EFFECT OF AEROBIC EXERCISE INTERVENTION ON PAINFUL DIABETIC NEUROPATHY

BY

MIN YOO

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Abstract

Painful diabetic peripheral neuropathy (DPN) is a common complication of diabetes. While the beneficial effect of exercise on diabetes has been well established, its effect specifically on painful DPN has not been thoroughly explored.

The objective of this pilot study is to examine the effect of aerobic exercise on pain in DPN.

Methods:

Twelve Sedentary individuals with type 2 diabetes mellitus between ages 40-70 with clinical diagnosis of DPN were enrolled in a 16-week, 3X week supervised aerobic exercise program.

Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DPN) was used to assess pain intensity (worst, least, average, now) and pain interference with daily life (activity, mood, walk, normal work, relationship, sleep, enjoyment of life) pre and post the intervention.

BMI, maximum oxygen uptake (VO_{2max}), hemoglobin A1c (HbA1c), and blood pressure were also measured pre and post the intervention as secondary outcomes of interest.

Results:

10 of 12 (83.3%) (5 males/5 females; age 57 ± 4.59 years; duration of diabetes 12.2 ± 5.94 years) participants reported pain due to DPN on the BPI-DPN and were included in the analysis. In these participants, significant reductions in pain interference on walking (4.95±2.83pre/2.8±2.74post, 0.0073), normal work (5.3±3.16pre/3.5±3.06post, P=0.0478), relationship with others (3.55±3.62pre/1±1.15post, P=0.0264), and sleep (5.05±2.77pre/3.2±3.12post, P=0.0407) were observed following the intervention.

The overall pain interference was also reduced (4.50±2.48pre/2.56±2.01post, P=0.0267). However, there was no change in pain intensity scores.

VO_{2max} showed a significant increase post-intervention, while BMI, HbA1c, and blood pressure remained unchanged.

Conclusion:

These preliminary results show reductions in perceived pain interference in people with painful DPN following an aerobic exercise intervention, without a change in pain intensity. Further validation by a randomized controlled trial is needed.

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Background

Introduction

In the United States, 18.8 million people are diagnosed with diabetes and an additional 7 million are estimated to have undiagnosed diabetes. The estimated cost of diabetes (combined direct and indirect) in the United States reached an astronomical figure of $174 billion in 2007, and continues to steadily climb as diagnosed cases of diabetes are projected to rise to nearly 33% of all citizens by 2050 [1].

Diabetic peripheral neuropathy (DPN) is a frequent complication of diabetes that affects 27-46% of diabetic patients in the United States [2]. Also referred to as "diabetic sensorimotor polyneuropathy (DSPN)", DPN is predominantly characterized by sensory symptoms in the "glove-and-stocking" distribution [3]. Diabetes causes DPN by promoting neuronal apoptosis and inhibiting nerve regeneration, which leads to significant deficits in tactile sensitivity, vibration sense, lower-limb proprioception, and kinesthesia [4]. Some DPN patients experience painful neuropathy, characterized by tingling, prickling, burning, or sharp-shooting sensations typically involving the lower limb and most commonly the foot. Painful diabetic neuropathy (PDN) is a common phenotype of DPN that affects up to approximately one-third of the general diabetic population [5, 6].

Neuropathic pain due to diabetes tends to be bilateral and predominantly involves foot and in some cases, upper extremities including fingertips and palms [7, 8]. This distribution pattern occurs because the longest sensory axons are usually the first to be affected by diabetes. Pain is often worse during the night, as well as under stress and fatigue [6, 8]. Patients typically describe their neuropathic pain by using words such as "hot", "burning", "electric", "jolts", "sharp", "tingling", and "pins and needles" [8]. It may also be accompanied by allodynia (painful response to normally non-painful stimuli) and hyperalgesia (exaggerated response to mild pain stimuli) [7].

Painful diabetic neuropathy poses a substantial and growing concern for patients and the health care system. PDN has been shown to be associated with significant reductions in overall quality of life in a cross-sectional study, where patients with PDN showed significantly poorer quality of life (Neuroquol questionnaire) compared to those without neuropathy and those with non-neuropathic pain [6]. The severity of PDN is associated with increasing levels of anxiety, depression, and sleep problems [9]. Painful neuropathy also causes considerable disability, with one-third of patients requiring a walking assist device such as a cane, walker, or wheelchair due to their neuropathy [8]. A study investigating gait function in type II diabetes mellitus patients with DPN found significantly greater gait variability and higher number of self-reported falls in DPN patients with painful neuropathy than in DPN patients without painful neuropathy, suggesting that pain by itself affects walking ability [10].

The exact mechanism by which diabetes causes painful neuropathy has not been clearly elucidated, but increased levels of advanced glycation end products (AGE) and protein kinase C (PKC) due to prolonged hyperglycemia are thought to be involved in peripheral nerve damage. A cascade of events following the nerve damage lead to altered expression of Na+, K+, and Ca2+ channels in the nociceptive neurons of the dorsal root ganglion, which causes exaggerated pain sensation [11]. Sodium channels also spread along the axon at the site of peripheral nerve damage and lead to ectopic neural discharge [11]. Pro-inflammatory cytokines including IL-6 and TNF-α are also thought to contribute to nerve cell damage and neuropathic pain [12]. Abnormal supraspinal modulation of sensory processing arising potentially due to damage from prolonged hyperglycemia may generate allodynia and hyperalgesia [13]. Presence of a possible genetic component in painful diabetic neuropathy has also been suggested [8].

Diagnosis and Treatment of Painful Diabetic Neuropathy

Various methods with differing sensitivities can be used to diagnose diabetic neuropathy, including nerve conduction test, 10-g Semmes-Weinstein monofilament examination [SWME],

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superficial pain sensation test, Electromyography (EMG), and several variations of vibration tests. A study comparing sensitivity and specificity of SWME, superficial pain sensation, vibration testing by the on-off method, and vibration testing by the timed method against the criterion standard of nerve conduction studies recommended SWME, superficial pain sensation, and vibration testing by the on-off method for annual screening of diabetic neuropathy in diabetes and primary care clinics, with 10g monofilament test as the single most practical predictor of neuropathy [14]. When diagnosing PDN, it is important to exclude all other etiologies of painful sensory neuropathy as diabetes patients are also at greater risks for conditions that may cause non-diabetic neuropathy, including chronic inflammatory demyelinating polyneuropathy, B12 deficiency, hypothyroidism, and uremia [15].

