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ASPECTS OF SARCOPENIA SYNDROME IN ONCOLOGICAL PRACTICE: DIAGNOSIS AND TREATMENT

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Abstract
Sarcopenia is diagnosed in 20-70% of patients with advanced neoplasms and is associated with a number of negative consequences. At the same time, this condition rarely comes to the attention of practicing oncologists, including due to diagnostic difficulties. Correcting sarcopenia requires a multidisciplinary approach, including optimal nutrition with adequate protein intake, micronutrients, and aerobic and strength-training exercise.

Keywords Sarcopenia, skeletal muscle, chemotherapy, parenteral nutrition.

INTRODUCTION

Malignant neoplasm (MN) has a significant impact on the patient's nutritional status up to the development of refractory cachexia, the most severe irreversible form of protein-energy malnutrition. Sarcopenia is diagnosed in 60-70% of patients with common neoplasms and is associated with a number of negative consequences. At the same time, this condition rarely comes to the attention of practicing oncologists, including due to diagnostic difficulties.

Three syndromes are causes of unintentional weight loss: 1) starvation, 2) cachexia, and 3) sarcopenia. The causes of weight loss in some cases may be a combination of these two or three syndromes [6]. Loss of muscle mass today (including due to sarcopenia) is one of the prognostic factors for the development of toxicity of antitumor treatment, as well as an unfavorable prognosis of cancer [33]. In 2000, sarcopenia cost American healthcare $18.5 million, representing approximately 1.5% of total healthcare costs [17].

The term "sarcopenia" was proposed in 1989 by the American scientist Irwin Rosenberg (USA). From the Greek words "Sarx, sarkos" - meat, muscles.

According to Russian and foreign authors, sarcopenia (wasting of skeletal muscles), sarcopenic obesity (SO) and myosteatosis have a negative impact on the results of surgical and drug

treatment of this group of patients.

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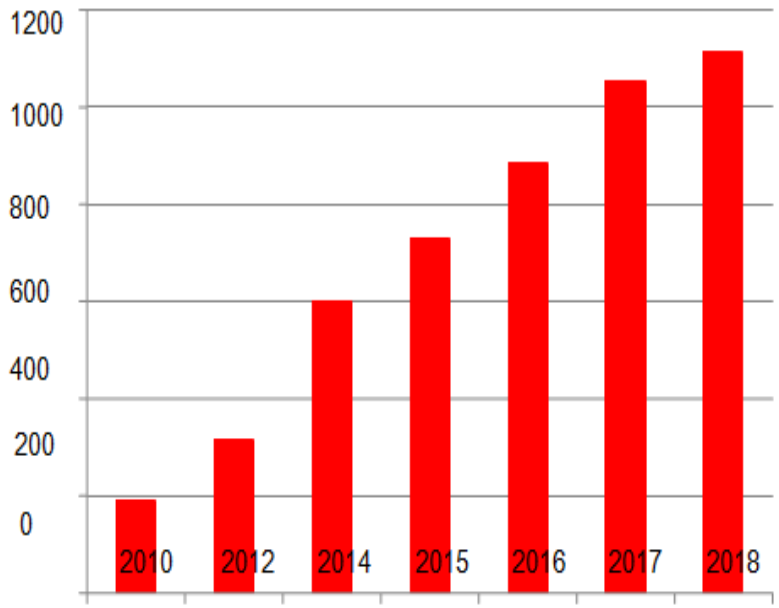


According to the American Center for Disease Control and Prevention, sarcopenia is one of the five main risk factors for morbidity and mortality in cancer patients [1]. IH Rosenberg proposed the term "sarcopenia" to describe the process of loss of skeletal muscle mass [2]. The term "sarcopenia" comes from the Greek. sarx – body and penia – loss [3]. Although sarcopenia primarily affects older people, it can develop in people of any age. For example, in various chronic inflammatory diseases, oncopathologies and deficiency of anabolic hormones [4, 13].

Sarcopenia - the progressive loss of muscle mass and strength - is associated with a high risk of adverse outcomes leading to disability (falls and fractures, low quality of life, type 2 diabetes, osteoporosis, cardiovascular disease, nocturia, etc.). Sarcopenia is not included in the current international classification of diseases of the circulatory system. 10th edition, but will be included in the next edition. This article presents issues of terminology and epidemiology of sarcopenia and for the first time examines the role of age-related deficiency of anabolic hormones (testosterone, hormone D, growth hormone (somatotropin)) in the pathogenesis of sarcopenia. In addition, the prospects for normalizing the level of these hormones during pathogenetic pharmacotherapy of sarcopenia are indicated.

