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Osteosarcopenia: epidemiology, risk factors and modern management strategies

D. Yu. Kurylo, N. V. Grygorieva

State Institution «D. F. Chebotarev Institute of Gerontology of the NAMS Ukraine», Kyiv

Osteosarcopenia is a combination of osteoporosis and sarcopenia that has been identified as a distinct geriatric syndrome, which has recently attracted increasing attention from the medical community. Unfortunately, to date, there are no unified criteria for defining this syndrome, which affects the determination of its epidemiology and prevention methods. The coexistence of osteoporosis and sarcopenia in an individual is associated with an increased risk of falls and fractures, reduced functional capabilities and quality of life, and a heightened risk of mortality; thus, it holds significant medical and social importance. The aim of this review was to analyze the current literature on osteosarcopenia, including its prevalence, pathogenesis, risk factors, and management. Methods. A review of literature sources was carried out in the electronic scientometric databases PubMed, Scopus, Web of Science and Google Scholar using the keywords: "osteoporosis", "sarcopenia", "osteosarcopenia", "sarcoporosis" for 2019-2024 with additional inclusion in the analysis of earlier publications which have a recognized scientific value. Both cohort and prospective studies, as well as meta-analyses and systematic reviews, were analyzed. The results of this work included clarifying terminology, determining the global prevalence of osteosarcopenia, and analyzing risk factors and key components of its pathogenesis, particularly in subjects with comorbidities (such as diabetes and obesity). Scientific studies on the most explored pharmacological and non-pharmacological approaches to treating osteosarcopenia were also reviewed, with a focus on methods that require further research to confirm their effectiveness. Conclusions. Given the prevalence of osteosarcopenia and the associated risks, further investigation, especially within the Ukrainian population, is highly relevant and necessitates new research to improve the management of this geriatric syndrome.

Остеосаркопенія є поєднанням остеопорозу та саркопенії, яке було виділено, як окремий геріатричний синдром, що останнім часом привертає все більше уваги медичної спільноти. На жаль, сьогодні немає єдиних критеріїв щодо його визначення, що впливає на вивчення епідеміології та методів профілактики. Поєднання остеопорозу та саркопенії в однієї особи асоційовано з підвищенням ризику падінь і переломів, зниженням функціональних можливостей та якості життя, зростанням ризику смертності, тому має вкрай важливе медико-соціальне значення. Мета. Проаналізувати сучасні літературні джерела, які вивчають остеосаркопенію, її поширеність, патогенез, фактори ризику та менеджмент. Методи. Огляд літератури здійснено в електронних наукометричних базах даних PubMed, Scopus, Web of Science та Google Scholar із використанням ключових слів: «остеопороз», «саркопенія», «остеосаркопенія», «саркопороз» за 2019–2024 роки з додатковим включенням до аналізу більш ранніх робіт за умови їх визнаної наукової цінності. Розглянуто як когортні та проспективні дослідження, так і метааналізи й систематичні огляди. Результатом цієї роботи є уточнення термінології, визначення поширеності остеосаркопенії у світі, аналіз факторів ризику й основних ланок патогенезу, зокрема і в осіб із супутньою патологією (цукровий діабет, ожиріння тощо). Проаналізовані наукові роботи стосовно найбільш вивчених медикаментозних і немедикаментозних підходів у лікуванні остеосаркопенії з розглядом методів, які потребують подальшого вивчення для підтвердження своєї ефективності. Висновки. Ураховуючи поширеність остеосаркопенії та ризики, які пов'язані з нею, її подальше вивчення, зокрема й в українській популяції, є вкрай актуальним і потребує проведення нових науково-дослідних розробок для покращення менеджменту цього геріатричного синдрому. Ключові слова. Остеопороз, саркопенія, остеосаркопенія, саркопороз.

