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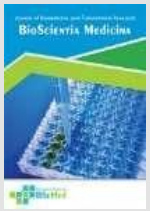

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Diagnosis and Management of Osteosarcopenia

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A B S T R A C T

Osteosarcopenia is a syndrome defined as a combination of low bone density and muscle mass as well as decreased strength and/or functional capacity. Osteoporosis and sarcopenia often coexist in the elderly, leading to a significantly worse prognosis. The epidemiology of osteosarcopenia is quite limited because the term is still new. Osteosarcopenia is more common in women than men and in malnutrition. Age-related immunological changes such as hormonal imbalance, chronic inflammation, increased oxidative stress, imbalance in protein metabolism, increased fat deposition, decreased physical activity, and poor nutritional status contribute to sarcopenia. Decreased bone density in osteoporosis can occur due to an imbalance between osteoblasts and osteoclasts. The diagnosis of osteosarcopenia is made based on the presence of osteoporosis and sarcopenia. Instrument strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC–F) are recommended for assessing sarcopenia and the fracture risk assessment tool (FRAX) for the risk of osteoporotic fracture. Management of osteosarcopenia is carried out holistically, including management of osteoporosis and sarcopenia both non-pharmacologically and pharmacologically.

1. Introduction

A healthy aging process is necessary to maintain the reserve capacity of various physiological systems. One of them is the musculoskeletal system, which helps mobility and also functions as a calcium deposit in the bones and muscles. However, when reaching the sixth decade of life, there is a progressive decline in bone density of approximately 1–1.5% per year, muscle mass of 1% per year, and a decrease in muscle strength of approximately 2.5–3% per year. This condition predisposes to osteoporosis and sarcopenia.[1] Osteoporosis is characterized by low bone mass density and damage to the microarchitecture of bone tissue. Sarcopenia is a condition of loss of muscle mass, strength, and function that increases the tendency to fall. sarco-osteopenia, now better known as osteosarcopenia, has been proposed as a new term to represent the elderly population with osteoporosis and sarcopenia.[4-6] Increasing evidence suggests that there is an overlap in the pathophysiology of osteoporosis and sarcopenia, increasing interest in managing these conditions simultaneously. The SarcoPhAge study showed subjects with sarcopenia had a five-fold higher risk of developing osteoporosis.[7,8] Research by Pereira et al. (2015), Lima et al. (2019), and Locquet et al. (2019) showed osteoporosis increases the risk of sarcopenia and vice versa.[9-11] Osteosarcopenia is a syndrome defined as a combination of low bone density and muscle mass as well as decreased strength and/or functional

capacity.[12,13] Because patients with osteosarcopenia represent individuals at higher risk of falls and fractures, an increasing elderly population, and the enormous socioeconomic impact of fractures, physicians are expected to become familiar with the terminology of osteosarcopenia as a new geriatric syndrome that requires early diagnosis and effective therapeutic intervention. Therefore, the author raised the title of this literature review to understand osteosarcopenia and how this condition can be prevented and treated.

Definition

Osteosarcopenia is a syndrome that describes the coexistence of osteoporosis and sarcopenia, two chronic musculoskeletal conditions associated with aging and decreased activity. Osteoporosis is a condition of damage to bone microarchitecture, which is characterized by a decrease in bone mass density until it exceeds the fracture threshold. Meanwhile, sarcopenia is a syndrome characterized by progressive loss of muscle mass and strength. These two conditions often occur together in the elderly, leading to a significantly worse prognosis.[6,14,15] In 2009, Binkley et al. identified an association between low bone mass and muscle mass, which was later referred to as "sarco–osteopenic or sarco–osteoporotic". In subsequent years, the term osteosarcopenia emerged as a way to encompass both concepts. However, there are difficulties in explaining the concept of osteosarcopenia and as a result, the determination of diagnostic criteria has become one of the main challenges for epidemiological studies and clinical characterization of patients.[16]

Epidemiology

The epidemiology of osteosarcopenia is quite limited because the term is still new. However, one major study by Huo et al. (2015) in 680 elderly patients with a history of falls found a prevalence of osteosarcopenia of 37%, and these patients had a higher frequency of comorbidities, mobility impairment, and depression. Osteosarcopenia was also associated with a significant increase in mortality in one study reported by Paintin et al. (2018) in 324 elderly patients in Korea with hip fractures. The 1-year mortality rate was 15.1% in patients with osteosarcopenia, more than in patients with osteoporosis alone (5.1%) or patients with sarcopenia alone (10.3%). Another study of 316 adults aged over 65 years in China found that 10.4% of men and 15.1% of women had osteosarcopenia.[6,22] According to Kirk et al. (2020), the prevalence of osteosarcopenia increases with age, in men in the age range 60–64 years by 14.3% to 59.4% in the age range ≥75 years, in women in the age range 60–64 years by 20.3% to 48.3% at age ≥75 years. Of the 46% of elderly patients with hip fractures, 17.1-96.3% showed the highest prevalence rate of osteosarcopenia.[1]

