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Interplay between Sarcopenia and Type 2 Diabetes: Mechanisms, Implications, and Therapeutic Prospects

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Abstract

Sarcopenia, characterized by the progressive loss of skeletal muscle mass and function, is both a significant risk factor for and a potential consequence of type 2 diabetes mellitus (T2D). The relationship between sarcopenia and T2D is complex and bidirectional, involving interconnected metabolic and molecular mechanisms that impair neuromuscular performance and muscle integrity during aging. The key pathways linking these conditions include insulin resistance, chronic low-grade inflammation, oxidative stress, and accumulation of advanced glycation end products. This review aims to critically examine the interplay between sarcopenia and T2D, with a focus on underlying pathophysiological mechanisms, nutritional determinants, and clinical implications. Dysregulated glucose metabolism, alterations in myostatin signaling, and activation of the ubiquitin–proteasome system are major contributors to muscle atrophy in this context. Furthermore, we highlight the role of targeted interventions, including resistance exercise, nutritional optimization, and emerging pharmacological strategies, in mitigating muscle loss and improving metabolic outcomes. A comprehensive understanding of these interconnected pathways is essential for developing integrated therapeutic approaches to improve the clinical outcomes and quality of life of affected individuals.

Keywords: Aging; Chronic inflammation; Nutrition; Neuromuscular; Sarcopenia; Type 2 diabetes

1. Introduction

Sarcopenia is an age-related condition characterized by the progressive loss of skeletal muscle mass, strength, and function. The nomenclature is derived from the Greek words *sarx* (flesh) and *penia* (loss). Sarcopenia is influenced by physiological, lifestyle, and environmental factors (1). With increasing life expectancy and a globally aging population, sarcopenia has become a significant public health concern. It is associated with adverse health outcomes, including functional decline, falls, fractures, disability, and increased mortality. Reduced muscle mass and strength impair an individual's capacity to perform daily activities, leading to a decline in autonomy and overall quality of life (2). Sarcopenia also increases the risk of falls and fractures, which may result in catastrophic repercussions, particularly among older adults. A key characteristic of sarcopenia is the imbalance between muscle protein synthesis and degradation. The responsiveness to anabolic stimuli, including exercise and dietary protein intake, declines with age, resulting in negative protein balance and muscle atrophy (2, 3).

Sarcopenia shares pathophysiological mechanisms with diabetes, a metabolic disorder characterized by impaired insulin function and abnormal glucose metabolism. Sarcopenia and diabetes involve a complex, bidirectional interaction between muscle integrity and metabolic homeostasis (4). These diseases share common risk factors, such as aging, physical inactivity, obesity, and chronic inflammation. Both conditions are more prevalent in older adults, as aging is linked to reduced muscle mass and function, as well as an increased risk of insulin resistance and type 2 diabetes (T2D) (5). The age-related hormonal changes also contribute to these disorders, while sedentary lifestyles and obesity exacerbate the risk. Chronic low-grade inflammation, commonly observed in obesity and aging, plays a pivotal role in the pathogenesis of both conditions by promoting muscle wasting, insulin resistance, and metabolic dysfunction.

Sarcopenia and diabetes are closely linked in their clinical manifestations and outcomes. Skeletal muscle is a major site for glucose uptake and disposal; however, reductions in muscle mass and quality impair insulin sensitivity and glucose metabolism, predisposing individuals to T2D and worsening glycemic control in those already affected (6). Conversely, insulin resistance and hyperglycemia in diabetes drive muscle protein breakdown and impair muscle regeneration, exacerbating sarcopenia. This bidirectional relationship creates a vicious cycle of muscle loss, metabolic dysfunction, and adverse health outcomes. The certain antidiabetic medications, including metformin and insulin sensitizers, may support muscle metabolism and function in patients with sarcopenia and diabetes.

In this review, we aimed to highlight the intricate connection between sarcopenia and T2D, emphasizing the need to address muscle health in diabetes management. By gaining insights into the cellular and molecular pathways underlying both conditions, together with targeted therapeutic strategies, the clinical outcomes and quality of life of the affected individuals can be enhanced.

2. Key contributors to neuromuscular dysfunction and muscle loss associated with aging

Sarcopenia exhibits substantial variability, shaped by genetic, environmental, and epigenetic influences (7). Notably, differences in the "stage of aging" observed among animals raised under identical conditions suggest that genetic factors may exert a more significant impact than epigenetic ones in determining the rate of biological aging in animal models (7, 8). Genetic variation plays a key role in the progression and severity of sarcopenia, with heredity accounting for approximately 64% of age-related differences in muscle strength (9).

Of note, the genetic variables listed in (**Table 1**) (10) include both genes particularly linked with age-related muscle decrease and those implicated in the overall etiology of sarcopenia, regardless

of age. While some genes, such as *ACTN3* and *IGF-1*, are strongly associated with aging-related changes in muscle structure and anabolic signaling, (11), (12) others, particularly inflammatory cytokines and metabolic regulators, contribute to sarcopenia in a variety of clinical settings, including chronic disease and metabolic disorders like T2D. Myostatin is a potential biomarker of sarcopenia (13), as it regulates transcription factors such as MEF2 and MyoD, consequently impairing myoblast proliferation and differentiation. Testosterone plays a crucial role in regulating muscle mass and strength, and its decline is closely linked to reductions in both muscle size and functional capacity (14). Skeletal muscle loss associated with inflammatory conditions is also correlated with elevated levels of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and interferon-gamma (IFN-γ) (15), which intensify protein breakdown and suppress protein synthesis in skeletal muscle, thereby promoting sarcopenia. Environmental and epigenetic factors significantly influence this progression. For example, diet and physical activity can significantly modulate the pace of sarcopenia (16). Both dietary restriction and exercise significantly attenuate aging-related changes in muscle tissue, potentially through the regulation of key molecules such as sirtuin 1 (SIRT1) (17).

Several chronic conditions such as chronic obstructive pulmonary disease (COPD), diabetes, chronic kidney disease, and chronic liver disease accelerate the progression of sarcopenia (**Fig. 1**) (18). COPD is associated with a gradual decline in muscle mass and function, compounded by systemic inflammation, which promotes sarcopenia. T2D, characterized by insulin resistance, chronic inflammation, accumulation of advanced glycation end products (AGEs), and increased oxidative stress, impairs skeletal muscle mass, strength, and function, thereby contributing to sarcopenia. Liver disease significantly disrupts the equilibrium between protein synthesis and proteolysis required to maintain muscle mass. Consequently, sarcopenia is highly prevalent among

liver transplant recipients and may persist even after successful transplantation (19). The coexistence of sarcopenia and osteoporosis has prompted some researchers to propose "osteosarcopenia" as a single disease entity (12). Molecular crosstalk among the muscle secretome, bone-derived cytokines, and adipokines further exacerbates muscle degradation, particularly in the case of obesity, where intramuscular lipid accumulation drives mitochondrial dysfunction and inflammatory responses (13).

Age-related alterations in the neuromuscular junction precede noticeable muscle loss and involve both structural changes and functional decline in motor neurons and muscle fibers (14, 20). Mitochondrial dysfunction and increased oxidative stress further impair the integrity of neuromuscular junction (NMJ), disrupting neurotransmission and compromising muscle performance (15). In addition, altered innervation of muscle fibers and motor units, together with chronic inflammation, are major contributors to the development of sarcopenia (16). Aging induces extensive remodeling of the NMJ, ultimately resulting in reduced motor unit activation (18). The accumulation of reactive oxygen species adversely affects motoneuron structure and promotes NMJ fragmentation (21). Aberrant neural activity and reduced central motor drive in aging may also compromise NMJ function (22). Overall, sarcopenia arises from a complex interplay of various mechanisms with varying timelines and etiologies across the human lifespan.

3. Association between sarcopenia and T2D

The association between sarcopenia and T2D is increasingly being recognized as a bidirectional and interdependent relationship, wherein each condition contributes to the onset and progression of the other (23). Moreover, lifestyle factors also play a critical role in linking sarcopenia and T2D. Physical inactivity and sedentary behavior contribute to both muscle atrophy and reduced insulin

sensitivity, while inadequate dietary intake, particularly insufficient protein consumption, impairs muscle protein synthesis and accelerates muscle loss.

