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Myokine imbalance and sarcopenia in patients with type 2 diabetes mellitus

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Abstract. Our understanding of skeletal muscle has undergone significant changes in recent years. It has been established that muscle tissue is a powerful endocrine organ, actively involved in regulating metabolic processes in other organs and tissues. Skeletal muscle is the largest organ in the human body. Muscle contraction causes a biomechanical response and also releases anti-inflammatory cytokines in response to this contraction, and this opens up new paradigms of skeletal muscle being an endocrine organ, through contraction stimulating the production and release of myokines and adipomyokines, which can influence other organs and systems. Sarcopenia is a progressive age-related decrease in the mass and functional capacity of skeletal muscle, which is associated with an increased risk of developing disability, falls, and metabolic disorders. An important role in the pathogenesis of this condition is played by an imbalance of myokines – signaling molecules secreted by muscle tissue. The results of recent epidemiological studies indicate that patients with type 2 diabetes mellitus (T2DM) are characterized, along with chronic complications, by loss of muscle tissue – sarcopenia. T2DM is a chronic disease that is a global pandemic affecting hundreds of millions of people worldwide, and its prevalence continues to increase. According to the World Health Organization, almost 422 million people worldwide suffer from diabetes mellitus. According to the 11th edition of the International Diabetes Federation Atlas, the number of people with T2DM among the Ukrainian population aged 20 to 79 years will increase to 2.1 million by 2050. According to the new American Diabetes Association guidelines for the treatment of diabetes, sarcopenia is associated with T2DM and diagnostic testing for this complication is recommended in this category of patients. Sarcopenia is now officially recognized as a disease in the International Classification of Diseases (ICD-10: M62). An imbalance between myokines, in particular irisin, myostatin, interleukins-6 and fibroblast growth factor 21, contributes to the development of sarcopenia, deterioration of glucose metabolism and increased insulin resistance. The article summarizes current data on the role of myokine imbalance in the pathogenesis of sarcopenia in DM, examines possible molecular mechanisms of interaction and promising areas of therapeutic correction.
Keywords: scelet muscle, myokine, sarcopenia, diabetes mellitus, irisin, myostatin.

Sarcopenia is a progressive, generalized skeletal muscle disease characterized by loss of muscle mass, strength, and function. This condition is associated with an increased risk of adverse outcomes, including falls, physical frailty, disability, and mortality [1, 2].

The definition of sarcopenia has evolved throughout time, with various research groups presenting divergent opinions and outlining different diagnostic criteria. Currently, sarcopenia is defined as loss of muscle mass with an emphasis on decreased muscle strength and functional impairment. Sarcopenia's pathophysiology is complicated and may be influenced by intrinsic factors, including age, comorbidities, ethnicity, and lifestyle, as well as extrinsic factors, such as the environment, country of residence, and living conditions.

According to recent research, sarcopenia affects 10-16% of the elderly worldwide. This disorder is more prevalent in patients with T2DM than in the general population [3]. Sarcopenia is a poorly understood metabolic condition with numerous risk factors affecting the elderly worldwide [4]. Sarcopenia can be caused by mitochondrial dysfunction, neuromuscular junction degeneration, age-related endocrine changes, and chronic inflammation. Mitochondrial dysfunction plays a key role in decreased mitochondrial biogenesis (due to reduced PGC-1α), impaired dynamics, oxidative stress accumulation, mitochondrial DNA damage, and impaired ATP production. These changes lead to reduced energy supply, apoptosis, and inflammatory signals, thus exacerbating the loss of muscle mass and strength. Sarcopenia can occur when pro-inflammatory cytokines increase and anti-inflammatory cytokines decrease, both of which are signs of chronic inflammation [5]. Chronic inflammation contributes to loss of muscle mass and strength [6]. Sarcopenia has been associated with elevated levels of pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin-6 (IL-6), and C-reactive protein. Inflammatory and immune cells secrete cytokines that contribute to the destruction of muscle fiber structure [7]. Sarcopenia's pathogenesis is multifactorial, involving the interaction of changes at the molecular, cellular, and systemic levels.

One of the central aspects is protein homeostasis imbalance, including age-related decline in anabolic signaling (particularly due to decreased IGF-1/PI3K/Akt/mTOR activity), enhanced proteolytic pathways through the ubiquitin-proteasome system (Atrogin-1, MuRF-1), and autophagy/lysosomal mechanisms [8].