Other than proper glycemic control for management of diabetes itself, current standard care for treatment of PDN focuses on pharmacological treatments aiming to relieve painful symptoms. Commonly used drugs include, but are not limited to, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), anticonvulsants (pregabalin and gabapentin), opioids, and tramadol (weak opioid agonist) [7, 11, 16]. While these regimens can be effective, they are often expensive and result in a number of adverse side effects [11]. Some medications may worsen or trigger mood disorders [16]. Dose appropriate for depression may be different from that for painful neuropathy, thus it may be difficult to administer these drugs to diabetic patients with coexisting depression. Tramadol has a potential to interact with most antidepressant medications [16]. Opioids are vulnerable to dose escalation due to rapid development of tolerance, and may cause constipation, sweating abnormalities, hypogonadism, and lowered immunity [16]. α-lipoic acid treatment of PDN shows conflicting study results, and there are concerns that it may alter insulin sensitivity [16]. Furthermore, there are multiple different guidelines with conflicting information for treatment of PDN [16]. Reviewing recent literature examining various old and new drugs for the treatment of PDN reveals that while a myriad of novel drugs have been introduced with many more in clinical stages of development,

finding appropriate pharmacologic therapies remains a strenuous effort [7]. Treatment of painful neuropathy continues to pose "enormous challenges" and is "currently inadequate" [11].

Exercise Intervention in People with Painful Diabetic Neuropathy

Physical exercise and a healthy diet have been shown to improve management of diabetes and its complications [17, 18]. A single bout of exercise has been shown to improve glycemic control – as measured by time spent in hyperglycemia – over the following twenty-four hours in type 2 diabetic patients with or without insulin treatment [19]. Other studies have demonstrated that 8-16 week-long aerobic and resistance exercise interventions can improve functional capacity, strength, and glycemic control [20, 21]. A meta-analysis of twelve aerobic training studies and two resistance training studies (fourteen total, of which eleven were randomized controlled trials) without drug co-interventions observed improved levels of HbA1c, but no change in body mass [22]. This result supports the idea that exercise has an effect on glycemic control in diabetes that is independent from weight control. However, despite being recommended as a major therapeutic modality, exercise still remains underutilized [23].

Patients with DPN can safely engage in exercise. Previously, weight-bearing exercise had been contraindicated among people with DPN [24], likely due to a greater perceived risk of foot injury that may develop unnoticed by the patients. However, several prospective cohort studies found no association between increased weight-bearing activity and risk of foot ulcers [25-27]. A following randomized controlled trial in 2008 showed that the intervention group who went through a self-monitored walking program and received motivational phone calls to promote weight-bearing activities did not have an increased incidence of foot ulcers compared to the control group that received only diabetes education and foot exams [24]. This has led to a recent change in exercise guidelines for people with DPN to allow moderate-intensity weight-bearing exercise [28].

Although exercise has been shown to be beneficial for diabetes control, its effects on DPN and especially the painful phenotype are not clear. Because poor glycemic control leading to nerve damage

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is thought to be one of the causes of DPN, it's possible to conjecture that exercise is protective against DPN. A randomized, controlled clinical trial involving diabetic patients without DPN enrolled in a prescribed and supervised 4-h/week exercise program for 4 years found that fewer participants in the exercise group developed neuropathy compared to the control group, which suggests exercise may delay or even prevent the onset of DPN in diabetic patients [29]. However, we cannot infer from this study whether exercise can reduce or reverse neuropathy in patients already affected by DPN. A mouse model study with four randomized groups (normal-sedentary, normal-exercise, STZ-sedentary, STZ-exercise) using streptozocin (STZ) to induce diabetes found that exercise training significantly decreases diabetes-associated neuropathic pain, including thermal hyperalgesia and mechanical allodynia in diabetic mice [12]. Compared to the STZ-sedentary group, the STZ-exercise group showed greater expression of Hsp72, a heat shock protein thought to protect against cell injury and repair damaged nerves [12]. Hsp72 may achieve this by acting as molecular chaperones to correct protein folding, and is elevated by skeletal muscle contraction [12, 30]. Despite of its feasibility and potential discovered in animal models, exercise as a therapeutic option for painful diabetic neuropathy involving human subjects has not been sufficiently addressed in previous literature.

Study Objective

The objective of this pilot study is to explore the effect of aerobic exercise on pain in DPN. We hypothesize that a supervised aerobic exercise intervention can reduce painful neuropathy due to diabetes.

Research Design

Subjects

As a part of an ongoing pilot study investigating the effect of an exercise intervention on diabetic peripheral neuropathy, participants with diabetic neuropathy were recruited for this exercise study through flyers posted in the community and electronically via websites and email (included in appendix), with the goal of 20 participants completing the study. The clinicians involved in the study utilized their clinical records to identify potential participants. We also utilized the Frontiers Research Participant Registry after approval from the Data Request Committee.

Once enrolled, participants were offered a $50 visa gift card at the midpoint (after completing baseline testing and the first 8 weeks of the program) and a $50 visa gift card at the completion of the 16-week intervention and the post-intervention tests (total of $100 in gift cards) to help with transportation and other expenses.

We enrolled subjects 40-70 years of age who reported a diagnosis of diabetes mellitus type II, with either a diagnosis of diabetic neuropathy or report of signs/symptoms consistent with neuropathy. In order to participate, all subjects were required to provide documentation from their physician that they were medically stable to participate in a supervised exercise program. The presence of neuropathy was confirmed with a nerve conduction testing and a clinical examination by a neurologist prior to enrollment. Subjects were also sedentary or under-active, as determined by a score of 5 or lower on the Telephone Assessment of Physical Activity (TAPA). [31]

At baseline, we assessed neuropathic pain due to diabetes, and the overarching pilot study also assessed plasma insulin, glucose, and lipid levels, insulin resistance, body composition, peripheral autonomic nervous system function (QSART), peripheral vascular function, fatigue, executive function, balance / fall risk, and intra-epidermal nerve fibers (IENF) density from skin biopsy. This led to a

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number of additional exclusion criteria not necessarily directly related to painful neuropathy, such as skin conditions or clotting disorders that would interfere with healing from the biopsy.