Recent evidence indicates that sarcopenia is not exclusively an age-related condition but can also occur at any stage of life in the presence of chronic diseases, a condition often referred to as secondary sarcopenia. The chronic disorders such as T2D, chronic kidney disease, cancer, and inflammatory diseases can accelerate muscle loss through mechanisms similar to those observed in primary age-related sarcopenia. These include persistent insulin resistance, systemic inflammation, oxidative stress, mitochondrial dysfunction, and activation of proteolytic pathways, all of which disrupt the balance between muscle protein synthesis and degradation. In particular, metabolic diseases such as T2D promote early onset of muscle impairment by altering glucose homeostasis and anabolic signaling pathways.

Skeletal muscle is the principal site of insulin-mediated glucose disposal, accounting for approximately 70–80% of postprandial glucose uptake (24). Consequently, reductions in muscle mass and quality have a direct and profound impact on glucose homeostasis and insulin sensitivity. Epidemiological studies indicate that individuals with T2D have a significantly higher prevalence of sarcopenia, with older adults exhibiting approximately a 1.5-fold increased risk compared with non-diabetic populations(25) (26). Conversely, sarcopenia itself predisposes individuals to the development of T2D. Loss of muscle mass reduces the body's capacity for glucose uptake and utilization, leading to impaired glucose tolerance and increased insulin resistance. Longitudinal cohort studies further support this association; for example, individuals in the lowest tertile of muscle mass index have been reported to exhibit up to two-fold higher risk of incident T2D than those in the highest tertile. These findings underscore the role of skeletal muscle not only as a target of metabolic dysfunction but also as a determinant of systemic metabolic health.

This bidirectional relationship poses significant challenges for the diagnosis, management, and overall understanding of both conditions. Glucose fluctuation, a hallmark of T2D, contributes to the development and progression of sarcopenia (27). These fluctuations induce endothelial dysfunction and chronic inflammation, impair muscle growth, and promote protein degradation (27). The accumulation of advanced glycation end products exacerbates muscle deterioration by promoting protein crosslinking, stiffness, and reduced contractility (28). Fluctuating hyperglycemia exacerbates pancreatic β-cell damage and apoptosis, thereby reducing the secretion of insulin and insulin-like growth factor-1, both of which are crucial for muscle health. Although hyperglycemia and glycemic variability are key clinical features of T2D and are associated with adverse effects on muscle health, these factors are considered part of the broader metabolic disturbances, discussed in subsequent sections. Similarly, increased inflammatory markers within skeletal muscle further contribute to apoptosis and structural damage in patients with poorly controlled glycemia (27).

Sarcopenia exacerbates the risk and severity of T2D. Muscle loss and dysfunction impair glucose metabolism, leading to insulin resistance and elevated insulin levels (29, 30). Sarcopenia and T2D are strongly correlated, with affected individuals exhibiting impaired glucose tolerance and increased T2D risk (31). In a cohort study of 6,895 adults (mean age: 52), those in the lowest third for muscle mass index had a two-fold increased risk of developing T2D compared with those in the highest muscle mass group. The prevalence of sarcopenia among older patients with T2D is significantly higher than that in nondiabetic individuals, underscoring the reciprocal relationship between these conditions (29, 30). This bidirectional association (32) contributes to functional decline, disability (33), and increased mortality (34). However, studies involving older patients with T2D and sarcopenia remain limited. Aging, a major risk factor for both conditions (35), is

characterized by progressive reductions in skeletal muscle mass and functional capacity (36), beginning around the age of 30 years and potentially resulting in a 30–50% loss by 80 years (36). Aging also reduces glucose utilization, thereby increasing T2D susceptibility. It disrupts the balance between muscle protein synthesis and degradation (37), resulting in net muscle loss. In addition, aging is associated with microstructural alterations, including shrinkage and a decline in the number of muscle fibers, particularly type II fibers (38). Such age-related muscle loss exacerbates glucose metabolism disorders (38). Aging is accompanied by changes in body fat distribution, shifting from subcutaneous to visceral fat deposition, including fat accumulation within skeletal muscle (39). Patients with diabetes often exhibit increased intramuscular fat stores, which contribute to sarcopenia and insulin resistance (40). Moreover, aging is associated with increased inflammation and oxidative stress, which are significant factors in the pathogenesis of diabetes and sarcopenia (41). Hormonal changes, such as decreased testosterone levels (2, 42), further accelerate muscle deterioration, particularly in diabetic males. Reduced energy intake and sedentary behavior in older adults also contribute to muscle loss and decreased insulin sensitivity (43). Vitamin D deficiency is another factor that mediates the development of both insulin resistance and sarcopenia (44). Conversely, cigarette smoking amplifies the risk of T2D and sarcopenia by adversely affecting body composition, insulin sensitivity, and skeletal muscle function (45).

4. Metabolic, pathophysiological, and nutritional perspectives

The systemic metabolic and pathophysiological alterations that link sarcopenia and T2D, including insulin resistance, chronic inflammation, oxidative stress, and nutritional factors, function as key drivers of disease progression (**Fig. 2**).

4.1. Insulin resistance

Insulin resistance is a central feature in the development of both sarcopenia and T2D (46). It arises from impairments in insulin signaling pathways, particularly disruption of glucose transporter type 4 translocation, which is essential for glucose uptake in skeletal muscle and adipose tissue (47). Impaired signaling reduces glucose absorption and hampers glycogen synthesis in muscle cells (47, 48), thereby compromising energy supply to muscles and increasing susceptibility to protein degradation during periods of increased energy demand (47, 48).

Insulin resistance exacerbates muscle wasting in individuals with sarcopenia or T2D (49), primarily by enhancing protein degradation and reducing protein synthesis in muscle tissue (49, 50). Several proteolytic pathways contribute to this process, including the ubiquitin-proteasome system, lysosomal autophagy, caspase-mediated hydrolysis, and calcium-dependent calpain activation (51, 52). Moreover, the metabolic disturbances associated with insulin resistance induce hyperglycemia, further aggravating muscle atrophy through multiple mechanisms. For example, hyperglycemia-induced downregulation of the E3 ubiquitin ligase WW domain-containing protein 1 (WWP1) decreases ubiquitin-dependent degradation of KLF15, a muscle-wasting–related transcription factor, thereby elevating KLF15 levels and promoting muscle loss (52, 53).

Insulin resistance disrupts key signaling pathways essential for muscle protein synthesis, particularly the IGF1–PI3K–Akt–mTOR axis (49, 54), leading to reduced protein synthesis, increased protein breakdown and consequent loss of muscle mass. It also promotes ectopic fat deposition, particularly within skeletal muscle, that aggravates inflammation and metabolic dysfunction. The accumulation of intramuscular fat stimulates the release of proinflammatory

cytokines and free fatty acids, impairing myogenesis and accelerating muscle degradation, thereby worsening the complications of both sarcopenia and T2D (55).

4.2. Inflammation

Chronic low-grade inflammation in T2D disrupts both glucose regulation and muscle homeostasis (56). It suppresses protein synthesis by inhibiting the phosphoinositide 3-kinase –Akt pathway and enhances protein degradation by activating the ubiquitin–proteasome pathway through FoxO transcription factors and downstream E3 ubiquitin ligases (57). Proinflammatory cytokines, such as TNF-α, IL-6, IL-1, and various chemokines, contribute to this process by promoting immune cell infiltration and muscle breakdown via nuclear factor-kappa B signaling (57).

