# Relationship Between Sarcopenia and Type 2 Diabetes Mellitus in Elderly Patients

## Yaşlı Hastalarda Sarkopeni ve Tip 2 Diabetes Mellitus Arasındaki İlişki

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## Abstract

Sarcopenia has been defined as a condition of decreased muscle strength, as measured by gait speed and grip strength, in the presence of low muscle mass. It is also known that the total muscle mass generally decreases by 1% after the age of 40 years. Type 2 diabetes mellitus (T2DM) is a global health concern that has continued to affect people even during 2018; its prevalence increases with age. Among the several factors that lead to sarcopenia in elderly patients, insulin resistance is one. However, it is still not clear whether this resistance is a coincidence or a consequence of diabetes. Common pathophysiological mechanisms between sarcopenia and diabetes make it difficult to distinguish the order of development of sarcopenia and T2DM. Prospective studies have demonstrated that low muscle mass and muscle strength may be associated with the development of T2DM. It has also been shown that T2DM exacerbates sarcopenia in elderly T2DM patients. Nevertheless, further research is needed to ascertain the exact nature of the relationship between sarcopenia and T2DM, so that their underlying causes may be minimized.

**Keywords:** Sarcopenia; type 2 diabetes mellitus; ageing; insulin resistance

## Özet

Sarkopeni, düşük kas kütlesinin varlığında yürüyüş hızı ve kavrama gücü ile ölçülen azalmış kas gücü durumu olarak tanımlanmıştır. Ayrıca, toplam kas kütlesinin 40 yaşından sonra genellikle %1 azaldığı da bilinmektedir. Tip 2 diabetes mellitus (Tip 2 DM), 2018 yılında hala insanları etkilemeye devam eden küresel bir sağlık sorunudur ve prevalansı yaşla birlikte artmaktadır. Yaşlı hastalarda sarkopeniye yol açan çeşitli faktörler arasında insülin direnci de bulunmaktadır. Bununla birlikte, bu direncin bir rastlantı mı yoksa diyabetin bir sonucu mu olduğu hâlâ net değildir. Sarkopeni ve diyabet arasındaki yaygın ortak patofizyolojik mekanizmalar sarkopeni ve Tip 2 DM gelişim sırasını ayırt etmeyi zorlaştırmaktadır. Prospektif çalışmalar, düşük kas kütlesinin ve kas gücünün Tip 2 DM'nin gelişimi ile ilişkili olabileceğini göstermiştir. Tip 2 DM varlığının yaşlı Tip 2 DM hastalarında sarkopeniyi artırdığı da gösterilmiştir. Bununla birlikte, sarkopeni ve Tip 2 DM arasındaki ilişkinin kesin doğasını saptamak için daha fazla detaylı araştırmaya ihtiyaç olduğu aşikârdır.

**Anahtar kelimeler:** Sarkopeni; tip 2 diabetes mellitus; yaşlanma; insulin rezistansı

## Introduction

Type 2 diabetes mellitus (T2DM) is a global health concern. Its prevalence has continued to increase even during 2018, and it has been predicted that it would affect 592 million individuals by 2035 (1). The occurrence of T2DM is at its peak during the age of 65 years in males and 75 years (2,3) in females. Among the elderly population, T2DM has been associated with decreased physical activity and low muscle strength. Although chronic conditions like hypertension, visual impairment, coronary heart disease, peripheral artery diseases, obesity, arthritis, and depression are major risk factors for T2DM, yet the reason for physical disability is still not completely understood (4). Approximately half the causes of physical disability among elderly T2DM patients remain unexplained (5). Studies on the musculoskeletal systems of elderly T2DM patients have presented conflicting results due to the pathogenetic com-

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plexity of the condition. Alterations in the muscular function of these patients may act as a pathophysiological pathway for the physical disability. Nevertheless, this possibility has not yet been thoroughly explored. The Health, Aging, and Body Composition (ABC) study investigated the body composition among adults aged 70 to 79 years and reported that older adults with T2DM have lower skeletal muscle strength and quality (6). In a study performed on diabetic patients with dementia, it was found that muscle strength and muscle quality decreased, although the muscle mass did not change (7). Furthermore, while it is known that skeletal muscle tissue is the largest insulin-dependent organ in the body, whether the loss of muscle mass and function leads to increased insulin resistance and, consequently, diabetes or vice versa still remain unclear. Therefore the present study attempts to understand the nature of this relationship.

## How can insulin resistance and diabetes lead to sarcopenia?

Several factors may cause sarcopenia in elderly patients, insulin resistance being one of them. Additionally, the presence of T2DM accelerates muscle loss and involves the presence of factors such as glucose toxicity, insulin resistance, reduced bone metabolism, increased inflammatory processes, and genetics. These factors cause wide variations in muscle mass and the degree of strength among individuals; therefore, the results of different studies related to this topic are inconsistent.

