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TOPICAL REVIEW

Physiological mechanisms of neuromuscular impairment in diabetes-related complications: Can physical exercise help prevent it?

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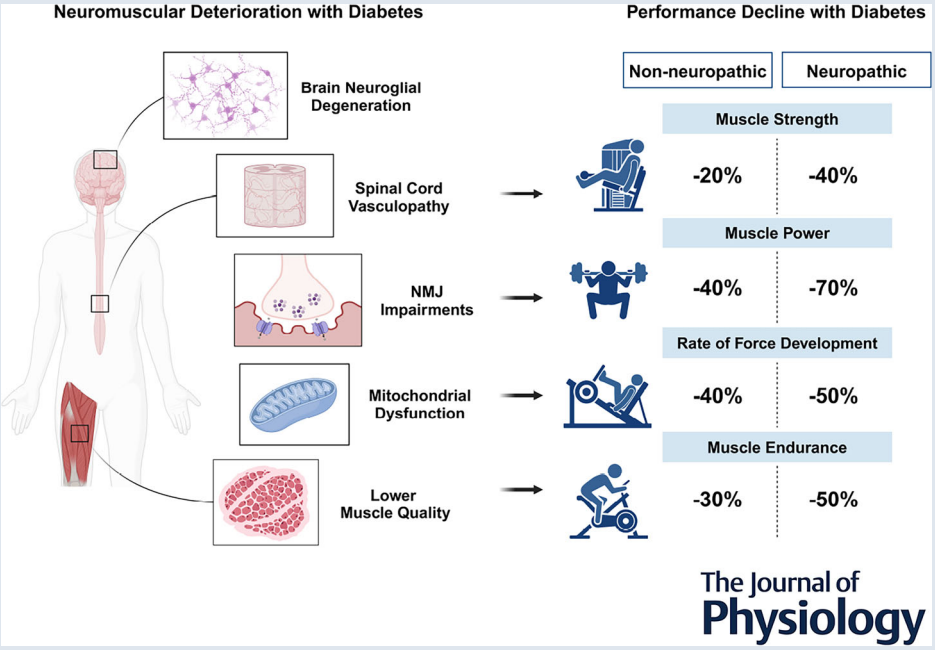

Abstract figure legend Diabetes-related complications affect the neuromuscular system across multiple structural levels. In the CNS, including the brain and spinal cord, complications primarily manifest as neuroglial degeneration and vasculopathy. This damage also extends to the neuromuscular junction (NMJ), mitochondrial function and muscle quality as a result of increased fat deposition and reduced myosin content. These physiological impairments contribute to an evident performance decline in both neuropathic and non-neuropathic diabetics compared to healthy individuals, leading to diminished muscle strength and power output, rate of force development and muscle endurance.

Abstract Diabetes mellitus is a chronic disorder that progressively induces complications, compromising daily independence. Among these, diabetic neuropathy is particularly prevalent and contributes to substantial neuromuscular impairments in both types 1 and 2 diabetes. This condition leads to structural damage affecting both the central and peripheral nervous systems, resulting in a significant decline in sensorimotor functions. Alongside neuropathy, diabetic myopathy also contributes to muscle impairment and reduced motor performance, intensifying the neuromuscular decline. Diabetic neuropathy typically implicates neurogenic muscle atrophy,

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motoneuron loss and clustering of muscle fibres as a result of aberrant denervation-reinervation processes. These complications are associated with compromised neuromuscular junctions, where alterations occur in pre-synaptic vesicles, mitochondrial content and post-synaptic signalling. Neural damage is intensified by chronic hyperglycaemia and oxidative stress, exacerbating vascular dysfunction and reducing oxygen delivery. These complications imply a severe decline in neuromuscular performance, evidenced by reductions in maximal force and power output, rate of force development and muscle endurance. Furthermore, diabetes-related complications are compounded by age-related degenerative changes in long-term patients. Aerobic and resistance training offer promising approaches for managing blood glucose levels and neuromuscular function. Aerobic exercise promotes mitochondrial biogenesis and angiogenesis, supporting metabolic and cardiovascular health. Resistance training primarily enhances neural plasticity, muscle strength and hypertrophy, which are crucial factors for mitigating sarcopenia and preserving functional independence. This topical review examines current evidence on the physiological mechanisms underlying diabetic neuropathy and the potential impact of physical activity in counteracting this decline.

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Introduction

Diabetes mellitus is a chronic metabolic disorder affecting millions worldwide, and it is associated with various complications (Harding et al., 2019; Ong et al., 2023; Shaw et al., 2010). Diabetic neuropathy (DN) is among the most common complications, progressively impairing both the central and peripheral nervous systems in type 1 (T1D) and type 2 diabetes (T2D) (Feldman et al., 2019). DN primarily affects somatic and autonomic nerves in a distal, symmetrical pattern, progressing according to fibre length (Forbes & Cooper, 2013; Said, 2007; Singh et al., 2014), ultimately resulting in impaired neural function, sarcopenia and neurogenic muscle fibre atrophy, implicating neuromuscular deconditioning (Allen et al., 2016; Haines et al., 2022; Wong et al., 2017).

Over time, both T1D and T2D are also linked to diabetic myopathy, a disorder affecting muscle mass and function as a result of chronic hyperglycaemia, altered muscle metabolism and reduced skeletal muscle regenerative capacity (D'Souza et al., 2013; Hernández & Camilo Vanegas, 2015; Monaco et al., 2019). Together with neuropathic complications, these factors contribute to the neuromuscular function decline associated with diabetes. In addition, long-term T2D is typically accompanied by older age (Assar et al., 2019), intensifying degenerative changes through the combined effects of ageing and diabetes (Hepple & Rice, 2016; Saeedi et al., 2019; Xu et al., 2018). This progressive neuromuscular deterioration notably impacts the quality of life and daily independence (Parasoglou et al., 2017; Wong et al., 2017), together with a marked decline in physical performance (Luo et al., 2022; Orlando et al., 2022).

In response to the multifactorial nature of neuromuscular deterioration in diabetes, there is growing interest in examining its physiological determinants and associated complications (Allen et al., 2016; Feldman et al., 2019; Le Corre et al., 2023; Orlando et al.,

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2022; Singh et al., 2014). Although prior reviews have addressed individual aspects of diabetic neuropathy, a comprehensive analysis encompassing central and peripheral mechanisms, alongside the potential of physical exercise to mitigate these adverse effects, remains limited. This topical review aims to synthesise current knowledge on structural and functional alterations associated with diabetic neuropathy in the advanced condition stage, offering an integrated perspective on its pathophysiology and the role of exercise in alleviating diabetes-related complications.

The literature search was conducted using the following terms on PubMed/MEDLINE/MeSH and Scopus: ('diabetes mellitus' OR 'diabetes' OR 'diabetic neuropathy' OR 'diabetes-related complications' OR 'diabetic complications') AND ('ageing' OR 'aging' OR 'older adults') AND ('neuromuscular' OR 'motor unit' OR 'muscle impairment' OR 'muscle weakness' OR 'sarcopenia' OR 'neuromuscular junction') AND ('exercise' OR 'physical activity' OR 'exercise intervention' OR 'resistance training' OR 'endurance training' OR 'aerobic exercise' OR 'combined exercise'). Additional articles suggested or related to these search results were also reviewed and included where relevant.

Differential pathogeneses in T1D and T2D

T1D typically manifests early in life, often during childhood or adolescence (peaking at ∼10–14 years of age), and is characterised by an acute and rapid onset of hyperglycaemia following autoimmune destruction of insulin-producing β-cells in the pancreas (Sempere-Bigorra et al., 2021). This autoimmune response is driven by genetic susceptibility and environmental factors, such as viral infections, implicating an absolute insulin deficiency (Ozougwu, 2013). Because of this sudden onset, individuals with T1D experience swift blood glucose fluctuations, underscoring consistent glycaemic control to mitigate the risk of complications (Cernea & Raz, 2021).

T2D develops gradually and is typically diagnosed in adulthood (peaking at ∼55–59 years of age), although rising obesity rates and sedentary lifestyles have led to increased incidence among younger populations (Sempere-Bigorra et al., 2021). T2D pathogenesis primarily depends on insulin resistance, where body tissues become less responsive to insulin. This condition usually initiates with prolonged prediabetes and hyperinsulinaemia as the pancreas compensates for insulin resistance. Over time, β-cell dysfunction ensues, resulting in a relative insulin deficiency. The slow progression of T2D, shaped by genetic predispositions, lifestyle factors and ageing, often leads to established neuropathic complications by the time of diagnosis (Ozougwu, 2013).

Neuropathy development in T1D and T2D. Although diabetic neuropathy is a prevalent complication in both types of diabetes, evidence highlights distinct pathogenetic mechanisms underlying this condition in T1D and T2D (Sempere-Bigorra et al., 2021; Zhu et al., 2024). The lifetime prevalence of diabetic neuropathy is high, affecting up to 30% of individuals with T1D and 50% of those with T2D, although the timing of onset varies between these groups. Neuropathy symptoms in T1D typically appear after a prolonged period (∼14–20 years post-diagnosis), with peak prevalence observed after 30 years of age, whereas, in T2D, symptoms emerge after a shorter duration (5–10 years post-diagnosis), peaking after 55 years of age (Feldman et al., 2019; Hicks & Selvin, 2019; Pop-Busui et al., 2017; Sempere-Bigorra et al., 2021).

The pathogenesis of T1D-related neuropathy is associated with disruptions in lipid biosynthesis and cholesterol metabolism, whereas, in T2D, it is linked to aberrant activity of nuclear factor-kappa B, peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) and mitogen-activated protein-kinase pathways involved in insulin signalling (Hur et al., 2016; Ng et al., 2024). Furthermore, studies analysing diabetes-related genes and pathways in the sciatic nerve of diabetic mice have identified distinct patterns of gene expression. In T1D, differentially expressed genes are primarily located in the nucleoplasm, affecting transcriptional regulation, whereas, in T2D, they are predominantly at cellular junctions and impact ion transport processes (Gu et al., 2018).

T1D and T2D present alterations in the neural system and the skeletal muscle (Fig. 1), contributing to a severe decline in motor performance, discussed in the next section.

