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THE ASSOCIATION OF SARCOPENIA AND OSTEOPOROSIS AND THEIR ROLE IN FALLS AND FRACTURES

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Ключевые слова: *саркопения, остеосаркопения, распространенность, метаболические нарушения, падения, переломы*

Abstract. The association of sarcopenia and osteoporosis and their role in falls and fractures (literature review). Povoroznyuk V.V., Dedukh N.V., Bystrytska M.A., Dzerovych N.I., Shapovalov V.S. *The progressive and generalized loss of skeletal muscle mass and strength leads to sarcopenia in elderly people. A new geriatric syndrome has been revealed – osteosarcopenia (osteosarcoporosis), which combines low bone mineral density with reduced muscle mass, strength and functional activity. The review presents data on the peculiarities of manifestation of these syndromes, the mechanisms of which are multifactorial and continue to be investigated. They are associated with genetic factors, lifestyle – lack of physical activity and malnutrition. The pathogenesis of sarcopenia involves mechanisms of chronic inflammation, changes in endocrine function, disturbance of neuromuscular connections and low reparation level. Sarcopenia correlates with low quality of life, disability, and death. The review analyzes the prevalence of sarcopenia which increases with age. However, there are conflicting results in the populations, which may be related to different clinical conditions, patient area, lifestyle and the use of different assessment criteria. The analysis of sarcopenia prevalence in men and women showed ambiguous results related to the studied population, involvement of different age groups of patients, different evaluation methods. Metabolic disorders in muscular and bone tissues were summarized on the basis of the analysis of the cross-influence of regulatory factors and metabolism products of these tissues; a close metabolic and functional association between them was shown. Fat infiltration of atrophied muscles and bone marrow is common in patients with sarcopenia and osteosarcoporosis, which affects muscle and bone tissue. Lipotoxicity and local inflammation stimulate the biosynthesis of pro-inflammatory cytokines. Literature analysis has shown controversial data on the association of sarcopenia and osteosarcopenia with falls and fractures, but based on meta-analysis data, which include an extensive body of information, it should be noted that individuals with sarcopenia and osteosarcopenia are more at risk of falls and fractures and require special special attention. The most common fracture in osteosarcopenia is the hip fracture.*

Реферат. Поєднання саркопенії та остеопорозу та їх роль при падіннях та переломах (огляд літератури). Поворознюк В.В., Дєдух Н.В., Бистрицька М.А., Дзерович Н.І., Шаповалов В.С. *Прогресуюча втрата скелетної м'язової маси й сили призводить до розвитку саркопенії в людей похилого віку. Виявлено новий геріатричний синдром – остеосаркопенія (остеосаркопороз), в якому поєднуються низька мінеральна щільність кісткової тканини зі зниженою м'язовою масою, силою і функціональною активністю. В огляді представлені дані про особливості проявів цих синдромів, багатофакторні механізми котрих знаходяться в стадії розширених досліджень. Їх пов'язують з генетичними факторами та способом життя – недостатньою фізичною активністю та неповноцінним харчуванням. У патогенезі саркопенії залучені механізми хронічного запалення, зміни ендокринної функції, порушення нейром'язових зв'язків і низький рівень репарації. Саркопенія тісно корелює з низькою якістю життя, інвалідністю, смертю. В огляді проаналізовано показники поширеності саркопенії, які збільшуються з віком. Однак у різних популяціях отримані суперечливі результати, які можуть бути пов'язані з різноманітними клінічними умовами, регіоном проживання пацієнтів, способом*

життя і використанням різних критеріїв оцінки. Аналіз поширеності саркопенії в чоловіків і жінок показав неоднозначні результати, зумовлені досліджуваною популяцією, залученням пацієнтів різних вікових груп і неоднаковими методами оцінки. Метаболічні порушення в м'язовій і кістковій тканинах узагальнені на основі аналізу перехресного впливу регуляторних факторів і продуктів метаболізму цих тканин, показано тісний метаболічний та функціональний зв'язок між ними. У пацієнтів із саркопенією й остеосаркопорозом поширена жирова інфільтрація атрофованих м'язів і кісткового мозку, що впливає на метаболізм м'язової і кісткової тканин. Ліпотоксичність і місцеве запалення стимулюють біосинтез прозапальних цитокінів. Аналіз літератури показав суперечливі дані про асоціацію саркопенії й остеосаркопенії з падіннями і переломами, однак ґрунтуючись на даних метааналізів, які включають великий масив інформації, слід зазначити, що особи з саркопенією й остеосаркопенією більш схильні до ризику падінь, переломів і вимагають особливої уваги. Найбільш тяжким переломом при остеосаркопенії є перелом проксимального відділу стегнової кістки.

