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The Effect of Exercise on Neuropathic Symptoms, Nerve Function, and Cutaneous Innervation in People with Diabetic Peripheral Neuropathy

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Abstract

Although exercise can significantly reduce the prevalence and severity of diabetic complications, no studies have evaluated the impact of exercise on nerve function in people with diagnosed diabetic peripheral neuropathy (DPN). The purpose of this pilot study was to examine feasibility and effectiveness of a supervised, moderately intense aerobic and resistance exercise program in people with DPN. We hypothesize that the exercise intervention can improve neuropathic symptoms, nerve function, and cutaneous innervation.

Methods—A pre-test post-test design was to assess change in outcome measures following participation in a 10-week aerobic and strengthening exercise program. Seventeen subjects with diagnosed DPN (8 males/9 females; age 58.4 ± 5.98 ; duration of diabetes 12.4 ± 12.2 years) completed the study. Outcome measures included pain measures (visual analog scale), Michigan

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Neuropathy Screening Instrument (MNSI) questionnaire of neuropathic symptoms, nerve function measures, and intraepidermal nerve fiber (IENF) density and branching in distal and proximal lower extremity skin biopsies.

Results—Significant reductions in pain (-18.1 ± 35.5 mm on a 100 mm scale, $p=0.05$), neuropathic symptoms (-1.24 ± 1.8 on MNSI, $p=0.01$), and increased intraepidermal nerve fiber branching ($+0.11 \pm 0.15$ branch nodes/fiber, $p=-.008$) from a proximal skin biopsy were noted following the intervention.

Conclusions—This is the first study to describe improvements in neuropathic and cutaneous nerve fiber branching following supervised exercise in people with diabetic peripheral neuropathy. These findings are particularly promising given the short duration of the intervention, but need to be validated by comparison with a control group in future studies.

Keywords

Exercise; Diabetic Peripheral Neuropathy; Intraepidermal nerve fiber density; Pain

Diabetic peripheral neuropathy (DPN) is a common complication of type 2 diabetes and is present in approximately one-third of people with diabetes aged 40 or older in the US. The most common form of DPN is a symmetrical distal degeneration of peripheral nerves combined with impaired nerve regeneration, with widespread involvement of both large and small nerve fibers that can lead to symptoms of pain and sensory loss. Pain is a primary complaint in approximately 1/3 of people with DPN. The sensory loss associated with DPN contributes to impaired balance and gait, and increased susceptibility to lower extremity injury and amputation.

It is well-established that lifestyle changes including healthy diet and exercise can significantly reduce the prevalence of diabetes and complications such as neuropathy. Recent large, randomized controlled trials have established that a combination of aerobic and resistance exercise improves physical fitness, glycemic control and insulin sensitivity in older adults and in people with diabetes. Exercise has long been recognized as a part of therapy in the management of diabetes, yet 31% of type 2 diabetic patients fail to participate in basic physical activity, and people with DPN may have difficulty participating in weight-bearing exercise because of pain or absent sensation. Although recent findings indicate that exercise may improve balance and trunk proprioception in people with DPN, no studies have directly evaluated the impact of exercise on nerve function in people with established DPN.

The effect of a 12-month healthy lifestyle intervention (dietary counseling and 150 minutes per week of unsupervised exercise) was investigated in subjects with neuropathy and pre-diabetic levels of impaired glucose tolerance. Several large-fiber and small-fiber outcome measures were assessed, but proximal intra-epidermal nerve fiber (IENF) density and foot sweat volume measured by quantitative sudomotor axon reflex testing (QSART) were the only measures of neuropathy noted to improve significantly following the intervention. Balducci et al. compared nerve function in people with diabetes (without neuropathy) who participated in a 4-year intense, individually prescribed and supervised aerobic exercise to control subjects with no intervention. The exercise group had improved large fiber outcome measures (nerve conduction velocity and vibration threshold), with fewer subjects developing neuropathy over the 4-year study. Although these results are encouraging, a 2010 update of a Cochrane database systematic review on the topic of “Exercise for People with Peripheral Neuropathy” concluded that there is a lack of high-quality evidence to evaluate the effect of exercise in people with peripheral neuropathy.

Exercise may positively influence the pathological factors associated with neuropathy by promoting microvascular dilation, reducing oxidative stress, and increasing neurotrophic factors, but it is unknown whether exercise will improve or worsen the signs and symptoms of DPN. The purpose of this pilot study was to examine feasibility of a supervised, moderately intense aerobic and resistance exercise program in people with diagnosed DPN. Our hypothesis was that the exercise intervention would improve neuropathic symptoms, nerve function, and cutaneous innervation.

