



E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2021; 3(1): 469-472
Received: 22-05-2020
Accepted: 24-06-2020

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The effect of therapeutic exercise on the treatment of symptoms and the delay of foot degeneration in patients with diabetic peripheral neuropathy: An evidenced-based physiotherapy review

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DOI: <https://doi.org/10.22271/27069567.2021.v3.i1h.184>

Abstract

Diabetic peripheral neuropathy (DPN) is a common complication of type 2 diabetes. It presents with a symmetrical peripheral degeneration of peripheral nerves. Pain is a major complaint in about 1/3 of people with DPN and DPN-related sensory loss contributes to impaired balance, gait problems, and increased sensitivity to injury. Recent research has shown that a combination of aerobic exercise and resistance training improves fitness, glycemic control and insulin sensitivity in older adults and people with diabetes. The aim of this review was to investigate the effect of exercise on improving the symptoms of patients with DPN and delaying the onset of foot degeneration. The PubMed and Science Direct databases were searched with the following keywords: Diabetic neuropathy, therapeutic exercise, physiotherapy, rehabilitation. The results of this review suggest that exercise can improve the symptoms of DPN by reducing pain as well as improving gait accuracy, enhancing lower limb strength and improving the quality of daily life of patients. Aerobic exercise seems to be the type of training that provides the most benefits. There is also evidence that exercise in diabetic patients may either prevent or delay the onset of peripheral neuropathy. However, further clinical trials are required.

Keywords: Diabetic neuropathy, therapeutic exercise, physiotherapy, rehabilitation

Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes and occurs in about 1/3 of people with diabetes aged 40 and over in the USA ^[1], with lower limb pain and loss of sensation caused by slow degeneration of peripheral nerves. The most common form of DPN is symmetrical peripheral degeneration of peripheral nerves combined with their attenuated regeneration ^[2]. As a consequence of DPN, people with long-term diabetes may have pain or significant deficits in tactile sensitivity, vibration and lower limb joint proprioception. These sensory deficits can contribute to impaired balance and gait, with an increased risk of falls, lower limb injury and amputation ^[3-5]. People with DPN are more likely to be inactive and less mobile ^[6].

Recent studies have shown that exercise has specific benefits in terms of glycemic control in people with DPN ^[1] as well as in the reduction of pain and sensory disorders. However, the research is small-scale and its results are controversial. In general, exercise in older adults with DPN has been shown to increase activity levels and improve their quality of life ^[7], improves balance, reduces the risk of falls ^[8], helps reduce fatigue and improve cardiovascular fitness, improves sleep quality, helps control body weight, plasma and vascular function. However, the results of the exercise in terms of the treatment of the symptoms as well as the treatment of the lesions resulting from the specific disorder in many areas are controversial, while there is often ambiguity regarding the type, intensity and dosage of the provided exercise ^[9]. The aim of this review was to investigate the effect of exercise on improving the symptoms of patients with DPN and delaying the onset of foot degeneration.

Method

The PubMed and Science Direct databases were searched with the following keywords: Diabetic neuropathy, therapeutic exercise, physiotherapy, rehabilitation.

This review included both clinical studies and systematic reviews applied to patients with DPN and in which at least one of the interventions contained exercises both individually and in combination with other therapies.

Literature review

The main findings of our review are analyzed below. Kluding *et al.* [6] conducted a small-scale study to investigate the side effects during moderate-intensity aerobic exercise in people with DPN. The aim of their research was also to study the changes in fatigue, aerobic fitness and other results after the intervention. Participants were 18 inactive people with type 2 diabetes and peripheral neuropathy (mean age = 58.1 years, SD = 5). They underwent a controlled 16-week aerobic exercise program (three times a week with an oxygen uptake reserve of 50% to 70%). The quality of sleep, maximal oxygen consumption ($\dot{V}O_2$ max), metabolic changes of the plasma, fatigue with the Multidimensional Fatigue Inventory, body mineral density with spectral imaging and function of the peripheral vascular system were the primary outcome measures of the study. The results of the measurements showed improvements in general fatigue, physical fatigue, $\dot{V}O_2$ max, total body fat, fat mass and peripheral blood flow. Although this research was a small-scale, non-experimental study, and the generalization of its results raises many questions, the authors state that it provides new data on the effect of supervised aerobic exercise on people with DPN. However, as the authors also note, it is important for physiotherapists to carefully prescribe the initial intensity of exercise and to closely monitor and properly train their patients to deal with side effects in the early stages of exercise in inactive individuals with DPN.

