УДК 616-009.17
https://doi.org/10.20538/1682-0363-2023-3-88-97

All you need to know about sarcopenia: a short guide for an internal medicine physician in questions and answers

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ABSTRACT

Sarcopenia is associated with social, economic, and individual burdens, including loss of independence, poor quality of life, and disability. In a short period of time, ideas about sarcopenia transformed from geriatric syndrome to disease. Initially, sarcopenia was considered in the context of gradual age-related deterioration in the functioning of all physiological systems. Over the years, it became clear that it can develop a second time, as a consequence of various diseases and pathological conditions.

To date, there have been no generally accepted diagnostic criteria for sarcopenia. There are several tests and tools available for screening sarcopenia, the choice of which depends on physical capabilities of the patient, capabilities of the medical institution, and the purpose for which it is detected (research or clinical practice).

From the point of view of human health, sarcopenia increases the risk of falls and fractures; impairs the ability to perform daily activities; is associated with the progression of major diseases and cognitive impairments; leads to movement disorders; contributes to a decrease in the quality of life, loss of independence or a need for long-term care. The presence of sarcopenia increases both the risk of hospitalization and hospitalization costs.

The aim of the literature review is to provide an analysis of up-to-date information on the causes, pathogenesis, screening, diagnosis, treatment, and consequences of sarcopenia, myosteatosis, and sarcopenic obesity. The search for literature containing information on relevant studies was conducted in PubMed and Google Scholar by the following keywords: sarcopenia, dynapenia, myosteatosis, sarcopenic obesity, nutritional status, malnutrition.

Keywords: sarcopenia, dynapenia, sarcopenic obesity, malnutrition, myosteatosis

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Bikbavova G.R., Livzan M.A., Tikhonravova D.V. All you need to know about sarcopenia: a short guide for an internal medicine physician in questions and answers. *Bulletin of Siberian Medicine.* 2023;22(3):88–97. https://doi.org/10.20538/1682-0363-2023-3-88-97.

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Все, что нужно знать о саркопении: краткий гид для современного терапевта в вопросах и ответах

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РЕЗЮМЕ

Саркопения связана с социальным, экономическим и индивидуальным бременем, включающим потерю независимости, низкое качество жизни и инвалидизацию. За короткий промежуток времени представления о саркопении преобразовались с гериатрического синдрома до заболевания. Изначально саркопения рассматривалась в контексте постепенного возрастного ухудшения работы всех физиологических систем. С годами стало понятным, что она может развиться вторично, как следствие различных заболеваний и патологических состояний.

На сегодняшний день общепринятых диагностических критериев саркопении не существует. Доступно несколько тестов и инструментов для скрининга саркопении, выбор которых зависит от физических возможностей пациента, возможности медицинского учреждения и цели, с которой проводится ее выявление (научно-исследовательская работа или практическая деятельность).

С точки зрения здоровья человека саркопения увеличивает риск падений и переломов; ухудшает способность выполнять повседневную деятельность; связана с прогрессированием основных заболеваний и когнитивными нарушениями; приводит к нарушениям подвижности; способствует снижению качества жизни, потере независимости или необходимости в длительном уходе. Наличие саркопении увеличивает риск госпитализации и стоимость лечения во время госпитализации.

Цель обзора – представить анализ актуальной информации о причинах, патогенезе, скрининге, диагностике, лечении и последствиях саркопении, а также миостеатозе и саркопеническом ожирении. Поиск литературы, содержащей информацию о соответствующих исследованиях, проводился в системах PubMed и Google Scholar по таким ключевым словам, как саркопения, динапения, миостеатоз, саркопеническое ожирение, нутритивный статус, мальнутриция.

Ключевые слова: саркопения, динапения, саркопеническое ожирение, мальнутриция, миостеатоз

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Бикбавова Г.Р., Ливзан М.А., Тихонравова Д.В. Все, что нужно знать о саркопении: краткий гид для современного терапевта в вопросах и ответах. *Бюллетень сибирской медицины.* 2023;22(3):88–97. https://doi.org/10.20538/1682-0363-2023-3-88-97.

