Review Article

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Exercise Therapy for Painful Diabetic Peripheral Neuropathy: A Bench-to-Bedside Evidence-Informed Review

Kumar Senthil P*, MPT; Adhikari Prabha, MD; Jeganathan PS***, PhD; Misri ZK****, DM (Neurology); D'Souza Sydney C**, MD**

Abstract

Diabetes is the leading cause for peripheral neuropathy and peripheral neuropathy is the leading complication of diabetes mellitus, which leads to chronic disabling pain, foot ulcers, infections and/or amputations. The objective of this review was to provide an evidence-informed literature update aimed at knowledge translation from experimental to clinical evidence for the use of exercise therapy in people with Diabetic peripheral neuropathy (DPN). PubMed-based search for studies was done using search terms '(diabetes OR diabetic) AND (neuropathy OR neuropathic) IN title, AND exercise IN title/abstract' to retrieve relevant evidence on experimental and clinical studies published in English. There were five laboratory-based studies and twenty clinical trials that evaluated the effects, efficacy and effectiveness of exercise therapy programs in population of PDPN. The review findings suggested that supervised aerobic exercise training might be beneficial for people with PDPN, although the heterogeneity of studies limited derivation of recommendations for practice. Other exercise techniques such as strengthening, stretching, balance training require further research prior to their evidence-informed use in clinical practice.

Keywords: Diabetic peripheral neuropathy; Physiotherapy; Rehabilitation; Exercise training; Evidence-informed practice.

Introduction

Diabetes is the leading cause for peripheral neuropathy and peripheral neuropathy is the leading complication of diabetes mellitus, which leads to chronic disabling pain, foot ulcers, infections and/or amputations.[1] The growing magnitude of personal suffering together with a global public health burden necessitated the recognition of DPN as a leading lifestyle-associated nerve dysfunction encountered in clinical practice of diabetes care.[2]

Painful diabetic peripheral neuropathy (PDPN) was recognized as a clinical consequence rather than a complication of diabetes mellitus, in which there is bilateral glove-and-stocking distribution of neuropathic pain in lower limbs, tingling and numbness, sensory and motor disturbances with/without autonomic dysfunction.[3] The PDPN patients had lower quality of life, higher levels of impairment of work productivity and activity, greater resource use, and higher total 3-year per-patient costs compared to other chronic painful coditions.[4]

Previous reviews on painful diabetic peripheral neuropathy were focused on clinical examination findings,[5] assessment scales,[6] medical/pharmacological management,[7] surgical management,[8] acupuncture,[9] and physiotherapy.[10] The objective of this review was to provide an evidence-informed literature update aimed at knowledge translation from experimental to clinical evidence for the use of exercise therapy

Author's Affiliation: *Associate professor, PhD Candidate, Dept of Physiotherapy, Kasturba Medical College (Manipal University), Mangalore, India, **Professor, Dept of Medicine, Kasturba Medical College (Manipal University), Mangalore-575001, India, ***Professor, Dept of Physiology, Kasturba Medical College (Manipal University), Mangalore-575001, India, *****Associate professor, Department of Neurology, Kasturba Medical College (Manipal University), Mangalore, India.

Reprint Request: Senthil P Kumar, Associate Professor, Dept of Physiotherapy, Kasturba Medical College (Manipal University), Mangalore-575001, India. Phone: 09341963889.

E-mail: senthil.kumar@manipal.edu

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in people with DPN.

Methods

A PubMed-based search for studies was conducted using search terms '(diabetes OR diabetic) AND (neuropathy OR neuropathic) IN title, AND exercise IN title/abstract' to retrieve relevant evidence on experimental and clinical studies published in English with available abstracts. Studies on exercise testing and/or autonomic neuropathy were excluded.

