

# LITERATURE REVIEW

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## SARCOPENIA AS A COMPLICATION OF TYPE 1 DIABETES MELLITUS

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## САРКОПЕНИЯ КАК ОСЛОЖНЕНИЕ САХАРНОГО ДИАБЕТА 1-ГО ТИПА

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The objective of this review is to systematize and summarize the available literature data on the problem of sarcopenia in patients with type 1 diabetes mellitus (DM 1). Sarcopenia is a progressive and generalized disease characterized by loss of muscle mass, strength, and decreased skeletal muscle function. More and more data reflecting the deterioration of a muscle mass condition and decreased muscle function and strength in patients with DM 1 have accumulated over the past few years. A hypothesis concerning impaired muscle con-

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dition and function in young patients with DM is put forward, thus, diabetic sarcopenia can be considered as a direct complication of DM 1.

Currently, diagnostics is based on the clinical algorithm proposed in the consensus of the European Working Group on Sarcopenia in Older People in 2019 (EWGSOP2). Despite numerous studies on sarcopenia, the issue of validated biomarkers used for early diagnosis and monitoring of sarcopenia remains unresolved.

**Keywords.** Sarcopenia, type 1 diabetes mellitus, complications of diabetes.

Систематизированы и обобщены имеющиеся в литературе данные по проблеме саркопении у пациентов с сахарным диабетом 1-го типа (СД 1). Саркопения – это прогрессирующее и генерализованное заболевание, характеризующееся потерей мышечной массы, силы и снижением функции скелетных мышц. За последние несколько лет все больше накапливается данных, отражающих ухудшение состояния мышечной массы и снижение функции и силы мышц у пациентов с СД 1. Выдвигается гипотеза о нарушении состояния и функционирования мышц у пациентов молодого возраста с СД, таким образом, диабетическая саркопения может рассматриваться как непосредственное осложнение СД 1.

В настоящее время диагностика основана на клиническом алгоритме, предложенном в консенсусе Европейской рабочей группы по саркопении пожилых людей 2019 г. (EWGSOP2). Несмотря на многочисленные исследования, посвященные саркопении, открытым остается вопрос валидированных биомаркеров, используемых для ранней диагностики и мониторинга саркопении.

**Ключевые слова.** Саркопения, сахарный диабет 1-го типа, осложнения диабета.

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### INTRUDCTION

Sarcopenia is a generalized progressive disease characterized by loss of muscle mass, strength, and function of skeletal muscles. Sarcopenia often worsens chronic comorbidities and is associated with an increased risk of adverse outcomes such as falls and fractures, and decreased ability to perform daily activities [1; 2].

Sarcopenia is associated with cardiovascular, respiratory diseases, cognitive impairment [2]. The presence of sarcopenia and dynapenia (decreased muscle strength) in a patient increases hospitalization costs for elderly patients by 5 times [3; 4]. According to a meta-analysis including 151 studies, sarcopenia develops in 10–27 % of people over 60 years of age, the prevalence of severe sarcopenia varies from 2 to 9 % depending on the diagnostic criteria and the population studied [4]. Despite the high incidence of this disease, there is no single diagnostic algo-

rithm, and no clear interpretation of tests has been established.

Primary sarcopenia associated with aging occurs in old age. However, in the presence of chronic diseases, loss of muscle mass, strength and muscle function begins already in young and middle age [5]. Over the past few years, more and more evidence has been accumulated reflecting the deterioration of muscle mass and a decrease in muscle function and strength in patients with type 1 diabetes mellitus (DM 1). Identification of factors influencing the development of sarcopenia will ensure the development of future strategies for the early detection of individuals at high risk of developing sarcopenia and, consequently, the implementation of preventive measures.