Subjects were excluded if they have any of the following conditions:

(1) Serious cardiac pathology such as recent myocardial infarction or heart surgery, uncontrolled cardiac arryhthmia, hypertrophic cardiomyopathy, symptomatic aortic stenosis or heart failure, unstable angina, acute pulmonary embolus or myocarditis, conduction abnormalities, or mitral valve prolapse;

(2) Serious musculoskeletal problems that would limit ability to exercise;

(3) Skin conditions, circulatory insufficiency, or open wounds in the leg that would interfere with healing from the biopsy;

(4) Open wounds on the weight bearing surface of the feet;

(5) Not able to ambulate independently;

(6) Stroke or other central nervous system pathology;

(7) Stage 2 hypertension (resting blood pressure $\geq$ 160 systolic or $\geq$ 100 diastolic);

(8) Lidocaine allergy;

(9) Anticipated difficulty with blood clotting due to Coumadin (Warfarin) use or blood clotting disorder;

(10) Body weight > 450 lbs;

(11) Inadequate cognition and communication abilities, defined as < 24 on the Mini Mental Status Exam (MMSE); or

(12) Pregnant or planning on becoming pregnant in the 18 weeks following enrollment.

The inclusion and exclusion criteria were reviewed with a phone screen (included in appendix)

prior to scheduling the initial visit. During the initial visit, prior to signing informed consent, the inclusion/exclusion criteria were confirmed via medical history, medication review, resting vital signs, Michigan Neuropathy Screening Instrument (MNSI -- includes visual exam of legs and feet), weight and height measures, and MMSE. After consent but prior to enrollment, participants completed the nerve conduction studies and quantitative sensory testing to confirm the presence of diabetic neuropathy, and participants also completed the graded maximal exercise test to confirm their ability to exercise safely. For female pre-menopausal subjects, a urine pregnancy test was completed prior to enrollment.

Once enrolled, a letter was sent to the participant's primary care physician (included in appendix) to inform them of the study procedures and inclusion/exclusion criteria.

Testing Schedule

Aerobic fitness was assessed with a graded maximal exercise test with a metabolic cart (Parvo Medics TrueOne 2400) and integrated ECG, using a standardized protocol with the total body recumbent stepper (TBRS, Nustep) for the exercise test [32, 33] approximately a week before the beginning of each subject's intervention program. We used the maximal workload obtained from this test as an outcome measure and also to calculate a moderate level of intensity and corresponding target heart rates (50-70% of VO_2 reserve) for the aerobic training program.

The graded maximal exercise test and assessment of outcome measures were completed primarily in the Clinical and Translational Science Unit (CTSU) in Kansas City, KS at baseline and following the 16-week intervention by study personnel and CTSU staff. A comprehensive testing schedule for each participant is described in Table 1.

Table 1: Participant Visit Schedule

	Before initial visit	Phone screening form with TAPA
Visit 1: CTSU (~ 3 hours, ~1 week before beginning intervention)	Pre-consent (1 hour)	Confirm inclusion/exclusion screening criteria
	Consent (30 min)	Informed consent review and signature

	Post-consent prior to enrollment (1 ½ hours)	Pregnancy test (if indicated) Nerve conduction studies Quantitative sensory testing Aerobic fitness via graded maximal exercise test
Visit 2: CTSU (~ 1 ½ hours, ~1 week before beginning intervention)	Post-enrollment	Blood draw (Fasting) *Snack provided Q-Sweat test iDXA scan Skin biopsy Questionnaires to take home (Pain, Fatigue, Fall history, DHI, ABC scale)
Visit 3: Georgia Holland REACH lab, G002 Hemenway (~ 1 ½ hours, ~2-3 days before beginning intervention)		*Retrieve questionnaires Peripheral vascular scan (Fasting) *Snack provided (glucose check) Executive function tests Balance tests
Intervention in Georgia Holland HEAL lab, G006 Hemenway		
Visit 4: REACH lab (~ 1 ½ hours, ~2-3 days after the intervention end)	Post-intervention	Peripheral vascular scan (Fasting) *Snack provided Executive function tests Balance tests Questionnaires to take home (Pain, Fatigue, Fall history, DHI, ABC scale)
Visit 5: CTSU (~ 2 ½ hours, ~1 week after the intervention end)	Post-intervention	*Retrieve questionnaires Medication review, resting vital signs, MNSI, weight and height Nerve conduction studies Quantitative sensory testing Aerobic fitness via graded maximal exercise test Skin biopsy
Visit 6: CTSU (~ 1 ½ hours, ~1 week after the intervention end)	Post-intervention	Blood draw *Snack provided Q-Sweat iDXA scan

TAPA = telephone assessment of physical activity; DXA = dual-energy X-ray absorptiometry; DHI = Dizziness Handicap Inventory; ABC Scale = Activities Balance Confidence Scale

Intervention

Subjects participated in 16 weeks of supervised aerobic exercise 3 times each week. Duration of the sessions progressed from 30 to 50 minutes and vital signs were closely monitored. The intensity of the aerobic activity was individually prescribed based on heart rate response during the graded maximal exercise test (progressing from 50 to 70% of VO_{2max} reserve), as shown in Table 2.

Participants were given an option to select from a variety of aerobic training equipment available in the Georgia Holland Health Exercise and Aging Lab in University of Kansas Medical Center, including cycle ergometers, treadmills, recumbent steppers, and elliptical trainers. The format of the aerobic exercise program was modified based on our previous experience to include only aerobic activities, with frequency, intensity, duration, and progression within the updated American College of Sports Medicine (ACSM) Guidelines [34], Joint Position Statement on Exercise and Type 2 Diabetes (ACSM and ADA,[35]), and ADA Standards of Medical Care (2012)[36]. Each exercise session started with brief stretching and/or a 5-minute warm up period, and finished with a 5-10 minute cool down period.

Resting blood pressure, heart rate, and rate of perceived exertion (RPE) were monitored for every subject before, during, and following the aerobic activity. A visual foot exam was performed each week to ensure absence of developing foot ulcers. Blood glucose check was performed on all participants prior to each exercise session according to recently updated ADA guidelines (2012):

*If hypoglycemic (<100 mg/dL), carbohydrates were provided and the participant proceeded to exercise if hypoglycemia resolved with retesting.