Main Findings

Effects of exercise in experimental diabetic neuropathy

Experimental models of diabetic neuropathy included Streptozotocin (STZ)-induced neuropathy in diabetic rats. Five laboratory-based studies evaluated the effects of exercises as follows;

Chen et al[11] studied STZ-induced male diabetic Wistar rats which were divided into 4 groups: normal sedentary rats, normal rats with exercise, sedentary STZ-diabetic (SS) rats, and STZ-diabetic rats with exercise. The exercise intervention consisted of daily run on a treadmill 30 to 60 min/d with an intensity of 20 to 25 m/min which significantly suppressed diabetes-induced blood glucose levels and body weight loss, and increased Hsp72 expression thereby markedly decreasing diabetes-associated neuropathic pain, including thermal hyperalgesia and mechanical allodynia.

Shankarappa et al[12] studied streptozotocin (STZ)-induced diabetic adult male rats which were either kept sedentary or forced-exercised (2-10 weeks, treadmill). The exercise group exhibited a 4-week delay in the onset of tactile hypersensitivity that was independent of glucose control. Forced-exercise markedly delayed the onset of diabetes-associated neuropathic pain by altering opioidergic tone.

Selagzi et al[13] studied the protective and therapeutic effects of aerobic physical activity (swimming) on the development of DPN using a STZ model where the rats were assigned to 5 groups: C (control), E (exercise), D (diabetic), DEx (exercise after diabetic), ExD (diabetic after exercise); and the results indicated that swimming exercise had no effect on glycemic control but restored body weight, CMAP amplitude and CMAP latency in the diabetic animals.

Snow et al[14] evaluated the effects of endurance exercise on myosin heavy chain (MHC) isoform expression in soleius muscles of diabetic rats with peripheral neuropathy. Male Sprague Dawley rats were randomly divided into four groups: control sedentary, diabetic sedentary, control exercise, and diabetic exercise. The exercised animals performed treadmill running five times per week for two weeks. The diabetic rats showed a significantly greater percentage of fast MHC than did the control groups, regardless of exercise status. The exercised animals showed greater expression of developmental MHC than did the sedentary animals.

van Meeteren et al[15] found that in acute EDN model, 24 days of exercise resulted in an enhanced return of motor function in the early phase of recovery and an increased sensory NCV after 250 days in the late phase. In chronic EDN, Moderate exercise training benfited diabetic rats, as evidenced by a superior motor function and an improvement in both motor and sensory NCV.

Effects of Exercise in Clinical Diabetic Neuropathy

Twenty clinical trials evaluated the effects, efficacy and effectiveness of exercise programs in DPN as follows;

Ahn and Song[16] studied 59 diabetic patients with neuropathy who were provided Tai chi exercises which comprised 1 hour of Tai Chi per session, twice a week for 12 weeks, and found that Tai Chi group had better total symptom scores, glucose control, balance, and

quality of life than their control (no intervention) counterparts.

Akbari et al[17] studied 10 diabetic patients with neuropathy and 10 age-matched healthy subjects who were treated with progressive Biodex stability and rocker and wobble-board training for 10 sessions, and found higher balance indices in the case group compared to control group, secondary to balance training.

Kluding et al[18] studied 17 DPN subjects using a 10-week aerobic and strengthening exercise program and found significant reductions in pain (visual analogue scale), neuropathic symptoms (Michigan neuropathy screening instrument), and increased intra-epidermal nerve fiber branching (proximal skin biopsy).

Shah and Mueller[19] compared the in-shoe peak plantar pressures (PPP) in 15 subjects with DM+PN during weight-bearing (treadmill walking, heel and toe raises, sit to stands, stair climbing, single leg standing) and non-weight-bearing exercises (stationary bicycling, balance ball exercise and plantar flexion exercise). The authors found that heel raises and increased walking speed were associated with high PPP, but both WB and NWB were safe, and feasible in this population.

Ites et al[20] in their systematic review included 6 articles that reported 4 physical therapy interventions-monochromatic infrared energy therapy, vibrating insoles, lower extremity strengthening exercises, and use of a cane. Lower extremity strengthening exercises was given a fair recommendation for clinical use in treating balance dysfunction in patients with DPN.

Tuttle et al[21] reported a patient of DM+PN successfully treated with moderate-intensity weight-bearing exercise (heart rate approximately 75% of maximum heart rate; rate of perceived exertion=11-13; 3 times per week) involving walking on a treadmill, balance exercises, and strengthening exercises for the lower extremities using body weight resistance, with improvements in muscle strength, physical function, and activity without causing any adverse injury.