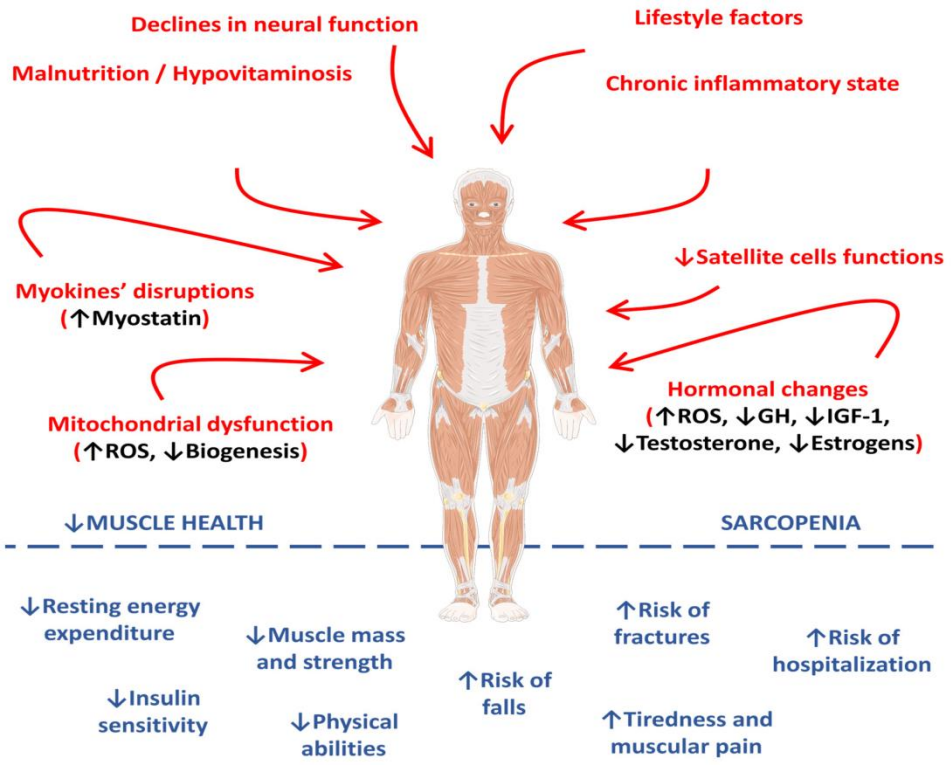
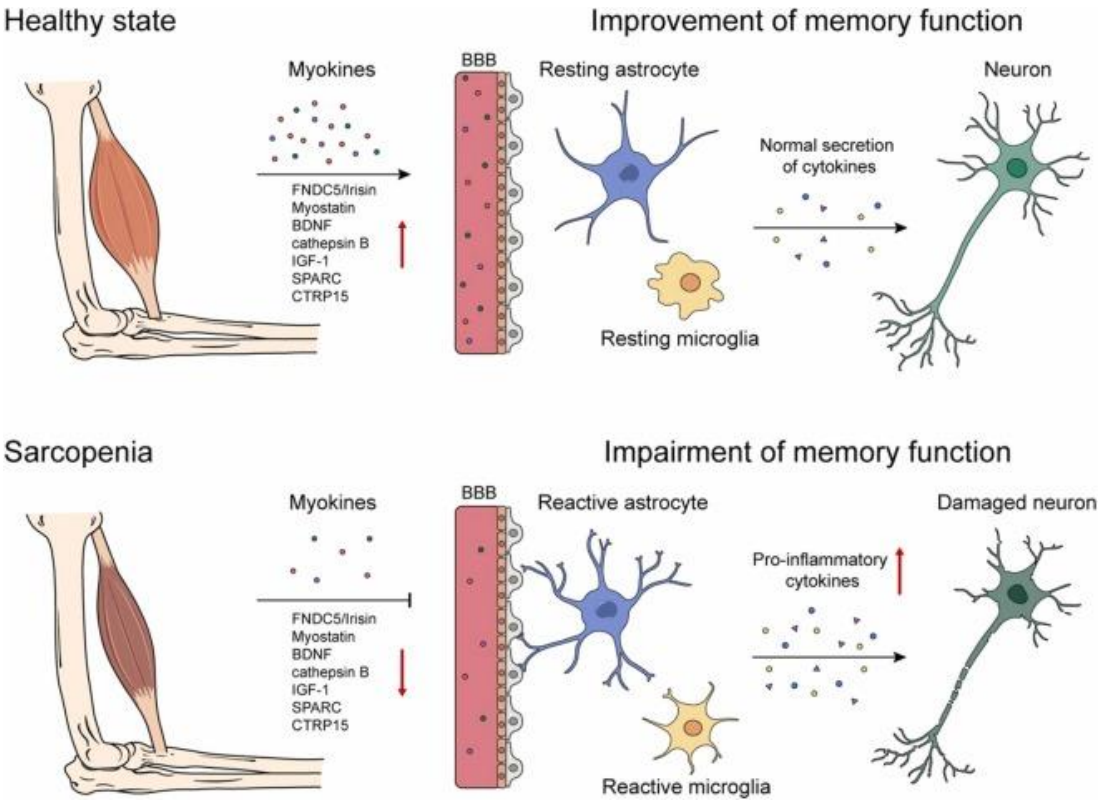