Satellite (muscle stem) cells age and experience functional exhaustion, resulting in decreased activation and differentiation, increased exposure to oxidative stress, and altered environments (extracellular matrix, inflammatory mediators), contributing to the reduced regenerative capacity of muscle tissue [9]. The research on sarcopenia has increased substantially in the recent decade with some evidence suggesting that sarcopenia is a complex pathological condition involving various simultaneously acting pathways, including satellite cell abnormality, alterations in the MPS pathway, biotransformation of muscle fibers, mitochondrial dysfunction, an increase in reactive oxygen species, an increase in fat deposition, an impaired motor-neuron activity, and chronic systemic inflammation [10] (**Fig. 1**).

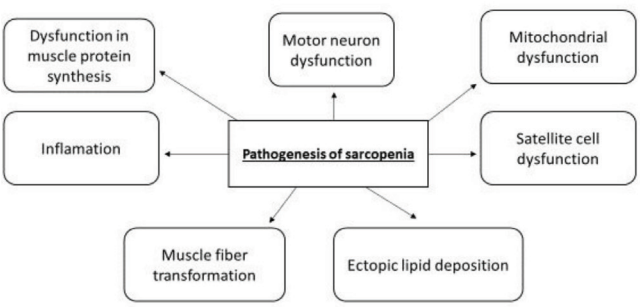

Fig. 1. Pathogenesis of sarcopenia [10].

The European Working Group on Sarcopenia in Older People recommends diagnosing sarcopenia using three key components: decreased muscle strength as the primary indicator, confirmation of the diagnosis based on a decrease in the quantity or quality of muscle mass, and an assessment of physical performance to determine the severity of the disease [4].

The European Working Group on Sarcopenia in Older People suggests using the SARC-F questionnaire to determine the risk of sarcopenia.

J.E. Morley created the SARC-F, a basic five-item self-report questionnaire [11]. The risk of sarcopenia is present when the sum of the scores on each of the five items exceeds or equals 4 points, with a maximum total score of 10 points [12]. However, due to its high specificity, the findings have been misinterpreted [13, 14]. As a result, recent in-

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vestigations have implemented an extended questionnaire that includes measuring thigh circumference. The findings indicate that this indicator substantially improves the sensitivity and accuracy of sarcopenia screening [15, 16].

Loss of muscle strength is usually measured using hand grip dynamometry and the five-times sit-to-stand test, whereas loss of muscle mass is usually measured using two-photon X-ray absorptiometry or bioimpedance analysis. Functional capacity is typically assessed using walking speed, short functional mobility tests (e.g., Short Physical Performance Battery, Timed Up and Go), or other similar methods. The application of these standard techniques enables a unified approach to detecting, comparing, and monitoring sarcopenia in different populations [4].

Sarcopenia and T2DM are two age-related diseases that are common among older adults and have a serious impact on their overall health and quality of life. Patients with T2DM and sarcopenia are more likely to suffer from metabolic disorders and have a higher probability of fractures and falls. These adverse effects can reduce their quality of life and increase the risk of mortality. DM and sarcopenia share common pathophysiology mechanisms. T2DM-specific signs include oxidative stress, the accumulation of advanced glycation end-products, and chronic inflammation, all of which accelerate muscle tissue degeneration. Sarcopenia affects healthy muscle, worsening glycemic regulation, and leading to the development and progression of T2DM [17, 18]. There is a relationship between T2DM and sarcopenia. The incidence of sarcopenia in patients with T2DM is significantly higher than in those without DM. Myosin breakdown exceeds myosin synthesis due to hyperglycemia and insulin resistance, leading to decreased muscle mass. Reduced skeletal muscle mass leads to decreased insulin sensitivity, which impairs the ability of peripheral tissues to process glucose and increases the risk of developing T2DM, forming a pathogenetic cycle between sarcopenia and DM [19, 20] (**Fig. 2**).

Obesity affects people with both sarcopenia and T2DM. Recent studies have shown that more than half of patients with DM are obese [21]. The presence of obesity, which is common in patients with T2DM, may complicate the timely diagnosis of sarcopenia. T2DM disrupts lipid metabolism in skeletal muscle, contributing to increased fat accumulation, also known as «myosteatosis».

