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SYSTEMATIC REVIEW

Exercise Intervention Studies in Patients with Peripheral Neuropathy: A Systematic Review

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Abstract
Introduction Peripheral neuropathies (PNPs) encompass a large group of disorders of heterogeneous origin which can manifest themselves with sensory and/or motor deficits depending on the predominantly affected nerve fiber modality. It represents a highly prevalent disease group which can be associated with significant disability and poor recovery. Exercise has the potential to improve side effects of PNP.
Objective Our objective in this systematic review was to analyze exercise interventions for neuropathic patients in order to evaluate the possible benefits of exercise.
Methods Three independent reviewers used PubMed, MEDPILOT® (MEDLINE), Cochrane, and relevant reference lists to obtain the data. Relevant studies were graded according to the Oxford Levels of Evidence.
Results Eighteen studies (ten randomized controlled trials and eight controlled clinical trials) met all inclusion criteria. Three (diabetic) studies were ranked very high quality [1b (A)], nine high quality (four diabetes, one cancer, four others) [2b (B)], while six (four diabetes, two others) showed low quality (4/C). Current data suggests that exercise is a feasible, safe, and promising supportive measure for neuropathic patients. This is best documented for patients with diabetic peripheral neuropathy (DPN), suggesting that endurance training has the potential to prevent the onset of and reduce the progression of DPN. In general, balance exercises showed the highest effect on the motor as well as sensory symptoms in all types of PNP.
Conclusion Overall, balance training appears to be the most effective exercise intervention. Studies focusing exclusively on strength, or a combination of endurance and strength, appear to have a lower impact. For metabolically-induced neuropathies, endurance training also plays an important role. Further research with high methodological quality needs to be conducted in order to establish evidence-based clinical recommendations for neuropathic patients.

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1 Introduction

Peripheral neuropathy (PNP) represents a group of diseases which affect motor, sensory and/or autonomous peripheral nerves. PNP can be subdivided by its etiology or by pathological features such as predominantly affected fiber modality. They can be further classified on the basis of primarily myelin or axonal damage resulting in demyelinating or axonal PNP. Furthermore, PNP is a highly prevalent disease; worldwide, approximately 168 million people are affected [1]. At the age of 55 years, around 5–8 % of all people suffer from symptomatic peripheral neuropathy, whereas in the age group above 65 years, almost one-third are estimated to have sensory symptoms attributed to peripheral neuropathy [1, 2]. Common symptoms include pain, altered sensation (numbness, burning, tingling, etc.), reduced or absent reflexes, muscle weakness,

reduced balance control, insecure gait, and higher risk of falling [3, 4]. All of these symptoms can affect activities of daily living and subsequently reduce a patient's quality of life [5].

PNP can develop genetically or be acquired. In approximately one-third of patients, PNP is caused by diabetes, another third results from a variety of factors such as medication (e.g. chemotherapeutic agents), genetics, autoimmune disorders, infections, nutritional deficiencies, and metabolic imbalance, whereas the remaining patients are termed idiopathic (cause unknown) [6]. PNP does not only have a severe impact on the activities of daily living, reducing patients' quality of life, but for some patients it can even influence their survival [6, 7].

For patients with diabetic peripheral neuropathy (DPN), who represent the largest group (50 % of all diabetic patients; 110 million people) [8], small and large nerve fibers are damaged to different degrees, causing foot ulcers and non-traumatic foot amputation [9].

In cancer patients, PNP is the most common [10] neurological and clinically relevant side effect. Peripheral neuropathy can occur as a paraneoplastic manifestation, but, much more frequently, PNP is induced by neurotoxic chemotherapeutic agents (platinum derivatives, vinca alkaloids, and taxanes, as well as bortezomib, thalidomide, and epothilones) [6, 11–13]. Not only do patients have to deal with the debilitating side effects that these drugs induce, but chemotherapy-induced peripheral neuropathy (CIPN) has become a decisive limiting factor for therapy, causing treatment delays, dose reductions, or even discontinuation of therapy, which can affect the outcome and compromise survival [6]. Therefore, the occurrence of PNP presents a diagnostic dilemma because, up to now, approved and effective treatment options are lacking [6, 13].

Even though PNP causes so many symptoms that may even lead to life-threatening consequences, little research has been done to investigate the potentially beneficial effects of specific exercises to counteract the described symptoms. Research has focused on pharmacological therapies aimed at reducing PNP or treat selected side effects [10, 14, 15]. While this has been helpful for neuropathic pain, it does not address the many other sensory and motor side effects of PNP [12, 14, 16, 17]. To the contrary, many of these agents have been shown to have additional negative side effects [13].

Previous studies have shown that exercise can attenuate motor deficits induced by PNP. Apart from the obvious effect of strength training preventing muscle loss, it also improves inter- and intramuscular coordination as well as neural control, contributing to improved stability and gait [18, 19]. Endurance training improves cardiovascular fitness but also has an influence on metabolic factors such as glycemic control, insulin sensitivity, lipid abnormalities, and hypertension [20, 21], and therefore may also be able to improve related neuromuscular parameters [22].

Alternative interventions such as sensorimotor training (SMT), whole-body vibration (WBV) or Tai Chi for instance, have not received much attention so far but have considerable potential as they not only target motor components but simultaneously address small and large sensory nerve fibers [23–25].