### SARCOPENIA AS A CHRONIC COMPLICATION OF TYPE 1 DIABETES MELLITUS

It is essential to understand the causes and pathogenetic mechanisms of sarcopenia

for developing strategies to prevent muscle loss. Skeletal muscles are composed of myofibrils formed by the fusion of satellite cells. Age-related muscle loss is caused by a decrease in the number of myofibrils; more than 80 % of muscles consist of a protein component, and therefore their atrophy or hypertrophy depends on their protein content [7].

Muscle protein anabolism is known to be mediated by amino acids, exercise, insulin, insulin-like growth factor-1 (IGF-1), testosterone, and estrogens [8]. In older people, muscle protein synthesis decreases even when the required Amount of amino acids is present in the blood, in other words, anabolic resistance develops [9]. It is noted that chronic inflammation develops with aging due to a decrease in immune function. It is characterized by moderately elevated levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL) -1 $\beta$ , IL-6 and IL-18, C-reactive protein (CRP). There is evidence of increased levels of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 in the blood by 2–4 times in elderly people compared to healthy young people [10]. Inflammatory cytokines cause the development of mitochondrial dysfunction and lead to excessive production of reactive oxygen species [11]. Chronic inflammation is believed to reduce muscle strength and function by increasing skeletal muscle infiltration by macrophages, decreasing muscle mass and increasing accumulation of ectopic fat [12]. The influence of additional factors on the pathogenetic mechanisms of sarcopenia development is noted in the presence of chronic diseases, in particular DM 1. In healthy people, the main part of glucose is absorbed by skeletal muscles against the background of hyperinsulinemia. Thus,

changes in muscle structure in patients with DM 1 may have a significant impact on glycemic control.

To date, information on the transformation of the muscular system in patients with DM 1 is limited. Some data indicate changes in skeletal muscles in adolescents and young adults with DM 1. C. Monaco et al. hypothesized that DM 1 can be considered a state of accelerated muscle aging; changes in the muscular system are similar to those observed in the muscles of older people, but in the presence of DM 1 they occur at a younger age. The authors draw attention to the presence of dysfunctional skeletal muscle mitochondria despite adequate physical activity and moderately controlled glycemia [13].

Mitochondrial dysfunction is involved in the pathophysiological mechanisms of aging and demonstrates a decrease in the functioning of the respiratory chain, which is the main source of reactive oxygen species. Changes in mitochondrial oxidation-reduction reactions in patients with DM 1 have been demonstrated in a study using a hyperinsulinemic euglycemic clamp. In the course of the study, no differences were found in the average blood glucose concentration and insulin levels between patients with DM 1 and the control group of healthy people, while glucose utilization was 50 % lower in patients with DM 1, insulin sensitivity was 53 % lower compared to the control group, proton flux through mitochondrial ATP synthase did not increase in patients with DM 1, but increased by 28 % in patients without diabetes [14]. Another group of researchers, when evaluating muscle properties in men with DM 1 and good glycemic control and a control group of healthy individuals, demonstrated a lower oxidative capacity in skeletal muscles in patients with DM 1 [15].

One of the negative consequences of hyperglycemia is the glycation of proteins, which leads to their chemical modification and the formation of advanced glycation end products (AGEPs), which are involved in the pathophysiology of the aging process of the muscular system and contribute to the development of late complications associated with DM 1 [16]. The study by H. Mori presents an analysis of the relationship between AGEP accumulation and decreased muscle function. The authors note that AGEP accumulation may be one of the causes of impaired muscle function in patients with DM 1 [17].

The decline in muscle function appears to begin early in life, with studies in children with DM 1 showing significant reductions in muscle strength and increased fatigue compared to their healthy peers [18]. Impaired muscle function from adolescence onwards suggests that sarcopenia is a direct complication of DM 1, regardless of the presence of other chronic complications.

Uncompensated glycemia due to insulin deficiency promotes catabolism of body proteins, primarily in skeletal muscle, as demonstrated in a study based on mass spectrometry of individual proteins undergoing degradation *in vivo* in the absence of insulin [19].

