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

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A B S T R A C T

Diabetic peripheral neuropathy (DPN) is a common condition that is associated with neuromuscular dysfunction and peripheral sensory impairment. These deficits predispose patients to sensory and motor system limitations, foot ulcers and a high risk of falls. Exercise 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 extremity muscles. Non-enzymatic glycation of motor proteins, impaired excitation–contraction coupling and loss of motor units have been indicated as the main factors underlying muscular dysfunction. Among the exercise-based solutions, aerobic training improves neural structure and function and ameliorates neuropathic signs and symptoms. Resistance training 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 evidence 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 muscular dysfunction is an early hallmark of diabetes and progresses 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 × 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 approximately 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 sensory-motor 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 re-innervation [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].
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 Ca2+ 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 sensory perception thresholds (VPT) at different sites (e.g., VPT halluces: –6 V) and improved symptomatology as measured by the Neuropathy Quality of Life (NeuQoL, 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.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Type of exercise</th>
<th>Intensity</th>
<th>Frequency (sessions/week)</th>
<th>Volume</th>
<th>Duration (weeks)</th>
<th>Neural effects</th>
<th>Muscular effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gholami et al. 2018⁹</td>
<td>RCT</td>
<td>AT</td>
<td>50–70% HRR</td>
<td>3</td>
<td>60–135 min/wk</td>
<td>12</td>
<td>SNCV</td>
<td>NR</td>
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<td>SNA = MNCV</td>
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<td>MNA = MDNS ↓</td>
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<tr>
<td>Dixit et al. 2014⁴³</td>
<td>RCT</td>
<td>AT</td>
<td>40–60% HRR</td>
<td>3–6</td>
<td>150–360 min/wk</td>
<td>8</td>
<td>SNCV</td>
<td>NR</td>
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<td>SNA = MNCV</td>
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<td>SNA = MNDL ↓</td>
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<tr>
<td>Fisher et al. 2007⁹⁹</td>
<td>Pre-post single group design</td>
<td>AT</td>
<td>40–75% VO₂₅₀₀</td>
<td>3</td>
<td>90 min/wk</td>
<td>24</td>
<td>SNCV</td>
<td>NR</td>
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<td>SNA = MNCV</td>
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<td>MNA = MDNS ↓</td>
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<tr>
<td>Hamed et al. 2014⁵⁵</td>
<td>RCT</td>
<td>AT vs HIIT</td>
<td>AT: 50–60% HR</td>
<td>3</td>
<td>AT: 150 min/wk</td>
<td>15</td>
<td>LANSS</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HIIT: 30 reps of 8 sec sprints and 12 sec of rest</td>
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<td>MNSI ↓</td>
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<td>12 reps maximum</td>
<td></td>
<td>HiIT: 60 min/wk</td>
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<td>VAS pain ↑</td>
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<tr>
<td>Handsaker et al. 2014⁵⁹</td>
<td>RCT</td>
<td>RT</td>
<td>30% 1-RM</td>
<td>3</td>
<td>1–3 sets of 30 sec</td>
<td>16</td>
<td>NR</td>
<td>SSG: ankle ↑</td>
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<td></td>
<td>knee ↑</td>
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<tr>
<td>Nadi et al. 2019⁶⁶</td>
<td>RCT</td>
<td>RT</td>
<td>60–80% VO₂₅₀₀</td>
<td>3</td>
<td>RT: 3–6 sets x 10 reps</td>
<td>12</td>
<td>MNCV</td>
<td>NR</td>
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<td></td>
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<td></td>
<td>RT: isokinetic knee extension (velocity of 90 s⁻¹)</td>
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<td>MNA = MNDL =</td>
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<td></td>
<td>CT: AT + RT</td>
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<td>RT, AT and CT: 90–135 min/wk</td>
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<td>SNCV = SNA =</td>
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</tr>
<tr>
<td>Stubbs et al. 2019⁵⁷</td>
<td>RCT</td>
<td>AT vs RT vs CT</td>
<td>AT: 50–70% VO₂₅₀₀</td>
<td>3</td>
<td>RT: 3–6 sets x 10 reps</td>
<td>12</td>
<td>MNCV</td>
<td>NR</td>
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<td>RT: isokinetic knee extension (velocity of 90 s⁻¹)</td>
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<td>MNA = MNDL =</td>
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<td></td>
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<td></td>
<td>CT: AT + RT</td>
<td></td>
<td>RT, AT and CT: 90–135 min/wk</td>
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<td>SNCV = SNA =</td>
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<tr>
<td>Kluding et al. 2012⁵³</td>
<td>Pre-post single group design</td>
<td>CT</td>
<td>AT: 50–70% VO₂₅₀₀</td>
<td>3–4</td>
<td>AT: 60–100 min/wk</td>
<td>10</td>
<td>IENFB</td>
<td>NR</td>
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<td></td>
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<td>RT: 7–10 RPE</td>
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<td>RT: 1 set = 10–20 reps. 10 upper and lower body exercises</td>
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<td>MNCV</td>
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<td>VAS pain ↓</td>
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</tbody>
</table>
Muscular effects

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Duration (weeks)</th>
<th>Volume</th>
<th>Frequency (sessions/week)</th>
<th>Intensity Type of Exercise</th>
<th>Neuraleffects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seyedizadeh et al. 2020</td>
<td>Pre-post single group design</td>
<td>8</td>
<td>NR</td>
<td>70 RCT CT IAT: 5–10 reps of 3 min at 50–65% HRR followed by 30 sec of rest + 12 NR Strength: trunk = lower body</td>
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<tr>
<td>Otterman et al. 2011</td>
<td>Pre-post single group design</td>
<td>3</td>
<td>3</td>
<td>AT: 40–65% HRR + RT: 8–12 reps maximum</td>
<td>AT: 40–65% 1-RM</td>
<td></td>
</tr>
<tr>
<td>Praet et al. 2008</td>
<td>Pre-post single group design</td>
<td>12</td>
<td>3</td>
<td>AT: 50–60% 1-RM + RT: 4–8 reps of 30 sec (50–60% of Wmax) followed by 60 sec of rest</td>
<td>AT: 50–60% 1-RM</td>
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</tbody>
</table>

Abbreviations: IAT, isokinetic resistance training; CT, conventional training; RCT, randomized controlled trial; HRR, heart rate reserve; Wmax, maximal workload; MFD, muscle fibre distribution; MNSI, Michigan Neuropathy Screening Instrument; VAS, Visual Analogue Scale; MNA, motor nerve amplitude; MNCV, motor nerve conduction velocity; MNDL, motor nerve distal latency; LEFS, lower extremity functional scale; IENF, intraepidermal nerve fibre density; SNDL, sensory nerve distal latency; SNCV, sensory nerve conduction velocity.

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.

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References


