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Pilot Study of Exercise Therapy on Painful Diabetic Peripheral Neuropathy

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Abstract

Objective—Painful diabetic peripheral neuropathy (DPN) is a common complication of diabetes. While the beneficial effect of exercise on diabetes is well established, its effect specifically on painful DPN has not been thoroughly explored. The objective of this pilot study was to examine the effect of aerobic exercise on pain in people with DPN.

Methods—Fourteen sedentary individuals (mean age 57±5.11 years) with painful DPN were enrolled in a 16-week, supervised aerobic exercise program. The 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 -intervention. Body mass index (BMI), maximum oxygen uptake (VO_{2max}), hemoglobin A1c (HbA1c), and blood pressure were also measured pre-and post-intervention as secondary outcomes of interest.

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Results—Significant reductions in pain interference were observed with walking (4.93±3.03 pre to 3.29±2.89 post, p=0.016), normal work (5.39±3.32 pre to 3.79±3.04 post, p=0.032), relationship with others (3.96±3.53 pre to 1.29±1.27 post, p=0.006), sleep (5.11±3.04 pre to 3.5±3.03 post, p=0.02), and the overall pain interference (4.65±2.70 pre to 2.97±2.22 post, p=0.013) following the intervention; however, there was no change in pain intensity. VO_{2max} increased significantly post-intervention (16.02±3.84ml/kg/min pre to 17.18±4.19ml/kg/min, p=0.028), while BMI, HbA1c, and blood pressure remained unchanged.

Conclusion—These preliminary results suggest that perceived pain interference may be reduced following an aerobic exercise intervention among people with painful DPN, without a change in pain intensity. Further validation by a RCT is needed.

Keywords

diabetic peripheral neuropathy; exercise; pain; pain interference

Introduction

As prevalence of diabetes is projected to rise to nearly 10% of the world population and 33% in the United States by 2030, diabetes and its complications pose an enormous burden to global health.[1] Diabetic peripheral neuropathy (DPN) is a frequent complication of diabetes that affects up to 50% diabetic patients in the United States.[2,3] The most common form of DPN is referred to as “diabetic sensorimotor polyneuropathy (DSPN)”, and is predominantly characterized by sensory changes in the “glove-and-stocking” distribution.[4] These symptoms may include significant deficits in tactile and pain sensitivity, vibration sense, lower-limb proprioception, and kinesthesia, caused by promotion neuronal apoptosis and inhibition of nerve regeneration in diabetes.[5] Pain is a common symptom with DPN, affecting 10–26% of the diabetic population.[6–8] Painful DPN (P-DPN) has been shown to have a significantly detrimental impact on anxiety and depression, gait variability, and overall quality of life.[7,9,10]

The current standard care for P-DPN focuses on providing symptomatic relief by utilizing pharmacological interventions. Commonly used medications for P-DPN include, but are not limited to, tricyclic antidepressants (TCA), anticonvulsants (pregabalin and gabapentin), opioids, and tramadol (a weak opioid agonist).[11,12] Treatment of P-DPN must be accompanied by proper glycemic control for management of the underlying cause in diabetes.[13] Administration of these regimens can be limited by a number of potential adverse side effects including triggering or worsening of mood disorders, lowered immunity, and development of addiction.[13] Furthermore, these drugs do not alter the progression of DPN. Only α-lipoic acid is a potential option targeting the etiology of P-DPN, although it has not been found to be superior to other drugs in randomized controlled trials.[14] Review of recent literature reveals that finding appropriate pharmacologic therapies for P-DPN remains a frustrated effort even though numerous novel drugs are newly developed and studied each year.[11] Currently, treatment of painful neuropathy continues to pose “enormous challenges” and is considered by clinicians to be “ inadequate”.[12]