Studies in healthy adults for instance, have revealed that SMT can induce supraspinal reorganization [26], regeneration of neuromuscular structures after injuries [27], reduction in reflex excitability [28], and diminish the prevalence of injuries [29], leading to improved proprioception [26], balance control, causing fewer falls [30], and increasing mobility. Similar effects have been shown with WBV. Kawanabe et al. [24] and Bogaerts et al. [31], for instance, showed that elderly people improve their gait after vibration exercises. Rittweger et al. [32] and Kirchner [33], found WBV to have a positive impact on pain reduction, while further studies showed an effect on deconditioned skeletal muscle [34], improved isometric strength [32, 35, 36], postural sway[37], and reduced fall frequency [31]. Tai Chi, a traditional Chinese martial art, improves balance [38], gait, reducing the risk of falling [39], inducing muscle strength [38], stabilization of the joints, flexibility [40], stamina, and coordination [41–45].

Nevertheless, the translation of those results to patients with neuropathic conditions is scarce. To date, treatment is predominantly symptom-orientated with little consensus regarding the benefits of the various exercises. Consequently, patients are uninformed as to how much exercise is advisable or if they should exercise at all during acute neuropathy.

Only in the last 3 years has the potential of exercise as a measure of supportive therapy gained more attention, for the first time enabling a systematic review based on sufficient evidence to derive preliminary recommendations.

This systematic review has the aim of analyzing all exercise interventions performed with neuropathic patients in order to critically review the exercises chosen and the influence they may have on the motor and sensory side effects of PNP. The intention is to improve future research and generate recommendations as to which exercises may be beneficial for which side effects of PNP, in order to better support neuropathic patients as well as the therapists guiding them, and improve their quality of life.

2 Methods

2.1 Literature Search

Three reviewers (FS, KM, and JR) independently searched the literature (April 2013–December 2013) using PubMed,

MEDPILOT® (MEDLINE), and the Cochrane Database in order to find exercise intervention studies for patients with peripheral neuropathy. Additionally, relevant reference lists were hand-searched. We used the terms 'peripheral neuropathy', 'PNP', 'CIPN', 'chemotherapy induced peripheral neuropathy', and 'diabetic neuropathy', and combined these by using AND with the terms 'physical activity', 'physical exercise', 'physical fitness', 'exercise', 'exercise program', 'exercise intervention', 'moving therapy', 'sports therapy', 'sport', 'endurance', 'aerobic training', 'resistance training', 'strength training', 'strength', 'balance', 'balance training', 'balance exercise', 'coordination', 'coordination exercises', 'gait', 'postural stability', 'postural control', and 'proprioception'. The German equivalents of all terms were also searched for.

To be included in the review, studies had to have examined the effect of an exercise intervention in patients with PNP, independent of the derivation. Animal studies, expert opinions without critical appraisal, or studies with less than ten patients, no control group, or combining exercise and nutrition, therapeutic footwear, medication for PNP, etc., therefore not enabling a clear interpretation of the results, were excluded. Reviews were excluded from analysis, yet analyzed for additional, possibly relevant, literature. Full-text articles of the studies meeting the inclusion criteria were then critically reviewed and graded according to the Oxford levels of evidence (see Table 1) by two authors (FS and FB) and, in case of doubt, by a third author (EZ), leading to grades of recommendation. This evaluation system by the Oxford Center for Evidence Based Medicine (OCEBM) was ranked most effective in a comparison by Atkins et al. in 2004 [46] and has been used for reviews in a similar context [47–50]. The evaluation is based on the study design, quality of the study, and its results, creating ten gradations of quality, which are then translated into four grades of recommendation (A = 1a, 1b; B = 2a, 2b, 3a, 3b; C = 4a, 4b; D = 5a, 5b) (see Table 1). Only high-quality studies [Level 1(A) and Level 2(B)] were considered to derive recommendations. Studies were abstracted for the tables to include the amount of study participants (*N*), type of exercise, duration, and frequency for which the exercise was performed, as well as the main outcome measures. Results given are based on intergroup comparison unless stated otherwise.

Table 1 Oxford levels of evidence and corresponding grades of recommendation

Level	Content	Grade of recommendation
1a	Systematic reviews with homogeneity of randomized controlled trials	A
1b	Individual randomized controlled trials (with narrow confidence interval)	
2a	Systematic reviews with homogeneity of cohort studies	B
2b	Individual cohort study (including low-quality, randomized controlled trials)	
3a	Systematic review with homogeneity of case-control studies	
3b	Individual case-control study	
4	Case-series (and poor-quality cohort and case-control studies)	C
5	Expert opinion without explicit critical appraisal	D

This table represents an overview of the standardized Oxford levels of evidence. The entire table can be obtained from the Centre for Evidence Based Medicine [51]

3 Results

We screened 8,701 search results in PubMed, as well as 959 in MEDPILOT® (MEDLINE and Cochrane) and 177 in relevant reference lists. After careful reviewing, the total number of studies meeting the inclusion criteria for this review was 18 studies: ten randomized controlled trials (RCT) and eight controlled clinical trials (CCT) (see Fig. 1) evaluated the effects of an exercise intervention on the side effects of PNP, assessing a total of 841 patients.

Eleven studies assessed patients with diabetes-induced neuropathies, one study considered CIPN, while six studies dealt with PNP of other derivation such as liver-transplanted familial amyloid polyneuropathy (FAP), sensory neuron disease, hereditary sensorimotor neuropathy (HMSN) (Charcot Marie Tooth disease 1 + 2), chronic acquired PNP, toxic neuropathy, or antimyelin-associated glycoprotein. No studies were found for any other causes of PNP such as HIV or alcohol (see Table 2).

Critical grading of the 18 studies revealed 12 high-quality (Level 1 and 2) studies (seven diabetic PNP, 1 CIPN, four other) and six of poor quality (Level 4) (four diabetic PNP, two others) (see Table 3).

3.1 Diabetic Peripheral Neuropathy

Eleven studies (seven RCT and four CCT), assessing 576 diabetic adults, were evaluated regarding the side effects of PNP. Three studies were graded 1b (A), four 2b (B) and four 4 (C) (see Table 4).