RESEARCH DESIGN AND METHODS

A pre-test post-test design was used for this pilot study, with all subjects participating in the intervention. This study was approved by the Human Subjects Committee/Institutional Review Board of the [blinded].

Subjects

Participants with self-reported diagnosis or symptoms of diabetic neuropathy (age 40–70) were recruited for the study. Several recruitment methods were utilized, including flyers posted in the community, broadcast emails, physician referrals, and contacting individuals in our lab database.

Prior to enrollment in the study, a clinical exam was performed by a neurologist (M.P.) to confirm the presence of DPN. As our participants had both signs and symptoms of DPN, they would be classified as “probable clinical distal sensorimotor polyneuropathy” as defined by the Toronto Expert Panel on Diabetic Neuropathy. Although we did perform nerve conduction studies on all of our participants, this was not used as the criteria for diagnosing or staging neuropathy severity in this study. Eligible subjects were enrolled into the study if they did not present with any of the following, as confirmed via communication with primary care provider: 1) serious cardiac pathology or musculoskeletal problems that would limit exercise ability; 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); or 6) history of lidocaine allergy. If eligible for the study, subjects were invited to participate and signed an institutionally-approved informed consent form. Subjects were offered a stipend of \$75 after completion of the intervention and the testing sessions to help offset transportation and other expenses.

Intervention

A 10-week exercise program with both aerobic and strengthening components, based on the American College of Sports Medicine Guidelines, was individually prescribed and is described in Table 1. The exercise intervention was supervised by individuals with basic cardiac life support certification and health professional training (e.g. physical therapists, exercise physiologists, medical students, or physical therapy students). These individuals monitored blood glucose level, blood pressure, heart rate, and rate of perceived exertion (RPE) during each exercise session.

Prior to beginning the intervention, subjects participated in a maximal graded exercise test using a cycle ergometer with a metabolic cart (Parvo Medics TrueOne 2400) and integrated ECG. The maximal workload obtained from this test was used to calculate a moderate level of intensity (50–70% of VO_2 reserve) for the aerobic training program.

Each exercise session included light stretching to warm up, followed by the aerobic or strengthening exercise. A variety of cardiovascular training equipment was available to subjects, including total body recumbent steppers (Nustep), upright cycle, recumbent cycle,

elliptical trainer, and treadmill (LifeFitness). Participants were encouraged to utilize different equipment over the course of the 10-week program, although subjects with absent protective sensation were encouraged to avoid repetitive weight-bearing activities such as treadmill walking.

Subjects performed strengthening exercises with resistance levels for each machine gradually increased to maintain RPE in a moderate range (7–8 out of 10) for each subject. Strength training included each of the following exercises: abdominal curls, biceps curls, chest presses, lat pulldowns, leg extensions, seated leg curls, seated rows, shoulder presses, squats, and triceps presses (LifeFitness).

Outcomes

Body mass index (BMI) and glycosylated hemoglobin (HbA1c) were assessed before and after the 10-week intervention, along with measures of neuropathic symptoms, peripheral nerve function, and cutaneous innervation:

1. Pain using an unmarked 100-mm visual analog scale to indicate the level of “current pain”, “usual pain over the past month”, and “worst pain over the past month”.
2. Michigan Neuropathy Screening Instrument (MNSI) symptom questionnaire with yes/no responses to 15 items to indicate the frequency and severity of neuropathic symptoms.
3. MNSI physical exam score to indicate abnormalities in the appearance of the feet, vibration sense, reflexes, and monofilament sensation.
4. Nerve conduction studies (NCS) of the sural, peroneal, and tibial nerves of the right lower extremity, including nerve conduction velocity, motor action potential amplitude, and latency (VikingQuest, Nicolet Biomedical).
5. Quantitative sensory testing (QST) of vibratory detection threshold, cooling detection threshold, and heat/pain threshold (TSA-II NeuroSensory Analyzer, Advanced Medical Systems).
6. Intraepidermal nerve fiber (IENF) density and epidermal axon branching from skin biopsies. The 3 mm punch skin biopsies were performed after injection of 2% lidocaine using sterile technique. Biopsies were obtained from the right leg proximally at the lateral thigh (20 cm from the iliac spine) and the distal part of the lateral ankle (10 cm above the lateral malleolus). The tissue was placed in freshly prepared Zamboni’s fixative (15% picric acid, 4% paraformaldehyde) for one hour, frozen and sectioned on a cryostat at 50 μ m, and processed for immunohistochemistry using rabbit anti-PGP9.5 primary antibody (1:3000; Chemicon, Temecula, CA). IENF density was quantified according to published guidelines (Lauria et al. 2010) by recording the linear IENF density (number of fibers/mm) in 3 separate sections. Epidermal fibers were recorded only if they were viewed to cross or originate at the dermal-epidermal junction. Axonal, branching was reported as the number of branch nodes per axonal fiber. All IENF processing and counting was performed by an experienced technician blinded to timing of tissue collection as pre- or post-test. It should be noted that biopsies were processed soon after they were acquired, so pre- and post-exercise biopsies were not processed at the same time.

