Neuromuscular dysfunction and exercise training in people with diabetic peripheral neuropathy: A narrative review

Giorgio Orlando [a,*], *Stefano Balducci* [b], *Andrew J.M. Boulton* [c,d], *Hans Degens* [a,e], *Neil D. Reeves* [a]

[a] *Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, UK*
[b] *Metabolic Fitness Association, Monterotondo, Rome, Italy*
[c] *Department of Medicine, Manchester Royal Infirmary, Manchester, UK*
[d] *Diabetes Research Institute, University of Miami, Miami, FL, USA*
[e] *Lithuanian Sport University, Kaunas, Lithuania*

A B S T R A C T

Diabetic peripheral neuropathy (DPN) is a common condition that is associated with neu-romuscular dysfunction and peripheral sensory impairment. These deficits predispose patients to sensory and motor system limitations, foot ulcers and a high risk of falls. Exer-cise training has been proposed as an effective tool to alleviate neural deficits and improve whole-body function. Here we review the effects of DPN on neuromuscular function, the mechanisms underlying this impairment, and the neural and muscular adaptations to exercise training. Muscle dysfunction is an early hallmark of DPN. Deficits in muscle strength, power, mass and a greater fatigability are particularly severe in the lower extrem-ity muscles. Non-enzymatic glycation of motor proteins, impaired excitation–contraction coupling and loss of motor units have been indicated as the main factors underlying mus-cular dysfunction. Among the exercise-based solutions, aerobic training improves neural structure and function and ameliorates neuropathic signs and symptoms. Resistance train-ing induces marked improvement of muscle performance and may alleviate neuropathic pain. A combination of aerobic and resistance training (i.e., combined training) restores small sensory nerve damage, reduces symptoms, and improves muscle function. The evi-dence so far suggests that exercise training is highly beneficial and should be included in the standard care for DPN patients.

Abbreviations: ACh, acetylcholine; AT, aerobic training; DPN, diabetic peripheral neuropathy; HIIT, high intensity interval training; IAT, interval aerobic training; IENF, intraepidermal nerve fibre; LANSS, Leeds assessment of neuropathic symptoms and signs scale; MDNS, Michigan diabetic neuropathy score; MNSI, Michigan neuropathy screening instrument; NeuroQoL, neuropathy quality of life; RCT, randomised control trial; RT, resistance training; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VAS, visual analogue scale; VPT, vibratory perception threshold

1. Introduction

Diabetic peripheral neuropathy (DPN) is a debilitating late complication of diabetes, affecting up to half of diabetic patients [1]. Loss of peripheral sensation, proprioception and impaired neuromuscular function are the main clinical features of this condition [2,3]. As a consequence, those patients with DPN often experience difficulty in safely performing basic activities of daily living resulting in a marked deterioration in the quality of life, and have an up to 20-fold higher risk of falls compared with age-matched healthy individuals [4,5].

The natural history of DPN is one of progressive loss of nerve function in a distal-proximal gradient, predominantly marked by sensory deficits that occur early in the disease, whereas motor deficits become more clinically evident at later stages of DPN [3]. Recent investigations show that mus-cular dysfunction is an early hallmark of diabetes and pro-gresses with the onset and severity of DPN [6,7]. It has been proposed that mechanisms other than motor nerve damage alone are also involved in the dysfunction of the muscular system in people with DPN.

Although there is currently no effective pathogenetic treatment for DPN [1], a number of cohort studies and clinical trials have shown that exercise training may partially restore neural and muscle function in people with DPN [8,9]. Based on these observations, exercise training has been proposed as a safe and effective strategy to slow the progression of DPN and to counteract its functional consequences.

The aim of this review is to provide an overview of the available evidence on the effects of DPN on neuromuscular function, the mechanisms underlying neuromuscular dysfunction and the adaptability of the nervous and muscular systems to exercise training.

2. Methods

A detailed search of PubMed, EMBASE, Scopus and Web of Science databases was conducted from their inception to March 2021 for the following key terms: 'diabetic neuropathies' OR 'diabetic peripheral neuropathy' OR 'diabetes' AND 'muscle' OR 'peripheral nerves' OR 'neuromuscular system' AND 'exercise training' OR 'aerobic training' OR 'resistance training' or 'combined training'. The systematic reviews and original research papers were selected according to their scientific relevance. The literature search was conducted mainly by the corresponding author (GO) of this study, with the co-authors vetting or/and providing additional suggestions and/or missed literature when necessary. Publications retrieved by manually back-searching from citations in relevant reviews and original research articles were also included. The inclusion criteria were: publications containing a patient diagnosis of type 1 (T1DM) or type 2 diabetes mellitus (T2DM) and DPN; characterisation of structure and function of the muscular and/or nervous systems. Publications were excluded if they were not written in English or not published in peer-reviewed journals. The focus of the literature review was the effects of exercise training in DPN, in terms of structured aerobic or resistance training alone or the combination of these modalities (combined training), on neuromuscular structure and function.

3. Neuromuscular function and diabetic peripheral neuropathy

Neuromuscular dysfunction is a typical complication of DPN, characterised by loss of muscle strength (i.e., force-producing capacity) and power (i.e., force $\times$ velocity) that is attributable to both a loss of muscle mass (atrophy) and poor muscle quality (i.e., low/reduced force per unit of muscle area) [10–16]. In addition to a progressive loss of contractile tissue (atrophy), there is also an accumulation of intra- and inter-muscular adipose tissue, capillary rarefaction and loss of oxidative capacity [11,13,17]. Muscle abnormalities first occur distally in the toes and feet before gradually spreading to the leg and thigh muscles [2]. Structural and functional deficits of the muscle progress with the severity of DPN [18]. Major detrimental effects have been documented in the ankle (i.e., ankle plantar flexors) and foot muscles (i.e., intrinsic foot muscles) [12,13,16] although a recent study has reported similar

strength reductions (-30%) in ankle and knee extensors in a mixed group of diabetic patients with and without DPN [17].

Loss of muscle power is one of the main functional neuromuscular performance deficits, as it declines more precipitously than muscle strength as not only the force generating capacity is reduced, but also perhaps the shortening velocity (power = force × velocity) [7,11]. Greater muscle fatigability (i.e., activity-induced reduction in strength or power) is another notable component of neuromuscular dysfunction in DPN [6,14,19]. These deficits are strongly correlated with sensory and motor nerve function, promoting the concept that muscle fatigability and deficits in muscle power are sensitive functional parameters reflecting the detrimental effects induced by the DPN on the neuromuscular system [6,7,15]. DPN patients may also display impaired motor control and this has been illustrated in some studies by delayed peak muscle activation despite an earlier "switching on" of muscles during functional tasks, such as level walking and when climbing stairs [20,21]. Together, these deficits are responsible for biomechanical changes leading to a gait pattern that is characterized by a slower, stiffer and unsteady gait, associated with focal areas of high foot pressure increasing the risk of foot ulcer development [5,22,23]. Consequently, DPN patients are at high risk of falling and developing foot complications.

