

# Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship

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**Abstract:** The incidence and prevalence of metabolic and musculoskeletal diseases are increasing. Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, inflammation, advanced glycation end-product accumulation and increased oxidative stress. These characteristics can negatively affect various aspects of muscle health, including muscle mass, strength, quality and function through impairments in protein metabolism, vascular and mitochondrial dysfunction, and cell death. Sarcopenia is a term used to describe the age-related loss in skeletal muscle mass and function and has been implicated as both a cause and consequence of T2DM. Sarcopenia may contribute to the development and progression of T2DM through altered glucose disposal due to low muscle mass, and also increased localized inflammation, which can arise through inter- and intramuscular adipose tissue accumulation. Lifestyle modifications are important for improving and maintaining mobility and metabolic health in individuals with T2DM and sarcopenia. However, evidence for the most effective and feasible exercise and dietary interventions in this population is lacking. In this review, we discuss the current literature highlighting the bidirectional relationship between T2DM and sarcopenia, highlight current research gaps and treatments, and provide recommendations for future research.

**Keywords:** type 2 diabetes mellitus, sarcopenia, metabolic health, muscle health, obesity

## Introduction

In 2017, it was estimated that 451 million adults globally had diabetes.<sup>1</sup> Approximately 90% of these individuals have type 2 diabetes mellitus (T2DM),<sup>2</sup> with the highest prevalence observed in older adults.<sup>3</sup> As populations age, incidence and prevalence of metabolic and musculoskeletal diseases increase.<sup>1,4</sup> Body composition changes during aging, resulting in significant losses of skeletal muscle mass and increased body fat percentage.<sup>5</sup> Collectively and independently, low muscle mass and adiposity are associated with higher incidence of metabolic disorders, including T2DM.<sup>6,7</sup> “Sarcopenia” describes age-related declines in muscle mass and function<sup>8–12</sup> and has been implicated as both a cause and consequence of T2DM.<sup>13</sup> T2DM is characterized by insulin resistance, increased advanced glycation end-products (AGEs), a proinflammatory phenotype and oxidative stress, which can lead to micro- and macro-vascular complications. These characteristics can interfere with normal cellular functioning and cause cell death<sup>14</sup>, which may lead to losses in skeletal muscle mass, strength, and function, potentially leading to the development of sarcopenia. Conversely, low muscle mass and function in sarcopenia can lead to poorer glucose disposal and decreased metabolic rate and physical activity, all of which may place older adults with sarcopenia at increased risk for developing T2DM.

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## Type 2 diabetes mellitus and sarcopenia

Currently, there is no consensus definition of sarcopenia; however, several definitions and criteria for diagnosis have been proposed, some of which are presented in Table 1. The most commonly used multi-component operational definition since 2010 is the European Working Group on Sarcopenia in Older People (EWGSOP) definition,<sup>8</sup> which has recently been revised.<sup>9</sup> The Asian Working Group for Sarcopenia (AWGS) definition<sup>12</sup> was derived from the EWGSOP definition but provides appropriate criteria for Asian populations. The International Working Group on Sarcopenia (IWGS)<sup>11</sup> definition is similar to the EWGSOP definition, but includes only low muscle mass and physical performance, not low strength. The only group to use statistical procedures to identify criteria for sarcopenia (low lean mass and handgrip strength), rather than expert consensus, is the Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project (FNIH).<sup>10</sup> Unsurprisingly, the different approaches taken to develop sarcopenia definitions results in poor agreement between them.

Recent meta-analyses indicate sarcopenia prevalence ranges from 10% to 40% in healthy men and women

aged  $\geq 60$ , and this variability is influenced by the operational definition applied and population assessed.<sup>15,16</sup> Our understanding of associations between sarcopenia and T2DM is similarly limited by lack of consistency in definitions applied. However, older adults with T2DM do appear to have an increased risk for sarcopenia. The prevalence of sarcopenia in Japanese and Chinese adults (aged  $\geq 65$  and  $>60$  years, respectively) with T2DM is 15% using the AWGS definition.<sup>17,18</sup> In the Korean Sarcopenic Obesity Study, individuals with T2DM had threefold higher odds of having low skeletal muscle mass relative to weight compared with non-diabetic controls after adjusting for multiple confounders.<sup>19</sup> In the Health ABC Study (n=2,675), older women with undiagnosed and confirmed T2DM demonstrated greater losses in thigh muscle cross-sectional area over five years compared with non-diabetic controls ( $-10.6 \pm 1.5$  and  $-9.3 \pm 1.2$  versus  $-5.2 \pm 0.4$  cm<sup>2</sup>, respectively).<sup>20</sup> Interestingly, the English Longitudinal Study of Ageing including 3,404 older adults recently demonstrated that diabetes predicted low handgrip strength eight years later in men (OR: 2.43 [95%CI: 1.5–3.95]), but not women (OR: 1.49 [95%CI: 0.83–2.68]), based on FNIH cut-points.<sup>21</sup>