In a crossover study involving 62 patients with a mean age of  $38 \pm 14$  years and the presence of DM 1, the prevalence of dynapenia was 23 %, sarcopenia – 8 % [20]. With an increase in the mean age of the test group, the incidence of sarcopenia increases. In a study of 812 patients with diabetes mellitus, the prevalence of sarcopenia in patients with DM 1 was 20 % among participants over the age of 65, significantly higher than in those with type 2 diabetes mellitus (8 %) [21]. Insulin pump use slows the progression of

muscle myopathy in patients with DM 1, according to a study of 32 people with DM 1. Muscle thickness in the insulin pump group was significantly higher than in patients on multiple insulin injections [22]. The main factors leading to the development of sarcopenia are shown in Fig. 1.

Studies reflecting accelerated muscle aging, decreased muscle strength, mass and function in patients with DM 1 are presented in Table 1 [13–22].

### **SCREENING AND ASSESSMENT OF SEVERITY OF SARCOPENIA**

In 2019, the European Working Group on Sarcopenia in Older People (EWGSOP2) updated the consensus on the diagnosis of sarcopenia by proposing a clinical algorithm that formed the basis for screening for sarcopenia in diabetes mellitus (Fig. 2) [2; 24].

At the first stage of the suspicion of sarcopenia, it is recommended to use the SARC-F questionnaire as a screening tool, which, when assessed with more than three points, allows detecting obvious signs of sarcopenia [2; 4; 24; 25]. In addition to the questionnaire, sarcopenia can be suspected in patients with risk factors, which include the presence of several chronic diseases, polypharmacy (taking more than five medications), malnutrition, and being in a nursing home [24].

In addition, specific risk factors for patients with diabetes include HbA1c levels above 8%, time since diagnosis of diabetes over five years, and the presence of diabetes complications [24].

In case of positive screening tests, the second step is to assess muscle strength. For this purpose, dynamometry and the chair rise test are used [24; 25].