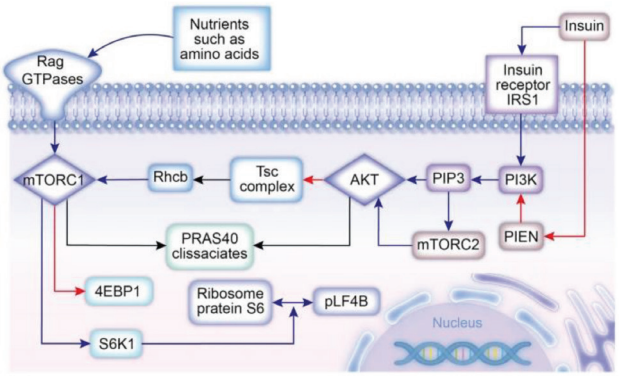

Fig. 2. Causal relationship between insulin resistance and sarcopenia [20].

Myosteatosis is a metabolic and structural phenomenon characterized by the pathological infiltration of skeletal muscle with lipids, which are localized both intracellularly and in the intermuscular space. The lipotoxic environment created by «myosteatosis» reduces muscle mass and strength, which leads to the appearance of typical signs of sarcopenia [17].

Myosteatosis is associated with a progressive decrease in the contractile capacity of muscle fibers, impaired oxidative metabolism, and insulin resistance, which contribute to cellular aging and mitochondrial dysfunction. It is a significant risk factor for the development of both sarcopenia and T2DM. Myosteatosis-associated insulin resistance is a primary defect that contributes to T2DM. Increased intramuscular adipose tissue causes more severe local inflammation and reduces skeletal muscle contractility [22]. Insulin resistance syndrome promotes ectopic fat accumulation that leads to local inflammation [22].

In 2022, the European Society for Clinical Nutrition and Metabolism and the European Association for the Study of Obesity (ESPEN-EASO) agreed to define sarcopenic obesity (SO) as loss of muscle mass and an increase in body fat [23].

Thus, the coexistence of SO and T2DM has become a common health problem. Recent studies have shown that the prevalence of SO in diabetic patients reaches 27% [24].

Obesity and T2DM are the major causes of impaired skeletal muscle stem cell regeneration, which is manifested by loss of muscle mass and progressive decline in glucose and lipid metabolism in skeletal muscle. These changes accelerate the development of T2DM [23]. Therefore, we should focus on early screening and detection of sarcopenia and SO in diabetic patients (**Fig. 3**) [25, 26].

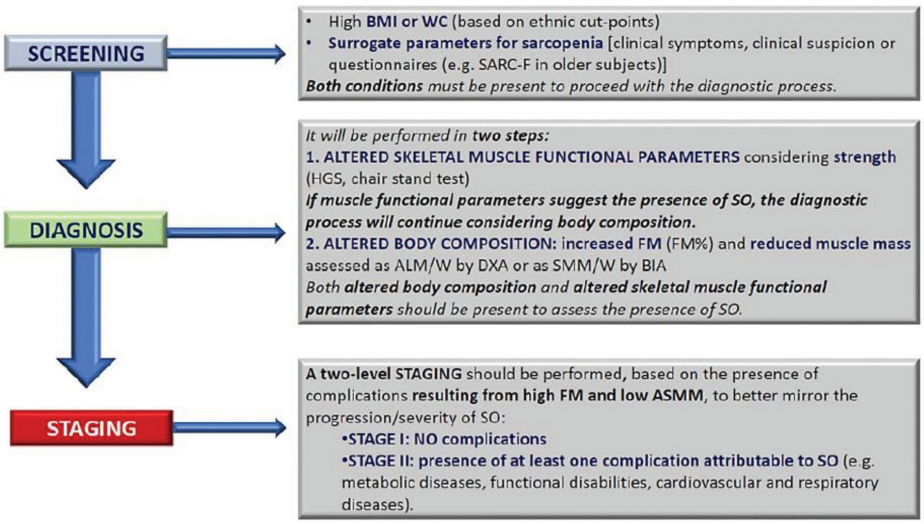

Fig. 3. Diagnostic procedure for the assessment of SO [26].

