

# The Association Between Sarcopenia and Diabetes: From Pathophysiology Mechanism to Therapeutic Strategy

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**Abstract:** Diabetes and sarcopenia are emerging as serious public health issues. Sarcopenia, an age-related disorder characterized by loss of skeletal muscle mass and function, is recognized as a new complication in elderly patients with type 2 diabetes mellitus (T2DM). Type 2 diabetes is characterized by insulin resistance, chronic inflammation, accumulation of advanced glycation products and increased oxidative stress, which can negatively affect skeletal muscle mass, strength and function leading to sarcopenia. There is a mutual interrelationship between T2DM and sarcopenia in light of pathophysiology mechanism and long-term outcome. T2DM will accelerate the decline of muscle mass and function, which will in turn lead to glucose metabolism disorders, reduced physical activity and the risk of diabetes. However, the specific mechanism involved has not been thoroughly studied. Therefore, this review aims to explore the pathophysiology and therapeutic strategy related to sarcopenia and diabetes and provide insight for future investigations, which is of great significance for improving the quality of life in the elderly with diabetes and concurrently reducing the incidence of related complications.

**Keywords:** type 2 diabetes mellitus, sarcopenia, insulin resistance, inflammation, gut microbiota, therapeutic strategy

## Introduction

Type 2 Diabetes mellitus (T2DM) is a metabolic disease characterized by chronic hyperglycemia due to insulin secretion and (or) utilization disorders. Epidemiological evidence shows that about 387 million adults are suffering from DM worldwide,<sup>1</sup> and it is estimated that it will increase to 693 million by 2045,<sup>2</sup> which has greatly burdened patients and society. Studies have found that both men and women with diabetes have lower bone mass index values<sup>3</sup> and the risk of sarcopenia in patients with T2DM is 1.5–2 times higher than that of non-diabetic people.<sup>4</sup> Currently, sarcopenia has been regarded as a new complication of T2DM,<sup>5</sup> which not only leads to poor quality of life but also increases the risk of physical disability and even death.<sup>6–8</sup>

The Asian Working Group for Sarcopenia (AWGS) 2014 consensus defined sarcopenia as “age-related decline of skeletal muscle plus low muscle strength and/or physical performance”,<sup>9</sup> which refers to age-related syndrome of progressive skeletal muscle loss with decrease in muscle strength and/or muscle function. It is a progressive and systemic skeletal muscle disorder that usually occurs as an age-related process in older adults<sup>10</sup> and is associated with serious consequences in the elderly such as frailty, falls, fractures, physical disability and death.<sup>11,12</sup> According to the latest diagnostic criteria of the Asian Working Group on Sarcopenia (AWGS) in 2019, the prevalence rates of suspected sarcopenia, sarcopenia, and severe sarcopenia in China are 38.5%, 18.6%, and 8.0%, respectively.<sup>13</sup> It is estimated that the prevalence of sarcopenia will increase significantly within the next 30 years,<sup>14</sup> becoming a major public issue. Sarcopenia and T2DM have a bidirectional relationship,<sup>15</sup> increase the risk of each other<sup>16</sup> and lead to functional decline and disability.<sup>17</sup> Recent studies have shown that patients with T2DM and sarcopenia have a higher mortality rate than

those without sarcopenia.<sup>18</sup> However, little attention has been paid to elderly T2DM patients with sarcopenia. Hence, it is important to study the pathogenesis of both for a proper management of this clinical complexity.

## The Converging Risk Factors for Sarcopenia and Diabetes

Aging is one of the most important risks of diabetes and sarcopenia.<sup>19</sup> One remarkable physiological sign of the aging process is the gradual loss of skeletal muscle mass and function,<sup>20</sup> which latently onset around the age of 30,<sup>21</sup> and will accumulate to 30–50% extremely loss in 80 years old.<sup>22</sup> The partial mechanism for this phenomenon may lie in the skeletal muscle, the major organ that possesses glucose transporter 4 (GLUT4) responsible for uptake of glucose, accounting for approximately 80% of glucose clearance,<sup>23,24</sup> and the utility of glucose also latently declines, increasing susceptibility to T2D.<sup>25</sup>

Unlike muscle tissue, the transformation of body fat occurs at a certain age.<sup>26</sup> The significant re-distribution of the adipose tissue is pivot to this change.<sup>12</sup> It is found that persistent localization switches from subcutaneous to visceral may lead to the ectopic accumulation of adipocytes and lipids in, such as bone marrow, liver, and especially skeletal muscle.<sup>12,27</sup> Compared with healthy elderly individuals, diabetic patients acquire up to 3-folds of the intramuscular fat stores,<sup>28</sup> a trend for the increased risk of sarcopenia and insulin resistance (IR).