Previous studies have observed a decrease in the genetic expression of insulin-like growth factor-1 (*IGF1*), ciliary neurotrophic factor (*CNF*), and insulin-like growth factor binding protein-5 (*IGFB5*) gene expression along with an increase in the expression of the *MSTN* gene. The *MSTN* gene gives instructions for controlling myostatin activity. A mutation in this gene results in decreased muscle function (8).

Another study demonstrated that other conditions including the increased expression of inflammation and apoptosis mediation genes such as the complement component fork-head box O3A (FOXO3A), galectin-1, CCAAT/enhancer binding-b (C/EBP-b) and 1q subcomponent peptide (C1Q-a) may also

exist (9). Yet, the number of genes suspected for sarcopenia possesses too many polymorphisms, with only a few of them being specific for sarcopenia. Therefore, careful isolation of significant genes is essential for pharmacogenetic intervention of sarcopenia in elderly T2DM patients.

Diabetic rat models have demonstrated altered metabolism and function of skeletal muscles; the main mechanism involved in this process is the reduced glucose uptake in type-1 fiber-rich muscles. Furthermore, fiber atrophy has been observed to occur in the fast and slow muscles among diabetic rats (10).

Several other studies have proved the existence of a common pathway between sarcopenia and an insulin-resistant state (11,12). These studies have revealed the dominance of myofiber lipid accumulation in both the conditions. Furthermore, the impaired synthesis of a myosin heavy chain has been observed to be connected with both, ageing and post-prandial insulin secretion. It has therefore been concluded that muscle protein synthesis is resistant to insulin action in the non-diabetic elderly patients. On the other hand, additive insulin resistance may play a role in sarcopenia in elderly diabetic patients (13).

Contrarily, some studies did not report any change in muscle protein synthesis and amino acid usage of muscles (14,15). Moreover, the cellular mechanism responsible for reduced protein synthesis, due to insulin resistance, in elderly diabetic patients has still not been established. However, it is possible that the regulation of gene translation signaling pathways may play a major role in this reduction. Insulin resistance is also associated with an impaired mitochondrial function in muscle tissue, and most diabetic patients experience a reduction in mitochondrial size.

It is a well-known fact that insulin resistance increases the cytoplasmic fatty acids in elderly patients, and this accumulation, in turn, increases the stress on cellular mitochondria. Such mitochondrial stress may be a common pathophysiological pathway in both insulin resistance and ageing. In addition, myosteatosis may also play a role. Myosteatosis is a condition characterized by lipid or adipose cell infiltration in muscle cells due to aging. It implicates increased stress on cellular mitochondria which in turn

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results in increased oxidative stress and the phosphorylation of insulin receptors that may cause impaired insulin binding to cells. Overall, these changes lead to impaired muscle function and may cause sarcopenia in diabetic patients (16,17).

Diabetes also leads to decreased motor-end plate innervation due to peripheral neuropathy, which may consequently result in a decrease in coordinated muscle contraction. Ageing may also contribute to a decrease in motor-end plates. The reductive impact of both, ageing and T2DM on IGF-1 levels and protein synthesis is a well-known fact among researchers. Moreover, the decline in IGF-1 level induces atherogenic activation and increased proteolysis. Low levels of bioavailable testosterone may play a crucial role in both ageing and T2DM patients in consideration of the fact that testosterone stimulates the inhibition of adipocyte production. In both these types of patients, exercise capacity is decreased and weight loss may cause muscle wasting. Anorexia is also commonly observed among elderly patients and may sometimes be considered as a physiological factor of ageing. However, if anorexia superimposes a disease, it may induce muscle atrophy and severe weight loss. Atherosclerosis, a common health problem among elderly patients, decreases blood flow to the muscles and leads to muscle hypoxia, which in turn causes tissues to become intolerant to exercise and, therefore, gather pro-inflammatory cytokines (18).

A general loss of self-management ability among T2DM patients may also play a role in the development of sarcopenia. It is well-known that T2DM may be associated with an impaired executive function (IEF) among patients with normal cognition, yet the mechanism of IEF in T2DM is not fully understood. Cerebral microvascular disease and chronic hyperglycemia are also possible confounding factors for functional neuronal dysfunction, which lead to IEF. Hence, a loss of self-management ability may be a responsible mechanism for the development of sarcopenia in patients with T2DM (19).