Several cross-sectional studies in large numbers of both T1DM and T2DM patients with DPN [6,10,14,24,25] have reported that neuromuscular dysfunction is an early, rather than a late complication of DPN as previously postulated by Andersen et al., [26], and that muscles that are seemingly not affected by peripheral neuropathy (e.g., upper body). may also be involved. For instance, 20% – 40% lower muscle strength during dynamic and static tasks was detected in both the upper (i.e., shoulder and arm muscles) and lower body (i.e., thigh and hip muscles) of patients with mild to moderate DPN compared to healthy individuals [10,14,25]. These findings indicate that muscle dysfunction is an early hallmark of DPN that is only partly explained by peripheral motor nerve damage. There is also evidence that muscle function impairment is an independent correlate not only of DPN but also of autonomic neuropathy and diabetic retinopathy, promoting the concept that the combination of more complications is related to the greatest muscle decline [6,24].

As discussed above, deterioration in muscle structure and function precede the onset of long-term complications in both T1DM and T2DM, but these deficits are exacerbated by DPN [17,27–30]. Recent studies reported an approximatively 20% lower isometric knee extensor muscle strength and endurance in a large group of diabetic patients without DPN compared with a well-matched group of healthy individuals [14,31]. Furthermore, they also found a 20–30% lower muscle function in people with mild to moderate neuropathy when compared with a group of non-neuropathic patients matched for age, diabetes duration, BMI, fat-free mass and physical activity level [14]. Lower muscle strength has also been documented in individuals with impaired glucose tolerance and in newly diagnosed T2DM compared to non-diabetic controls [28]. Similarly, adolescents with T1DM display lower muscle function compared with their age-matched counterparts [27]. Finally, there is evidence of a lower quadriceps muscle volume (–22%) and higher intramuscular fat content (+10%) in the calf muscles in a group of diabetic patients without DPN [17]. The above observations are, however, not unequivocal, as some studies observed that non-neuropathic patients had a similar quadriceps muscle strength, volume and quality compared with healthy individuals [13,18]. The possible causes for this discrepancy are not clear, although it should be noted that these studies were not only limited by the small number of participants but also did not consider physical activity level.

Although more research is required, the above observations suggest that muscle dysfunction in DPN may be due to a synergistic effect of hyperglycaemia and motor nerve damage on the muscular system. Because muscle deficits occur in muscles of the upper and lower body, it has been suggested that diabetes induces a systemic effect on the muscular system. Finally, considering the strong relationship between chronic hyperglycaemia and muscle structure and function [32,33], it is hypothesised that the systemic effects on muscle are more pronounced in DPN compared with non-neuropathic patients, as these patients are typically characterised by worse cardiometabolic health and a longer period of diabetes.

4. Neural and muscular factors underlying the loss of neuromuscular performance

Although the mechanisms underlying the impaired neuromuscular function in diabetes and DPN are complex and not entirely clear, it is important to note that chronic hyperglycaemia is capable of altering the vascular and sensorymotor systems. Indeed, as showed in Fig. 1, chronic hyperglycaemia may cause not only denervation by damage of the peripheral nerves but may also alter muscle fibre function through several mechanisms among which non-enzymatic glycation of skeletal muscle proteins.

In the last few decades, DPN has been shown to be responsible for several structural and functional alterations in motor neurons, causing neuromuscular transmission impairment or failure, which in turn leads to muscle dysfunction and atrophy [15,34-36]. The neuronal dysfunction due to axon and myelin degeneration is further compounded by a progressive deterioration of the ability of the nervous system to regenerate itself, resulting in insufficient compensatory reinnervation [34,35]. Consequently, the number of functioning motor units in the tibialis anterior and the first dorsal interosseous has been estimated to be reduced by up to 60% and 30%, respectively, in people with severe DPN compared to healthy controls [35,36]. Interestingly, although electrophysiological studies highlight motor units loss, it is equivocal whether there are any histological changes in motor neurons in DPN [37], and most studies did not observe any reduction in the number of motor neurons cell bodies. This suggests that in contrast with the well-documented loss of sensory neurons, motor neurons could be partially preserved during neuropathy because cell bodies are located within the spinal cord and therefore protected by circulating molecules from the blood–brain barrier [37].

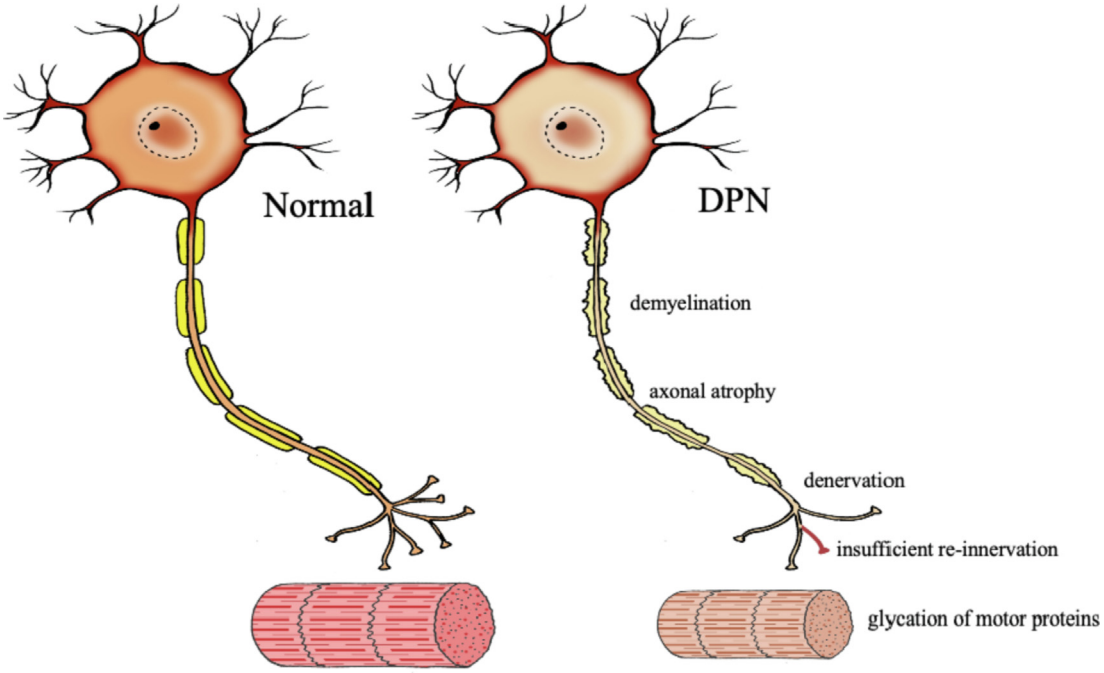

Fig. 1 – Effects of diabetic peripheral neuropathy on motor nerve and muscle fibre. Fig. 1 is a diagrammatic representation of the changes induced by diabetic peripheral neuropathy (DPN) on motor nerve and muscle fibre. During this condition, motor neurons are subject to progressive axonal degeneration and segmental demyelination, leading to axonal atrophy, terminal denervation and, eventually, if no reinnervation takes place, muscle fibre loss. The neuronal dysfunction is further compounded by a progressive deterioration of the ability of the nervous system to regenerate. At muscular level, mitochondrial dysfunction, capillary rarefaction, and non-enzymatic glycation of myofibrillar proteins (brown colour) are typical manifestation of diabetes and DPN. These contribute synergistically to muscle dysfunction and atrophy. In particular, glycation of the myofibrillar proteins actin and myosin is linked to impairment of the muscle fibre force-generating capacity and reduction in maximal shortening velocity that synergistically reduce the power generating capacity of the muscle fibres. Muscle dysfunction in DPN is the result of a synergistic effect from hyperglycaemia and motor nerve damage on the muscular system.