WHAT IS SARCOPENIA? BACKGROUND, DEFINITION, AND TERMINOLOGY

Sarcopenia is generally regarded as an age-related progressive condition characterized by impaired skeletal muscle function and weight loss, associated with an increased risk of falls, fractures, hospitalization, and mortality. M. Critchley described the loss of muscle mass in elderly people in 1931. The term sarcopenia was proposed by the American professor I. Rosenberg in 1989 (Greek “sarx” – body, flesh and “penia” – deficiency) [1]. In 2010, the European consensus on definition and diagnosis proposed the first definition of sarcopenia. This term is understood as a condition characterized by progressive and generalized skeletal muscle disorder with increased risk of adverse outcomes, such as deterioration in the quality of life, physical disability, and mortality [2]. In 2016, sarcopenia was officially recognized as a disease in the International Classification of Diseases (ICD-10: M62.84).

So, in a short period of time, ideas about sarcopenia were transformed from a geriatric syndrome to a disease. The status of the disease gives “increased

awareness" of this problem [3] and stimulates research interest and commercial interest of pharmaceutical companies in the development of new drugs. According to experts, sarcopenia will become a global problem by 2045, which is associated with an increase in human life expectancy [4].

Primary sarcopenia is a consequence of age-related changes in the muscle tissue. In certain cases, it can develop a second time, as a consequence of other diseases and pathological conditions (cancer, chronic heart failure, liver cirrhosis, inflammatory bowel diseases, etc.) due to systemic inflammation, limited physical activity (bed rest), malabsorption syndrome, obesity, endocrine disorders, and nutrient deficiency [5].

Sarcopenia can be acute, lasting less than 6 months, and chronic, lasting at least 6 months [6]. There is a term presarcopenia, which is defined as an isolated decrease in muscle mass with normal muscle strength and function. Classifying sarcopenia into acute, chronic, and presarcopenia is necessary for early intervention and management of the disease using available methods to improve the quality of life and life expectancy of patients.

It is reasonable to separate the use of such sarcopenia characteristics as muscle mass (quantitative disorder) and muscle strength and function (qualitative disorder), since muscle strength depends not only on their mass [7]. To define muscle strength, it is proposed to use the term dynapenia [8], while the term sarcopenia is a broader concept [9]. Some scientists suggest_using the term dynapenia only in relation to elderly and senile people [10]. However, the Foundation for the National Institutes of Health, which is established by the US Congress, suggests using the term dynapenia in patients of any age [9].

The combination of sarcopenia and obesity is called sarcopenic obesity (SO). It is a loss of muscle mass and fat accumulation that synergistically increase life-threatening consequences. SO is associated with an increased risk of disability, cardiovascular diseases, metabolic syndrome, and mortality [11]. The ability of adipose tissue to produce signaling molecules and influence metabolism, that is, to work as an organ of the endocrine system, was discovered relatively recently, becoming one of the main achievements in this field [12]. Among the effector organs is muscle tissue, the paracrine regulation of which is implemented by adipocytes. Under physiological conditions, muscle tissue contains a minimal amount of fat which is used as an energy source during aerobic activity, while excessive pathological muscle fat infiltration is called myosteatosis [13]. Fat deposition in the muscles can occur between the muscles (intermuscularly), in the extracellular region, but within the same muscle (intramuscularly), and inside cells (intracellularly). Thus, there is a change in muscle architectonics and a significant decrease in the functional activity of muscles [14].

WHAT IS THE PREVALENCE OF SARCOPENIA?

The prevalence of sarcopenia varies from 5 to 13% among people over 60–70 years and from 11 to 50% among people over 80 years [15, 16]. According to other studies, the prevalence of sarcopenia among the elderly is 29% and among individuals living in long-term care institutions – 33% [17]. The International Clinical Guideline on Sarcopenia recommends annual screening in all persons over 65 years of age in hospitals and clinics using the SARC-F questionnaire (A Simple Questionnaire to Rapidly Diagnose Sarcopenia) [18].

WHAT ARE THE RISK FACTORS FOR SARCOPENIA?

Muscle mass starts to decrease from the third to the fourth decade and progresses at a rate of 0.5–1% per year with a drastic decline after the eighth decade [19]. Muscle strength also decreases in parallel, but not in direct proportion to the loss of muscle mass. Such factors as malnutrition, physical inactivity, and polymorbidity in the elderly are involved in the development of primary sarcopenia, while taking medication, malabsorption syndrome, systemic inflammations, endocrine disorders, obesity, and malnutrition are involved in the development of secondary sarcopenia (Figure).