Inflammatory markers particularly IL-6, TNF-α, and C-reactive protein levels are commonly elevated in individuals with T2D and are closely linked to insulin resistance (58). Increased levels of these mediators negatively impact muscle mass and function (59). For example, IL-6 promotes muscle catabolism; experimental administration of low-dose IL-6 into mouse muscle induces muscle atrophy (60, 61). In older adults with T2D, accelerated loss of leg muscle mass and strength has been reported, with IL-6 and TNF-α identified as contributory factors (62). IL-6 influences muscle both directly and indirectly, including through effects on neurons and blood vessels. Chronic elevation of IL-6 maintains phosphorylation of STAT3, triggering muscle protein degradation via the Janus kinase/signal transducers and activators of transcription (JAK/STAT) and nuclear factor kappa B (NF-κB) pathways (63). Furthermore, IL-6–initiated inflammatory cascade activates additional cytokines, such as TNF and IL-1, through NF-κB, forkhead box O4 (FOXO4), and related signaling networks, further exacerbating muscle atrophy (49, 64). Despite its anti-inflammatory characteristics, IL-10 inhibits mTOR signaling and induces mitophagy,

which may contribute to muscle atrophy. However, the precise molecular mechanisms by which C-reactive protein (CRP) impairs muscle tissue remain unclear (61). Indeed, the inflammatory milieu in T2D disrupts muscle homeostasis, promoting muscle loss and weakness, with IL-6 playing a significant role.

4.3. Oxidative stress and AGEs

T2D is characterized by increased oxidative stress, a condition in which reactive oxygen species (ROS) overwhelm the body's antioxidant defenses (65). Oxidative stress is a major contributor to the onset and progression of myopathy in individuals with T2D (46, 51). Multiple factors, including lipid metabolism disorders, insulin resistance, accumulation of AGEs, and mitochondrial dysfunction, contribute to this imbalance (46, 51).

In T2D, hyperglycemia triggers the overproduction of superoxide anions through various mechanisms, including upregulation of specific genes associated with muscle damage (50). Hyperglycemia-induced oxidative stress leads to muscle damage and exacerbates mitochondrial dysfunction. Patients with T2D exhibit impaired mitochondrial function, evidenced by a longer recovery half-life of phosphocreatine after exercise and reduced mitochondrial density in first-degree relatives of patients with T2D (50). AGEs are generated via non-enzymatic reactions between glucose and proteins, lipids, or nucleic acids, and their accumulation further contributes to oxidative stress and muscle dysfunction (65). The precise mechanisms underlying AGE-induced muscle disorders remain unclear; however, they might increase the crosslinking of proteins, impair muscle contractility, and promote inflammation.

4.4. Nutritional perspective

The association between anthropometric measurements, recorded using nutritional assessment tools including the Subjective Global Assessment (SGA), European Society for Clinical Nutrition and Metabolism (ESPEN) criteria, and Global Leadership Initiative on Malnutrition (GLIM) framework, and sarcopenia has been examined in older patients with T2D (66). These studies also evaluated the predictive accuracy of these indicators for identifying sarcopenia. The findings demonstrated that malnutrition, defined by the SGA, ESPEN, and GLIM criteria, and adductor pollicis muscle thickness (APMT) below the fifth percentile were significantly associated with sarcopenia. Notably, overweight patients exhibited a lower risk of sarcopenia (67). The study underscored the importance of comprehensive assessment in hospital settings to avoid misclassification of nutritional status in older patients with T2D. Despite a significant proportion of overweight patients and those with good nutritional status according to body mass index and SGA, respectively, a notable percentage developed sarcopenia, reflecting the challenge of sarcopenic obesity (66). Anthropometric indicators such as mid-upper arm circumference and APMT were inversely associated with sarcopenia (68). However, after statistical adjustments, the association with mid-upper arm muscle circumference lost statistical significance. Malnutrition assessed using the GLIM criteria substantially increased sarcopenia risk, while the combination of SGA and APMT below the fifth percentile remained strongly associated with sarcopenia, even after adjustments (66).

Supplementation with amino acids, particularly β-hydroxy-β-methyl butyrate, leucine, glutamine, and arginine, improves muscle strength and mass in older individuals with sarcopenia, potentially reducing T2D risk (69). Plant-based proteins may be preferable for older adults with or at risk of T2D. In addition, branched-chain amino acids such as leucine, as well as nutrients such as omega-3 fatty acids and vitamin D, can help prevent muscle mass loss and improve metabolic health (70).

However, further research is needed to establish optimal doses and combinations of these nutrients for effective management of sarcopenia and T2D (**Fig. 3**).

4.5. Sarcopenic obesity

Sarcopenic obesity refers to the simultaneous presence of diminished skeletal muscle mass and function alongside excess adiposity, forming a distinct metabolic condition that combines features of both sarcopenia and obesity (71-73). It is increasingly observed in individuals with T2D and is linked to more severe metabolic disturbances than either condition alone. The underlying mechanisms are multifactorial, with visceral and intramuscular fat playing a central role by releasing free fatty acids and lipid intermediates that induce lipotoxicity and impair insulin signaling, particularly along the IRS–PI3K–Akt pathway. This disruption reduces glucose uptake and weakens anabolic processes in the muscle (74-76). At the same time, adipose tissue acts as an endocrine organ, producing proinflammatory cytokines such as TNF-α and IL-6, along with dysregulated adipokines that together promote chronic inflammation, inhibit protein synthesis, and accelerate muscle breakdown. Mitochondrial dysfunction and oxidative stress further worsen this imbalance by limiting energy production and increasing ROS, leading to cellular damage and heightened insulin resistance. These effects are compounded by reduced physical activity and anabolic resistance, which together drive a cycle of progressive muscle loss and fat accumulation. Clinically, sarcopenic obesity is associated with poor glycemic control, increased cardiovascular risk, reduced physical function, and increased mortality. Standard measures such as body mass index may fail to detect this condition, underscoring the importance of comprehensive assessments that account for both muscle mass and body composition (77-80).

5. Cellular and molecular mechanisms underlying sarcopenia and T2D

Sarcopenia and T2D arise from interconnected mechanisms involving impaired protein homeostasis, chronic inflammation, mitochondrial dysfunction, and disrupted insulin signaling (**Fig. 4**) (51). At the cellular level, sarcopenia is characterized by an imbalance between muscle protein synthesis and degradation (18). The age-related changes, such as reduced satellite cell activity and decreased anabolic hormone production, further impair muscle regeneration and repair (65, 81). Concurrently, elevated pro-inflammatory cytokines, including TNF-α and IL-6, enhance proteolysis and inhibit myogenesis, accelerating muscle loss (82). In T2D, insulin resistance impairs glucose uptake in skeletal muscle primarily through disruption of the PI3K/Akt signaling pathway, leading to defective glucose transporter type 4 (GLUT4) translocation to the plasma membrane (82), (83). This results in reduced glucose utilization and persistent hyperglycemia. Chronic hyperglycemia promotes the accumulation of reactive oxygen species and advanced glycation end products, which exacerbate oxidative stress and cellular damage in muscle tissue (83). Mitochondrial dysfunction further aggravates this condition by impairing adenosine triphosphate (ATP) production and increasing oxidative damage.

Insulin signaling plays a central role in maintaining muscle mass by stimulating protein synthesis and inhibiting degradation via the mechanistic target of rapamycin complex 1 pathway (84, 85). However, insulin resistance suppresses these anabolic effects, contributing to muscle wasting. Additionally, activation of stress-related pathways such as c-Jun N-terminal kinase and NF-κB amplifies inflammation and insulin resistance, thereby linking metabolic and degenerative processes in both sarcopenia and T2D (84).

5.1. GLUT4 pathway and glucose–WWP1 interaction

Impaired glucose uptake is a key feature of insulin resistance in sarcopenia and T2D (86) (**Fig. 5)**. The skeletal muscle, the primary site of glucose disposal, depends on insulin-mediated activation of the IRS–PI3K–Akt pathway for GLUT4 translocation (49, 87). In sarcopenic muscle, reduced insulin receptor activity and impaired IRS phosphorylation weaken this signaling cascade, resulting in decreased GLUT4 translocation and diminished glucose uptake (49, 84). Consequently, defective glucose metabolism contributes to energy deficiency and muscle degeneration (49).