Diabetic-related complications of the neural system

Individuals affected by diabetic neuropathy experience complications that extend beyond the peripheral nerves, impacting the spinal cord and supraspinal areas (Selvarajah et al., 2006; Ved et al., 2018). This widespread impairment disrupts both motor and somatosensory functions, contributing to motor deficits and neuropathic pain (Feldman et al., 2017; Leitzelar & Koltyn, 2021; Meacham et al., 2017; Woolf, 2011; Zhang et al., 2021). Numerous mechanisms contribute to the neuromuscular impairments observed in both neuropathic and non-neuropathic diabetic individuals.

Anatomical determinants. Diabetic neuropathy primarily targets sensory nerves (Ramji et al., 2007; Zochodne et al., 2001), with motoneurons being affected at a later stage (Feldman et al., 2019; Forbes & Cooper, 2013). This progression is attributed to the anatomical

positioning of sensory neurons in the dorsal root ganglia, which lie outside the blood–brain barrier, becoming highly vulnerable to diabetes-related oxidative stress. By contrast, the cell bodies of spinal motoneurons reside within the ventral horn and are somewhat protected (Ballabh et al., 2004; Feldman et al., 2017). Additionally, neuropathic impairments are more pronounced in the lower limbs, probably as a result of the combined effects of lower glucose clearance compared to the upper extremities and the longer nerve fibre length (Forbes & Cooper, 2013; Olsen et al., 2005; Sacchetti et al., 2013).

Diabetic neuropathy is characterised by vascular deterioration, which includes a high incidence of atherosclerosis, capillary basement membrane thickening and endothelial hyperplasia, all of which contribute to reduced oxygen tension (Badrah et al., 2022; Li et al., 2022; Li et al., 2023; Rask-Madsen & King, 2013). Although vascular involvement is widely accepted as a primary cause of neuropathy, there is evidence suggesting that these complications may be secondary to a more pronounced neuroglial disorder occurring in anatomical sites with poor vascularisation (Forbes & Cooper, 2013; Pittenger et al., 2004; Shun et al., 2004).

Structural impairment. Although neuropathy symptoms primarily develop in peripheral structures, evidence indicates that central impairments are already present even with non-neuropathic diabetes and the early stages of diabetic neuropathy. These impairments often coincide with dysfunctions in motor and somatosensory systems, contributing to neuromuscular decline (Allen et al., 2016; Feldman et al., 2019).

Structurally, significant decreases in motor cortex volume have been observed in both T1D (Hughes et al., 2013) and T2D (Peng et al., 2015; Zhang et al., 2022), even in the absence of a neuropathy diagnosis. However, neuropathic patients experience a more severe reduction in motor cortex volume, accompanied by spinal cord atrophy (Selvarajah et al., 2011, 2023; Zang et al., 2023). Structural alterations have also been noted in somatosensory regions, including reduced connectivity between the thalamus and cortex, as well as lower thalamic

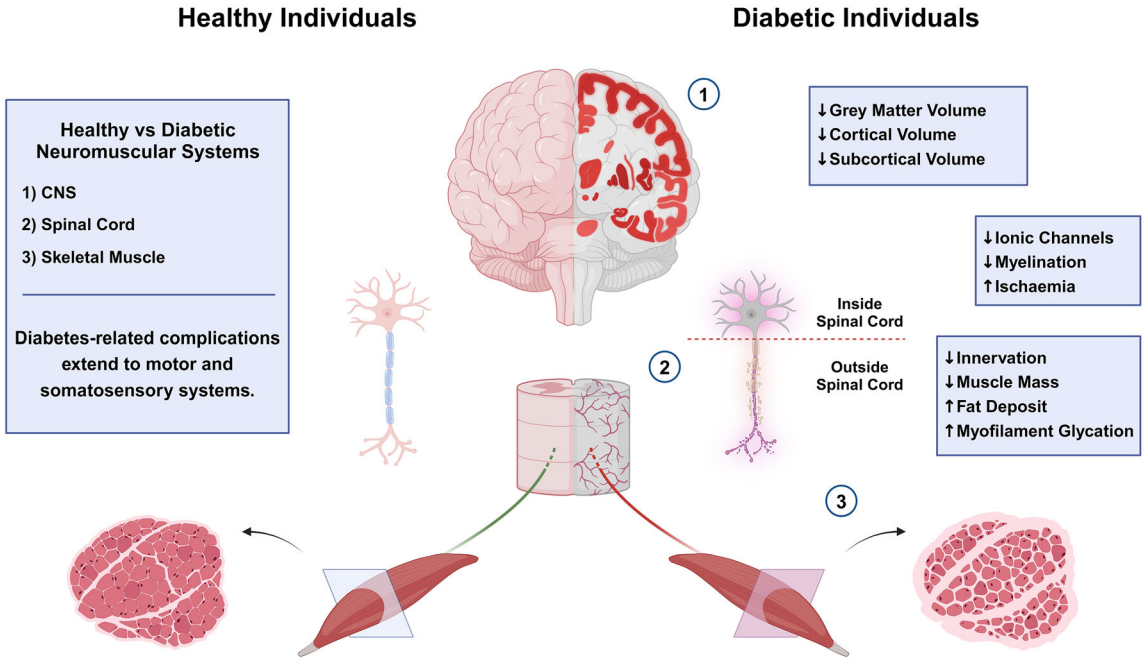

Figure 1. Neuromuscular deterioration observed with diabetes-related complications
(1) In healthy individuals (left), the CNS exhibits adequate grey matter in cortical and subcortical regions. By contrast, diabetic individuals (right) present a significantly lower grey matter volume of cortical and subcortical structures. These alterations suggest neuron and synapse loss alongside disruption of neural networks, potentially impairing cognitive, motor and sensory functions. (2) In healthy subjects, spinal neurons are well-myelinated with adequate ion channels for efficient nerve signal transmission. Myelin facilitates rapid nerve conduction, and good blood perfusion prevents ischaemic phenomena. Diabetic individuals present fewer ion channels and reduced myelination, impairing nerve signal transmission and resulting in slower conduction velocity. Increased ischaemic events indicate reduced blood flow to nerve tissue, exacerbating neuronal damage. (3) Diabetes-related complications impair muscle innervation at the muscular level, reducing contractile capacity and co-ordination. Decreased muscle mass and increased intramuscular fat reflect metabolic imbalance and deteriorated muscle health. Created with BioRender.

grey matter volume in the presence of painful diabetic neuropathy compared to painless neuropathy (Feldman et al., 2019; Selvarajah et al., 2014). Moreover, decreased somatosensory cortex thickness has been reported in both painful and painless neuropathic patients compared to healthy individuals (Selvarajah et al., 2023), with significant axonal degeneration of central somatosensory tracts observed in T2D patients (Fang et al., 2021).

It has also been suggested that vascular damage within the spinal cord, resulting from hyperglycaemia-induced reductions in the vascular endothelial growth factor (VEGF)-A/VEGF receptor 2 signalling cascade, may contribute to neuropathic pain by compromising vascular support to the somatosensory system (Ved et al., 2018). Nonetheless, the precise roles of diabetes *vs*. ischaemia in these degenerative processes remain unclear, particularly regarding the effects on cerebral neurons and glial cells, including perivascular and mitochondrial swelling (Muramatsu, 2020).

In long-term diabetic patients, spinal motoneurons present severe impairments, including swollen or displaced nuclei and cytoplasmic fat deposits (Reske-Nielsen et al., 1966). These factors significantly contribute to the progression of neuropathy (Andersen, 1999; Said, 2007; Selvarajah et al., 2019). This pathological process, affecting both T1D and T2D individuals, is characterised by motor axon loss, demyelination and neuronal apoptosis (Zhu et al., 2024), resulting in neurogenic muscle atrophy and subsequent declines in motor function (Allen et al., 2013; Allen, Kimpinski, et al., 2014; Picconi et al., 2018; Wong et al., 2017). In addition, spinal neurons exhibit hyperexcitability to peripheral stimuli, with morphological changes such as increased dendritic spine length, head diameter, density and redistribution observed in the presence of diabetic neuropathy, as demonstrated in animal models (Tan et al., 2012). Furthermore, the loss of the motor end plate associated with denervation significantly reduces the number of functional motor units in these individuals (Francis et al., 2011; Muramatsu, 2020). This condition deteriorates in older adults, implicating a severe decline in neuromuscular function as a result of the combined effects of neuropathy and ageing in long-term diabetic individuals (Aagaard et al., 2010; Hepple & Rice, 2016).

Functional impairment. Structural damages typically implicate functional alterations, including deafferentation, impaired somatosensory pathway and reduced thalamic feedback, all contributing to altered pain processing (Feldman et al., 2019). Nociceptive information processing within the spinal cord is regulated by a descending pain modulatory system (Bannister, 2019), where brainstem projections either inhibit or facilitate nociceptive transmission at the spinal level (Bannister & Dickenson, 2017; West et al., 2015). Dysfunctions in this pathway have been linked to the chronic pain frequently experienced by individuals with neuropathy (Feldman et al., 2019; Ossipov et al., 2014; Tao et al., 2019). The involvement of glial cells and astrocytes in diabetic neuropathy remains poorly understood. However, it has been hypothesised that these cells contribute to altered neural signalling and neuromodulation of somatosensory pathways through the production and release of various chemical factors (Salter & Beggs, 2014).

Altered functionality of somatosensory neurons results in broader input from spontaneously active nociceptors, increased synaptic transmission within the spinal cord and amplified processing of nociceptive signals, complications collectively known as sensitisation (Woolf, 2011; Zang et al., 2023). Impaired sensory feedback probably arises from hyperexcitability or the generation of afferent signals in the absence of external stimuli, leading to dysfunctional stimulus-response coupling (Ørstavik et al., 2006). Hyperexcitability appears to be a primary pathophysiological driver of neuropathic pain (Feldman et al., 2019). This dysfunction is associated with the altered activity of specific sodium and calcium voltage-gated channels involved in nociceptor electrical signalling, as well as the amplification of sensory feedback (Blair & Bean, 2002; Dubin & Patapoutian, 2010; Jagodic et al., 2007; Messinger et al., 2009; Orestes et al., 2013).

