Neuromuscular dysfunction in type 2 diabetes: underlying mechanisms and effect of resistance training

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Summary

Diabetic patients are at higher risk of developing physical disabilities than non-diabetic subjects. Physical disability appears to be related, at least in part, to muscle dysfunction. Several studies have reported reduced muscle strength and power under dynamic and static conditions in both the upper and lower limbs of patients with type 2 diabetes. Additional effects of diabetes include a reduction in muscle mass, quality, endurance and an alteration in muscle fibre composition, though the available data on these parameters are conflicting. The impact of diabetes on neuromuscular function has been related to the co-existence of long-term complications. Peripheral neuropathy has been shown to affect muscle by impairing motor nerve conduction. Also, vascular complications may contribute to the decline in muscle strength. However, muscle dysfunction occurs early in the course of diabetes and affects also the upper limbs, thus suggesting that it may develop independently of micro and macrovascular disease. A growing body of evidence indicates that hyperglycaemia may cause an alteration of the intrinsic properties of the muscle to generate force, via several mechanisms. Recently, resistance exercise has been shown to be an effective strategy to counteract the deterioration of muscular performance. High-intensity exercise seems to provide greater benefits than moderate-intensity training, whereas the effect of a power training is yet unknown. This article reviews the available literature on the impairment of muscle function induced by diabetes, the underlying mechanisms, and the effect of resistance training on this defect. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords type 2 diabetes; muscle strength; muscle endurance; diabetic neuropathy; resistance exercise

Abbreviations T2DM, type 2 diabetes mellitus; DPN, diabetic peripheral neuropathy; IGT, impaired glucose tolerance; T1DM, type 1 diabetes mellitus; HbA1c, haemoglobin A1c; PRT, progressive resistance training; 1RM, 1-repetition maximum

Introduction

Diabetes is perhaps the most common metabolic disorder in the world, to the point that it is considered a global public health emergency. Recently, the International Diabetes Federation has reported that the number of people
suffering from type 2 diabetes mellitus (T2DM) has reached 382 million and it is expected to rise up to 590 million by 2035 [1]. The presence of chronic complications is the main cause of the high level of mortality and disability in this population.

The increased risk of physical disability associated with diabetes in older individuals [2] appears to depend, at least in part, on muscle weakness, which is a typical feature of the disease. This has been confirmed by numerous studies showing that diabetes is associated with a decrease in muscle strength, power, mass and quality predisposing patients to falls [3], fractures [4] and long-term hospitalisation [5]. Moreover, given the increasing incidence of T2DM in young individuals [6], it is possible, although still to be proven, that the neuromuscular deficit associated with the disease may negatively affect their physical capacities earlier during their productive years.

Of note, a recent study has shown that the muscle strength deficit is associated with an increased likelihood of metabolic syndrome in men, suggesting that muscle strength measurements may be helpful in identifying subjects at risk of chronic disorders [7].

Chronic, long-term complications of diabetes, particularly diabetic peripheral neuropathy (DPN), have been implicated in the pathogenesis of muscle impairment. However, a growing body of evidence supports the concept that hyperglycaemia directly impacts on the intrinsic properties of the muscle to generate force [8,9].

Recently, physical exercise has been shown to be an effective tool for the prevention and treatment of diabetes [10]. Indeed, in addition to improving glycaemic control and other modifiable cardiovascular risk factors [11–13], physical exercise, particularly resistance training, has been shown to ameliorate neuromuscular performance in T2DM patients, although to a lower extent than in non-diabetic subjects [14–17].

The purpose of this article is to review the available literature on the impairment in muscle function induced by T2DM, the underlying mechanisms and the effect of resistance training on this defect.

### Muscle dysfunction in T2DM

A large body of evidence has shown that T2DM is associated with multiple muscular defects, including reduced muscle strength, power, mass, quality and endurance and altered fibre type composition.

### Muscle strength and power

Clinical and experimental studies have demonstrated that T2DM is associated with a reduction in muscle strength (Table 1). This impairment was shown to occur both in the upper [9,18–23] and lower limbs [8,9,18,20,24–29], although the detrimental effect of diabetes differs between the upper and lower appendicular musculature, as reported also for muscle metabolism [30,31]. Similar results have been reported in subjects with impaired glucose tolerance (IGT) and in newly diagnosed T2DM, suggesting that the defect of muscle strength affects diabetic patients since the early stages of the disease [22].