Hyperglycemia further activates the glucose–WWP1 signaling axis, linking metabolic dysfunction to protein degradation (52, 88). The increased flux through the hexosamine biosynthetic pathway elevates UDP-N-acetylglucosamine (UDP-GlcNAc) levels, thereby enhancing glycosylation and stabilizing WWP1. Elevated WWP1 level promotes ubiquitination and degradation of key proteins, including IRS-1, thereby impairing insulin signaling and exacerbating insulin resistance (84, 88). In addition, WWP1 targets myogenic regulatory factors such as MyoD and myogenin, suppressing muscle regeneration, and negatively regulates the Akt/mTOR pathway, further inhibiting protein synthesis (49, 84), (89). These combined effects accelerate muscle wasting in sarcopenia and T2D.

5.2. Myostatin-mediated regulation

Myostatin, a negative regulator of muscle growth, plays a critical role in sarcopenia progression (13), (90). The binding of myostatin to the activin type II receptor activates Smad2/3 signaling, which suppresses protein synthesis and enhances proteolysis through activation of muscle-specific E3 ubiquitin ligases (91). Beyond its direct catabolic effects, myostatin promotes inflammation and oxidative stress by increasing the production of cytokines such as TNF-α and IL-6 and

inducing ROS generation (92, 93), (94, 95). It also impairs mitochondrial biogenesis by downregulating PGC-1α and inhibits satellite cell proliferation through upregulation of cell cycle inhibitors (p21 and p27), thereby limiting muscle regeneration (96), (97). Furthermore, suppression of myogenic regulatory factors, including MyoD and myogenin, contributes to reduced regenerative capacity (98). Genetic and epigenetic modifications, such as polymorphisms, DNA methylation, and histone acetylation, further regulate myostatin expression and influence susceptibility to sarcopenia (99).

5.3. Ubiquitin-proteasome pathway

The ubiquitin–proteasome pathway (UPP) is the primary system responsible for protein degradation in skeletal muscle and plays a central role in sarcopenia [90]. This system involves sequential enzymatic actions of E1, E2, and E3 enzymes that tag proteins with ubiquitin for degradation by the 26S proteasome. Dysregulation of this pathway disrupts protein turnover, favoring degradation over synthesis (100). The key E3 ubiquitin ligases, including MuRF1 and Atrogin-1, are markedly upregulated in muscle atrophy conditions (100). MuRF1 targets structural proteins such as myosin heavy chain and troponin, while Atrogin-1 promotes degradation of proteins involved in muscle growth and regeneration, including MyoD and eIF3f (100), (101). In addition to enhanced ubiquitination, proteasome dysfunction contributes to sarcopenia. Alterations in proteasome composition and reduced expression of subunits such as PSMA7 and PSMB5 impair proteolytic efficiency, leading to accumulation of damaged proteins (102). The oxidative modifications, including carbonylation, nitration, and glycation, further compromise proteasome activity and exacerbate muscle degeneration (103).

6. Clinical perspectives on sarcopenia in T2DM

The clinical manifestations of sarcopenia in T2D present significant challenges. Sarcopenia often coexists with T2D, and their interaction contributes to a wide range of clinical complications (51). One of the primary manifestations is muscle weakness and functional decline. Sarcopenia-related muscle wasting impairs physical performance and functional capacity, leading to difficulties in daily activities, such as walking, stair climbing, and lifting objects (51, 104). Individuals with both conditions often experience decreased muscle strength, particularly in the lower extremities, compromising mobility and increasing the risk of falls and fractures. These impairments significantly affect independence and autonomy, often resulting in increased healthcare utilization and costs.

Impaired glucose regulation and metabolic dysfunction are additional complications of sarcopenia in T2D (105). Muscle wasting and insulin resistance exacerbate metabolic dysregulation by impairing glucose metabolism in skeletal muscle, promoting hyperglycemia, glucose intolerance, and disease progression (24, 82). Furthermore, sarcopenia-related changes in muscle composition increase intramuscular fat accumulation, and reduced oxidative capacity worsen metabolic dysfunction and insulin resistance, thereby accelerating T2D–related complications.

The cardiovascular complications and mortality risk are elevated in individuals with sarcopenia and T2D owing to the combined effects of muscle wasting, insulin resistance, and metabolic dysfunction on cardiovascular health (106). Muscle loss in sarcopenia is associated with an increased prevalence of cardiovascular risk factors, including hypertension, dyslipidemia, and endothelial dysfunction, which contribute to atherosclerosis, coronary artery disease, and myocardial infarction (107). Furthermore, sarcopenia-related inflammation, oxidative stress, and insulin resistance promote vascular inflammation, endothelial dysfunction, and thrombotic events,

further compounding cardiovascular complications in T2D (108). Frailty and functional decline resulting from sarcopenia are also independent predictors of mortality in older adults with T2D, underscoring the importance of early detection and management of sarcopenia to improve clinical outcomes and extend survival in this population.

6.1. Diagnostic approaches for assessment of sarcopenia in T2D

A comprehensive assessment of sarcopenia in T2D requires a multidimensional approach that integrates clinical evaluation, functional assessment, imaging techniques, and biomarker measurements (109) (Table 2). Clinical evaluation and physical examination form the cornerstone of diagnosis, while functional assessments are essential for evaluating muscle strength and function in individuals with T2D (110). Standardized tests such as handgrip strength, chair stand test, and timed up-and-go test are widely used to measure muscle strength, power, and overall functional capacity. These assessments also facilitate longitudinal monitoring of muscle function and assessment of intervention effectiveness in patients with T2D. Imaging modalities such as dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging, and computed tomography provide accurate measurements of muscle mass and composition, offering further insights into muscle status in the context of T2D and sarcopenia (111). DEXA scanning allows for the measurement of lean body mass and fat mass, enabling detection of changes in muscle mass and adiposity associated with aging and metabolic disorders (112). MRI and CT imaging enable detailed assessments of muscle quality, including muscle density, intramuscular fat infiltration, and muscle fiber composition (113).

In recent years, omics studies have focused on biomarker discovery to improve the diagnosis and management of sarcopenia in T2D (114). Serum biomarkers such as creatine kinase, lactate

dehydrogenase, and myostatin may reflect muscle damage, inflammation, and impaired regeneration in sarcopenia. Circulating inflammatory markers, such as CRP, IL-6, and TNF-α, provide further insights into the inflammatory status and metabolic dysregulation associated with sarcopenia and T2D (114). Moreover, nutritional assessments, including serum albumin, prealbumin, and vitamin D levels, are essential for identifying malnutrition and micronutrient deficiencies that contribute to muscle wasting and functional decline in individuals with T2D.

6.2. Therapeutic approaches for sarcopenia in T2D

The therapeutic approaches, including antidiabetic medications and anabolic agents, offer promising strategies for managing sarcopenia in T2D by improving muscle health, metabolic function, and overall well-being (115). Antidiabetic drugs such as metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium–glucose cotransporter-2 (SGLT-2) inhibitors not only improve glycemic control but also exert favorable effects on muscle metabolism and function in individuals with T2D-related sarcopenia (116). In addition, anabolic agents, including selective androgen receptor modulators (SARMs), growth hormone secretagogues, and myostatin inhibitors, enhance muscle growth and function by modulating critical pathways involved in protein synthesis and regeneration (104, 117). Nutritional supplements and dietary interventions may complement pharmacological therapy by providing essential nutrients and promoting muscle preservation in individuals with sarcopenia and T2D.

Antidiabetic medications are central to the management of T2D and may also contribute to the preservation of muscle mass and function in individuals with sarcopenia. Oral antidiabetic agents such as metformin, sulfonylureas, and thiazolidinediones help regulate blood glucose levels by suppressing hepatic glucose production, improving insulin sensitivity, and enhancing glucose

uptake in peripheral tissues, including skeletal muscle (117). Metformin, the first-line therapy for T2D, supports muscle health by activating AMP-activated protein kinase, a key regulator of energy metabolism and mitochondrial function in skeletal muscle (118). This activation promotes mitochondrial biogenesis, oxidative metabolism, and muscle glucose uptake, thereby improving muscle function and insulin sensitivity in T2D and sarcopenia.