Another therapeutic modality for P-DPN, which remains inadequately explored, is exercise intervention. A strong body of evidences in literature shows that physical exercise and a healthy diet can improve management of diabetes and its complications, including other forms of DSPN.[15–17] A randomized, controlled clinical trial involving diabetic patients without DPN in a long-term, supervised exercise program showed promising results suggesting that exercise may delay or even prevent the onset of DPN in diabetic patients.[18] Randomized studies of weight-bearing exercise in those with DSPN have found such exercise to be well tolerated and not associated with increases in foot ulcers or falls, both common complications of DPN; however, they did not study those with P-DPN.[19,20] A recent streptozotocin (STZ)-induced diabetic mouse model study found that exercise training significantly decreased diabetes-associated neuropathic pain, including thermal hyperalgesia and mechanical allodynia.[21] Despite its' safety, feasibility and potential effectiveness discovered in animal models, exercise as a therapeutic option for painful diabetic neuropathy involving human subjects has not been sufficiently addressed in previous intervention studies.[22] A recent controlled study utilizing a visual analog scale (VAS) to assess neuropathic pain observed that 6 months of a balanced exercise program demonstrated medium-sized effects without statistical significance, compared to an education group.[23]

The purpose of this pilot study was to explore the effect of a supervised, moderate-intensity aerobic exercise training intervention on pain and pain interference in daily life, specifically in people with P-DPN. We hypothesized that our exercise intervention would be associated with reduction of pain in DPN.

Materials and Methods

This study was part of a larger project that investigated the effect of exercise in people with DPN on a variety of outcome measures that will be reported elsewhere, including plasma metabolic and lipid markers, body composition, and intra-epidermal nerve fibers (IENF) density from skin biopsy. This study had IRB approval from the University of Kansas Medical Center. The result of exercise on pain and pain interference outcomes for the subset of individuals with painful DPN are reported here. All individuals participated in the intervention in this pre-post test design project.

Participants

Individuals were recruited for this study through flyers posted in the community and electronically via websites, by phone, and by email. The clinicians involved in the study utilized their databases to identify potential participants, and the University of Kansas Frontiers Research Participant Registry was utilized with approval. Individuals were invited to participate in further screening after signing an institutionally-approved informed consent form if they: (1) were between 40–70 years of age, (2) reported a diagnosis of type 2 diabetes mellitus, (3) reported either a diagnosis of diabetic neuropathy or signs/symptoms consistent with neuropathy, and (4) were sedentary or under-active, as determined by a score of 5 or lower on the Telephone Assessment of Physical Activity (TAPA).[24] Following consent, the presence of neuropathy was confirmed with a comprehensive neurological

examination by an experienced neurologist (M.P.), nerve conduction studies and quantitative sensory testing, prior to enrollment.[25] Individuals were excluded if they had any of the following conditions: (1) Serious cardiac pathology, such as cardiac autonomic neuropathy, or musculoskeletal problems that would limit ability to exercise; (2) Open wounds on the weight bearing surface of the feet; (3) Inability to ambulate independently; (4) Stroke or other central nervous system pathology; (5) Stage 2 hypertension (resting blood pressure ≥ 160 systolic or ≥ 100 diastolic); (6) Body weight > 204 kg; (7) Pregnant or planning on becoming pregnant in the 18 weeks following enrollment; and (7) Impaired cognition and communication abilities, defined as < 24 on the Mini Mental Status Exam (MMSE). Additional exclusion criteria were applied due to potential contraindications for the skin biopsy outcomes (not reported in this paper), including skin conditions, lidocaine allergy, and blood clotting disorder.

Prior to enrollment, each participant underwent a graded maximal exercise test using a standardized protocol that has been validated against the gold standard Bruce protocol. The protocol utilized the total body recumbent stepper (TBRS, NuStep) with a metabolic cart (Parvo Medics TrueOne 2400) and integrated ECG.[26,27] The exercise test consisted of gradual increases in resistance in the recumbent stepper while the participants were asked to maintain a stepping speed of 110–120 steps/min until two of the three termination criteria were met, which were (1) maximum heart rate within 10 beats/min of predicted maximum; (2) plateau of VO2 max; (3) respiratory exchange ratio ≥ 1.10. The test was also terminated if the participants were unable to maintain the stepping rate of 110 steps/min with verbal cues and encouragement. The maximal workload obtained from this test was used to calculate a moderate level of intensity (50–70% of VO_2reserve) and corresponding heart rate for the aerobic training program. The participants received $50 at halfway point of their exercise program, and another $50 at the completion of the program, with a compensation of $100 for each participant.

In this paper, we report on the subgroup of people who (in addition to the above) had painful neuropathy, as defined by answering ‘yes’ on Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DPN) regarding the presence of neuropathic pain from diabetes and according to the study neurologist’s assessment.