The theory of the emergence of sarcopenia is discussed taking into account the impact of internal and external risk factors. Internal factors include the influence of proinflammatory cytokines, oxidative stress, mitochondrial dysfunction, and insulin resistance. In addition, double-blind studies have shown that the heritability of some parameters of muscle mass and strength reaches 80%. External risk factors for sarcopenia include exposure to radiation, dietary habits, smoking, alcohol and / or drug abuse, infectious agents, social environment, and physical activity. The interaction of internal and external factors is a complicated, parallel, and dynamic process that leads to an imbalance between protein synthesis and proteolysis in skeletal muscles [20].

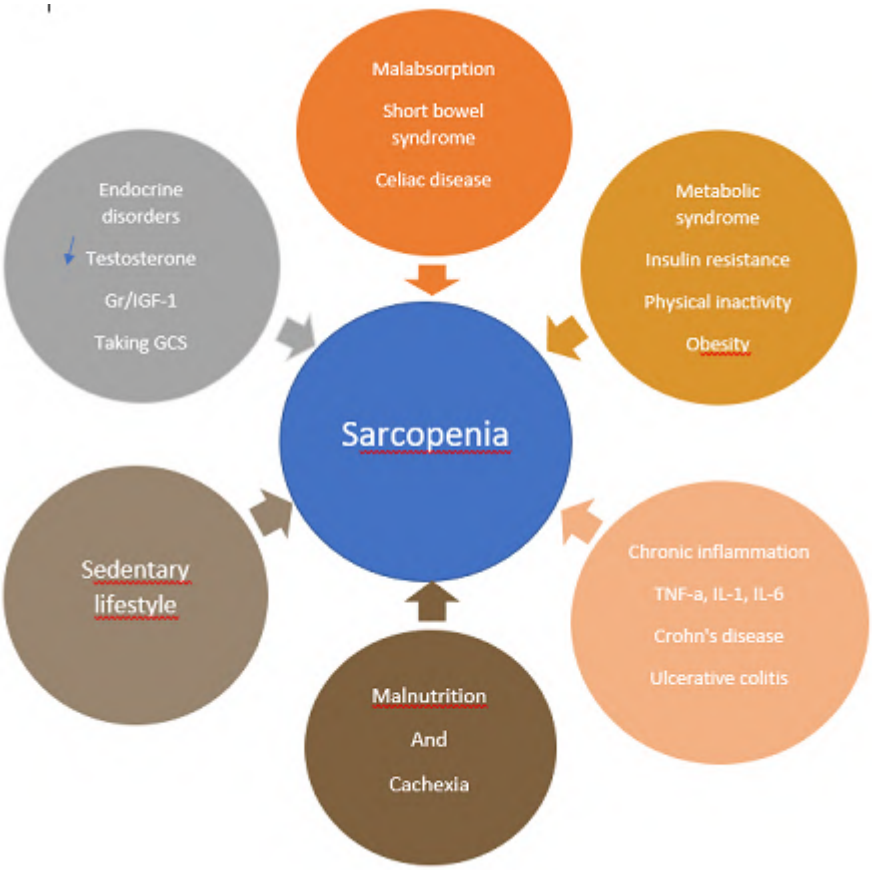

Figure. Factors contributing to the development of sarcopenia

METHODS OF SARCOPENIA DIAGNOSIS / HOW TO DIAGNOSE SARCOPENIA?

Currently there are no generally accepted diagnostic criteria for sarcopenia. There are several tests and tools available for screening sarcopenia, the choice of which depends on the physical capabilities of the patient, the capabilities of the medical institution, and the purpose for which it is detected (research or clinical practice). Sarcopenia should be diagnosed from the moment when the patient reports about such symptoms as falling, slow walking speed, difficulty getting up from a chair, weight loss, exhaustion, and weakness [22].

To identify sarcopenia, the European Consensus recommends using the SARC-F questionnaire which includes five questions concerning the degree of difficulty in performing routine activities (strength, walking, chair stand test, climbing stairs, falling during the previous year). The SARC-F questionnaire has good sensitivity and high specificity [22]. Its advantages are reliability, simplicity of use, convenience for screening, fast results, and low cost [23].

The Ishii screening test is a method that evaluates the probability of sarcopenia using three variables: age, grip strength, and calf circumference [24]. The calculation includes two steps and is represented by the following equations. Calculation of probability points: for men $0.62 \times (\text{age} - 64) - 3.09 \times (\text{grip strength} - 50) - 4.64 \times (\text{calf circumference} - 42)$; for women $0.80 \times (\text{age} - 64) - 5.09 \times (\text{grip strength} - 34) - 3.28 \times (\text{calf circumference} - 42)$.