Emerging classes of antidiabetic medications, such as GLP-1 RAs and SGLT-2 inhibitors, present promising therapeutic strategies for addressing sarcopenia in individuals with T2D (119). GLP-1 RAs, including liraglutide and semaglutide, exert pleiotropic benefits on muscle health by stimulating muscle protein synthesis, inhibiting muscle protein degradation, and improving mitochondrial function within skeletal muscle. In addition, they improve glycemic control, reduce body weight, and mitigate cardiovascular risk factors, making them attractive agents for managing sarcopenia in T2D (119). Similarly, SGLT-2 inhibitors, such as empagliflozin and dapagliflozin, promote muscle glucose uptake, reduce intramuscular fat deposition, and enhance muscle function (119). Beyond their metabolic effects, SGLT-2 inhibitors exert cardioprotective effects, reduce heart failure risk, and improve exercise capacity, further enhancing their utility in managing T2D-related sarcopenia.

Anabolic agents represent a promising pharmacological approach for promoting muscle growth and function in sarcopenia (120). These agents, including selective SARMs, growth hormone secretagogues, and myostatin inhibitors, enhance muscle hypertrophy by targeting critical pathways involved in muscle protein synthesis, satellite cell proliferation, and muscle regeneration. SARMs, such as enobosarm and RAD140, selectively bind to androgen receptors in skeletal muscle and bone, resulting in increased lean body mass, improved muscle strength, and enhanced physical performance (121).

6.3. Therapeutic strategies

Elucidating the molecular mechanisms underlying sarcopenia offers critical insights for developing targeted therapeutic strategies. Interventions that modulate the IGF-1/PI3K/Akt/mTOR signaling pathway, such as myostatin inhibitors, SARMs, and growth hormone secretagogues hold promise for promoting muscle growth and mitigating muscle wasting (104, 115-118, 122). Furthermore, anti-inflammatory agents, antioxidants, and mitochondria-targeted therapies may counteract the chronic inflammation, oxidative stress, and mitochondrial dysfunction that drive the progression of sarcopenia.

Myostatin is a promising target for drug development in sarcopenia (90). Inhibition of myostatin activity can increase muscle mass by promoting muscle fiber hypertrophy and reducing protein breakdown. Several approaches are being explored, including monoclonal antibodies, soluble receptor forms, and small molecules that disrupt myostatin signaling. Monoclonal antibodies, such as bimagrumab and domagrozumab, have shown promising results in clinical trials, increasing lean body mass and improving muscle strength in older adults with sarcopenia (123). These antibodies bind to myostatin, preventing receptor interaction and thereby promoting muscle growth. Similarly, soluble forms of the myostatin receptor, such as ACE-031, have shown potential in preclinical studies by sequestering circulating myostatin and blocking its binding to muscle cells (124).

Small molecules that target myostatin pathways, such as activin receptor antagonists and follistatin analogs, are also being explored (124). These compounds modulate the activity of myostatin and related proteins, promoting muscle growth and function. Early findings are promising; however,

further research is needed to establish the long-term safety and efficacy of myostatin inhibitors in sarcopenia treatment.

6.4. Role antidiabetic drugs in sarcopenia

Given the high prevalence and significant adverse effects of sarcopenia in individuals with diabetes, optimizing muscle quality and function is essential in clinical management. Beyond underlying pathophysiological mechanisms, increasing attention has been directed toward the effects of commonly prescribed antidiabetic agents on skeletal muscle, as patients are being exposed to these drugs daily. Notably, sulfonylureas and glinides have been reported to negatively impact muscle health and should be avoided in patients with diabetes who also have sarcopenia.

Several classes of antidiabetic drugs are being investigated for their potential to counteract sarcopenia and promote muscle health (125). Metformin has shown promise owing to its anti-inflammatory and insulin-sensitizing properties. By improving insulin sensitivity and reducing chronic inflammation, it may help preserve muscle mass and function in individuals at risk of sarcopenia, however, the study revealed that metformin does not improve physical performance in older adults with probable sarcopenia and frailty, thus, alternative interventions for maintaining mobility and function in this vulnerable population need to be explored (126). Thiazolidinediones also exert insulin-sensitizing effects that could theoretically support muscle health. GLP-1 RAs might indirectly benefit muscle mass by reducing inflammation and enhancing overall metabolic health. DPP-4 inhibitors, which increase incretin hormone levels, have favorable effects on muscle metabolism and may help preserve muscle tissue. Insulin therapy remains a cornerstone of diabetes management owing to its potent effects on glycemic control. Beyond blood sugar regulation, insulin significantly stimulates muscle protein synthesis. In a study on Japanese patients, insulin

therapy attenuated the decline in lower extremity muscle strength; however, no effect was observed in the upper extremities, supporting its clinical use to reduce sarcopenia risk in patients with T2D (127). Sulfonylureas and glinides, which stimulate insulin secretion by inhibiting ATP-sensitive potassium channels, have been associated with adverse effects on skeletal muscle mass and function. While insulin therapy may help preserve muscle mass, it does not consistently improve muscle function (128). Future clinical trials should prioritize the development of standardized methods and indices for evaluating sarcopenia. In clinical practice, muscle quality assessments should be integrated with glycemic control, particularly in patients who experience significant weight loss following pharmacological interventions. Incorporating these proactive strategies into routine care may help mitigate sarcopenia risk and contribute to the establishment of robust datasets for future research.

7. Conclusions and future prospects

The complex interplay between sarcopenia and T2D underscores the need for integrated management strategies that simultaneously address both conditions. This review highlights that the progressive decline in skeletal muscle mass and function associated with sarcopenia exacerbates the risk and severity of T2D. Central metabolic pathways, including insulin resistance, chronic inflammation, oxidative stress, and accumulation of AGEs, form the basis of this bidirectional relationship. These processes impair glucose homeostasis while accelerating muscle degradation and functional decline. From a clinical perspective, early recognition and management of sarcopenia in patients with T2D are critical to improving therapeutic outcomes. Interventions aimed at preserving muscle mass and function such as resistance exercise, sufficient protein intake, optimized nutrition, and appropriate pharmacological agents are essential. These measures not

only combat sarcopenia but also improve glycemic control and slow T2D progression. In summary, a holistic, multidisciplinary approach that integrates metabolic regulation, nutritional support, and structured physical activity is fundamental to addressing the dual burden of sarcopenia and T2D. Future research should focus on further elucidating the molecular mechanisms linking these conditions and on evaluating targeted interventions to enhance clinical care and quality of life in affected individuals.

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Competing interests

The authors declare that they have no competing interests.

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Figure legends

Fig. 1. Factors contributing to sarcopenia: an overview of neuromuscular impairment and age-related influences

Several diseases, such as COPD, diabetes, chronic kidney disease, and chronic liver disease, exacerbate sarcopenia. COPD, chronic obstructive pulmonary disease; neuromuscular junction

Fig. 2. Systems overview of metabolic, inflammatory, and nutritional factors in sarcopenia–T2D interaction

This schematic illustrates the bidirectional relationship between sarcopenia and T2D, highlighting key contributing factors including insulin resistance, chronic inflammation, oxidative stress, and nutritional imbalance. Impaired insulin signaling and reduced GLUT4 translocation lead to decreased glucose uptake and enhanced muscle protein degradation, while proinflammatory cytokines (e.g., IL-6, TNF-α) further accelerate muscle catabolism via NF-κB and STAT3 pathways. Hyperglycemia-induced oxidative stress and advanced glycation end products exacerbate mitochondrial dysfunction and structural muscle damage. In parallel, malnutrition, reduced protein intake, and vitamin D deficiency contribute to muscle loss and metabolic dysregulation. T2D, type 2 diabetes

Fig. 3. Metabolic and pathophysiological perspectives in the relationship between sarcopenia and T2D