Five studies (Lee et al. [4], Akbari et al. [54], Song et al. [55], Allet et al. [56], and Richardson et al. [59]) assessed the influence of balance training on the side effects of PNP, showing a significant impact on balance control. Two studies (Song et al. [55] and Allet et al. [56]) also showed improved gait parameters, while Lee et al. [4] compared two interventions—WBV and a combination of WBV with balance

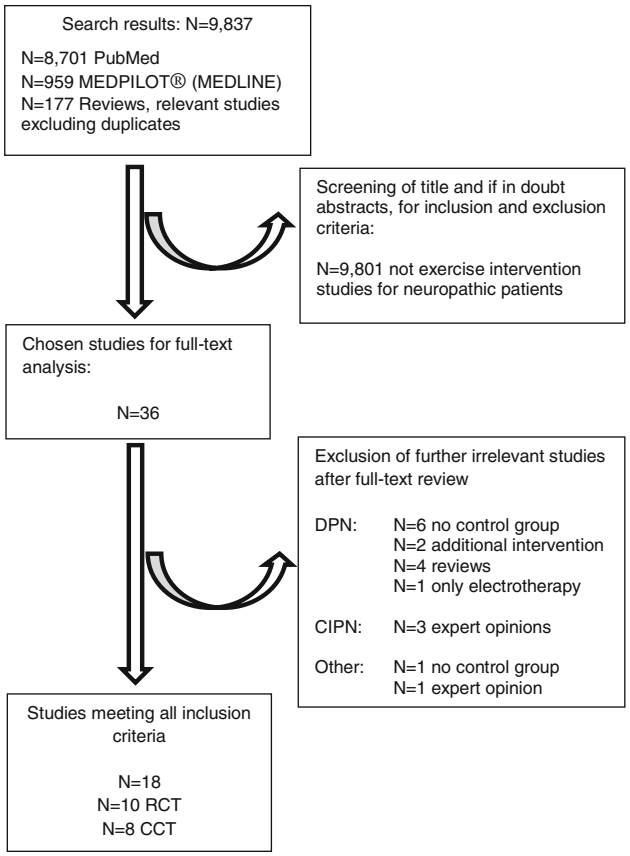

Fig. 1 Procedure of literature search and selection of studies for the systematic review. *DPN* diabetic peripheral neuropathy, *CIPN* chemotherapy-induced peripheral neuropathy, *RCT* randomized controlled trial, *CCT* clinical controlled trial

exercises—with a control group. A further two studies (Ahn and Song [25] and Hung et al. [57]) chose Tai Chi as the intervention and showed improved motor, sensory, and metabolic symptoms of PNP. Kruse et al. [58] and Mueller et al. [53] chose a combination of endurance, balance, and strengthening exercises. Both groups performed progressive balance, flexibility, strengthening and aerobic exercises, although one group conducted the exercises standing or walking [weight-bearing group (WB; $N = 15$)], while the other group [non-WB group (NWB; $N = 14$)] was sitting or lying. Positive effects on motor performance could only be detected if exercises were performed standing or walking. Kruse et al. [58] instructed patients in leg strengthening and balance exercises as well as a graduated, self-monitored walking program for eight sessions, and then monitored patients while they continued home-based for 12 months. No significant intergroup differences were found.

The only existing preventive study was conducted by Balducci et al. [22], evaluating 78 diabetic patients over 4 years of endurance training (brisk walking on a treadmill at 50–85 % heart rate reserve). Intergroup comparison with the control group revealed significant sensory improvements.

No adverse events were reported by Dixit et al. [52], Ahn and Song [25], Kruse et al. [58], and Balducci et al. [22]. Mueller [53] reported that one patient sustained a calf strain during treadmill walking but was able to continue to exercise with lower intensity. Allet et al. [56] declared two patients had developed pain in their Achilles tendon, making it necessary to slow down the progression for 'toe walking' and 'one leg stance' exercises. The remaining five studies (Lee et al. [4], Akbari et al. [54], Song et al. [55], Hung et al. [57] and Richardson et al. [59]) did not indicate adverse events.

3.2 Chemotherapy-Induced Peripheral Neuropathy

So far, only one RCT, graded 2b (see Table 5), has assessed the effects of exercise intervention in patients suffering from CIPN. Streckmann et al. [60] was the first to show beneficial effects of exercise (sensorimotor, endurance, and resistance training) on motor as well as sensory side effects of CIPN in cancer patients (lymphoma). The number of patients with reduced deep sensitivity could be diminished significantly in the intervention group by 87.5 %, while no changes (0 %) were observed in the control group. Furthermore, patient's quality of life as well as their level of activity were also improved significantly. No adverse events occurred.

3.3 Neuropathy of Other Derivation

Six studies (two RCT and four CCT) investigated 204 adults with neuropathies due to various causes [61–66]. Grading revealed four 2b (B) studies and two 4a (C) studies (see Table 6).

Apart from two studies that focused on liver-transplanted FAP (Tomás et al. [62]) and HMSN (Matjacic and Zupan [61]), all other studies evaluated a heterogeneous collective.

Only three studies were able to achieve improvements through the exercise regime chosen. Tomás et al. [62] and Nardone et al. [64] were able to improve balance and gait parameters, while Graham et al. [63] showed improved knee extensors and total work load. Tomás et al. [62] chose a combination of endurance, resistance, and balance exercises. Intergroup differences in favor of the exercising groups were shown for their walking capacity. Nardone et al. [64] compared neuropathic patients with patients with vestibular disorder. Both groups performed ten sessions of balance exercises on a powered platform, as well as Cawthorne–Cooksey and Frenkel exercises. Due to a crossover design, both groups received the same exercises, only in a different order. Regardless of the treatment order, both groups were able to improve their balance.