Neuropathic complications also include impaired nerve regeneration, primarily as a result of delayed and dysfunctional Wallerian degeneration. Such delays result in reduced reinnervation of target tissues and dysfunctions in neurons and Schwann cells, adversely affecting nerve impulse transmission (Sango et al., 2017; Terada et al., 1998; Yang et al., 2023). A clinical marker of peripheral diabetic neuropathy is reduced nerve conduction velocity (NCV), which is employed to assess the severity of the condition (Lawrence & Locke, 1961; Li et al., 2023; Yorek et al., 2014). Notably, NCV declines progressively with the duration of diabetes and chronic hyperglycaemia in the presence of neuropathy (Feldman et al., 2019; Hamid et al., 2021). The physiological mechanisms underlying reduced NCV include microvascular damage, axonal swelling, dysfunction of the NA^+/K^+ ATPase pump, and altered membrane permeability to sodium and calcium ions (Coppey et al., 2000; Feldman et al., 2019; Forbes & Cooper, 2013; Sima & Brismar, 1985).

Diabetic-related complications of the skeletal muscle

Persistent diabetes leads to impaired skeletal muscle structure and function in both T1D and T2D, with the associated complications progressively reducing

muscle mass, quality and functional capacity. These impairments stem from both neurogenic (neuropathy) and non-neurogenic (myopathy) factors, further damaging motor performance deficits in affected individuals.

Neurogenic disorder in skeletal muscle. The primary cause of reduced muscle mass with diabetes is the accelerated loss of motor axons that mirrors patterns observed with ageing (Allen et al., 2016). This phenomenon arises from cycles of denervation and reinnervation (i.e. sprouting), where certain muscle fibres remain unsuccessfully reinnervated for unknown reasons, contributing to sarcopenia and muscle fibre atrophy (Hepple & Rice, 2016). A more rapid loss of muscle mass probably occurs in both T1D and T2D compared to healthy older adults (Le Corre et al., 2023), who already experience a progressive clustering of fibres within a given motor unit. Therefore, the loss of muscle mass associated with diabetic neuropathy is linked to a dysfunctional sprouting process characterised by accelerated denervation and decreased reinnervation of orphaned muscle fibres (Andersen et al., 1998; Muramatsu, 2020). A lower number of muscle fibres implies a consequent decrease in myosin content, resulting in a significant decline in strength per muscle area, comprising a deconditioning process comparable to that observed in older age and periods of immobilisation (D'Antona et al., 2003).

Non-neurogenic disorder in skeletal muscle. A critical aspect of motor dysfunction is attributed to diabetic myopathy, resulting from multiple physiological determinants, including metabolic and vascular factors (D'Souza et al., 2013; Hernández & Camilo Vanegas, 2015). The progression of diabetic myopathy involves several interrelated mechanisms, including hyperglycaemia-induced oxidative stress, chronic inflammation, excessive fat deposits, decreased mitochondrial density and disrupted extracellular matrix remodelling (Andersen et al., 1998; Hernández & Camilo Vanegas, 2015; Lesniewski et al., 2003; Mesinovic et al., 2019; Perry et al., 2016; Sacchetti et al., 2013).

Chronic hyperglycaemia is associated with the production of reactive oxygen species, leading to mitochondrial dysfunction and promoting a pro-oxidant state that impairs protein synthesis and satellite cell function (D'Souza et al., 2013). This condition can also accelerate muscle protein degradation through the ubiquitin–proteasome pathway, contributing to sarcopenia (Kalyani et al., 2015; Le Corre et al., 2023). Furthermore, persistent hyperglycaemia has been associated with myofilament glycation, which implicates a reduced speed of the power stroke. This condition implicates a structural modification in the catalytic domain of the myosin head observed following *in vitro* exposure to glucose (Ramamurthy et al., 2001, 2003). This complication, combined with impaired microcirculation, compromises the delivery and distribution of metabolic substrates, further worsening the decline in muscle quality (Orlando et al., 2022; Suzuki et al., 2022).

Long-term inflammation is driven by elevated pro-inflammatory cytokines, such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α, which further disrupt muscle function by promoting insulin resistance and reducing regenerative capacity (Hernández & Camilo Vanegas, 2015; Monaco et al., 2019). Furthermore, the accumulation of advanced glycation end-products (AGEs) intensifies inflammation, oxidative stress and muscle degradation, impairing muscle progenitor cell functionality (Hernández & Camilo Vanegas, 2015; Monaco et al., 2019). Increased levels of plasminogen activator inhibitor-1 and collagen are typically observed with diabetes-related complications of the skeletal muscle, implicating disrupted extracellular matrix remodelling and impaired muscle regeneration. In addition, prolonged oxidative stress drives the conversion of muscle stem cells into adipocytes, leading to muscle wasting and metabolic inflexibility (D'Souza et al., 2013; Hernández & Camilo Vanegas, 2015; Monaco et al., 2019).

Although this condition affects both diabetes types, T1D and T2D present a differential diabetic myopathy progression. In T1D, the autoimmune-driven destruction of pancreatic β-cells and subsequent insulin deficiency primarily contribute to the associated complications, which may appear as accelerated muscle ageing with structural changes analogous to those observed in older adults, including mitochondrial dysfunction and muscle atrophy. T2D, by contrast, is often associated with insulin resistance, obesity and increased fat deposition in muscle, leading to metabolic inflexibility and accelerated sarcopenia, especially in older adults (Hernández & Camilo Vanegas, 2015; Monaco et al., 2019). Additionally, T1D-related myopathy often manifests with impaired regenerative responses and reduced muscle satellite cell function, whereas T2D muscles frequently exhibit increased glycolytic fibres and lipid infiltration, contributing to functional decline (D'Souza et al., 2013).

Neuromuscular junction impairments

Motor function decline in diabetic neuropathy is also attributable to dysfunctional neuromuscular junctions (NMJs) (Fig. 2). Age-related NMJ remodelling reduces reinnervation capacity (Pratt et al., 2021) and similar alterations are observed with diabetes, including impaired functionality and a lower number of vesicles

and pre-synaptic mitochondria, as shown in murine models (Estrada-Bonilla et al., 2020; Fahim et al., 1998, 2000; Kimura et al., 1993). As a result, diabetes-related deterioration of NMJ includes diminished calcium sequestration by mitochondria and lower ATP production rate, contributing to impaired excitation–contraction coupling, mirroring NMJ impairments associated with ageing (Anagnostou & Hepple, 2020; Miao et al., 2024; O'Connor et al., 2023). Additionally, lower levels of acetylcholinesterase, which is the enzyme responsible for breaking down ACh outside axon terminals, have been observed in diabetic individuals and correlated with muscle weakness (Garcia et al., 2012).

Post-synaptic alterations include disruptions in nicotinic ACh receptors (nAChRs), resulting in defective ACh–receptor pairing. This disruption weakens the stability and efficiency of neuromuscular transmission, ultimately contributing to reduced motor function (Marques & Neto, 2002). A critical marker of NMJ health is the C-terminal agrin fragment (CAF), a molecule that interacts with the low-density lipoprotein receptor-related protein 4 receptor. Together with the muscle-specific kinase, CAF initiates signalling essential for clustering nAChRs at the post-synaptic membrane, ensuring optimal receptor density and alignment for effective synaptic transmission (Monti et al., 2023). Elevated levels of CAF in serum reflect NMJ degeneration, indicative of breakdown and reduced function of these synaptic structures. Studies have found these elevated CAF levels in both older adults (Pratt et al., 2022) and individuals with diabetes (Qaisar et al., 2024; Racha et al., 2022), suggesting that NMJ deterioration follows a similar pattern in both conditions. This observation reinforces the concept of diabetes-related neuromuscular complications as a model of accelerated ageing because NMJ function diminishes more rapidly and parallels age-related degeneration.

Neural control with diabetic neuropathy. Motor control is accomplished when descending neural signals elicit co-ordinated muscle responses to generate planned movements. Afferent and efferent signals integrate at both spinal and supraspinal levels, influencing the output of spinal motoneurons to muscle fibres (Avaltroni et al., 2024; Gandevia, 2001; McLean et al., 2007; Osseward & Pfaff, 2019). Upon reaching the motor end plate, these signals trigger calcium release from the sarco/endoplasmic reticulum, prompting muscle fibres to generate tension (Calderón et al., 2014). A single motoneuron and the muscle fibres it innervates represent the motor unit, which is recognised as the final common pathway for motor command (Duchateau & Enoka, 2011; Liddell & Sherrington, 1925;

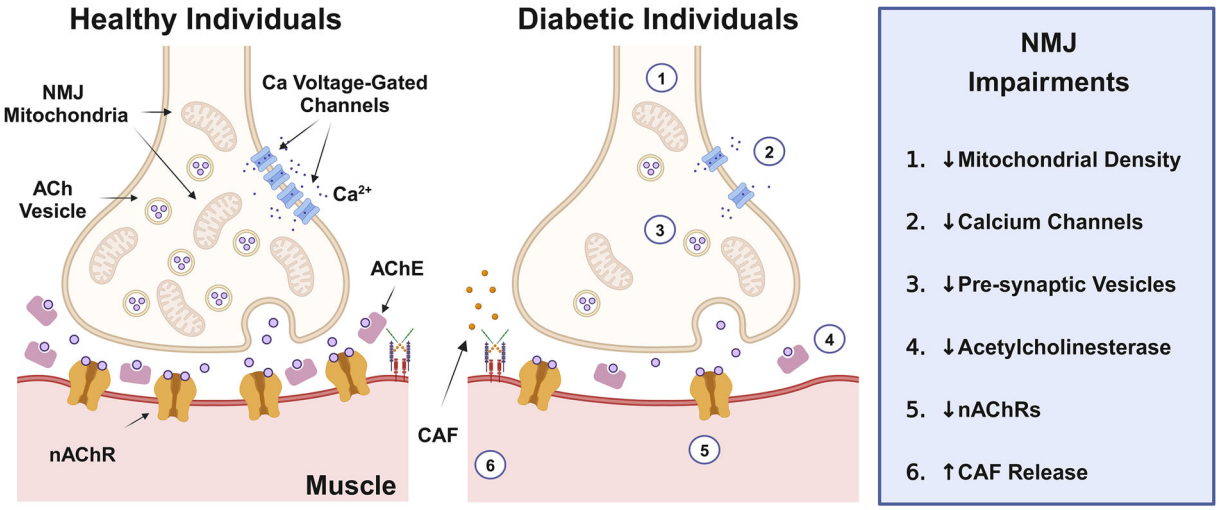

Figure 2. Neuromuscular junction deterioration in diabetic individuals
In healthy individuals (left), neuromuscular junctions show a well-organised structure with a homogeneous distribution and a high density of post-synaptic nicotinic ACh receptors. The abundant presence of calcium channels and pre-synaptic vesicles ensures efficient synaptic transmission together with a proper mitochondrial density, supporting energy demands and calcium buffering in the axonal terminal. Acetylcholinesterase activity allows rapid degradation of ACh, maintaining synaptic balance and optimal muscle function. In diabetic individuals (right), neuromuscular junction (NMJs) are significantly impaired, presenting lower mitochondrial density (1), limiting energy production capacity and calcium sequestration. Decreased calcium channels (2) and pre-synaptic vesicles (3) further impair neuromuscular transmission. Lower acetylcholinesterase content (4) reduces the ACh degradation rate, impairing proper reuptake. Furthermore, a lower density of post-synaptic nicotinic ACh receptors (5) implicates decreased vesicle-releasing-binding coupling. The increased release of C-terminal agrin fragment (CAF) is used as a serum biomarker of NMJ deterioration (6). AChE, acetylcholinesterase; Ca^{2+}, calcium (ion); nAChR, nicotinic ACh receptor.