This figure illustrates the metabolic and pathophysiological mechanisms underlying the intricate relationship between sarcopenia and T2D. It highlights multifaceted interactions between insulin resistance, inflammation, oxidative stress, advanced glycation end products (AGEs), and

nutritional factors in the development and progression of sarcopenia in individuals with T2D. It also depicts the cellular and molecular pathways implicated in sarcopenia–T2D comorbidity, including dysregulation of the GLUT4 pathway, altered myostatin regulation, and enhanced activity of the ubiquitin-proteasome pathway. T2D, type 2 diabetes

Fig. 4. Molecular mechanisms underlying sarcopenia and T2D

The overall schematic presentation illustrates the molecular mechanisms proposed to contribute to the association between sarcopenia and T2D. The central pathways involved include glucose metabolism and insulin resistance, which play critical roles in regulating protein synthesis and degradation in muscle tissues. The various signaling cascades are depicted, highlighting their regulatory effects on the intricate balance between the synthesis and degradation of muscle protein. T2D, type 2 diabetes

Fig. 5. Depiction of molecular interplay between impaired insulin signaling and WWP1-mediated ubiquitination in skeletal muscle

The disruption of the IRS-1/PI3K/Akt pathway limits GLUT4 translocation, while hyperglycemia-driven activation of WWP1 exacerbates insulin resistance and protein degradation, collectively contributing to muscle wasting in sarcopenia and T2D. T2D, type 2 diabetes; WWP1, WW domain-containing protein 1

Table 1. Genetic factors implicated in sarcopenia with functional relevance and aging association [129]

Gene category	Genes	Primary relevance	Functional role in sarcopenia	Ref
Structural and metabolic genes	*ACTN3*	Aging-related & general	Regulates muscle fiber composition and contractile performance	78, 130
	ACE	General	Influences muscle efficiency, vascular function, and physical performance	131-133
	APOE	Aging-related	Associated with lipid metabolism and age-related muscle degeneration	134-136
	CAV	General	Involved in membrane signaling and muscle cell integrity	137, 138
	CNTF	Aging-related	Supports neuromuscular function and motor neuron survival	139, 140
	MTHFR	General	Regulates homocysteine metabolism, affecting muscle function	141, 142

	NRF2	Aging-related	Controls oxidative stress response and antioxidant defense	143-145
Growth factor-related genes	Myostatin	General & aging-related	Negative regulator of muscle growth; promotes protein degradation	146-148
	IGF-1	Aging-related	Stimulates muscle protein synthesis and regeneration	78, 149, 150
Hormone-related genes	Testosterone	Aging-related	Regulates muscle mass, strength, and anabolic signaling	151, 152
	Thyroid hormones	General	Influence metabolic rate and muscle energy balance	153, 154
	Cortisol	General	Promotes protein catabolism and muscle breakdown	78, 155
	Leptin	General	Regulates energy balance and muscle metabolism	156, 157
	Adiponectin	General	Modulates insulin sensitivity and inflammation	158-160
	Irisin	Aging-related	Promotes muscle hypertrophy and metabolic regulation	161-163

	Vitamin D receptor	Aging-related	Regulates muscle function and calcium homeostasis	164-166
Inflammatory cytokine-related genes	Tumor necrosis factor-alpha	General & aging-related	Promotes inflammation-induced muscle catabolism	167-169
	Interleukin-1β	General	Contributes to inflammatory muscle degradation	170-172
	Interleukin-6	General & aging-related	Mediates chronic inflammation and muscle atrophy	173-175
	Interferon-gamma	General	Regulates immune-mediated muscle damage	176-178

Table 2. Diagnostic approaches for assessment of sarcopenia

Diagnostic Approach	**Parameter Measured**	**Methodology / Tool**	**Parameter / Metric**	**Clinical Relevance**	**Advantages / Limitations**
Muscle Mass Assessment	Skeletal muscle quantity	DXA	Appendicular lean mass (ALM), Lean Mass Index (LMI)	Detects muscle wasting, correlates with metabolic risk	High precision, low radiation; costly and limited availability

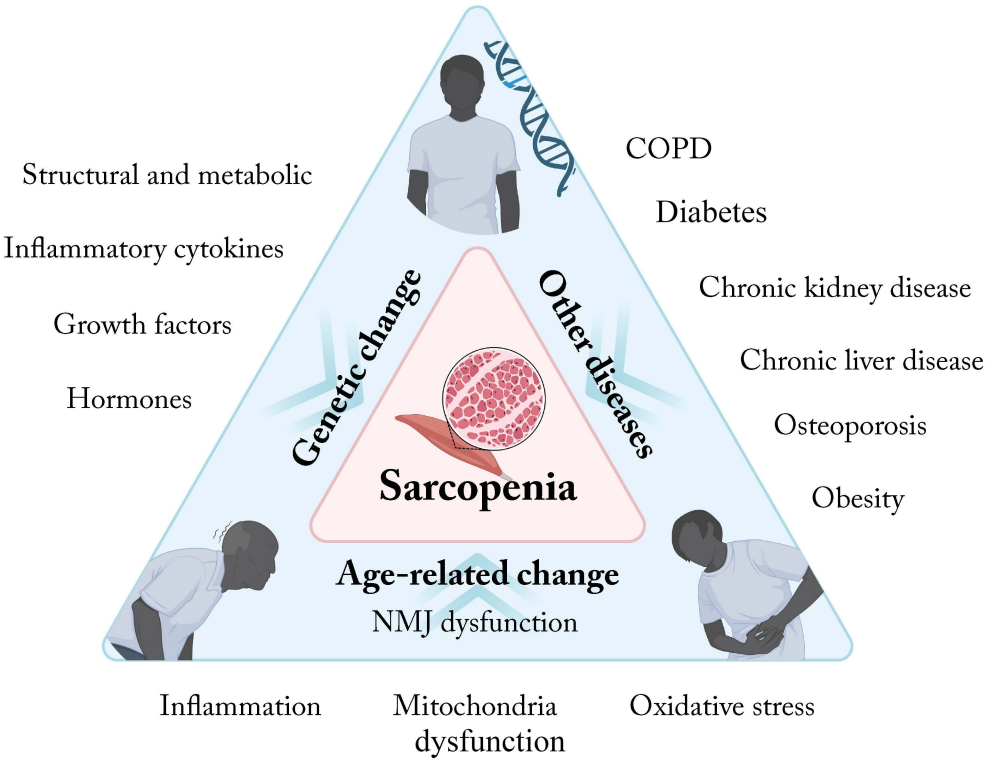
		BIA	Skeletal Muscle Mass Index (SMI), Phase Angle	Quick estimation of total body muscle; correlates with functional status	Portable, non-invasive; influenced by hydration and obesity
		CT / MRI	Cross-sectional muscle area, muscle volume, and intramuscular fat fraction	Quantitative evaluation of regional muscle mass and quality	Gold standard; expensive, radiation exposure (CT)
Muscle Strength Assessment	Grip strength	Hand dynamometer	Maximum voluntary contraction (MVC), peak force	Early marker of sarcopenia; predicts falls and disability	Simple, inexpensive; single-joint measure
	Knee extension strength	Isokinetic dynamometry	Peak torque, rate of force development	Predicts lower limb function and	Requires equipment; not

				mobility impairment	widely available
Physical Performance	Gait speed	4- or 6-meter walk test	Average walking speed (m/s), stride length	Correlates with functional limitation and fall risk	Quick, low-cost; influenced by comorbidities
	Short Physical Performance Battery (SPPB)	Chair stand, balance, gait speed	Composite score (0–12), chair rise time	Functional assessment of sarcopenia-related impairment	Comprehensive; requires training and time
	Timed Up and Go (TUG)	3-meter walk, sit-to-stand	Time to complete (s), gait initiation speed	Measures mobility and fall risk	Minimal equipment; may miss early sarcopenia
Muscle Quality Assessment	Muscle architecture	Ultrasound	Pennation angle, fascicle length, muscle thickness	Detects structural changes and intramuscular fat	Portable, radiation-free; operator-dependent