Key words. Osteoporosis, sarcopenia, osteosarcopenia, sarcoporosis

Introduction

As human life expectancy has increased due to improved living conditions and medical advances, the proportion of the elderly in the world population has increased significantly. According to current projections, the number of people aged 60 years and older will continue to increase, from 1.1 billion in 2023 to 1.4 billion in 2030 [1]. This will contribute to a rise in the number of age-associated diseases and conditions, and their study is becoming increasingly relevant. The main geriatric syndromes include cognitive impairment, depression, chronic pain, polypharmacy, certain functional limitations, urinary or fecal incontinence, constipation, orthostatic hypotension, syncope, pressure ulcers, vision, hearing or sensory impairment, falls, frailty, malnutrition, or loss of muscle mass and strength (sarcopenia) [2–4]. The presence of the latter in combination with osteoporosis in one person has been singled out as a separate geriatric phenomenon, which has been combined with the terms "osteosarcopenia" (OSP) or "sarcoporosis" [6]. However, today there is no consensus in the world on the definition of this condition. Some scientists define OSP as a combination of osteoporosis, instrumentally confirmed by two-photon X-ray absorptiometry (DXA) and sarcopenia, others in the presence of low bone mineral density (BMD, osteopenia or osteoporosis) and sarcopenia or in the case of an osteoporotic low-traumatic fracture in combination with sarcopenia [7–10]. OSP poses a threat to the elderly due to the increased risk of a number of complications characteristic of both diseases, therefore it requires more attention and in -depth study. In recent years, there has been an increasing number of high-quality studies studying this syndrome. Regrettably, the Ukrainian-language literature contains only limited research on the study of OSP as evidenced by references [11, 12].

Purpose: to analyze modern literary sources on osteosarcopenia, its epidemiology, pathogenesis, risk factors and possible ways of prevention and treatment.

Material and methods

A review of literature sources was carried out in the electronic scientometric databases PubMed, Scopus, Web of Science and Google Scholar using the keywords: "osteoporosis", "sarcopenia", "osteosarcopenia", "sarcoporosis" for

2019–2024 with additional inclusion in the analysis of earlier studies provided that their recognized scientific value was recognized. Both cohort and prospective studies, as well as meta-analyses and systematic reviews, were analyzed.

Results

Definition of osteosarcopenia

As noted above, OSP combines two diseases: sarcopenia and osteoporosis.

The term "sarcopenia" was first proposed to describe the loss of skeletal muscle mass by I. Rozenberg in 1989, and in 1998 R. Baumgartner used this term to characterize a syndrome associated with an increased risk of falls and physical weakness [13, 14]. According to the latest European guidelines issued by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2019, it is a progressive and generalized skeletal muscle disease associated with an increased risk of falls, fractures, impaired motor activity and mortality [15].

The definition of "osteoporosis" was first proposed by the World Health Organization (WHO) in 1994 [16]. This disease is characterized by a decrease in bone density and impaired bone microarchitecture and leads to an increased risk of falls and fractures, and, as a result, to disability and increased mortality [17].

To describe the combination of osteoporosis and sarcopenia, G. Duque and colleagues first proposed the term "osteosarcopenia" [18]. The latter is characterized by low BMD (according to WHO standards osteopenia (according to the assessment of DRA values by T-criterion from –1 to –2.5 standard deviations (SD)) or osteoporosis (T-criterion ≤ -2.5 SD) or the presence of a low-energy osteoporotic fracture regardless of the state of bone tissue and low muscle mass and decreased function (sarcopenia)), which are established using criteria related to muscle mass, strength and functional capabilities of the subject.

However, there is still ongoing debate about the definition of OSP, and studies use different inclusion criteria to identify patients, which makes it difficult to compare its incidence and consequences. For example, in a meta-analysis by N. Veronese et al. [7], osteoporosis and sarcopenia are combined for the diagnosis of OSP, using generally accepted criteria for their establishment. In another meta-analysis by S. Chen et al., other OSP criteria were used for consideration: a combination of sarcopenia with low BMD (osteopenia or osteoporosis) or sarcopenia with osteoporosis [10]. In some publications, scientists define OSP as a combination of sarcopenia and low BMD (osteopenia or osteoporosis) [19–23], while other scientists consider the presence of sarcopenia and osteoporosis as criteria for determining OSP [24–28].

It should be noted that different researchers use not only different data on the assessment of bone tissue status (osteopenia, osteoporosis or low-traumatic fractures), but also different criteria for determining sarcopenia (EWGSOP, Asian Working Group for Sarcopenia (AWGS), Foundation for the National Institutes of Health Sarcopenia Project (FNIH), Sarcopenia Definitions and Outcomes Consortium (SDOC), etc.). Differences in the definition of OSP complicate the study of its epidemiology and require a unified approach, including outlining management and prognosis strategies.

Epidemiology of Osteosarcopenia

A meta-analysis by N. Veronese et al., which included 14,429 individuals (mean age 70 years, 64.5 % women, OSP criteria included a combination of osteoporosis by DXA and sarcopenia), showed that the prevalence of OSP was 12.72 % (95 % confidence interval (CI): 9.65–15.78) [7]. Another observation [10] analyzed data from 64,404 individuals aged 46.6–93 years to determine the overall incidence of OSP in the adult population worldwide and used different combinations of criteria. The results showed that the overall prevalence of this syndrome was 18.5 % (95 % CI: 16.7–20.3 %), including 15.3 % (95 % CI: 13.2–17.4) in men and 19.4 % (95 % CI: 16.9–21.9) in women. The authors found significant differences in the prevalence of OSP among people who were hospitalized (24.7 %) and living in the community (12.9 %) ($p = 0.001$).