Fig.1. Multifactorial etiopathogenesis of sarcopenia [32]



Rice. 2. Functions of muscle tissue [40]

The incidence of sarcopenia in the population increases steadily with age: from 14% among people aged 65–70 years to 53% or higher in people aged 80 years [14, 17]. First of all, sarcopenia leads to a deterioration in the functionality of fast muscle fibers, which are responsible for maintaining balance when the position of the center of gravity changes. This, in turn, increases the risk of spontaneous falls: in cancer patients, the incidence of falls increases by 10% [18, 22]. Falls cause serious injuries in 10–15% of cases, and fractures in 5% of cases [23]. According to statistics, 5.3% of all hospitalizations and 90% of proximal femur fractures are caused by falls from one's own height, and among the risk factors for non-vertebral fractures, falls are more significant than a decrease in bone mineral density [24, 25]. Sarcopenia is also significantly associated with the incidence of osteoporosis, fractures and falls, which increases all-cause mortality and sharply reduces survival [26, 28].

Etiopathogenesis of sarcopenia: the role of mitochondrial dysfunction and hormonal disorders

The mechanisms of sarcopenia continue to be actively studied, and it is already clear that there is no universal mechanism for loss of quantity and quality of muscle mass [29, 32]. Sarcopenia is a multifactorial syndrome with a complex interdisciplinary pathogenesis. According to modern concepts, muscle tissue acts as one of the most significant human organs, since it produces a large amount of biologically active substances, hormonoids and special cytokines (myokines). The latter are cellular regulators of growth and decay and support the function of muscle mitochondria [33, 40].

Any moderate, constant physical activity improves the quality of life and even prolongs it. It has been proven that moderate physical activity promotes the biogenesis of mitochondria in skeletal muscles, activating their antioxidant properties, the production of endorphin and serotonin - hormones of joy and happiness, and also reduces the manifestations of insulin resistance and oxidative stress. Thus, in rodents kept in cages with a squirrel wheel, after six months of voluntary jogging, the activity of telomerase (an enzyme that stabilizes the end sections of cell chromosomes) in the heart tissue increased 1.7 times, and the level of the p53 protein (pro-oncogene) decreased by half.

A decrease in muscle mass in cancer patients, especially in modern conditions of physical inactivity and muscle detraining, begins very early. This is due to the lack of adequate biogenesis of myocyte mitochondria. With increasing influence of oxidative stress, mitochondrial dysfunction of muscle tissue steadily increases, which turns from functional to morphological. This, in turn, contributes to a further deterioration of metabolism and leads to clinical manifestations of a deficiency in the quantity and quality of muscle tissue [2, 6]. In striated muscles, with mitochondrial dysfunction, abnormally enlarged mitochondria accumulate, which is accompanied by muscle ischemia or anoxia. When stained with Gomori trichrome, they are detected in muscle tissue biopsies in the form of characteristic "broken red threads" [41,43].

Receptors for many hormones (glucocorticosteroids, estrogens, androgens, thyroid hormones, hormone D) are found in mitochondria of various cell types. Hormones not only influence cells through genomic mechanisms, activating certain nuclear DNA genes, but also have a non-genomic effect on cell mitochondria, the main producers of cellular energy and the most powerful intracellular antioxidants [19, 42]. For example, age-related deficiency of thyroid hormones (hypothyroidism) has a number of negative consequences. The fast (non-genomic) effects of stimulating the respiratory chain and the slow genomic effects of mitochondrial biogenesis are weakened, and the mass of mitochondria is increased due to the direct effect of T3 on nuclear transcription proteins and mitochondria. At the same time, an increased level of cortisol, characteristic of an aging person and reflecting an increase in age-related oxidative stress, potentiates

the negative impact of age-related hypothyroidism on the function of myocyte mitochondria [13].