Ageing is associated with a decrease in insulin secretion by 0.7% per year. In a patient with T2DM, this reduction can even reach up to 50%. Persistent hyperglycemia leads to the increased production of advanced glyca-

tion end products (AGEs) which accumulate in the muscle, resulting in muscular stiffness and reduced muscle function. These AGEs may play a role in sarcopenia through the up-regulation of inflammation as well as endothelial dysfunction in the microcirculation of skeletal muscles (20). In light of the above information, it can be said that the variety of pathophysiological mechanisms involved in both these processes cause difficulty in distinguishing the precise order of development of sarcopenia and T2DM.

### Does sarcopenia cause insulin resistance?

Prospective studies have demonstrated that low muscle mass and strength may be associated with the development of T2DM (21). It has been determined that an assessment of the presence of sarcopenia can be used as both, primary and secondary forms of prevention of T2DM in elderly patients (22). Moreover, it is advantageous to study older adults with T2DM to assess the presence of sarcopenia in these patients when they show a poor metabolic response to exercises. As mentioned previously, the skeletal muscle is the largest insulin-dependent tissue of the body. Furthermore, sarcopenia promotes insulin resistance regardless of obesity. The presence of both, sarcopenia and obesity, together causes more severe insulin resistance; (23) again making it difficult to distinguish the relationship between sarcopenia and insulin resistance. Further, regarding the action of insulin on mitochondrial proteins, it has been observed that insulin is a major regulating factor for mitochondrial oxidative phosphorylation in skeletal muscles. Thus, insulin resistance is involved in muscle protein loss related to ageing and may lead to sarcopenia (24).

### Therapeutic approaches for elderly diabetic sarcopenic patients

Exercise may play an important role in reversing sarcopenia and improving glucose regulation among elderly patients. An exercise regimen including strength and power training as well as balance exercises may improve functional capacities and metabolic profiles in patients. However, the role of tight glycemic control still remains unclear. Uncontrolled diabetes (HbA1c ≥8.0% or ≥8.5%) has been associated with low walking speed while good glycemic control

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(HbA1c <7%) has been associated with better performance (25). Ozturk et al. (26) have demonstrated that lowering HbA1c levels may positively affect the muscle mass of elderly diabetic patients. However, other studies have not observed any positive impact of tight glycemic control on physical function; although tight glycemic control may be associated with an increased risk of hypoglycemia, falls, and fractures (27,28). Sarcopenia, which develops in geriatric patients, is often associated with changes in the endocrine and nervous system. Klinefelter syndrome or motor neuron disease (e.g., amyotrophic lateral sclerosis) is known to be associated with impaired muscle structure and decreased physical performance. Therefore, these diseases are used as prototypic disease models to study the isolated endocrinological and neurodegenerative causes of sarcopenia (29).

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Pharmacological interventions have not been proven to be superior to exercise training regimens, and their benefits for improving appetite are limited. For example, hormone replacement therapy involving androgens and growth hormones has failed to have a positive impact on the frailty of elderly patients. On the other hand, several antidiabetic drugs have shown positive effects on sarcopenia (31). For example, it has been speculated that metformin may cause muscle strength improvement among T2DM patients (32). Furthermore, glitazones and dipeptidyl peptidase-4 inhibitors may improve the blood supply of muscles (33,34). On the other hand, it has been shown that sulfonylureas, especially glibenclamide, and glinides may have an atrophic effect on muscles (35). Lastly, although insulin increases protein synthesis in young adults, this effect has not been observed among elderly individuals (36). In addition, new therapies such as testosterone, selective androgen receptor modulators, myostatin inhibitors, ghrelin analogs, vitamin K and mesenchymal stem cell therapy have been observed to be promising treatments (37).

## Conclusion

The prevalence of sarcopenia and T2DM among contemporary elderly population continues to increase. Oxidative injury, mitochondrial dysfunction, lipid and AGE accumulation, the dysregulation of several genetic pathways, a loss of self-management, hormonal changes particularly testosterone deficiency, and decreased motor-end plates are all major factors in the development of both, sarcopenia and diabetes. These common pathophysiological mechanisms between sarcopenia and diabetes make it difficult to determine the exact nature of the relationship between sarcopenia and T2DM. Thus, this distinction must remain an active area of research. Future studies should attempt to distinguish more clearly, the order of development of sarcopenia and diabetes in order to minimize the common underlying causes of both these disorders.

## Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

## Authorship Contributions

Idea/Concept: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; Design: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; Control/Supervision: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; Data Collection and/or Processing: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; Analysis and/or Interpretation: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; Literature Review: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; Writing The Article: Zeynel Abidin Sayiner,

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Zeynel Abidin Öztürk; Critical Review: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; References And Fundings: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk; Materials: Zeynel Abidin Sayiner, Zeynel Abidin Öztürk.

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