Sherrington, 1906). Therefore, motor output is shaped by multiple inputs converging on spinal motoneurons, including neural feedback from receptors and signals from spinal and supraspinal areas (Farina & Gandevia, 2024; Gandevia, 2001; Gandevia et al., 1990; Heroux et al., 2022; Proske & Gandevia, 2012). As a result, neuromuscular function relies on co-ordinated motor unit activation and firing patterns to ensure precise control of muscle contraction (Enoka & Fuglevand, 2001; Heckman & Enoka, 2012; Henneman, 1957). Extensive research has demonstrated that this finely tuned system is severely compromised by diabetic neuropathy, resulting in numerous pathophysiological consequences that affect both the motor and somatosensory nervous systems (Andersen et al., 1996, 2004, 2012; Hilton et al., 2008; Ho et al., 2013; Malone, 2016; Muramatsu, 2020).

Diabetes-related complications on motor unit function. Recording motor units offers valuable insights into motoneuron properties (Farina & Gandevia, 2024). This is accomplished by analysing individual motor unit activity, reflecting the one-to-one association between action potentials generated by an alpha motoneuron and those received by its innervated muscle fibres (Martinez-Valdes et al., 2023). Such recordings facilitate the understanding of the peripheral motor control deterioration observed in diabetic individuals. Impaired motor unit characteristics include suppressed firing rates, reduced post-activation potentiation (Allen et al., 2016) and inefficient recruitment during sustained contractions, where the same limited pool of motor units is repeatedly activated (Watanabe et al., 2012).

Evidence obtained using high-spatial resolution electromyography confirmed lower discharge rates, marked by higher firing fluctuations and impaired force steadiness in neuropathic individuals compared to healthy controls (Favretto et al., 2023; Senefeld et al., 2020). More recently, reduced firing rates during recruitment and sustained contraction phases have also been observed in young individuals with T1D compared to healthy individuals despite comparable maximal voluntary force levels (Valli et al., 2025). However, a meta-analysis discussing EMG studies evaluating lower limb function with diabetic neuropathy revealed significant result heterogeneity, highlighting the need for further research to fully elucidate the physiological mechanisms underlying motor impairments across different stages of neuropathy (Haque et al., 2020).

The effect of diabetes-related complications on performance decline. The neurogenic deterioration of skeletal muscle quality is widely recognised as the primary factor contributing to impaired neuromuscular function in diabetic neuropathy (Parasoglou et al., 2017). The degenerative processes associated with diabetes-related complications are significantly intensified in the presence of neuropathy. The resulting pathological alterations lead to a dysfunctional integration of somatosensory inputs and motor responses, culminating in impaired motor unit functioning (Allen, Kimpinski, et al., 2014; Favretto et al., 2023; Le Corre et al., 2023; Watanabe et al., 2012). This disruption of the motor-sensory system initiates a cascade of complications that progressively deteriorate neurophysiological function, contributing to neuromuscular performance decline. Such a decline is particularly critical for maintaining motor function and independence in individuals with long-term diabetes, who also experience age-related physiological deterioration (Forbes & Cooper, 2013).

Muscle strength, power and rate of force development. Impaired neuromuscular function in diabetes is associated with a suppressed force generation capacity, ∼20% lower in uncomplicated diabetic individuals compared to healthy counterparts (Andersen et al., 1996; Orlando et al., 2016). This impairment is attributed to diminished muscle quality in both T1D and T2D, resulting in a progressive and accelerated decline in muscle strength, reaching an up to ∼40% decrease in neuropathic individuals compared to healthy counterparts (Andreassen et al., 2006; Le Corre et al., 2023). Non-neuropathic diabetic individuals present ∼40% lower muscle power and rate of force development (RFD) than healthy controls (Favretto et al., 2019; Sacchetti et al., 2013; Senefeld et al., 2020). These reductions are even more severe in neuropathic patients, with an ∼70% lower power output and an RFD reduced by ∼50% (Favretto et al., 2019; Hilton et al., 2008; Le Corre et al., 2023).

Muscle endurance. Diabetes and associated complications negatively affect muscle endurance, inducing significant decreases in the time to task failure in both types of diabetes (T1D: ∼30% in mixed samples; T2D: ∼30% in males and ∼20% in females) and larger force decrease (i.e. fatigue index) (both T1D and T2D: ∼20%) compared to healthy counterparts (Bazzucchi et al., 2015; Orlando et al., 2017, 2017a, 2017b). Individuals with neuropathic complications exhibit lower muscle endurance and higher force decrease, ∼20% and 35% lower than in non-neuropathic T1D (Orlando et al., 2017b) and T2D (Orlando et al., 2022). Furthermore, neuropathic individuals exhibit ∼50% lower muscle endurance than healthy controls (Orlando et al., 2017b). The evidence presented above indicates that T1D and T2D result in a comparable decline in performance, whereas a more severe loss of function is observed with neuropathy (Fig. 3). This decline is further exacerbated by ageing in diabetic individuals, with performance reducing

up to 50% more than in healthy ageing, according to longitudinal investigations (Seok et al., 2007).

Physiological determinants of neuromuscular performance decline. Reduced performance is hypothesised to be influenced by preferential denervation of type II muscle fibres (Allen, Major, et al., 2014; Le Corre et al., 2023), although neural impairments also play a significant role. Nevertheless, RFD relies on both neural and contractile properties (Del Vecchio et al., 2024; Maffiuletti et al., 2016), with the speed of motoneuron recruitment and maximal discharge rate being essential for rapid force generation (Del Vecchio et al., 2019), both of which are compromised with neuropathic and non-neuropathic diabetes. A possible explanation for the pronounced decline in RFD and power output is the lower muscle fibre conduction velocity observed in diabetic individuals (Hilton et al., 2008; Sacchetti et al., 2013). Furthermore, the greater reduction in muscle power compared to RFD is attributable to impaired cross-bridge kinetics and reduced muscle shortening speed in diabetes. Power is assessed during dynamic contractions, whereas RFD is typically measured during isometric contractions (Le Corre et al., 2023; Sacchetti et al., 2013). The decline in muscle power precedes that of force in the presence of diabetes, a condition that worsens with ageing, long-term diabetes and neuropathy (Hepple & Rice, 2016; Le Corre et al., 2023; Lesniewski et al., 2003; Sacchetti et al., 2013). These findings underscore the need for further research into the effects of physical activity on