	Intramuscular fat	CT / MRI	Hounsfield units (HU), fat fraction	Predicts myosteatosis and functional decline	Accurate; expensive and less feasible for routine use
Biochemical / Molecular Markers	Myostatin / Follistatin ratio	ELISA	Serum concentration (ng/mL)	Regulates muscle protein synthesis; biomarker for early muscle loss	Non-invasive; limited routine availability
	Inflammatory markers	IL-6, TNF-α, CRP	Plasma/serum concentration (pg/mL or mg/L)	Chronic inflammation accelerates sarcopenia progression	Widely available; non-specific, must be interpreted with functional measures
	IGF-1 / Hormonal profile	Serum assays	Insulin-like growth factor-1 (IGF-1),	Reflects anabolic-catabolic balance in muscle	May guide therapeutic interventions; influenced by

testosterone, cortisol

systemic disease


Structural and metabolic
Inflammatory cytokines
Growth factors
Hormones
COPD
Diabetes
Chronic kidney disease
Chronic liver disease
Osteoporosis
Obesity
Genetic change
Other diseases
Sarcopenia
Age-related change
NMJ dysfunction
Inflammation
Mitochondria dysfunction
Oxidative stress

Insulin Resistance

↓ GLUT-4 Translocation
↓ Protein Synthesis
↑ Protein Degradation

Ectopic Fat

Ubiquitin-Proteasome

Autophagy

Lysosomal Pathway

Calcium-dependent Calpain

- **KLF15** ↑ (E3 Ubiquitin Ligase)
- Lysosomal Pathway
- Calcium-dependent Calpain
- **KLF15** ↑ (E3 Ubiquitin Ligase)

Inflammation

↑ IL-6, TNF-α, CRP
NF-κB Activation

- Increased Inflammator Markers
- Immune Cell Infiltration
- ↑ STAT3 Activation
- ↑ NF-kB Activation

- Increased Inflammator Markers
- ↑ STAT3 Activation
- ↑ NF-kB Activation
- ↑ Muscle Atrophy

Hyperglycemia

Sarcopenia

- Muscle Loss
- Frailty

Bidirectional Link

Type 2 Diabetes (T2D)

- Insulin Resistance
- ↑ Hyperglycemia

Oxidative Stress & AGEs

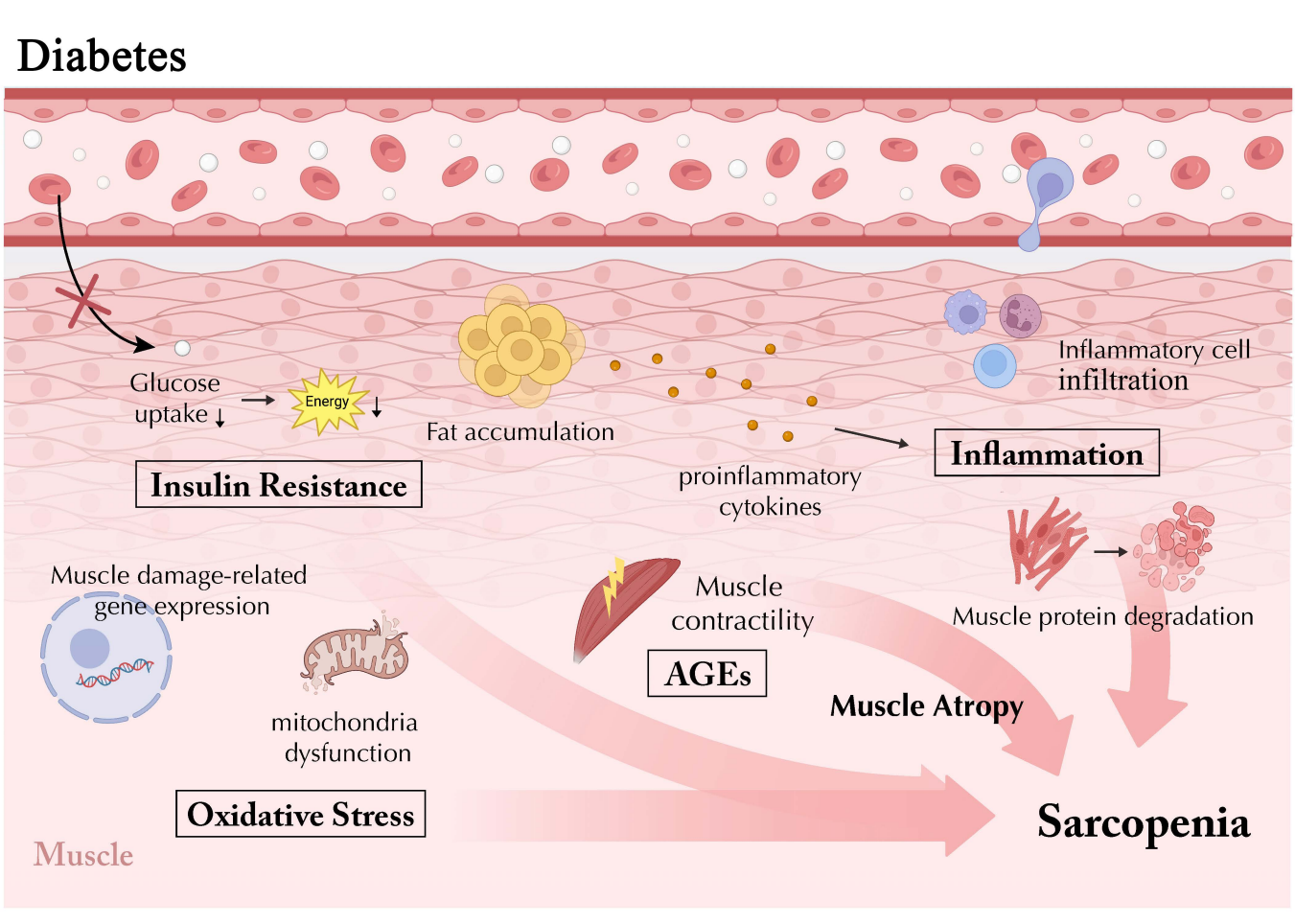
- Reactive Oxygen Species
- ↑ Nutrortnion of AGEs
- ↑ ROS Production
- ↑ Mitochondril/Dyfunction
- ↑ Protein Crosslinking