I.H. Rosenberg first described sarcopenia as a loss of skeletal muscle mass with age [32]. In 2016, sarcopenia was included in the International Classification of Diseases (10th edition, code M62.84) [5, 13]. This pathology is characterized by progressive generalized skeletal muscle mass and strength loss, which is reflected in their function, manifested by general weakness, increased risk of falls, fractures, disability and increased mortality.

The diagnostic criteria for sarcopenia were proposed by the European Working Group on Sarcopenia (EGSOP) [36]. These include hand-grip dynamometry, gait speed and muscle mass. The most commonly used questionnaires for diagnosis are SarQol (Sarcopenia and Quality of Life) and SARC-F (Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls).

Epidemiology

Prevalence. The number of older people around the world are steadily increasing and sarcopenia is the leading disease at this age, although it may also manifest itself at younger ages. Sarcopenia is considered to be a skeletal muscle pathology, including osteoporosis, and also develops with neoplasms, chronic obstructive pulmonary disease, chronic renal failure, etc.

The development of sarcopenia is facilitated by many factors affecting the loss of muscle mass and strength at any age, such as lack of physical activity, poor nutrition, endocrine system and metabolic disorders, chronic inflammation, as well as genetic factors [2]. With age, the biosynthesis of muscle proteins and regulatory factors decreases, which slows down reparative processes in muscle tissue.

The number of patients in Europe is expected to increase from 20 to 32.3 million by 2045 [39]. In the USA 12-14% of people have sarcopenia (about 50 million people) and a doubling of number of patients by 2050 is predicted. As reported in 2014 by of the European Working Group on Sarcopenia in Older People (EWGSOP) and International Working Group on Sarcopenia (IWGS) prevalence of sarcopenia was registered in 1-29% of those in community-dwelling populations of older adults, 14-33% in long-term care institutions and 10% in the acute hospital-care population [28]. The prevalence of sarcopenia was 19.2% in males and 8.6% in females aged >65 [38]. Other studies have shown that sarcopenia prevalence was from 2% to 37% in communities [31, 41]. A high percentage of sarcopenia (32.8%), of which 68% were men, was found among people aged 70 years and living in communities. The disease was registered in 50% of people aged > 80 years [36].

Prevalence of sarcopenia among apparently healthy Ukrainian women, as shown for other populations, increases with age. Sarcopenia indicatots were 4.1% among 50-59 years old (y/|o), 3.7% – 60-69 y/o, 18.4% – 70-79 y/o, 30.8% – 80-89 y/o [1]. In estimating the prevalence of sarcopenia in men and women, there are controversial results, which may be related to the studied population and different age groups [31].

Falls and fractures in sarcopenia. Sarcopenia also affects a person's tendency to fall, which in some cases ends in a fracture [3, 33]. An imbalance is a strong risk factor for falling. The ability to maintain balance requires the interaction of the motor (muscular), nervous and sensory systems, the functions of which decrease with age. In a cross-sectional study in Australia in 2015 involving 680 elderly people with sarcopenia, falls were recorded in 40% of individuals [27]. Meta-analysis data, which included 2,771 literature sources are presented [33]. Individuals with sarcopenia were found to have a higher risk of falling (OR 1.60; 95% CI 1.37-1.86, P<0.001, I2=34%) and fractures (OR 1.84; 95% CI 1.30-2.62, P=0.001, I2=91%) compared to patients without sarcopenia.