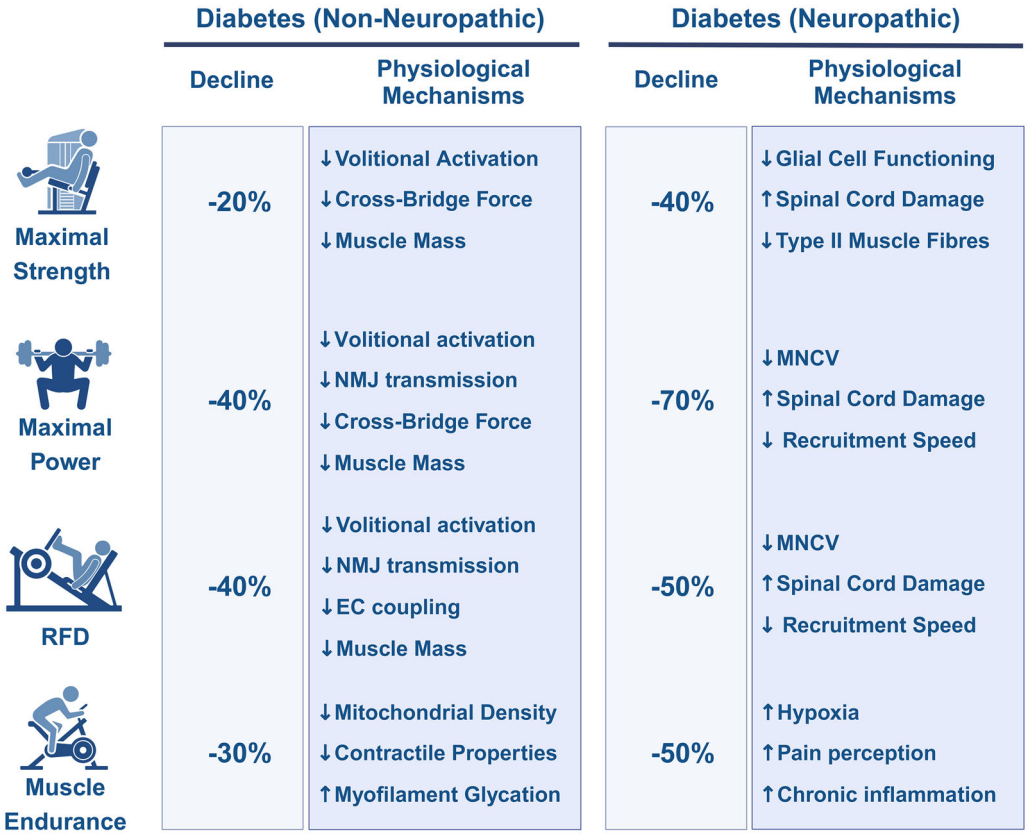

Figure 3. Performance decline with diabetes-related complications
Four aspects of muscular performance, (1) maximal strength, (2) maximal power, (3) rate of force development (RFD) and (4) muscle endurance, are primarily impaired in diabetic individuals. (1) Maximal strength is reduced by 20% in diabetes as a result of decreased grey matter, lower muscle activation and muscle mass. In diabetic neuropathy, strength reduction reaches 40%, attributed to glial cell dysfunction, spinal cord damage, and type II fibre loss. (2) Maximal power decreases by 40% in diabetes, linked to lower muscle activation, neuromuscular junction (NMJ) transmission and excitation–contraction (EC) coupling; this reduction reaches 70% with neuropathy as a result of slower motor unit recruitment and reduced nerve conduction. (3) RFD is reduced by 40% in diabetes and by 50% in neuropathy, with the latter linked to more severe spinal damage and slower motor recruitment. (4) Muscle endurance is lowered by 30% in diabetes as a result of decreased mitochondrial density, contractile properties and myofilament glycation, whereas neuropathy results in a 50% decrease, exacerbated by hypoxia, pain and chronic inflammation. The data compare affected adults to healthy controls. MNCV, motor nerve conduction velocity. Data from Allen et al. (2015, 2016); Allen, Major et al. (2014); Bazzucchi et al. (2015); Hilton et al. (2008); and Orlando et al. (2016, 2017b, 2017a).

Table 1. Mechanisms of central and peripheral fatigue with diabetes-related compilations

	Determinant	Impact on fatigue
Central mechanisms	↓ Grey matter volume	↓ Motor control ↓ Neural input integration
	↓ Neural connectivity	↓ Motor co-ordination ↓↑ Fatigue perception
	↑ Spinal cord vasculopathy	↓↑ Spinal signalling ↓ Motoneuron activation
Peripheral mechanisms	↑ Spinal nerve atrophy	↓↑ Neural transmission ↓↑ Integration-response tasks
	↓ NMJ function	↓↑ Neuromuscular transmission
	↓↑ Pain perception	↑ Discomfort ↑ Perceived fatigue
	↓ Mitochondrial density	↓ ATP availability ↑ Early fatigue onset
	↓ Muscle vascularisation	↑ Oxygen flow ↓ Metabolite disposal
	↑ Myofilament glycation	↓ Force output ↑ Effort
	↓ Calcium availability	↓↑ E–C coupling

↓, reduced; ↑, increased; ↓↑, altered; E–C, excitation–contraction; NMJ, neuromuscular junction.

the progression of diabetes-related complications and the implication for mitigating symptoms and performance decline.

Mechanisms of fatigue in diabetic-related complications

It is essential to differentiate exercise-induced fatigability from the trait fatigue commonly associated with diabetes. Exercise-induced fatigability results from temporary, task-driven muscle exhaustion. Trait fatigue is a persistent fatiguing state influenced by glycaemic dysregulation, depression and lifestyle (Behrens et al., 2023). Although exercise-induced fatigability occurs during physical exertion and primarily depends upon physiological training conditioning, trait fatigue persists regardless of physical activity and can significantly impact daily functioning and quality of life (Behrens et al., 2023; Fritschi & Quinn, 2010; Kalra & Sahay, 2018). In particular, task-induced fatigue encompasses central and peripheral mechanisms that influence both motor performance and perceived dimensions.

Motor performance fatigue is defined as a measurable decline in motor output, such as reduced maximal voluntary contraction or decreased endurance, attributed to impairments within the neuromuscular system. This type of fatigue is objective, resulting directly from physiological limitations in neural and muscular functions. By contrast, perceived motor fatigue refers to the subjective sensation of tiredness or a need to reduce effort, influenced by psychophysiological factors such as mood, motivation and discomfort signals from sensory feedback (Behrens et al., 2023). In the presence of diabetes, in particular, diabetic neuropathy, these conditions are typically interdependent as a result of psychophysiological decline, nerve dysfunctions and cardiometabolic impairments (Fritschi & Quinn, 2010; Kalra & Sahay, 2018).

Central and peripheral mechanisms of fatigue do not operate in isolation but instead interact in a way that intensifies the overall experience of fatigue in diabetic individuals (Table 1). Central deficits impair motor control and signal co-ordination, placing greater strain on the peripheral musculature to maintain performance. Simultaneously, peripheral muscle dysfunctions, including reduced mitochondrial function, impaired blood flow and structural abnormalities, feedback to the CNS through altered sensory inputs. This feedback can exacerbate perceived fatigue, leading to an early sensation of exhaustion, further intensified by altered pain perception (Allen et al., 2015; Feldman et al., 2019; Fritschi & Quinn, 2010).

Central mechanisms of fatigue. Central fatigue in diabetes and diabetic neuropathy primarily results from neurological impairment that affects neural transmission, co-ordination and motor control (Allen et al., 2015; Fritschi & Quinn, 2010). Reduced grey matter volume in the cortex, commonly observed in individuals with diabetes, diminishes voluntary activation and the capacity of the CNS to perform sustained, high-intensity tasks (Fritschi & Quinn, 2010; Muramatsu, 2020). This impairment limits cognitive-motor integration,

which is critical for maintaining optimal motor output. Additionally, decreased connectivity between cortical and subcortical areas weakens the communication between regions responsible for motor planning, control and feedback (Fritschi & Quinn, 2010; Kalra & Sahay, 2018). Furthermore, the efficiency in motor unit recruitment from the CNS is reduced as a result of a detrimental synchronisation in these brain networks, leading to a faster onset of fatigue and a reduced ability to sustain motor performance over time (Fritschi & Quinn, 2010; Kalra & Sahay, 2018; Watanabe et al., 2012).

Further complicating these central mechanisms, spinal cord vasculopathy and atrophy compromise blood flow and nutrient delivery to spinal neurons, which are essential for maintaining motor unit recruitment during physical activity (Allen et al., 2015; Ved et al., 2018). With diabetic neuropathy, this spinal cord impairment affects both the neural transmission along the spinal pathways and the feedback mechanisms that normally regulate motor unit activation (Muramatsu, 2020). As a result, the CNS is forced to increase cortical activation for motor output, which is inherently unsustainable over prolonged periods. Diabetic neuropathy also introduces specific disruptions in motor unit recruitment patterns, with irregular motor unit firing, a condition requiring increased energy expenditure to achieve consistent force output (Favretto et al., 2019, 2023; Watanabe et al., 2012). This dysfunction further amplifies central fatigue as the CNS struggles to co-ordinate and sustain motor output in a condition of irregular and inefficient neural signalling.

Peripheral mechanisms of fatigue. Structural and functional impairments contribute to peripheral fatigue as a result of diabetes-related complications, particularly at the muscle fibres and NMJ level. Sensory and motor nerve atrophy, along with the degeneration of motor end plates, significantly affects neuromuscular transmission (Allen et al., 2015; Le Corre et al., 2023). Loss of motor end plate integrity means that, even with adequate neural drive, the muscular response is compromised, accelerating fatigue onset during physical exertion. Compounded by impaired NMJ function, the transmission of action potentials to muscle fibres is weakened, further impacting excitation–contraction coupling (Anagnostou & Hepple, 2020; Miao et al., 2024; Orlando et al., 2022). These complications contribute to performance fatigue as muscle fibres become less responsive to neural signals, necessitating greater effort to sustain contraction and maintain performance.

Peripheral fatigue is also marked by myofilament glycation, a process dependent on chronic hyperglycaemia that structurally alters myosin filaments within muscle fibres (Ramamurthy et al., 2001, 2003). This glycation reduces the efficiency of cross-bridge cycling, leading to a weakened and slower rate of force production and compelling the body to expend additional energy for the same mechanical output level (Orlando et al., 2022). Dysfunctional excitation–contraction coupling, partly as a result of calcium release abnormalities in the sarcoplasmic reticulum, compounds these peripheral limitations by further reducing contractile efficiency, thereby accelerating fatigue onset (Orlando et al., 2022).

Compromised supply and health of muscle fibres observed with diabetic neuropathy further exacerbate peripheral fatigue, with vascular damage impacting perfusion, oxygen tension (Li et al., 2023) and reduced mitochondrial density, limiting ATP production necessary for muscle contractions (Andersen, 1999; Li et al., 2023). Energy sources become insufficient to meet performance demands, leading to early muscle fatigue as energy reserves are depleted, particularly during prolonged tasks.

Together, these peripheral impairments form a substantial barrier to sustained muscle activity because both structural and metabolic complications undermine the muscular ability to maintain prolonged contractions.

Perceived fatigue in diabetic individuals. Perceived fatigue reflects the subjective sense of exhaustion or weariness, which can arise independently of physical exertion (Behrens et al., 2023). In the presence of diabetes, perceived fatigue significantly limits physical performance because it is heavily influenced by the underlying pathophysiology of diabetes-related complications. The combination of metabolic, sensory and emotional factors creates both physical and cognitive experiences of fatigue, disrupting motor performance and exercise tolerance (Kalra & Sahay, 2018). Unlike performance fatigue, which is directly measurable through objective metrics, perceived fatigue in diabetic individuals closely aligns with the subjective feeling of energy depletion, often resulting in a mismatch between perceived effort and actual performance levels (Barakou et al., 2023).

Neuropathic complications further exacerbate this issue by disrupting afferent signals that communicate muscle status to the CNS, leading to an amplified sense of effort, particularly in those with diabetic neuropathy (Barakou et al., 2023; Fritschi & Quinn, 2010). These sensory disruptions increase the perceived effort for simple motor tasks, such that even daily activities may feel as demanding as moderate to intense exercise. This altered sensory feedback affects proprioceptive inputs, increasing the subjective experience of fatigue and lowering the threshold for exhaustion during physical exertion.

