

Review Article

Lower-limb muscle-specific alterations in type 2 diabetes: A fiber-type-dependent perspective on structural atrophy, functional decline, and targeted resistance training in humans

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Abstract

Type 2 diabetes mellitus (T2DM) adversely affects skeletal muscle, contributing to weakness, functional decline, and reduced mobility. Although lower-limb muscles are essential for locomotion and independence, it remains unclear whether diabetes affects these muscles uniformly or whether certain muscle groups are more vulnerable. Resistance training (RT) is widely recommended for individuals with T2DM. This narrative review synthesizes evidence from human studies on structural and functional alterations in the quadriceps, gastrocnemius, and soleus muscles in adults with T2DM. We propose that fiber-type composition may be a key determinant of muscle-specific vulnerability. Because the soleus is composed predominantly of type I (slow-twitch, oxidative) fibers, which are particularly susceptible to mitochondrial dysfunction, impaired glycogen metabolism, and chronic metabolic stress, we propose the hypothesis that it may undergo earlier and more pronounced deterioration than muscles with a more mixed fiber composition. Current evidence consistently demonstrates reduced quadriceps size, strength, and muscle quality in T2DM, whereas studies of the calf muscles remain limited despite their critical role in gait and balance. Emerging imaging and mechanistic evidence suggest that the soleus may exhibit early diabetes-related microstructural alterations. RT improves muscle strength, physical function, and metabolic health; however, no human study has directly compared the responses of the quadriceps, gastrocnemius, and soleus to the same RT protocol. Overall, available evidence supports regional heterogeneity rather than uniform lower-limb involvement in T2DM. A fiber-type-informed, muscle-specific perspective may improve understanding of diabetes-related muscle dysfunction and guide the development of more targeted resistance training strategies to preserve mobility and functional independence.

Key Words: Type 2 diabetes mellitus, Skeletal muscle, Resistance training, Fiber-type composition, Lower-limb muscles

Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disorder characterized by chronic hyperglycemia and insulin resistance. In addition to its well-established effects on glucose homeostasis, T2DM is now widely recognized as a condition that compromises skeletal muscle health. Given that skeletal muscle is the primary site of insulin-stimulated glucose disposal and plays a central role in mobility and functional independence, diabetes-related impairments in muscle can have substantial metabolic and clinical consequences (Castillo Í et al., 2025; Lopez-Pedrosa et al., 2024; Yang et al., 2025).

Growing evidence shows that adults with T2DM commonly experience declines in muscle strength, reduced muscle quality, and changes in muscle morphology (Castillo Í et al., 2025). These abnormalities are associated with impaired mobility, poorer physical performance, a higher risk of falls, and reduced quality of life. Notably, the loss of muscle strength in T2DM is not always proportional to the reduction in muscle mass, suggesting that structural and functional deterioration may arise through, at least in part, distinct underlying mechanisms (Goodpaster et al., 2006; Liu et al., 2024; Muvhulawa et al., 2023).

The lower limbs are of particular clinical importance because they play a vital role in locomotion, balance, stair climbing, and other activities of daily living (Hortobágyi et al., 2015). However, increasing evidence suggests that diabetes-related changes are not evenly distributed across lower-limb muscle groups (Castillo Í et al., 2025). The quadriceps femoris (quadriceps) have been studied most extensively and consistently show both structural and functional impairments (Lopez-Pedrosa et al., 2024). By comparison, the gastrocnemius and soleus are also likely to be clinically important but have received considerably less attention in human studies (Monaco et al., 2020). As a result, it remains uncertain whether the apparent differences between muscle groups reflect true muscle-specific susceptibility or simply the unequal distribution of existing research (Castillo Í et al., 2025; Monaco et al., 2020).

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Notably, evidence from animal models of diabetes provides direct support for the concept of fiber-type-dependent muscle vulnerability. In a comparative study of rat skeletal muscles, Bozkurt et al. (2010) demonstrated that the soleus muscle, which is composed predominantly of oxidative type I fibers, exhibited more pronounced compositional, structural, and functional alterations than the predominantly glycolytic extensor digitorum longus (EDL) muscle in response to diabetes (Bozkurt et al., 2010). Similarly, Hardin et al. (1993) reported that the decrease in GLUT4 glucose transporter content was significantly greater and occurred more rapidly (as early as day 2) in the soleus compared to muscles with higher type II fiber composition (Hardin et al., 1993). These mechanistic findings from animal studies, together with human imaging evidence showing early microstructural changes in the soleus of T2DM patients (Zhao et al., 2022; Zuo et al., 2012), provide a strong biological rationale for the hypothesis that the soleus may be particularly vulnerable to diabetes-related deterioration.

Although previous reviews have described skeletal muscle atrophy and dysfunction in T2DM, none has systematically examined whether fiber-type composition contributes to muscle-specific patterns of deterioration or influences responses to resistance training. Skeletal muscle is a heterogeneous tissue composed of fibers with distinct metabolic and contractile properties, broadly classified as slow-twitch (type I, oxidative) and fast-twitch (type II, glycolytic). In this review, we use the term 'fiber-type-specific' in two distinct contexts: first, to describe the differential vulnerability of muscle fibers to diabetes-related metabolic disturbances (fiber-type-dependent vulnerability), and second, to describe the differential adaptive responses of muscle fibers to resistance training (fiber-type-aligned training). Individuals with T2DM typically exhibit a shift in fiber-type composition, characterized by a reduction in oxidative type I fibers and a relative increase in glycolytic type II fibers (Frankenberg et al., 2022; Oberbach et al., 2006). Type I fibers also differ from type II fibers in glucose handling and protein localization under diabetic conditions (Frankenberg et al., 2022).

In this review, we propose the hypothesis that the soleus muscle, owing to its exceptionally high proportion of type I fibers (approximately 80–90%), may be particularly susceptible to diabetes-related metabolic disturbances, including insulin resistance, mitochondrial dysfunction, and chronic inflammation. As a result, we suggest that it may undergo earlier and more pronounced structural and functional deterioration than the quadriceps or gastrocnemius. Importantly, this hypothesis is supported by converging evidence from animal models and human imaging studies, as detailed above. However, it must be emphasized that direct comparative longitudinal studies in humans are currently lacking and this framework should therefore

be viewed as a testable hypothesis rather than an established pathophysiological fact. We further suggest that adaptations to resistance training are likely to depend, at least in part, on muscle fiber composition. Specifically, high-volume, low-to-moderate load training may be better suited to the soleus, whereas high-intensity, explosive training may produce greater benefits in the gastrocnemius and quadriceps. This review evaluates the evidence supporting this fiber-type-based framework and presents a muscle-specific approach to resistance training that may help guide future research and clinical practice.

Lower-limb muscle dysfunction in T2DM is likely driven by multiple factors, including insulin resistance, chronic low-grade inflammation, mitochondrial dysfunction, intramuscular fat accumulation, reduced physical activity, and diabetes-related neuropathic changes (Liu et al., 2024; Veluthakal et al., 2024). The relative contribution of these mechanisms may vary across muscle groups according to their fiber-type composition, metabolic profile, and functional role (Hansen et al., 2025).

Resistance training (RT) is widely recognized as one of the most effective non-pharmacological strategies for preserving skeletal muscle health in individuals with T2DM (Feng et al., 2025; Pfeifer et al., 2022). Beyond improving glycemic control, RT can increase muscle strength, stimulate hypertrophy, enhance neuromuscular function, and improve physical performance (Amaravadi et al., 2025; Morihara et al., 2025). However, it remains unclear whether these adaptations occur uniformly across individual lower-limb muscles.