One of the powerful hormones that have a pronounced anabolic effect on muscle mass is growth hormone - somatotropin, the role of which in the pathogenesis of many diseases continues to be actively studied. The problem of age-related decrease in somatotropin secretion is widely discussed in the literature, but has not yet found proper clinical application. It is known that a decrease in the synthesis of growth hormone leads to a decrease in the secretion and level of insulin-like growth factor 1 (IGF-1), or somatomedin C, the laboratory determination of which is now available and is used to diagnose growth hormone deficiency.

Levels of somatotropin and IGF-1 decrease with age. Given the anabolic effect of these hormones, their therapeutic effect in sarcopenia is assumed. It has been shown that the administration of somatotropin in pharmacological doses increases muscle mass and strength by increasing protein synthesis in myocytes and improving the function of their mitochondria [30, 31]. In addition, the relationship between somatotropin and other hormones that have an anabolic effect on muscle tissue is being studied [22–35].

Low levels of sex hormones are significantly associated with obesity and hyperinsulinemia (insulin resistance) through the mechanisms of sarcopenia (deficiency in the quantity and quality of skeletal muscle), since glucose utilization occurs mainly in muscle tissue. Stimulation of endogenous testosterone secretion by human chorionic gonadotropin has been shown to improve insulin sensitivity within 48 hours [32].

Methods for diagnosing sarcopenia

Increasing clinicians' awareness of the high prevalence of the above conditions is key to developing preventive measures, as well as adjusting the treatment of patients with malignant tumors.

Skeletal muscle is the most massive organ, occupying 40-50% of body weight, consuming 20% of the energy entering the body at rest, and possessing enormous metabolic potential [28]. Over time, the definition has changed significantly, moving from a purely gerontological concept to the presentation of sarcopenia as a clinical condition manifested by significant muscle deficits affecting functional status and depending on comorbidities, exogenous factors and lifestyle[21]. Lisa Martin et al. (2013) define sarcopenia as “severe muscle wasting” [23]. This term combines both processes occurring at the cellular level (denervation, mitochondrial dysfunction, inflammation, hormonal changes) and their consequences: decreased muscle strength, physical activity and mobility; increasing weakness, risk of falls; reducing the body's energy needs. Sarcopenia in people over 60 years of age is diagnosed in 13–24% of cases, in people aged 80 years and older - in more than half [24]. The International Working Group on Sarcopenia defines sarcopenia as the presence of low muscle mass and decreased muscle function as measured by walking speed. Sarcopenia may be associated with increased fat mass, but this is not necessarily the case [14].

According to the European consensus, “sarcopenia is a decrease in lean body mass and a decrease in muscle function (strength and performance) due to age-related, neurohumoral changes, nutritional disorders or muscle catabolism” [9, 29]. Sarcopenic loss of muscle mass is divided into physiological (the volume of skeletal muscles after 30 years decreases by 1% per year) and pathological [27]. Loss of muscle mass is a serious complication of many chronic diseases, including cancer, and leads to the development of weakness, decreased physical activity, loss of independence from others, and an increased risk of death. Sarcopenia also contributes to the progression of frailty syndrome. Currently, experts identify a special condition - presarcopenia, defined as dynopenia, in which there is a decrease in muscle strength without impaired mobility [27]. According to some authors, sarcopenia is much more common in men than in women: 61 and 31%, respectively [4]. Aspects of the pathogenesis of sarcopenia are enhanced by a number of negative effects on the body during systemic antitumor therapy, worsening its results and the quality of life of patients [23, 33]. However,