The red flag method [25] is used for screening sarcopenia during a standard medical consultation. Table 1 presents the main components of this technique. In addition to collecting complaints and examining a patient, eating habits (for example, whether the patient consumes enough protein-containing foods) and physical activity (playing sports, working in the country or in the garden in the spring – autumn period and / or walking) are analyzed. The authors of the method suggest proceeding to more complex procedures for assessing sarcopenia when red flags are identified.

Table 1

The red flag method for screening sarcopenia

Parameter	Red flags
Examination	Weakness
	Visual identification of muscle loss
	Reduced gait speed
Complaints and anamnestic data	Weight loss
	Decreased muscle strength in the arms and legs
	Fatigue
	Falls
	Impaired mobility
	Loss of energy
	Difficulties doing exercises and daily activities
Clinician's assessment	Nutrition
	Body mass
	Physical activity

Determination of skeletal muscle strength: hand-grip dynamometry (grip strength) is a simple, reliable, and inexpensive method that is recommended for practical use. Levels lower than 27 kg in men and 16 kg in women are diagnostically significant in sarcopenia. Low grip strength is a predictor of long hospital stays, functional limitations, poor quality of life, and mortality [26, 27]. In cases where the use of hand-grip dynamometry is not possible, it is recommended to use the chair stand test. The patient is offered to get up from the chair 5 times in a row and sit down without the help of hands, while measuring the time during which the patient will be able to complete the task. A time interval greater than 15 seconds is diagnostically significant. Another version of the test with a chair is when times the patient gets up and sits down on a chair within 30 seconds are counted [25].

Such criteria as the total mass of skeletal muscles, the mass of appendicular muscles (muscle mass of skeletal muscles of the upper and lower limbs), and the cross-sectional area of muscles in various zones are important in order *to determine the mass of skeletal muscles*. There are several imaging techniques that make it possible to evaluate the above criteria; these include magnetic resonance imaging (MRI), computed tomography (CT), dual-energy X-ray absorptiometry (DXA), bioimpedance analysis, and ultrasound.

The procedure for conducting and describing the results obtained with MRI and CT is time-consuming, therefore, a method for calculating the lumbar index at the third lumbar vertebra (L3) was developed and tested [25]. The advantage of this method is its accuracy, reproducibility of the results, as well as the fact that the lumbar index can be determined during CT or MRI performed for other purposes (for example, in cancer patients). The disadvantages of these methods are rare application in primary health care due to their high cost, requirements for highly qualified personnel, and ionizing radiation load, which makes it difficult to use them during follow-up in response to prescribed treatment. An important point is that the cut-off points of low muscle mass are not currently defined [28].

Dual Energy X-Ray Absorptiometry (DXA) is also used to quantify sarcopenia (muscle mass) and calculate the content of adipose tissue. Abroad, this method is considered as the method of choice due to low radiation doses, speed of implementation, and non-invasiveness. The disadvantages of this technique include the facts that the equipment is not mobile and that different manufacturers report different results [6].

The bioimpedance analysis is less accurate for measuring quantitative parameters of sarcopenia, since this technique evaluates the distribution of fluid in the body, while the rest of remaining values are calculated ones, so there can be an error in measurement. Another disadvantage of the method is that its accuracy is affected by the position of the electrodes, room temperature, and body temperature [29].

Currently, methods for ultrasound diagnosis of sarcopenia are being actively developed, however, despite the improvement of equipment and software, the technique is operator-dependent, which has a significant impact on the representativeness of the results [30]. At the same time, the European Working Group on Sarcopenia in Older People [6] recommends this examination due to its reliability, convenience, cost, and timing, indicating its future potential. During the study, the thickness and cross-sectional area of the pennate (feather-like) muscles, echogenicity, beam length, and angle of inclination, for example, of the quadriceps femoris, are evaluated [31].

The measurement of calf circumference in the elderly is also useful as a diagnostic indicator in conditions where other methods for determining the quantitative characteristics of muscle mass are not available [32]. With all the conventions of the interpretation, the size of the calf less than 31 cm in general suggests a decrease in muscle mass [33].