Furthermore, Kluding *et al.* [1] conducted a pilot study to evaluate the effect of a 10-week resistance and endurance program on 17 people diagnosed with DPN (eight men and nine women, age 58.4 ± 5.98 , duration of diabetes 12.4 ± 12.2 years). Lower limb biopsies were performed before and after the intervention to assess the density and branching of intraepidermal fibers. Other measurements that were taken at the same time points included the general function of the nerves in the area and pain, which was assessed with the Visual Analog Scale and the Michigan Neuropathy Screening Instrument questionnaire. The results showed significant reductions in pain, improvement of neuropathic symptoms and improvement of intraepidermal nerve fiber branching from a proximal skin biopsy. This was the first study to describe improvements in neuropathic and cutaneous nerve fiber branching following supervised exercise in people with DPN. These findings are particularly promising given the short duration of the intervention, but need to be validated compared to a control group in a future larger-scale study.

In another study, Seyedizabeh *et al.* [13] focused on the effects of combined resistance-aerobic training on serum kinesin-1 and physical function in patients with type 2 diabetes and DPN. The study involved 24 women with DPN, who were randomly divided into two groups (intervention and control). The intervention group followed a combined resistance-aerobic exercise program for a total of eight weeks with three sessions performed in that time span. Regarding the exercise protocol, it was divided into two parts. The aerobic exercises had a duration of three minutes and 5-10 repetitions per set (30 seconds of rest

between each set) and were performed at 50-65% of heart rate reserve (HRR). The resistance training contained a variety of relevant exercises at 6-7 stations. Each exercise included 8-12 repetitions with 2-3 sets (3-5 minutes of rest between each set). The results showed that kinesin-1 levels and aerobic endurance improved after eight weeks of combined exercise. However, this improvement was not overall statistically significant. More specifically, the lower body strength improved significantly, in contrast to the upper body strength, which did not exhibit significant change. In reference to change, the combined exercise program caused small adjustments, which can prove beneficial due to DPN being a progressive condition.

In the study of Handsacer *et al.*, [11] the authors report that patients with diabetes and DPN place their feet less accurately while walking, which may contribute to an increased risk of falling. In a clinical study, they examined the efficacy of a combined exercise program in the gait accuracy of patients with diabetes and DPN. The 29 participants included eight patients with DPN, 11 patients with diabetes but no neuropathy and 10 healthy adults. Gait accuracy was measured before and after the intervention through a small stepping walkway, comprising of six stepping targets. The duration of the intervention was 16 weeks with one-hour weekly sessions. The program implemented included high-intensity resistance exercises and visual-motor training. The results of this study showed that both diabetic patients with DPN and diabetic patients without DPN, who participated in the intervention, improved their gait accuracy compared to healthy participants, in whom no significant differences in gait accuracy were found. Exercise for improved gait accuracy is, according to researchers, an effective method of training to improve gait stability in people with DPN and can help reduce the risk of falls.

The study of Balducci *et al.* [12] studied the effects of long-term exercise on the treatment or onset delay of DPN in type 1 and 2 diabetic patients. The study included 78 diabetic patients without peripheral DPN signs and symptoms. The participants were randomized into two groups. The first group (exercise group) consisted of 31 diabetic participants who followed a supervised exercise protocol that included brisk walking one hour four times a week on a treadmill at 50-85% HRR. Η 2^η ομάδα αποτελούνταν από 47 διαβητικούς; The second group consisted of 47 diabetic patients who did not receive any treatment. This study had a duration of four years. Vibration perception threshold, nerve distal latency, nerve conduction velocity, and nerve action potential amplitude in the lower limbs were evaluated before and after treatment. The percentage of diabetic patients who developed motor neuropathy and sensory neuropathy during the four years of the study was significantly higher in the control group than the exercise group (17% vs. 0.0%, $p < .05$ and 29.8% vs. 6.45%, $p < .05$ respectively). In conclusion, this study noted that long-term aerobic exercise training can prevent the onset or modify the course of development of DPN.