### Table 1. Summary of studies examining the effects of type 2 diabetes on muscle strength

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Diabetes duration (years)</th>
<th>Limb evaluated (Upper/Lower)</th>
<th>Contraction mode (Static/Dynamic)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatef et al. [28]</td>
<td>18</td>
<td>52.11 ± 9.2</td>
<td>4.8 ± 2</td>
<td>Lower</td>
<td>Static</td>
<td>↓ KE</td>
</tr>
<tr>
<td>Leenders et al. [18]</td>
<td>12</td>
<td>59.17 ± 7.1</td>
<td>15.5 ± 7</td>
<td>Upper</td>
<td>Dynamic</td>
<td>↓ KE/KF</td>
</tr>
<tr>
<td>Sacchetti et al. [9]</td>
<td>12</td>
<td>71 ± 1</td>
<td>NR</td>
<td>Upper</td>
<td>Static</td>
<td>↓ HG</td>
</tr>
<tr>
<td>Kalyani et al. [8]</td>
<td>321</td>
<td>58.2 ± 17.5</td>
<td>16.7 ± 16.4</td>
<td>Lower</td>
<td>Dynamic</td>
<td>↓ KE</td>
</tr>
<tr>
<td>Izerman et al. [27]</td>
<td>39</td>
<td>58.2 ± 17.5</td>
<td>16.7 ± 16.4</td>
<td>Lower</td>
<td>Static/Dynamic</td>
<td>↓ EF, ↓ KE</td>
</tr>
<tr>
<td>Volpato et al. [24]</td>
<td>95</td>
<td>62 ± 7</td>
<td>NR</td>
<td>Lower</td>
<td>Dynamic</td>
<td>↓ KE</td>
</tr>
<tr>
<td>Shah et al. [19]</td>
<td>60</td>
<td>73.9 ± 6.2</td>
<td>6.56 ± 5.86</td>
<td>Lower</td>
<td>Static</td>
<td>↓ KE/AE/AF</td>
</tr>
<tr>
<td>Izerman et al. [29]</td>
<td>15</td>
<td>73.9 ± 6.2</td>
<td>6.56 ± 5.86</td>
<td>Lower</td>
<td>Static</td>
<td>↓ KE/AE/AF</td>
</tr>
<tr>
<td>Park et al. [26]</td>
<td>305</td>
<td>73.5 ± 2.7</td>
<td>NR</td>
<td>Lower</td>
<td>Dynamic</td>
<td>↓ HG</td>
</tr>
<tr>
<td>Park et al. [20]</td>
<td>485</td>
<td>73.8 ± 2.9</td>
<td>6.0 (median)</td>
<td>Lower</td>
<td>Static</td>
<td>↓ KE</td>
</tr>
<tr>
<td>Cetinireç et al. [23]</td>
<td>76</td>
<td>50.1 ± 7.6</td>
<td>5.94 ± 6.18</td>
<td>Upper</td>
<td>Static</td>
<td>↓ HG</td>
</tr>
</tbody>
</table>

NR, not reported; KE, knee extensors; KF, knee flexors; HG, handgrip; AE, ankle extensors; AF, ankle flexors.

↓ Decreased in muscle strength.

" Unchanged.

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A longitudinal study showed a 50% faster age-related decline in strength in diabetic patients than in healthy controls [26]. This defect has been documented in both dynamic [8,9,18,20,24–26,28] and static conditions [9,18–23,27–29]. However, some authors have reported no statistically significant differences in maximal isometric strength between diabetic and non-diabetic subjects [9,26,28].

A recent study assessing the torque-velocity relationship in the upper and lower limbs of patients with both type 1 diabetes mellitus (T1DM) and T2DM has reported a major decline in strength versus the non-diabetic control group at higher contraction speeds. This study showed that, in addition to a reduced ability to express maximum muscle strength, diabetes also has a negative influence on muscle power at both the upper and lower limb level [9] (Figure 1).