Risk factors

In women aged >50 years and in men >70 years, etiological factors begin to cause loss of musculoskeletal tissue and show symptoms of loss of physical capacity and function.[16,23] Osteosarcopenia is more common in women than men. The association with the female gender is mainly caused by a lack of estrogen at the time of menopause, which causes a decrease in muscle strength.[16,22] Kirk et al. (2020) reported a population-based study of 2353 adults, also finding that body mass index and physical activity were inversely associated with osteosarcopenia. Meanwhile, higher fat mass increases the risk of osteosarcopenia in men by 1.46 times and women by 2.25 times. In another study among 148 geriatric inpatients, individuals with osteosarcopenia were at greater risk for malnutrition compared with osteoporosis or sarcopenia alone.[1] Research by Huoet et al. (2015) used the instrument mini nutritional assessment (MNA) and found that individuals with osteosarcopenia had a two-fold higher risk of malnutrition with an MNA score <12 compared to controls. As age increases, the prevalence of sarcopenia decreases, while osteosarcopenia increases sharply, as shown in the diagram below.[16,22]

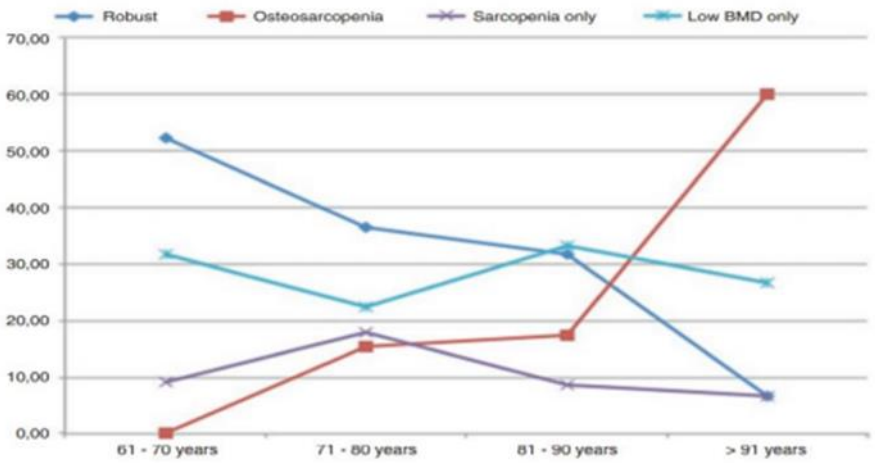

Figure 1. Prevalence of osteosarcopenia, sarcopenia, and osteopenia/osteoporosis.[16]

Pathophysiology

Sarcopenia is a progressive degenerative disease with diverse etiologies. Age-related immunological changes such as hormonal imbalance, chronic inflammation and increased oxidative stress, imbalance in protein metabolism, increased fat deposition, decreased physical activity, and poor nutritional status contribute to sarcopenia. On the other hand, decreased bone density in osteoporosis is thought to originate from an imbalance between osteoblast bone-forming cells and osteoclast bone-resorbing cells. Hormonal factors, especially estrogen, parathyroid hormone, and testosterone, decrease after menopause, which are involved in the development of osteoporosis. Decreased physical activity and poor nutritional status, such as lack of protein, vitamin D, and calcium intake, also contribute to this bone disorder.[1] The mechanostat theory states that muscle exerts a mechanical force on the bone, with a certain threshold determining whether bone will form or reabsorb. Both osteoporosis and sarcopenia can occur due to reduced physical activity during the aging process.[6] More recent research suggests a role for paracrine or endocrine activity. An important hormone that mediates this role is growth hormone, insulin-like growth factor–1 (IGF – 1), gonadotropin hormone, and vitamin D. Muscles and bones also secrete certain factors known as myokines and osteokines, which help communication between muscles and bones. The myokine studied is myostatin, a member of the growth factors transforming growth factor beta (TGF–β), which inhibits skeletal muscle growth but also has effects on bones and tendons. Additionally, low testosterone and estrogen are linked to muscle atrophy and bone loss in both men and women.[1,6] Growth hormone – insulin-like growth factor – 1 axis is a major regulator of bone and muscle growth. Genetic polymorphism of various genes also contributes to the pathogenesis of osteosarcopenia, as quoted by Kirk et al. (2020), namely genes Glycinec – N – Acyltransferase (GLYAT)Methyltransferase Like 21C (METTL21C), peroxisome proliferator–activated receptor gamma coactivator 1 – Alpha (PGC-1α), and myocyte enhancer factor – 2 (MEF2C) is associated with muscle atrophy and bone loss. The risk factors for osteoporosis and sarcopenia have heritabilities in the range of 60%–70%.[1,25] Physical activity decreases with age, with nearly 80% of time spent sedentary in older people, leading to loss of mechanical load and resulting bone and muscle loss. Calorie intake decreases by around 25% at age 40–70 years. Decreased vitamin D levels and protein intake correlate with decreased muscle strength. Smoking and alcohol are important risk factors for osteoporosis, with intake of 3 units of alcohol per day increasing the risk of fracture. In the figure below can be seen the pathophysiology of osteosarcopenia.[6]