The other three studies (Matjacic and Zupan [61], Ruhland and Shields [65], and Lindeman et al. [66]) did not

Table 2 Numbers of studies and reported effects of exercise interventions on different types of neuropathy

Type of neuropathy	Studies showing beneficial effects of exercise	Studies showing no beneficial effects of exercise	Studies that did not report on differences between groups[a]
Diabetic	9 [4, 22, 25, 52–57]	1 [58]	1 [59]
CIPN	1 [60]	0	0
HMSN	0	1 [61]	0
Liver transplanted FAP	1 [62]	0	0
Inflammatory peripheral neuropathy after GBS or stable CIDP	1 [63]	0	0
Mixed aetiologies	1 [64]	2 [65, 66]	0
HIV, alcohol, chronic kidney disease, amyloidosis, lyme disease, diphtheria, etc.	0	0	0

CIPN chemotherapy-induced peripheral neuropathy, *HMSN* hereditary motor and sensory neuropathy, *FAP* familial amyloid polyneuropathy, *GBS* Guillain-Barré Syndrome, *CIDP* chronic inflammatory demyelinating polyradiculoneuropathy, *HIV* human immunodeficiency virus

[a] Not included in percentage of beneficial studies

Table 3 Quality of studies on exercise interventions for neuropathic patients, based on Oxford levels of evidence

Grade of recommendation	LOE	Cancer	Diabetes	Others
A	1b	0	3	0
B	2b	1	4	4
C	4	0	4	2
D	5	Excluded	Excluded	Excluded
Total $N = 18$		1	11	6

LOE levels of evidence

detect any significant intergroup results. The earliest study by Lindeman et al. [66] in 1995 investigated the effects of strength training. In 1997, Ruhland and Shields [65] also assessed the effects of strength training but combined it with endurance and stretching exercises. Patients were advised to train daily for 6 weeks (home-based). Matjacic and Zupan [61] combined strength training with passive stretching and dynamic balance exercises. Both groups performed the same exercises. They solely differed in dynamic balance training; the control group was managed by a physiotherapist, while the intervention group performed the exercises on a balance trainer.

Graham et al. [63] did not report any adverse events. All other authors (Tomás et al. [62], Nardone et al. [64], Matjacic and Zupan [61], Ruhland and Shields [65], and Lindeman et al. [66]) did not indicate adverse events.

4 Discussion

Although PNP is a highly prevalent and debilitating disease, affecting 168 million people worldwide [1], predominantly expert opinions and poor-quality studies have dominated the research field, hinting at the potential of exercise interventions for patients with PNP. It is only in the last 3 years that more and more high-quality studies have confirmed this presumption. Consequently, previous evidence has been insufficient to generate a systematic review until now. The only other existing review from 2010 [52] merely found one study that met the inclusion criteria.

Summarizing, one can say that the evidence for exercise interventions in neuropathic patients has improved, although study quality is diverse. Overall, the quality of the 18 included studies is 2b. Evidence is best in patients with diabetes and neuropathy, revealing most RCTs and therefore the highest quality in the field of neuropathic patients. With only one study on CIPN to date, results are promising but evidence is low. This also applies to the studies on the many other causes of PNP. Diseases such as HMSN or FAP, for instance, are also only represented in one study, while the many other causes of PNP are either merely represented with very few individuals in a heterogeneous patient group or not at all (see Table 2).

The current data suggests that exercise is feasible, safe, and beneficial (see Table 2) for patients with PNP. Overall, exercise-compliance was good and only two studies, both in diabetic patients, reported mild adverse events (Mueller et al. [53] and Allet et al. [56]), due to which patients had to modify their training schedule temporarily on account of pain in the Achilles tendon or the calf.

Currently, there is little evidence for a beneficial effect of supportive therapies such as vitamin E or high-dose vitamin B [67], electrolyte infusions (Ca/Mg), or electrotherapy in patients with PNP. Even neuroprotective treatments such as amifostine, nerve growth factors, or corticosteroids are not well evaluated or failed to demonstrate beneficial effects in clinical trials [13, 68, 69].

Table 4 Exercise interventions for patients with diabetic neuropathy

Reference	*N*	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup differences)	LOE	Grade of recommendation
Dixit et al. [52]	87 40 IG 47 CG	RCT	Diabetics	Endurance on treadmill at 40–60 % HRR	8 weeks	3–6×/week 150–360 min	↑ Distal peroneal nerve conduction velocity ↑ Sural sensory nerve conduction velocity ↑ MDNS ↔ Latency, duration and amplitude	2b	B
Lee et al. [4]	55 19 WBV + BE 18 BE 18 CG	RCT (two interventions, one control)	Diabetics	WBV + balance exercises or balance exercises solely	6 weeks	Balance exercises 2×/week for 60 min WBV: 3×/week for 3 min at 15–30 Hz; 1–3 mm	WBV comp to BE and CG ↑ Postural sway ↑ BBS ↑ TUG ↑ Five times sit-to-stand ↑ HbA_{1C} WBV and BE comp to CG ↑ FRT ↑ One-leg stance	2b	B
Mueller et al. [53]	29 15 WB 14 NWB	RCT (two exercise groups)	Diabetics	Balance, flexibility, strengthening, and aerobic exercise conducted Sitting or lying (NWB), or standing and walking (WB)	12 weeks	3×/week	WB group ↑ 6 MW ↑ Average daily step counts NWB group ↑ HbA_{1c}	1b	A
Akbari et al. [54]	20 10 IG 10 CG	CCT (age-matched)	Diabetics	Balance: Biodex stability and rocker and wobble-board	10 sessions	1–2×/session	↑ Stability indices (open and closed eyes)	4	C
Ahn and Song [25]	39 20 IG 19 CG	CCT (non-equivalent CG)	Diabetics	Tai Chi	12 weeks	2×/week for 1 h	↑ Balance ↑ Quality of life ↑ Total neuropathic symptom score ↑ Glucose control	4	C
Song et al. [55]	38 19 IG 19 CG	RCT	Diabetics	Balance exercise program	8 weeks	2×/week for 32 min	↑ Balance and trunk proprioception: decreased sway paths ↑ Unipedal stance ↑ Dynamic balance ↑ Fkt reach test ↑ Timed up-and-go ↑ 10 m walk ↑ Less trunk repositioning errors	2b	B