**Muscle mass and quality**

Type 2 diabetes mellitus has been shown to be associated with a significant reduction in muscle mass and quality (i.e. muscle strength per unit of regional muscle mass), with three times greater prevalence than in healthy subjects [32], predisposing the diabetic patient to more severe physical disability [33]. This decline has been documented in both cross-sectional and longitudinal studies and appears to affect primarily the appendicular musculature and particularly the lower limbs [18,34]. However, the few studies that have investigated longitudinal changes of muscle mass and quality in both the upper and lower limb of diabetic patients reported a significant reduction only for the lower limb [26]. The possible causes for this...
discrepancy are not clear, although it should to be noted that T2DM is responsible for a muscle-specific defect that differs between upper and lower body muscle groups [18,34]. A 6-month study, in addition to reporting a significant reduction in limb muscle mass, documented a more rapid decline of the cross-sectional area of the thigh among diabetic than non-diabetic women [34]. This decline was comparable with that of non-diabetic men, suggesting that the greater propensity to maintain muscle mass in women is lost in diabetic women. This study also demonstrated that a decrease in muscle mass occurred since the initial stages of the disease, as a significant defect was detected even in patients with undiagnosed diabetes.

Muscle endurance

Muscular endurance is an important factor for the activities of daily life. In parallel with impaired muscle strength, diabetic patients can also experience premature muscle fatigue, with consequent reduction in work capacity [35]. However, the effect of diabetes on muscular endurance has not been clearly defined yet, because of the limited number of available studies and the contrasting results obtained. Of these studies, one conducted on a sample of eight insulin-dependent diabetic subjects reported a significant reduction in muscular endurance of the knee extensors [36]. Similar results have been reported by Ijzerman et al., who demonstrated a reduction in isokinetic muscular endurance in 34 T2DM patients, which was significant only for the knee flexor muscles [27]. Other authors documented a greater fatigability of the distal segments of the upper limbs, as assessed using an isometric protocol [19], whereas a diminished muscle endurance at the ankle was also recently observed in neuropathic patients [37]. In T1DM patients, Almeida et al. found a reduction in muscular endurance during sub-maximal isometric contractions of the lower limb muscles [38].

These data appear in contrast with those by Andersen et al., who recorded greater muscular endurance during isokinetic contractions of the knee and ankle extensors in insulin-dependent diabetic patients than in non-diabetic control subjects [39]. Likewise, another, very recent, study reported greater isokinetic muscular endurance of the knee flexor muscles in patients suffering from diabetes for more than 10 years [28]. However, the same muscle group under static conditions was found less resistant to fatigue. Based on the aforementioned evidence, it appears that T2DM is associated with greater fatigability, although it remains to be clarified if and how this depends on the type of muscle contraction, on the body region considered and on the presence of co-morbidities affecting neuromuscular function.

Altered muscle fibre type composition

Another possible effect of diabetes is an alteration of muscle fibre composition. However, there is no consensus on this, because numerous authors have reported an increase in the percentage of type II fibres, in particular IIx, and a reduction in the percentage of type I fibres [40–46], while others have found no significant difference [18,47–52]. A summary of the findings from the studies reporting fibre type composition in diabetic patients is reported in Table 2. Data are conflicting also for IGT and insulin-resistant subjects, because some studies have documented a higher proportion of type II fibres [53–55], whereas others have observed no significant difference [42,56–58].

Most studies on the histological properties of diabetic muscle have investigated the vastus lateralis, whereas only a few have been conducted on different muscle group. Of these, a recent study conducted on the gastrocnemius muscle showed that diabetes does not affect fibre composition at this level [49]. Similar results have been reported by Rabol et al., who have compared fibres type composition of deltoideus and vastus lateralis between T2DM patients and healthy subjects reporting no significant difference between groups [47]. Interestingly, muscle fibre type proportion between upper and lower limb was different only in diabetic subjects while no difference was reported in control subjects. Based on this, it may be hypothesized that diabetes is responsible for a muscle-specific alteration in fibre composition. However, because there is no scientific evidence as to whether or not diabetes has a selective effect on muscle morphology, this remains just a speculation.