To identify relevant literature, we conducted a systematic search of PubMed, Scopus, and Web of Science databases up to March 2026 using combinations of the following keywords: 'type 2 diabetes,' 'skeletal muscle,' 'lower limb,' 'quadriceps,' 'gastrocnemius,' 'soleus,' 'muscle atrophy,' 'muscle strength,' 'muscle quality,' 'fiber type,' 'resistance training,' and 'exercise.' We included human studies published in English that examined structural or functional alterations in lower-limb muscles in adults with T2DM, as well as intervention studies investigating the effects of resistance training on muscle outcomes. We also manually searched reference lists of relevant reviews and included key animal studies providing mechanistic insights. Given the hypothesis-generating nature of this review, we used a narrative synthesis approach, integrating evidence from cross-sectional, longitudinal, and interventional studies to develop a fiber-type-informed framework for understanding muscle-specific vulnerability and training responses.

This narrative review synthesizes current evidence from human studies on muscle-specific structural and functional alterations in the lower-limb muscles of adults with T2DM, with a particular focus on the quadriceps and calf muscles. It also explores the

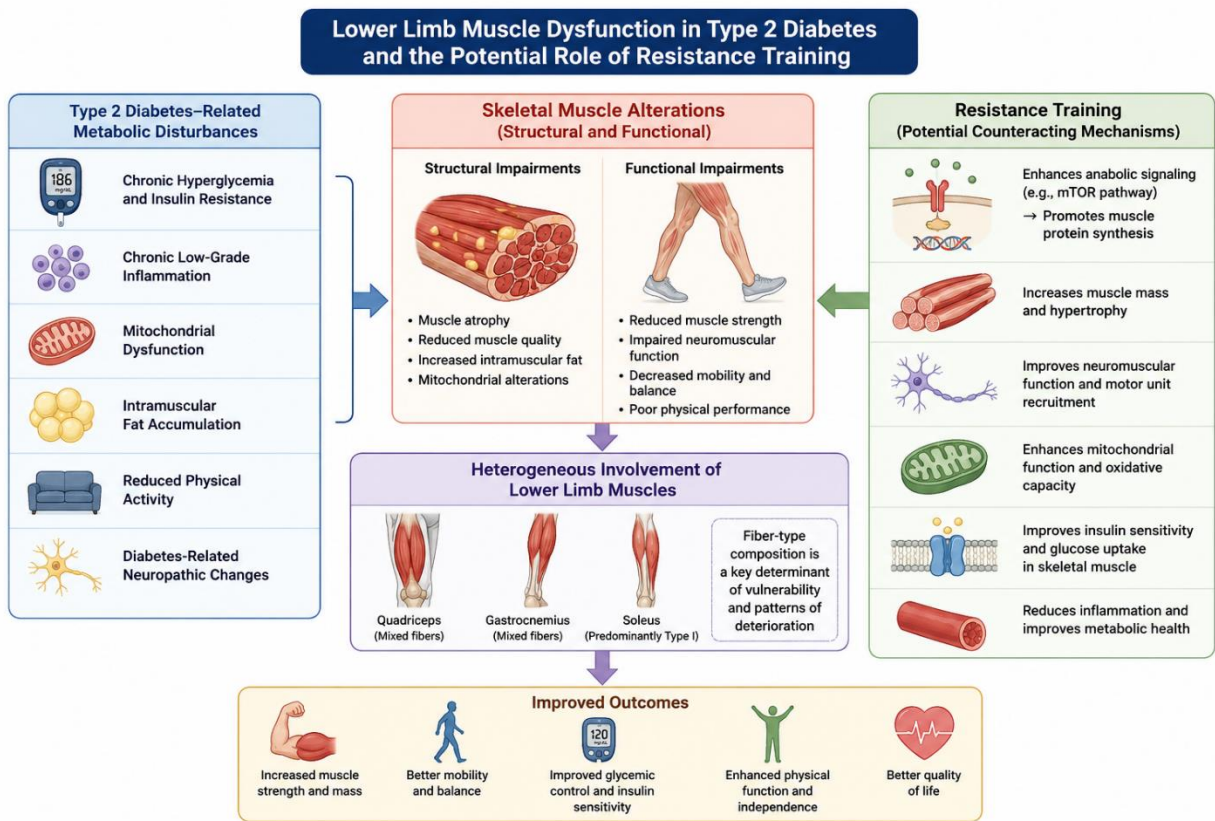


Figure 1. Conceptual overview of lower-limb muscle dysfunction in T2DM and the potential counteracting effects of resistance training.

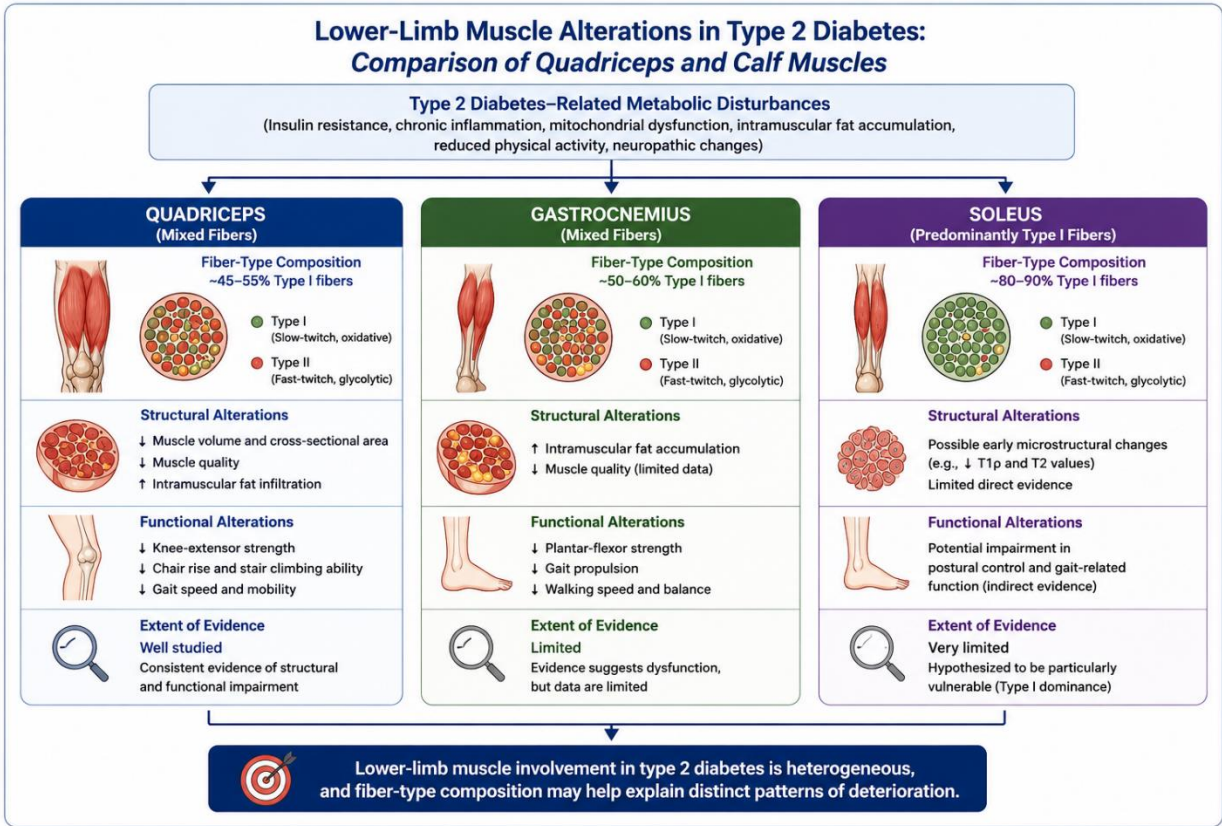


Figure 2. Comparison of structural and functional alterations in the quadriceps, gastrocnemius, and soleus muscles in T2DM, highlighting fiber-type-dependent vulnerability.