Functional and structural changes of the neuromuscular system may be detectable in diabetic patients long before the clinical presentation of DPN [29,38-40]. One electrophysiological abnormality is the lower motor unit number in the foot muscles of T1DM patients who do not yet present clinical evidence of DPN [38]. Some attempts at regeneration during these early stages of DPN is evident as a high prevalence of A-waves, indicators of the neurogenic process, may be found during stimulation of the tibial nerves in non-neuropathic T2DM patients [39]. In addition to the loss of motor units, the behaviour of motor units and neural drive in diabetes is also changed as reflected by a greater variability in the torque signal and the single motor unit discharge rate during isometric contractions in T2DM patients [29]. At the level of the neuromuscular junction, changes are also detectable such as terminal denervation, endplate degeneration and evidence of collateral re-innervation in newly diagnosed T1DM patients without clinical signs of neuropathy [40]. Similarly hyperglycaemia in rodents was associated with a decreased motor nerve conduction velocity, a reduced number of acetylcholine (ACh)-containing vesicles and ACh receptor expression, marked swollen mitochondria with irregular cristae indicative of mitochondrial degeneration at the nerve terminals, motor endplate abnormalities and disrupted t-tubules [41,42]. These observations suggest that neuromuscular junctions are an important target of diabetes-induced hyperglycaemia and that compensatory mechanisms are present to alleviate denervation.

Although muscle dysfunction in diabetes has been well characterised, the mechanisms underlying this defect need to be elucidated. Muscle dysfunction is only partly explained by the loss of muscle mass and hence also qualitative changes in muscle must contribute to the muscular dysfunction in diabetes [30,33] Of course, part of it could be the above-discussed problems with the neural drive, but it has also been hypothesised that hyperglycaemia has a negative impact on both the force and power-generating capacity of the remaining muscle tissue. Although the effects of diabetes on single skeletal muscle fibre contractile properties have so far been conducted only in animal models, these studies do support the hypothesis that hyperglycaemia induces a reduced ability to generate force [43,44]. Non-enzymatic glycation of skeletal muscle proteins, sarcoplasmic reticulum dysfunction, abnormalities in mitochondrial ultrastructure and bioenergetics and alterations of muscle membrane electrical properties and dysfunction of microcirculation leading to an impairment of the delivery and distribution of metabolic substrates have all been proposed to contribute to skeletal muscle dysfunc-

tion in diabetes [2,45,46]. In particular, glycation appears to impair muscle fibre function, where *in vitro* studies have shown that the speed at which actin is propelled by myosin in *in vitro* motility assays is decreased significantly after exposure to glucose, consequent to structural modifications in the catalytic domain of the myosin head [47,48]. Such a glycation-induced slowing of muscle fibres will have a significant impact on the power generating capacity of a muscle fibre, since power is the product of force and velocity. There is evidence that particularly types II fibres are glycated in diabetes [45], and as type II fibres produce higher power than type I fibres [49], this glycation of type II fibres may significantly contribute to the marked decline in muscle power documented in diabetes and DPN. A recent study [50] additionally showed that cardiac fibres of people with diabetes had lower mechanical performance and higher post-translational glycation of myofilaments caused by methylglyoxal, a by-product of glycolysis. Moreover, *ex vivo* exposure to relevant doses of methylglyoxal resulted in reduced contractility and Ca^2 + sensitivity. It is therefore hypothesised that glycation of myofilaments is directly linked to reduced contractile function in patients with diabetes [50].

Although the above circumstantial evidence suggests that hyperglycaemia is a significant cause of muscle fibre dysfunction in diabetes and DPN, the impact of long-standing hyperglycaemia on the contractile properties of single skeletal muscle fibre in humans remains unknown. Similarly, there is a paucity of information about the relationship between motor denervation and muscle fibre function. New studies in the field of the effects of diabetes and DPN on contractile properties of skeletal muscle are necessary.

5. Neural and muscular adaptations to exercise training

There are currently no effective treatments to prevent or slow the progression of DPN. Improvement and stabilization of glycaemic control, pain relief via pharmacological therapy and reduction of cardiovascular risk factors are the only available options to manage the condition [1]. Furthermore, since DPN patients have a high risk of falling and often have severe functional limitations, particular attention should be given to identify strategies that improve the capacity of the neuromuscular system [2].

Exercise training is undoubtedly a unique therapeutic strategy which has the potential to elicit several beneficial effects in patients with DPN through various positive adaptations of cardiovascular and neuromuscular systems and metabolism [51]. Clinical trials have shown that exercise may improve muscle performance and several electrophysiological parameters, as well as ameliorate symptoms in diabetic patients with and without DPN [52–55]. It has been shown that peripheral nerve function improved after four years of regular exercise and was associated with a lower risk of developing DPN [55]. Two recent systematic reviews also indicate that a combination of aerobic and/or resistance exercises with balance exercises improves postural control [56,57]. Taken together, this suggests that exercise induces nerve and muscle benefits, thus preventing or alleviating sensory-motor deficits and their functional consequences. Notably, several studies have shown that exercise training may induce nerve regeneration also without any improvement in glycaemic control, thus supporting the hypothesis that exercise may partially mediate nerve plasticity through mechanisms independent of glucometabolic status [58,59]. Indeed, studies in animal models support the hypothesis that exercise induces systemic nerve adaptations via restoration of levels of circulating neurotrophic factors, reducing oxidative stress and inflammation, and improving microvascular function [60-62].

As shown in Table 1, aerobic training (AT), resistance training (RT) and a combination of AT and RT (combined training, or CT), together with standard pharmacological treatment, appear to be effective tools to alleviate neuropathic complications, compared to standard care alone [9,52-54,59,63-67]. A systematic review reported that AT impacts nerve function positively and causes minimal adverse effects, thus indicating it as a potent strategy to manage DPN [68]. However, the authors highlighted the poor quality of most of the studies, as well as high heterogeneity between the exercise protocols performed, indicating the necessity of further investigations.