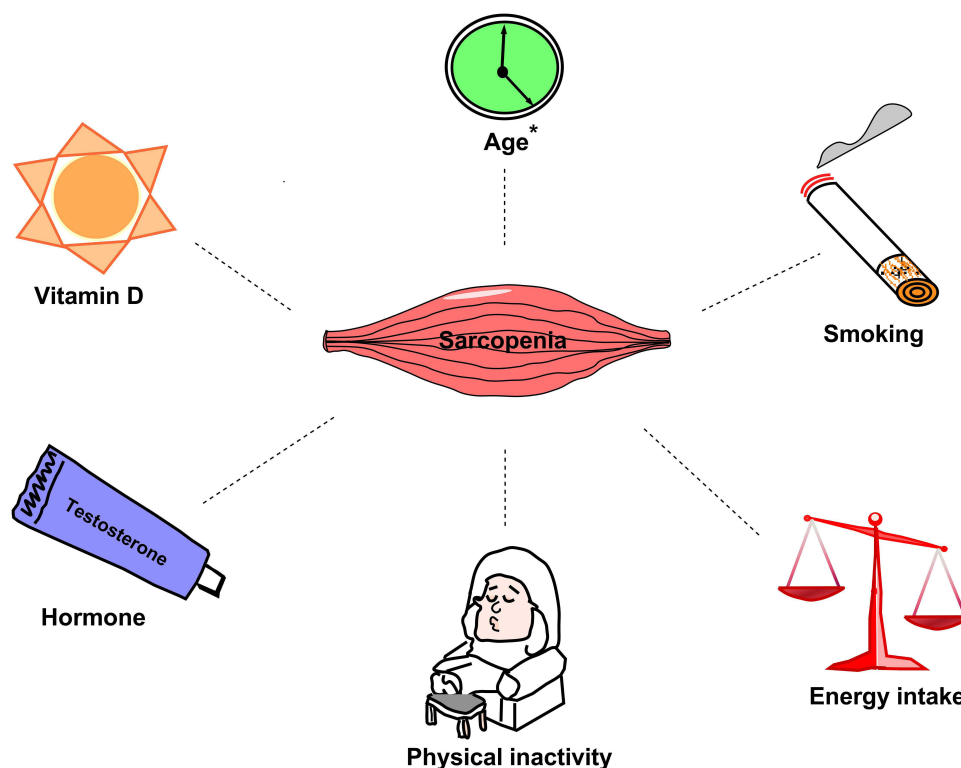
In addition, the imbalance between muscle protein anabolic and catabolic pathways paves way for the overall loss of skeletal muscle in aging. Microstructure alterations include the shrinkage and reduction of myofibers, particularly type II myofibers.<sup>25</sup> Aging also promotes the satellite cells decrease, as well as the shift from type II to type I myofibers.<sup>29</sup> This is more overt in the functional change of muscle fibers, especially type IIb, which release certain proteins and myokines that influence glucose metabolism in a more direct manner. Thus, loss of skeletal muscle mass due to aging or underlying diseases can exacerbate disarrangement of glucose metabolism.<sup>30</sup>

Due to the decreased protection mechanism or the other agents, aging is also accompanied by an increase in inflammatory markers and oxidative stress, both of which have been implicated as significant pathophysiological changes in DM and sarcopenia.<sup>31,32</sup> Specifically, mitochondrial dysfunction and advanced glycation products associated with aging may adversely affect muscle quality and glycemic levels.<sup>17</sup> Concurrently, changes in hormone levels also contribute to chronic inflammation.<sup>33</sup> For instance, reduced testosterone levels impaired self-renewal of satellite cell in muscle.<sup>34</sup> It is noteworthy that decline in serum testosterone levels in males with diabetes may be more significant.<sup>35</sup> Therefore, testosterone deficiency is closely associated with sarcopenia in aged diabetic patients.

Besides, both energy requirements and intake decrease with aging. Between the ages of 40 and 70, energy intake decreases by an average of 25%. This reduction inevitably leads to weight and muscle loss, which adversely affects strength and physical performance,<sup>36</sup> which in turn has an effect upon glucose metabolism. In addition, a sedentary lifestyle during aging is also a major contributor to the decline of skeletal muscle mass and insulin sensitivity.<sup>37</sup>

Vitamin D, a dietary precursor of 1,25 (OH)<sub>2</sub>D<sub>3</sub>, is often considered an important nutrient for maintaining proper bodily function.<sup>38</sup> Vitamin D may affect metabolism and muscle health. Low vitamin D levels are associated with poorer physical function,<sup>39</sup> worse glycemic control<sup>40</sup> and an increased risk of developing diabetes in elderly adults.<sup>41</sup> Inversely, vitamin D deficiency is common in patients with T2DM.<sup>42</sup> Vitamin D plays many critical roles in the function of skeletal muscle, such as maintaining muscle excitability through intracellular calcium, the proliferation and differentiation of skeletal muscle stem cells, and so on.<sup>43,44</sup> Multiple studies have also demonstrated that vitamin D supplementation can improve muscle strength and prevent atrophy of type II fibers where vitamin D is deficient.<sup>45</sup> These evidences suggest that vitamin D emerges as a critical risk factor mediating the development of IR and sarcopenia, but the conclusion remains to be determined.