**Table 1** Comparison of current definitions of sarcopenia

	Low muscle strength	Low muscle mass	Poor physical performance
<b>EWGSOP<sup>8</sup></b>	Hand grip strength: $<30$ kg (men) and $<20$ kg (women)	ALM/height <sup>2</sup> : $<7.26$ kg/m <sup>2</sup> (men) $<5.50$ kg/m <sup>2</sup> (women) OR Skeletal muscle mass/height <sup>2</sup> : $<8.87$ kg/m <sup>2</sup> (men) $<6.42$ kg/m <sup>2</sup> (women)	Gait speed $\leq 0.8$ m/s (4-m course) OR SPPB score: $\leq 8$ points
<b>EWGSOP2<sup>9</sup></b>	Hand grip strength: $<27$ kg (men) and $<16$ kg (women) OR Chair stands time: $>15$ s (5 rises)	ALM: $<20$ kg (men) and $<15$ kg (women) OR ALM/height <sup>2</sup> : $<7.00$ kg/m <sup>2</sup> (men) $<6.00$ kg/m <sup>2</sup> (women)	Gait speed: $\leq 0.8$ m/s (4-m course) OR SPPB score: $\leq 8$ points OR TUG: $\geq 20$ s OR 400 m walk: $\geq 6$ min or non-completion
<b>FNIH<sup>10</sup></b>	Hand grip strength: $<26$ kg (men) and $<16$ kg (women)	ALM/BMI: $<0.789$ kg/BMI (men) $<0.512$ kg/BMI (women)	-
<b>IWGS<sup>11</sup></b>	-	ALM/height <sup>2</sup> : $\leq 7.23$ kg/m <sup>2</sup> (men) $\leq 5.67$ kg/m <sup>2</sup> (women)	Gait speed: $<1.0$ m/s
<b>AWGS<sup>12</sup></b>	Hand grip strength: $<26$ kg (men) and $<18$ kg (women)	ALM/height <sup>2</sup> : $<7.0$ kg/m <sup>2</sup> (men) $<5.4$ kg/m <sup>2</sup> (women)	Gait speed: $\leq 0.8$ m/s (6-m course)

**Abbreviations:** EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP2, European Working Group on Sarcopenia in Older People Updated Definition; FNIH, Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project; IWGS, International Working Group on Sarcopenia; AWGS, Asian Working Group for Sarcopenia; ALM, Appendicular Lean Mass; BMI, Body Mass Index; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go.

In addition to the risk of sarcopenia being increased in T2DM patients, older adults with sarcopenia may have increased risk of developing T2DM. In 113,913 Korean men and 89,854 women (mean age of 40 years), individuals in the lowest skeletal muscle mass relative to body weight quartiles had a twofold greater risk of developing T2DM compared with individuals in the highest quartile.<sup>6</sup> Additionally, the Korean Genome Epidemiology Study in 6,895 adults (mean age of 52 years) showed that individuals in the lowest muscle mass index tertile (defined by weight-adjusted appendicular lean mass [ALM]) had two-fold higher odds of incident T2DM after adjusting for confounders.<sup>22</sup> Furthermore, comorbid presence of obesity and low muscle mass conferred even greater risk of incident T2DM in this population.<sup>22</sup> Lower hand grip strength normalized to body weight was also predictive of elevated fasting glucose ( $>5.56$  mmol/L or treatment with glucose-lowering drugs) in 17,703 Chinese men and women aged over 40 years.<sup>23</sup>

Muscle deficits may affect metabolic health through altered glucose disposal, as skeletal muscle accounts for ~80% of glucose clearance during euglycemic and hyperinsulinemic conditions.<sup>24</sup> Therefore, greater quantities of muscle increase glucose disposal and potentially delay the onset of T2DM. Once established, however, T2DM leads to various pathophysiological manifestations that have bidirectional relationships with components of sarcopenia.

## Insulin resistance

Insulin resistance is a hallmark of T2DM that results in poor glycemic control, which potentially affects components of sarcopenia. In the MrOS study, men aged  $\geq 65$  years without T2DM but in the highest quartile for insulin resistance had two-fold higher odds of losing  $\geq 5\%$  total lean mass over approximately five years.<sup>25</sup> In the NHANES study, gait speed decreased across increasing quartiles of insulin resistance in non-diabetic older men, but not women.<sup>26</sup> Conversely, in 968 Italian men and women with a mean age of 67 and 68 years, respectively, insulin resistance was negatively associated with handgrip strength normalized to BMI in women, but not men.<sup>27</sup> Thus, insulin resistance may be a predictor of poor muscle health, irrespective of diabetes status, although further research is required to clarify sex-specific associations of insulin resistance and components of sarcopenia.

Glycated hemoglobin (HbA1c) is a measure of long-term glycemic control.<sup>28</sup> In older Korean men aged  $\geq 65$

years with T2DM, poor glycemic control ( $\text{HbA1c} \geq 8.5\%$ ) was associated with poor lower-limb muscle quality and physical performance.<sup>29</sup> Similar associations have been reported for Caucasian and Black individuals; in the Baltimore Longitudinal Study of Ageing, knee extensor strength was lower across increasing quartiles of HbA1c.<sup>30</sup> Interestingly, total body and leg lean mass remained the same across all quartiles of HbA1c in adjusted models that included body weight as a covariate. However, this is a potential over-adjustment and could explain the lack of association between HbA1c and lean mass, despite the relationship with muscle strength.<sup>30</sup> Loss of muscle strength and mass in individuals with poor glycemic control likely occurs due to increased protein degradation<sup>31</sup> and decreased protein synthesis.<sup>32</sup> Impaired protein metabolism is therefore exacerbated in individuals with T2DM, and particularly in individuals with undiagnosed T2DM, who typically have greater glucose variability. The negative effects of poor glycemic control on muscle health are compounded as it often occurs alongside other adverse characteristics of T2DM, including inflammation.

## Inflammation

T2DM is associated with chronic, low-grade systemic inflammation which may negatively affect glucose and muscle homeostasis.<sup>33–35</sup> Inflammatory markers including interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and C-reactive protein (CRP) are often elevated in individuals with T2DM.<sup>36,37</sup> These inflammatory markers are associated with adiposity and insulin resistance<sup>38</sup> and are elevated in obese and non-obese individuals with T2DM.<sup>36</sup> Visceral adipose tissue (VAT) secretes IL-6 and TNF- $\alpha$ ,<sup>39</sup> and it is therefore likely to be a major contributor to inflammation in T2DM. We recently demonstrated that waist circumference (an indirect measure of VAT) was negatively associated with muscle strength, quality, and performance in 84 overweight and obese older adults.<sup>40</sup> However, it is unclear whether these negative associations were driven in part by increased inflammation.