of resistance training to mitigate these impairments, introduces a fiber-type-informed training framework, and identifies key priorities for future research. We emphasize that the proposed fiber-type-informed framework is hypothesis-generating and requires validation through direct comparative human studies. A conceptual overview of the pathways linking T2DM to lower-limb muscle dysfunction, along with the potential counteracting effects of resistance training, is presented in Figure 1.

Muscle-specific structural and functional alterations in the lower limb

Skeletal muscle dysfunction in T2DM involves both structural and functional abnormalities (Castillo Í et al., 2025; Wasir et al., 2025). Although these aspects are closely interconnected, they do not represent the same phenomenon and should be considered separately (Jeong et al., 2025). Structural changes typically include reductions in muscle size, muscle thickness, cross-sectional area, and overall muscle quality (Feng et al., 2025), whereas functional impairment is characterized by decreased force-generating capacity, impaired mobility and balance, and reduced performance during daily activities (Yigit et al., 2025). In many individuals with T2DM, muscle weakness is greater than would be expected from the loss of muscle mass alone, indicating that neural and metabolic factors also play an important role in the development of functional decline (Dantas et al., 2025).

Multiple pathophysiological mechanisms are thought to contribute to lower-limb muscle dysfunction in T2DM. Chronic insulin resistance disrupts anabolic signaling and suppresses protein synthesis (Murphy et al., 2015), whereas persistent low-grade inflammation may accelerate muscle protein breakdown (Ciaraldi et al., 2016). Mitochondrial dysfunction, reduced oxidative capacity (Houzelle et al., 2021), intramuscular adipose accumulation (Huang et al., 2023), and diabetes-related neuropathic changes further compromise muscle structure and function. Because lower-limb muscles differ in their fiber-type composition, mechanical demands, and metabolic profile, the impact of these pathological processes is unlikely to be uniform across muscle groups (Frankenberg et al., 2022). Figure 2 summarizes the heterogeneous involvement of the lower-limb muscles, with particular emphasis on the quadriceps and calf muscles.

Quadriceps

The quadriceps are the most extensively investigated lower-limb muscle group in adults with T2DM and consistently exhibit both structural and functional impairments (Guerrero et al., 2016; Shahrjerdi et al., 2020). Numerous studies have documented reductions in quadriceps volume, cross-sectional area, and muscle quality, together with diminished knee extensor strength

(Orlando et al., 2023; Shahrjerdi et al., 2020). These changes are of particular clinical importance because the quadriceps are essential for everyday tasks such as rising from a chair, climbing stairs, walking, and maintaining functional independence (Hoveizavi et al., 2025; Shahrjerdi et al., 2020).

Beyond the loss of muscle mass, alterations in muscle composition appear to play a critical role. Increased intramuscular fat infiltration and declining muscle quality can reduce force-generating capacity even when muscle mass is relatively well preserved (Bittel et al., 2015; Huang et al., 2023). This may explain why reductions in muscle strength in individuals with T2DM are often greater than would be expected based on muscle mass loss alone (Huang et al., 2023; Orlando et al., 2016).

The quadriceps may be especially affected because of their major role in weight-bearing and mobility-related activities (Hoveizavi et al., 2025; Senefeld et al., 2020). However, the available evidence does not conclusively indicate that the quadriceps are inherently more susceptible to diabetes-related pathology than other lower-limb muscles (Gui et al., 2025; Senefeld et al., 2020). Instead, their apparent prominence may partly reflect the fact that they have been investigated more extensively than other muscle groups (Gui et al., 2025; Hoveizavi et al., 2025).

From a fiber-type perspective, the quadriceps, particularly the vastus lateralis, consist of a mixed distribution of type I and type II fibers, with type I fibers accounting for approximately 45–55% of the total. In individuals with T2DM, this distribution shifts toward a lower proportion of type I fibers and a higher proportion of type II fibers, especially type IIX fibers (Frankenberg et al., 2022). This transition may represent a metabolic adaptation that favors glycolytic over oxidative metabolism. In addition, type I fibers in T2DM contain lower levels of diffusible glycogen and exhibit altered localization of glycogen-associated proteins compared with healthy controls, pointing to fiber-type-specific metabolic disturbances (Frankenberg et al., 2022; Oberbach et al., 2006). Together, these observations suggest that the mixed fiber composition of the quadriceps may make this muscle vulnerable to both oxidative and glycolytic impairments, which could contribute to its consistent involvement across studies.

Calf muscles

The calf muscles, particularly the gastrocnemius and soleus, are essential for gait propulsion, ankle stability, and postural control (Volpato et al., 2012). Despite their critical functional roles, they have been studied far less extensively than the quadriceps in individuals with T2DM, leaving their structural and functional involvement less well understood (Houzelle et al., 2021).