According to the 2014 Surgeon General's Report, active smokers are at higher risk of developing T2D by 30–40% when compared to non-smokers.<sup>46</sup> Cigarette smoking impacts body weight and composition, peripheral insulin sensitivity, and pancreatic  $\beta$  cell function.<sup>47</sup> Numerous studies have described the vicious effects of smoking on skeletal muscle function and morphology, especially, the thigh muscles.<sup>48</sup> The partial consequence is degeneration in muscle fatigue resistance<sup>49</sup> associated with compromised muscle oxidative capacity,<sup>50</sup> and a transition from slow twitch to fast twitch fiber type.<sup>51</sup> Furthermore, smoking could promote skeletal muscle wasting via smoking-induced inflammation that facilitate protein breakdown and suppress protein synthesis<sup>52</sup> (Figure 1).



**Figure 1** The converging risk factors between sarcopenia and diabetes. Sarcopenia was variably associated with some risk factors, notably age (marked with\*).

## The Metabolic Pathophysiology for Sarcopenia in T2DM Insulin Resistance (IR)

The main mechanism for T2DM is insulin resistance (IR). Skeletal muscle is one of the target organs for insulin action and insulin resistance.<sup>53</sup> Impaired insulin action may promote protein degradation and hamper protein synthesis, resulting in both mass and strength drops of muscle.<sup>4</sup> IR in skeletal muscle is the most important factor exacerbating sarcopenia in T2DM patients.<sup>54</sup>

The main proteolytic pathways in muscle involve the ATP-dependent ubiquitin proteasome pathway (UPP), lysosomal autophagy pathway, caspase hydrolysis pathway and calcium-dependent calpain pathway, of which were mainly mediated by IL6/STAT, TNF&IL6/NFκB, myostatin/Smad2/3 and FoxO1/3 signaling pathways.<sup>55</sup> Insulin itself reduces proteasome catalytic activity in muscles.<sup>56</sup> In the case of IR, high blood glucose levels may cause muscle atrophy via the proteolytic pathway of the ubiquitin-proteasome.<sup>57</sup> Metabolic dysregulation due to insulin resistance<sup>58</sup> leads to hyperglycemia and muscle atrophy via the WWP1/KLF15 pathway.<sup>59</sup> WWP1 is a member of the ubiquitin ligase protein family. Studies have shown that hyperglycemia upregulates KLF15 protein in skeletal muscle of diabetes models of animals by downregulating the E3 ubiquitin ligase WWP1, followed by inhibition of ubiquitin-dependent degradation of KLF15. KLF15 is a protein associated with muscle wasting. The abundance of the transcription factor KLF15 and the expression of genes associated with muscle atrophy were increased in skeletal muscle of diabetic mice, and mice with muscle-specific KLF15 deficiency were protected from diabetes-induced muscle atrophy.<sup>60</sup> This pathway may serve as a therapeutic target for insulin resistance-induced sarcopenia.

Muscle protein synthesis is mainly regulated by two factors: insulin-like growth factor 1 (IGF1) and myostatin.<sup>61,62</sup> Protein synthesis inhibition is mediated by inhibition of the IGF1-PI3K-Akt-mTOR and SC-Gai2 pathways.<sup>55</sup> The signaling system of IGF1 and a series of intracellular components plays a crucial role in the regulation of skeletal muscle growth. Akt kinase, also known as protein kinase B (PKB), is a central component of this cascade, controlling protein synthesis through mammalian target of rapamycin (mTOR) and glycogen synthase kinase 3 (GSK3), and through FoxO family of transcription factors for protein degradation.<sup>63</sup> IR inhibits mammalian targets of rapamycin pathway,<sup>64</sup> while

simultaneously stimulating the ubiquitin-proteasome system to upregulate protein catabolism through proteins belonging to FoxO family, and their downstream E3 ubiquitin ligases, resulting in decreased muscle mass.<sup>65</sup> As skeletal muscle mass decreases, IR increases lipolysis, releases free fatty acids (FFA) from adipose tissue, and inhibits the growth hormone (GH)-insulin-like growth factor (IGF1) axis that promotes protein synthesis in skeletal muscle.<sup>66</sup>

Myostatin, a member of the transforming growth factor  $\beta$  (TGF- $\beta$ ) superfamily, downregulates mTORC1 signaling and increases AMPK $\alpha$ 2 phosphorylation, both processes could lead to dysregulation of protein synthesis and enhance autophagic proteolysis.<sup>67</sup> Myostatin binds to its cognate receptor, the activin II receptor type B (ActRIIB), and thereby exerts multiple effects. After activation of Smad2/Smad3 and dephosphorylation of Akt, muscle protein ubiquitination and proteasomal degradation as well as autophagy will be induced by Atrogin-1 and MuRF1, resulting in process favors for protein degradation.<sup>68,69</sup> Additionally, myostatin also inhibits the mammalian target of rapamycin complex 1 (mTORC1).<sup>68,69</sup> Besides, caspase, an apoptotic enzyme specific for caspase-3, is overexpressed in T2DM. Myostatin-induced apoptosis was shown to be elicited via activation of the p38-caspase pathway, leading to increased protein degradation.<sup>69,70</sup> Hyperinsulinemia caused by IR increases the content of myostatin,<sup>71</sup> thereby reducing skeletal muscle through the above-mentioned pathway.