The ilSIRENTE study evaluated the relationship between sarcopenia and 2-year risk of falling among 260 persons aged 80 and over [34]. Sarcopenia was found in 66 participants (25.4%), 18 of whom (27.3%) reported falling incidents during the 2-year observation period. It was found that persons with sarcopenia were more than three times prone to falling.

A survey of a group of 2000 men in the community aged ≥65 found that sarcopenia was

associated with an increased risk of fractures (OR 1.87; 95% CI 1.26-2.79) regardless of bone mineral density (BMD) and other clinical risk factors [45]. Another study based on meta-analysis has shown that sarcopenia is a risk factor for falling among older people living in communities (OR=1.52, CI: 1.32-1.77) [14].

However, there are sporadic studies that do not show a connection between sarcopenia, falls and fractures. In a study of 498 adult men and women, a weak association between sarcopenia and falls was shown and no connection with fractures was found [37]. Another study also showed no correlation between sarcopenia and fracture in the distal end of the forearm bones, but found a strong correlation with BMD [20].

That is, sarcopenia's association with falls is presented in a variety of ways, but based on meta-analyses that include a vast array of information, it should be noted that people with sarcopenia are more likely to fall and fracture.

At the same time, the development of sarcopenia may also be associated with a previous fracture. A review has been carried out on the PubMed and Cochrane databases to analyze and generalize data on the prevalence of sarcopenia in low-energy fracture patients and to identify fracture risk factors in sarcopenia patients [43]. The prevalence of sarcopenia after fracture ranged from 12.4% to 95% in men and from 18.3% to 64% in women. Two studies have shown that sarcopenia was a significant risk factor for low-trauma fracture at low BMD, but only in men. The authors believe that there is an urgent need for further research into the relationship between sarcopenia and low-energy fracture risk, in order to better understand its pathophysiological mechanisms.

In a Spanish study, sarcopenia incidence in patients with low-energy hip fracture was 17.1% (12.4% in men, 18.3% in women) [30]. The prevalence of sarcopenia in patients with hip fracture in the Chinese population was 73.6% in males and 67.7% in females, and 20.8% and 12.4%, respectively, as defined by the Asian Sarcopenia Working Group [29]. In the Taiwanese population of 139 patients with hip fracture, 70 (50.3%) had sarcopenia [40]. Sarcopenia has also been associated with an increased risk of vertebral fractures [11]. These data suggest that fractures in old age can be considered a risk factor for sarcopenia.

In addition, there is a study showing that after proximal femur fractures, older patients with sarcopenia need more blood for transfusion during the perioperative period and longer postoperative hospitalization [12].

Mechanisms of the interrelation of the bone and muscular systems

The bone and muscular systems are closely linked. Bone remodeling is not only dependent on the gravitational load, but also on the functional activity of the muscles and the close metabolic connection between the two systems. The concept of "musculoskeletal unit" has been developed, which is based on linear relationships at different ages between BMD and muscle mass, and the cross-influence of these tissues.

An association study (GWAS) has shown that some genes are associated with both sarcopenia and osteoporosis. These include polymorphisms of genes encoding myostatin (MSTN), α-actinin 3 (ACTN3), glycine-N-acyltransferase (GLYAT), and methyltransferase-like protein 21C (METTL21C), coactivator of 1-alpha receptor, proliferator-activated by peroxisome proliferators, gamma (PGC-1α) and myocyte enhancer factor 2C (MEF-2C) [18, 23].

Myokines, humoral cytokines and growth factors expressed by skeletal muscles affect bone metabolism. Among them are myostatin, insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), interleukins (1, 6, 15), osteoglycin, osteonectin, the family of proteins FAM5C, irisin, transmembrane protein 119 (Tmem 119), matrix metalloproteinase-2, activin, follistatin, monocyte chemoattractant protein (MCP)-1, transforming growth factor-β (TGF-β), bone morphogenetic proteins (BMPs), ciliary neurotrophic factor (CNTF) and others. The functions of many of them are not fully understood [21, 22].

Myostatin plays an important role in bone remodeling. It reduces bone formation and stimulates resorption, influencing the proliferation of osteoclasts by stimulating the expression of genes producing the RANKL by osteoblasts, receptor integrin αVβ3, dendrocyte expressed seven transmembrane protein (DCSTAMP) and calcitonin receptor.

