Pilot Study of Exercise and Peripheral Nerve Function in People with Diabetes

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Background

- Diabetes is a leading cause of adult disability in the United States.[1]
- Diabetic neuropathy (DN) is a complication of Type 1 and Type 2 diabetes in over 50% of people who have had the disease for 20 years.[2]
- The most common form of DN is a symmetrical distal degeneration of peripheral nerves combined with impaired nerve regeneration leading to impaired balance, altered gait patterns, and increased risk of falling [2]. increased susceptibility to injury, gangrene, and amputation.[3]
- Several studies have demonstrated improved glycemic control following aerobic and resistance exercise in people with diabetes, yet participation in regular physical activity remains an underutilized therapy.[4]
- Because of complications associated with regular exercise, including foot ulceration, few studies have looked at the effectiveness of exercise in people with diabetic neuropathy.[5]

Summary of Preliminary Studies

- Our preliminary work evaluated ankle proprioception and cutaneous innervation in people with Type 2 Diabetes.
- Our lab reported the following proprioceptive baseline measures on a sample of 26 participants (n=9 healthy subjects; n=9 diabetic with neuropathy and n=3 diabetic with no neuropathy). Table 1 illustrates the error on proprioceptive testing at 2 different ankle positions. We found a significant difference between nondiabetic and diabetic without neuropathy (one-way ANOVA).

Table 1

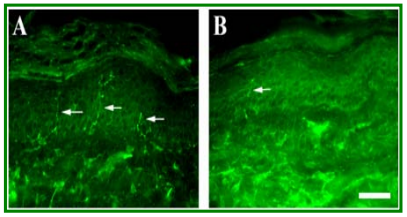
	15°	30°
Nondiabetic (n=12)	3.11 +/- 1.5	3.97 +/- 2.13
Diabetic with neuropathy (n=8)	*6.17 +/- 3.6	5.62 +/- 3.0
Diabetic without neuropathy (n=6)	3.11 +/- 1.2	3.29 +/- 2.0

- Furthermore, skin biopsy data (Table 2) demonstrated a significant difference in Intra Epidermal Nerve Fibers (IENF) from nondiabetic and diabetic without neuropathy (one-way ANOVA).

Table 2

	IENF
Nondiabetic (n=9)	19.16 ± 5.01 SEM
Diabetic with neuropathy (n=9)	*4.06 ± 4.19 SEM
Diabetic w/ no neuropathy (n=3)	13.71 ± 12.90 SEM

- A subset of patients in this preliminary study (20) had a 3mm skin biopsy above the ankle. This biopsy tissue was processed for immunocytochemistry to quantify intraepidermal nerve fiber (IENF) density by Dr. Wright's laboratory (Fig. 1).



Purpose

The purpose of our current study is to initiate an exercise intervention that will improve nerve function and cutaneous innervation in people with diabetic neuropathy.

Methods

- A pre-test post-test design has been used for this pilot study, with all subjects participating in the intervention.
- Clinical neurological examination performed by Dr. Pasnoor
- Quantitative sensory testing (TSA-II NeuroSensory Analyzer, Advanced Medical Systems)
- Nerve conduction velocity studies
- Proprioceptive control by measuring passive joint position sense on the dominant ankle joint using an isokinetic dynamometer (Pic 1,2).

Picture 1

Picture 2

Subjects

- Thirty participants with diabetic neuropathy (age 40-70), will be recruited for this study through flyers posted in the community (e.g. at the local ADA chapter offices, at diabetes support group meetings, in the Cray Diabetes Center, in Wyandotte County safety net clinics, and in other physician offices).
- To date, 6 subjects have been recruited and began the intervention. Their baseline measurements are found in Table 3.

Table 3

Subject	Age	Sex	Weight (kg)	HbA1c	Peroneal Nerve Conduction	VO_2 Peak ml/kg/min
1	48	F	140	7	40m/s	12.0
2	55	M	104	8.4	46m/s	16.0
3	64	M	98	7.8	40m/s	24.7
4	64	M	99	7.3	40m/s	28.6
5	59	F	74	5.6	47m/s	16.4

Intervention

- A 10-week exercise program, supervised by members of the research team, is individually prescribed, supervised, and progressed. Subjects initially participate 3 times each week, and progress to 4 times each week.
- Intensity is based on a a maximal graded exercise test. The maximal workload obtained from this test is used to calculate a moderate level of intensity (50-70% of VO2 reserve) for the aerobic training program.
- Exercise sessions include stretching to warm up, aerobic or strengthening exercise, and cool down (Picture 3).
- Exercise sessions are progressed from 30 to 50 minutes based on the American College of Sports Medicine Guidelines[6] (Picture 4). A 10 repetition maximum weight will be established for each subject will be gradually progressed to 20 (Picture 5 and 6).
- Resting blood pressure, heart rate, and rate of perceived exertion (RPE) will be monitored for every subject before, during, and following the aerobic activity. Participants will perform a blood glucose check prior to each exercise session and will not exercise if values are below 70 or above 250.[4]

Picture 3

Picture 4

Picture 5

Picture 6

Outcome Measures

- Nerve function will be characterized at baseline and following the intervention by Quantitative sensory testing (QST), and nerve conduction studies (NCS) of the sural, peroneal, and tibial nerves
- Quantitative proprioception testing measure passive joint position sense on the dominant ankle joint using an isokinetic dynamometer (Biodex Medical systems Inc, Shirley, NY).
- Total dermal and epidermal innervation will be quantified with a punch skin biopsy from distal lateral ankle and the proximal lateral thigh using a 3 mm disposable circular punch (Miltex, York, PA).
- The tissue will be sectioned at 50 µm and processed for immunohistochemistry using rabbit anti-PGP9.5 primary antibody (1:3000; Chemicon, Temecula, CA). In addition, sections will be coded in order to carry out the analysis in a blinded fashion and quantified.

Implications

Such exercise interventions may be an efficient and cost effective way to increase proprioceptive sense and neuronal innervation in participants with Type 2 Diabetic Neuropathy.

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