Increased IR increases ectopic fat accumulation and promotes the production of pro-inflammatory factors that inhibit myogenesis and increase muscle catabolism.<sup>72</sup> In skeletal muscle, insulin binds to the insulin receptor (GLUT4), allowing glucose uptake by the muscle cells. In the case of IR, its uptake is reduced, leading to hyperglycemia.<sup>57</sup>

## Inflammation

Type 2 Diabetes Mellitus (T2DM) is characterized by chronic low-grade inflammation<sup>73</sup> which disrupts glucose and muscle homeostasis.<sup>57</sup> This inflammation leads to a downregulation of protein anabolism via the PI3K-Akt pathway, while simultaneously upregulating protein catabolism through the stimulation of the ubiquitin-proteasome system by FoxO family proteins and their downstream E3 ubiquitin ligases.<sup>74</sup> The main inflammatory molecules involved in inflammation are TNF- $\alpha$ , IL-6, IL-1 and chemokines, which promote inflammatory cell infiltration and muscle degeneration through NF- $\kappa$ B.<sup>75</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>76,77</sup> and associated with IR.<sup>78</sup> Increases in pro-inflammatory factors such as IL-6, TNF- $\alpha$ , and CRP have been shown to adversely affect muscle mass and function.<sup>79</sup> IL-6 can increase muscle catabolism.<sup>80</sup> In an animal experiment, low concentrations of IL-6 were injected into the muscles of mice. The muscles exposed to IL-6 subsequently atrophied due to protein breakdown.<sup>81</sup> In addition, clinical studies have also shown that compared with non-diabetic controls, older adults with T2DM have greater loss of leg muscle and strength over 3 years. After adjusting for cytokines including IL-6 and TNF- $\alpha$ , these associations were only partially attenuated.<sup>82</sup> IL-6 is associated with increased loss of muscle and strength in T2DM, probably due to direct effects on myocytes, as well as indirect effects on neurons and vasculature. Furthermore, IL-6 in chronically low levels controls signal transducer and activator of transcription 3 (STAT3) phosphorylation through a negative feedback mechanism leading to protein catabolism in muscle via JAK/STAT<sup>81</sup> and NF- $\kappa$ B-dependent pathways.<sup>83</sup> The inflammatory cascade begins with the activation of other interleukins, such as TNF and IL1, which act through NF $\kappa$ B, FOXO4 and other signaling pathways, resulting in muscle atrophy.<sup>55</sup> Although IL-10 inhibits mTOR activity, it induces mitophagy, which leads to muscle atrophy.<sup>84</sup> The specific molecular mechanisms underlying the adverse effects of CRP on muscle require further investigation.

## Oxidative Stress

Oxidative stress, caused by increased reactive oxygen species (ROS) and decreased antioxidant effects,<sup>85</sup> is considered an important contributor to aging and diseases. Muscle cells produce ROS (hydroxyl radicals, peroxides, and superoxides) as a by-product of normal metabolism and are more susceptible to oxidative stress.<sup>54</sup> While T2DM is associated with increased oxidative stress,<sup>57</sup> hyperglycemia in T2DM triggers increased production of ROS.<sup>86</sup> ROS activates the ubiquitin-proteasome system and accelerates the degradation of muscle proteins,<sup>87</sup> which leads to sarcopenia. It has been shown that increased oxidative stress impairs muscle repair,<sup>88</sup> satellite cell differentiation and DNA in diabetic rat.<sup>89</sup>

Furthermore, oxidative stress inhibits the Akt/mTOR pathway and its downstream targets, subsequently inhibiting protein synthesis and promoting muscle atrophy.<sup>90</sup>

Mitochondrial dysfunction is another age- and T2DM-related factor associated with oxidative stress leading to deterioration of both metabolic and muscle health.<sup>91,92</sup> Mitochondria play an important role in muscle function and metabolism. Compared with younger generation, the oxidative capacity per muscle unit is reduced by 50% in the elderly,<sup>93</sup> and accompanied by increased incident of mitochondrial DNA mutations.<sup>94</sup> Diabetes-induced mitochondrial dysfunction leads to myocyte apoptosis,<sup>95</sup> thereby increasing the risk of sarcopenia. Furthermore, loss of Ca<sup>2+</sup> homeostasis can activate non-lysosomal Ca<sup>2+</sup>-regulated calpains due to increased oxidative stress (another marker of T2DM).<sup>96</sup> In diabetic patients, abnormally activated calpain leads to muscle atrophy through its activation of the ubiquitin-proteasome pathway (UPP) and inhibition of the Akt pathway.<sup>97</sup>