Table 4 continued

Reference	*N*	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup differences)	LOE	Grade of recommendation
Allet et al. [56]	71 35 IG 36 CG	RCT	Diabetics	Balance and gait exercises with function-orientated strengthening	12 weeks	2×/week	↑ Gait speed ↑ Dynamic balance (walk over beam and balance index), Biodex sway index ↑ Performance-oriented mobility ↑ Degree of concern about falling ↑ Hip flexion mobility ↑ Hip and ankle plantar flexor strength	2b	B
Kruse et al. [58]	79 41 IG 38 CG	RCT	Diabetics	Leg strengthening, balance exercises and graduated, self-monitored walking program	3 months supervised 12 months home-based	1×/week 8 instructive sessions	↔ Between the groups for strength, balance, participant-reported falls	1b	A
Hung et al. [57]	60 28 IG diabetics 32 CG healthy	CCT (age-matched)	Diabetics	Tai Chi Chuan	12 weeks	3×/week	↑ Fasting blood glucose levels ↑ Nerve conduction velocities ↑ Motor nerve conduction velocities ↔ Amplitudes	4	C
Balducci et al. [22]	78 31 IG 47 CG	RCT (preventive)	Diabetics	Endurance (long-term) Brisk walking on a treadmill (50–85 % heart rate reserve)	4 years	4 × 1 h/week	Exercise group ↑ Less development of PNP ↑ Vibration perception threshold ↑ Nerve conduction velocity (peroneal and sural)	1b	A
Richardson et al. [59]	20 10 IG 10 CG	CCT (first ten placed in IG, followed by CG)	Diabetics	IG: balance exercises CG: seated exercises—neck flexion and rotation, strengthening exercises of upper extremities, low frequency	3 weeks	Daily	Only intragroup results given ↑ 3 clinical measures of balance ↔ ABC Scale ↔ Motor response amplitudes (tibial, sural, peroneal)	4	C

LOE levels of evidence, *RCT* randomized controlled trial, *HRR* heart rate reserve, *CCT* clinical controlled trial, *IG* intervention group, *PNP* peripheral neuropathy, *CG* control group, *MDNS* Michigan Diabetic Neuropathy Score, *WBV* whole-body vibration, HbA_{1C} glycosylated hemoglobin, *BE* balance exercise group, *BBS* Berg Balance Scale, *TUG* timed up-and-go test, *FRT* functional reach test, *fkt* function, *WB* weight-bearing, *NWB* non-weight-bearing, *6 MW* 6-min walk test, *fkt* functional, *ABC* activities-specific balance confidence ↑ indicates improvement, ↔ indicates no change

Specific treatment for nerve damage is currently not available [70] and the efficacy of available pharmaceutical interventions is limited. In DPN, for instance, 90 % of patients require two or more medications, and despite high prescription compliance, only 27 % respond to those pharmaceutical treatments [71–73]. There is no consensus regarding the treatment of PNP. To the contrary, most medication exerts additional side effects [10, 74]. Oncological patients with CIPN, for instance, were asked to report on the effect of supportive measures during rehabilitation. Patients reported that walking through granulated material as well as balance and gait exercises were most effective [75]. Therefore, exercise is currently a promising option in supportive therapy, which should be taken more seriously.

In general, the patient cohorts were quite heterogeneous with regard to symptoms and underlying cause. Therefore, future intervention studies should consider this shortcoming in study design. Groups should at least consist of patients with similar symptoms, not mixing diverse mechanisms or patients with symptoms only in the hands or face, for instance, with patients experiencing numbness in their feet, as most assessments performed are consequently biased.

Most studies reported on side effects caused by dysfunction of motor nerve fibers. All studies showing an additional impact on the sensory symptom balance control chose balance exercises as the intervention method, revealing improved parameters of balance control such as decreased sway paths, improved unipedal stance, less failed attempts and trunk repositioning errors, faster reaction time, better performance-orientated mobility, improved static and dynamic balance, and reduced concern regarding falling [4, 54–56, 60, 64]. Apart from specific gait training, balance exercises were also able to improve gait parameters such as gait speed, walking distance in the six- and ten-meter walk, and improved timed up-and-go. Lee et al. [4] showed additive effects of balance training when combined with WBV. Two studies by Ahn and Song [25] and Hung et al. [57] suggest that Tai Chi also targets balance control due to the high demand on balance control during the monopedal stances and weight-shifting movements.

A combination of strength and endurance training, not including any balance indices, was performed in two CCT studies (Graham et al. [63] and Tomás et al. [62]). They revealed improvements on the knee extensors and total work load as well as walking capacity. Lindeman et al. [66] detected significant improvements for knee torques in the HMSN group. These three studies only achieved improvements regarding muscle atrophy in general though not for specific PNP-related symptoms.

Interestingly, studies assessing either a combination of strength and endurance training, or strength training alone [Kruse et al. [58] (RCT), Matjacic and Zupan [61] (RCT), and Ruhland and Shields [65] (CCT)] did not detect any significant intergroup differences.