Psychological factors also contribute to higher perceived fatigue in diabetic patients, influencing cognitive and physical domains. Diabetes-related psychological distress, encompassing diabetes distress,

anxiety and depression, is prevalent in this population, further increasing perceived fatigue (Kalra & Sahay, 2018). The chronic mental load required to manage blood glucose, dietary restrictions and medication schedules results in persistent cognitive fatigue (Barakou et al., 2023; Fritschi & Quinn, 2010), directly impacting motor performance by reducing the individual's mental resilience and the ability to sustain effort during exercise.

Older females with diabetes generally report higher perceived exertion than males in comparable conditions (Huebschmann et al., 2015). Furthermore, in controlled exercise settings, such as endurance step tests at 50–90% of the maximal workload, no significant differences have been reported in male diabetic individuals (50—60 years of age, non-neuropathic) in terms of both absolute heart rate and heart rate relative to the maximum. Similarly, no differences emerged in perceived exertion across each test level for these male participants (Schwensfeier et al., 2023). Discrepancies in perceived fatigue across studies probably arise from variations in testing conditions, demographics and individual health factors. Sex-specific physiological and psychological differences and distinct study designs may influence the mentioned outcomes. Moreover, the diverse impact of diabetes-related complications such as neuropathy and individual approaches to diabetes management suggest the need for additional research for a comprehensive characterisation of precise determinants of perceived fatigue in this population.

Glycaemic control and the protective role of physical activity

Managing blood glucose levels prevents and mitigates micro- and macrovascular complications in diabetic individuals (Le Corre et al., 2023). Dysglycaemia is associated with a higher risk of developing endothelial dysfunctions, contributing to a greater incidence of cardiovascular complications (Li et al., 2023). Both long-term and short-term glycaemic control are crucial in supporting cardiovascular health and preventing complications such as diabetic neuropathy (Feldman et al., 2019; Forbes & Cooper, 2013).

Impaired long-term glucose control is responsible for adverse cardiometabolic events, commonly recognised as glucotoxicity (Rossetti et al., 1990), implicating consequences such as reduced insulin sensitivity and secretion, as well as decreased β-cell mass and functionality (Bensellam et al., 2012; Robertson et al., 2003). These mechanisms progressively lead to insulin resistance and impaired glucose uptake in T2D individuals. Moreover, glucotoxicity is associated with increased oxidative stress, cellular damage, endothelial dysfunction and inflammation, heightening the risk of both microvascular and macrovascular complications in individuals with either T1D or T2D (Le Corre et al., 2023; Li et al., 2023).

It is fundamental to note that other factors may influence the appearance of microvascular complications in diabetic individuals. Short-term glycaemic variability is typically associated with an increased risk of developing neuropathic complications (Zhang et al., 2021). In particular, individuals with diabetic neuropathy have demonstrated higher variability in glycated haemoglobin (HbA1c) compared to those without complications (Su et al., 2018). Daily fluctuations in glucose levels contribute to increased oxidative stress and elevated circulating inflammatory factors (e.g. IL-6, TNF-alpha and IL-18), as well as adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin), collectively raising the incidence of cardiovascular complications in both types of diabetes (Ceriello et al., 2004, 2010; Ceriello & Ihnat, 2010).

Postprandial periods amplify the consequences of glycaemic variability, with glucose levels often exceeding normal ranges. This underscores the relevance of managing post-meal glucose levels to improve overall cardiometabolic health in diabetic individuals and reduce complications (Ceriello et al., 2004). In these terms, exercise and diet are essential for reducing the post-meal glucose response and glycaemic variability, lowering the risk of developing vascular complications (Bellini et al., 2024; Syeda et al., 2023; Yorek et al., 2014; Zhang et al., 2021). For example, it has been recently highlighted that prolonged moderate-intensity exercise starting soon after eating (i.e. 30–60 min after) can significantly reduce the postprandial glucose peak (Bellini et al., 2021). Therefore, implementing physical activity right after a meal would benefit cardiometabolic health.

Technological advances are also helpful in glycaemic management, particularly through continuous glucose monitoring systems. These systems allow diabetic individuals to more effectively manage glucose fluctuations, increasing time within the target glycaemic range and decreasing daily variability (Yapanis et al., 2022). Additionally, continuous glucose monitoring is helpful in monitoring glucose levels during exercise, allowing real-time adjustments that enhance exercise safety. This capability may improve adherence to exercise programs because fear of hypoglycaemic events during physical activity is a common reason for exercise avoidance in diabetic populations (Cigrovski Berkovic et al., 2021; Zaharieva & Addala, 2022).

The benefits of exercise in diabetic individuals extend beyond managing glucose and lipid metabolism, and diverse physiological adaptations result from long-term exercise programs (Praet et al., 2007). Both resistance and endurance exercises have been associated with beneficial effects for neuropathic symptoms, glycaemic control,

and physical fitness (Li et al., 2024; Pedersen, 2017; Su et al., 2023). These beneficial effects are achieved through specific physiological responses to different physical training modalities summarised in Fig. 4.

Aerobic training. People diagnosed with diabetes mellitus typically present a lower exercise capacity by ∼20% (Wei et al., 1999; Zaccardi et al., 2015), manifested with a reduced $\dot{V}_{O_2max}$ and time-to-exhaustion compared to healthy, age and physically-activity-matched control groups (Nesti et al., 2020). Decreased exercise capacity includes deficiencies in the cardiovascular and respiratory systems to supply oxygen, as well as the inability of tissues to extract oxygen (Nesti et al., 2020; Reusch et al.,

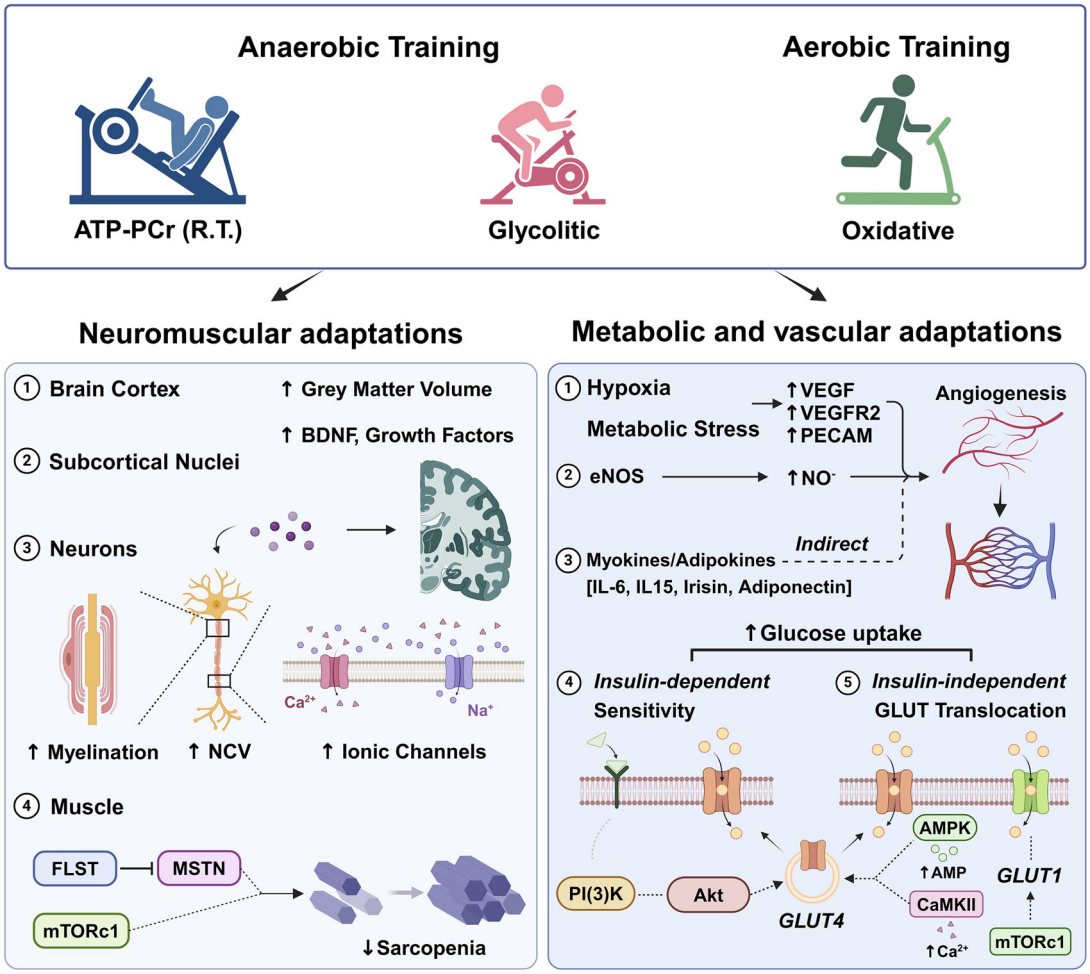

Figure 4. Physiological and molecular changes induced by physical exercise
Both anaerobic (i.e. resistance training/ATP-PCr, glycolitic energy systems) and aerobic (oxidative energy system) training promote neuromuscular (right) and metabolic/vascular adaptations (left). Right: the neuromuscular effects of exercise highlight changes in the central and peripheral nervous system. Exercise promotes the increase in grey matter and brain-derived neurotrophic factor (BDNF) in the cerebral cortex (1) and subcortical nuclei (2), as well as an increase in other beneficial growth factors. The release of these substances at the neuronal level (3) induces an improvement in myelination, an increase in nerve conduction velocity (NVC) and an enhancement of ion channels. As a result of the combined effect of mechanical overload and time under tension, molecular signalling of mechanistic target of rapamycin complex 1 (mTORc1) and follistatin (inhibiting myostatin), exercise reduces sarcopenia and improves muscle function. Left: exercise-induced hypoxia (1) and metabolic stress (2) lead to a significant increase in the expression of angiogenic factors, such as vascular endothelial growth factor (VEGF), VEGFR2 (VEGF receptor) and endothelial plaque cell adhesion molecule (PECAM), as well as endothelial nitric oxide synthase and nitric oxide (2). These changes and the secretion of myokines and adipokines (3) facilitate angiogenesis, improving blood flow and nutrient supply to muscle tissue. In addition, there is an improvement in glucose uptake mediated by both insulin-dependent (4) and insulin-independent glucose transporter type 4 (GLUT-4) receptors (5), which contributes to increased energy availability and optimised metabolic function. AMPK, adenosine monophosphate kinase; eNOS, endothelial nitric oxide synthase; FLST, follistatin; IL, interleukin; MSTN, myostatin; NO, nitric oxide; PCr, phosphocreatine; R.T., resistance training. Created with BioRender.