Interestingly, IL-6 is also produced by myocytes during exercise, and transient increases in IL-6 assist in nutrient mobilization and muscle hypertrophy.<sup>41–43</sup> Contrary to this, IL-6 has been reported to cause muscle atrophy when localized to the tibialis anterior of Sprague-Dawley rats, independent of systemic inflammation.<sup>35</sup> In the Framingham Heart Study consisting of 558 older adults aged 72–92 years, IL-6 predicted two-year lean mass losses in women, but not men.<sup>44</sup> In 115 older adults aged  $>60$  years, ALM loss

over five years was fivefold and fourfold greater in individuals with IL-6 and CRP concentrations in the top tertile of the cohort, respectively.<sup>45</sup> Park et al demonstrated that older adults with T2DM had greater losses in leg muscle mass and strength over three years compared with non-diabetic controls, and these associations were partially attenuated after adjusting for cytokines including IL-6 and TNF- $\alpha$ .<sup>46</sup>

In addition to being negatively associated with muscle mass, inflammatory markers are also negatively associated with muscle strength, which is now considered the principal component of sarcopenia.<sup>9</sup> Visser et al reported that in 2,746 generally well-functioning Black and Caucasian men and women from the USA aged 70–79 years, handgrip strength was between 1.1 and 2.4 kg lower per standard deviation increase in IL-6 concentration.<sup>47</sup> TNF- $\alpha$  was negatively associated with grip strength in Black and Caucasian women, but not men.<sup>47</sup> In the English Longitudinal Study of Ageing, CRP was negatively associated with handgrip strength in women, and chair stand time in both sexes.<sup>48</sup> Taken together, inflammation associated with T2DM may independently affect muscle mass and strength.

## Oxidative stress

Aging is associated with reduced antioxidant capacity, which has been implicated in the pathogenesis of sarcopenia.<sup>49</sup> T2DM is also associated with increased oxidative stress,<sup>50</sup> which can lead to myopathy. Oxidative stress in T2DM can occur through dyslipidemia and altered lipid metabolism, insulin resistance, increased AGEs and mitochondrial dysfunction.<sup>50</sup> In diabetic rats, increased oxidative stress impairs muscle repair.<sup>51</sup> In 107 pre- and post-menopausal women increased oxidative stress (measured by lipid peroxide concentrations) was negatively associated with skeletal muscle mass adjusted for height (SMI).<sup>52</sup> Given that oxidative stress also has the capacity to impair satellite cell differentiation and damage DNA,<sup>53</sup> it is evident that myopathy in T2DM is caused by the disruption of numerous cellular pathways, and further research is required to clarify how they work, and determine whether they are perhaps suitable targets for interventions.

Another age- and T2DM-related factor implicated in the progression of metabolic and muscle health deterioration through oxidative stress is mitochondrial dysfunction.<sup>54,55</sup> Older individuals have up to 50% lower oxidative capacity per unit of muscle<sup>56</sup> and increased mitochondrial DNA mutations<sup>57</sup> compared with younger

adults. Interestingly, when compared with BMI-matched controls, individuals with T2DM had a 45% lower phosphocreatine recovery half-time (a measure of mitochondrial function) immediately after exercise.<sup>58</sup> Furthermore, this study also reported that fasting plasma glucose and HbA1c were positively associated with phosphocreatine recovery half-time ( $r=0.42$  and  $r=0.48$ , respectively).<sup>58</sup> Impairments in oxidative capacity lead to decreased metabolism of macronutrients, and, more importantly, poorer physical performance. Interestingly, T2DM has intergenerational effects on mitochondria; young, lean offspring of individuals with T2DM had 38% lower skeletal muscle mitochondrial density compared with insulin-sensitive offspring from non-diabetic parents.<sup>59</sup> Additional studies investigating links between T2DM, sarcopenia and mitochondrial dysfunction in humans are required given the important role of mitochondria in muscle function and metabolism.

## Advanced glycation end-products

Non-enzymatic reactions between glucose and amino groups in proteins, lipids, and nucleic acids can lead to the formation of AGEs.<sup>60</sup> AGEs are positively associated with insulin resistance, obesity, and age.<sup>61,62</sup> Currently it is unclear how AGEs contribute to poor muscle health; however, it has been proposed that AGE-associated muscle weakness arises through increased protein cross-linking within muscle, thereby interfering with contractility, and also increasing inflammation and oxidative stress.<sup>14,61,61</sup> Indeed, AGE concentrations within skeletal muscle increase across the lifespan.<sup>61</sup> Skin autofluorescence is a common, surrogate measure of AGEs, which is representative of long-term glycaemic control.<sup>63</sup> Skin autofluorescence was higher (indicating higher AGEs) in a cross-sectional study of 166 Japanese adults (mean age of 63 years) with T2DM and sarcopenia when compared with non-sarcopenic T2DM controls, and was associated with low muscle strength and total body lean mass.<sup>64</sup> Another study in 232 Japanese adult men reported that higher skin autofluorescence was associated with lower hand grip strength and leg extension power.<sup>65</sup> In 9,203 Japanese men and women with a mean age of 58 years, SMI was inversely correlated with skin autofluorescence.<sup>66</sup> Furthermore, in a subpopulation of this study consisting of 1,934 participants aged >60 years, skin autofluorescence was negatively associated with grip and hip flexion and abduction strength.<sup>66</sup> Currently, reliability of skin autofluorescence as a proxy for AGE concentrations is questionable due to measurement variability associated with factors including skin



pigmentation, presence of body creams and changes in blood flow.<sup>67,68</sup> Nevertheless, skin autofluorescence is a quick, non-invasive measurement, and there is some evidence of a link between poor metabolic and muscle health through AGE accumulation within skeletal muscle. However, longitudinal studies assessing the effect of AGEs on components of sarcopenia using more robust measures of AGE concentrations (tissue biopsy and serum/urinary samples) are required.