The use of different criteria in the study of the epidemiology of OSP significantly affected the frequency of diagnosis of the syndrome. Thus, the prevalence of sarcopenia combined with osteopenia or osteoporosis was 20.7 % (95 % CI: 17.1–24.4), and sarcopenia alone with osteoporosis confirmed by DXA was 16.1 % (95 % CI: 13.3–18.9) [10]. Another meta-analysis that studied the prevalence of OSP was conducted by T. Huang et al. [29]. They analyzed 31 studies involving 15,062 subjects aged 64.1 to 84.8 years. The following diagnostic criteria for sarcopenia were used: 8 studies — AWGS, 16 — EWGSOP, 2 —FNIH, 3 — Japan Society of Hepatology (JSH), and the remaining 2 — two other sets of diagnostic scales. In 16 studies, OSP was considered the combination of sarcopenia and low BMD, and in 15 — the presence of osteoporosis and sarcopenia. Thirteen studies were conducted in Asia, 8 in Europe, 6 in Oceania, and 4 in the Americas. The prevalence of OSP ranged from 1.5 to 65.7 % with an overall rate of 21 % (95 % CI: 0.16–0.26). It was higher in women, at 28 % (95 % CI: 21–35 %), and in men, at 14 % (95 % CI: 9–20 %). It has been shown to be more common in European populations (26 %; 95 % CI 11–45 %) than in Asian populations (18 %; 95 % CI 13–24 %). It is higher in South America (23%; 95 % CI 5–48 %) than in North America (11 %; 95 % CI 8–15 %), while in Oceania it is 21 % (95 % CI 10–34 %). Among those living in the community, the prevalence of OSP was lowest (12 %; 95 % CI 7–18 %), compared with those receiving inpatient (26 %; 95 % CI 18–36 %) or outpatient care (33 %; 95 % CI 16–53 %) [29].

The heterogeneity of the results of the above-mentioned meta-analyses on the epidemiology of OSP is apparently related to differences in the populations included in the analysis, study designs (cohort, cross-sectional), and criteria for defining OSP. According to some scientists, the presence of an osteoporotic fracture is an important criterion for OSP. Thus, B. Kirk et al. found that the prevalence of OSP among the elderly living in the community varies within 5–37 %, with the most significant indicators in patients with a history of fractures: ~46 % for people with low-traumatic fractures and from 17.1 to 96.3 % with a femur fracture [9]. The inclusion criteria for this study were the definition of OSP, which included the combination of osteopenia or osteoporosis according to DXA or a current low-energy fracture regardless of BMD together with sarcopenia. In a later study by this author, which included 481 community-dwelling individuals (mean age 78 years, 75.9 % women), the inclusion factors for determining the prevalence of OSP were the combination of osteoporosis or osteopenia and sarcopenia diagnosed according to the SDOC or EWGSOP2 criteria. When the former was used to define sarcopenia, the prevalence of OSP was 37.2 %, and when the latter was used, it was 25.6 % [30].

Thus, to date, the results of individual publications and meta-analyses indicate significant variability in the frequency of OSP, which is caused by different approaches to its definition. Currently, the prevalence of this syndrome in Ukraine has not been studied, which requires research to determine its medical and social significance in our country.

Pathogenesis of osteosarcopenia

A substantial body of evidence has been accumulated, indicating a close connection between muscles and bones. In addition to mechanical influence, genetic and molecular associations and the influence of many endocrine factors are important [31, 32].

The most explained and studied is the mechanical factor in the development of OSP, since such an interaction between muscle and bone is obvious and is emphasized by the “mechanostat” hypothesis. According to this theory, the muscle acts on the bone

with a mechanical force with a certain threshold, which determines the activity of the osteosynthesis or resorption process. An increase in muscle mass leads to stretching of collagen fibers and periosteum, which causes stimulation of osteosynthesis. A decrease in muscle mass and, as a result, a decrease in the mechanical effect on the bone, respectively, activates the processes that cause a decrease in BMD [33].