*If hyperglycemic (> 300 mg/dL) and participant was not on insulin, exercise was permitted with close monitoring of blood glucose every 10-15 minutes. If blood glucose rose with activity, exercise was stopped.

*If hyperglycemic (> 300 mg/dL) and the participant was taking insulin, urine was checked for ketosis. If positive for ketones, exercise was postponed. If negative for ketones, exercise was permitted with close monitoring of blood glucose every 10-15 minutes.

Table 2: Aerobic Exercise Intervention Schedule

WEEK	Day 1	Day 2	Day 3
1	50% VO_2R, 30 min	50% VO_2R, 30 min	50% VO_2R, 35 min
2	50% VO_2R, 35 min	50% VO_2R, 35 min	50% VO_2R, 40 min
3	50% VO_2R, 40 min	50% VO_2R, 40 min	50% VO_2R, 45 min
4	50% VO_2R, 45 min	60% VO_2R, 45 min	60% VO_2R, 45 min
5	60% VO_2R, 45 min	60% VO_2R, 45 min	60% VO_2R, 45 min
6	70% VO_2R, 45 min	70% VO_2R, 45 min	70% VO_2R, 45 min
7	70% VO_2R, 50 min	70% VO_2R, 50 min	70% VO_2R, 50 min
8 - 16	70% VO_2R, 50 min	70% VO_2R, 50 min	70% VO_2R, 50 min

Primary Outcome Assessment

Painful neuropathy was measured using the Brief Pain Inventory Short Form for Diabetic Peripheral Neuropathy (BPI-DPN). This scale has been specifically validated in this population [37, 38], and consists of 4 pain intensity items (worst, least, average, and current pain severity) and a 7-item pain interference scale (impact of diabetic neuropathic pain on quality of life, described by general activity, mood, sleep, walking ability, relationships, and enjoyment of life). Overall interference with life by painful neuropathy from DPN was assessed by the average of the 7 interference items. The entire questionnaire took approximately 5-10 minutes to complete for each participant.

Secondary Outcome Assessment

Each participant's BMI, aerobic fitness (indicated by VO_{2max}), blood pressure, and glycemic control (indicated by Hemoglobin A1c) were measured as secondary outcomes of interest. Pre and post the exercise intervention.

Documentation of AEs

During each study visit (testing session or exercise session), subjects were asked about adverse events, including falls, change in medical status, or problems that resulted from study procedures. Any adverse events that occurred during the testing or exercise sessions were documented. An AE form (included in Appendix) was utilized to help classify these events as follows:

- Related to study procedure as determined by the PI or unrelated to study procedure (related instead to underlying disease, pre-existing conditions, or other factors)
- Anticipated (included in consent form) or unanticipated (not included in consent form
- Serious (SAE, Grade 4 using CTCAE v3.0) or not serious (AE, Grade 1, 2 or 3 using CTCAE v3.0)

Any AEs that were related to study procedures, unanticipated, or serious were reported to the medical monitor and to the Human Subjects Committee (HSC). A report that summarizes the frequency of all AE's was provided to the medical monitor on a quarterly basis.

Statistical Analysis

All pre vs post outcome comparisons, including BPI-DPN intensity, BPI-DPN interference, BMI, VO_{2max}, blood pressure, and Hemoglobin A1c were analyzed with matched-pair t-test using JMP® Pro 9.0.2.

Results

Subject Enrollment and Baseline Characteristics

72 people were contacted and screened, of whom 37 people met the eligibility (Figure 1). 12 of 37 eligible people declined to participate. Of the remaining 25 people, 8 could not participate due to one of the following reasons: abnormality detected during the baseline exercise test, absence of neuropathy in the nerve conduction and sensory testing, unstable hyperglycemia (blood glucose > 300 mg/dL and positive ketone test) during the first screening visit, AE unrelated to the study prior to starting intervention, and scheduling conflicts. As a result, 17 people were able to start the exercise program. As of 4/1/2013, 10 participants have completed their intervention as well as pre and post outcome assessments. These 10 participants had an average exercise completion rate of 81.9 ± 10.1%. The baseline measurements of the 10 participants are shown in Table 3. 6 additional participants are scheduled to complete the study by June 2013.
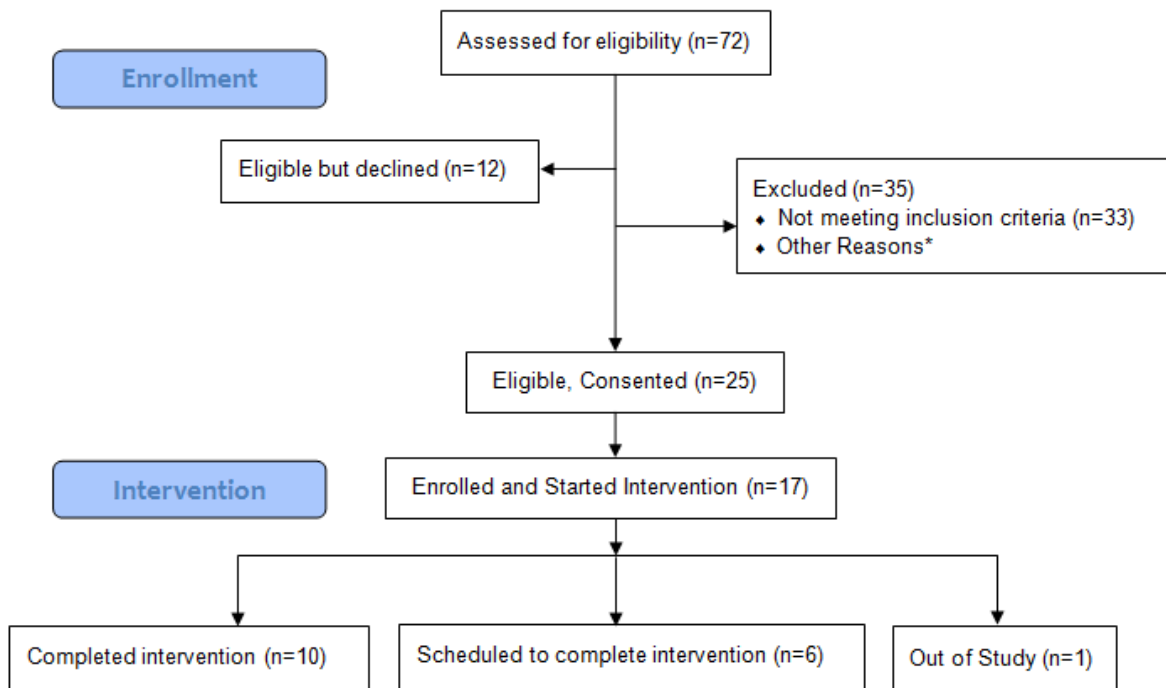
Figure 1: Flowchart of Subject Recruitment and Enrollment