Statistical Analysis

Analyses were performed using SPSS 16.0 for Windows. For each of the outcome measurements, descriptive statistics (mean, standard deviation) were calculated and scatter plots were examined visually to find outliers potentially caused by data entry or other errors. Normal distribution of variables was confirmed through visual analysis of histograms, calculations of skewness indices, and the Kolmogorov-Smirnov Z statistic for baseline data. The use of parametric statistical tests was justified for this small data set, as no significant difference was found between a normal distribution and the distribution of each variable, with a probability of the Z statistic more than 0.05 in all cases (range, 0.06 to 0.96). The pre-intervention and post-intervention scores were compared using a 2-tailed paired t test, with significance set at $\alpha = 0.05$.

RESULTS

Subjects

Informed consent forms were signed by 30 individuals, and 19 subjects completed the intervention. Three subjects were disqualified during baseline testing because of health issues that prevented participation in the exercise test ($n=2$) or the absence of neuropathic signs or symptoms ($n=1$). Six subjects withdrew before starting the intervention because of schedule conflicts or transportation issues. Two subjects withdrew because of the onset of medical issues that interfered with exercise participation (chronic bronchitis, pulmonary hypertension). No serious unanticipated adverse events occurred with testing or intervention (e.g. Grade 3 or 4 on the CTC III Common Toxicity Criteria Reporting Guidelines). The most common Grade 2 adverse events (mild severity requiring minimal intervention) included: hyperglycemia or hypoglycemia prior to exercise; high resting blood pressure prior to exercise; pain in legs, knees, back, or hands with exercise; pain or itching at biopsy site. No infection or delayed healing noted at any biopsy site, and no foot ulcerations were noted during the study.

Two subjects completed post-testing although they participated in $<75\%$ of the sessions; therefore their data was not included in the analysis. One subject missed several exercise sessions because of leg pain, another missed exercise sessions for a variety of reasons including hyperglycemia and doctor's appointments.

The 17 subjects (8 males, 9 females) who participated in $>75\%$ of the intervention (average attendance = 95%) had a mean age of 58.4 ± 5.98 years, and were diagnosed with diabetes an average of 12.4 ± 12.2 years previously. All subjects were taking prescribed hypoglycemic agents, and 24% (4/17) were on insulin. The race of these subjects was primarily white (15/17 or 88%), with 1 (6%) African American, and 1 (6%) not indicated. Hispanic ethnicity was reported in 3 (17%) subjects. The subjects had a baseline aerobic fitness of 17.2 ± 5 ml/kg/m. Four subjects (24%) had absent sural nerve function at baseline, and a majority of participants (10 out of 17, or 59%) had painful neuropathy, as defined by the neurologist's clinical determination of "prominent complaint of burning or pain in both feet for the past 6 months".

Outcomes

Changes in selected outcome measures following the intervention are presented in Table 1. Subjects were obese at entry into the study, and no change in BMI, waist circumference, or waist:hip ratio were found following the intervention. Baseline HbA1c indicated moderate control of diabetes (7.8%), with significant improvement following the intervention (7.1%, $p=0.031$).

Significant improvements were found in ratings of the worst pain over the past month (62.4 to 44.3mm, $p=0.05$), MNSI symptom score (5.2 to 4 points, $p=0.01$), and IENF branching at the proximal biopsy site (0.16 to 0.27 branch nodes/fiber, $p=0.008$). Individual results of changes in neuropathic symptoms and IENF branching are presented in Figures 1–3. No significant changes in any of the nerve conduction study or quantitative sensory testing outcomes were found following the intervention.