Furthermore, since muscle and bone are derived from mesenchymal stem cells, they are influenced by the same genetic factors [34]. Genome-wide association studies (GWAS) have confirmed the pleiotropic effects of some genes on bone and muscle. These include genes for growth/differentiation factor 8 (GDF8), glycine-N-acyltransferase (GLYAT), methyltransferase-like 21 C (METTL21C), gamma coactivator 1-alpha (PGC-1α), myocyte enhancer factor-2 C (MEF2C), sterol regulatory element-binding transcription factor 1 (SREBF1), and others [20, 35]. Vitamin D receptor polymorphisms have also been shown to be associated with sarcopenia and osteoporosis [36].

The relationship between bone and muscle tissue can be mediated by several autocrine, endocrine and paracrine mechanisms. Muscle secretes "myokines" — factors that affect other tissues, including bone metabolism. On the other hand, factors synthesized in bone tissue — "osteokines" (in particular, osteocalcin, osteoprotegerin and sclerostin) — have a regulatory effect on muscle tissue metabolism. Some myokines (insulin-like growth factor-1, irisin, follicle-stimulating hormone, interleukin (IL)-15, etc.) have a positive effect on bone formation, while other myokines (myostatin, IL-6) have a negative regulatory effect on its remodeling [33, 37].

Myostatin (growth and differentiation factor 8) is a well-studied myokine [38, 39] that inhibits skeletal muscle growth and also affects tendons and bones. It not only inhibits muscle differentiation and growth, promotes protein breakdown, affects adipogenesis and bone remodeling, but is also a potent anti-osteogenic factor and a direct modulator of osteoclast differentiation. Myostatin can activate SMAD and protein kinase signaling pathways, suppressing the Wnt/β-catenin pathway to synergistically regulate muscle and bone growth and metabolism, and is currently being studied as a therapeutic target to inhibit osteoclast formation [39].

Thus, current knowledge about the pathogenesis of OSP allows us to confirm the complex relationships between bone and muscle tissue, and common hormonal and humoral mediators are the object of study as therapeutic targets for the possible treatment of this syndrome.

Risk factors for osteosarcopenia

In recent years, increased interest in OSP among clinical researchers has led to an increase in the number of publications on its risk factors. As noted above, the relationship between decreased muscle mass and low BMD is explained by the mechanical effect of muscles on the stimulation of osteosynthesis and the humoral dependence of muscle and bone tissue. Therefore, decreased muscle mass and the presence of sarcopenia are important risk factors for osteoporosis, and therefore OSP.

This thesis is confirmed by numerous studies. Thus, in the publication of D. Scott et al. involving 3,334 people (mean age 70 years), it was confirmed that patients with sarcopenia had significantly lower BMD of the lumbar spine and femur, distal radius and tibia than the group without defined sarcopenia and with its probable presence (all $p < 0.05$) [40]. Other studies also confirmed that probable and severe sarcopenia was associated with osteoporosis ($p < 0.05$). At the same time, low muscle strength, as measured by hand dynamometry, and low physical capacity, as assessed by the 4-meter test, were associated with osteoporosis ($p < 0.02$).

Low muscle strength and physical capacity were associated not only with osteoporosis ($p < 0.001$) but also with osteopenia ($p < 0.05$). In addition, probable sarcopenia was associated with osteopenia at the femoral neck ($p < 0.01$) [41].

Sung-Young Jang et al. found an association between low muscle mass and osteoporosis in the lumbar spine and femoral neck in both men (lumbar spine: odds ratio (OR) = 1.73; 95 % CI: 1.08–2.76; femoral neck: OR = 3.39; 95 % CI: 1.69–6.80) and women (lumbar spine: OR = 1.52; 95 % CI 1.17–1.97; femoral neck: OR = 2.09; 95 % CI 1.56–2.80). The association between low muscle mass and osteoporosis was significant in men and women across age groups, except for men aged 50–64 years [42].

A retrospective cohort study of 140 postmenopausal women demonstrated that the most common risk factors for OSP were insufficient protein intake (79.3 %) and dietary calcium intake (65.7 %), low physical activity as measured by the SPPB test (53.6 %), and hyperlipidemia (33.6 %). It was also found that dynamometry indicators are decisive for the occurrence of OSP (relative risk (RR) = 0.86; 95 % CI: 0.80–0.92), and a decrease in handgrip strength using a hand dynamometer by one unit increases the risk of OSP by 1.16 times (95 % CI: 1.09–1.25) [19]. Similar results were obtained by T. Tiftik et al.,

who found a relationship between low dynamometry values (< 22 kg) and a 1.6-fold increase in the risk of osteoporosis [43].