2013). Endurance training is considered safe and effective in enhancing glycaemic control, exercise capacity, and well-being status in complicated and uncomplicated diabetic individuals (Colberg et al., 2016; Kanaley et al., 2022). Aerobic exercise promotes the decrease in HbA1c and fasting plasma glucose levels (Boulé et al., 2003; Umpierre et al., 2011) in a dose-dependent association with modifications in training volume and/or intensity (Delevatti et al., 2019).

Improvements in aerobic exercise capacity are mainly related to modifications in the oxygen cascade, with an augmented capacity of oxygen transportation and extraction observed in diabetic individuals (Nesti et al., 2020). For example, a study investigating cardiac modifications following a high-intensity interval training program has shown that diabetic individuals had greater cardiac output at rest, which was accompanied by improvement in left ventricular filling and emptying capacity, as well as an increase in stroke volume (Wilson et al., 2019). Nevertheless, it has been shown how both continuous and interval training were effective strategies to improve oxygen extraction in the diabetic population (Van Ryckeghem et al., 2022) and these findings pointed out reduced blood flow to skeletal muscle as a contributing factor to exercise tolerance in T1D and T2D patients (Goulding et al., 2020; Nesti et al., 2020).

Despite vascular damage induced by chronic hyperglycaemia, it has been suggested that aerobic exercise performed at both moderate and high intensity promotes angiogenesis, decreases capillary rarefaction and reduces pericapillary membrane thickness (Basu et al., 2014; Mortensen et al., 2019). Among several underlying mechanisms involving glycaemic and AGEs control, inflammation management, and apoptosis regulation (Callaghan & Feldman, 2013; Dixit et al., 2014; Gholami et al., 2018; Olver et al., 2014), reactive oxygen species, myokinases and the upregulation of endothelial nitric oxide synthase promoting nitric oxide (NO^{-}) synthesis are the leading candidates inducing vascular adaptations in response to exercise (Groen et al., 2014; Prior et al., 2014; Qi et al., 2022; Song et al., 2024). Nevertheless, these findings remain highly speculative in people affected by diabetes mellitus because these individuals typically present NO resistance (Bahadoran et al., 2023).

However, the development of microvascular complications with diabetes is associated with increased production of reactive oxygen species (Baynes, 1991; Giugliano et al., 1996), disrupting the balance between free-radical generation and antioxidant activity (Giacco & Brownlee, 2010). A long-term endurance training program has been associated with decreased oxidative stress among people with T2D by modifying the systemic oxidative stress profile (Nojima et al., 2008) and selectively upregulating antioxidant enzymes compared to other training modalities (de Oliveira et al., 2012).

Aerobic training effectively reduces fat content in diabetic patients, as demonstrated by reductions in visceral and subcutaneous adipose tissue following an aerobic training program (Bacchi et al., 2012). These adaptations were also observed in another study on diabetic individuals (Seung et al., 2005), outlining modifications in both absolute and relative terms. Altered fat mass in diabetic individuals may result from changes in cytokine levels (i.e. TNF and IL-6), which commonly have inhibitory effects on insulin secretion, leading to insulin resistance (Hajer et al., 2008). Indeed, higher levels of IL-6 are typically observed after acute exercise, which suppresses the production of TNF and enhances insulin secretion with a concomitant effect on glycaemic function through stimulation of glucagon-like peptide-1 from pancreatic -cells (Karstoft & Pedersen, 2016). Constant and regular exercise practice indirectly affects chronic inflammation through improvements in body composition, physical fitness and metabolic function (Colberg et al., 2016; Pedersen & Saltin, 2015), modulating the activity of pro-inflammatory cytokines (Papagianni et al., 2023). Moderate-intensity aerobic training programs promote reductions in C-reactive protein (Balducci et al., 2010; Choi & Rush, 2012) and resistin levels (Giannopoulou et al., 2005), as well as IL-6 and TNF, as previously outlined. The above findings point out the effects of regular endurance training on the damage exerted by chronic hyperglycaemia in diabetic individuals.

Moreover, aerobic training promotes the activation of PGC-1α, which is critical in mediating mitochondrial biogenesis and neuronal cell survival (Halling & Pilegaard, 2020; You et al., 2024). These adaptations have been observed in people with both types of diabetes in response to various aerobic training modalities, even though to a lower extent than in healthy individuals (Jingjing et al., 2023; Lin et al., 2024; Minnock et al., 2022), implicating greater oxidative capacity of the skeletal muscle (Lundby & Jacobs, 2016). Mitochondrial function enhancements have been observed in response to moderate-intensity endurance training, evidenced by a higher creatine phosphate recovery rate. This improvement is further supported by elevated insulin-stimulated glucose oxidation and reduced fat oxidation (Meex et al., 2010). Another study examining the effects of low-volume, high-intensity interval training reported increased citrate synthase activity alongside other skeletal muscle mitochondrial capacity markers. However, when comparing moderate- and high-intensity training programmes in diabetic mice, no significant differences in mitochondrial function were found (Chavanelle et al., 2017). These findings, however, await confirmation in human studies.

It has been reported that 6 months of aerobic exercise mitigates the deterioration of brain structures in the T2D

population. In particular, a lesser duration of physical activity (hours/week) is associated with a lower volume of cortical and subcortical structures, which is not dependent on HbA1c (Moreno et al., 2023). Furthermore, diabetic individuals with and without neuropathy undertaking aerobic exercise significantly improved NCV (Balducci et al., 2006; Gholami et al., 2018), leading to enhanced functionality in both sensory and motor nerves because of the positive effect of exercise (Beigi et al., 2023; Streckmann et al., 2022). These findings support the notion of physical training safety and effectiveness in restoring neural functioning in diabetic individuals with neuropathic compilations. Moreover, aerobic exercise promotes several *exerkines*, such as irisin, adiponectin and interleukins, which have been recognised as a primer for molecular signalling of injured tissue regeneration (Chen et al., 2022).

Aerobic exercise also induces motor cortical neuroplasticity in diabetic individuals, comprising a critical adaptation in mitigating neural deterioration occurring with neuropathic complications (McDonnell et al., 2013; Yamazaki et al., 2019; Yang et al., 2019). This is probably induced by the exercise role in promoting brain-derived neurotrophic factor (BDNF), which is responsible for neuronal survival, proliferation, maturation, and outgrowth in both the central and peripheral nervous systems, including beneficial effects for spinal cord injuries (Bilchak et al., 2021; Cefis et al., 2023; Chang et al., 2019; Chen et al., 2022; English et al., 2014; McGregor & English, 2019).

To date, no studies assessing NMJ modification following exercise intervention have been performed in diabetic individuals. However, healthy young and older adults exhibited enhanced pre-synaptic nerve terminal branching and the number of vesicles, along with a greater number of post-synaptic receptors, with significant responses observed after endurance exercise (Deschenes, 2019; Yamaguchi et al., 2024).

Resistance training. The increases in muscle strength in response to resistance training are accompanied by a higher muscle fibre conduction velocity in diabetic individuals, indicative of enhanced recruitment of higher-threshold motor units (Bazzucchi et al., 2015). These adaptations are particularly evident in lower limbs compared to upper limbs as a result of differences in fibre morphofunctional features, as well as sarcolemmal excitability (Orlando et al., 2016). In this context, performance enhancements from training can result from spinal and supraspinal adaptations, as well as enhanced anaerobic capacity of skeletal muscle (Škarabot et al., 2021; Zanuso et al., 2017), although the evidence of the effect of exercise on these outcomes in individuals with neuropathy remains to be explored.

Reduced pain sensation and electrophysiological dysfunction, accompanied by increases in neurotrophic factors, have been observed in response to resistance training, although to a lesser extent compared to aerobic training (Cefis et al., 2023; Dobson et al., 2014; Groover et al., 2013; Ma et al., 2019; Zhang et al., 2021). The physiological effects associated with neurotrophic factor secretions promote reversing myelinic damage and restoring Ca^{2+} ionic channels, explaining the enhanced neural input transmission (Shankarappa et al., 2011).

The role of resistance training on the NMJ is currently unknown. However, it has been reported that NMJ responses to resistance training primarily regard structural expansion, particularly in the post-synaptic density of higher-threshold motor units (Deschenes, 2019). These modifications may also be beneficial for diabetic individuals with respect to to mitigating the detrimental effects of diabetes-related complications on neuromuscular transmission.

Neurogenic sarcopenia and muscle atrophy are critical in diabetes-related complications, which are primarily mitigated through resistance training (Zacker, 2005). Indeed, the overloading of muscle structures induces hypertrophy, enhanced body mass index, waist circumference and fat mass (Acosta-Manzano et al., 2020). Furthermore, resistance training induces musculoskeletal adaptations through the combined effect of mechanical overload (Roberts et al., 2023) and time under tension (Burd et al., 2012), resulting in the upregulation of mechanistic target of rapamycin complex 1 (mTORc1) and follistatin, which is responsible for inhibiting myostatin (Amthor et al., 2004; Rodino-Klapac et al., 2009).

Resistance training is also associated with the production of exerkines, which is responsible for tissue regeneration and remodelling, paramount for mitigating diabetes-related complications (Chow et al., 2022; Robbins & Gerszten, 2023). As a result, the increase in muscle strength, accompanied by enhanced muscle quality and functionality, directly depends on the protective and preventive action of exercise training. Nevertheless, it is crucial to note that resistance training adaptations are severely attenuated with ageing, although a significant protective effect has been recognised (Hepple & Rice, 2016).

Combined exercise training. The physiological mechanisms associated with the beneficial effects of combined aerobic and resistance training on diabetic individuals directly incorporate the abovementioned evidence of either isolated exercise modalities. However, combining these training modalities represents an additional strategy for optimising gains from both in diabetic individuals. Recent findings indicate that combined exercise training induces a significant reduction

in the body mass index of ∼0.98 kg m^{-2}, accompanied by lower body fat percentage and a preserved muscle mass (Zhao et al., 2021). The observed effects depend on the physiological response to mechanical overload in promoting hypertrophy and the higher metabolic rate promoted by aerobic exercise, further contributing to physical fitness, weight management and individual independence (Coffey & Hawley, 2017; Huiberts et al., 2024; Maiorana et al., 2002). Combined exercise also promotes significant reductions in both systolic and diastolic blood pressure and enhancements in lipid profiles in diabetic individuals (Zhao et al., 2021). These modifications contribute to reduced cardiovascular risk, improved vascular health and overall enhancements in blood lipid regulation in diabetic individuals, especially those with T2D, as a result of the close association with a sedentary lifestyle (Pinto et al., 2023).