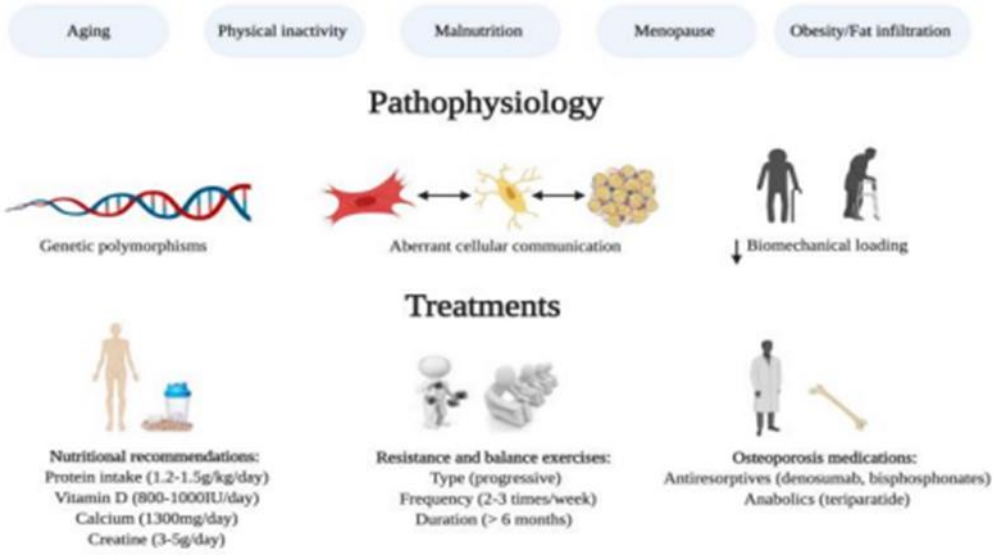

Figure 2. Pathophysiology of osteosarcopenia.[26]

Clinical manifestations

Body composition

In patients with osteosarcopenia, muscle mass and bone mineral densitometry (BMD) is low. Patients with osteosarcopenia have low body mass index (BMI) and fat mass. Several studies evaluating BMI in elderly people with osteosarcopenia show that the average BMI is lower than in individuals with sarcopenia and osteoporosis alone. According to Mathieu et al. (2021), 34 osteosarcopenia patients had lower BMI and fat mass than patients without osteosarcopenia.[16,22,27]

Physical function

In patients with osteosarcopenia, muscle strength decreases. Huo et al. (2015) observed an average grip strength of 16.6 Kgf in osteosarcopenia compared to 18.7 Kgf in sarcopenia, and Wang et al. (2015) showed the same trend. These findings suggest that low muscle strength is a characteristic of osteosarcopenia patients.[16,22,28] Most studies have shown that the average walking speed of individuals with osteosarcopenia is lowest compared to other phenotypes, regardless of the criteria used to diagnose sarcopenia, namely European Working Group on Sarcopenia in Older People (EWGSOP) or Asian Working Group for Sarcopenia (AWGS). Huo et al. (2015) showed that the average walking speed was significantly lower than the osteoporosis and control groups and very similar to the sarcopenia group. Meanwhile, Wang et al. (2015) described lower walking speeds in the osteosarcopenia group compared to individuals with osteoporosis and sarcopenia alone.[22,28,29] Low mobility is a common clinical feature of osteosarcopenia, and, according to research, is one of the specific clinical characteristics. Huo et al. (2015) found the risk of decreased mobility was about three times higher in osteosarcopenia patients compared to the control group, but sarcopenia did not have a significant relationship with decreased mobility.[22,29]