## Advanced Glycation End-Products (AGEs)

AGEs, a few of heterogeneous molecules, which are derived from non-enzymatic products of the reaction of glucose or other sugar derivatives with proteins or lipids, are biomarkers of aging, and utilized as assessment of disease status.<sup>98</sup> Hyperglycemia in T2DM patients develops with chronic accumulation of AGEs, which are associated with IR and aging.<sup>99,100</sup> Accumulation of AGEs has been shown to lead to skeletal muscle atrophy and dysfunction in both basic experiments<sup>101</sup> and human studies.<sup>102</sup> The formation of AGEs is irreversible, and accumulates in various neuromusculoskeletal tissues, such as bone, cartilage, muscle, tendons, ligaments, and nerves, where they significantly affect biomechanical properties of those tissues.<sup>98</sup> The accumulation of AGEs in diabetes affects skeletal muscle health through pathways such as mitochondrial dysfunction and induction of cell death.<sup>17</sup> In addition, AGEs also interfere with muscle contractility by causing charge changes and increasing intramuscular protein cross-linking. By binding to AGEs receptors (RAGE) on skeletal muscle cell membranes, AGEs induce inflammation and activate NADPH oxidase through intracellular signal transduction, which increases the amount of circulating reactive oxygen species (ROS) that promotes oxidative stress.<sup>98</sup> Recently, a study shows that higher skin AGEs are associated with a higher prevalence of sarcopenia.<sup>103</sup> Whether AGEs measurement can be used to detect pathological changes in skeletal muscle caused by hyperglycemia and aging remains to be further investigated.

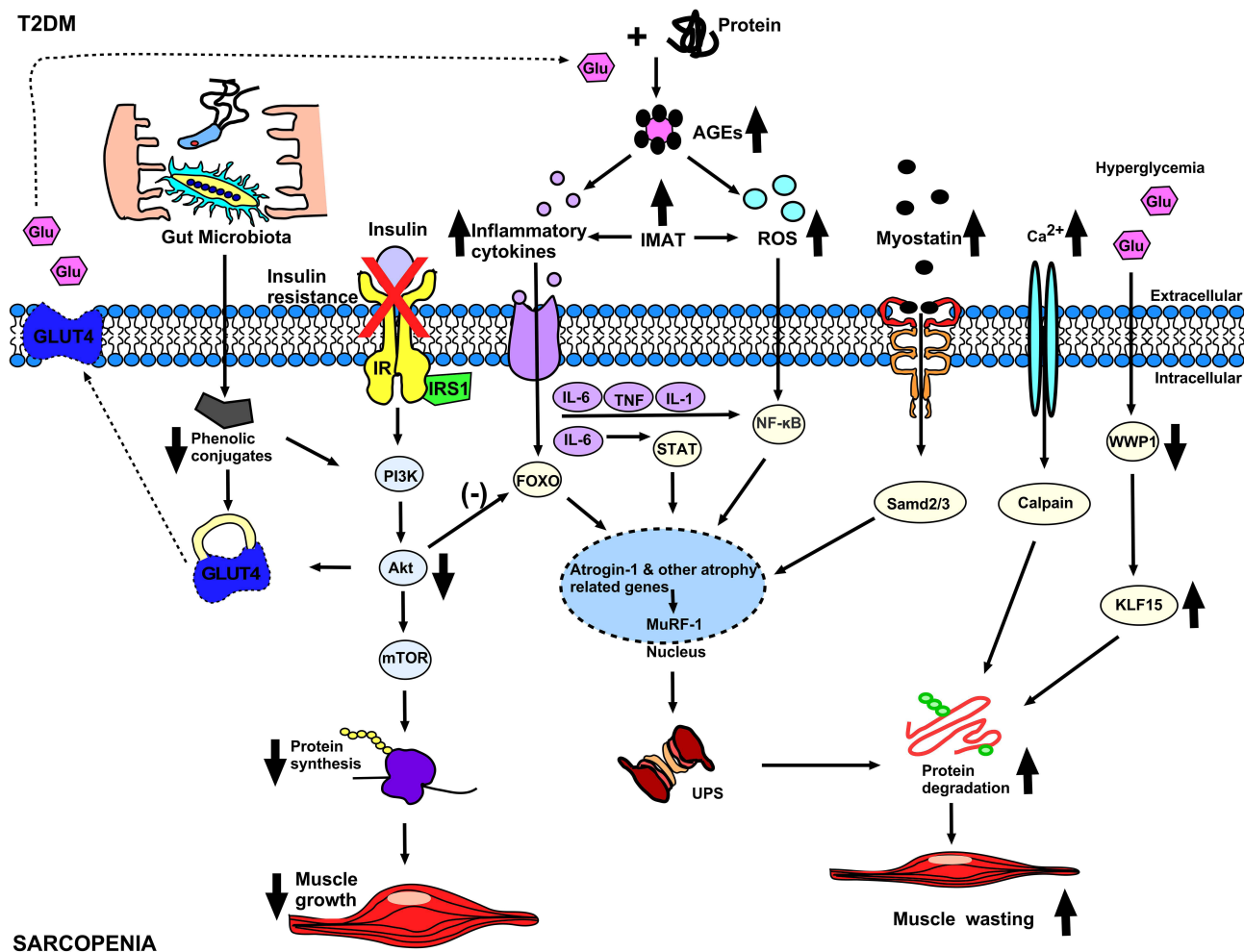
## Intramuscular Adipose Tissue (IMAT)