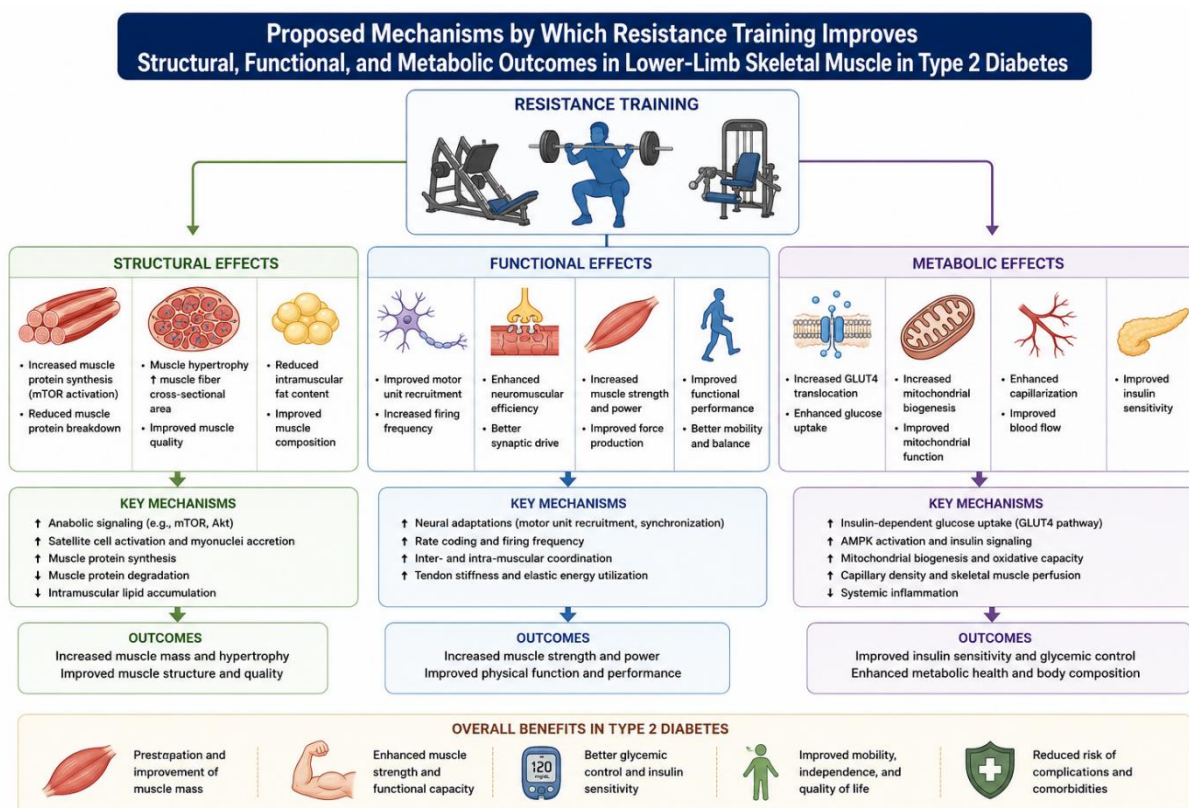


Figure 3. Proposed mechanisms by which resistance training improves muscle structure, function, and metabolic health in T2DM.

Conceptual Clinical Framework for Evaluating Lower Limb Muscle Involvement and Guiding Resistance Training in Individuals with Type 2 Diabetes

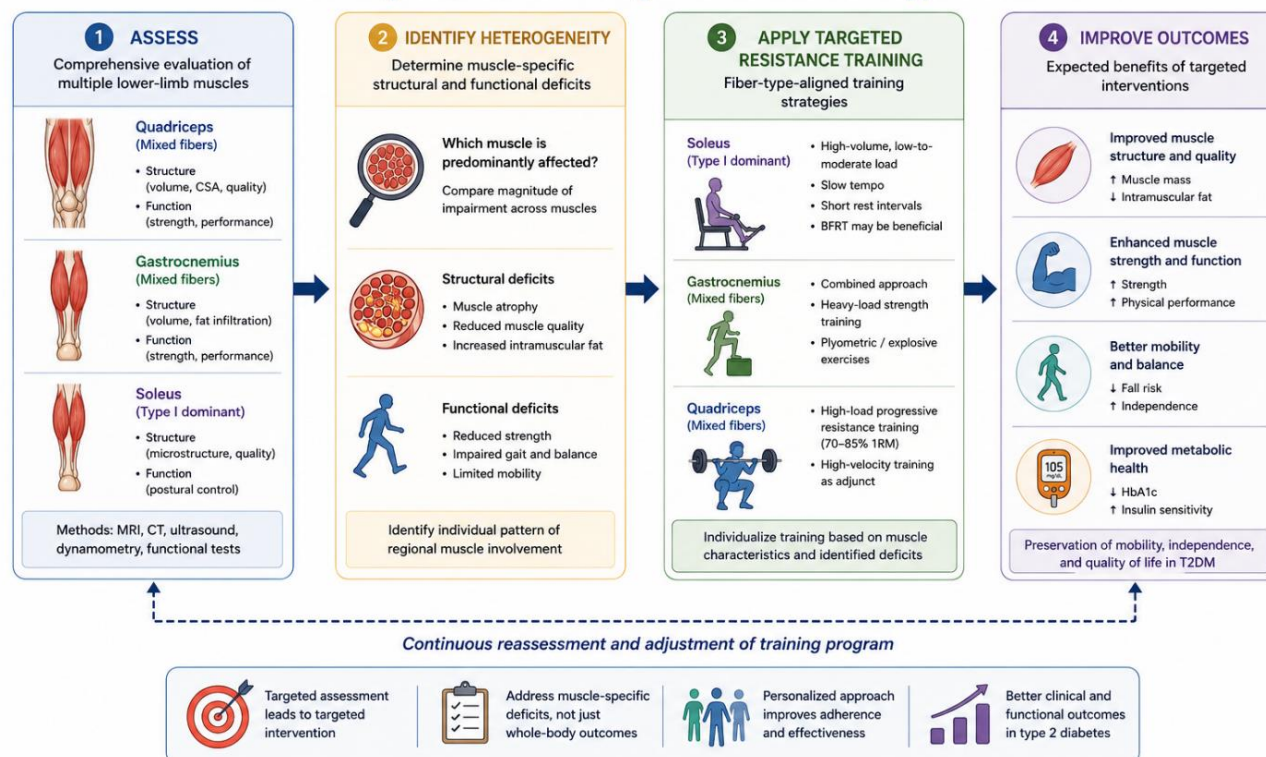


Figure 4. Stepwise clinical framework for evaluating lower-limb muscle involvement and guiding fiber-type-aligned resistance training in individuals with T2DM.

Available evidence indicates that the calf muscles may undergo declines in muscle quality, increased intramuscular fat infiltration, and functional impairments that contribute to gait dysfunction (Almurdhi et al., 2016; Bittel et al., 2015). As the plantar flexors generate much of the propulsive force required for walking, impairment of these muscles can adversely affect walking efficiency and overall mobility (Błażkiewicz et al., 2015; Francia et al., 2015).

Soleus: The overlooked type-I dominant muscle

The soleus warrants particular attention because it is composed predominantly of oxidative type I fibers (approximately 80–90%) and is continuously engaged in maintaining posture (Zhao et al., 2022; Zuo et al., 2012). The hypothesis that the soleus is particularly vulnerable to T2DM-related deterioration is supported by mechanistic evidence from animal models. Bozkurt et al. (2010) used FTIR spectroscopy to show that in diabetic rats, the soleus muscle, due to its high mitochondrial content and reliance on oxidative phosphorylation, underwent more severe structural and functional alterations compared to the glycolytic extensor digitorum longus (EDL) muscle (Bozkurt et al., 2010). Furthermore, Hardin et al. (1993) demonstrated that GLUT4 content decreased by approximately 50% in the soleus as early as day 2 of diabetes induction, whereas this reduction was minimal in predominantly type II muscles (Hardin et al., 1993). These findings indicate that oxidative muscles are preferentially vulnerable to the metabolic disturbances of diabetes, reflecting a fiber-type-dependent vulnerability.

Although direct evidence of soleus-specific alterations in T2DM remains limited, the available findings are informative. Zuo et al. (2012) reported significantly lower T2 values in the soleus muscle of patients with T2DM, with T2 values showing an inverse association with both the presence of diabetes and HbA1c levels, but not with body mass index or regional lipid content (Zuo et al., 2012). These observations suggest that microstructural changes in the soleus are more closely related to glycemic status than to obesity. More recently, Zhao et al. (2022) used T1ρ magnetic resonance imaging to identify microstructural alterations in the soleus that were associated with diabetes duration and insulin resistance (Zhao et al., 2022).

From a mechanistic standpoint, type I fibers rely heavily on oxidative metabolism and efficient mitochondrial function. Mitochondrial dysfunction is a well-recognized feature of T2DM and is characterized by reduced oxidative enzyme activity and impaired mitochondrial architecture (Houzelle et al., 2021). Because type I fibers contain a high mitochondrial density and depend primarily on oxidative phosphorylation for energy production, they may be especially susceptible to diabetes-related mitochondrial dysfunction. Consistent with this concept,

the proportion of slow oxidative fibers in the skeletal muscle of individuals with T2DM is reduced by approximately 16%, whereas the proportion of fast glycolytic fibers increases by 49% (Oberbach et al., 2006). This shift in fiber-type composition may reflect the preferential loss or atrophy of oxidative fibers, with potentially important consequences for the soleus muscle.