### Vascular complications

Micro- and macrovascular complications of T2DM result from chronic hyperglycemia, AGE accumulation, inflammation, and oxidative stress and have the capacity in their own right to affect skeletal muscle.<sup>69,70</sup> Healthy vasculature is crucial for the transfer of nutrients, removal of waste products and oxygenation of tissues, including skeletal muscle. Micro- and macrovascular complications are strongly interconnected in T2DM.

### Microvascular complications

Neuropathy, retinopathy, and nephropathy are common microvascular complications in T2DM. Damaged nerve cells innervating skeletal muscle can impair muscle contractility, resulting in reduced muscle strength. A recent study reported that in men and women aged >50 years with T2DM, individuals with neuropathy had lower knee extension strength relative to body weight compared to individuals without neuropathy.<sup>71</sup> In addition to impairing muscle strength, nerve damage also causes muscle atrophy.<sup>72</sup> Both of these muscle impairments contribute to poor physical performance. In support, a cross-sectional analysis of the Health ABC study including 2,364 older adults (aged 73–82 years) demonstrated that poor peripheral nerve function was independently associated with poor physical performance outcomes including Short Physical Performance Battery (SPPB) scores, gait speed and standing balance ratio.<sup>73</sup> In the same study, individuals with T2DM also had poorer physical performance when compared with controls, and although adjusting for peripheral nerve function attenuated the relationship between T2DM and physical performance measures, it still remained significant.<sup>73</sup> Thus, neuropathy is one of the various T2DM complications that contributes to poor muscle health and ultimately, sarcopenia.

Although diabetic retinopathy does not appear to inherently affect muscle function, it can affect vision, which is a key component of balance. Balance is important for both locomotion and physical performance. Unsurprisingly,

impaired vision in T2DM contributes to increased falls risk.<sup>74</sup> In a cross-sectional analysis of the Singapore Epidemiology of Eye Diseases Study (n=9,481, aged 40–80 years), adults with T2DM and diabetic retinopathy had higher odds (OR:1.31 [95%CI:1.07–1.60]) of falling compared to individuals without diabetes in a fully adjusted model.<sup>74</sup> Additionally, individuals with diabetes and mild (OR:1.81 [95%CI:1.23–2.67]) and moderate (OR:1.89 [95%CI:1.16–3.07]) non-proliferative diabetic retinopathy had increased falls risk when compared to individuals that had diabetes without diabetic retinopathy.<sup>74</sup> Falls have an enormous economic burden<sup>75</sup> and they contribute to a large proportion of global injury-related deaths.<sup>76</sup> There are very few studies that have explored the relationship between diabetic retinopathy and sarcopenia; however, a small cross-sectional study in 316 Japanese adults with T2DM (aged >20 years) reported that diabetic retinopathy increased odds for prevalent sarcopenia (OR:7.78 [95%CI:1.52–39.81]) and low muscle strength (OR:6.25 [95%CI:1.15–33.96]) and was negatively associated with muscle quality defined by hand grip strength relative to SMI ( $\beta=-0.136$ ;  $P=0.005$ ).<sup>77</sup> Due to the small sample size of this study, there is insufficient evidence to conclude that there is a definitive relationship between diabetic retinopathy and sarcopenia. Further studies in large T2DM and sarcopenic populations that include measures of diabetic retinopathy are required.

Diabetic nephropathy causes chronic kidney disease (CKD),<sup>78</sup> which contributes to muscle wasting.<sup>79</sup> In 387 older Asians (mean age 68 years) with T2DM, diabetic nephropathy was associated with 2.5-fold (95% CI:1.35–5.13) higher odds of prevalent sarcopenia defined by AWGS criteria.<sup>80</sup> Sarcopenia prevalence has been reported to increase with CKD severity<sup>81</sup> and depending on the definition utilized, also predicts mortality in CKD patients.<sup>82</sup> Pathophysiological mechanisms that are thought to contribute to sarcopenia in CKD include increased inflammation and protein loss, reduced vitamin D synthesis, mitochondrial dysfunction, and metabolic acidosis.<sup>79</sup> In 100 CKD patients not on dialysis, high sensitivity CRP was associated with ALM/BMI ( $r=-0.268$ ).<sup>81</sup> In another study of 148 adult CKD patients (aged  $\geq 18$  years) not on dialysis, glomerular filtration rate was positively associated with lean mass, appendicular SMI and ALM.<sup>83</sup> In addition to losses in muscle mass, respiratory capacity of muscle also appears to be lower in CKD, which could further contribute to development and/or progression of sarcopenia. Muscle biopsies taken in

a cohort of adults with stage 5 CKD patients demonstrated that mitochondrial volume density is lower in individuals with CKD compared with non-CKD controls.<sup>84</sup> Targeting muscle mass and mitochondrial biogenesis may improve mortality rates in this population.