Note. ALM/W – appendicular lean mass adjusted to body weight; ASMM – absolute skeletal muscle mass; BIA – bioelectrical impedance analysis; BMI – body mass index; DXA – dual X-ray absorptiometry; FM – fat mass; HGS – handgrip strength; SMM/W – total skeletal muscle mass adjusted by weight; WC – waist circumference; SARC-F – strength, assistance with walking, rising from a chair, climbing stairs and falls.

Management of sarcopenia and myokines

Dietary protein intake is beneficial for older adults with sarcopenia and T2DM. Increased dietary protein intake not only helps to control blood sugar levels and maintain muscle mass, but it also promotes weight regulation, reduces inflammation, and increases insulin sensitivity.

Numerous studies have consistently shown that adequate dietary protein intake can stimulate muscle protein synthesis, while reducing muscle protein breakdown and enhancing the efficient processing of nutrients in the muscle [27].

Amino acids are the fundamental building blocks of muscle protein. Consequently, the effect of dietary protein intake on muscle protein synthesis is primarily limited to essential amino acids [28].

Vitamin D plays a crucial role in maintaining muscle health and directly influences muscle development. Vitamin D is a fat-soluble substance that improves bone health by facilitating the absorption of essential minerals such as calcium and phosphorus. Research has shown that vitamin D deficiency is associated with an increased risk of sarcopenia [29].

Exercise is considered a safe and effective method for the prevention and treatment of DM complicated by sarcopenia [30].

A substantial body of research has brought attention to the potential role of omega-3 fatty acids in maintaining and regulating skeletal muscle quality and function. A study of diet and its relation to grip strength in community-dwelling older men and women found a positive correlation between fatty fish consumption and increased grip strength. Participation in any form of physical activity can significantly improve sarcopenia in older adults, as supported by numerous studies [31].

Since the Food and Drug Administration has not yet approved any pharmacological treatments for sarcopenia, effective methods to preserve healthy aging are required [32].

Investigations into myokines' potential to prevent muscle loss are ongoing. Irisin, derived from fibronectin type III domain-containing protein 5 (FNDC5), is a particularly promising option. Research on experimental animals has shown that the administration of recombinant irisin or the overexpression of FNDC5 enhance insulin sensitivity, reduce fasting glucose levels, and inhibit hepatic gluconeogenesis by activating the PI3K/Akt pathway. The physiological benefits of irisin include antimetastatic effects related to its anti-inflammatory action, neuroprotective effects, and attenuation of oxidative stress [33]. Irisin has an antioxidant action, protecting skeletal muscle from oxidative damage and chronic inflammation, a critical mechanism for maintaining muscle homeostasis and counteracting atrophy [34].

Irisin, a hormone-like molecule produced during exercise, has been proposed as a potential biomarker of sarcopenia and muscle damage due to its strong positive correlation with skeletal muscle mass and strength [35].

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A review of the literature suggests that circulating irisin levels are lower in patients with T2DM than in normoglycemic individuals, regardless of body mass index. They are associated with adverse lipid profiles and insulin resistance markers. In view of this, irisin can be considered a biomarker of impaired glucose homeostasis or used for monitoring metabolic abnormalities in T2DM [36].

Thus, irisin has been shown to reduce circulating glucose levels and increase insulin secretion and sensitivity. Irisin affects the pathophysiological processes in the development of T2DM and sarcopenia.

The findings suggest that irisin plays a potentially important role in the regulation of energy homeostasis and carbohydrate metabolism, which makes it a promising biomarker and therapeutic target in T2DM.

A decrease in its level may be a consequence of reduced physical activity, skeletal muscle dysfunction, or a compensatory response to chronic hyperglycemia [37].

However, clinical results remain controversial. Some studies have shown a positive correlation between irisin concentration and insulin resistance indices, while others have shown no statistically significant associations [38].

The differences may be attributed to different irisin measurement methods and disease durations, as well as small sample sizes. Further large prospective studies using standardized approaches to irisin measurement are required to determine its diagnostic value and therapeutic potential.

In human studies, irisin may serve as a potential diagnostic marker for sarcopenia in elderly and postmenopausal women.

In addition, increased levels of irisin, a myokine released into the bloodstream during exercise, can promote skeletal muscle growth. Moreover, animal and cell experiments have shown that increased irisin levels help improve muscle mass.