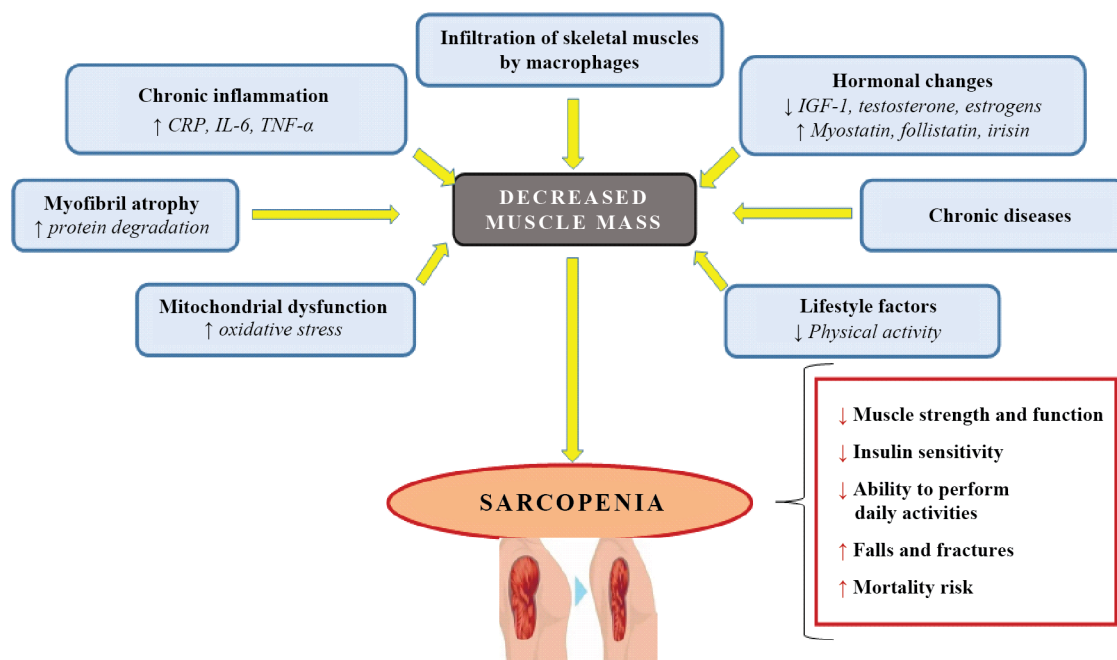


Fig. 1. Factors involved in the process of occurrence and progression of sarcopenia, and consequences of sarcopenia (adapted from [23])

Table 1

**Studies demonstrating changes in skeletal muscle in patients with type 1 diabetes mellitus**

Author	Year	Basic Provisions
Monaco C.M.F. et al.	2019	DM 1 promotes accelerated skeletal muscle aging despite adequate physical activity and moderately controlled glycemia
Kacarovskiy M. et al.	2011	A study using a hyperinsulinemic euglycemic clamp has proven changes in mitochondrial oxidation-reduction reactions in patients with DM 1
Crowther G.J. et al.	2003	A lower oxidative capacity in skeletal muscle has been proven in patients with DM 1
Krause M.P. et al.	2011	Hyperglycemia promotes glycation of proteins, which leads to their chemical modification and the formation of AGEp, which are involved in the aging processes of the muscular system
Mori H. et al.	2017	An analysis of the relationship between AGEp accumulation and decreased muscle function in patients with DM 1 showed a prevalence of sarcopenia of 16.6 %
Lukács A. et al.	2012	Studies conducted in children with DM 1 show significant reductions in muscle strength and increased fatigue compared to their healthy peers
Robinson M.M. et al.	2016	Uncompensated glycemia due to insulin deficiency promotes protein catabolism in skeletal muscles
Andreo-López M.C. et al.	2023	In a study involving 62 patients with a mean age of 38 ± 14 years and the presence of DM 1, the prevalence of dynapenia was 23 %, sarcopenia – 8 %
Hiramine Y. et al.	2022	In a study of 812 patients with diabetes mellitus, the prevalence of sarcopenia in patients with DM 1 was 20 % among participants aged over 65 years
Tan S. et al.	2022	In the group of patients on insulin pump therapy, muscle thickness measurements were significantly higher ( $p < 0.05$ ) than in the group using syringe pens

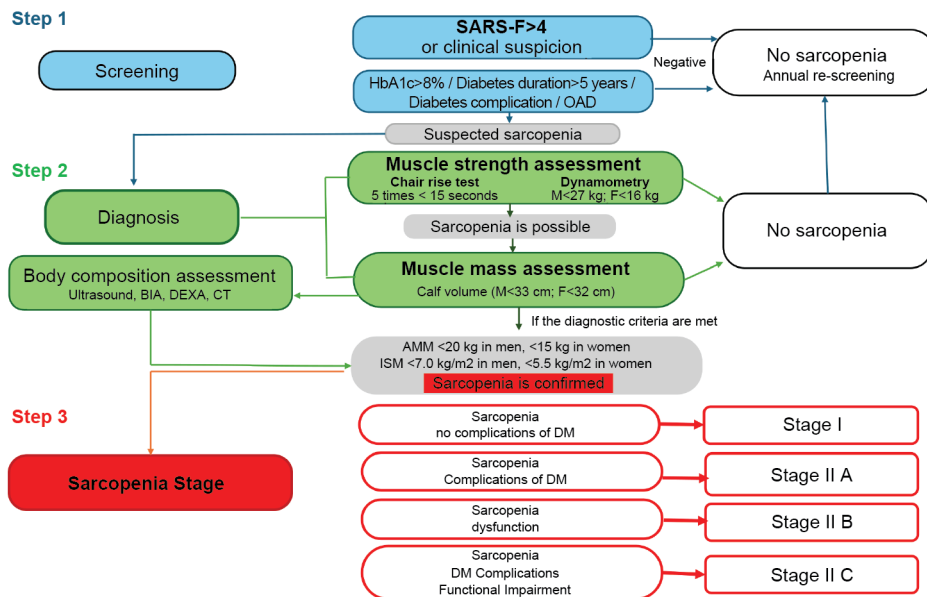


Fig. 2. Algorithm for screening and diagnosing sarcopenia in diabetes mellitus (adapted from [24])