Table 3: Baseline measurements

Age	57 ± 4.59 years
Years with Diabetes	12.2 ± 5.94 years
Race	White (40%)/African-American (30%)/Hispanic (30%)
Years with DPN	7.2 ± 3.77 years
HbA1c	7.96 ± 2.32 %
Systolic Blood Pressure	130.6 ± 15.82 mmHg
Diastolic Blood Pressure	74.7 ± 10.48 mmHg
Gender	Male (50%)/Female (50%)
Insulin Use	Yes (80%)/No (20%)

Primary Outcome Variables

Pain intensity ratings at baseline (Worst=5.45, least= 3.65, average=3.95, now=3.35, mean of four items=4.1) were similar or somewhat lower compared to results found in a previous study that validated BPI-DPN (Worst=5.5, least=4.0, average=5.0, now=4.4, mean of four items=4.7)[38], and another study assessing burden of illness associated with painful diabetic neuropathy using BPI-DPN (mean of four items=5.0)[39]. Pain interference ratings at baseline (General activity=3.8, Mood=4.0, Walking=4.95, Normal work=5.3, Relationship=3.55, Sleep=5.05, Average interference=4.5) were also similar or slightly lower than results from the BPI-DPN validation study (General activity=4.7, Mood=4.9, Walking=5.6, Normal work=5.3, Relationship=3.7, Sleep=5.2, Average interference=4.9) [38], and the burden of illness study (Average interference=5.0) [39].

Despite an overall downward trend, there was no statistically significant change in any of the pain intensity items (Figure 2) (Table 4). There were significant reductions in 4 of the 7 pain interference items (Figure 3), including walking (p=0.0073), normal work (p=0.0478), relationship with

others (p=0.0264), and sleep (p=0.0407), while the remaining 3 items (general activity, mood, enjoyment of life) did not change. Average of the 7 pain interference items was also significantly reduced after the exercise intervention program (p=0.0267).

BPI-DPN Pain Intensity
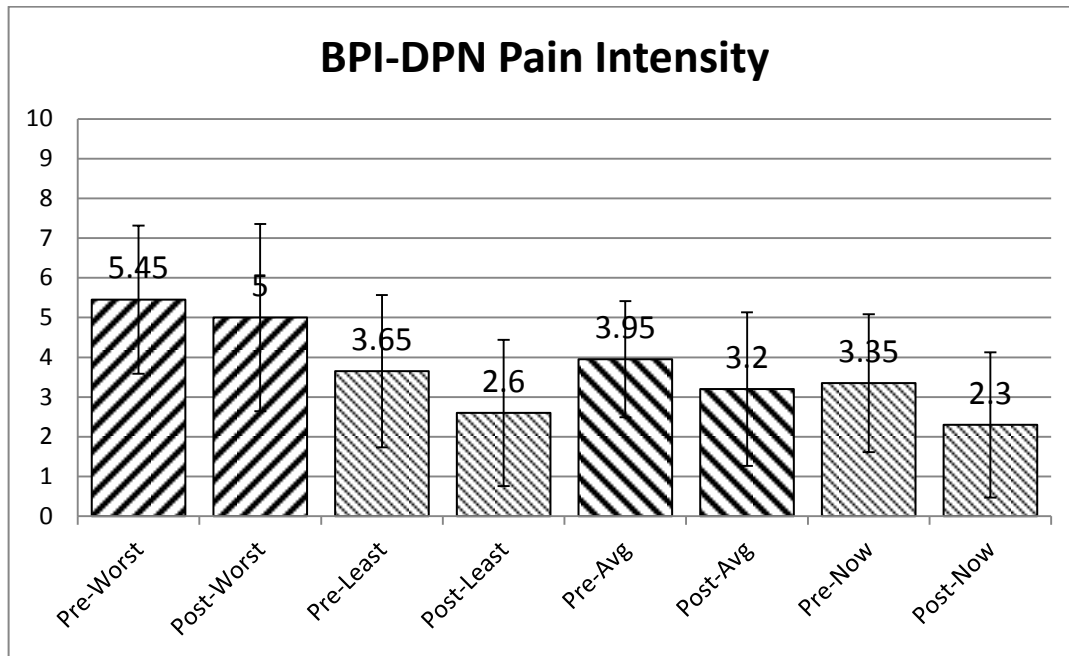
Figure 2: Changes in BPI-DPN Pain Intensity Items