Based on the available mechanistic evidence, including mitochondrial vulnerability, fiber-type composition, and impaired glycogen handling in type I fibers (Oberbach et al., 2006) and early microstructural changes detected by MRI (Zhao et al., 2022; Zuo et al., 2012). We propose the hypothesis that the soleus may be one of the first lower-limb muscles to undergo structural deterioration in T2DM. Nevertheless, this hypothesis requires direct validation through comparative longitudinal studies evaluating the trajectories of soleus and quadriceps deterioration within the same cohort.

Gastrocnemius: The mixed-fiber propulsive muscle

The gastrocnemius has a mixed fiber-type composition, with approximately 50–60% type I fibers, and plays an essential role in gait propulsion, ankle stability, and balance control (Volpato et al., 2012). Dysfunction in this muscle may directly impair walking efficiency and increase fall risk (Błażkiewicz et al., 2015; Francia et al., 2015). Available evidence indicates that the gastrocnemius exhibits increased intramuscular fat accumulation and reduced plantar-flexor strength in individuals with T2DM (Almurdhi et al., 2016; Bittel et al., 2015). These deficits may be particularly relevant for dynamic balance and propulsive force generation during walking. Unlike the soleus, which is primarily involved in postural control and sustained low-level activity, the gastrocnemius is recruited during higher-intensity, explosive movements such as walking propulsion, stair climbing, and jumping.

The mixed fiber composition of the gastrocnemius may explain its dual vulnerability- a concept that captures two distinct pathways of impairment. First, the metabolic vulnerability of its type I fibers makes them susceptible to diabetes-related mitochondrial dysfunction, insulin resistance, and oxidative stress, similar to the soleus but to a lesser degree given the lower proportion of type I fibers. Second, the neuromuscular vulnerability of its type II fibers arises from reduced neural drive, impaired motor unit recruitment, and disuse-related atrophy, which are common in T2DM and may be exacerbated by physical inactivity and peripheral neuropathy. This dual vulnerability may contribute to the impaired gait propulsion and reduced walking speed frequently reported in individuals with T2DM (Błażkiewicz et al., 2015; Francia et al., 2015). This dual vulnerability concept is consistent with findings from animal models demonstrating fiber-type-dependent metabolic and neuromuscular impairments in response to diabetes (Bozkurt et al., 2010; Hardin et al., 1993).

Table 1. Muscle specific involvement

Muscle Group	Fiber-Type Composition	Structural Findings	Functional Findings	Extent of Study	Evidence for RT Response	Proposed Vulnerability Mechanism	Key references
Quadriceps	Mixed (~45–55% type I)	• Reduced volume and CSA • Decreased muscle quality • Increased intramuscular fat	• Decreased knee extensor strength • Impaired chair-rise and gait	Extensive	Moderate (hypertrophy and strength gains documented)	Mixed vulnerability: • Type I: metabolic dysfunction • Type II: disuse/neuromuscular factors	(Guerrero et al., 2016; Huang et al., 2023; Shahrjerdi et al., 2020)
Gastrocnemius	Mixed (~50–60% type I)	• Increased intramuscular adipose infiltration	• Reduced plantar-flexor strength • Impaired gait propulsion	Limited	Very limited	Dual vulnerability: • Metabolic (type I) • Neuromuscular (type II) • Critical for gait propulsion	(Almurthi et al., 2016; Bittel et al., 2015; Francia et al., 2015)
Soleus	Type I dominant (~80–90% type I)	• Limited structural data • Microstructural changes on MRI (T2*, T1ρ)	• Postural control impairment (indirect)	Very limited	Unknown	Highest vulnerability: • Type I fibers most susceptible to mitochondrial dysfunction, insulin resistance, and oxidative stress	(Houzzelle et al., 2021; Oberbach et al., 2006; Zhao et al., 2022; Zuo et al., 2012)

Table 2. Hypothesis-generating fiber-type-aligned training framework.

Muscle	Dominant Fiber Type	Proposed Training Modality	Rationale
Soleus	Type I (~80–90%)	High-volume, low-to-moderate load; slow tempo; short rest intervals; BFR may be particularly beneficial (Trinks et al., 2026)	Enhances oxidative capacity and mitochondrial function; aligns with type I fiber recruitment patterns; BFR specifically improves mitochondrial oxidative capacity
Gastrocnemius	Mixed (~50–60% type I)	Combined approach: heavy-load strength training + plyometric/explosive exercises	Addresses both metabolic (type I) and neuromuscular (type II) vulnerabilities; critical for gait propulsion and balance
Quadriceps	Mixed (~45–55% type I)	Traditional high-load progressive RT (70–85% 1RM); adjunctive high-velocity training may further improve functional outcomes (Khan et al., 2022; Lin et al., 2022)	Well-supported by existing evidence, high-load training effectively recruits type II fibers and promotes hypertrophy

Overall interpretation

Current evidence indicates that lower-limb muscle involvement in T2DM is heterogeneous rather than uniform (Henriksen et al., 2018; Tuttle et al., 2012). The quadriceps consistently exhibit both structural and functional impairments (Ding et al., 2026; Lin et al., 2022), whereas the calf muscles are increasingly recognized as clinically important despite remaining comparatively understudied (Ding et al., 2026). This regional heterogeneity suggests that different muscles may be affected through distinct pathophysiological pathways, and that uniform approaches to assessment and intervention may be insufficient. We propose that fiber-type composition may be a major factor underlying this heterogeneity. The soleus, with its exceptionally high proportion of type I (oxidative) fibers, may be particularly susceptible to mitochondrial dysfunction, oxidative stress, and impaired glycogen handling, as supported by animal models and human imaging studies (Bozkurt et al., 2010; Hardin et al., 1993; Zhao et al., 2022; Zuo et al., 2012). In contrast, the quadriceps, with its mixed fiber composition, may be vulnerable to impairments affecting both oxidative and glycolytic pathways, including metabolic disturbances in type I fibers and neuromuscular dysfunction or disuse-related atrophy in type II fibers. The gastrocnemius, which also contains a mixed fiber profile but serves distinct functional demands particularly gait

propulsion and explosive movements may exhibit deficits arising from a combination of metabolic dysfunction and neuromuscular impairment, consistent with a dual vulnerability concept. However, it is important to emphasize that existing evidence does not conclusively demonstrate that any single lower-limb muscle is selectively more vulnerable than the others in T2DM (Frankenberg et al., 2022). Rather, the available data indicate that different muscles may exhibit distinct patterns of structural deterioration, fat infiltration, neuromuscular impairment, and functional decline (Orlando et al., 2016; Tuttle et al., 2012). Accordingly, a fiber-type-informed, muscle-specific perspective should be viewed as a framework for understanding regional heterogeneity rather than as evidence that one muscle group is consistently the most affected across all individuals with T2DM (Orlando et al., 2016). This framework is supported by converging evidence from animal models and human imaging studies, but remains a testable hypothesis requiring direct comparative validation in humans. Table 1 summarizes the muscle-specific findings reported in the available studies.

