserable," and "intolerable." Remember, pain can have a low intensity but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **unpleasant** sensation imaginable ("intolerable")

19. We want you to give us an estimate of the severity of your deep versus surface pain over the past week. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No **deep** pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **intense deep** pain sensation imaginable

HOW INTENSE IS YOUR *SURFACE* PAIN?

No **surface** pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **intense surface** pain sensation imaginable

20. Pain can also have different time qualities. For some people, the pain comes and goes and so they have some moments that are completely without pain; in other words the pain "comes and goes". This is called **intermittent** pain. Others are never pain free, but their pain types and pain severity can vary from one moment to the next. This is called **variable** pain. For these people, the increases can be severe, so that they feel they have moments of very intense pain ("breakthrough" pain), but at other times they can feel lower levels of pain ("background" pain). Still, they are never pain free. Other people have pain that really does not change that much from one moment to another. This is called **stable** pain. Which of these best describes the time pattern of your pain (please select only one):

( ) I have **intermittent** pain (I feel pain sometimes but I am pain-free at other times).
( ) I have **variable** pain ("background" pain all the time, but also moments of more pain, or even severe "breakthrough pain or varying types of pain).
( ) I have **stable** pain (constant pain that does not change very much from one moment to another, and no pain-free periods).

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APPENDIX G

SUBJECT NAME: _____

PRE- TREATMENT ***DATE:*** _____ ***& TIME:*** _____

MONOFILLAMENT:

THIRD METATARSAL HEAD

YES OR NO

FIFTH METATARSAL HEAD

YES OR NO

POST- TREATMENT ***DATE:*** _____ ***& TIME:*** _____

MONOFILLAMENT:

THIRD METATARSAL HEAD

YES OR NO

FIFTH METATARSAL HEAD

YES OR NO

APPENDIX H

LLU Neuropathic Therapy Center: INF Study

Patient ID: _____

Date: _____ Treatment #: _____

Distal Posterior Tibial Artery (Proximal to Medial Malleolus)

- *Angle of insolnation to be 60 degrees for vessel*
- *No constricting clothing*
- *Record best of 2-3 measurements*

Please circle: Left or Right

	Pre-Treatment	Image #	Post-Treatment	Image #
PI Anterograde				
PI Retrograde				
PSV Anterograde				
PSV Retrograde				
Volume Flow Anterograde				
Volume Flow Retrograde				
RI Anterograde				
RI Retrograde				
Waveform				