Other myokines that affect the muscular system should also be considered. Myostatin is a myokine that regulates muscle growth and development. It acts as a negative regulator of muscle hypertrophy, limiting muscle size by inhibiting its growth. Myostatin normally functions as an inhibitor, suppressing the division and growth of muscle cells (myocytes) [39]. This suggests that myostatin is further involved in myogenesis, as it is present both prenatally in the growing myotome and postnatally in adult muscle. With age, myostatin levels tend to increase, contributing to the development of sarcopenia, which is a decrease in muscle mass and strength. This decrease in muscle function is largely due to an imbalance between catabolism and anabolism in muscle. Studies suggest that myostatin inhibition using genetic or pharmacological methods may enhance muscle mass and improve functional capacity in older adults. Physical activity, particularly resistance training, has been shown to be an effective strategy for reducing myostatin levels and preventing the development of sarcopenia. However, despite these promising results, the mechanisms of myostatin regulation and its effects on other tissues, including the heart, require further investigation to optimize therapeutic approaches [40, 41].

IL-6 is a cytokine that plays a key role in regulating inflammatory processes and metabolism. Elevated levels of IL-6 are associated with the development of numerous age-related diseases, including sarcopenia. Increased levels of IL-6 manifest chronic inflammation, contributing to the degeneration of muscle fibers and their decreased regenerative capacity. This leads to accelerated catabolism of muscle proteins, in particular through the activation of mechanisms associated with apoptosis and muscle protein breakdown. In addition, IL-6 can affect myofibril metabolism, increasing oxidative stress in muscle cells and contributing to the development of insulin resistance, which worsens the condition of patients with sarcopenia. Reducing IL-6 levels by pharmacological or physical methods can be an effective strategy to slow or prevent sarcopenia [42, 43].

FGF21 is a metabolic regulator primarily secreted by the liver, but is also found in adipose tissue and muscle. FGF21 regulates energy metabolism, affecting glucose, lipid, and protein metabolism, and maintains metabolic homeostasis [44]. Given its ability to influence metabolic pathways, it has recently been shown that FGF21 can also influence the development of sarcopenia. Recent studies suggest that elevated FGF21 levels can improve muscle function by stimulating oxidative pathways and activating mechanisms that contribute to maintaining muscle mass. However, loss of sensitivity to FGF21, which may occur with age or due to the development of insulin resistance and T2DM, reduces the regenerative and adaptive capacity of muscle. Pharmacological strategies aimed at increasing FGF21 levels or improving its sensitivity have promising potential for use in the treatment or prevention of sarcopenia, although further clinical studies are needed to confirm their efficacy [45].

Obesity treatment is an important aspect of DM and sarcopenia. Current therapeutic guidelines recommend a drug with a relevant therapeutic effect. Glucagon-like peptide-1 (GLP-1) is a peptide hormone that has antidiabetic effects, enhances insulin secretion by pancreatic β-cells, improves insulin sensitivity, regulates appetite and gastric emptying, and promotes muscle growth [46]. GLP-1 agonists can increase muscle mass. Recent studies suggest that GLP-1 can directly affect skeletal muscle [47]. GLP-1 receptors are absent in human skeletal muscle, so the effects must be indirect. They promote muscle remodeling, enhance postprandial muscle protein synthesis, increase muscle blood flow, and improve muscle insulin resistance through weight loss [48]. However, current studies have shown that the administration of GLP-1 drugs results in weight loss that can reduce muscle mass by 20–50% in some people, especially if lifestyle changes are not implemented [49]. Significant weight loss raises concerns about the negative impact on muscle mass, health, and function, especially in more vulnerable patients. Thus, sarcopenia may be a major problem and contraindication for the administration of GLP-1 receptor agonists. By inhibiting gastric emptying and reducing dietary food intake, GLP-1 receptor agonists can significantly inhibit nutrient absorption, potentially leading to a decrease in muscle mass and the development of sarcopenia [50].

Conclusions

1. The study provides a review of the existing research on the pathogenesis of sarcopenia in people with diabetes and possible treatment strategies. Type 2 diabetes mellitus leads to the progression of sarcopenia, and, conversely, sarcopenia exacerbates diabetes mellitus. There is a complex relationship between these two conditions.