Exercise Intervention

Subjects participated in 16 weeks of supervised aerobic exercise 3 times each week. All sessions were supervised by members of the research team who are health professionals or health professional students with current CPR certification. Adherence to study protocol was monitored by the study PI through a training period for new exercise supervisors, informal observation of exercise sessions, and regular review of exercise logs. Duration of the sessions progressed from 30 to 50 minutes, and heart rate was measured before and after each session with pulse oximeter and continuously during the exercise using the heart rate monitor on each exercise machine. Blood pressure was checked before and after each session, and every 10–15 minutes during the exercise if the participant’s resting blood pressure was elevated to near stage 2 hypertension levels. The intensity of the aerobic activity was individually prescribed (Table 1) based on heart rate response during the graded

maximal exercise test as previously described. Participants were given an option to select from a variety of aerobic training equipment, including cycle ergometers, treadmills, recumbent steppers, and elliptical trainers. The frequency, intensity, duration, and progression of the aerobic exercise program followed established guidelines for people with diabetes.[28,29,30] 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. Blood glucose, blood pressure, heart rate, and rate of perceived exertion (RPE) were monitored during every session, and a visual foot exam was performed each week to ensure absence of developing foot ulcers.

Outcomes

Pain and pain interference were measured using the Brief Pain Inventory Short Form for Diabetic Peripheral Neuropathy (BPI-DPN). BPI-DPN is a scale specifically validated in this population,[31,32] and consists of 4 pain intensity items (worst in past 24 hours, least in past 24 hours, 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 in the past 24 hours). Each item is scaled 0 (“no pain”) to 10 (“pain as bad as you can imagine”) for pain intensity and 0 (“no interference”) to 10 (“complete interference”) for pain interference. Overall interference with life by painful neuropathy from DPN was assessed by the average of the 7 interference items.

To supplement the BPI-DPN, we developed a separate questionnaire for the participants to report the frequency of their neuropathic pain, to identify the pain as unilateral or bilateral, to categorize the pain with descriptors such as “burning”, “electric shock-like”, “pins and needles” and “painful sensation to light touch”. Participants were asked to rate the severity of each type of pain ranging 0 (“none”), 1 (“hardly noticed”), 2 (“slightly”), 3 (“moderately”), 4 (“strongly”), and 5 (“very strongly”).

Each participant’s BMI, aerobic fitness (indicated by VO_{2max} on the graded maximal exercise test), blood pressure, and glycemic control (indicated by Hemoglobin A1c) were secondary outcomes of interest before and after the exercise program. Blood pressure was recorded by a single reading in the seated position after each participant rested comfortably for a minimum of 10 minutes and prior to the VO_{2max} test. Hemoglobin A1c was measured with a disposable fingerstick blood testing kit (A1cNow, Bayer, Whippany, New Jersey) prior to the VO_{2max} test.

Statistical Analysis

Analyses were performed using SPSS 16.0 for Windows. Normal distribution of variables was tested through visual analysis of histograms and Shapiro-Wilk statistics. Due to the small sample size of the study and because several of the BPI-DPN variables were not normally distributed, we calculated median values of these variables, and non-parametric analyses were utilized. Pre-intervention versus post-intervention outcome comparisons, including BPI-DPN intensity and BPI-DPN interference, were analyzed with two-tailed Wilcoxon signed-rank test with significance set at $\alpha = 0.05$. Since they were normally and

homogenously distributed, BMI, Hemoglobin A1c, VO_{2max}, blood pressure pre-intervention vs post-intervention comparisons were analyzed with paired Student's t-test with significance set at $\alpha = 0.05$.

Results

Enrollment and Baseline Characteristics

A total of 20 people enrolled in the larger study, which included people with non-painful DPN and painful DPN, and 18 completed the intervention and all post-intervention measurement sessions. A total of 15 people who completed the intervention (83.3%) had painful DPN. However, one person was identified as an outlier because of a large increase in pain intensity following the intervention, well outside the range of other participants. This individual described some emotional trauma due to family issues that arose during the intervention period which may have influenced her pain ratings during the post-intervention measurement session. Analysis of results with and without this individual had no effect on the results. The baseline measurements of the 14 subjects are shown in Table 2. These participants had an average exercise session attendance rate of 74.6±13.21% of total possible sessions offered.