Only three RCTs (Dixit et al. [52], Streckmann et al. [60], and Balducci et al. [22]) demonstrated improvement on small and large sensory nerve fiber function. A combination of endurance, strength, and SMT revealed improved peripheral deep sensitivity in cancer patients (lymphoma) (Streckmann et al. [60]).

Balducci et al. [22] found that long-term, supervised endurance training was able to prevent the onset of PNP in diabetics, while Dixit et al. [52] achieved positive effects with moderate intensity (40–60 % heart rate reserve) aerobic exercise on the progression of DPN.

The underlying mechanisms for the beneficial effects of exercise on PNP have not yet been fully understood. Explanations may include positive modulation of regenerative mechanisms such as altered expression of growth factors, induction of remyelination, or accelerating axonal regeneration [76, 77]. Recently, it has been demonstrated that treadmill exercise has the potential to improve the regeneration of transected nerves by altered expression of neurotrophic growth factors such as nerve growth factor [78].

However, we will presumably have to address two different mechanisms of PNP in order to best target the symptoms. When analyzing the current data, it is noticeable that studies showing the effects of endurance exercises on sensory symptoms of PNP target DPN, which is metabolically induced, whereas the other types of PNP better respond to balance training. Exercise recommendations will probably have to differ, whether we desire to primarily target metabolically-induced PNP, such as DPN, or whether we have to target nerve cells damaged by toxins directly, as in CIPN.

In metabolically-induced PNP, exercise, especially endurance training, can induce glycemic control and reduce body weight. DPN, for instance, is attributed, amongst other mechanisms, to prolonged hyperglycemia, causing up to fourfold higher neuronal glucose levels [79] and additionally initiating an accumulation of sorbitol. Glucose and sorbitol in such concentrations disturb the homeostasis and cause neuronal damage [52]. Additionally, sorbitol requires a higher amount of antioxidants in order to detoxify, thereby contributing to enhanced oxidative stress, which leads to neuronal cell damage. Previous studies have shown that aerobic exercise has the potential to reduce the glucose level, therefore modulating the polyol-sorbitol pathway and increasing antioxidative capacity, consequently preventing and restoring neuronal damage [52, 80]. Recent studies have also revealed that neurons can alternatively use lactate as a substitute for glucose and therefore reduce the level of neuronal glucose and oxidative stress

Table 5 Exercise intervention studies for patients with chemotherapy-induced peripheral neuropathy

Reference	*N*	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup differences)	LOE	Grade of recommendation
Streckmann et al. [60]	61 30 IG 31 CG	RCT	Lymphoma	Sensorimotor training, endurance and strength	36 weeks	2×/week	↑ QOL ↑ Peripheral deep sensitivity ↑ Higher reduction and total number of CIPN ↑ Static, dynamic and perturbed balance control ↑ Aerobic performance level ↑ Level of activity (outside intervention)	2b	B

LOE levels of evidence, *QOL* quality of life, *RCT* randomized controlled trial, *CIPN* chemotherapy-induced peripheral neuropathy, *IG* intervention group, *CG* control group, ↑ indicates improvement

[81]. Endurance exercises, inducing a steady state of lactate and additionally removing surplus glucose, may therefore enhance the use of this alternative metabolic pathway and contribute to regulation of the glucose level. Consequently, the intensity and duration will also play a substantial role as a certain lactate level (presumably ≥2 mmol/l, in order to create the required gradient as the brain holds a lactate state of 1.9 mmol/l [82]) will have to be sustained. Therefore, the type of endurance exercise is probably secondary to the intensity necessary for each individual to obtain an effective lactate state. Furthermore, exercise also increases the blood flow through distal muscle groups, increasing oxygenation to the peripheral tissue.

Dixit et al. [52] even detected an influence of endurance exercise on the amount of oral hypoglycaemic agent (OHA) and insulin necessary. Further studies comparing this observation with exercise interventions would be highly desirable.

Whereas for non-metabolically-induced PNP, specific balance training such as SMT or whole-body vibration will probably play a more crucial role as they have the potential to induce neural adaptations [26]. The underlying mechanisms must also still be elucidated. Although one possibility could lie in the regenerative effect of SMT on nerve fibers [83]. A further possibility is attributed to the nervous system's plasticity: (i) an increase in the density of receptors; (ii) activating deafferented neurons [83] by increasing metabolism; (iii) lowering the threshold for excitability [84]; or (iv) inducing supraspinal learning effects (Taube 2008).

Especially regarding the small and large sensory nerve fibers, the intensity, frequency, and choice of exercises seem to be crucial. Presumably, not every type of balance training will be able to induce sensory changes.

As previous studies on SMT in healthy adults have shown, neural stimulation is only achieved if exercises are performed within a range of 20–40 s, not exceeding five exercises, and allowing for sufficient regeneration time between exercises in order to prevent neural fatigue [23, 26].

The indication 'balance training' is very diverse and can include many different variations, targeting different effects. For this reason, studies should specify the balance training performed, and indicate frequency and duration in order to enable comparison and generate better recommendations in the future.

All studies applied the intervention at least twice a week (2–3×/week balance; 4–6×/week endurance) for at least 6 weeks (6–36 weeks balance; 8 weeks–4 years endurance).

This review also has limitations. Although the studies were ranked by three independent reviewers in order to minimize subjectivity, selection bias cannot be ruled out completely. It must also be considered that ranking according to the criteria of the Oxford Levels of Evidence-Based Medicine was hampered due to lack of access to the raw data in the papers. Many studies lacked confidence intervals and indications regarding adverse events. Consequently, studies were difficult to interpret and rank and may therefore be under- or over-rated. However, those limitations are well-known and also apply at different degrees for other evaluation strategies [86, 87].