Risk factors that influence the development of OSP were also investigated by T. Huang et al. [29]. The results showed that female gender (OR = 5.10; 95 % CI: 2.37–10.98; p < 0.0001), older age (OR = 1.12; 95 % CI: 1.03–1.21; p = 0.008), and history of fractures (OR = 2.92; 95 % CI: 1.62–5.25; p = 0.0003) significantly increased the risk of developing OSP, while elevated parathyroid hormone (PTH) levels (OR = 2.41; 95 % CI: 0.59–9.87; p = 0.22) and high body mass index (BMI) (OR = 1.01; 95 % CI: 0.63–1.62; p = 0.97) did not have a statistically significant association with OSP. On the other hand, low BMI was found to be a significant factor associated with the development of OSP, according to the results of a retrospective study by H. Okamura et al. (OR = 1.71; 95 % CI: 1.46–2.00; p < 0.01) in all age groups (65–74, 75–84 and 85 years and older) [25]. In a publication by P. Suriyaarachchi et al. with the participation of 400 subjects (mean age 79 years, 65 % women), it was reported that individuals with elevated blood PTH levels and normal calcium were more common in the OSP group than in the group without sarcopenia and osteopenia (OR = 6.88; 95 % CI: 1.9–9.2) [23]. This suggests that elevated PTH levels may be a risk factor for the development of OSP, but this suggestion requires further study.

A study of 2,353 community-dwelling Australians identified risk factors associated with OSP, such as physical inactivity (OR: 0.64; 95 % CI: 0.46–0.88), low BMI (OR: 0.84; 95 % CI: 0.81–0.88 for men and 0.77; 95 % CI: 0.74–0.80 for women), increased body fat (1.46; 95 % CI: 1.11–1.92 for men and 2.25; 95 % CI: 1.71–2.95 for women) and older age (in men, prevalence ranged from 14.3 % in the 60–64 age group to 59.4 % at age 75) and older. In women, the corresponding figures ranged from 20.3 to 48.3 %, p < 0.05) [9].

Osteosarcopenia and comorbidity

Osteosarcopenia and obesity

Since scientific studies [9] have shown that increased fat mass is a risk factor for OSP, and fat, muscle, and bone cells originate from the same mesenchymal precursors, it is worth considering the relationship between adipose tissue and OSP.

Fatty infiltration of bones and muscles is common in patients with osteoporosis and sarcopenia. With age, the composition of body tissues changes with an overall increase in the percentage of fat in the body and a decrease in muscle mass, while total body weight may remain stable. This condition is commonly called "sarcopenic obesity," and its presence leads to impaired functional capacity and increased disability among older people [44]. That is why in recent years the combination of sarcopenia, osteoporosis and obesity has been increasingly studied as a condition called "osteosarcopenia obesity".

Today, it is known about the protective effect of adipose tissue on bone mass, which can be partially explained by the well-documented relationship between the level of extraglandular estrogen synthesis and the number of adipocytes. According to some authors, muscle strength in obese individuals may be greater than in people without it. This may indicate a positive effect of excessive adipose tissue on muscles, associated with chronic overload, which can increase muscle size and strength [44]. Thus, in the study by H. Okamura et al., not a single patient from the OSP group had obesity [25], which could indirectly indicate the absence of its negative effect on the development of OSP and isolated cases of combination with OSP. But in the observation of A. Polito with the participation of 1,344 postmenopausal women aged 50 years and older, the prevalence of osteosarcopenic obesity was 32 % [45].

A cross-sectional study of 542 community-dwelling Southeast Asians aged 21–90 years reported that the prevalence of OSP and osteosarcopenic obesity was 1.8 % and 0 % in those aged 21–59 years; 12.9 % and 2.8 % in those aged ≥ 60 years; 17.3 % and 4.1 % in those aged ≥ 65 years; and 25.5 % and 7.0 % in those aged ≥ 75 years, respectively [20]. It was also found that the risk of osteosarcopenic obesity was influenced not only by age, sex, and race, but also by alcohol consumption. However, it was not a reliable predictor of functional impairment in the subjects.

It has now been proven that bone and muscle homeostasis is linked to adipose tissue through neurohumoral connections. High levels of adipose tissue, independent of BMI, are lipotoxic, affecting the function and structure of other tissues. Lipotoxicity and local inflammation are reflected in the biosynthesis of proinflammatory cytokines, including IL-6 and tumor necrosis factor-α [46]. Adipokines, including leptin, resistin, and adiponectin, which are released from adipose tissue, are also able to regulate both muscle and bone metabolism. Exercise-induced stimulation of bioactive cytokines through the interaction of muscle, bone, and fat enhances muscle anabolism, bone formation, mitochondrial biogenesis, glucose utilization, and fatty acid oxidation, and attenuates chronic inflammation. At the same time, the release of lipolytic myokines (IL-6, irisin, and leukemia inhibitory factor) induced by physical exercise activates thermo-

genesis, promoting the transformation and darkening of adipocytes [37].