However, despite the established pathways of myokines' influence on bone metabolism, this direction requires further research, which will contribute to accurate diagnostics and development of methods for treatment of muscle and bone diseases, such as sarcopenia and osteoporosis.

Sarcopenia increases the expression of pro-inflammatory TNF-α and C-reactive protein molecules that directly or indirectly affect musculoskeletal metabolism [44]. The state of muscle tissue is affected by mitochondrial dysfunction observed in sarcopenia, associated with increased apoptosis, which is accompanied by low reparative ability [35].

Growth hormone, sex hormones, and pathological conditions such as excess glucocorticoids and diabetes affect both muscles and bones [21].

There is also a reverse pathway of the influence of bone tissue on muscle tissue through the secretion of osteoblasts and osteocytes of osteokines, among which: prostaglandin E2, sclerostin and osteocalcin [21]. Osteocalcin stimulates the proliferation of β-cells of the pancreas, which secrete insulin, affecting the metabolism of muscle tissue. Myoblasts proliferation is also affected by the secretion of vascular endothelial growth factor (VEGF) by mesenchymal stromal cells of the bone marrow. Protein of the signaling pathway Wnt-3a expressed by bone cells also affects muscle function, but this pathway has not been sufficiently studied.

The effect of vitamin D deficiency on muscle and bone tissue has been studied and evaluated, which is accompanied not only by a decrease in BMD, but also by a decrease in muscle strength, lengthening the relaxation phase of muscle contraction. Vitamin D affects muscle and bone cells both directly through receptor (VDR) and indirectly, affecting calcium homeostasis, phosphate and parathyroid hormone (PTH) secretion [7].

Closely related homeostasis of bone, muscle and adipose tissue is supported through neuro-humoral connections. In patients with sarcopenia and osteoporosis, fat infiltration of atrophied muscles and bone marrow is widespread, affecting muscle and bone tissue. Lipotoxicity and local inflammation stimulate biosynthesis of proinflammatory cytokines, among which are interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [18]. In clinical practice, sarcopenia in combination with osteopenia/osteoporosis and other disorders of body composition (high fat mass) are quite common. These states are defined as sarcopenic obesity or osteosarcopenic obesity [4].

Osteosarcopenia

Given the close relationship and commonality of osteoporosis and sarcopenia pathogenesis, the term "osteosarcopenia" or "sarcoporosis" is now widely used [9]. Osteosarcopenia has been described as a new geriatric syndrome that combines low BMD with reduced muscle mass, strength and functional activity [16, 23]. No specific markers of this pathology have been revealed, however, it has been established that such patients have lower levels of testosterone, vitamin D and hemoglobin in comparison with isolated pathology – osteoporosis or sarcopenia [2]. The development of osteosarcopenia is influenced by endocrine diseases, alimentary insufficiency, obesity and corticosteroid intake.

In a study published in 2019, which included 3,334 elderly people, it was demonstrated that individuals with a confirmed sarcopenia diagnosis had lower BMD rates and bone architecture disorders in various anatomical skeletal areas compared to those without sarcopenia [6].

The prevalence of osteosarcopenia in the elderly living in community is 4.7% in Japan, 28% in Germany, ranging from 7% to 13% in China, with the highest rates of 40% in Australia and 34% in Iran [14, 19, 26]. Osteosarcopenia incidence increases with age, in men it ranges from 14.3% (60-64 years) to 59.4% (> 75 years), in women it is 20.3% (60-64 years) to 48.3% (> 75 years) [24].

However, in another study, higher rates of osteosarcopenia were recorded in women, ranging from 2.5 to 82.6%, compared with 16.4 to 32.0% for men [15].

The prevalence of sarcopenia depended on the criteria used to establish the diagnosis. Cases of sarcopenia (92 patients, mean age 66±10 years, 90% of women) according to core muscle index (CMI) criteria were found in 65% of patients (9% had sarcopenia, 56% had osteopenia), only 22% had osteopenia/osteoporosis, 13% – without these pathologies [8]. In terms of handgrip strength, sarcopenia was found in 60% of individuals, in gait speed – 45% and by SARC-F score (A Simple Questionnaire to Rapidly Diagnose Sarcopenia) – 40%. Osteosarcopenia according to handgrip strength was found in 51%, gait speed – 34% and SARC-F score – 32%.