It is recommended to assess muscle mass to diagnose possible sarcopenia. The simplest method is to measure the anticnemion circumference adjusted for body mass index (BMI), but at present the diagnostic value of this method in patients with DM 1 is poorly studied. A decrease in muscle mass can be assumed with a calf circumference of less than 33 cm in men and less than 32 cm in women adjusted for BMI.

Next, a study of the body composition is carried out with the calculation of appendicular muscle mass, which is the sum of the muscle mass of the limbs in kg (AMM), and the skeletal muscle index - SMI, calculated as the ratio of appendicular muscle mass to the square of the patient's height (kg/m<sup>2</sup>). The threshold values for confirming sarcopenia are AMM values less than 20 kg in men and less than 16 kg in women, SMI values less than 7 kg/m<sup>2</sup> in men and less than 5.5 kg/m<sup>2</sup> in women [24].

The gold standard for noninvasive assessment of muscle mass is computed tomography

(CT), but it is not used routinely due to the high radiation exposure and cost of the examination. Dual-energy X-ray absorptiometry and bioelectrical impedance analysis are more accessible.

The third step after confirming sarcopenia is to determine the stage (severity), depending on the presence of diabetes complications and muscle function. Stage I corresponds to patients with sarcopenia without diabetes complications and without impaired muscle function. Stage II includes three sublevels: A, B and C. Stage II A is characterized by the presence of diabetic complications, but without impairment of muscle function. Stage II B is determined in the presence of impairment of muscle function, but without complications of diabetes. Stage II C is established in the presence of impairment of muscle function in combination with the presence of diabetic complications [24].

The diagnosis of decreased muscle function is made using various physical performance tests. The Short Physical Performance Battery (SPPB)

includes three tests: assessment of the patient's balance, determination of the 4 m walking speed, the "Chair Rise" test. The "Get Up and Go" test and the 400 m walking speed are also used [24; 25]. This algorithm allows the use of available screening methods to identify risk groups for the development of sarcopenia, promotes timely diagnosis and early prevention of the disease in patients with diabetes mellitus.

#### **ANALYSIS OF BIOCHEMICAL MARKERS INDICATING THE PRESENCE OF SARCOPENIA**

Biomarkers that reflect the presence or absence of sarcopenia can be divided into two groups. The first group includes markers that assess the skeletal-muscular condition - these are myokines, such as myostatin, follistatin, irisin. These are specific peptides produced by muscle fibers that have autocrine, paracrine or endocrine effects. Myokines provide a connection between muscles and other organs, and also affect the metabolism of lipids and glucose.

The second group includes markers that suggest causal factors in the development of the disease - these are adipokines, hormones, inflammatory mediators and acute phase proteins [26]. Studies show that myostatin, also known as growth differentiation factor-8 (GDF-8), simultaneously activates protein degradation and inhibits protein synthesis in skeletal muscles [27]. According to H.R. Bergen et al., higher concentrations of myostatin are found in older women compared to younger women, and lower concentrations are found in older men compared to younger men. In addition, the researchers found higher concentrations of myostatin in older women suffering from sarcopenia than in the corresponding groups of men [28]. When muscle mass decreases to the level of sarcopenia, higher levels of GDF-8 are recorded, such data were

presented in a prospective cohort study involving 878 volunteers [29]. It is also known that myostatin affects lipid metabolism and promotes intracellular lipid accumulation in muscles by increasing the expression of certain genes [30]. In addition, in their study A.G. Dial et al. determined the level of myostatin in patients with DM 1 and in a control group of healthy people: according to the data obtained, myostatin in the blood serum is significantly elevated in adults with DM 1 compared to comparable individuals without diabetes [31]. The authors also note that glycemic control, as measured by glycated hemoglobin (HbA1c), did not affect myostatin expression in serum or skeletal muscle. Similar data were obtained in a study of myokine in adolescents with DM 1. Myostatin levels were significantly elevated in the presence of DM 1 compared to healthy children in the control group [32].