IMAT is an ectopic fat deposit, which has been associated with poor outcome of metabolism<sup>104</sup> or health of muscle.<sup>105</sup> A hallmark pathophysiology of diabetes is obesity and ectopic deposition of fat in many insulin target tissues including skeletal muscle.<sup>106</sup> Accumulation of ectopic lipids in skeletal muscle increases the risk of skeletal muscle IR.<sup>107</sup> Obese adults with T2DM and peripheral neuropathy had higher calf muscle IMAT content compared with age-matched obese controls.<sup>108</sup> Fat accumulation increases adipokine secretion and low-grade inflammation, which leads to both insulin signaling and mitochondrial dysfunction in skeletal muscle, which in turn leads to muscle atrophy.<sup>109</sup> Abnormal mitochondrial morphology caused by impaired lipid metabolism leads to membrane stiffness and increased ROS production in the process of muscle degeneration.<sup>110</sup> In addition, IMAT is composed of non-contractile tissue and infiltration of fat into muscle affects the elasticity of skeletal muscle.<sup>111</sup> The role of IMAT in sarcopenia and T2DM among the elderly is significant and should be prioritized as a crucial outcome measure in upcoming intervention studies.

## Gut Microbiota

Human gut microbiota is able to influence host physiology by regulating multiple processes, including nutrient absorption, inflammation, oxidative stress, immune function, and anabolic balance.<sup>112</sup> Dysbiosis of the gut microbiota plays an important role in the pathogenesis of IR and T2D through multiple mechanisms,<sup>113</sup> which involve increased intestinal permeability, low-grade endotoxemia, short-chain fatty acids (SCFAs) or changes in the production of branched-chain amino acids (BCAAs), bile acid metabolism, and/or effects on gut hormone secretion.<sup>114</sup> Compositional and functional changes in the gut microbiota have been observed in patients with T2DM and prediabetes.<sup>115,116</sup> Additionally, fecal microbiota transplantation from healthy donors to patients with metabolic syndrome was associated with increased microbial diversity, improved glycemic control, and insulin sensitivity.<sup>117</sup> Recent studies have shown that the gut





**Figure 2** The possible mechanism of diabetes and sarcopenia. In diabetes, insulin resistance inhibits protein synthesis pathways leading to decreased muscle mass. The increase of inflammatory cytokines, ROS, Myostatin and Calpain related to diabetes will not only inhibit the protein synthesis pathway, but also increase the protein catabolism pathway, thereby causing further decline in muscle mass. Hyperglycemia causes decrease of WWP1, which leads to increase of KLF15, which further aggravates the protein catabolism pathway and leads to muscle atrophy.

**Abbreviations:** IR, insulin receptor; AGEs, Advanced glycation end-products; IMAT, Intermuscular adipose tissue; GLUT4, glucose transporter 4; UPS, ubiquitin-proteasome system; X, insulin resistance; Down arrow, decrease; Up arrow, increase; Dotted Arrow, Move; (-), inhibit.

microbiota also influences the onset and progression of sarcopenia.<sup>118,119</sup> An in vitro study showed that phenolic conjugates produced by the microbiota increase glucose uptake in muscle fibers by upregulating GLUT4 and PI3K and induce an anabolic response that increases muscle mass.<sup>120</sup> Intake of probiotics and prebiotics modulates skeletal muscle mass and function by modulating gut permeability and the gut-muscle axis.<sup>121</sup> Thus, the gut microbiota may be an essential contributor involved in the pathogenesis of sarcopenia and diabetes (Figure 2).

## The Therapeutic Strategy for Sarcopenia in T2DM

### Non-Pharmacological Approaches

#### Physical Exercise

Exercise is the most cost-effective lifestyle intervention for the prevention and treatment paradigm of diabetes.<sup>122</sup> Numerous studies have shown that exercise can also retard muscle loss by attenuating the activation of NF- $\kappa$ B.<sup>123,124</sup> The 2018 clinical practice guidelines strongly recommend physical exercise as the primary treatment for sarcopenia.<sup>125</sup> Both aerobic and resistance exercise can prevent and treat the decline in muscle mass and strength that occurs with aging.<sup>126</sup> Aerobic exercise decreases the level of HbA1c, fasting blood glucose, and IR, as well improves skeletal muscle mass, especially leg strength. Resistance exercise (RE) can effectively enhance muscle strength while ameliorating IR, fat

accumulation, and maintaining mitochondrial function in patients with T2DM.<sup>127,128</sup> Current clinical experiments have proven short-term moderate-intensity resistance exercise (Each exercise consisted of (i) 5 min of warm-up; (ii) 30 min of RE: biceps (left hand 12 times × 3 groups; right hand 12 times × 3 groups; 1–2 min rest between each group); posterior neck arm extension (12 times × 3 groups, 1–2 min rest between each group); static squat (30s × 3 groups, 1–2 min rest between each group); standing upright against the wall for 10 min; and (iii) 5 min of stretching) is an effective and safe form of exercise. This type of exercise can reduce glycemic levels and its fluctuations, as well as hypoglycemia risks in elderly patients with T2DM and sarcopenia, improving the time in target range (TIR).<sup>129</sup> It is noteworthy that for the elderly or (and) patients with neurological diseases, high-intensity exercise is difficult to implement; however, blood flow restriction (BFR) training can be used as an alternative to traditional exercise, and even low strength training also significantly increases muscle strength.<sup>130</sup>