sarcopenia has not been sufficiently studied and oncologists, lacking knowledge, do not pay due attention to it in clinical practice. At a young age, skeletal muscle occupies 40-50% of the total body weight, but with age it regresses, and by the age of 75-80 it makes up only 25% of the total body weight [42, 43]. Age-related loss of skeletal muscle tissue is a process of reduction in the number and size of muscle fibers, which occurs due to multifactorial effects: decreased physical activity; chronic inflammation; deficiency of macronutrient intake (primarily protein); hormonal changes; so-called oxidative stress (physiological stress caused by oxidative reactions that are not typical for humans). natural metabolism) [8, 37, 39]. To date, it has been established that age-related sarcopenia (AS) is characterized by atrophy and necrosis of type II muscle fibers [45]. LB Verdijk et al. showed that degradation of type II muscle fibers is associated with a reduction in the satellite cell pool [45]. However, other authors have not noted changes in the number of satellite cells during myogenesis in elderly people [45]. However, most studies have demonstrated an age-related decrease in the regenerative potential of skeletal muscles due to a slowdown in the processes of proliferation and differentiation of satellite cells [43]. A number of possible mechanisms for the development of VS have been described, but the specific contribution of each of them to the overall process remains unclear. The pathogenesis of sarcopenia is shown in Fig. 1. Recent data indicate that an age-related decrease in the expression of "positive" regulators (anabolism regulators) (Akt kinase, MRTF-s and serum response factor) is an important factor in the progression of sarcopenia [34, 37, 38]. On the contrary, it was not possible to prove an increase in the activity of "negative" regulators (catabolism regulators) (atrogin1, myostatin, calpain proteolytic enzymes) in the muscles of aging mammals. Among age-related hormonal changes, a deficiency of steroid hormones has a decisive influence on muscle metabolism. It is known that testosterone has an anabolic effect, which is also expressed in muscle hypertrophy. Age-related declines in testosterone levels result in decreased muscle strength in both men and women. Also, with age, the secretion of the insulin-like growth factor IGF-I progressively decreases, causing a decrease in somatropin levels, which also contributes to the progression of sarcopenia [13, 34]. The insulin-like growth factor IGF-I is one of the most important mediators of muscle tissue synthesis and remodeling, realized through the Akt-mToR-p70S6K signaling pathway [30].

Diagnosis of sarcopenia Routine body mass index (BMI) and anthropometric measurements (circumference and calypmetric methods) are not valid for the diagnosis of sarcopenia, since sarcopenia has been shown to occur at various BMI levels, including overweight and obesity. Thus, a Canadian study by VE Baracos et al., which included 441 patients, demonstrated a significant incidence of sarcopenia in patients with stage III–IV non-small cell lung cancer (46.8%) [4]. At the same time, sarcopenia was recorded at various BMI indicators, including overweight and obesity. With a BMI below 18.5, sarcopenia was diagnosed in only 7.5% of patients [4]. VC. Lyadov et al., determining the media, diagnosed sarcopenia in 70% of patients with pancreatic cancer. The authors also noted the lack of correlation between BMI and the presence of sarcopenia [1]. Today, screening scales and instrumental methods are used to diagnose sarcopenia. As a screening for this pathological condition, the SARC-F rating scale, convenient in clinical practice, has been proposed, consisting of only five indicators (Table 1) [22]. A test result of four points or more suggests the presence of sarcopenia [22]. Other tests have also been proposed to assess the functional state of muscles (Table 2). To analyze the component composition of the body, clinicians have bioimpedance analysis (BIA), densitometry, dual-energy X-ray absortiometry, magnetic resonance imaging, computed tomography (CT), and PET-CT at their disposal. The most common method for diagnosing sarcopenia is the determination of the Skeletal Muscle Index (SMI) during CT. Skeletal muscle area is calculated from two axial sections taken at the level of the third lumbar vertebra (L3). All striated muscles are outlined on computer sections, and the computer program calculates the

sum of their areas and the arithmetic mean. The ratio of the resulting indicator of skeletal muscle area at the L3 body level to the square of the patient's height is defined as the skeletal muscle index (SMI L3) [1, 40]. The principle of BIA is that an alternating current of a certain frequency is passed through a tissue mass, followed by measuring the electrical impedance (resistance) of the tissue. At the same time, the impedance of tissue fluids is low, and the impedance of adipose and bone tissue is high. Thus, BIA allows you to determine the total fluid content in the body and calculate fat and fat-free (lean) mass. Lean mass in sarcopenia in men is less than 14.6 kg/m2, in women it is less than 11.4 kg/m2 [2]. Dual-energy X-ray Absorptiometry (DXA) is often used in the clinic due to its relative low cost and minimal radiation exposure. DXA also determines the mass media (the sum of the measured muscle mass of the upper and lower extremities).

CONCLUSION

According to the literature and research results, sarcopenia, caused by changes in the structure and function of muscle tissue, makes a significant negative contribution to the pathogenesis of most diseases, especially in patients with malignant tumors. It dramatically worsens the quality of life, significantly increasing the risk of falls, reducing a person's functionality and ability to self-care. Sarcopenia leads to constantly progressive mitochondrial dysfunction of all cells of the body against the background of steadily increasing insulin resistance and disorders in the mitochondria of myocytes (the most energy-consuming cells of muscle tissue) and a deficiency of most anabolic hormones, primarily sex steroid hormones, hormone D, growth hormone (somatotropin), sleep hormone (melatonin). Increasing life expectancy poses an important challenge for 21st century medicine – to ensure activity and independence. Therefore, against the backdrop of the development of new methods for the treatment of osteoporosis, atherosclerosis and cancer, more attention should be paid to the pathogenetic therapy of sarcopenia.

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