Characterization of Pain

The majority of the participants described their neuropathic pain as bilateral (91%), intermittent (50%) or constant with intermittent exacerbations (50%). All subjects reported having at least one of the four types of pain ("burning", "electric shock-like", "pins and needles" and "painful sensation to light touch"). Half of the subjects (7) reported experiencing of all four types of pain, and "burning" was the most common type of pain (10/14 or 71%) reported. The severity of each type of pain was the highest for "pins and needles" (median =2.0) and "burning" (2.0). There was no notable pattern of changes in these characterizations of pain post intervention.

Change in Pain and Pain Interference

There were no statistically significant changes in any of the pain intensity items (Table 3). However, pain interference was significantly reduced in 4 of the 7 pain interference items, including walking, normal work, relationship with others, and sleep (Table 4). The remaining 3 pain interference items (general activity, mood, enjoyment of life) did not change. Median value of the combined pain interference scale (average of the 7 pain interference items) was also significantly reduced after the exercise intervention program (Pre 4.29±2.70, Post 2.36±2.22, p=0.013).

Change in Other Variables

The participants' aerobic fitness, as measured by their VO_{2max}, showed a moderate, statistically significant (p=0.028) improvement (Table 5). Non-significant changes in BMI, blood pressure, and HbA1c were observed after the intervention.

Discussion

In this pilot exercise intervention study, we found 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. The small size of our sample limits the interpretation of non-significant reductions in pain severity, which may be clinically important. An exercise adherence rate of 74.6% in people with significant chronic painful DPN is a strength of this study. This successful engagement of the previously inactive and chronically debilitated population in a routine 16-week exercise program suggests that supervised exercise programs are viable in people with DPN, while also posing a question regarding whether the results may have differed with greater adherence to protocol or an intervention of greater duration.

Our findings show significant reductions in how the participants reported that 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 may have played a role in abating the impact of pain on quality of daily life. Absence of significant changes in pain intensity suggests that the decrease in neuropathic pain interference may have had a psychological component. The participants may have experienced less overall distress and increased confidence in walking, normal work, relationship with others, and sleep despite persisting pain. While we did not include a measure of 'coping with pain', it is also possible that the participants learned to cope better with their neuropathic pain. Future studies should include such measures. Since pain is multifaceted and all-encompassing experience, subjects may have reported significant change in pain interference due to a change in their frame of reference with respect to the ramification of their pain on their activities. Due to the lack of a significant impact on pain intensity by the exercise intervention, it was unclear whether the intervention actually improved functional status, or just changed the participants' perception toward the pain-function relationship.

This study did not address the underlying physiology of the changes we have reported. Increased levels of advanced glycation end products (AGE) and protein kinase C (PKC) due to prolonged hyperglycemia are thought to lead to peripheral nerve damage in DPN.[21] Central pain processing mechanisms in P-DPN has also been suggested by recent studies.[33] Assessing objective measures of brain functioning along with self-reported pain measures may provide a better understanding of physiological changes and should be investigated in future studies.

The lack of change in HbA1c levels of our subjects suggests that improvement in hyperglycemia was not the mechanism producing improvement in pain interference items. While previous studies that provided exercise interventions to people with diabetes improved glycemic control as indicated by reductions in HbA1c levels,[34–37] a prior exercise intervention study among those with DPN found similar results.[20]

We observed minor, non-significant decrease in average BMI and a significant improvement in overall aerobic fitness. Meta-analyses of clinical trials providing exercise intervention 3 to

12 months in duration have concluded that aerobic exercise alone is not an effective weight loss therapy.[38] While this appears to hold true in our sample, participants appear still to have benefited from the intervention although they did not lose weight. These secondary outcome findings imply that the reduction in pain interference could be independent of weight loss and glycemic control.

Pain intensity and pain interference ratings at baseline were similar or somewhat lower compared to results found in a previous study by Zelman et al. that validated the BPI-DPN pain inventory (Worst=5.6±2.8), least=4.0±2.9, average=5.0±2.5, now=4.4±2.9, mean of four severity items=4.7±2.6) (Average interference=4.9±2.8),[32] and another study assessing burden of illness associated with painful diabetic neuropathy using BPI-DPN (mean of four pain severity items=5.2) (Average interference=5.0±2.6).[39] Using categories of pain severity identified by the BPI-DPN validation study, there was no change in category of pain intensity ratings, while most of the pain interference ratings saw improvements from "moderate" (4–6 in BPI-DPN) to "mild" (1–3).[32]

Our study had several limitations. First, the trial lacked a comparison group, which means that the presence and the absence of changes in our outcome measures could be partially attributed to placebo response or regression toward the mean. In addition, these results may not be generalizable to the many people with P-DPN because people with very severe diabetic complications or with significant co-morbidities may have failed to meet the inclusion criteria for this study, or may have been reluctant to participate due to perceived inability to exercise. On the other hand, participants in our study participated three times per week in a 16 week 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. We believe that our findings are nevertheless clinically meaningful due to the enormous growth in recent years of diabetes and the prevalence of painful DPN that is resistant to treatment. Future randomized studies should be conducted to confirm these findings and test their applicability in a wider population.