Therefore, the association of OSP with obesity continues to arouse interest in the scientific community, prompting the emergence of new studies regarding osteosarcopenic obesity.

Osteosarcopenia and diabetes mellitus

Recent study has shown that type 2 diabetes mellitus (T2DM) is a significant risk factor for OSP. A. Moretti et al. [47] in a case-control study demonstrated that postmenopausal women with T2DM had a 5-fold increased risk of OSP compared with those without T2DM (50 vs. 17 %; OR = 5.0; 95 % CI: 1.05– 23.79; p = 0.04), and their hand strength was significantly lower ((10.09 ± 4.02) kg vs. (18.40 ± 6.83) kg, respectively; p = 0.001) [47].

L. M. Pechmann et al. in the observation with the inclusion of women and men with DM2 (mean age (65.1 ± 8.2) and (68.8 ± 11.0) years) also confirmed a higher prevalence of OSP (11.9 vs. 2.14 %, respectively, p = 0.01), sarcopenia (12.9 vs. 5.4 %, respectively, p < 0.03) and fractures (29.9 vs. 18.5 %, respectively, p = 0.02) in patients with DM2 compared to the control group and lower hand strength indicators ((24.4 ± 10.3) kg vs. (30.9 ± 9.15) kg, respectively, p < 0.001). The mean Trabecular Bone Score (TBS) values were (1.272 ± 0.11) and (1.320 ± 0.12), respectively (p = 0.001). According to multivariate analysis, age, larger waist circumference, fractures and osteoporosis increased the risk of low TBS. TBS was also found to be associated with complications of T2DM (p = 0.03), but not with its duration or glycemic control [48]. According to the results of studies highlighted in the systematic review by A. Polito et al., T2DM patients with TBS have lower BMI, waist circumference, body fat percentage and worse β-cell function. It has been concluded that β-cell function may be a factor in counteracting the development of OSP, and the focus on its preservation in individuals with DM2 is a preventive measure to prevent the development of OSP [45].

Therefore, considering that DM2 has an adverse effect on muscle and bone health, which leads to the development of OSP and, as a result, impaired functional ability of patients, there is a need to timely establish algorithms for the detection of this condition, its treatment and prevention.

Osteosarcopenia and the risks of falls and fractures

In a study by W. Sepúlveda-Loyola et al. involving 253 individuals (77 % women; mean age (77.9 ± 0.42) years), a significant association between sarcopenia and the risk of falls was demonstrated, and OSP classified as severe sarcopenia significantly increased the frequency of falls (OR = 2.83–3.63; p < 0.05) [8]. Similar results were obtained by other researchers. Thus, according to the observational data of B. Kirk et al., the presence of OSP increases the risk of falls by 54 % (hazard ratio (HR) = 1.54; 95 % CI: 1.20–1.97) [9]. An even greater increase in the risk of falls in individuals with OSP was demonstrated in the study by Z. Teng et al. (OR = 1.62; 95 % CI: 1.28–2.04) [49].

On the other hand, OSP has been associated with fracture risk. The disease was classified as severe sarcopenia (according to the EWGSOP2 and FNIH definitions) and resulted in an increased fracture rate (OR = 3.86–4.38; p < 0.05) [8].

A significant increase in fracture risk in the presence of OSP was found in the publication by B. Kirk et al. (HR = 2.13; 95 % CI: 1.61–2.81; pooled results of 7 studies) [9], while a later follow-up found that the probability of recurrent fractures (≥ 2 vs 0–1) was significantly higher in individuals with OSP compared with those with osteopenia or osteoporosis regardless of definition, after adjustment for age, sex, alcohol intake, smoking, BMI, lowest DXA T-score, physical activity, and comorbidities (SDOC: HR = 1.63; 95 % CI: 1.03–2.59; p = 0.04; EWGSOP2: HR = 1.83; 95 % CI: 1.12–3.01, p = 0.02) [30]. An even greater increase in fracture risk in individuals with OSP was demonstrated in a study by Z. Teng et al. (OR = 2.46; 95 % CI: 1.83–3.30) [49].

Osteosarcopenia and mortality risk

To date, the results of existing publications indicate that OSP not only affects the functional activity and quality of life of patients, but also increases the risk of mortality.

Thus, in a meta-analysis conducted by N. Veronese et al. with the participation of 14,429 people (mean age (70 ± 6) years, 64.5 % women), it was found that OSP significantly increased the risk of mortality by 53 % (OR = 1.53; 95 % CI 1.28–1.78) [7].