Among the randomized controlled trials (RCTs) exploring the effects of AT, recent studies reported an increased sensory nerve conduction velocity (+2.1 m/s) and improved Michigan Diabetic Neuropathy Score (MDNS, − 4.3 points) after 12 weeks of moderate AT [9,54]. Dixit et al. noted improved sensory (+7.7 m/s) and motor nerve (+3 m/s) conduction velocities, decreased MDNS (ranging from −5 to −7 points), lower vibratory perception thresholds (VPT) at different sites (e.g., VPT halluces: −6 V) and improved symptomatology as measured by the Neuropathy Quality of Life (NeuroQoL, total score: −8.4 points) after 8 weeks of moderate AT [58,63,64]. A further study comparing the effects of continuous moderate AT with high intensity interval training (HIIT) for 15 weeks indicated that HIIT was more effective at reducing neuropathic pain as assessed by the Leeds Assessment of Neuropathic Symptoms and Signs Pain scale (LANSS, −3.6 points) in a large group of obese women with DPN [65]. In addition to improving conduction velocities and symptomatology, one pre-post single group study of 24 weeks found that AT increases the action potential amplitudes of both the motor and sensory nerves (motor amplitude: +0.9 mV; sensory amplitude: +1.2 μV) in a small group of people with moderate to severe neuropathy [59].

These findings show that AT of moderate intensity (i.e., 40–60% of maximal oxygen uptake) may induce functional and structural benefits in the sensory and motor nerves. DPN patients should perform from 60 to 360 min weekly of aerobic exercises spread over three to six sessions per week [9,63]. Neural benefits may be evident after eight weeks of intervention and translate into an improvement in neuropathic signs that will be further enhanced with longer intervention durations (e.g., 24 weeks) [59,63]. Interestingly, AT appeared particularly effective in patients with severe DPN, supporting the concept that exercise also elicits marked beneficial effects on the nervous system in diabetic patients with severe nerve involvement [59]. At present, the capacity of aerobic training to induce muscle adaptations remain to be addressed.

As is widely documented in healthy individuals, RT appears to be the best modality to enhance muscle strength, promote muscle hypertrophy and neuromuscular remod-

Table 1 – Summary of studies exploring neural and muscular adaptations to exercise training in people with diabetic peripheral neuropathy.

Reference	Study design	Type of exercise	Intensity	Frequency (sessions/week)	Volume	Duration (weeks)	Neural effects	Muscular effects
Gholami et al. 2018[9]	RCT	AT	50–70% HRR	3	60–135 min/wk	12	SNCV ↑ SNA = MNCV = MNA =	NR
Gholami et al. 2020[54]	RCT	AT	50–70% HRR	3	90–135 min/wk	12	MDNS ↓	NR
Dixit et al. 2014[63]	RCT	AT	40–60% HRR	3–6	150–360 min/wk	8	SNCV ↑ SNA = SNDL = MNCV ↑ MNA = MNDL = MDNS ↓	NR
Dixit et al. 2014[58]	RCT	AT	40–60% HRR	5–6	150–360 min/wk	8	NeuroQoL ↓ MDNS ↓	NR
Dixit et al. 2019[64]	RCT	AT	40–60% HRR	3–6	150–360 min/wk	8	VPT: alluces ↑ malleoli ↑ 1-MTP ↑	NR
Fisher et al. 2007[59]	Pre-post single group design	AT	40–75% VO_{2R}	3	90 min/wk	24	SNCV ↑ SNA ↑ MNCV ↑ MNA ↑ F-latencies ↑	NR
Hamed et al. 2014[65]	RCT	AT vs HIIT	AT: 50–60% HR HIIT: 30 reps of 8 sec sprints and 12 sec of rest	3	AT: 150 min/wk HIIT: 60 min/wk	15	LANSS ↑ LEFS =	NR
Handsaker et al. 2014[52]	RCT	RT	12 reps maximum	1	3 sets × 12 reps. 3 lower body exercises	16	NR	SSG: ankle ↑ knee ↑
Nadi et al. 2019[66]	RCT	RT	30% 1-RM	3	1–3 sets of 30 sec	12	MNSI ↓	NR
Stubbs et al. 2019[67]	RCT	AT vs RT vs CT	AT: 60–80% VO_{2peak} RT:isokinetic knee extension (velocity of 90 s^{-1}) CT: AT + RT	3	RT: 3-6 sets x 10 reps RT, AT and CT: 90–135 min/wk	12	MNCV = MNA = MNDL = SNCV = SNA = SNDL = VPT = HPT = CDT =	NR
Kluding et al. 2012[53]	Pre-post single group design	CT	AT: 50–70% VO_{2R} + RT: 7–10 RPE	3–4	AT: 60–100 min/wk RT: 1 set × 10–20 reps. 10 upper and lower body exercises	10	IENFB ↑ MNCV = MNA = MNDL = SNCV = SNA = SNDL = VPT = HPT = CDT = MNSI ↓ VAS pain ↓	NR

Table 1 – (continued)

Reference	Study design	Type of exercise	Intensity	Frequency (sessions/week)	Volume	Duration (weeks)	Neural effects	Muscular effects
Seyedizadeh et al. 2020[70]	RCT	CT	IAT: 5–10 reps of 3 min at 50–65% HRR followed by 30 sec of rest + RT: 8–12 reps maximum	3	IAT: 50–100 min/wk RT: 2–3 sets × 8–12 reps. 7 upper and lower body exercises	8	NR	Strength: trunk = lower body ↑
Otterman et al. 2011[71]	Pre-post single group design	CT	AT: 40–65% HRR + RT: 40–65% 1-RM	3	AT: 90 min/wk RT: 2–3 sets × 10–15 reps. 5 upper and lower body exercises	12	NR	Strength: knee ↑
Praet et al. 2008[72]	Pre-post single group design	CT	RT: 50–60% 1-RM + IAT: 4–8 reps of 30 sec (50–60% of W_{max}) followed by 60 sec of rest	3	CT: 135 min/wk RT: 2 sets × 10 reps. 4 upper and lower body exercises	12	NR	Strength: upper body↑ lower body ↑ MFD=

Abbreviations: ↑ increased; =, unchanged; ↓, decreased; NR, not reported; 1-RM: one-repetition maximum; 1-MTP: first metatarsal phalanx; AT: aerobic training; CDT: cooling detection threshold; HPT: heat pain threshold; IAT: interval aerobic training; LANSS: Leeds assessment of neuropathic symptoms and signs scale; HIIT: high intensity interval training; HR: heart rate; HRR: heart rate reserve; IENFB, intraepidermal nerve fibre branching; LEFS: lower extremity functional scale; MFD: muscle fibre distribution; MDNS: Michigan diabetic neuropathy score; MNA: motor nerve amplitude; MNCV: motor nerve conduction velocity; MNDL: motor nerve distal latency; MNSI: Michigan neuropathy screening instrument; NeuroQoL: neuropathy quality of life; RCT: randomised control trial; RPE: rate of perceived exertion; RT: resistance training; SSG: speed of strength generation; SNA: sensory nerve amplitude; SNCV: sensory nerve conduction velocity; SNDL: sensory nerve distal latency; VAS: visual analogue scale; VPT: vibratory perception threshold; W_{max}: maximal workload capacity.

elling also in people with DPN [69]. The last of these effects of RT may be mediated by the RT-induced reduction in several factors causing or accelerating DPN progression, such as hyperglycaemia, dyslipidaemia, insulin resistance, systemic inflammation and neuro-hormonal growth factor deficiency [51]. RT may be more suitable than AT for DPN patients, as they are commonly highly deconditioned and experience mobility problems. Improving their muscle strength may help to prepare DPN patients to be better able to undertake AT.