Critical appraisal of the evidence

While the literature consistently demonstrates impairments in lower-limb muscles in T2DM, a critical appraisal of the evidence base reveals several important limitations and apparent contradictions.

First, conflicting findings exist regarding the magnitude of structural versus functional decline. For instance, while most studies report reduced quadriceps strength, the association between muscle cross-sectional area and strength is not always linear, with some investigations showing strength deficits exceeding mass loss, suggesting that factors beyond atrophy (e.g., neural dysfunction, fat infiltration) play significant roles (Huang et al., 2023; Orlando et al., 2016). Similarly, while some resistance training trials demonstrate significant hypertrophy, others report minimal or no structural changes despite substantial strength gains (Botton et al., 2018; Orlando et al., 2023). These discrepancies likely arise from differences in participant characteristics (e.g., disease duration, glycemic control, presence of neuropathy), training protocols (intensity, volume, duration), and measurement techniques (e.g., MRI vs. ultrasound vs. DXA).

Second, methodological limitations are pervasive across the literature. Most cited studies use cross-sectional designs, which preclude causal inferences about the temporal sequence of muscle deterioration. Sample sizes are frequently small, particularly in studies utilizing advanced imaging (e.g., MRI T1p mapping) or muscle biopsy, limiting statistical power and generalizability. Notably, a major gap is the scarcity of studies that simultaneously assess multiple lower-limb muscles within the same cohort, making it difficult to ascertain whether the observed differences between muscle groups reflect true biological heterogeneity or simply between-study variability. Furthermore, few studies have specifically examined the soleus or gastrocnemius in isolation, and those that do often lack functional outcome measures or direct comparisons with the quadriceps.

Third, evidence quality varies considerably across muscle groups. Quadriceps dysfunction is supported by numerous randomized controlled trials and large cross-sectional cohorts, constituting relatively high-level evidence. In stark contrast, evidence for the gastrocnemius and, particularly, the soleus relies heavily on small-scale cross-sectional imaging studies or extrapolation from animal models, representing lower-level evidence. The lack of longitudinal data tracking the progression of calf muscle deterioration over time represents a critical knowledge gap.

These limitations underscore that while the hypothesis of fiber-type-dependent vulnerability is biologically plausible and supported by convergent lines of evidence, it remains preliminary and requires confirmation through well-designed, adequately powered, longitudinal comparative studies. Future research should prioritize prospective cohort designs, standardized multi-muscle assessment protocols, and the inclusion of both structural and functional outcome measures to establish the true trajectory of muscle-specific deterioration in T2DM.

Resistance training as a therapeutic strategy

Resistance training (RT) is one of the most widely recommended exercise interventions for individuals with T2DM because it directly targets skeletal muscle, the primary site of insulin-stimulated glucose disposal and a key determinant of physical function (Al Ozairi et al., 2023; Shahrjerdi et al., 2020). In addition to improving glycemic control, RT may help counteract several processes involved in diabetes-related muscle dysfunction, including muscle atrophy (Shabkhiz et al., 2021), reduced neuromuscular activation, mitochondrial dysfunction (Sparks et al., 2013; Trinks et al., 2026), and loss of muscle strength (Qian et al., 2024). Figure 3 summarizes the proposed structural, functional, and metabolic effects of resistance training on the lower-limb muscles.

Effects on Muscle Structure

Evidence from human intervention studies indicates that RT can induce beneficial structural adaptations in skeletal muscle. Reported improvements include increases in lean muscle mass, muscle thickness, and cross-sectional area, particularly when training is performed at adequate intensity and for a sufficient duration (Al Ozairi et al., 2023; Botton et al., 2018; Orlando et al., 2023; Takenami et al., 2019). However, structural adaptations are not consistent across all studies (Magalhães et al., 2021; Pandey et al., 2015). Differences in participant characteristics, disease severity, training protocols, and assessment methods are likely to account for much of this variability (Botton et al., 2018; Orlando et al., 2023; Rosa et al., 2026; Shahrjerdi et al., 2020). In addition, increases in muscle size do not necessarily translate into equivalent improvements in functional performance, suggesting that hypertrophy is only one aspect of the overall adaptive response to RT (Botton et al., 2018; Geirsdottir et al., 2012; Orlando et al., 2023; Reich et al., 2020).

Effects on muscle function

The most consistent and well-established benefit of RT in individuals with T2DM is the improvement of muscle function. Human intervention studies have consistently reported substantial gains in lower-limb strength, particularly in the knee extensors, along with improvements in functional performance, including chair-rise ability, walking capacity, and other mobility-related tasks (Khan et al., 2022; Lin et al., 2022). These improvements are likely mediated by multiple mechanisms. In addition to stimulating muscle hypertrophy, RT induces neural adaptations, including enhanced motor unit recruitment, increased firing frequency, and improved neuromuscular coordination (Dabbagh Nikookheslat et al., 2017; Shahrjerdi et al., 2020). These neural adaptations may be especially important during the early stages of training and could explain why gains in muscle strength often exceed increases in muscle size (Takenami et al., 2019).

Table 3A. Summary of human studies on quadriceps and fiber-type-specific investigations in T2DM

Reference	Muscle Group	Study Design	Sample (T2DM/Control)	Main Findings	Strengths	Weaknesses / Gaps
Guerrero 2016 (Guerrero et al., 2016)	Quadriceps	Cross-sectional	100 / 39	Premature loss of quadriceps mass and strength in T2DM, independent of disease duration	Large sample; direct isokinetic dynamometry	Cross-sectional design; no follow-up; only quadriceps assessed
Shahrjerdi 2020 (Shahrjerdi et al., 2020)	Quadriceps	RCT (6-week RT)	20 T2DM / 20 healthy	RT improved neuromuscular efficiency and peak torque in knee extensors	Controlled trial; objective EMG measurement of neural adaptation	Short intervention (6 weeks); small sample size; no calf muscle assessment
Orlando 2023 (Orlando et al., 2023)	Quadriceps	Pilot RCT (8-week RT + HIIT)	12 T2DM (no control)	RT increased quadriceps volume (+5.9%), but muscle quality gains were inconsistent	MRI-based volume measurement (gold standard)	Pilot study; no control group; very small sample; only quadriceps measured
Huang 2023 (Huang et al., 2023)	Quadriceps	Cross-sectional	158 T2DM	Low thigh muscle strength correlated with myosteatosis; strength deficits exceeded mass loss	Direct CT assessment of intramuscular fat; relatively large sample	Cross-sectional; causality not established; no calf data
Dantas 2025 (Dantas et al., 2025)	Vastus lateralis	Cross-sectional biopsy	T2DM patients	Deubiquitinating enzymes regulate mitochondrial quality control and insulin sensitivity in T2DM muscle	Novel molecular mechanism; direct human tissue	Small sample; single muscle; no functional outcome
Frankenberg 2022 (Frankenberg et al., 2022)	Fiber-type specific (vastus lateralis)	Cross-sectional biopsy	10 T2DM / 10 control	Type I and Type II muscle fibers show different glucose handling in T2DM, indicating fiber-type specific pathology	Direct human muscle biopsy; cell-level mechanistic data	Small sample; single muscle (vastus lateralis); not translated to whole-muscle function

Table 3B. Summary of Human Studies on Calf Muscles (Gastrocnemius and Soleus) and Mixed Lower-Limb Interventions in T2DM.