The combined benefits of aerobic and resistance training increase confidence and satisfaction with physical capabilities, which is positively associated with exercise adherence in a relatively long-term intervention (Balducci et al., 2010). Improved adherence strengthens the likelihood of continued metabolic and functional benefits, supporting the long-term health of diabetic patients. However, mild musculoskeletal discomfort or the aggravation of pre-existing conditions, such as osteoarthritis, can occur, particularly in unsupervised settings (Zhao et al., 2021). Although these events are typically minor, proper supervision and individualised adjustments to exercise regimens are recommended to minimise risk, emphasising the importance of individualised, guided exercise programs for the diabetic population.

The role of physical exercise in glycaemic control. To mitigate the detrimental effects of glycaemic variability, 150–300 min of moderate-intensity or 75–150 min of vigorous-intensity aerobic exercise per week and at least two sessions per week of resistance exercise have been suggested in people with diabetes (Kanaley et al., 2022; Pinto et al., 2023). The aim is to minimise sedentary habits by performing activity breaks or any movement, based on the motto 'every move counts' (Bull et al., 2020). This is achieved through aerobic exercise, resistance training and combining both approaches (Coffey & Hawley, 2017; Kanaley et al., 2022; Maiorana et al., 2002).

Aerobic training, including continuous or interval-based exercise, is strongly associated with improved glycaemic control in both healthy and diabetic individuals. Regular aerobic exercise has been linked to reductions in HbA1c and fasting glucose levels, alongside enhanced insulin sensitivity and lipid management, which are particularly beneficial in the diabetic population (Ashcroft et al., 2024; Bellini et al., 2024; Bird & Hawley, 2017; Haxhi & Bellini, 2024; Van Dijk & Van Loon, 2015).

At the molecular level, aerobic exercise promotes glucose uptake in skeletal muscle primarily through the activation of AMP-activated protein kinase (AMPK), a pathway that facilitates the translocation of glucose transporter type 4 GLUT (GLUT4) to the cell membrane (Fueger et al., 2007; Kennedy et al., 1999; Leprivier & Rotblat, 2020). This insulin-independent mechanism of GLUT4 mobilisation is essential for improving glycaemic control, particularly in individuals with impaired insulin signalling. Although exercise does not appear to affect insulin receptor activity (Treadway et al., 1989), GLUT4 translocation has been suggested to depend on NO signalling and calmodulin-dependent protein kinase pathways associated with muscle contraction (Knudsen et al., 2020; Richter & Hargreaves, 2013; Sjøberg et al., 2017). Notably, this insulin receptor-independent action contributed to the recognition of physical exercise as the most potent stimulus to increase skeletal muscle GLUT4 expression, thereby improving glycaemic control and underscoring the protective role of exercise in diabetes-related complications.

Aerobic exercise also stimulates IL-6 release from muscle, which subsequently enhances glucagon-like peptide-1 secretion from intestinal L-cells and the pancreas, indirectly improving insulin response and glycaemic regulation (Holst, 2007; Morettini et al., 2017; Müller et al., 2019). This cascade reduces systemic inflammation, improves fat oxidation and enhances cardiovascular health, further supporting glucose homeostasis and long-term metabolic health in diabetic individuals (Karstoft & Pedersen, 2016).

Resistance training also enhances glycaemic control through different mechanisms from aerobic exercise. Unlike aerobic training, resistance exercise does not primarily rely on AMPK activation but rather on mTOR-related pathways, which are stimulated by the muscle contractions and microtears characteristic of strength exercises (Röhling et al., 2016). This mTOR pathway activation enhances glucose transport into skeletal muscle cells, improving insulin sensitivity and aiding in glycaemic control. Resistance training also enhances the release of myokines, comprising proteins that play a role in muscle signalling and metabolic regulation. Myokines released following resistance exercise modulate inflammation, promote fat oxidation and improve -cell function, helping to reduce endothelial dysfunction and mitigate cardiovascular risks associated with diabetes (Karstoft & Pedersen, 2016; Pedersen, 2017).

Even though exercise substantially improves life quality in diabetic individuals, many patients do not exercise regularly. One of the leading causes of poor exercise program adherence is fear of hypoglycaemic events during the session, especially among T1D individuals (Riddell et al., 2017). Hyper- and hypoglycaemic events during exercise are relevant issues that these patients have to

Table 2. Training strategies for diabetic individuals

Training	Prescription	Adaptation	References
Endurance training continuous activity at moderate and high-intensity of running/swimming/cycling	55–75%HRmax RPE 12–13 >150 min week^{-1} | 3–7 days week^{-1} 75–95%HRmax RPE 14–16 75–150 min week^{-1} 3–7 days week^{-1} No more than 48 h of rest	HbA1c level ↓ Insulin sensitivity ↑ Blood pressure ↓ Lipid profile ↑ Fat mass ↓ Glycaemic control ↑ Mitochondrial density ↑	(Colberg et al., 2016; Rodino-Klapac et al., 2009)
Strength training Resistance machines, free weights, resistance bands, and/or body weight as resistance exercises	1–3 sets, 10–15 repetitions OMNI 7–8 8–10 exercises per session 1–3 sets, <8 repetitions OMNI 8–9 8–10 exercises per session Minimum 48 h of rest	HbA1C ↓↓ Fat mass ↓ Strength ↑↑ Sarcopenia ↓↓↓ Body composition ↑↑	(Acosta-Manzano et al., 2020; Kanaley et al., 2022; Syeda et al., 2023)
HIIT High-intensity repeated bouts of running/swimming/cycling or resistance training	10 s to 4 min, high-intensity (75–95%HRmax) 12 s to 5 min, active/passive rest (30–60%HRmax) 3 days week^{-1} for vigorous aerobic 2 days week^{-1} for resistance training	Glycaemic control ↑↑ Oxidative capacity ↑↑ Insulin sensitivity ↑↑ Stroke volume ↑	(Van Ryckeghem et al., 2022; Wilson et al., 2019)
Combined training (strength + aerobic) resistance training (weight loaded) + aerobic exercises (i.e. walking, cycling)	Circuit training 7 laps, strength + aerobic Strength (60%1RM, 15 repetitions) Aerobic 70–80%HRmax 3 sessions week^{-1} 1 h per session	HbA1 ↓↓ Glycaemia ↓ Strength ↑ Waist: hip ratio ↓ Skinfold ↓↓ Body composition ↑↑ $\dot{V}_{O_2max}$ ↑	(Coffey & Hawley, 2017; Huiberts et al., 2024; Maiorana et al., 2002; X. Su et al., 2022)

↑ Slight increase, ↑↑ moderate increase, ↑↑↑ high increase, ↓ slight decrease, ↓↓ moderate decrease, ↓↓↓ high decrease. Classification was made based on Colberg et al. (2016) and Syeda et al. (2023). The OMNI scale has been adapted according to Helms et al. (2016); Lagally & Robertson (2006); Naclerio et al. (2011); and Robertson et al. (2003). HbA1C, haemoglobin A1C; HIIT, high-intensity interval training; HRmax, maximum heart rate; RM, repetititon maximum; RPE, rating of perceived exertion.

deal with. Technological advances and the most recent studies on exercise safety have widely helped reduce these events and increase glucose control during exercise. In particular, evidence suggests that aerobic exercise elicits a greater glucose reduction during and several hours after the session compared to resistance exercise in T1D (Yardley et al., 2012) and T2D individuals (Bellini et al., 2023, 2024). This has mainly been associated with more production of growth hormone in response to resistance exercise, which mitigates broad excursions of glucose levels (Yardley et al., 2012). Therefore, it is paramount to consider combined exercise strategies to guarantee blood glucose stability both acutely (Minnock et al., 2020) and chronically (Minnock et al., 2022). Although the importance of exercise in managing blood glucose levels in diabetic individuals has been broadly discussed, evaluating its impact on neuropathic complications still requires more investigation, underlining the physiological relevance of the beneficial effects promoted by physical exercise.

Guidelines for exercise prescription in diabetic individuals are reported in Table 2.

Practical applications

Regular exercise is crucial for treating diabetes-associated complications and shall be considered as the leading approach for therapeutic benefits (McGee & Hargreaves, 2020). Aerobic exercise improves vascular health, enhancing blood flow and oxygen delivery to tissues, and also promotes the release of BDNF, which supports

nerve health and function. Resistance training helps prevent and manage sarcopenia by enhancing muscle strength and preserving fat-free mass. These combined effects lead to better glycaemic control, reduced neuropathic symptoms and improved overall physical health . The abovementioned information finds applications throughout various exercise training modalities that shall be individualised and applied based on patients' needs.

Conclusions

Diabetic neuropathy is associated with deterioration in both the structural and functional aspects of the neuromuscular system, manifesting through impairments at the central and peripheral nervous systems, defective neuromuscular junction and accelerated loss of muscle fibres. These complications contribute to a severe decline in performance and independence, burdening the affected population. Current knowledge highlights the significant impact of hyperglyacemia-induced oxidative stress, impaired nerve regeneration and vascular complications on neuromuscular integrity. Although the precise mechanisms, particularly regarding CNS involvement, remain partially understood, evidence supports the critical role of glycaemic control in mitigating these complications. Notably, regular physical exercise emerges as a promising intervention, potentially counteracting neuromuscular decline by promoting muscle strength, hypertrophy, metabolic health and nerve regeneration. Future research should aim to elucidate the detailed pathways of neuromuscular deterioration to optimise the exercise protocols and therapeutic benefits for diabetic individuals and also include motor unit assessment over a broad range of modalities to elucidate the mechanisms underlying the loss of functional properties.

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Additional information

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The authors declare that they have no competing interests.

Author contributions

E.L. designed and conceived this review. All authors drafted and critically revised the article. All authors have approved the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

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