There were small, non-significant reductions in each of the four perceived pain intensity items (worst, least, average, now) by the participants after the completion of 16-week aerobic exercise intervention.
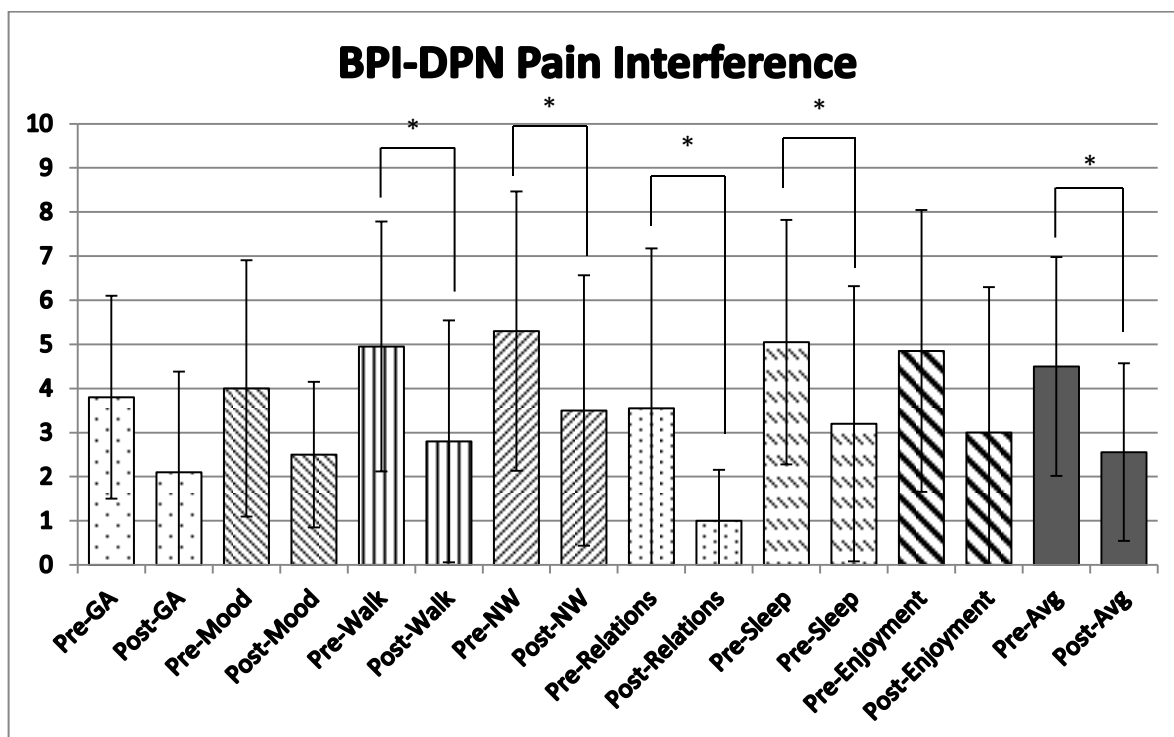
Figure 3: Changes in BPI-DPN Pain Interference Items

(GA=General activity, NW=Normal work, Relations=Relationship with others, Enjoyment=Enjoyment of life, Avg=Interference average). Interference by painful neuropathy due to diabetes on walking, normal work, relationship with others, and sleep showed significant reductions post-intervention, while interference by painful neuropathy due to diabetes on general activity, mood, and enjoyment of life showed statistically non-significant, but potentially clinically important reductions. Overall interference (average of the 7 interference items) rating was also reduced significantly. * denotes $p<0.05$.

Table 4: BPI-DPN Pain Intensity Outcome

	Pre-Intervention	Post-Intervention	Change	P-value
Pain Intensity (Worst)	5.45±1.86	5.0±2.36	-0.45±2.50	0.58
Pain Intensity (Least)	3.65±1.92	2.6±1.84	-1.05±2.31	0.19
Pain Intensity (Average)	3.95±1.46	3.2±1.93	-0.75±2.23	0.31
Pain Intensity (Now)	3.35±1.73	2.3±1.83	-1.05±2.31	0.19

Table 5: BPI-DPN Pain Interference Outcome

	Pre-Intervention	Post-Intervention	Change	P-value
General Activity	3.8±2.30	2.1±2.28	-1.7±3.02	0.11
Mood	4±2.91	2.5±1.65	-1.5±3.50	0.21
Walk	4.95±2.83	2.8±2.74	-2.15±1.97	0.0073*
Normal Work	5.3±3.16	3.5±3.06	-1.8±2.49	0.0478*
Relationship with Others	3.55±3.62	1±1.15	-2.55±3.04	0.0264*
Sleep	5.05±2.77	3.2±3.12	-1.85±2.45	0.0407*
Enjoyment of Life	4.85±3.20	3±3.30	-1.85±3.42	0.12
Average	4.50±2.48	2.56±2.01	-1.94±2.34	0.0267*

*Denotes significant changes

Secondary Outcome Variables

A small, non-significant reduction in BMI was observed after the intervention (-0.523 kg/m^2±1.27, p=0.23) (Table 6). Both systolic and diastolic blood pressure showed non-significant increases (Systolic: +6.5±13.13mmHg, p=0.15, Diastolic: +2.9±8.24mmHg, p=0.29), while Hemoglobin A1c remained essentially identical (-0.06±0.79%, p=0.82), suggesting that the participants did not benefit in their glycemic control from the exercise program. However, the participants' aerobic fitness, as measured by their VO$_{2max}$, showed a moderate (8.6%), statistically significant (p=0.04) improvement.

Table 6: Changes in Secondary Outcomes

	Pre-Intervention	Post-Intervention	Change	P-value
BMI	34.96±5.05kg/m^2	34.43±5.32kg/m^2	-0.523±1.27kg/m^2	0.23
VO$_{2max}$	16.21±4.40ml/kg/min	17.6±4.71ml/kg/min	1.39±1.85ml/kg/min	0.04*
Blood Pressure (Systolic)	130.6±15.82mmHg	137.1±11.53mmHg	6.5±13.13mmHg	0.15
Blood Pressure (Diastolic)	74.7±10.48mmHg	77.6±9.56mmHg	2.9±8.24mmHg	0.29
HbA1c	7.96±2.32%	7.9±2.11%	-0.06±0.79%	0.82

*Denotes a significant change

Adverse Events

No Grade 3 or Grade 4 adverse events (AE) occurred during screening and testing sessions or intervention. Grade 2 AE's (clinical symptoms that required minimal, non-invasive intervention) consisted of episodes of transient hypoglycemia (BG < 100 mg/dL) after exercise, which were shortly resolved with administration of carbohydrates, hyperglycemia (BG > 300 mg/dL) with positive ketone test, mild joint discomforts, muscle cramp, fatigue, and transient hypertension at rest.

One participant developed knee swelling with pain during the intervention period. This participant was referred to an orthopedist and recovered without needing surgery, but decided to stop the intervention at this point. Another participant developed a unilateral dorsal foot swelling with mild pain after an active day at home, after which the participant's physician was contacted, and the exercise intervention was halted. After examination, the physician concluded that the participant could return to exercise after a brief period of resting, and the participant completed the intervention without any further related AE's. This participant's data was not included in the analysis.

Discussion

The results imply that while the participants' perceived pain intensity from DPN did not change, they felt less hindered in certain aspects of their life by the painful neuropathy after the 16-week exercise intervention. It is also possible that the non-significant reductions in pain severity items could not be detected due to our limited sample size, but are still clinically important.