Reference	Muscle Group	Study Design	Sample (T2DM/Control)	Main Findings	Strengths	Weaknesses / Gaps
Almurdhi 2016 (Almurdhi et al., 2016)	Calf (plantar flexors)	Cross-sectional	20 T2DM / 20 control	Reduced plantar flexor strength without volume loss; increased intramuscular fat	Detailed MRI-based muscle volume and strength assessment	Small sample; only male participants; no quadriceps comparison
Bittel 2015 (Bittel et al., 2015)	Calf	Cross-sectional	79 obese T2DM	Higher intermuscular adipose tissue in the calf correlated with poorer physical function (6-min walk, stair power)	Well-phenotyped obese T2DM cohort; functional outcomes	Cross-sectional; no longitudinal data; no intervention
Zhao 2022 (Zhao et al., 2022)	Soleus	Cross-sectional MRI	41 T2DM / 20 control	T1ρ mapping detected soleus microstructure changes correlated with diabetes duration and insulin resistance	Novel MRI technique; specific focus on understudied soleus muscle	Only male participants; no functional correlation; no comparison to other muscles
Zuo 2012 (Zuo et al.) (Zuo et al., 2012)	Soleus	Cross-sectional MRI	T2DM patients	Reduced T2* values in soleus inversely correlated with HbA1c, suggesting altered oxygen metabolism.	Novel MRI technique; specific focus on soleus.	Cross-sectional; no functional outcomes; no comparison to other muscles.
Khan 2022 (Khan et al., 2022)	Lower limb (knee extensors)	RCT (12-week RT), assessor-blinded	109 T2DM (with/without DPN)	Progressive RT improved knee extensor strength (+10.3 Nm in DPN group) and motor function	Large RCT; included diabetic neuropathy patients; clinically relevant outcomes	Did not measure individual calf muscles; no muscle-specific hypertrophy data
Kobayashi 2023 (Kobayashi et al., 2023)	Whole body	RCT (9-month RT vs. aerobic)	186 normal-weight T2DM	Strength training reduced HbA1c (-0.44%) and increased lean mass more than aerobic exercise	Long duration; large sample; normal-weight subgroup	No lower-limb muscle-specific outcomes; whole-body DXA only
Trinks 2026 (Trinks et al., 2026)	Lower limb	RCT (12-week BFR-RT)	T2DM patients (exact n not specified)	BFR-RT improved mitochondrial capacity, oxidative capacity, and muscle strength	Direct ex vivo mitochondrial respiration measurement; novel BFR technique	Small sample; no comparison between different lower-limb muscles

From a clinical standpoint, improvements in muscle strength are particularly important, as muscle weakness is closely associated with reduced mobility, a greater risk of falls, and loss of functional independence in older adults with T2DM (Jang, 2019; Rahimi et al., 2019).

Metabolic benefits

The benefits of RT extend beyond improvements in the musculoskeletal system. An increase in muscle mass expands the body's capacity for glucose uptake, while repeated muscle contractions enhance insulin sensitivity through both insulin-dependent and insulin-independent mechanisms (AfshounPour et al., 2015; Pandey et al., 2015). RT has also been linked to better glycemic control, reduced insulin resistance, and favorable changes in body composition (Hamasaki et al., 2015a, 2015b; Kobayashi et al., 2023; Pandey et al., 2015). These metabolic improvements may indirectly support the long-term preservation of muscle health by limiting exposure to the metabolic disturbances that drive muscle dysfunction (Kobayashi et al., 2023; Olver & Laughlin, 2016). A summary of the characteristics of the resistance training studies cited in this section – including training parameters, targeted muscles, and primary outcome measures – is presented in Table 4.

Muscle-specific responses to resistance training

Despite the growing body of evidence supporting RT as a therapeutic intervention for T2DM, muscle-specific adaptations to training remain poorly understood (Hansen et al., 2025). Most intervention studies have focused on overall lower-limb strength or whole-body outcomes rather than examining adaptations within individual muscle groups (Orlando et al., 2023; Sambashivaiah et al., 2019). Consequently, it remains uncertain whether the quadriceps, gastrocnemius, and soleus similarly adapt to RT or whether some muscles possess greater structural or functional plasticity than others (Koh et al., 2018). Answering this question is an important priority for future research, as it could provide the basis for more precise, muscle-specific exercise prescriptions (Czajkowska et al., 2024).

Fiber-type-aligned responses to resistance training: A proposed framework

The principle of training specificity states that the characteristics of the training stimulus largely determine the nature of the physiological adaptations. From a fiber-type perspective, type I (oxidative) fibers respond more favorably to high-volume, low-to-moderate load, and slow-velocity training, whereas type II (glycolytic) fibers are more responsive to high-load, low-volume, and explosive exercise. This well-established principle of exercise physiology has important implications for RT prescription in individuals with T2DM, particularly given the fiber-

Type-dependent vulnerabilities discussed in section 2, and the fiber-type-aligned training adaptations discussed here. Recent evidence also supports the concept of fiber-type-specific training adaptations in T2DM. For example, high-intensity interval training (HIIT) has been shown to reduce subsarcolemmal lipid droplet size in a fiber-type-specific manner in individuals with T2DM, whereas moderate-intensity endurance training does not produce the same effect (Koh et al., 2018). In addition, the transcriptional response to HIIT is attenuated in type IIA myonuclei in people with T2DM, suggesting that diabetes impairs training adaptations in a fiber-type-specific manner (Hansen et al., 2025).

Low-load blood-flow restriction training (BFRT) has recently emerged as a promising approach that may be especially well suited for the soleus. In a 12-week randomized controlled trial, Trinks et al. (2026) reported that BFRT produced improvements in muscle strength comparable to those achieved with conventional resistance training, despite requiring a substantially lower training load. Notably, BFRT also enhanced the oxidative capacity of skeletal muscle and adipose tissue, increased muscle mitochondrial content, and elicited more pronounced transcriptional changes in angiogenesis-related pathways (Trinks et al., 2026). These findings suggest that BFRT may provide an effective low-load strategy for improving mitochondrial oxidative capacity, muscle strength, and body composition in individuals with T2DM. Given the predominantly type I fiber composition and high oxidative demands of the soleus, this training modality may offer particular benefits for this muscle.

Table 2 proposes fiber-type-aligned training framework for lower-limb muscles in T2DM based on the available evidence and the principle of training specificity. This fiber-type-informed training framework has yet to be evaluated in direct comparative studies involving individuals with T2DM. To date, no human study has compared the hypertrophic or functional adaptations of the quadriceps, gastrocnemius, and soleus to the same RT protocol while accounting for differences in fiber-type composition. This framework should therefore be viewed as a hypothesis-generating proposal that requires direct validation in future comparative trials. Future randomized controlled trials should directly compare these muscle groups using standardized outcome measures, including muscle volume, cross-sectional area, intramuscular fat content, and fiber-type-specific molecular markers.