Follistatin should be considered together with myostatin. Follistatin concentrations are increased in patients with sarcopenia, as shown in a large study in postmenopausal women [33].

The myokine that causes muscle hypertrophy is irisin. Numerous studies have shown that its levels are significantly reduced in patients with sarcopenia [34; 35].

Adipokines may be a factor in the development of sarcopenia. These are biologically active substances specific to adipose tissue, the main representatives of which are adiponectin and leptin. A recent meta-analysis involving 1,389 people, of whom 557 were people with sarcopenia and 832 were from the control group, revealed that patients with sarcopenia are characterized by significantly higher levels of adiponectin [36]. Therefore, the constant presence of adiponectin in the blood serum will contribute to the decrease in muscle mass and the development of sarcopenia.

Leptin is an adipokine that improves the immune response and induces lipid catabolism. Low blood leptin levels are correlated with decreased square area of muscle mass in older adults [37]. Hormones play an important role in muscle anabolic and catabolic processes.

Decreased levels of insulin-like growth factor-1 (IGF-1) are considered a possible factor contributing to the development of sarcopenia [38]. IGF-1 is partially synthesized in skeletal muscle and regulates muscle growth in an autocrine and paracrine manner. Studies have shown that decreased levels of IGF-1 are associated with decreased skeletal muscle mass and the development of sarcopenia in elderly patients [39]. A study aimed at determining the incidence of sarcopenia in patients with DM 1 found that IGF-1 levels were significantly lower in patients with sarcopenia [40].

An equally important role in the diagnosis of sarcopenia is given to determining the level of dehydroepiandrosterone sulfate (DHEA-S). Serum DHEA-S concentrations peak in young adulthood and then gradually decline over time. In a retrospective study of 108 elderly patients, patients with sarcopenia had significantly lower DHEA-S concentrations [41]. Chronic inflammation is one of the most important mechanisms to consider in the pathogenesis of sarcopenia. Inflammatory cytokines promote muscle atrophy by causing protein catabolism and suppressing muscle tissue synthesis. A meta-analysis with a total of 11,249

participants showed significantly higher CRP levels in patients with sarcopenia [42]. Somewhat later, new data were published confirming that higher levels of CRP, IL-6, TNF- $\alpha$  were significantly associated with low skeletal muscle strength and muscle mass [43]. Based on this, an increase in the level of inflammatory cytokines is associated with a higher risk of developing sarcopenia.

In order to improve the quality of life of patients and timely diagnosis of the disease, further research is needed to develop a panel of validated biomarkers.

### CONCLUSIONS

Sarcopenia is a chronic progressive disease with high prevalence. Patients with DM 1 are at particular risk for developing sarcopenia. In recent years, more and more data have emerged on the pathogenetic mechanisms of accelerated muscle aging in patients with absolute insulin deficiency, and issues have been raised about considering sarcopenia as a late complication of DM 1. Due to the low routine diagnosis of decreased muscle mass, strength and function, patients have a higher risk of falls and fractures, worsening of chronic diseases and increased length of hospitalization.

Thus, the implementation of a simple algorithm for diagnosing sarcopenia will allow the implementation of a strategy for the prevention of this condition in patients with DM 1.

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Lyapunova A.I. – literature search, collection and processing of information, writing of the manuscript.

Alieva O.O. – literature search, writing of the manuscript.

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