## The Nutrition Supplements

Although the exact mechanism is not yet clear, adequate energy and protein intake can help prevent loss of muscle mass. Animal protein intake is associated with an increased overall risk of T2DM compared with plant protein intake.<sup>131</sup> Therefore, protein derived from plant may be the most appropriate source to ensure protein needs in older adults with or at risk of T2DM. Notably, leucine exhibits strong insulinotropic properties that increase amino acid availability for muscle protein synthesis, reduce muscle protein breakdown, and enhance glucose disposal to help maintain glycemic homeostasis.<sup>132</sup> A recent study showed that the branched-chain amino acids valine, leucine, and isoleucine longitudinally reduce the odds of muscle mass loss.<sup>133</sup> Therefore, supplementation with branched-chain amino acids, leucine, or leucine-rich proteins is one of the most common interventions for the treatment of sarcopenia in older adults.<sup>134</sup>

In addition, intake of other specific nutrients, including Omega-3 fatty acids, nicotinamide adenine dinucleotide (NAD<sup>+</sup>) precursor, vitamin D, foods containing anti-inflammatory and antioxidants and dietary fiber can modify insulin sensitivity, oxidative stress and inflammation to maintain muscle mass and improve glycemic level.<sup>37</sup> Omega-3s are polyunsaturated fatty acids, mainly derived from marine fish, that increase muscle mass and function in healthy older adults.<sup>135</sup> Omega-3 supplementation alone and in combination with exercise can substantially improve metabolic and muscle health. Omega-3 supplementation affects muscle directly by increasing muscle protein synthesis<sup>136</sup> and indirectly by reducing systemic inflammation.<sup>137</sup> Opacity, type and dose of Omega-3 supplements are most effective in the prevention and treatment of sarcopenia, thus, more prospective cohort studies are needed.

Vitamin D can improve muscle mass and function and is beneficial for patients with sarcopenia.<sup>138</sup> Therefore, adequate vitamin D intake is recommended for elderly diabetic patients, especially those with sarcopenia.<sup>139</sup> However, the optimal dose and frequency of administration, as well as the duration of treatment, remain unclear.<sup>4</sup> In a study conducted on older adults with sarcopenia, it was found that combining exercise with daily intake of whey protein (22 g), essential amino acids (11 g, including 4 g leucine) and vitamin D (100 IU) resulted in a gain of almost 2 kg greater in lean mass compared to exercise alone. Additionally, the group that received the combination treatment showed significant improvements in hand grip strength and a reduction in CRP levels. In addition, it was reported that low intake of vitamins B1 and B12 increased the chance of sarcopenia in elderly patients with T2D.<sup>8</sup> Further research is needed on whether vitamin B1 and B12 supplementation improves metabolic and muscle health issues. Inversely, the results of vitamin A and E in different studies are still controversial, where the sample size needs to be further expanded. Interestingly, reduced speed of eating was associated with an increased risk of sarcopenia in aged T2D patients.<sup>140</sup> Recent studies have shown potential benefits of low-dose lithium (Lithium) in T2D and sarcopenia,<sup>141</sup> while specific mechanisms need further study.

Although sarcopenia and T2DM are prevalent in the modern population, the current evidence for nutritional intervention is not consistent. The complement of evidences in the future research and practice will assist successful management of sarcopenia and diabetes.

## Pharmacotherapy

There are currently no approved specific drugs for the therapy of sarcopenia. Possible therapeutic targets include hormonal interventions such as transdermal testosterone gels<sup>142</sup> and selective androgen receptor modulators

(SARMs).<sup>143</sup> Transdermal testosterone gel increases the blood concentration of androgens, which has a favorable anabolic effect on skeletal muscle.<sup>144</sup> However, adverse side effects exist, such as dyslipidemia, benign prostatic hypertrophy and uterine hyper-proliferation.<sup>145</sup> Androgens are important for building and maintaining skeletal muscle, and due to their anabolic effects on muscle, they are considered superior in the potential treatment of sarcopenia.<sup>146</sup> SARMs have an acceptable safety profile and positive effects on body composition and function in clinical trials.<sup>143,146</sup> Hepatotoxicity and off-target effects on genitalia were major treatment-limiting side effects.<sup>147</sup> Nonetheless, even if drugs are approved for the treatment of sarcopenia in the future, lifestyle modification will likely remain the mainstay for T2DM and sarcopenia.