Mechanisms responsible for the decline in neuromuscular function

Older studies have attributed the impairment of neuromuscular function associated with diabetes to the chronic long-term complications of the disease, particularly DPN, based on the involvement of the distal segments of the lower limbs and the late occurrence of loss of muscle strength. Peripheral artery disease, that also affects these body segments, may aggravate muscle weakness and atrophy [59]. However, more recent surveys have documented that muscle dysfunction occurs also at the upper limb level and in subjects with newly diagnosed T2DM, thus prompting the hypothesis that diabetes is directly responsible for an impairment of muscle structure and function, which is further augmented by the presence and severity of DPN and other complications.
Diabetic peripheral neuropathy

Diabetic peripheral neuropathy is one of the most severe micro-vascular complications, occurring in 30–50% of all diabetic patients [60]. This complication is responsible for a muscle strength deficit, associated with atrophy of the distal segments of the lower limbs, because of denervation caused by loss of motor axons combined with insufficient re-innervation [61]. This reduction affects the flexor and extensor muscles of the ankle under dynamic and static conditions [62–65]. DPN has also been shown to be responsible for a significant reduction in strength of more proximal muscle groups, in particular of the flexor and extensor muscles of the knee [62,63].

By way of contrast, a cross-sectional study reported a significant reduction in maximum isometric strength of the upper limb [66]. However, studies examining the impact of diabetes on the upper limbs focused on neuromuscular function in dynamic conditions, reporting no significant effects of DPN on muscle strength of the elbow and wrist joints [62,63]. Because the possible factors responsible for this discrepancy are unclear, further studies, possibly of larger size, are needed to clarify whether the upper limbs are affected and to characterize neuromuscular function in both dynamic and static conditions.

With regard to the effects of DPN on muscle mass, numerous clinical and experimental research demonstrated that diabetes is responsible for an accelerated decline in muscle mass that occurs first in the foot muscles and thereafter invariably progresses to the lower legs [61,67]. This decline is related to the degree of DPN and is more pronounced distally. This supports the concept that the neuropathic process might depend on the length of the nerve [63]. In a long-term follow-up study, neuropathic patients showed an annual decline of muscle volume of ankle dorsal and plantar flexors of 4–5%, whereas in non-neuropathic patients, the decline was 2%. Likewise, in the intrinsic foot muscles, the reduction was of 3% in neuropathic patients and nearly 1% in non-neuropathic subjects [61].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Diabetes duration</th>
<th>Therapy</th>
<th>Muscle biopsied</th>
<th>Fibre type proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mørin et al. [46]</td>
<td>15 M/14 F</td>
<td>54.2 ± 2</td>
<td>27.9 ± 0.7</td>
<td>&lt;6 month</td>
<td>OHA</td>
<td>VL</td>
<td>I †, IIA †, IIX †</td>
</tr>
<tr>
<td>Nyholm et al. [55]</td>
<td>16 M/9 F</td>
<td>36.6 (21–55)</td>
<td>26.2 (21–30)</td>
<td>&gt;4 years</td>
<td>OHA/Insulin</td>
<td>VL</td>
<td>I lla †, IIX †</td>
</tr>
<tr>
<td>Cederholm et al. [51]</td>
<td>9 M/9 F</td>
<td>62 ± 11</td>
<td>29 ± 0.8</td>
<td>7 years</td>
<td>Insulin</td>
<td>VL</td>
<td>I, II</td>
</tr>
<tr>
<td>Gaster et al. [44]</td>
<td>8 M</td>
<td>53.8 ± 1.0</td>
<td>32.7 ± 1.2</td>
<td></td>
<td>OHA</td>
<td>VL</td>
<td>I l, II</td>
</tr>
<tr>
<td>He et al. [48]</td>
<td>9 M/11 F</td>
<td>52 ± 2</td>
<td>31.8 ± 0.8</td>
<td></td>
<td>OHA</td>
<td>VL</td>
<td>I, Ila, IIX</td>
</tr>
<tr>
<td>Van Loon et al. [50]</td>
<td>8 M</td>
<td>54.3 ± 2.5</td>
<td>29.9 ± 1.2</td>
<td>&gt;5 years</td>
<td>OHA</td>
<td>VL</td>
<td>I, II</td>
</tr>
<tr>
<td>Mogensen et al. [43]</td>
<td>10 M</td>
<td>55 ± 2</td>
<td>31 ± 1</td>
<td></td>
<td>OHA/Insulin</td>
<td>VL</td>
<td>I lla †, IIX †</td>
</tr>
<tr>
<td>Oberbach et al. [40]</td>
<td>4 M/6 F</td>
<td>58.7 ± 6.4</td>
<td>32.1 ± 3.4</td>
<td></td>
<td>NR</td>
<td>VL</td>
<td>I, II</td>
</tr>
<tr>
<td>Segerström et al. [42]</td>
<td>39 M</td>
<td>65.5 ± 1.5</td>
<td>27.1 ± 3.9</td>
<td></td>
<td>OHA/Insulin</td>
<td>VL</td>
<td>I l, IIX †, IIX †</td>
</tr>
<tr>
<td>Rabøl et al. [47]</td>
<td>8 M/2 F</td>
<td>52.3 ± 2.7</td>
<td>30.1 ± 1.2</td>
<td></td>
<td>OHA</td>
<td>VL/DE</td>
<td>I, II</td>
</tr>
<tr>
<td>Chomentowski et al. [56]</td>
<td>5 M/6 F</td>
<td>44.0 ± 2.7</td>
<td>34.3 ± 0.8</td>
<td></td>
<td>OHA</td>
<td>VL</td>
<td>I, II</td>
</tr>
<tr>
<td>Solomon et al. [57]</td>
<td>10 M/10 F</td>
<td>65 ± 2</td>
<td>32.8 ± 0.7</td>
<td></td>
<td>OHA</td>
<td>VL</td>
<td>I, II</td>
</tr>
<tr>
<td>Leenders et al. [18]</td>
<td>60 M</td>
<td>71 ± 1</td>
<td>27.3 ± 0.4</td>
<td></td>
<td>OHA</td>
<td>VL</td>
<td>I, II</td>
</tr>
<tr>
<td>Andreassen et al. [49]</td>
<td>13 M/6 F</td>
<td>58 (28–67)</td>
<td>28 (24–44)</td>
<td>12 years</td>
<td>OHA/Insulin</td>
<td>GM</td>
<td>I, II</td>
</tr>
</tbody>
</table>