Conclusion

Our single group clinical trial is unique in that it examined supervised aerobic exercise intervention as a potential therapeutic modality for P-DPN while assessing the intensity of neuropathic pain and the impact of neuropathic pain on various aspects of people's lives. 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 aerobic fitness in our participants, but did not lead to changes in BMI, HbA1c, and blood pressure. We feel that the natural extension of these pilot data should be validation in different subgroups with painful DPN (such as patients with limited English proficiency who may rate pain differently), followed by randomized controlled trial with a larger sample size in a less restrictive sample to confirm the applicability of these findings in a wider population.

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References

1. Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2011. 2011, 2013.
2. Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell AS. Epidemiology, public health burden, and treatment of diabetic peripheral neuropathic pain: a review. Pain medicine (Malden, Mass). Sep; 2007 8(Suppl 2):S50–62.
3. Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes/metabolism research and reviews. Feb; 2012 28(Suppl 1):8–14. [PubMed: 22271716]
4. Morales-Vidal S, Morgan C, McCoyd M, Hornik A. Diabetic peripheral neuropathy and the management of diabetic peripheral neuropathic pain. Postgraduate medicine. Jul; 2012 124(4):145–153. [PubMed: 22913903]
5. Bansal V, Kalita J, Misra UK. Diabetic neuropathy. Postgraduate medical journal. Feb; 2006 82(964):95–100. [PubMed: 16461471]
6. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes care. Oct; 2011 34(10):2220–2224. [PubMed: 21852677]
7. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care. Jul; 2006 29(7):1518–1522. [PubMed: 16801572]
8. Hartemann A, Attal N, Bouhassira D, et al. Painful diabetic neuropathy: diagnosis and management. Diabetes & metabolism. Nov; 2011 37(5):377–388. [PubMed: 21820345]
9. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. Journal of pain and symptom management. Oct; 2005 30(4):374–385. [PubMed: 16256902]
10. Lalli P, Chan A, Garven A, et al. Increased gait variability in diabetes mellitus patients with neuropathic pain. Journal of diabetes and its complications. Dec 3.2012
11. Ziegler D. Painful diabetic neuropathy: advantage of novel drugs over old drugs? Diabetes care. Nov; 2009 32(Suppl 2):S414–419. [PubMed: 19875591]
12. Mendell JR, Sahenk Z. Clinical practice. Painful sensory neuropathy. The New England journal of medicine. Mar 27; 2003 348(13):1243–1255. [PubMed: 12660389]
13. Hovaguimian A, Gibbons CH. Clinical Approach to the Treatment of Painful Diabetic Neuropathy. Therapeutic advances in endocrinology and metabolism. Feb; 2011 2(1):27–38. [PubMed: 21709806]
14. Tesfaye S, Vileikyte L, Rayman G, et al. Painful Diabetic Peripheral Neuropathy: Consensus Recommendations on Diagnosis, Assessment and Management. Diabetes/metabolism research and reviews. Jun 21.2011
15. Kim HJ, Jung TS, Jung JH, et al. Improvement of glycemic control after re-emphasis of lifestyle modification in type 2 diabetic patients reluctant to additional medication. Yonsei medical journal. Mar 1; 2013 54(2):345–351. [PubMed: 23364966]