Lindberg *et al.* [14] studied the effect of a weight-free exercise program on people with severe peripheral neuropathy and diabetic foot ulcers. The participants were five men (mean (SD) age 68.2 (7.1) years) with diabetes, severe DPN and active foot ulcer, who participated in a 10-week exercise program. Adherence to the program, patient satisfaction, healing of foot ulcers, side effects, ability to

perform activities of daily living and changes in muscle strength were assessed before and after the intervention. According to the results of the study, all participants completed the program with session attendance at 85-95% and with high satisfaction. Only minor side effects occurred, while ulcers decreased in all participants. The distance on the stationary bike improved from an average of 3.30 (1.1) to 5.36 (0.5) kilometers. The ability to perform in self-selected activities of daily living was improved, while the maximal isometric muscle strength of the knee extension was improved by 23%. The authors concluded that a weight-free exercise program for people with diabetes, severe DPN and foot ulcers seems feasible and safe. Further studies are needed to confirm these findings.

In a systematic review/meta-analysis, Melese *et al.* [15] examined the effect of therapeutic exercise on gait in patients with DPN. The researchers analyzed nine randomized controlled trials with 370 participants. Eight of these studies demonstrated the efficacy of exercise and improvement in gait in people with DPN. The findings of this study showed that the implementation of combined exercise programs that included resistance training and range of motion exercises in balance and flexibility significantly improves gait in people with DPN.

Aerobic exercise improves vascular endothelial function in people with type 2 diabetes. There is little information available on vascular health in people with type 2 diabetes and DPN. So, Billinger *et al.* [16] conducted a study whose primary goal was to determine whether a 16-week aerobic exercise intervention could improve vascular health in people with type 2 diabetes and DPN. A secondary objective was to investigate the relationship between changes in flow-mediated dilation and the number of years since the diagnosis of DPN. The measurements showed that aerobic exercise was beneficial in improving vascular health measures, but these were not statistically significant. The size of the change depends on the length of time since the onset of DPN.

The effect of aerobic exercise on pain in people with DPN was the focus of the study of Yoo *et al.* [10] The study included 14 sedentary individuals (mean age 57 ± 5.11 years) with painful DPN, who participated in a 16-week supervised aerobic exercise program. The Brief Inventory Pain-Diabetic Peripheral Neuropathy questionnaire for assessing pain intensity and reduced functioning in daily life, body mass index (BMI), hemoglobin A1c (HbA1c) and blood pressure were assessed before and after the intervention. The results of the study showed a reduction in pain when walking, at work and during sleep. $\dot{V}O_2$ max increased significantly after the intervention, while BMI, HbA1c and blood pressure remained unchanged. These preliminary results suggest that perceived interference with pain may be reduced after an aerobic exercise intervention in people with painful DPN. Further research is needed to determine the exact effects of exercise.

Lastly, Dixit *et al.* [17] in a clinical study examined the effects of eight weeks of moderate-intensity aerobic exercise on the vibration perception threshold in type 2 diabetic patients with DPN. A total of 87 people participated in the study; 37 people in the intervention group and 47 people in the control group. The intervention group exercised at 40-60%HRR, while the control group received standard medical care, foot care training and followed the same diet as the intervention group. Both groups were evaluated at

baseline and after eight weeks. The results showed that aerobic exercise had an enhancing effect on peripheral nerve vibration, which has a mitigating effect on DPN in type 2 diabetes.

Conclusions

The above studies suggest that aerobic exercise in particular can improve the symptoms of DPN as well as reduce pain, [10] improve gait accuracy [11] and lower limb strength [12] and generally affect the quality of daily lives of patients [1]. There is also evidence that exercise in diabetic patients may either prevent or delay the onset of peripheral neuropathy [1]. However, further clinical trials are required.

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