CONCLUSIONS

This is the first study to describe improvements in outcomes related to neuropathic symptoms and cutaneous nerve fiber branching following supervised exercise in people with diabetic peripheral neuropathy. The exercise intervention was feasible for the subject participants screened using the study criteria, as the study was completed by 63.3% of subjects who signed the consent form, and no serious unanticipated adverse events occurred with maximal or submaximal levels of exercise.

Despite the short duration of our study, 10-weeks of exercise significantly improved selected measures of peripheral nerve function (“worst” pain levels and MNSI score), glycemic control (HbA1c), and resting heart rate. The reduction in pain and neuropathic symptoms support feasibility of an exercise intervention in people with DPN, as it was previously unknown whether exercise would increase pain or neuropathic symptoms. The pain assessment measures asked participants to reflect on their pain levels over the past month, which may have underestimated improvements in pain during this 10-week intervention. Further, the lack of a control group in our study limits the interpretation of improvement in symptoms, as we can not rule out a possible Hawthorne effect of attention. An important next step in this research would be to include a non-exercise control group with equivalent attention.

At baseline, the participants in this study had DPN of varying severity, with decreased IENF density in comparison to recently published normative values. Our participants had a distal IENF density of 3.83 fibers/mm, compared to a median of 8.9 – 9.8 in healthy 50–59 year olds. In fact, our participants were within the 5th percentile cut off values of 3.5 – 4.3 for healthy subjects in this age range, used for diagnosis of small fiber neuropathy. Significant improvements were observed following exercise in the number of branches per fiber in the proximal biopsy site, although no significant improvements were noted in the distal IENF measures or proximal IENF density. This may reflect less extensive damage in proximal nerve fibers, or earlier response of these fibers to exercise-induced plasticity in a 10-week intervention. Although the change in IENF density was not statistically significant, the observed increase in this measure is consistent with modest 30% increase in IENF density following 1 year of lifestyle intervention (Smith et al. 2006). Another study with a 4-year intervention of supervised, moderately intense (50–85% of heart rate reserve) treadmill exercise in participants with diabetes but no neuropathy found improved nerve conduction measures compared to the no-exercise the control group. These subjects did not have pain or neuropathic symptoms at baseline, and the researchers did not assess IENF measures via skin biopsy. Future studies may benefit from counting branching and/or fragments of epidermal axons, as current guidelines of IENF quantification may limit the ability to detect important changes in epidermal interventions such as exercise. Finally, it should be noted that biopsies from pre- and post-exercise time points were not processed and evaluated together, which could add potential bias to the quantification of IENF density. Future studies should be designed to avoid this potential bias by processing biopsies before and after the intervention at the same time.

As expected, the participants who completed the intervention in our study had significant improvements in HbA1c and resting heart rate. Moderately intense levels of aerobic and resistance training have been found to be effective at improving glycemic control in older adults and in people with diabetes. In fact, our subjects demonstrated similar improvement in A1C levels to that reported in a meta-analysis of 14 randomized controlled trials of exercise intervention for people with diabetes. As the A1C measure gives an indication of glycemic control over the previous 3 months, the change following a 10-week intervention may be underestimated.

The baseline aerobic fitness for our subjects is classified as “very poor”, less than the lowest 1 percentile of VO₂max levels for healthy men and women in either age 50–59 or age 60–69 comparison groups. VO₂max levels below the 20th percentile are associated with increased risk of death from all causes. Although we did not perform a second maximal exercise test to determine change in aerobic fitness following the intervention, the significant reduction in resting heart rate may reflect increased cardiovascular efficiency.

In addition to the short duration of the intervention, the limitations of our study include the small sample size, lack of a control group, and limited knowledge of potential mechanisms for the observed improvements in neuropathic symptoms and cutaneous innervation. The mechanisms are likely multi-factorial and may include the direct effect of improved glycemic control on nerve fibers, change in vascular function, body composition changes, or psychological/social factors.

In conclusion, this pilot study of a 10-week supervised aerobic and resistance exercise program found significant improvements in measures of pain, neuropathic symptoms, and cutaneous fiber branching in people with diabetic peripheral neuropathy. These promising findings support the need for future research in this area to explore the long-term effects and possible mechanisms of these changes.