To date, special recommendations regarding exercise interventions for neuropathic patients are scarce. Solely from a DPN point of view, the American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM) have released a statement [70] recommending patients do 150 min/week of moderate-

Table 6 Exercise intervention studies for patients with heterogeneous causes of neuropathy

References	*N*	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup difference)	LOE	Grade of recommendation
Tomás et al. [62]	39 23 IG (8 supervised/ 15 home-based) 16 CG	CCT	Liver-transplanted FAP	Aerobic (treadmill, bicycle, rowing) <15 RPE, resistance training with Thera-Band, FlexBar, and stability trainer	24 weeks	3×/week for 1 h	↑ Body composition ↑ Walking capacity	4	C
Nardone et al. [64]	33 19 IG: PNP 14 CG: vestibular disorder	CCT (crossover: both groups received exercise, only in the other order)	Ménière, sensory neuron disease, Ramsey-Hunt, Charcot Marie Tooth, diabetes, nutritional, entrapment neuropathy, tomaculous nephropathy, antimyelin-associated glycoprotein	Powered platform and Cawthorne-Cooksey (vestibular disorder) and Frenkel (PNP) balance exercises	10 sessions	2 sessions daily/ 30 min	↑ Improved balance, regardless of order	2b	B
Graham et al. [63]	26 16 IG: PNP 10 CG: healthy	CCT (both exercised)	Inflammatory peripheral neuropathy after GBS or stable CIDP	Unsupervised, community-based strengthening, aerobic and functional exercise	12 weeks (36 sessions)	3×/week for 1 h	↑ Knee extensors ↑ Total work load after exercise Significant baseline difference ↑ ODSS scores ↑ Physical functioning (SF-36) ↑ Fatigue	2b	B
Matjacic and Zupan [61]	16 8 IG 8 CG	RCT (both groups received exercise)	HMSN	Both groups: passive stretching, muscle strengthening Dynamic balance training differed: CG: managed by physiotherapist IG: performed on balance trainer	12 days	6 days/1 day rest/6 days for 40 min	↔ Intergroup results Intragroup ↑ Berg Balance Scale ↑ TUG ↑ 10-m walk test	2b	B

Table 6 continued

References	*N*	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup difference)	LOE	Grade of recommendation
Ruhland and Shields [65]	28 14 IG 14 CG	CCT (only partially randomized)	Chronic acquired peripheral neuropathy, HMSN, toxic neuropathy	Home exercise: strengthening with Thera-Band, stretching, aerobic conditioning	6 weeks	Advised daily	↔ Intergroup results Intragroup results ↑ Average muscle score	4	C
Lindeman et al. [66]	58 29 IG 29 CG	RCT (matched according to muscle strength and stair-climbing performance and then randomized into IG or CG)	30 MYD 28 HMSN	Strength-training	24 weeks	3×/week	↔ In MYD group ↔ Yimed motor performance ↑ Knee torques in HMSN group	2b	B

LOE levels of evidence, *IG* intervention group, *RCT* randomized controlled trial, *CCT* clinical controlled trial, *CG* control group, *TUG* timed up-and-go test, *FAP* familial amyloid polyneuropathy, *RPE* received perception of exertion, *PNP* peripheral neuropathy, *GBS* Guillain-Barré Syndrome, *CIDP* chronic inflammatory demyelinating polyradiculoneuropathy, *ODSS* overall disability sum score, *SF-36* Short-Form health survey, *MYD* myotonic dystrophy, *HMSN* hereditary motor and sensory neuropathy, ↑ indicates improvement, ↔ indicates no change

intensity exercise, or to refrain from non-weight-bearing activities such as swimming, bicycling, or arm exercises in case of foot injuries. Other than that, Internet sites, as well as ADA personnel, advise patients with diabetes and PNP to 'be careful when exercising' as 'some physical activities are not safe for people with neuropathy' [88]. Possible risks are mentioned, such as an increased risk of skin breakdown and infection as well as Charcot joint destruction, due to reduced sensitivity in the extremities [70]. However, current studies reveal that mild adverse events only occurred in 2 of 18 studies. Furthermore, patients exercising do not seem at higher risk for skin breakdown or foot ulceration, nor have weight-bearing exercises induced a higher risk than non-weight-bearing activities. Additionally, the efficacy of non-weight-bearing activities is low [53].

The large heterogeneity of the existing studies makes it difficult to define evidence-based recommendations, not only for peripheral neuropathy in general but also for the various subgroups. In order to give precise training guidelines, including duration, frequency, and intensity, more studies will be necessary. It is challenging to compare the various exercise programs of the individual studies as data is insufficient for the subgroups and a general comparison may be biased due to the potentially diverse underlying mechanisms of PNP that could alter the response to exercise. Furthermore, the studies differ in terms of the interventions, duration, frequency, heterogeneous inclusion- and exclusion criteria as well as outcome measures, which could also influence the effects. Since most neuropathies are characterized by a chronic disease course, exercise interventions at different timepoints during the disease course may impact their potential treatment benefit. Nevertheless, we will try to present some prevailing directions and therefore generate preliminary recommendations that will have to be confirmed by further studies.

According to the current evidence (see Table 7), balance exercises seem to have the highest effect on the crucial side effects of PNP, especially in primarily non-metabolic neuropathic disorders. Therefore, balance exercises should be included in exercise interventions and supportive care for PNP patients. Possible interventions to obtain this aim could be, for example, SMT, Tai Chi, and vibration exercises as these target the same mechanisms. Additionally, the type of exercises within the balance training will also have to be chosen carefully according to the symptom one wishes to address.

For patients with neuropathies of primarily metabolic origin, endurance exercises will presumably best target the onset as well as the progression of DPN. This is likely to also apply to other metabolically-induced neuropathies. Additional balance exercises or WBV [4] should be considered.