Screening tools such as the Timed Up and Go (TUG) test are used *to determine physical performance*. When measuring the gait speed, the patient walks 4 meters at a normal speed, the medical staff records the walking time and calculates the speed (in m / s) [34]. The recommended cut-off point for determining severe sarcopenia is 0.8 m / s or less. The TUG test involves getting up from the chair, walking 3 meters to the mark, turning around, returning, and sitting back on the chair [35]. An indicator of severe sarcopenia is the time ≥ 20 seconds. The Short Physical Performance Battery (SPPB) test is a comprehensive test, but it is more often used in research than in clinical assessment, as it takes at least 10 min to complete it. The SPPB test includes an assessment of gait speed, a balance test, and a chair stand test. The maximum score is 12, and a score of ≤ 8 indicates poor physical performance [25].

Several international groups are currently involved in the development of screening and diagnostic criteria for sarcopenia: the European Working Group on Sarcopenia in Older People (EWGSOP); the Asian Working Group on Sarcopenia (AWGS), the International Working Group on Sarcopenia (IWGS), the Foundation for the National Institutes of Health (FNIH) established by the US Congress. The diagnostic criteria for sarcopenia which were offered by these groups are presented in Table 2.

Table 2

Diagnostic criteria for sarcopenia proposed by various research teams studying this problem

Research team	Definition	Criteria		
		Muscle mass	Muscle strength	Physical performance
EWGSOP-2 [6]	Probable sarcopenia – criterion 1. The diagnosis is confirmed additionally by criterion 2. If the patient has criteria 1, 2, and 3, then sarcopenia is severe. 1. Low muscle strength 2. Low muscle quantity or quality 3. Low physical performance	Appendicular Skeletal Muscle Mass Index (AMMI): the ratio of the total skeletal muscle mass of the upper and lower extremities to the patient's height per square, kg / m²: M < 7.0 kg / m² W < 5.5 kg / m² (DXA)	M < 27 kg W < 16 kg (dynamometry)	Gait speed M and W ≤ 0.8 m / s SPPB – total score ≤ 8 TUG ≥ 20 seconds
FNIH [9]	Combination of low muscle mass and weakness	AMMI M < 0.789 or < 19.75 kg (DXA) W < 0.512 or < 15.02 kg (DXA)	M < 26 kg W < 16 kg (dynamometry)	Gait speed M and W < 0.8 m / s
IWGS [36]	Combination of low muscle mass and reduced physical performance	M < 7.23 kg / m² W < 5.67 kg / m² (DXA) M < 7.23 kg / m² W < 5.67 kg / m² (BIA)	–	Men and women < 1 m / s

Note: M – men, W – women.

The European Working Group on Sarcopenia in Older People (EWGSOP) conducted its second meeting in 2018 [6]. Since their first meeting in 2010, researchers and clinicians have accumulated information, studied in detail many aspects of this problem, and identified issues that required resolution. One of the issues is, for example, that many practitioners are aware of sarcopenia and may suspect it in a patient, however no unique diagnostic criteria and management methods have been presented, while the consequences of sarcopenia are quite alarming [37–39].

Another important achievement was the understanding that timely diagnosis of muscle strength deficiency is still of paramount importance when comparing the significance of such sarcopenia parameters as muscle strength and muscle mass [40]. Measuring muscle strength is more applicable from a practical point of view, while measuring muscle mass is technically difficult due to reasons described above. In addition, according to studies, muscle strength is a more significant marker in terms of predicting poor patient outcomes [26, 27]. Scientists pay attention to the fact that the practical significance of this characteristic will also increase with the improvement of tools and methods for assessing the quantitative characteristics of muscle mass.

HOW TO TREAT SARCOPENIA?

Primary and secondary sarcopenia are a consequence of many diseases both in elderly or younger patients with comorbidities of varying severity, so the focus should be placed on the

treatment of underlying diseases. The positive impact of treatment strategies aimed at controlling diabetes mellitus, reducing inflammatory status, decreasing weight in obesity, and enriching diet with foods rich in various nutrients is obvious [41].

There is no doubt that physical activity and moderate strength workouts are beneficial for the elderly, which has a positive effect on muscle strength, muscle mass, and performance [25]. Moreover, strength workout is the most effective and available method for preventing the progression of sarcopenia that improves many aspects of overall health [42]. There are no studies in the field of standardization of physical activity, which creates difficulties in assigning the amount of physical activity that a particular patient needs. Only EWGSOP pays attention to the fact that the duration of physical exercise should be at least 3 months and combined programs should be recommended for patients with a sedentary lifestyle [6].