## Macrovascular complications

A key macrovascular complication in T2DM is atherosclerosis. Atherosclerosis appears to progress faster in individuals with T2DM, as it is exacerbated by poor metabolic health.<sup>85</sup> Additionally, chronic hyperglycemia inhibits nitric oxide-mediated vasodilation through increased oxidative stress, AGE accumulation, and direct actions on endothelial nitric oxide synthase.<sup>86</sup> Both of these complications increase the risk for hypertension, which can lead to end organ damage.<sup>87</sup> In 365 hypertensive Turkish adults aged >18 years without T2DM, skeletal muscle mass was negatively associated with hypertensive retinopathy, a measure of end organ damage, in both adults and older adults.<sup>88</sup> However, in this same study, SMI was not associated with hypertensive end organ damage. It is plausible that hypertension can damage myocytes; however, there is also evidence that suggests muscle mass can influence blood pressure. A recent study demonstrated that increased muscle mass induced via myostatin knockout leads to reduced systolic and diastolic blood pressure and mean arterial pressure in an obese mouse model (*db/db*), independent of adiposity and body weight.<sup>89</sup> The positive effects of increased muscle mass on blood pressure were thought to be due to improved renal function resulting from metabolic improvements attributed to increased muscle mass. It is possible that increased muscle mass would confer similar vascular benefits in humans; however, this is difficult to determine given that muscle mass is currently increased in humans primarily through exercise. Hence, it is unclear whether increases in muscle mass, or other beneficial effects of exercise are improving vascular health, although both are likely to contribute. Nevertheless, interventions targeting muscle hypertrophy may have the additional benefit of improving vascular health.

Peripheral artery disease (PAD) is another macrovascular complication associated with T2DM that affects up to a quarter of diabetes patients.<sup>90</sup> PAD measured using ankle-brachial index (an indirect, non-invasive measure of PAD) has been associated with lower hip extension and knee and hip flexion strength in older adults.<sup>70</sup> It has also been reported that older adults with PAD have slower gait

speed compared to controls without PAD.<sup>91</sup> Reduced blood flow in PAD can result in ischemia, leading to poorer muscle strength, mass and performance outcomes.<sup>92</sup> Also, PAD can lead to reduced physical activity and exercise due to the pain associated with this complication, which may further contribute to poor muscle health outcomes. Further studies investigating the relationship between micro- and macrovascular complications and sarcopenia outcomes including muscle composition and function are required in T2DM populations.

## IMAT and T2DM

Muscle quality is an underappreciated component of sarcopenia.<sup>9</sup> Parallel to muscle loss with aging, numerous neuromuscular changes contribute significantly to reduced force-production capacity, including inter- and intramuscular adipose tissue (IMAT). IMAT is an ectopic fat depot associated with poor metabolic<sup>93</sup> and muscle health outcomes.<sup>94,95</sup> Obese and T2DM individuals have greater amounts of thigh IMAT compared with lean controls, and IMAT is associated with insulin sensitivity.<sup>96</sup> In overweight and obese non-diabetic adults, calf IMAT was negatively associated with insulin sensitivity in both men ( $r = -0.40$ ) and women ( $r = -0.43$ ) using gold-standard MRI and glucose clamp techniques.<sup>93</sup> In comparison, subcutaneous adipose tissue, a considerably larger fat depot, does not appear to predict insulin sensitivity.<sup>96</sup> In a cross-sectional analysis of the Look AHEAD study ( $n = 183$ ), overweight and obese men and women with T2DM had greater IMAT at higher levels of total-body adiposity when compared with non-diabetic overweight and obese controls.<sup>97</sup> In addition to influencing insulin sensitivity, various studies have reported that IMAT is an independent predictor of physical function<sup>94,95</sup> and falls risk.<sup>98,99</sup> In fact, IMAT is a stronger predictor of mobility function in older adults than lean mass.<sup>95</sup> In a cross-sectional study ( $n = 79$ ), obese adults with T2DM and peripheral neuropathy had higher amounts of calf muscle IMAT and lower subcutaneous fat when compared with obese age-matched controls both with and without T2DM.<sup>100</sup> The authors suggested that IMAT may exacerbate peripheral neuropathy through increased concentrations of localized cytokines, including TNF- $\alpha$  and IL-6,<sup>100</sup> which have been implicated in disrupted nerve cell homeostasis and neuropathy.<sup>101</sup> IL-6 is associated with an increased loss of muscle mass and strength in T2DM,<sup>46,47</sup> and this is likely due to direct effects on myocytes, alongside indirect effects on neurons and vasculature. Given that IMAT consists of non-contractile tissue, fat infiltration into

skeletal muscle affects elastic properties of skeletal muscle.<sup>102</sup> It is clear that IMAT makes an important contribution to the relationship between sarcopenia and T2DM in older individuals, and should be considered as a key outcome measure in future interventional studies.

Impaired muscle function may contribute to high levels of sedentary behavior in T2DM patients and contribute to a positive feedback loop where functional impairments lead to metabolic impairments, and vice versa. This positive feedback loop can be broken using lifestyle interventions with proven effectiveness for improving metabolic and musculoskeletal health.

## Treatment and prevention of T2DM and sarcopenia

T2DM is commonly treated using glucose-lowering medications. Some of these may influence muscle mass (Table 2), but for the majority, their effects on sarcopenia components are unclear. Metformin increases AMP-activated protein kinase activity,<sup>103</sup> which inhibits the mechanistic target of rapamycin (mTOR), a key factor in muscle growth.<sup>104</sup> However, metformin is being investigated as an adjunct therapy to resistance training in older adults,<sup>105</sup> as it may assist in the mobilization of M2 macrophages, which could have anti-inflammatory properties in skeletal muscle.<sup>105</sup> In the MrOS study, men with diabetes treated with metformin alone and metformin plus thiazolidinediones (insulin sensitizers) over 3.5±0.7 years follow-up had an attenuated loss of total lean mass and ALM compared to men with diabetes that were not treated with insulin sensitizers, and men with untreated diabetes.<sup>106</sup> Thus, it is unclear whether metformin has positive, negative, or negligible effects on muscle mass and strength in humans. Insulin has anabolic effects on muscle mass and protein metabolism in young and non-insulin resistant men and women;<sup>32,107</sup>

however, this does not seem to occur for individuals with T2DM.<sup>32,108</sup> Indirectly, insulin therapy may improve muscle health by reducing blood glucose concentrations, which, as described above, can have negative effects on muscle through inflammation, oxidative stress and increased AGEs if chronically elevated. Sulfonylureas have been reported to cause muscle atrophy in a very small proportion of users;<sup>109</sup> however, to the best of our knowledge there are no clinical trials investigating this relationship in a controlled setting. Overall, there is a paucity of data pertaining to the relationship between glucose-lowering medication and muscle health in humans, but purported effects on body weight and muscle mass in T2DM are described in Table 2.