Tuttle et al[22] studied physical activity levels (average daily step count) in 22 patients with DM+PN to determine the relationship among step count, intermuscular adipose tissue volume (IMAT), muscle performance (peak torque, power), and physical function. The average daily step count was inversely related to IMAT, and IMAT was inversely related to muscle performance and overall physical function.

Kruse et al[23] studied the effects of weight-bearing exercise on foot ulceration in people with DM+PN, by comparing the effects of a lower-extremity exercise and walking intervention on balance, lower-extremity strength (force-generating capacity), and fall incidence. The training program had a minimal effect on participants' balance and lower-extremity strength, but not the rate of falling.

Xhauflaire-Uhoda et al[24] evaluated skin temperature, skin surface water loss (SSWL), the Corneometer(®) average capacitance (CMAC) and skin capacitance mapping (SCM) before and after moderate physical exercise in 20 healthy subjects and at rest in 20 patients with DM+PN. The authors found that Diabetic neuropathy appeared at rest as an increased (compensatory) SCM on the forearms without obvious modification on the hypohidrotic legs.

Rutkove[25] reported a 52-year old woman with DM+PN who was treated symptomatically by improving the metabolic profile through weight loss, exercise, and alpha lipoic acid medications that helped slow neuropathy progression.

Lemaster et al[26] studied 79 patients with DM+PN who were given leg strengthening and balance exercises; a graduated, self-monitored walking program (part 1); and motivational telephone calls every 2 weeks (part 2) in addition to diabetic foot care education, Weight-bearing activity did not lead to significant increases in foot ulcers thus establishing its therapeutic safety.

Fisher et al[27] studied 5 patients with DM+PN who completed a 8-week program of

a supervised moderate exercise program (40-75% of maximal 02 uptake reserve) with a subsequent 16-week program of monitored similar exercise. There were significant improvements in aerobic exercise capacity and motor conduction velocities and amplitudes, sensory conduction velocities, and F-wave latencies in the exercise group.

Balducci et al[28] studied 78 subjects (31 diabetic participants who performed a prescribed and supervised 4 h/week brisk walking on a treadmill at 50% to 85% of the heart rate reserve (exercise group: EXE), and a control group of 47 diabetic participants who did not perform exercise. The authors demonstrated that long-term aerobic exercise training could modify the natural history of DPN, with significant differences not only on Delta (delta) in NCV for both peroneal and sural motor nerve between the EXE and CON groups but also the incidence of motor neuropathy and sensory neuropathy during the 4 years of the study was significantly higher in the CON than the EXE group.

Kanade et al[29] compared 23 subjects with diabetic neuropathy (DMPN), 23 patients with current diabetic foot ulcers, 16 patients with partial foot amputations and 22 patients with trans-tibial amputations, and found total heart beat index (THBI) increased and gait velocity and daily stride count fell with progression of foot complications. The maximum peak pressures over the affected foot of patients with diabetic foot ulcers and partial foot amputations were higher than in the group with DPN. The authors suggested that walking exercise should be prescribed together with protective footwear, supplemented by partial or non-weight-bearing exercises.

Smith et al[30] studied 32 subjects with impaired glucose tolerance (IGT) who were given individualized diet and exercise counseling, and at 1-year follow-up improvements in cutaneous reinnervation measured using skin biopsy and pain relief were noted.

Pfeifer et al[31] used a treatment algorithm based on anatomic site and neuropathophysiological source of the neuropathic pain in which they categorized the types of pain into three groups (superficial, deep, and muscular) on 53 patients who were treated with imipramine +/- mexiletine for deep pain, capsaicin for superficial pain, and stretching exercises and metaxalone +/- piroxican for muscular pain, and 22 who were treated as controls. The treated group had significant change of scores in: total pain, deep pain, superficial pain, muscular pain, and sleep. 21% became pain-free (total pain < 2) in the treated group.