2. Disturbances in myokine secretion may play a significant role in the pathogenesis of age-related and metabolic diseases, including type 2 diabetes mellitus, sarcopenia, and sarcopenic obesity. Aging leads to a decrease in the secretion of most myokines, including irisin. Therefore, it is important to further study the role of irisin in patients with diabetes mellitus and sarcopenia, the diseases that affect the elderly population and require timely detection, treatment, and prevention. Recent studies have shown that irisin can be used as a biomarker of sarcopenia and sarcopenic obesity, as well as for early screening of age-related muscle changes.

3. The findings suggest the link between sarcopenia and irisin, with the latter having an impact on sarcopenia treatment. However, the mechanism of irisin action in sarcopenia treatment is not fully understood.

4. The decrease in irisin levels, often observed in sarcopenia, may limit the adaptive capacity of muscles, worsen tissue trophism, and increase insulin resistance. Thus, the study of myokine regulatory mechanisms presents opportunities for discovering new therapeutic strategies in the prevention and treatment of sarcopenia and type 2 diabetes mellitus.

5. The findings suggest that irisin has a potential therapeutic effect in sarcopenia and may become a promising treatment for sarcopenia in the future. However, at present, there is a lack of high-quality studies on the administration of irisin in sarcopenia treatment, and the corresponding mechanisms of action have not yet been elucidated. Therefore, further research is necessary to establish the relationship between irisin and sarcopenia in patients with type 2 diabetes mellitus.

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Abbreviations

DM – Diabetes mellitus
FGF21 – Fibroblast growth factor 21
GLP-1 – Glucagon-like peptide-1
IL-6 – Interleukin-6
SO – Sarcopenic obesity
T2DM – Type 2 diabetes mellitus

Міокіновий дисбаланс і саркопенія у хворих на цукровий діабет 2-го типу

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Резюме. Погляд на скелетну мускулатуру за останні роки суттєво змінився. Встановлено, що м'язова тканина є потужним ендокринним органом, який бере активну участь у регуляції метаболічних процесів в інших органах та тканинах. Скелетні м'язи – це найбільший орган людського тіла. Скорочення м'язів викликає біомеханічну реакцію, а також у відповідь на це скорочення виділяє протизапальні цитокіни, і саме це відкриває нові парадигми того, що скелетні м'язи – це ендокринний орган, який через скорочення стимулює вироблення і вивільнення міокінів та адипоміокінів, які можуть впливати на інші органи та системи. Саркопенія – це прогресуюче вікове зниження маси та функціональної здатності скелетних м'язів, яке асоціюється з підвищеним ризиком розвитку інвалідизації, падінь та метаболічних порушень. Важливу роль у патогенезі цього стану відіграє дисбаланс міокінів – сигнальних молекул, що секретуються м'язовою тканиною. Результати останніх епідеміологічних досліджень свідчать, що для хворих на цукровий діабет (ЦД) 2-го типу (ЦД2) поряд із хронічними ускладненнями характерна і втрата м'язової тканини – саркопенія. ЦД2 – це хронічне захворювання, яке є глобальною пандемією, що вражає сотні мільйонів людей по всьому світу, і його поширеність продовжує зростати. За даними Всесвітньої організації охорони здоров'я майже 422 мільйона людей у всьому світі страждають на ЦД. За оцінкою Атласу Міжнародної федерації діабету в 11-му виданні серед населення України від 20 до 79 років кількість хворих на ЦД2 зросте до 2,1 мільйона до 2050 року. Згідно з новими рекомендаціями Американської діабетичної асоціації з питань лікування ЦД, зазначено, що саркопенія асоціюється із ЦД2 та в цієї категорії пацієнтів рекомендується проводити діагностичний пошук цього ускладнення. Саркопенія тепер офіційно визнана захворюванням у Міжнародній класифікації хвороб (МКХ-10: М62). Порушення рівноваги між міокінами, зокрема іризином, міостатином, інтерлейкінами-6 і фактором росту фібробластів 21 сприяє розвитку саркопенії, погіршенню глюкозного обміну та посиленню інсулінорезистентності. У статті узагальнено сучасні дані щодо ролі міокінового дисбалансу в патогенезі саркопенії при ЦД, розглянуто можливі молекулярні механізми взаємодії та перспективні напрями терапевтичної корекції.

Ключові слова: скелетні м'язи, міокіни, саркопенія, цукровий діабет, іризин, міостатин.

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