Although RT has the potential to counteract neural and muscular damage with DPN, only few investigations, exclusively RCTs, have been conducted in this regard, with only one exploring nerve function through electrophysiological measures. Handsaker et al. [52] observed that a high-load RT strategy is safe and markedly increased the speed of ankle (stair ascent, +27%; stair descent, +78%) and knee (stair ascent, +35%; stair descent, +60%) force generation during stair ascent and descent in patients with moderate DPN [52]. A more recent study conducted by Nadi et al. documented improvements in pain and tingling as measured by the reduction of Michigan Neuropathy Screening Instrument (MNSI) score after 12 weeks of low intensity RT [66]. Finally, Stubbs et al. reported that 12 weeks of isokinetic RT focused on the quadriceps muscles did not improve nerve conduction and quantitative sensory testing in a small group of people with moderate to severe DPN [67]. It is important, however, to note that the RT protocol used, considered only the involvement of a specific muscle group, thus limiting the capacity of RT to induce systemic metabolic adaptations.

This evidence indicates that RT is a safe and an effective tool to counteract muscle dysfunction, alleviates some neuropathic symptoms (i.e., pain and tingling) and thereby may improve functional performance during daily life tasks. While it is conceivable that multiple sets (3 sets of 12 repetitions) of high-load RT (75–80% of one-repetition maximum) once a week for as short as 16 weeks may induce a marked increase in muscle performance [52]. However, low intensity RT is a safe and well-tolerated strategy and should be considered as a first choice in high-deconditioned DPN patients [66]. Although this evidence promotes RT as a strategy to elicit benefits on some sensory-motor deficits, it should be interpreted carefully as it results from a small number of studies. Finally, further studies are required to uncover the adaptability of sensory and motor nerve damage to RT.

Research has shown that CT elicits superior metabolic control than AT or RT alone and may induce cardiorespiratory adaptations in people with diabetes [51]. To the best of our knowledge, few studies have explored the effectiveness of CT to counteract neuromuscular complications of DPN. Kluding et al., in a pre-post single group study, showed that 10 weeks of moderate CT increased intraepidermal nerve fibre branching (IENF: +0.11 ± 0.15 nodes/fibre) and reduced neuropathic symptoms as assessed by MNSI (-1.25 points) and Visual Analogue Scale (VAS) score (pain, −18.1 points) [53]. No changes, however, were detected in nerve conduction velocity and quantitative sensory testing. In addition, a RCT has shown an improvement, albeit minimal (+6%), only in the lower body muscle strength after 8 weeks of CT [70]. Similarly, a feasibility study has observed a 11% (14 Nm) increase of the maximal voluntary knee extensor torque after 12 weeks

of training [71]. Finally, Praet et al. found a 10% and 18% strength increase in the upper and lower body, respectively, and no changes in muscle fibre distribution and cross-sectional area, after 10 weeks of a combination of moderate RT and interval aerobic training [72].

The above-stated findings support the notion that CT partially restores small sensory nerve damage, ameliorates symptoms and improves muscle function. Although the current evidence promotes the use of CT in people with DPN, investigations with a more robust study design are necessary. Nervous and muscular adaptations to CT may be evident with aerobic and resistance exercises of moderate intensity (AT: 40–70% of maximal oxygen uptake; RT: 40–60% of one-repetition maximum), relatively short duration (10–12 weeks), and high frequency of intervention (3–4 sessions/week) [53,71]. CT should include 50 to 100 min of aerobic exercise per week combined with a single (one set of 10–20 repetitions)[53] or multiple sets (2–3 sets of 8–12 repetitions) [71] of 5–10 strength exercises. Since no effects have been found in the larger nerve fibres, the capacity of CT to counteract sensory and motor deficits is questionable. Although CT could have an impact on muscle performance, it appears that these adaptations are not comparable with those observed with RT alone. This is consistent with the current debate on the adaptability of the muscular system with CT. Indeed, it has been suggested that AT may dampen RT-induced adaptations (e.g. muscle strength and growth)[73], but others report minimal interference between modalities [74,75]. More research is needed to test the effectiveness of CT on alleviating muscular dysfunction in DPN.

6. Conclusions

It appears that muscular dysfunction in DPN is caused by a synergistic effect of the diabetic state and motor nerve damage. Such deficits present in the early stages of DPN and progress with the severity of peripheral nervous system damage. Loss of functional motor units, neuromuscular transmission impairment and glycation of myofibrillar proteins in muscle fibres have been proposed as the primary factors contributing to muscular system impairments in diabetes patients. Muscle function deficits are particularly severe in the lower extremities. Given the significant role of neuromuscular complications in impaired physical function, these deficits should be monitored, and strategies aimed at alleviating them should be included in the standard care of DPN patients.

Exercise training can partially restore sensorimotor damage in people with DPN and is often accompanied by improvements in muscle performance and neuropathic symptoms, leading to better physical function. Specifically, AT elicits several benefits at the nervous system level, improve neuropathic signs and reduce symptomatology promoting AT as a strategy to slow the progression of DPN, however, its potential to counteract muscle dysfunction is unclear. RT is the most promising strategy to counteract muscle dysfunction and may also alleviate some neuropathic symptoms. Finally, CT may partially restore small sensory nerve damage, ameliorate symptomatology and improve muscle function. Although the current evidence promotes exercise training as an effective tool for alleviating sensory-motor deficits, high-quality studies are required and the mechanisms underlying nervous and muscular adaptations to exercise need to be addressed.

Author contributions

GO was primarily responsible for drafting the manuscript, with contributions and input to specific sections by all authors. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Sarah Reeves for production of the original figure.

REFERENCES

[1] Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: A position statement by the American diabetes association. Diabetes Care 2017;40 (1):136–54. https://doi.org/10.2337/dc16-2042.

[2] Orlando G, Balducci S, Bazzucchi I, Pugliese G, Sacchetti M. Neuromuscular dysfunction in type 2 diabetes: Underlying mechanisms and effect of resistance training. Diabetes Metab Res Rev 2016;32(1):40–50. https://doi.org/10.1002/dmrr.2658.

[3] Boulton AJM, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. Diabetes Care 2004;27(6):1458–86. https://doi.org/10.2337/diacare.27.6.1458.