Currently convincing evidence of the impact of various therapeutic diets on the course of sarcopenia has not been obtained yet. However, observational studies have shown that an increasing protein intake to 1.2 g / kg daily in the elderly has a positive effect on muscle mass and, to a lesser extent, on muscle strength. Weak old people or old people with acute or chronic diseases need more dietary protein (1.2–1.5 g / kg of body weight per day) [43]. It has been suggested that dietary supplements, such as β-hydroxy-β-methylbutyrate, creatine, and vitamin D, have an impact on physical performance. It has been proven that supplements of β-hydroxy-β-methylbutyrate apparently increase muscle mass, while their effect on muscle strength and physical performance is controversial [44]. The meta-analysis demonstrated that vitamin D supplements increase muscle strength but do not affect their mass [45]. Based on this information, it seems reasonable for clinicians and / or nutritionists to pay attention to the calorie content, the quality and quantity of incoming protein, as well as the level of vitamin D in the elderly and consider the possibility of personalized prescription of dietary supplements.

Precision medicine is defined as a new paradigm that focuses on personalized, predictive, and preventive approaches and represents a completely new way to treat sarcopenia. Modern innovative technologies including smartphone software, neuromuscular electrical stimulation, smart home technologies, and interactive games with virtual reality elements help to personalize sarcopenia treatment programs [46]. These methods will help the elderly to remain independent and at the same time receive adequate physical activity and control their diet depending on individual needs. For example, the software, including remote measurements and monitoring of the intensity of physical activity, helps doctors remotely obtain information about the activity of patients and monitor their compliance with a scheduled treatment plan and progress in exercise. Robotic devices can also become useful tools in passive and active patient education [47]. A smart home includes many connected devices that can help older people stay independent by providing them with better experiences than regular exercise. For example, smart refrigerators have the function of helping old people maintain adequate nutrition by tracking daily food intake, providing them with individual meal plans and purchasing groceries through online systems. Of course, further research is needed to determine the role of currently available technologies in the treatment of sarcopenia.

The Food and Drug Administration (FDA) has not approved any specific drugs for the treatment of sarcopenia. The possibility of using such drugs as growth hormone, anabolic or androgenic steroids, selective androgen receptor modulators, protein anabolic agents, appetite stimulants, myostatin inhibitors, β-receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, and troponin activators is being considered.

These groups of drugs have different efficacy. For example, growth hormone increases muscle protein synthesis and muscle mass but does not improve muscle strength or function [48]. The effects of anabolic steroid supplements differed between genders: an increase in weight and muscle mass in men and weight gain mainly due to increased fat mass in women [49]. In both men and women, testosterone supplements increased muscle strength [50]. Herbal supplements, such as curcumin, alkaloids, catechins, proanthocyanidin, gingerols, and segaols, have shown a moderate effect on skeletal muscle function [51]. Ghrelin and megestrol acetate, which are used as appetite stimulants, can increase body weight and muscle mass [52]. Myostatin, produced by muscles, prevents muscle anabolism [53]. Bimagrumab, a human monoclonal antibody that modulates activin type IIB receptors, increases muscle volume, muscle mass, and physical performance [54]. ACE inhibitors and troponin activators have a positive effect on muscle mass [55].

CONCLUSION

Scientific and technological progress in medical technology has made it possible to find out the causes of many diseases, decipher their pathogenesis, create new drugs, and develop preventive strategies. This has led to an increase in the life expectancy of the world's population [56]. However, population aging has emerged and requires a comprehensive public health response. Muscle mass and strength tend to decrease with age after the peak in adolescence. Thus, the term sarcopenia was coined. In a short period of time, ideas about sarcopenia have transformed from a geriatric syndrome to a disease. Initially, sarcopenia was considered in the context of gradual age-related deterioration of all physiological systems, leading to reduction of individual vitality reserves, which causes increased vulnerability to stress factors and increases the risk of adverse health consequences. Over the years, it became clear that in certain cases it can develop a second time, as a consequence of other diseases and pathological conditions.

At the moment, there are still many gaps in our knowledge about sarcopenia, namely the mechanisms of its occurrence, universal screening methods, diagnostic tools, validated control points, cut-off points, and outcomes. The research results gradually provide answers to the questions, but at the same time new problems appear and require further research and study.

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Received 21.01.2023;
approved after peer review 31.01.2023;
accepted 16.02.2023