There are no approved pharmacological treatments for sarcopenia. Possible therapeutic targets include hormonal interventions such as a transdermal testosterone gel<sup>116</sup> and selective androgen receptor modulators.<sup>117,118</sup> Transdermal testosterone gels increase serum concentrations of androgens, which have well-documented anabolic effects on skeletal muscle.<sup>119</sup> However, these have undesirable side effects in regions such as the prostate gland and seminal vesicles, and have virializing side effects in women.<sup>120</sup> Thus, selective androgen receptor modulators (SARMs) that only bind with androgen receptors within skeletal muscle are an attractive therapeutic.<sup>121</sup> SARMs have acceptable safety profiles, and positive effects on body composition and physical function in clinical trials.<sup>117,118</sup> Other novel treatments for sarcopenia undergoing clinical trials in humans include activin type IIB receptor antagonists<sup>121</sup> and myostatin blockades (NCT01963598), which inhibit myostatin action. Myostatin is a negative regulator of myogenesis, and its inhibition significantly increases skeletal muscle mass in various animal knockouts.<sup>89,122</sup> Improving muscle mass, quality and function using these treatments could also lead to indirect improvements in

**Table 2** Direct effect of glucose-lowering medications on body weight and muscle mass in type 2 diabetes

Glucose-lowering medications	Body weight	Muscle mass
<b>Metformin</b>	Decreases <sup>110</sup>	Unclear <sup>103,106</sup>
<b>Sulphonylureas</b>	Increases/neutral <sup>160</sup>	Decreases <sup>109</sup>
<b>Insulin</b>	Increases <sup>111</sup>	Unclear/increases <sup>112</sup>
<b>Dipeptidyl peptidase 4 inhibitors</b>	Neutral <sup>113</sup>	Unclear
<b>Sodium-glucose co-transporter 2 inhibitors</b>	Decreases <sup>114</sup>	Unclear
<b>Thiazolidinediones</b>	Increases <sup>111</sup>	Unclear <sup>106</sup>
<b>Glucagon-like peptide 1 receptor agonists</b>	Decreases <sup>115</sup>	Unclear

metabolic health; however, further studies are required to establish their safety and efficacy. Even if pharmacological agents are approved for the treatment of sarcopenia in the future, lifestyle modification will likely remain the primary therapy for the management of T2DM and sarcopenia.

## Physical activity and exercise

Higher levels of physical activity are protective against the development of T2DM and sarcopenia. In the US Diabetes Prevention Program which included 3,234 non-diabetic adults, a lifestyle modification program (low-calorie, diet-induced weight loss of 7% of initial body weight and  $\geq 150$  min moderate-intensity physical activity per week) resulted in 58% reduced incidence of T2DM over three years, which was significantly more effective than metformin, a first-line glucose-lowering drug.<sup>123</sup> In addition to reducing the incidence of T2DM, lifestyle interventions also achieve remission of T2DM.<sup>124</sup> In the Look AHEAD study, approximately 12% of individuals completing a lifestyle intervention (aerobic activity for  $\geq 50$  min/week in the first month and  $\geq 175$  min/week after 6 months, alongside a weight loss goal of  $\geq 10\%$ ) experienced partial or complete remission of T2DM compared with diabetes support and education (control).<sup>124</sup> Similarly, a meta-analysis has reported that any engagement in physical activity reduces the likelihood of incident sarcopenia (OR:0.45 [95%CI:0.37–0.55]) in adults older than 40 years.<sup>125</sup> Recent findings from the Look AHEAD study demonstrated that the lifestyle intervention resulted in better lower-limb performance, and lower likelihood (adjusted OR: 0.84 [95%CI:0.71–0.99]) of having poor gait speed ( $<0.8$  m/s) in individuals with T2DM after 11 years. However, lifestyle intervention did not improve hand grip strength when compared with controls.<sup>126</sup> This is unsurprising given aerobic exercise is generally not effective for improving muscle strength, despite its ability to improve metabolic health.<sup>127</sup>

Indeed, a recent network meta-analysis including 2,208 individuals  $\geq 18$  years of age with T2DM reported that supervised aerobic and strength training were both effective at reducing HbA1c compared with no exercise.<sup>127</sup> However, the greatest reductions in HbA1c were experienced by individuals undertaking combined resistance and aerobic exercise.<sup>127</sup> Furthermore, a recent randomized control trial (RCT) in 137 pre-diabetic adults (mean age 59 years) reported that two-year supervised resistance training alone (HR:0.35 [95%CI:0.15–0.79]) and in

combination with aerobic training (HR:0.26 [95%CI:0.11–0.62]) were as effective as aerobic training alone (HR:0.28 [95%CI:0.13–0.64]) in preventing progression to T2DM.<sup>128</sup> Resistance training is the most effective strategy for improving both muscle mass and function in sarcopenic individuals,<sup>129</sup> and is similarly effective for improving muscle strength, size, and quality and metabolic health in older adults with T2DM.<sup>130</sup> Resistance training may therefore reduce the risk of developing sarcopenia in T2DM patients.