[4] MacGilchrist C, Paul L, Ellis BM, Howe TE, Kennon B, Godwin J. Lower-limb risk factors for falls in people with diabetes mellitus. Diabet Med 2010;27:162–8. https://doi.org/10.1111/j.1464-5491.2009.02914.x.

[5] Reeves ND, Orlando G, Brown SJ. Sensory-Motor Mechanisms Increasing Falls Risk in Diabetic Peripheral Neuropathy. Medicina (B Aires) 2021;57:457. https://doi.org/10.3390/medicina57050457.

[6] Orlando G, Sacchetti M, D'Errico V, Haxhi J, Rapisarda G, Pugliese G, et al. Muscle fatigability in patients with type 2 diabetes: relation with long-term complications. Diabetes Metab Res Rev 2020;36(2). https://doi.org/10.1002/dmrr.v36.210.1002/dmrr.3231.

[7] Sacchetti MS, Balducci S, Bazzucchi I, Carlucci F, Di Palumbo AS, Haxhi J, et al. Neuromuscular dysfunction in diabetes: Role of nerve impairment and training status. Med Sci Sports Exerc 2013;45(1):52–9. https://doi.org/10.1249/MSS.0b013e318269f9bb.

[8] Kluding PM, Bareiss SK, Hastings M, Marcus RL, Sinacore DR, Mueller MJ. Physical Training and Activity in People With Diabetic Peripheral Neuropathy: Paradigm Shift. Phys Ther 2016;97:31–43. https://doi.org/10.2522/ptj.20160124.

[9] Gholami F, Nikookheslat S, Salekzamani Y, Boule N, Jafari A. Effect of aerobic training on nerve conduction in men with type 2 diabetes and peripheral neuropathy: A randomized controlled trial. Neurophysiol Clin 2018;48(4):195–202. https://doi.org/10.1016/j.neucli.2018.03.001.
[10] Ferreira JP, Sartor CD, Leal ÂMO, Sacco ICN, Sato TO, Ribeiro IL, et al. The effect of peripheral neuropathy on lower limb muscle strength in diabetic individuals. Clin Biomech 2017;43:67–73. https://doi.org/10.1016/j.clinbiomech.2017.02.003.
[11] Hilton TN, Tuttle LJ, Bohnert KL, Mueller MJ, Sinacore DR. Excessive Adipose Tissue Infiltration in Skeletal Muscle in Individuals With Obesity, Diabetes Mellitus, and Peripheral Neuropathy: Association With Performance and Function. Phys Ther 2008;88:1336–44. https://doi.org/10.2522/ptj.20080079.
[12] Moore CW, Allen MD, Kimpinski K, Doherty TJ, Rice CL. Reduced skeletal muscle quantity and quality in patients with diabetic polyneuropathy assessed by magnetic resonance imaging. Muscle Nerve 2016;53(5):726–32. https://doi.org/10.1002/mus.24779.
[13] Stouge A, Khan KS, Kristensen AG, Tankisi H, Schlaffke L, Froeling M, et al. MRI of skeletal muscles in participants with type 2 diabetes with or without diabetic polyneuropathy. Radiology 2020;297(3):608–19. https://doi.org/10.1148/radiol.2020192647.
[14] Orlando G, Balducci S, Bazzucchi I, Pugliese G, Sacchetti M. The impact of type 1 diabetes and diabetic polyneuropathy on muscle strength and fatigability. Acta Diabetol 2017;54(6):543–50. https://doi.org/10.1007/s00592-017-0979-9.
[15] Allen MD, Major B, Kimpinski K, Doherty TJ, Rice CL. Skeletal muscle morphology and contractile function in relation to muscle denervation in diabetic neuropathy. J Appl Physiol 2014;116(5):545–52. https://doi.org/10.1152/japplphysiol.01139.2013.
[16] Andreassen CS, Jakobsen J, Ringgaard S, Ejskjaer N, Andersen H. Accelerated atrophy of lower leg and foot muscles-a follow-up study of long-term diabetic polyneuropathy using magnetic resonance imaging (MRI). Diabetologia 2009;52(6):1182–91. https://doi.org/10.1007/s00125-009-1320-0.
[17] Almurdhi MM, Reeves ND, Bowling FL, Boulton AJM, Jeziorska M, Malik RA. Reduced lower-limb muscle strength and volume in patients with type 2 diabetes in relation to neuropathy, intramuscular fat, and Vitamin D levels. Diabetes Care 2016;39(3):441–7. https://doi.org/10.2337/dc15-0995.
[18] Andersen H, Nielsen S, Mogensen CE, Jakobsen J. Muscle strength in type 2 diabetes. Diabetes 2004;53(6):1543–8.
[19] Allen MD, Kimpinski K, Doherty TJ, Rice CL. Decreased muscle endurance associated with diabetic neuropathy may be attributed partially to neuromuscular transmission failure. J Appl Physiol 2015;118(8):1014–22. https://doi.org/10.1152/japplphysiol.00441.2014.
[20] Brown SJ, Handsaker JC, Bowling FL, Maganaris CN, Boulton AJM, Reeves ND. Do patients with diabetic neuropathy use a higher proportion of their maximum strength when walking ? J Biomech 2014;47(15):3639–44. https://doi.org/10.1016/j.jbiomech.2014.10.005.
[21] Handsaker JC, Brown SJ, Bowling FL, Cooper G, Maganaris CN, Boulton AJM, et al. Contributory factors to unsteadiness during walking up and down stairs in patients with diabetic peripheral neuropathy. Diabetes Care 2014;37(11):DC_140955. https://doi.org/10.2337/dc14-0955.
[22] Reeves ND. Gait and Exercise Training in Diabetic Peripheral Neuropathy. Foot Diabetes 2020:187–200. https://doi.org/10.1002/9781119445821.ch11.
[23] Fernando M, Crowther R, Lazzarini P, Sangla K, Cunningham M, Buttner P, et al. Biomechanical characteristics of peripheral diabetic neuropathy: A systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. Clin Biomech 2013;28(8):831–45. https://doi.org/10.1016/j.clinbiomech.2013.08.004.
[24] Balducci S, Sacchetti M, Orlando G, Salvi L, Pugliese L, Salerno G, et al. Correlates of muscle strength in diabetes. Nutr Metab Cardiovasc 2014;24(1):18–26.
[25] IJzerman TH, Schaper NC, Melai T, Meijer K, Willems PJB, Savelberg HHCM. Lower extremity muscle strength is reduced in people with type 2 diabetes, with and without polyneuropathy, and is associated with impaired mobility and reduced quality of life. Diabetes Res Clin Pract 2012;95(3):345–51. https://doi.org/10.1016/j.diabres.2011.10.026.
[26] Andersen H. Motor neuropathy. first ed. Elsevier B.V.; 2014. 10.1016/B978-0-444-53480-4.00007-2.
[27] Maratova K, Soucek O, Matyskova J, Hlavka Z, Petruzelkova L, Obermannova B, et al. Muscle functions and bone strength are impaired in adolescents with type 1 diabetes. Bone 2018;106:22–7. https://doi.org/10.1016/j.bone.2017.10.005.
[28] Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DIW, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? Diabetes Care 2005;28(10):2541–2. https://doi.org/10.2337/diacare.28.10.2541.
[29] Senefeld JW, Keenan KG, Ryan KS, D'Astice SE, Negro F, Hunter SK. Greater fatigability and motor unit discharge variability in human type 2 diabetes. Physiol Rep 2020;8:1–15. https://doi.org/10.14814/phy2.14503.
[30] Volpato S, Bianchi L, Lauretani F, Lauretani F, Bandinelli S, Guralnik JM, et al. Role of muscle mass and muscle quality in the association between diabetes and gait speed. Diabetes Care 2012;35(8):1672–9. https://doi.org/10.2337/dc11-2202.
[31] Orlando G, Balducci S, Bazzucchi I, Pugliese G, Sacchetti M. Muscle fatigability in type 2 diabetes. Diabetes Metab Res Rev 2017;33(1):e2821. https://doi.org/10.1002/dmrr.v33.110.1002/dmrr.2821.
[32] Kalyani RR, Metter EJ, Egan J, Golden SH, Ferrucci L. Hyperglycemia Predicts Persistently Lower Muscle Strength With Aging. Diabetes Care 2015;38(1):82–90. https://doi.org/10.2337/dc14-1166.
[33] Yoon JW, Jang HC. Hyperglycemia is associated with impaired muscle quality in older men with diabetes: The Korean Longitudinal study on health and aging (Diabetes Metab J 2016;40:140–6). Diabetes Metab J 2016;40:250–1. https://doi.org/10.4093/dmj.2016.40.3.250.
[34] Andersen H, Stålberg E, Gjerstad MD, Jakobsen J. Association of muscle strength and electrophysiological measures of reinnervation in diabetic neuropathy. Muscle Nerve 1998;21(12):1647–54.
[35] Allen MD, Kimpinski K, Doherty TJ, Rice CL. Length dependent loss of motor axons and altered motor unit properties in human diabetic polyneuropathy. Clin Neurophysiol 2014;125(4):836–43. https://doi.org/10.1016/j.clinph.2013.09.037.
[36] Allen MD, Choi IH, Kimpinski K, Doherty TJ, Rice CL. Motor unit loss and weakness in association with diabetic neuropathy in humans. Muscle Nerve 2013;48(2):298–300. https://doi.org/10.1002/mus.23792.
[37] Muramatsu K. Diabetes mellitus-related dysfunction of the motor system. Int J Mol Sci 2020;21:1–26. https://doi.org/10.3390/ijms21207485.
[38] Picconi F, Mataluni G, Ziccardi L, Parravano M, Di Renzo A, Ylli D, et al. Association between early neuroretinal dysfunction and peripheral motor unit loss in patients with type 1 diabetes mellitus. J Diabetes Res 2018;2018:1–9. https://doi.org/10.1155/2018/9763507.
[39] Cai Q, Aimair G, Xu W-X, Xiao P-Y, Liu L-H, Liang Y-X, et al. The Physiological Significance of A-Waves in Early Diabetic