Antidiabetic drugs may affect muscle mass; however, the mechanism for most of them on sarcopenia is still unknown. Metformin is a drug widely used in the treatment of T2DM, and different studies have also shown it has positive effects on muscle mass and muscle strength.<sup>148,149</sup> However, in the elderly, inconveniences such as digestive intolerance, dysgeusia, hyperoxia, and vitamin b12 deficiency may hamper their prospect widely utilization in these populations.<sup>150</sup> Sulfonylureas predispose to muscle atrophy and should be avoided in patients with sarcopenia or in patients with diabetes at risk of developing sarcopenia.<sup>151,152</sup> Glinides have a similar mechanism of action to sulfonylureas<sup>153</sup> and should also be avoided. Thiazolidinediones act as insulin sensitizers, and some studies have shown that thiazolidinediones are beneficial for muscle performance in diabetics. Pioglitazone improves skeletal muscle energy expenditure by reducing intramuscular lipid content and improving fatty acid metabolism,<sup>154</sup> but increases risk of fractures and decompensated heart failure.<sup>155</sup> Dipeptidyl peptidase-4 inhibitors (DPP-4) have positive effects on muscle mass and glycemic control,<sup>156</sup> which may be related to the ability to enhance the action of GLP-1 or inhibit DPP-4 activity itself, or both.<sup>149</sup> DPP-4 inhibitors have few side effects and exhibit minimal risk of hypoglycemia.<sup>157</sup> Thus, such drugs may serve as a promising approach for T2DM with sarcopenia. Glucagon-like peptide 1 agonists (GLP-1RA) have anti-inflammatory and antioxidant properties, and the mechanism of their effects on skeletal muscle is still a matter of debate.<sup>153</sup> Sodium-Glucose Cotransporter 2 Inhibitors (SGLT-2i) have been shown to be good therapeutic options for the treatment of aged T2D patients. In animal experiments, SGLT2i not only improved hyperglycemia but also improved fatty acid metabolism in muscle, thereby preventing muscle atrophy.<sup>158</sup> Regardless of this proposed preclinical studied merit, the effects of SGLT-2i on muscle are still unclear in limited follow-up duration of clinical trials.<sup>159</sup> Insulin is actually the most powerful hypoglycemic drug known so far. In limited studies, it claimed that long-term application of insulin therapy may negatively affect muscles encompassing mechanism such as inflammation, oxidative stress and increased ACEs, while its effect on bodyweight may be favored for low BMI patients. Therefore, there is currently no homogenous evidence that insulin therapy is beneficial for sarcopenia in older adults<sup>153</sup> (Table 1).

**Table 1** Effects of Drug Therapy on Muscle and Adverse Side Effects in Diabetics

Medication	Effect on Muscle Mass	Adverse Side Effects
<b>Transdermal testosterone gels</b>	Increases <sup>144</sup>	Dyslipidemia, benign prostatic hypertrophy, and uterine hyper-proliferation <sup>145</sup>
<b>Selective androgen receptor modulators (SARMs)</b>	Increases <sup>143,146</sup>	Hepatotoxicity and off-target effects on genitalia <sup>147</sup>
<b>Metformin</b>	Increases	Digestive intolerance, dysgeusia, hyporexia, and vitamin b12 deficiency <sup>150</sup>
<b>Thiazolidinediones</b>	Increases <sup>154</sup>	Fractures and decompensated heart failure <sup>155</sup>
<b>Sulfonylureas</b>	Decreases <sup>151,152</sup>	Hypoglycemia, weight gain
<b>Glinides</b>	Decreases <sup>153</sup>	Potential hypoglycemia with combination therapy
<b>DPP-IVis</b>	Increases <sup>156</sup>	Minimal risk of hypoglycemia <sup>157</sup>
<b>GLP-1RA</b>	Inconclusion <sup>153</sup>	/
<b>SGLT-2i</b>	Inconclusion <sup>159</sup>	/
<b>Insulin</b>	Decreases <sup>153</sup>	Hypoglycemia



## Future Directions

Mitochondrial-targeted antioxidants are another potential therapy to reverse oxidative dysfunction, lower ATP levels and restore protein synthesis and muscle mass.<sup>160</sup> In addition, myostatin (MYO) plays a powerful role as a negative muscle growth regulator. This is supported by studies showing that MYO gene knockout mice exhibit abnormal muscle hypertrophy and MYO overexpression can lead to severe muscle atrophy.<sup>161</sup> In preclinical models, follistatin, a myostatin antagonist, was associated with reduced myostatin expression and increased muscle mass and protein synthesis.<sup>162</sup> Endothelin-1 (ET-1) may play a critical role in mediating myopathy and adipose inflammation through the release of IL-6, TNF- $\alpha$ , or adipokines, visfatin, which involve PI3K/Akt/miR-let-7g-5p pathways in elderly individuals with diabetes.<sup>163</sup> These findings can promote conceptualization and development of novel approaches or strategies for sarcopenia and with its related diseases in the future.

## Conclusion

T2DM and sarcopenia are interrelated and entangled each other. Aging, insulin resistance, inflammation, oxidative stress, accumulation of AGEs, ectopic fat, vitamins and other factors could obviously affect muscle health. Impaired muscle health may also contribute to the development and progression of T2DM. Therefore, specific exercise methods and protein-rich nutrition combination-specific plans should be adopted, and appropriate hypoglycemic drugs selected to be individualized. The evidences backup the most effective and feasible interventions for patients complicated with both diseases are relatively sparse, and important directions in the future needed including intensive exploring underlying comprehensive cellular and molecular pathways and their interrelationships for two diseases, the advancement in developing biomarkers, the accuracy of diagnosis throughout whole life-span. Only by solving these techniques and knowledge limits, could prevention and treatment of sarcopenia and T2DM pierce the chaos of cognitive and practice cave.

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## Disclosure

The authors declare no conflicts of interest in this work.

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