Our findings show significant reductions in how the participants felt their diabetic neuropathic pain interfered with their daily activities including walking, normal work, relationships with others, and sleep. A significant reduction in average pain interference scale reveals that the intervention was successful in abating the impact of pain on quality of life. Absence of significant changes in pain intensity suggests that the decrease in neuropathic pain interference may be psychological. The participants may be experiencing less overall distress in, walking, normal work, relationship with others, and sleep despite persisting pain. It is also possible that the participants learned to cope better with their neuropathic pain. On the other hand, the fact that all four of the pain intensity items showed modest, non-significant decreases points to another possibility that our sample size was simply too small to detect a potentially clinically important improvement in perceived pain.

A minor, non-significant decrease in average BMI supports a meta-analysis of clinical trials involving 12-week to 12-month duration exercise programs, which concluded aerobic exercise alone is not an effective weight loss therapy [40]. However, our hemoglobin A1c results do not agree with findings of previous studies that showed exercise was beneficial for improving glycemic control as indicated by reductions in HbA1c levels [19-22]. The reason for this is unclear. The participants' overall aerobic fitness improved, showing that they still benefited from the intervention although they did not lose weight. These secondary outcome findings also imply that the reduction in pain interference could be independent of weight loss and glycemic control.

The exercise compliance rate of our participants (81.9%) was comparable to the average rate found in a meta-analysis of 27 exercise studies for type 2 diabetes mellitus patients (86%) [41]. Our slightly lower number may be attributed to the fact that only 12 of the 27 studies actually declared their compliance rate. The meta-analysis also included studies involving aerobic, resistance, and aerobic-resistance training rather than just aerobic exercise. Furthermore, frequencies, durations, eligible subject profile (Presence of DPN was necessary to participate in our study) and exact protocols of these studies were different. We believe that the exercise compliance rate in our study and the fairly low drop-out rate (1 out of 13 participants) support the idea that regular exercise intervention is feasible in people with painful DPN.

At baseline, the participants reported experiencing slightly lower levels of pain intensity and pain interference due to DPN compared to previous studies using BPI-DPN to assess pain in painful DPN patients. These differences may be attributed to a selection bias in our study because people with very severe diabetic complications were likely either excluded because they did not meet the inclusion/exclusion criteria, or declined to participate partially due to being in poor physical shape. Another possible explanation for the difference is that the previous studies included both type 1 and type 2 diabetes mellitus patients, while our study only enrolled type 2 patients. This leads to a potential limitation in generalizability. Because our subject pool only included participants who were physically able to do moderate intensity aerobic exercise, patients with severe, longstanding diabetes or patients with significant co-morbidity such as cardiac disease were excluded. The idea that our subject pool cannot be generalized to patients with severe diabetes is supported by the average HbA1c level of our participants at baseline (7.96%), which was approximately one percent below what would be considered by CDC as "poorly controlled diabetes" [1]. The subjects in our study also gave informed consent to participate in a three-times-a-week, 16 week-long exercise program, which would suggest that despite being previously sedentary, they may have been more motivated to improve their health compared to the general diabetic population. However, we believe that our findings are still significant because with the

enormous, growing prevalence of diabetes and DPN, even after excluding patients who physically cannot or are not willing to exercise regularly, a large population would be able to benefit from the exercise programs.

Conclusion

These preliminary results show reductions in perceived pain interference in people with painful DPN following an aerobic exercise intervention, without a change in pain intensity. The intervention also improved VO_{2max} in our participants, but did not lead to changes in BMI, HbA1c, and blood pressure. We feel that the natural extension of our pilot data should be a follow-up randomized controlled trial with a larger sample size for further validation.

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Appendix A: Recruitment Flyer

Exercise for People with Diabetic Neuropathy

Georgia Holland
Health, Exercise and Aging Lab
University of Kansas Medical Center

- Researchers at the University of Kansas Medical Center (KUMC) are looking for 30 subjects to describe the effect of a 16-week exercise program on nerve function and skin nerve fibers in people with leg nerve damage from diabetes.

- What are the criteria?
  - Pain or numbness in both feet with diabetes, age 40-70
  - **No** open wounds on the feet, or serious heart or lung problems

- What would I have to do?
  - Attend 3 measurement sessions (1 ½ - 3 hours each) at the Clinical Research Center or on KUMC campus at the beginning and end of the program
  - Attend 16 weeks of exercise sessions, 3 times each week (1 hour each) on KUMC campus

- **Contact Linda at 913 945-6630 for more information!**

Appendix B: 30-Second Radio Script for Recruitment

If you or someone you know has diabetes and has problems with pain or numbness in their feet, then you may be interested in a research study that is being conducted at the University of Kansas Medical Center. I'm Dr. Patricia Kluding, a physical therapist and researcher at KU Med, urging you to contact us at 913-945-6630 to see if you would be eligible to participate in this exercise study.

There will be no cost to you or your insurance company for these supervised exercise sessions or other expenses related to the study. If you have diabetes and pain or numbness in your feet, pick up the phone and call us at 913-945-6630.

You deserve to get the most out of life. Take charge of your diabetes.

Appendix C: Phone Screening Form

PHONE SCREENING

Exercise and Neuropathy Research Group version 2 (ENRGy2) Project

Greetings: "We are conducting a study to see if exercise will improve nerve function in people with diabetes who have problems with their nerves in the legs and feet. The exercise sessions are 3 days per week for 16 weeks here at KUMed. May I have your permission to ask you some preliminary questions to see if you may be eligible for the study?"

If yes:

Name	
Date of contact	

If criteria is not met for any of the following items: "I am sorry you do not meet the entry criteria for this study. Thank you for calling."