According to X-ray bone densitometry and skeletal muscle index (skeletal muscle mass divided by height in meters, squared, SMI), sarcopenia was found in persons with normal BMD in 40%, with osteopenia – 64%, with osteoporosis – 76%. When comparing the frequency of pathology by sex, gender-specific features were identified, sarcopenia was recorded in 69% of women and 33% of men (p=0.034). Patients with osteosarcopenia and sarcopenia had lower body weight indices, skeletal muscle mass and appendicular mass (limb muscle mass) as well as skeletal muscle index compared to patients with osteopenia/osteoporosis or without this pathology [8].

Among the 2,353 individuals living in the community, risk factors associated with osteosarcopenia included older age (men: 14.3% (60-64 years) to 59.4% (≥75 years); women: 20.3% (60-64 years) to 48.3% (≥75 years); physical inactivity (cumulatively men and women (OR): 0.64, 95%, CI 0.46-0.88), low body mass index (OR: males: 0.84, 95%, CI 0.81-0.88; females: 0.77, 95%, CI 0.74-0.80) and higher fat mass (males: 1.46, 95%, CI 1.11-1.92; females: 2.25, 95%, CI 1.71-2.95) [24].

The data are controversial with respect to the risk of fall and fracture in osteoporosis (compared to sarcopenia and osteoporosis). In a prospective cohort study the Osteoporotic Fractures in Men (MrOs),

which lasted from 2001 to 2013 and included 2,000 individuals (≥65 years), it was found that men with osteoporosis have a 3.5 times greater risk of fractures than men with sarcopenia or only osteoporosis [45].

A study in Australia (253 individuals, 77% of whom were 77.9±0.42 years old women) found that the risk of fall (ODs: 2.83-3.63; p<0.05) and fracture (ODs: 3.86-4.38; P < 0.05) was significantly higher in osteosarcopenia patients than in those without this pathology [42]. The combination of osteoporosis and sarcopenia resulted in a significant increase in the risk of fracture (OR 3.49, 95% CI 1.76-6.90) in comparison with persons with normal BMD and without sarcopenia [45].

Osteosarcopenia was high – 5 to 37% in older people (≥65 years) living in communities. Sarcopenia following low-trauma fractures was found in 46% of patients, of whom 17.1-96.3% had hip fractures [24]. The hip fracture is associated with increased mortality in osteosarcopenia patients [25].

In the comparative analysis of the risk of fractures and falls in 1575 men with osteosarcopenia aged over 70 years, no distinctive features were revealed in comparison with osteopenia/osteoporosis and sarcopenia groups [10]. The participants were contacted for 2 years, and for radiologically confirmed fracture incidents – every 4 months for 6±2 years.

The relationship of osteosarcopenia with serum PTH levels and falls was found. Of the 400 patients surveyed, 24% had high PTH levels with normal adjusted calcium levels. These individuals reported more falls per year and had low levels of muscle strength, gait rate and BMD [17].

When osteoporosis and sarcopenia are combined, different results concerning the risk of falls and fractures are obtained. These data indicate a need for in-depth research in this area.

Thus, sarcopenia is regarded as a separate nosologic form presented in the International Classification of Diseases 10 (ICD-10) as a syndrome that may manifest itself as a primary or secondary condition. The manifestation of sarcopenia is associated with loss of muscle mass, strength and is combined with an increased risk of falls and fractures. In turn, fractures may be a pathogenetic factor in sarcopenia. Numerous signaling pathways leading to disturbance of metabolism and muscle structure have been described and the close metabolic and functional association between muscle and bone tissue has been demonstrated. The concept of osteosarcopenia as a new geriatric syndrome has been developed. Osteosarcopenia is widespread in various populations and is associated with serious health consequences in terms of quality of life: general weakness, increased risk of falls, fractures and mortality.

Conflict of interests. The authors declare no conflict of interest.

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