McCarty[32] opined that "low-fat, whole-food vegan diet, coupled with daily walking exercise, leads to rapid relapse of neuropathic pain in the majority of type 2 diabetics; and there is indeed evidence that vegan diets, as well as exercise training, tend to decrease the viscosity of both whole blood and plasma; reductions in hematocrit and in fibrinogen may contribute to this effect. The fact that vegan diets decrease the white cell count is suggestive of an improvement in blood filterability as well; filterability improves with exercise training owing to an increase in erythrocyte deformability."

Tesfaye et al[33] measured sural sensory conduction velocity was recorded in 12 non-neuropathic diabetic subjects, 15 diabetic subjects with established neuropathy and 16 age-matched normal control subjects, before and after exercise to 80% age/sex predicted maximum heart rate, and found SNCV increased significantly after exercise in normal subjects and non-neuropathic diabetic subjects but not in neuropathic subjects.

Kremser et al[34] studied the exercise response of seven diabetic humans having peripheral sensory and cardiac autonomic neuropathy, eight diabetics without neuropathy, and eight normal subjects and reported that patients with diabetic neuropathy had a reduced VO2max than non neuropathic diabetics with no difference in ventilatory anaerobic threshold.

Kumar et al[35] in their observer-blinded pilot randomized sham-controlled clinical trial

with concealed allocation studied 34 PDPN patients who were randomly administered nerve sliders and nerve massage to one lower limb while sham intervention of passive joint movements was performed for the other limb. The experimental side was found to have a greater reduction of vibration and thermal perception thresholds compared to the sham side. The changes between immediate post-treatment and 15-min post-treatment were not significant for all three measurements which suggested the carry-over effects of the intervention.

Discussion

The objective of this review was to provide an evidence-informed literature update aimed at knowledge translation from experimental to clinical evidence for the use of exercise therapy in people with DPN, and the review findings were encouraging the growth in evidence witnessed in terms of increase in both quantity and quality of clinical studies. Exercise had long been recognized as a part of the therapeutic management of diabetes, and exercise had the potential to delay and/or prevent the development of painful DPN.[36]

Individualizing exercise prescription depending upon subject characteristics such as age, gender and other anthropometric and socio-demographic characteristics is essential for a successful treatment adherence. Older adults require strengthening exercises and coordination training in addition to their routine exercise program.[37]

There were no established treatment guidelines for exercises in DPN in spite of numerous consensus statements and there is a need for foot care guidelines incorporating exercise prescription for patients with DPN who present with insensate feet[38] which were evidence-informed and based upon biopsychosocial approach to management.[39]

Manual therapy had been long recognized to play an inherent role under the profession of physical therapy,[40] and treatment methods in manual therapy such as neurodynamic mobilization (nerve sliders and nerve massage) were shown to be beneficial in a range of neuropathic pain conditions.[41]

Neurodynamic examination findings were reported to be altered in people with DPN,[42] which suggested presence of peripheral nerve mechanosensitivity and they were related to impaired neurophysiological findings, neuropathic pain and quality of life.[43] Only one published study by Kumar et al[35] evaluated efficacy of neurodynamic mobilization in DPN and there is scope for more high quality research in this area.

Application of therapeutic techniques should be based upon an evidence-informed clinical reasoning-based decision-making approach both in physical therapy[44] and manual therapy practice,[45] which is essential for extrapolation into exercise therapy for DPN.

This review was the first of its kind on exercise therapy for DPN and it has few limitations in its non-systematic approach, and it was based only upon bench-to-bedside translation of knowledge from research to practice towards better care of people with DPN. Future high quality clinical trials utilizing homogenous participant characteristics and outcome measures would enable meta-analyses of reviewed studies to provide a quantitative summary of evidence.

Conclusion

Supervised aerobic exercise training was shown to be beneficial for people with DPN, although the heterogeneity of studies limited derivation of recommendations for practice. Other exercise techniques such as strengthening, stretching, balance training require further research prior to their evidence-informed use in clinical practice. Role of manual therapy as an adjunct to exercise therapy is open for future scientific investigations on its physiological and clinical effects in people with DPN.

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