M, male; F, female; BMI, body mass index; NR, not reported; OHA, oral hypoglycaemic agent; VL, vastus lateralis; DE, deltoideus; GM, gastrocnemius medialis.
†Increased.
‡Decreased.
*Unchanged.

Table 2. Summary of studies reporting fibre type composition in patients with type 2 diabetes

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the authors found also no relationship between various nervous and vascular parameters and the proportion and diameter of muscles fibres, thus concluding that the alteration in muscle morphology is independent of the presence of DPN. However, it should be noted that this study was not only limited by the small number of participants but also it did not include subjects with a severe degree of DPN, which could in part explain the lack of relationship between nervous parameters and fibre diameter because DPN is responsible for atrophy only late in the progression of the disease.

A cross-sectional analysis of subjects with T1DM and T2DM, encompassing a wide range of peripheral nerve function and various degrees of micro and macrovascular complications, has shown that upper and lower body strength correlated independently with male gender and, inversely, with age and several sensory and autonomic nerve function parameters [66]. It is unclear whether these nerve function defects directly affect muscle strength or simply reflect a, yet, unrecognized motor nerve impairment. Interestingly, a recent cross-sectional study has shown that reduced heart rate variability is associated with both early and late measures of DPN, particularly sural sensory nerve dysfunction [68]. In addition, diabetes, and to a lesser extent age-induced reduction in handgrip strength was associated with significantly impaired autonomic function and forearm and skin blood flow during and after isometric exercise [69]. The autonomic nervous system, together with the intrinsic vascular smooth muscle cell myogenic response and endothelial cell autoregulation, plays a major role in capillary recruitment, a central mechanism favouring muscle metabolism during contraction. In this context, even early, subclinical autonomic nervous system alterations might affect contraction by reducing blood supply to the exercising muscle. Decreased blood flow results in oxidative stress, which causes mitochondrial damage, as well as in the production of pro-inflammatory cytokines, which play a fundamental role in promoting muscle cell proteolytic activity and apoptosis [70,71]. Moreover, it has been hypothesized that there might be a relationship between microvascular damage and muscle morphology, based on the increase in type II fibres, which parallels the reduced capillary density of the vastus lateralis muscle [46]. In addition to its action on muscle perfusion, the autonomic nervous system affects the contractility of muscle fibres, modulates the proprioceptive information arising from the muscle spindle receptors and, under certain conditions, nociceptive information [72].