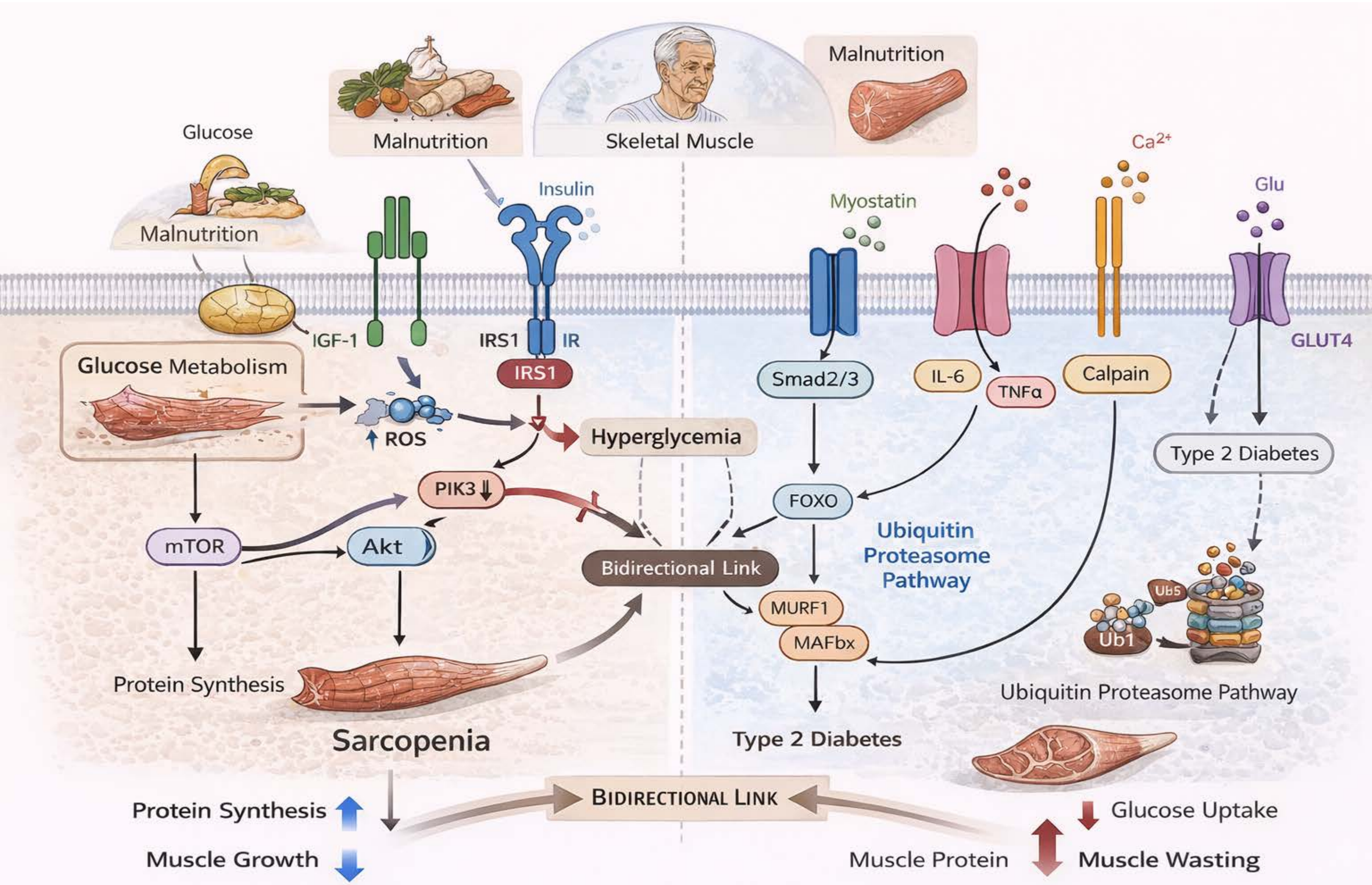
Bidirectional Link

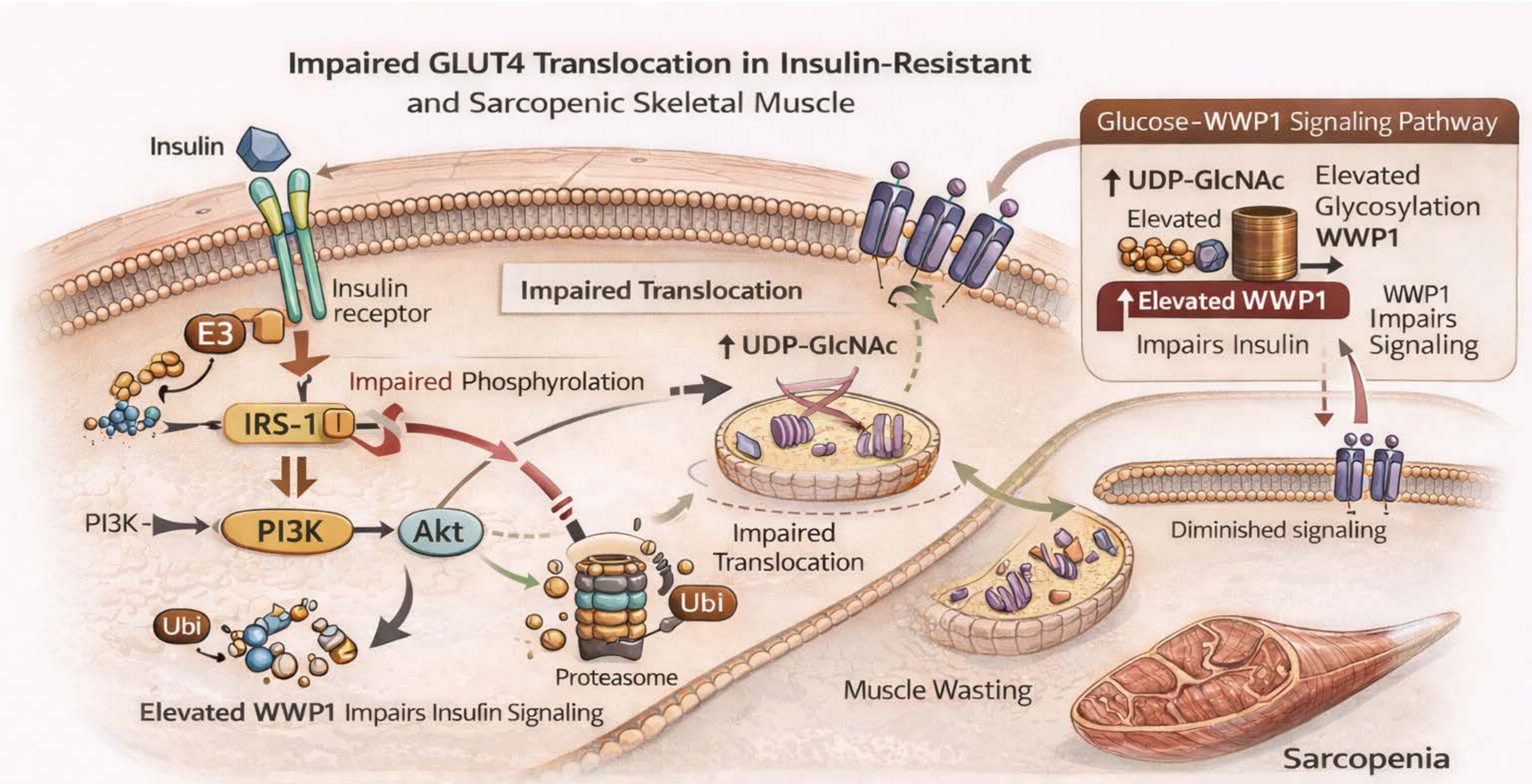
↑ Functional Decline
↑ Mortality

Nutritional Factors

- Malnutrition
- ↓ Muscle Mass Sarcopenic Obesity
- Unbalanced Diet
- ↓ Protein Intake
- ↑ Vitamin D Deficiency


Diabetes
Glucose uptake
Energy
Insulin Resistance
Fat accumulation
proinflammatory cytokines
Inflammation
Inflammatory cell infiltration
Muscle damage-related gene expression
mitochondria dysfunction
Oxidative Stress
Muscle contractility
AGEs
Muscle protein degradation
Muscle Atropy
Sarcopenia
Muscle


Malnutrition
Skeletal Muscle
Malnutrition
Glucose
Malnutrition
Insulin
Myostatin
Ca2+
Glu
IGF-1
IRS1
IR
IRS1
Glucose Metabolism
ROS
Hyperglycemia
Smad2/3
IL-6
TNFα
Calpain
GLUT4
Type 2 Diabetes
PIK3
FOXO
mTOR
Akt
Bidirectional Link
Ubiquitin Proteasome Pathway
MURF1
MAFbx
Ub5
Ub1
Protein Synthesis
Ubiquitin Proteasome Pathway
Sarcopenia
Type 2 Diabetes
Protein Synthesis
Muscle Growth
BIDIRECTIONAL LINK
Glucose Uptake
Muscle Protein
Muscle Wasting


Impaired GLUT4 Translocation in Insulin-Resistant
and Sarcopenic Skeletal Muscle
Insulin
Insulin receptor
E3
IRS-1
PI3K
PI3K
Akt
Impaired Phosphyrolation
Impaired Translocation
↑ UDP-GlcNAc
Impaired Translocation
Ubi
Ubi
Proteasome
Elevated WWP1 Impairs Insulin Signaling
Glucose-WWP1 Signaling Pathway
↑ UDP-GlcNAc
Elevated
Elevated Glycosylation WWP1
↑ Elevated WWP1
Impairs Insulin
WWP1 Impairs Signaling
Diminished signaling
Muscle Wasting
Sarcopenia