Vulnerability

In 2015, a study in China by Wang et al. showed that osteosarcopenia was found in 26.3% of men and 38.5% of women with frailty, and the risk is about 4 times greater for frailty. However, unlike other studies, the risk of frailty and the consequences of sarcopenia were also significant, similar to those observed in osteosarcopenia.[28] Penelitian Yoo et al. (2018) found a higher mortality rate in individuals with osteosarcopenia of 15.1% compared to osteoporosis of 5.1%, 10.3% in sarcopenia alone, and 7.8% in the normal group. The mortality rate in this study was

25.8% in men with osteosarcopenia and 2.1% in men without osteosarcopenia. In the figure below can be seen the hypothesized relationship between the etiology, clinical manifestations, and outcomes of osteosarcopenia.[30]

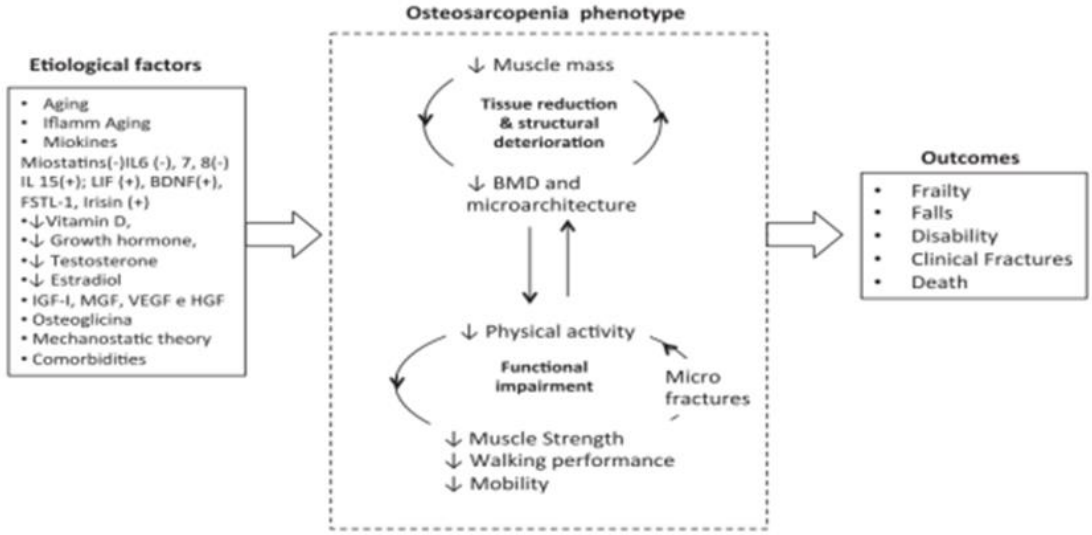

Figure 3. The hypothesis of the relationship between etiology, clinical manifestations, and outcome of osteosarcopenia.[16]

Diagnosis

In diagnosing osteosarcopenia, a thorough medical history assessment is carried out, including the history of falls, risk factors, physical examination, functional assessment, and specific investigations. The next important assessment is regarding possible causes of osteosarcopenia, such as decreased activity, comorbidities, malnutrition, use of medications, symptoms of weakness, fatigue, reduced mobility, decreased function, falls and fractures, as well as the impact of reduced quality of life, and mood disorders.[1,26]

A comprehensive fall assessment involves a thorough history and physical examination aimed at addressing modifiable risk factors for falls. Physical assessments include muscle strength such as grip strength, sit-stand tests, or functional capacities such as gait speed, short physical performance battery (SPBB), walking time test, and 4-meter walking test. However, the most widely studied physical assessment is muscle strength in the form of hand grip strength in kg using hand–held dynamometer. In addition, physical performance was assessed by walking speed in m/s over 4 meters.[26] It has been recommended for implementation strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC – F) assesses sarcopenia and fracture risk assessment tool (FRAX) for fracture risk. SARC–F is recommended because of its moderate sensitivity and high specificity, SARC–F is most accurate in detecting individuals suffering from severe sarcopenia. The SARC–F has been validated for use internationally and in multiethnic populations. There are seven tools recommended for risk stratification in individuals with osteoporosis, but FRAX is the most widely used. FRAX can be applied without BMD and has been recommended in 80% of the global population.[1,26]