Do you have diabetes?		If yes, continue
Do you have neuropathy or symptoms of numbness, pain or tingling in the feet?		If yes, continue
How old are you?		If between 40 and 70, continue
Have you been hospitalized with a heart attack or heart surgery in the preceding 3 months?		If no, continue
Do you have any other serious heart problems?		If no, continue
Have you had any chest discomfort (pressure or pain) in the last 3 months?		If no, continue
Do you have any bone, joint, or muscle problems that limit your		If no, continue

ability to exercise? If yes, please describe.		
Do you have any open wounds on the soles of your feet?		If no, continue
Can you walk without anyone helping you? (cane, walker, leg brace is ok)		If yes, continue
Have you ever had a stroke or other disease of the brain or nervous system? (Examples: multiple sclerosis, Parkinson's disease)		If no, continue
What is your blood pressure?		If systolic < 160 and diastolic <100, or if unknown, continue
Are you allergic to Lidocaine?		If no, continue
What is your current weight?		If <450 lbs. continue
Do you use Coumadin or have a clotting disorder		If no, continue
Are you currently pregnant or plan on becoming pregnant in the next 18 months?		If no, continue
Is there anything else we need to know about you or your medical history?		

Telephone Assessment of Physical Activity

I am going to ask you about the amount and level of physical activity you usually do. In this survey, we define physical activities as activities where you move and increase your breathing or heart rate. These are activities you do for pleasure, work, or for getting around. I will read a statement about activities, and you can tell me whether the statement describes you by answering *yes* or *no or not sure*

The first statement is:

1	I rarely or never do any physical activities. Does this describe you?	Yes ▫	No ▫	Not Sure ▫

The next statements are about three types of activities: light, moderate, and vigorous. Light activities are activities when your heart beats only slightly faster than normal and you can still talk and sing during them. Some examples of light activities are walking leisurely, light vacuuming, light yard work, or light exercise such as stretching. Here are two statements about light activity,

2a	I do some **light** physical activities, but not every week. Does this describe you?	Yes ▫	No ▫	Not Sure ▫
3	I do some **light** physical activity every week. Does this describe you?	Yes ▫	No ▫	Not Sure ▫

Next are moderate activities. Moderate activities are activities when your heart beats faster than normal. You can still talk but not sing during such activities. Some examples of moderate activities are fast walking, aerobics class, strength training, or swimming gently. I have four statements about moderate activities. The first one is,

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		Yes	No	Not Sure
2b	I do some **moderate** physical activities, but not every week. Does this describe you?	☐	☐	☐
4a	I do some **moderate** physical activities every week, **BUT** less than 30 minutes per day. Does this describe you?	☐	☐	☐
4b	I do some **moderate** physical activities every week, **BUT** less than 5 days per week. Does this describe you?	☐	☐	☐
6	I do 30 minutes or more per day of **moderate** physical activities, 5 or more days per week. Does this describe you?	☐	☐	☐

If yes to #6: "I am sorry you do not meet the entry criteria for this study. Thank you for calling."

If no to #6: continue

The next three statements are about vigorous activities. Vigorous activities are activities when your heart rate increases a lot. You typically can't talk or your talking is broken up by large breaths. Some examples of vigorous activities are jogging, running, using a stair machine, or playing tennis, racquetball, badminton

		Yes	No	Not Sure
5a	I do some **vigorous** physical activities every week, **BUT** less than 20 minutes per day. Does this describe you?	☐	☐	☐
5b	I do some **vigorous** physical activities every week, **BUT** less than 3 days per week. Does this describe you?	☐	☐	☐
7	I do 20 minutes or more per day of **vigorous** physical activities, 3 or more days per week. Does this describe you?	☐	☐	☐

If yes to #7: "I am sorry you do not meet the entry criteria for this study. Thank you for calling."

If no to #7: continue on next page

If interested in study and meet criteria, collect additional information:

Phone Number (home / cell / work)	
Address	
Email Address	
Preferred mode for sending directions and other information (mailing address or email)	
Contact Person (if desired)	
Birthdate	
Unique Subject Code	
Testing session 1: Date/ time	
Testing session 2: Date/ time	
Testing session 3: Date / time	
Preferred days and time for exercise program	

Name of person completing this form _____

Appendix D: Physician Letter

[insert date]

Dear [*insert Physician/Health Care Provider's name*],

Your patient *[insert name, date of birth]* would like to participate in a research project at the University of Kansas Medical Center, "Pilot Study of Exercise and Peripheral Nerve Function in People with Diabetes" (Human Subjects Committee approval # 11385 and CTSU approval # 105). This project involves a graded maximal exercise test and a supervised 16-week aerobic exercise program.

The purpose of this research study is to determine the effect of an aerobic exercise intervention on nerve function in people with diabetic peripheral neuropathy, including assessment of changes in cutaneous innervation, vascular and metabolic outcomes, body composition, and other outcome measures.

We have reviewed your patient's medical history and list of current medications to confirm the absence of pathological conditions that would be a contraindication to exercise in your patient. Your patient has completed a graded maximal exercise with ECG monitoring and a metabolic cart to confirm their ability to exercise safely and to determine their level of aerobic fitness to prescribe an appropriate exercise intensity. During all exercise sessions, we will monitor blood glucose, heart rate, and blood pressure.

We will be recruiting up to 30 participants with diabetic peripheral neuropathy for this study, age 40-70. In addition to receiving supervised exercise sessions without cost, subjects will be given a total of $100 in gift cards once the study is completed. I would be happy to answer any questions you may have about the study, and please let me know if you have any specific concerns regarding your patient.

Sincerely,

Patricia Kluding PT PhD

Associate Professor, Department of Physical Therapy and Rehab Science

913-588-6918 or pkluding@kumc.edu

Linda D'Silva, PT

Study Coordinator

913-945-6630 or ldsilva@kumc.edu

Georgia Holland Health Exercise and Aging Lab

Department of Physical Therapy and Rehabilitation Science

Appendix E: Adverse Event Form

ADVERSE EVENT FORM

ENRGy2 STUDY

Subject ID: _____   Date: _____

Information gathered in person or via phone or email? _____

Brief Description of Adverse Event and Action Taken:

Is AE related to study procedures? □ Yes   □No

      Comment:

Is AE anticipated from risks described in consent form? □ Yes   □No

      Comment:

Is AE severity: □ Mild (asymptomatic, transient)

                     □ Moderate (symptomatic, interferes with function, requires treatment)

                     □ Severe (disabling, life-threatening, requires hospitalization)

      Comment:

*If AE is moderate or severe, notify study coordinator and PI immediately.

*Use additional paper to continue with comments or to follow up as indicated.

Person completing form: _____

Signature: _____ Date: _____