Neuropathy: Assessment of Motor Nerve Fibers by Neurophysiological Techniques. Front Syst Neurosci 2021;15. https://doi.org/10.3389/fnsys.2021.63391510.3389/fnsys.2021.633915.s001.
[40] Reske-Nielsen E, Gregersen G, Harmsen A, Lundbaek K. Morphological abnormalities of the terminal neuromuscular apparatus in recent juvenile diabetes. Diabetologia 1970;6:104–9. https://doi.org/10.1007/BF00421437.
[41] Fahim MA, Hasan MY, Alshuaib WB. Early morphological remodeling of neuromuscular junction in a murine model of diabetes. J Appl Physiol 2000;89(6):2235–40. https://doi.org/10.1152/jappl.2000.89.6.2235.
[42] Francis GJ, Martinez JA, Liu WQ, Zochodne DW, Hanson LR, Frey WH, et al. Motor end plate innervation loss in diabetes and the role of insulin. J Neuropathol Exp Neurol 2011;70(5):323–39. https://doi.org/10.1097/NEN.0b013e318215669a.
[43] Stephenson GM, O'Callaghan A, Stephenson DG. Single-fiber study of contractile and biochemical properties of skeletal muscles in streptozotocin-induced diabetic rats. Diabetes 1994;43(5):622–8. https://doi.org/10.2337/diabetes.43.5.622.
[44] RodríGuez-Reyes N, RodríGuez-Zayas AE, Javadov S, Frontera WR. Single muscle fiber contractile properties in diabetic rat muscle. Muscle Nerve 2016;53(6):958–64. https://doi.org/10.1002/mus.24988.
[45] Suzuki A, Yabu A, Nakamura H. Advanced glycation end products in musculoskeletal system and disorders. Methods 2020. https://doi.org/10.1016/j.ymeth.2020.09.012.
[46] Monaco CMF, Gingrich MA, Hawke TJ. Considering Type 1 Diabetes as a Form of Accelerated Muscle Aging. Exerc Sport Sci Rev 2019;47:98–107. https://doi.org/10.1249/JES.0000000000000184.
[47] Ramamurthy B, Höök P, Jones AD, Larsson L. Changes in myosin structure and function in response to glycation. FASEB J 2001;15(13):2415–22. https://doi.org/10.1096/fj.01-0183com.
[48] Ramamurthy B, Jones AD, Larsson L. Glutathione reverses early effects of glycation on myosin function. In Vitro 2003;285(2):C419–24. https://doi.org/10.1152/ajpcell.00502.2002.
[49] Gilliver SF, Degens H, Rittweger J, Sargeant AJ, Jones DA. Variation in the determinants of power of chemically skinned human muscle fibres. Exp Physiol 2009;94:1070–8. https://doi.org/10.1113/expphysiol.2009.048314.
[50] Papadaki M, Holewinski RJ, Previs SB, Martin TG, Stachowski MJ, Li A, et al. Diabetes with heart failure increases methylglyoxal modifications in the sarcomere, which inhibit function. JCI Insight 2018;3(20). https://doi.org/10.1172/jci.insight.12126410.1172/jci.insight.121264DS1.
[51] Zanuso S, Sacchetti M, Sundberg CJ, Orlando G, Benvenuti P, Balducci S. Exercise in type 2 diabetes: Genetic, metabolic and neuromuscular adaptations. A review of the evidence. Br J Sports Med 2017;51(21):1533–8. https://doi.org/10.1136/bjsports-2016-096724.
[52] Handsaker JC, Brown SJ, Bowling FL, Maganaris CN, Boulton AJM, Reeves ND. Resistance exercise training increases lower limb speed of strength generation during stair ascent and descent in people with diabetic peripheral neuropathy. Diabet Med 2016;33(1):97–104. https://doi.org/10.1111/dme.12841.
[53] Kluding PM, Pasnoor M, Singh R, Jernigan S, Farmer K, Rucker J, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. J Diabetes Complications 2012;26(5):424–9. https://doi.org/10.1016/j.jdiacomp.2012.05.007.
[54] Gholami F, Nazari H, Alimi M. Cycle Training improves vascular function and neuropathic symptoms in patients with type 2 diabetes and peripheral neuropathy: A randomized controlled trial. Exp Gerontol 2020;131:110799. https://doi.org/10.1016/j.exger.2019.110799.
[55] Balducci S, Iacobellis G, Parisi L, Di Biase N, Calandriello E, Leonetti F, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Complications 2006;20(4):216–23. https://doi.org/10.1016/j.jdiacomp.2005.07.005.
[56] Dixit S, Gular K, Asiri F. Effect of diverse physical rehabilitative interventions on static postural control in diabetic peripheral neuropathy: a systematic review. Physiother Theory Pract 2020;36(6):679–90. https://doi.org/10.1080/09593985.2018.1491078.
[57] De Oliveira Lima R.A., Piemonte G.A., Nogueira C.R., Nunes-Nogueira V.DS. Efficacy of exercise on balance, fear of falling, and risk of falls in patients with diabetic peripheral neuropathy: A systematic review and meta-analysis. Arch Endocrinol Metab 2021;65:198–211. 10.20945/2359-3997000000337.
[58] Dixit S, Maiya A, Shastry B. Effect of aerobic exercise on quality of life in population with diabetic peripheral neuropathy in type 2 diabetes: A single blind, randomized controlled trial. Qual Life Res 2014;23(5):1629–40. https://doi.org/10.1007/s11136-013-0602-7.
[59] Fisher MA, Langbein WE, Collins EG, Williams K, Corzine L. Physiological improvmente with moderate exercise in type II diabetic neuropathy. Electromyogr Clinical Neurophysiol 2007;47(1):23–8.
[60] Li H, Shen Z, Lu Y, Lin F, Wu Y, Jiang Z. Muscle NT-3 levels increased by exercise training contribute to the improvement in caudal nerve conduction velocity in diabetic rats. Mol Med Rep 2012;6:69–74. https://doi.org/10.3892/mmr.2012.897.
[61] Malysz T, Ilha J, Severo do Nascimento P, Faccioni-Heuser MC, De Angelis K, D'agord Schaan B, et al. Exercise training improves the soleus muscle morphology in experimental diabetic nerve regeneration. Muscle Nerve 2011;44(4):571–82. https://doi.org/10.1002/mus.22133.
[62] Tsai KL, Huang PC, Wang LK, Hung CH, Chen YW. Incline treadmill exercise suppresses pain hypersensitivity associated with the modulation of pro-inflammatory cytokines and anti-inflammatory cytokine in rats with peripheral nerve injury. Neurosci Lett 2017;643:27–31. https://doi.org/10.1016/j.neulet.2017.02.021.
[63] Dixit S, Maiya AG, Shastry BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: A single blind, parallel group randomized controlled trial. J Diabetes Complications 2014;28(3):332–9. https://doi.org/10.1016/j.jdiacomp.2013.12.006.
[64] Dixit S, Maiya A, Shastry BA. Effects of Aerobic Exercise on Vibration Perception Threshold in Type 2 Diabetic Peripheral Neuropathy Population Using 3-sites Method: Single-blind Randomized Controlled Trial. Altern Ther Health Med 2019;25:36–41. https://doi.org/10.1136/bmj.291.6493.487-b.
[65] Hamed NS, Raoof NALA. Effect of high intensity interval training on diabetic obese women with polyneuropathy: a randomized controlled clinical trial. Phys Ther Rehabil 2014;1:4. https://doi.org/10.7243/2055-2386-1-4.
[66] Nadi M, Bambaeichi E, Marandi SM. Comparison of the effect of two therapeutic exercises on the inflammatory and physiological conditions and complications of diabetic neuropathy in female patients. Diabetes, Metab Syndr Obes Targets Ther 2019;12:1493–501. https://doi.org/10.2147/DMSO.S206454.
[67] Stubbs EB, Fisher MA, Miller CM, Jelinek C, Butler J, McBurney C, et al. Randomized controlled trial of physical exercise in diabetic veterans with length-dependent distal symmetric polyneuropathy. Front Neurosci 2019;13. https://doi.org/10.3389/fnins.2019.00051.