16. Conn VS, Hafdahl AR, Mehr DR, LeMaster JW, Brown SA, Nielsen PJ. Metabolic effects of interventions to increase exercise in adults with type 2 diabetes. Diabetologia. May; 2007 50(5): 913–921. [PubMed: 17342472]
17. Tanaka S, Tanaka S, Iimuro S, et al. Cohort Profile: The Japan Diabetes Complications Study: a long-term follow-up of a randomised lifestyle intervention study of type 2 diabetes. International journal of epidemiology. May 18.2013
18. Balducci S, Iacobellis G, Parisi L, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. Journal of diabetes and its complications. Jul-Aug;2006 20(4):216–223. [PubMed: 16798472]
19. Mueller MJ, Tuttle LJ, Lemaster JW, et al. Weight-bearing versus nonweight-bearing exercise for persons with diabetes and peripheral neuropathy: a randomized controlled trial. Arch Phys Med Rehabil. May; 2013 94(5):829–838. [PubMed: 23276801]
20. LeMaster J, Mueller MJ, Reiber GE, Mehr D, Conn VS, Madsen R. Effect of weight bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: the Feet First Randomized Controlled Trial. Physical therapy. 2008
21. Chen YW, Hsieh PL, Chen YC, Hung CH, Cheng JT. Physical exercise induces excess hsp72 expression and delays the development of hyperalgesia and allodynia in painful diabetic neuropathy rats. Anesthesia and analgesia. Feb; 2013 116(2):482–490. [PubMed: 23302966]
22. Lemaster JW, Mueller MJ, Reiber GE, Mehr DR, Madsen RW, Conn VS. Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial. Physical therapy. Nov; 2008 88(11):1385–1398. [PubMed: 18801859]
23. Toth C, Brady S, Gagnon F, Wigglesworth K. A Randomized, Single-Blind, Controlled, Parallel Assignment Study of Exercise Versus Education as Adjuvant in the Treatment of Peripheral Neuropathic Pain. The Clinical journal of pain. Jul 24.2013
24. Mayer CJ, Steinman L, Williams B, Topolski TD, LoGerfo J. Developing a Telephone Assessment of Physical Activity (TAPA) questionnaire for older adults. Preventing chronic disease. Jan.2008 5(1):A24. [PubMed: 18082013]
25. Cornblath DR, Chaudhry V, Carter K, et al. Total neuropathy score: validation and reliability study. Neurology. Nov 10; 1999 53(8):1660–1664. [PubMed: 10563609]
26. Billinger SA, Loudon JK, Gajewski BJ. Validity of a total body recumbent stepper exercise test to assess cardiorespiratory fitness. Journal of strength and conditioning research / National Strength & Conditioning Association. Sep; 2008 22(5):1556–1562. [PubMed: 18714232]
27. Billinger SA, Tseng BY, Kluding PM. Modified total-body recumbent stepper exercise test for assessing peak oxygen consumption in people with chronic stroke. Phys Ther. Oct; 2008 88(10): 1188–1195. [PubMed: 18772275]
28. American College of Sports M. ACSM's Guidelines for Exercise Testing and Prescription. 8. Philadelphia: Lippincott Williams & Wilkins; 2010.
29. Medicine ACoS, American Diabetes A. Joint Position Statement: Exercise and Type 2 Diabetes. Med Sci Sports Exerc. 2010; 42(12):2282–2303. [PubMed: 21084931]
30. American Diabetes A. Standards of Medical Care in Diabetes. Diabetes Care. 2012; 35(S1)
31. Hoffman D, Sadosky A, Dukes E, Alvir J. How do changes in pain severity levels correspond to changes in health status and function in patients with painful diabetic peripheral neuropathy? Pain. 2010; 149:194–201. [PubMed: 20303665]
32. Zelman D, Gore M, Dukes E, Kei-Sing T, Brandenburg N. Validation of a modified version of the Brief Pain Inventory for painful diabetic peripheral neuropathy. Journal of Pain and Symptom Management. 2005; 29(4):401–410. [PubMed: 15857744]
33. Fischer TZ, Waxman SG. Neuropathic pain in diabetes--evidence for a central mechanism. Nature reviews. Neurology. Aug; 2010 6(8):462–466. [PubMed: 20625378]
34. van Dijk JW, Manders RJ, Canfora EE, et al. Exercise and 24-h Glycemic Control: Equal Effects for All Type 2 Diabetic Patients? Medicine and science in sports and exercise. Nov 27.2012
35. Maiorana A, O'Driscoll G, Goodman C, Taylor R, Green D. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabetes research and clinical practice. May; 2002 56(2):115–123. [PubMed: 11891019]

36. Tessier D, Menard J, Fulop T, et al. Effects of aerobic physical exercise in the elderly with type 2 diabetes mellitus. Archives of gerontology and geriatrics. Oct 1; 2000 31(2):121–132. [PubMed: 11090907]

37. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA : the journal of the American Medical Association. Sep 12; 2001 286(10):1218–1227. [PubMed: 11559268]

38. Thorogood A, Mottillo S, Shimony A, et al. Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. The American journal of medicine. Aug; 2011 124(8):747–755. [PubMed: 21787904]

39. Sadosky A, Schaefer C, Mann R, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. Diabetes, metabolic syndrome and obesity : targets and therapy. 2013; 6:79–92.