Other researchers demonstrate even higher mortality rates in patients with OSP. In the work of B. Kirk et al. it was confirmed that OSP significantly increases the risk of mortality (OR = 1.75; 95 % CI: 1.34–2.28, analysis based on the results of 5 observations) [9]. A significant increase in the risk of mortality in the presence of OSP was also demonstrated by the results of the study by Z. Teng et al. (OR = 1.66; 95 % CI: 1.23–2.26) [49]. It is clear that the results of these studies are important to consider when examining patients to ensure timely detection and treatment of OSP. In addition, the proven high risks of falls, fractures and mortality in people with

OSP emphasize the urgency of continuing to study this syndrome with a targeted focus on its timely diagnosis and treatment.

Osteosarcopenia therapy

There are presently two methodologies utilized for the treatment of OSP: non-pharmacological and pharmacological interventions.

The most effective non- pharmacological approach is to ensure rational physical activity, which has been shown to improve bone [50] and muscle strength [51]. In addition, according to some researchers, the use of nutritional supplements enriched with nutrients, in particular sufficient amounts of vitamin D and protein, can improve physical performance and be an effective tool for the prevention and treatment of OSP [36].

The randomized controlled trial FrOST (Franconian osteopenia and sarcopenia trial) evaluated the effect of dynamic resistance exercise on the treatment of OSP in elderly men. For this purpose, BMD and appendicular fat-free mass index (AFMI) were studied in 43 subjects aged 73–91 years who led a sedentary lifestyle. Physical training in the study group was performed on simulators with high intensity, speed and resistance twice a week, and both groups (study and control) received sufficient amounts of protein, calcium and vitamin D daily. After 12 months of observation, the exercise group showed preservation of BMD at the level of the lumbar spine, while the control group was diagnosed with its decrease ($p < 0.001$; standardized mean difference (SMD) = 0.90). The IAMS index increased in the study group, while it decreased in the control group ($p < 0.001$; SMD = 1.95). Proximal femoral BMD did not differ significantly between groups ($p = 0.06$; SMD = 0.65), while changes in maximal hip extensor strength were significant ($p < 0.001$; SMD = 1.92) in the high-intensity resistance exercise group [51]. The results of this randomized trial suggest that dynamic resistance exercise may be a promising tool for the treatment of OSP. It should be noted that strategies aimed at preventing falls in patients with OSP may also have important practical value. These may include the addition of balance training exercises, safety assessment and risk reduction in the home, and the use of assistive devices that reduce falls. However, there is a lack of high-quality work examining this issue in individuals with OSP.

Currently, much attention is paid to the development of the effectiveness of dietary strategies, in particular the rational consumption of various macro- and micronutrients in the management of both sarcopenia and osteoporosis, but there are no studies that would study the feasibility of using these strategies in the prevention of OSP.

It has now been proven that vitamin D supplementation affects the increase in muscle strength, reducing the risk of falls and mortality, and this relationship is stronger in older people and people who are deficient in this vitamin. To ensure the maintenance of bone and muscle health, daily intake of vitamin D_3 at a dose of 800–1000 IU/d; calcium 1300 mg/d; 1.2–1.5 g/kg protein/d (with 2.5–3 g leucine at each meal) is recommended [9]. Addressing vitamin D deficiency in older adults and promoting its optimal intake through diet or supplementation may be a valuable tool in the management of OSP.

Currently, some studies suggest that adding creatine to resistance training increases gains in both muscle strength and mass compared with exercise training alone. A recently published meta-analysis of randomized clinical trials demonstrated a positive effect of creatine supplementation with resistance training on both upper (4 studies, $n = 97$, $p = 0.05$) and lower body strength (4 studies, $n = 100$, $p = 0.03$) compared with a control group, provided that the follow-up period was at least 24 weeks [52]. Although this approach requires further scientific evidence, creatine supplementation has also been suggested by other authors [9] to increase muscle strength (3–5 g/d) in older adults.

It is likely that a combination of high-intensity resistance exercise, balance exercises, protein supplements, vitamin D, calcium, and creatine may be an effective treatment for OSP in the elderly, but this issue requires further detailed study.