[68] Gu Yu, Dennis SM, Kiernan MC, Harmer AR. Aerobic exercise training may improve nerve function in type 2 diabetes and pre-diabetes: A systematic review. Diabetes Metab Res Rev 2018:e3099.(3):e3099. https://doi.org/10.1002/dmrr.3099.

[69] Maestroni L, Read P, Bishop C, Papadopoulos K, Suchomel TJ, Comfort P, et al. The Benefits of Strength Training on Musculoskeletal System Health: Practical Applications for Interdisciplinary Care. Sport Med 2020;50(8):1431–50. https://doi.org/10.1007/s40279-020-01309-5.

[70] Seyedizadeh SH, Cheragh-Birjandi S, Hamedi Nia MR. The Effects of Combined Exercise Training (Resistance-Aerobic) on Serum Kinesin and Physical Function in Type 2 Diabetes Patients with Diabetic Peripheral Neuropathy (Randomized Controlled Trials). J Diabetes Res 2020;2020:1–7. https://doi.org/10.1155/2020/6978128.

[71] Otterman NM, van Schie CHM, van der Schaaf M, van Bon AC, Busch-Westbroek TE, Nollet F. An exercise programme for patients with diabetic complications: a study on feasibility and preliminary effectiveness. Diabet Med 2011;28:212–7. https://doi.org/10.1111/j.1464-5491.2010.03128.x.

[72] Praet SFE, Jonkers RAM, Schep G, Stehouwer CDA, Kuipers H, Keizer HA, et al. Long-standing, insulin-treated type 2 diabetes patients with complications respond well to short-term resistance and interval exercise training. Eur J Endocrinol 2008;158(2):163–72. https://doi.org/10.1530/EJE-07-0169.

[73] Larose J, Sigal RJ, Khandwala F, Kenny GP. Comparison of strength development with resistance training and combined exercise training in type 2 diabetes. Scand J Med Sci Sports 2012;22(4):e45–54. https://doi.org/10.1111/j.1600-0838.2011.01412.x.

[74] Piasecki M, Ireland A, Piasecki J, Degens H, Stashuk DW, Swiecicka A, et al. Long-term endurance and power training may facilitate motor unit size expansion to compensate for declining motor unit numbers in older age. Front Physiol 2019;10. https://doi.org/10.3389/fphys.2019.00449.

[75] Hendrickse PW, Krusnauskas R, Hodson-Tole E, Venckunas T, Degens H. Regular endurance exercise of overloaded muscle of young and old male mice does not attenuate hypertrophy and improves fatigue resistance. GeroScience 2021;43(2):741–57. https://doi.org/10.1007/s11357-020-00224-x.