Table 1

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

*VO_2R: Oxygen Reuptake Reserve

Each participant's individualized target heart rates were determined based on his/her VO_2R, and gradually progressed from 50% VO_2R to 70% by week 6. Length of each exercise session was also increased from 30 minutes to 50 minutes by week 7.

Table 2

Participant Characteristics

Age	57 ± 5.11 years
Years with Diabetes	12.2 ± 5.94 years
Race / Ethnicity	White (42.9%) African-American (21.4%) Hispanic (35.7%)
Years with DPN	7.2 ± 3.77 years
Gender	Male (35.71%) Female (64.29%)
Insulin Use	Yes (57.14%) No (42.86%)

Table 3

Changes in Pain Intensity Items in BPI-DPN (Median and Mean Values)

BPI-DPN Measure		Pre-Intervention	Post-Intervention	P-value (two-tailed Wilcoxon signed- rank test, $\alpha = 0.05$)
Pain Intensity (Worst)	Median	5.5±2.47	5.5±2.75	0.34
	Mean	5.68±2.47	5.21±2.75	
Pain Intensity (Least)	Median	3.0±1.84	2.5±1.74	0.10
	Mean	3.54±1.84	2.43±1.74	
Pain Intensity (Average)	Median	3.0±1.76	3.0±1.68	0.19
	Mean	4.04±1.76	3.29±1.68	
Pain Intensity (Now)	Median	3.0±2.22	2.5±1.79	0.13
	Mean	3.54±2.22	2.43±1.79	

* BPI-DPN: Brief Pain Inventory - Diabetic Peripheral Neuropathy

Table 4

Changes in Pain Interference Items in BPI-DPN (Median and Mean Values)

BPI-DPN Measure		Pre-Intervention	Post-Intervention	P-value (two-tailed Wilcoxon signed- rank test, α = 0.05)
General Activity	Median	4.5±2.91	2.0±2.80	0.08
	Mean	4.32±2.91	2.86±2.80	
Mood	Median	4.0±2.96	3.0±2.15	0.17
	Mean	4.14±2.96	3.0±2.15	
Walk	Median	5.0±3.03	4.0±2.89	0.016*
	Mean	4.93±3.03	3.29±2.89	
Normal Work	Median	6.0±3.32	3.0±3.04	0.032*
	Mean	5.39±3.32	3.79±3.04	
Relationship with Others	Median	3.5±3.53	1.5±1.27	0.006*
	Mean	3.96±3.53	1.29±1.27	
Sleep	Median	4.0±3.04	3.0±3.03	0.02*
	Mean	5.11±3.04	3.5±3.03	
Enjoyment of Life	Median	4.0±3.04	2.5±3.02	0.10
	Mean	4.68±3.04	3.21±3.02	
Average	Median	4.29±2.70	2.36±2.22	0.013*
	Mean	4.65±2.70	2.97±2.22	

BPI-DPN: Brief Pain Inventory - Diabetic Peripheral Neuropathy

* denotes a significant change

Table 5

Changes in Secondary Outcomes

	Pre-Intervention	**Post-Intervention**	**Change**	**P-value (Paired Student's t-test, α = 0.05**
Body Mass Index (BMI) [kg/m^2]	35.24±4.61	34.67±4.72	−0.57±1.20	0.10
Maximum Oxygen Uptake (VO_{2max}) [ml/kg/min]	16.02±3.84	17.18±4.19	1.16±1.68	0.028*
Systolic Blood Pressure [mmHg]	129.43±13.77	136.07±12.69	6.64±15.27	0.13
Diastolic Blood Pressure [mmHg]	74.57±10.35	77.29±8.22	2.71±8.50	0.25
Glycosolated Hemoglobin (HbA1c) [%]	7.59±2.11	7.73±1.93	0.14±0.83	0.51

* denotes a significant change