Primary muscular defects

Given the neuromuscular deficit documented on diabetic patients, an alteration of the intrinsic properties of the muscle to generate force has been hypothesized [9,27] (Figure 2). Clearly, insulin resistance and diabetes have the potential to impact negatively on the muscle fibres by several mechanisms, going from the alteration of the metabolic machinery to the morphological and functional modifications of the muscle fibres. These defects may be investigated by analyzing the mechanical and biochemical properties at the single muscle fibre level, as already performed in non-diabetic individuals [73,74]. Unfortunately, these studies have been conducted only on diabetic rats. The results support the hypothesis that diabetes is responsible for muscle-specific abnormalities through an alteration in the temporal parameters of contractions in the soleus (constituted primarily of type I fibres) and a reduced ability to develop strength in the extensor muscle of the fingers (characterized by a prevalence of type II fibres) [75–80].

Glycation of skeletal muscle myosin was shown to impair both the structural and functional properties of this contractile protein, with increased myosin cross-linking and reduced in vitro motility speed, respectively [81]. In addition, data from animal models suggest an alteration of Na⁺–K⁺ ATPase activity [82], an increase in the concentration of intracellular sodium [82], a reduction in intracellular ATP [77,82], an impairment of calcium handling by sarcoplasmic reticulum [75,78], a reduction in resting membrane potential and resting membrane conductance [83] and an alteration in the permeability to calcium of the sarcolemma [78]. An additional factor is deterioration in mitochondrial function. This dysfunction has been shown to be muscle-specific as reported by a study that observed differences in mitochondria respiration only at the vastus lateralis while no differences was seen at the deltoid [47].

At the vastus lateralis, some authors have reported a reduction in succinate dehydrogenase and an increase in glycolytic activity [40,84], while others have reported significant differences only for oxidative activity [48,85,86]. A study reported a significant reduction in activity of rotenone-sensitive NADH:O₂ oxidoreductase, an enzyme that reflects the overall activity of the respiratory chain, thus showing that T2DM is associated with an impaired bioenergetic capacity of skeletal muscle mitochondria [85]. This study also demonstrated that T2DM is responsible for a significant alteration of mitochondrial morphology, as documented by both a reduction in mitochondrial size and an alteration of internal membrane structure, including wider cristae [85]. In addition, a selective reduction in inter-myofibrillar mitochondria in IGT and in T2DM subjects has been recently reported [56]. However, other investigators did not find significant differences in mitochondrial density between diabetic and non-diabetic individuals [57,87]. Finally, one of the possible mechanisms responsible for the shift
from type I to type II fibres is hyperinsulinemia, because according to studies in both human and animal models, insulin infusion is associated with an increase in myosin heavy chain IIx mRNA expression [88, 89].

Effects of resistance exercise on neuromuscular performance

Numerous studies have shown that strength training is an effective tool for improving glyco-metabolic profile. This type of exercise has been shown to provide significant benefits to haemoglobin (Hb) A1c and basal and post-load glucose and insulin levels [90–92]. In addition to improving glycaemic control, resistance training appears to elicit significant changes in neuromuscular function in T2DM patients. Numerous studies have clearly shown that muscle strength and power deficit can be significantly counteracted in diabetic patients who undergo a resistance exercise programme. Castaneda et al. showed a 33% increase in strength after subjecting diabetic patients to 16 weeks of high-intensity progressive resistance training (PRT) [15]. Similar results were reported by Dustan et al., who documented a 42% increase in upper limb strength and a 28% increase in lower limb strength. In that study, participants trained at an intensity of 50–60% 1-repetition maximum (1RM) for the first weeks and up to 75–80% 1RM during the final weeks [93]. More recently, Larose et al. observed a 65% increase in the strength of the knee extensor muscles and a 57% increment in that of the pectoral muscles after 6 months of PRT in a large sample of T2DM patients [14]. Lower, although significant improvements have been reported by
several authors who used workouts of more moderate intensity [94,95]. In addition to increasing strength, resistance training has also a positive impact on muscle mass. Thus, because the muscle is the major site of glucose uptake and hence clearance, exercise-induced increase in muscle mass is beneficial for improving not only functional motor capacities, but also glucose homeostasis by favouring muscle glucose utilization and glycogen synthesis. One of the first studies to examine the metabolic effect of a period of resistance training in T2DM patients, reported an increase in thigh circumference and in the diameter of type II fibres, as compared with a sedentary control group [96]. Similar results were reported by Brooks et al., who reported also an increase in muscle quality, in addition to an increase in the diameter of both type I and type II fibres [97]. Based on the aforementioned findings, it is clear that resistance training is an effective tool for improving muscle strength and quality in diabetic patients, with high-intensity protocols obtaining the greatest effects on muscle performance, as compared with more moderate intensities.