Combining resistance and aerobic training with diet-induced weight loss may be the most effective strategy for improving metabolic and musculoskeletal health in obese older adults. Resistance training may prevent or minimize muscle mass losses commonly associated with diet-induced weight loss,<sup>131</sup> which needs to be avoided in older adults at risk of sarcopenia, including those with T2DM. In dieting obese older adults, combined resistance and aerobic training led to a 21% improvement in physical performance,<sup>132</sup> and improved strength and preserved muscle mass more than aerobic training alone.<sup>132</sup> Similarly, in obese older adults intentionally losing weight over 18 months, resistance training combined with caloric restriction resulted in less loss of lean mass ( $-1.5\%$ ) than caloric restriction combined with aerobic training ( $-3.1\%$ ) and caloric restriction alone ( $-2.0\%$ ).<sup>133</sup> Nevertheless, the effect of exercise and diet-induced weight loss interventions on metabolic and muscle health in older adults with T2DM and sarcopenia is largely unexplored.

## Diet

Caloric restriction is an effective strategy for weight loss in overweight and obese individuals.<sup>134</sup> While weight loss can lead to remission of T2DM,<sup>135</sup> as described above, it can lead to significant losses in muscle mass.<sup>131</sup> To an extent, muscle mass losses may be commensurate to decreased loading as a result of losses in fat mass; however, muscle mass losses during caloric restriction may also result from inadequate protein intake.

Protein is important for the maintenance and growth of skeletal muscle. In older adults, there is evidence to suggest that recommended daily intake (RDI) of protein should be between  $\sim 1.2$ – $1.6$  g/kg/day,<sup>136</sup> despite the RDI in many countries being  $\sim 0.8$  g/kg/day.<sup>137,138</sup> In the Health ABC study, older adults in the highest quintile of energy-adjusted protein intake ( $1.2 \pm 0.4$  g/kg/day) lost approximately 40% less ALM and total lean mass over three years when



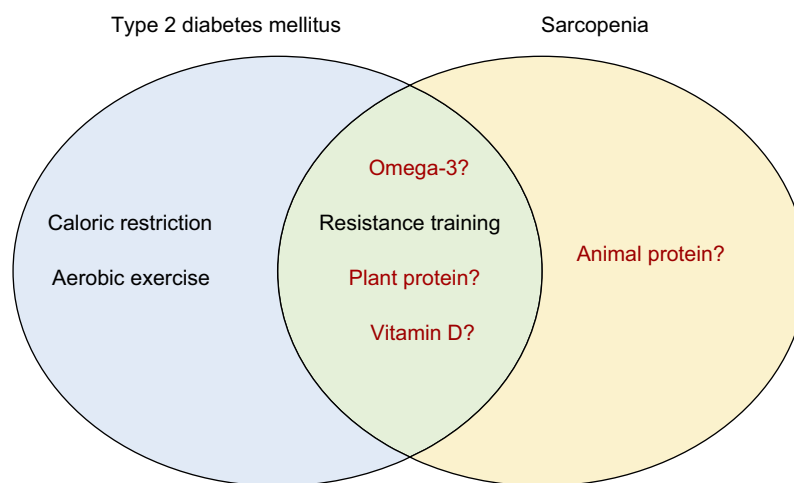
compared with individuals in the lowest quintile for protein intake ( $0.8 \pm 0.3$  g/kg/day).<sup>139</sup> Different protein sources may also affect the risk for incident T2DM. Findings from the Melbourne Collaborative Cohort Study (MCCS) and a meta-analysis showed that individuals in the highest animal and total protein intake category had increased pooled risk ratios for incident T2DM (RR:1.19 [95%CI:1.11–1.28] and RR:1.09 [95%CI:1.06–1.13], respectively), compared with the lowest intake category. Interestingly, individuals in the highest plant protein intake category had reduced, albeit not significantly, risk for incident T2DM (RR:0.95 [95%CI:0.89–1.02]) compared with individuals in the lowest intake category.<sup>140</sup> It was also reported that in the MCCS cohort alone ( $n=21,523$ ), plant protein was negatively associated with incident T2DM in women (OR:0.60 [95%CI:0.37–0.99]), but not men (OR:1.26 [95%CI:0.75–2.13]). Thus, to ensure older adults with, or at risk of, T2DM are meeting protein requirements, increases in protein intake from primarily plant sources may be most appropriate. Plant protein appears to have a lower skeletal muscle anabolic response when compared with animal protein; however, proposed strategies to augment the anabolic properties of plant protein include fortification of plant-based protein sources with amino acids, selective breeding of plants to improve amino acid profiles, and consuming a combination of plant protein sources.<sup>141</sup>

The efficacy of combining protein supplementation with resistance training to enhance exercise-related muscle outcomes in older adults with and without sarcopenia is still unclear. A recent meta-analysis by Morton et al demonstrated that protein supplementation was effective for improving lean mass in resistance-trained adults, but appears to have very little effect on muscle outcomes in older adults.<sup>142</sup> This meta-analysis also reported that protein intake beyond  $\sim 1.6$  g/kg/day did not further increase changes in lean mass.<sup>142</sup> Interestingly, Beaudart et al recently reported that an additional effect of protein supplementation combined with exercise on muscle mass and strength in older adults with sarcopenia was only evident in 3/12 RCTs included in their systematic review.<sup>143</sup> Nevertheless, ensuring adequate protein intake is important for muscle maintenance and, potentially, growth, which in turn is beneficial for metabolic health.

Vitamin D may also affect metabolic and muscle health. Low vitamin D has been linked to poor physical function<sup>144</sup> and glycemic control.<sup>145</sup> Vitamin D receptors are located within the pancreas and skeletal muscle, suggesting a role in both glucose and muscle homeostasis.