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Figure 1. Individual change in neuropathic symptom scores using the Michigan Neuropathy Screening Instrument questionnaire. Pre-intervention measures are labeled as #1 and post-intervention measures are labeled as #2; exercise duration was 10 weeks.

Figure 2. Individual change in intraepidermal nerve fiber (IENF) branching at proximal biopsy site. Pre-intervention measures are labeled as #1 and post-intervention measures are labeled as #2; exercise duration was 10 weeks.

Figure 3. Increased cutaneous nerve fibers after exercise in an individual subject with DPN. PGP 9.5+ fibers (arrows) in the epidermis before (A) and after (B) 10 weeks of exercise. Scale bar equals 50 μm .

Table I

Description of progressive exercise training program.

WEEK	AEROBIC EXERCISE	RESISTANCE EXERCISE	DAYS/WK
1	30 minutes, 50% VO_2R $\times$ 2 days	10 reps $\times$ 1 day	3
2	35 minutes, 50% VO_2R $\times$ 1 day	10 reps $\times$ 1 day, 15 reps $\times$ 1 day	3
3	35 minutes, 50% VO_2R $\times$ 2 days	15 reps $\times$ 1 day	3
4	40 minutes, 50% VO_2R $\times$ 2 days	15 reps $\times$ 2 days	4
5	40 minutes, 60% VO_2R $\times$ 2 days	15 reps $\times$ 2 days	4
6	45 minutes, 60% VO_2R $\times$ 2 days	15 reps $\times$ 2 days	4
7	45 minutes, 60% VO_2R $\times$ 2 days	20 reps $\times$ 2 days	4
8	45 minutes, 70% VO_2R $\times$ 2 days	20 reps $\times$ 2 days	4
9	50 minutes, 70% VO_2R $\times$ 2 days	20 reps $\times$ 2 days	4
10	50 minutes, 70% VO_2R $\times$ 2 days	20 reps $\times$ 2 days	4

 VO_2R = reserve aerobic capacity, reps = repetitions

Table II

Change in outcome measures before and after the exercise intervention.

		Pre-intervention	Post-intervention	<i>P</i> value
	Body mass index, kg/m ²	35.3±5.7	3.53±5.5	0.95
	Waist circumference, cm	114±10.4	113.8±9.5	0.41
	Waist:Hip ratio	0.94±0.11	0.95±0.11	0.86
	HbA1c, %	7.8±1.0	7.28±0.83	0.031*
	Resting heart rate, bpm	77.3±8.2	72±9.6	0.036*
Symptoms	Pain (current), mm	15.1±9.6	9.9±14.8	0.26
	Pain (usual), mm	34.7±23.4	23.6±21.9	0.11
	Pain (worst), mm	62.4±26.7	44.3±35.1	0.05*
	Symptom score (MNSI)	5.24±1.4	4±2	0.01*
	Physical exam score (MNSI)	3.03±1.3	2.94±1.7	0.78
Nerve conduction	Sural nerve amplitude, μ V	6.41±5.9	5.59±5.14	0.35
	Sural nerve latency, ms	2.99±1.8	2.69±1.8	0.23
	Peroneal nerve amplitude, mV	4.48±2.5	4.53±2.6	0.85
	Peroneal nerve latency, ms	4.1±1.25	4.1±1.17	1.0
	Peroneal nerve conduction velocity, m/s	39.6±11.5	38.9±10.9	0.46
	Tibial nerve amplitude, mV	6.66±5.3	6.6±5.2	0.85
	Tibial nerve latency, ms	3.63±1.04	3.69±1.13	0.58
	Tibial nerve conduction velocity, m/s	35.1±10.8	38.4±10.8	0.71
QST	Heat pain threshold, °C	46.8±2.97	46.3±2.68	0.076
	Cooling detection threshold, °C	27.7±4.8	27.8±3.2	0.76
	Vibration detection threshold, dB	35.9±36	33.5±39.9	0.71
Cutaneous	IENF density (proximal), fibers/mm	8.56±4	10.24±5.3	0.09
	IENF branching (proximal), branch nodes/fiber	0.16±0.15	0.27±0.19	0.008*
	IENF density (distal), fibers/mm	3.83±3.3	3.85±3.7	0.99
	IENF branching (distal), branch nodes/fiber	0.09±0.12	0.12±0.13	0.4

P 0.05 with 2-tailed, paired *t* test. MNSI = Michigan Neuropathy Screening Instrument.

QST = Quantitative Sensory Testing. IENF = Intraepidermal nerve fiber.