Indeed, it is interesting to consider that an increase in the intensity of exercise, through an increase of movement execution velocity, that is, focussing on developing high levels of power, can play an important role in inducing significant modifications in the muscle function of diabetic patients. In this regard, Ibanez et al. examined the effects of 16 weeks of PRT on muscle strength and power in T2DM and healthy subjects. The training protocol included three to five series of 10–15 repetitions performed at 50–70% 1RM for the first 8 weeks, then three to five series of 5–6 repetitions at 70–80% 1RM for the last 8 weeks. During the last 8 weeks, the focus was on muscle power, through the performance of three or four series of 6–8 repetitions at 30–50% 1RM but at maximum velocity [16]. The results clearly showed that 16 weeks of PRT can increase muscle strength and power in both the upper and lower limbs. Furthermore, the same study revealed a similar increase in muscle power in diabetic and control subjects, leading the authors to hypothsize that diabetic patients have lower strength trainability compared with healthy subjects, although muscle power appears to be maintained [16]. In this regard, however, recent data on T2DM patients suggest a greater strength deficit and a lower training effect of conventional PRT programmes at higher contraction velocities [9].

Based on the evidence discussed earlier, and given the paucity of data on the neuromuscular system’s adaptive response and on metabolic control following power training compared with strength training traditionally used in protocols to improve physical fitness of diabetic patients, new studies are needed to clarify this issue. Regarding the glycometabolic effects of power training, Mavros et al. recently investigated the effects of 12 months of high-velocity PRT compared with a traditional low-intensity protocol on body composition and insulin sensitivity on a large sample of T2DM patients [98]. The power protocol included three series of eight repetitions at 80% 1RM. The participants were instructed to perform the concentric phase as quickly as possible, while the eccentric phase was performed at a controlled velocity over a period of about 4 s. Results showed that power training significantly increased muscle mass, together with HbA1c and insulin sensitivity, as compared with low-intensity training [98].

**Conclusions**

Based on the evidence reviewed, a marked and accelerated deterioration in neuromuscular function affects diabetic patients since the early stages of the disease [22]. As a result, these individuals experience a reduction in muscle strength, power and quality, which affects the upper and especially the lower limbs.

Another effect of diabetes on neuromuscular function is reduced muscular endurance, which also appears to affect both the upper and lower limbs. However, to our knowledge, no study has investigated concurrently the effect of diabetes on muscle endurance of the upper and lower limbs in dynamic and static conditions. With regard to the contrasting results on the alteration in fibre composition induced by diabetes, there is the need for larger studies in diabetic individuals well-characterized for treatments and complications.

Diabetic peripheral neuropathy has been shown to affect the muscle by impairing motor nerve conduction, and also vascular complications may contribute to the decline in muscle strength. However, muscle dysfunction occurs early in the course of diabetes and affects also the upper limbs, thus suggesting that it may develop independently of micro and macrovascular disease. The mechanisms behind muscle dysfunction are unclear, although studies conducted in animal models have suggested an alteration of the muscle’s mechanical and electrical components [75,78]. Future studies aimed at understanding the possible causes responsible for this decline should examine the mechanical and biochemical properties of individual muscle fibres from diabetic patients. In addition to the intrinsic inability of the muscle to generate force, diabetes has been shown to be responsible for an alteration of mitochondria morphology and function.

The decrease in neuromuscular performance is further augmented by the presence and severity of neuropathic complications. DPN affects proximal and distal segments of the lower limb, and according to some authors, the upper limbs as well. To understand whether the upper limb
muscles are affected, further investigations will have to examine neuromuscular function in various experimental conditions on large samples.

Numerous studies have clearly shown that strength training can improve both glycaemic control and the neuromuscular function. High-intensity protocols appear to have greater effects on muscle strength, power and quality compared with moderate-intensity protocols. However, to date, there is no evidence on the effect of a power training protocol on neuromuscular performance.

**Conflict of interest disclosure**

All authors declare no potential conflicts (financial, professional or personal) that are relevant to the manuscript.

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