Clinical implications and future directions

A critical caveat must be explicitly stated: the central hypothesis that the soleus is particularly vulnerable to T2DM-related deterioration is currently supported by indirect mechanistic and imaging evidence rather than by direct comparative human trials. While animal models and human MRI studies provide convergent

Table 4. Summary of resistance training studies in T2DM: Parameters, targeted muscles, and outcome measures

Reference	Training Protocol	Intensity	Volume	Frequency	Duration	Targeted Muscles	Outcome Measures
Shahrjerdi (Shahrjerdi et al., 2020)	Resistance training	70–80% 1RM	3 sets × 8–12 reps	3×/week	6 weeks	Knee extensors	Neuromuscular efficiency, peak torque
Botton (Botton et al., 2018)	Resistance training	60–80% 1RM	3 sets × 8–12 reps	3×/week	12 weeks	Lower limb	Muscle strength, neuromuscular parameters
Khan (Khan et al., 2022)	Progressive resistance training	70–85% 1RM	3 sets × 8–10 reps	2×/week	12 weeks	Knee extensors	Isometric strength, motor function
Orlando (Orlando et al., 2023)	Concurrent RT + HIIT	RT: 70–80% 1RM; HIIT: 85–95% HRmax	RT: 3 sets × 8–12 reps; HIIT: 4 × 4 min	3×/week	8 weeks	Lower limb	Quadriceps volume (MRI), muscle quality
Kobayashi (Kobayashi et al., 2023)	Strength training	70–85% 1RM	3 sets × 8–10 reps	3×/week	9 months	Whole body (multi-joint)	HbA1c, lean mass (DXA)
Trinks (Trinks et al., 2026)	BFR resistance training	30–40% 1RM	4 sets × 15 reps	3×/week	12 weeks	Lower limb	Mitochondrial capacity, muscle strength
Takenami (Takenami et al., 2019)	Low-intensity resistance training	50% 1RM	3 sets × 10–15 reps	2–3×/week	12 weeks	Lower limb	Muscle function, glycemic control
Al Ozairi (Al Ozairi et al., 2023)	Home-based resistance training	Progressive (unspecified)	3 sets × 10–12 reps	3×/week	12 weeks	Whole body	Muscle strength, glycemic control

support, no study to date has directly compared the longitudinal trajectories of structural atrophy, functional decline, or metabolic alterations between the soleus, gastrocnemius, and quadriceps within the same cohort. Therefore, this framework should be regarded as a hypothesis-generating model that requires rigorous testing in future prospective, comparative studies. Recognizing regional heterogeneity in lower-limb muscle dysfunction has important clinical implications. Assessment approaches that rely solely on measures of total muscle mass may fail to detect clinically meaningful deficits in specific muscle groups (Chen et al., 2021; Kataoka et al., 2020). Likewise, exercise interventions aimed at improving overall physical fitness may not adequately target the muscle-specific impairments that contribute to functional limitations (Volpato et al., 2012). Figure 4 presents a conceptual framework for evaluating regional involvement of the lower-limb muscles and guiding targeted resistance training in individuals with T2DM.

For clinical assessment, we recommend a multi-muscle approach using accessible tools: ultrasound or MRI for muscle cross-sectional area and fat infiltration (with ultrasound being more practical for routine use), isokinetic or hand-held dynamometry for knee extensor and plantar flexor strength, and functional tests such as the chair-rise test (quadriceps) and gait speed or stair-climbing tests (calf muscles). For exercise prescription, we propose a targeted approach: for the soleus, high-volume, low-to-moderate load training with slow tempo and short rest intervals, potentially combined with BFRT; for the

a combined strategy of heavy-load strength training and explosive exercises; for the quadriceps, conventional progressive high-load RT (70–85% 1RM). These recommendations are hypothesis-generating and require validation in future trials.

Future research should adopt standardized approaches to evaluate muscle structure, muscle quality, and muscle function across multiple lower-limb muscles (de Luis Román et al., 2024; Sharath et al., 2026). Greater emphasis should also be placed on the calf muscles, which remain relatively understudied despite their essential contributions to gait and balance (Wei et al., 2023; Zhao et al., 2022). In particular, the soleus, as a predominantly type I fiber muscle, warrants priority in future investigations because of its proposed vulnerability to T2DM and the limited evidence currently available. Longitudinal studies are also needed to examine how changes in muscle morphology, strength, mobility, and glycemic control are related over the course of T2DM (Ferrari et al., 2020; Sugimoto et al., 2021). Such studies could help determine whether structural and functional impairments develop in parallel or follow distinct trajectories as the disease progresses (Tan et al., 2022). Findings of the mentioned human studies were summarized in Table 3A and 3B.

Conclusion

Lower-limb muscle dysfunction is an important, yet often overlooked, complication of T2DM. Current evidence indicates that structural deterioration, reduced muscle quality, and functional

weakness affect multiple lower-limb muscle groups, although the severity and pattern of involvement appear to differ across regions. The quadriceps remain the most extensively studied muscle group and provide the strongest evidence of diabetes-related impairment, whereas the calf muscles are increasingly recognized as clinically important despite receiving far less attention. Overall, the available evidence supports the concept of regional heterogeneity rather than uniform involvement of the lower-limb muscles.

A central proposal of this review is that fiber-type composition may be a key determinant of muscle-specific vulnerability in T2DM. Converging evidence from animal models and human imaging studies supports the hypothesis that the predominantly type I soleus muscle may be particularly susceptible to diabetes-related mitochondrial dysfunction, oxidative stress, and metabolic impairment. However, this hypothesis awaits direct confirmation through comparative longitudinal human studies, which are urgently needed to determine whether the soleus indeed deteriorates earlier or more profoundly than other lower-limb muscles (Bittel et al., 2015; Frankenberg et al., 2022; Oberbach et al., 2006; Shabkhiz et al., 2021; Zhao et al., 2022; Zuo et al., 2012). Resistance training is an effective therapeutic strategy for improving muscle strength, functional performance, and metabolic health in individuals with T2DM. Although evidence for structural adaptations is promising, muscle-specific and fiber-type-specific responses to RT remain poorly understood. To date, no human study has directly compared the hypertrophic or functional adaptations of the quadriceps, gastrocnemius, and soleus to the same resistance training protocol in individuals with T2DM.

We propose that clinicians and researchers move beyond a "one-size-fits-all" approach by considering fiber-type-informed, muscle-specific exercise prescriptions. For the soleus, high-volume, low-to-moderate load training, potentially combined with BFRT, may provide particular benefits. For the gastrocnemius, a training strategy that addresses both metabolic and neuromuscular impairments may be the most appropriate. For the quadriceps, conventional progressive high-load RT remains the best-supported approach based on the current evidence. Overall, adopting a fiber-type-informed, muscle-specific perspective may improve our understanding of diabetes-related muscle dysfunction and help guide the development of more targeted exercise interventions aimed at preserving mobility, functional independence, and quality of life in adults with T2DM. Well-designed comparative trials are now needed to validate this hypothesis-generating framework.

What is already known on this subject?

Structural and functional impairments of skeletal muscle are well

documented in individuals with T2DM, and resistance training is widely recognized as an effective intervention for improving muscle strength, physical function, and metabolic health. However, previous reviews have generally considered lower-limb muscles as a homogeneous group and have not systematically examined whether fiber-type composition influences muscle-specific vulnerability or adaptive responses to resistance training.

What does this study add?

This review proposes a novel fiber-type-informed framework to explain regional heterogeneity in lower-limb muscle involvement in T2DM. We hypothesize that the soleus, because of its predominantly type I fiber composition, may be particularly susceptible to diabetes-related metabolic disturbances and may require a different resistance training strategy than the gastrocnemius or quadriceps. By integrating current human evidence with exercise physiology, this review provides a muscle-specific conceptual framework that may guide future mechanistic studies and the development of more targeted exercise prescriptions.

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