Table 7 Preliminary recommendations for patients with neuropathy based on the measured effects of current studies

Neuropathy	Symptoms	Interventions	Effects of exercise on sensory function	Effects of exercise on motor function	Other effects of exercise	Duration	Frequency, intensity	References
Chemotherapy-induced peripheral neuropathy (platinum derivatives, vinca alkaloids, taxanes, bortezomib, thalidomide, epothilones)	Decreased sensation Pins/needles/itching sensation Painful paresthesia or numbness Cold-induced dysesthesia Reduced or absent reflexes (Achilles and patellar) Loss of balance control Gait instability More falls and injuries Weakness	Sensorimotor training	Improved peripheral deep sensitivity and balance control (static, dynamic and perturbed)		QOL Higher level of activity	36 weeks, 2×/week	3–5 exercises: 20–40 s ≥40 s rest between each repetition ≥1 min rest between each exercise	Streckmann et al. [60]
		Endurance		Aerobic performance level	QOL Higher level of activity	36 weeks, 2×/week	10–30 min (60–70 % max. hf)	Streckmann et al. [60]
		Strength			QOL Higher level of activity	36 weeks, 2×/week	4 exercises, 1 min max. force	Streckmann et al. [60]
Diabetic neuropathy	Hypoesthesia, pin sensation, pain, reduced or absent reflexes (Achilles and patellar) Loss of balance control Autonomic dysfunction	Balance	Improved balance	Gait	NA	8 weeks 2×/week	30 min	Song et al. [55]
		Endurance	Preventive: less development, PNP, Better vibration, perception threshold, Improved nerve conduction velocity	NA	NA	Preventive: 4 years, 4×/week	Preventive: 60 min (brisk walking at 50–85 % heart rate reserve)	Balducci et al. [22]
			Progressive: nerve conduction velocity, distal and sural sensory MDNS			Progressive: 8 weeks/ 3–6×/weeks 150–300 min	Progressive: on treadmill (40–60 % heart rate reserve)	Dixit et al. [52]
		Combination (balance + strength)	Improved balance	Gait-orientated mobility	Reduced concern about falling	12 weeks 2×/week		Allet et al. [56]
		(balance + strength + endurance)	NA	Gait	NA			Mueller et al. [53]
		WBV + balance exercises	Postural sway BBS	TUG Five times sit-to-stand	HbA_{1C}	3× WBV +2× balance	WBV: 3 min; 15–30 Hz balance: 60 min	Lee et al. [4]

Table 7 continued

Neuropathy	Symptoms	Interventions	Effects of exercise on sensory function	Effects of exercise on motor function	Other effects of exercise	Duration	Frequency, intensity	References
Neuropathy of other causes Charcot Marie Tooth (hereditary mutation of axonal and/or myelin proteins)	Motor and sensory symptoms (depending on the subtype), no pain, chronic progressive	Balance	Improved balance	NA	NA	10 sessions twice daily	30 min Powered platform and Cawthorne Cooksey or Frenkel exercises	Nardone et al. [64]
FAP (extracellular deposition of insoluble amyloidal fibers, mostly synthesized within the liver [62])	Autonomic dysfunction, pain, hypoesthesia, paresis	Strength	NA	Knee torques (only in HSMN group)	NA	24 weeks 3×/week		Lindeman et al. [66]
		Combination balance + strength	No effect	No effect	No effect	12 days		Matjacic and Zupan [61]
		Combination strength + endurance	NA	Knee extensors Total work load	NA	12 weeks 3×/week	60 min unsupervised	Graham et al. [63]

QOL quality of life, *max hf* maximum heart rate, *PNP* peripheral neuropathy, *NA* not assessed, *FAP* familial amyloid polyneuropathy, *HSMN* hereditary motor and sensory neuropathy, *MDNS* Michigan Diabetic Neuropathy Score, *WBV* whole-body vibration, *BBS* Berg Balance Scale, *TUG* timed up-and-go test, HbA_{1C} glycosylated hemoglobin

In accordance with other reviews on exercise interventions for various causes [47], better results were achieved if training was supervised rather than home-based or community-based [58, 68]. It also seems that exercises need to be repeated at least twice a week, preferably for 12 weeks or longer, as studies with very short interventions (12 days to 6 weeks) and less frequency (once a week) [58, 61, 65] fail to produce significant intergroup effects. Of course, it depends on the intervention and the aim. For instance, SMT is known to impact balance control in healthy older adults after just 4 weeks [30]. Further studies should evaluate the individual types of exercises and determine whether combinations of exercises, such as endurance and SMT, could have additive effects, as well as the intensity and duration necessary to achieve the highest effect for this specific patient cohort. Furthermore, the potential of exercise in various phases of the disease (preventive, acute, and rehabilitation) needs to be evaluated.

Scientists should preferably choose a control group that has the same disease but does not participate in the exercise intervention. If offering an intervention to the control group is desired, the intervention should not target the outcome measurements as intergroup results will be too weak and biased [61].

The recommendations generated are based on rather low evidence and very heterogeneous studies and can thus only present a preliminary direction. Therefore, many more studies will be necessary to develop comprehensive clinical exercise recommendations. Nevertheless, exercise is currently an effective supportive measure for neuropathic patients and a good alternative to pharmaceutical approaches. Therefore, the translation of the present knowledge into practice should be initiated. The various societies responsible ought to contribute to the education and instruction of therapists and physicians in order to guarantee the best possible support for patients. Interdisciplinary collaborations are essential in striving towards standardization of exercise in supportive therapy.

5 Conclusion

Exercise is feasible, safe, and effective for neuropathic patients. Balance training has the potential to improve sensory and motor symptoms in PNP, while in PNP of metabolic etiology, endurance training can prevent the onset and delay the progression of PNP. Exercise is therefore a supportive therapy for neuropathic patients that should be taken more seriously.

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