The literature does not provide well-defined strategies for the pharmacotherapy of OSP or sarcopenia. On the other hand, both antiresorptives (bisphosphonates, denosumab, etc.) and bone formation stimulants are used to treat osteoporosis and its complications. Recently, reports have appeared confirming the positive effect of antiresorptives not only on BMD, but also on the state of skeletal muscles and the risk of falls, which may be promising in the treatment of OSP. Thus, in a retrospective cohort study conducted by T. Rupp et al. [53], a positive effect of denosumab was demonstrated not only on BMD, but also on changes in hand muscle strength ($p < 0.001$), which was also observed in the group using bisphosphonates (alendronate and ibandronate) ($p = 0.001$). However, in patients who used denosumab, the results were better than in the case of using bisphosphonates or placebo (the dynamics of changes in muscle strength per year in the control group was (–6.05 ± 10.22) %; during treatment with

bisphosphonates (+0.78 ± 8.23) %; with denosumab (+5.14 ± 25.49)%). In addition, treatment with denosumab resulted in better results in the sit-stand test and a significant increase in lower limb strength compared with the group that received bisphosphonates (the dynamics of changes per year was in the control group (+5.82 ± 12.74) %; in the group of patients that received bisphosphonates, (+0.95 ± 8.61) %, denosumab (+8.20 ± 14.38) %). However, the dynamics of the time index during this test did not show significant differences between the three groups [53].

The positive effect of denosumab on lower limb muscle strength may explain the reduction in the risk of falls during its use, which is confirmed by the results of a placebo-controlled study conducted by P. Chotiyarnwong et al. [54], but this relationship still needs further study.

In a prospective study conducted by M. Pizzonia et al., the effects of alendronic acid and denosumab on BMD, TBS and AFMI were compared in 98 patients over 65 years of age with osteoporotic hip fracture. According to the results, an early trend towards improvement in BMD and its quality was observed in the group receiving alendronic acid compared with those receiving denosumab (femoral neck BMD: 64.0 vs. 46.7 %; total femur: 68.0 vs. 53.3 %; lumbar spine: 84.0 vs. 53.3 %, respectively); TBS (48.0 vs. 20 %, respectively). However, the denosumab group showed better results in the AFMI index [55]. In a study by N. Bonnet et al., appendicular muscle mass (AMM) and hand strength were assessed in postmenopausal women treated for osteoporosis for three years. Both denosumab and bisphosphonates (alendronate and zoledronate) resulted in improvements in BMD compared with the control group, in which no medication was administered ((0.12 ± 0.29) g/cm^2 and (0.04 ± 0.12) g/cm^2 vs. (–0.07 ± 0.19) g/cm^2, respectively, both $p < 0.05$). In contrast, only the denosumab group showed an increase in BMD and strength in both hands ((0.66 ± 2.2) kg and (3.22 ± 10.0) kg, respectively, versus (–0.06 ± 0.39) kg and (–0.07 ± 6.6) kg with bisphosphonates; and (–0.36 ± 1.03) kg and (–1.39 ± 2.4) kg, respectively, in untreated patients, both $p < 0.05$). Changes in BMD and hand strength correlated with changes in lumbar spine BMD ($r^2 = 0.82$ and $r^2 = 0.81$, both $p < 0.001$) only in the denosumab group [56].

There is little scientific evidence to support the positive effects of denosumab on muscle strength, but the available studies encourage further study of its mechanisms to expand the possibilities of drug treatment of OSP in the future. And a combination of non-pharmaceutical and pharmaceutical approaches in treatment, with individual selection of the most effective drug, will provide the best result in OSP treatment.

Conclusion

With an aging population, OSP is a significant global issue, impacting quality of life and increasing healthcare system burdens. Given the mechanisms of OSP development, it is necessary to ensure a multidisciplinary approach for the timely detection, effective treatment and prevention of this important geriatric syndrome. Continued research in these fields is essential to establish clear protocols and standardized recommendations for managing patients with OSP and individuals at increased risk of its occurrence in the near future.

Conflict of interest. The authors declare that there is no conflict of interest.

Prospects for further research. An analysis of the available literature indicates the important medical and social significance of osteosarcopenia, however, data on its epidemiology are contradictory, and those related to its management are insufficient. The above is the basis for further research in Ukraine on the study of epidemiology, risk factors of osteosarcopenia and possibilities of its prevention and treatment.

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OSTEOSARCOPENIA: EPIDEMIOLOGY, RISK FACTORS AND MODERN MANAGEMENT STRATEGIES

D. Yu. Kurylo, N. V. Grygorieva

State Institution «D. F. Chebotarev Institute of Gerontology of the NAMS Ukraine», Kyiv

✉ Darina Kurylo: kurilodarina@ukr.net; https://orcid.org/0009-0005-8075-2644A

✉ Nataliia Grygorieva, MD, Prof.: crystal_ng@ukr.net; https://orcid.org/0000-0002-4266-461X