A recent randomized controlled trial in older adults with low vitamin D concentrations ( $\geq 8$  and  $\leq 20$  ng/mL) reported that vitamin D supplementation (800 IU/d) for 12 months did not affect lower-extremity power, strength or lean mass.<sup>146</sup> On the contrary, meta-analyses by Stockton et al<sup>147</sup> and Rabenda et al<sup>148</sup> suggest that vitamin D supplementation can improve muscle strength, but only in individuals with baseline 25-hydroxyvitamin D [25(OH)D]  $< 25$  and  $< 30$  nmol/L, respectively. Interestingly, vitamin D also shows potential as an adjunct therapy during exercise. In a meta-analysis by Antoniak and Greig, minor improvements in lower limb muscle strength (standard mean difference: 0.98 [95%CI: 0.73–1.24]) were evident with combined vitamin D and exercise versus exercise alone; however, for the timed up and go test (TUG), there were no additive effects of vitamin D combined with exercise compared with exercise alone.<sup>149</sup> Only three studies were included in the analysis of lower limb muscle strength, and two studies were included in the analysis of TUG, highlighting the need for further research into the effects of combined vitamin D supplementation and exercise. There is also a need for more RCTs investigating the effect of vitamin D on muscle in vitamin D deficient populations, both with and without T2DM and sarcopenia.

Regarding direct effects of vitamin D on metabolic health, a recent RCT utilizing gold-standard measures of insulin sensitivity and high-dose vitamin D supplementation (100,000 IU initial bolus; 4,000 IU/d) reported no effects on insulin sensitivity in 54 non-diabetic, vitamin D deficient ([25(OH)D]  $\leq 50$  nmol/L) overweight and obese adults.<sup>150</sup> Furthermore, a subgroup analysis ( $n=23$ ) was performed in this study in participants with baseline 25 (OH)D concentrations  $< 30$  nmol/L; however, there was no effect of vitamin D supplementation on insulin sensitivity.<sup>150</sup> It should be noted that this sub-analysis was likely underpowered. Also, vitamin D supplementation has been reported to have no effect on insulin sensitivity in vitamin D deficient individuals ([25(OH)D]  $\leq 50$  nmol/L) with T2DM.<sup>151</sup> Meta-analyses have reported conflicting findings; with vitamin D supplementation influencing glucose regulation in prediabetes and diabetes<sup>145,152–154</sup> but not in other populations.<sup>155</sup> Future studies in larger T2DM and non-T2DM populations with moderate to severe vitamin D deficiency ([25(OH)D]  $< 30$  or 25 nmol/L) may help establish whether there is an effect of vitamin D supplementation on various aspects of glucose metabolism, and whether this effect is limited to individuals with poorer metabolic health.



**Figure 1** Lifestyle interventions for type 2 diabetes mellitus and sarcopenia.

Lastly, omega-3 supplementation alone and in combination with exercise may improve metabolic and muscle health. Omega-3 supplementation can affect muscle directly by increasing muscle protein synthesis<sup>156</sup> and indirectly by decreasing systemic inflammation.<sup>157</sup> In 118 postmenopausal women, 6 months of fish oil-based supplementation (rich in omega-3 fatty acids) was associated with improved gait speed compared with placebo ( $3 \pm 16$  vs  $-3.5 \pm 14\%$ ).<sup>158</sup> Furthermore, in 60 healthy older adults (aged 60–85 years), 6 months of fish oil-based omega-3 supplementation increased thigh muscle volume (mean change: 3.6% [95% CI:0.2–7.0%]), handgrip strength (mean change: 2.3 kg [95% CI:0.8–3.7 kg]) and composite 1 repetition maximum muscle strength scores (mean change: 4.0% [95% CI:0.8–7.3%]).<sup>159</sup> However, RCTs have also reported that omega-3 supplementation alone has no effect on muscle health in older populations.<sup>160,161</sup> Similar to vitamin D supplementation, omega-3 supplementation has shown some potential as an adjunct therapy during exercise. In 51 older adults (mean age 64 years) that completed a 12-week resistance training program combined with flaxseed oil-derived alpha-linolenic acid (ALA) supplementation (rich in omega-3 fatty acids) or placebo, ALA supplementation resulted in a small increase in knee flexor muscle thickness, and a decrease in IL-6 concentrations in men.<sup>162</sup> Although, it is still unclear what type and dosage of omega-3 supplement is most effective for preventing and treating sarcopenia. Regarding the effect of omega-3 supplementation on metabolic health, studies assessing the effect of omega-3 supplementation on fasting glucose,<sup>159</sup> insulin resistance,<sup>163</sup> and T2DM<sup>164</sup> have reported little, or no effect. There are also limited data on nutritional interventions in individuals with

comorbid T2DM and sarcopenia. Further studies in well-defined populations, particularly those with nutritional deficiencies, will help clarify the effect of the aforementioned nutritional interventions on metabolic and muscle health.

## Conclusion

There are numerous bidirectional links between T2DM and sarcopenia, and the existence of one condition may increase the risk of developing the other. Factors such as insulin resistance, inflammation, AGE accumulation, increased oxidative stress and vascular complications can all affect various components of muscle health; and impaired muscle health can also contribute to development and progression of T2DM. The use of different operational definitions of sarcopenia clouds our understanding of this relationship, and therefore, development of a consensus definition is paramount. Evidence suggests that several lifestyle interventions (identified in Figure 1) can improve and maintain functional and metabolic health in individuals with T2DM and sarcopenia, but evidence for the most effective and feasible interventions in those with both conditions is lacking. Further research is needed to better understand, treat and prevent comorbid sarcopenia and T2DM, the beneficial outcomes of which would include increased independence and quality of life in these individuals.

## Author contributions

All authors contributed to conception and design, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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