An important requirement for assessing osteosarcopenia is determining the best method for assessing muscle and bone composition. Magnetic resonance imaging (MRI), computed tomography (CT), dual energy X–Ray absorptiometry (DXA), and

Ultrasound all have important variables in assessing sarcopenia and osteoporosis and can provide useful information for clinical decision-making. In the figure below can be seen the osteosarcopenia diagnosis algorithm.[31]

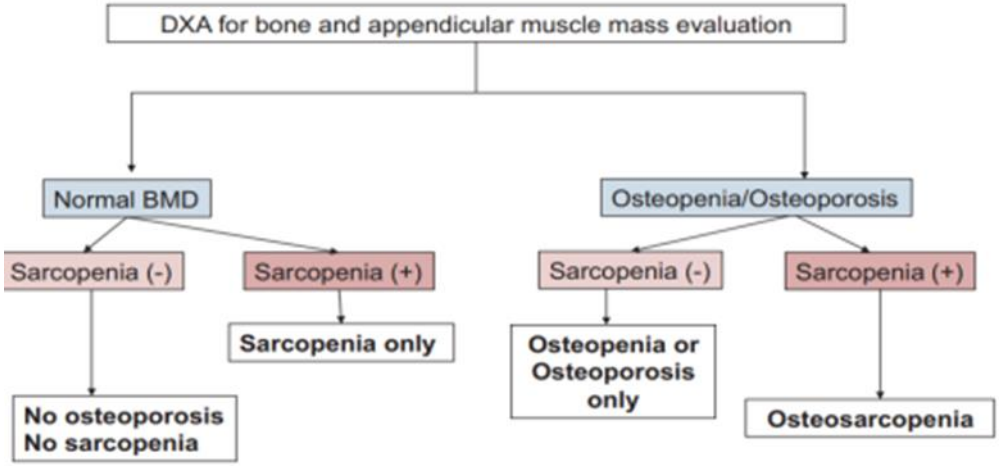

Figure 4. Algorithm for the diagnosis of osteosarcopenia.[16]

Diagnosis osteoporosis

To diagnose osteoporosis, a complete evaluation is required, such as anamnesis, physical examination, bone biochemistry, measurement of bone mass density, radiological examination, and the function of several related organs such as the kidneys, liver, gastrointestinal tract, and thyroid. In history, the main complaint can usually lead directly to a diagnosis, such as a femoral column fracture in the elderly. Other factors can be asked, such as fractures with minimal trauma, long immobilization, decreased height in the elderly, lack of sun exposure, and poor nutritional intake.[14] Drugs consumed in the long term must also be considered, such as corticosteroids, thyroid hormones, antacids containing aluminum, heparin, and anticonvulsants. The habit of drinking alcohol and smoking also does not forget to ask. In addition, there are diseases associated with osteoporosis, such as kidney disease, gastrointestinal tract, liver, endocrine, and pancreatic insufficiency. Age and history of menstruation, menopause, and use of contraceptive drugs must also be considered. And finally, a family history of osteoporosis is also an important thing to pay attention to.[14] Further assessments include height and weight, gait, bone deformity, leg–length inequality, spinal pain, and scar tissue in the neck. Osteoporosis sufferers often exhibit dorsal kyphosis or gibbus (Dowager's hump) and decreased height. Apart from that, abdominal protuberance, paravertebral muscle spasms, and thin skin were also found.[14] Biochemical examination of bones consists of total calcium in serum, calcium ions, phosphorus levels in serum, urine calcium, urine phosphate, serum osteocalcin, urine pyridinoline, parathyroid hormone, and vitamin D. Biochemical bone turnover markers (BTM) is a biomolecule released into the circulation during bone resorption and formation. This biomolecule is categorized as a marker of bone formation and bone resorption. In clinical practice, BTM measurements can aid diagnostic and therapeutic decisions and support therapy monitoring. However, the lack of standardization and substantial analytical and preanalytical variability hinder the wider clinical use of BTM in daily practice.[32] Radiological examination in assessing bone mass density is not sensitive. Often, a decrease in spinal bone mass density of >50% does not provide a specific radiological appearance. Typical radiological features of osteoporosis are thinning of the cortex and more lucent trabecular areas. The vertebral bones will provide an illustration picture–frame

vertebra. Bone densitometry is an accurate and precise examination to assess bone mass density, so it can be used to assess prognosis, predict fractures, and diagnose osteoporosis.[14] In 1994, the World Health Organization (WHO) operationally defined osteoporosis with DXA if the bone mass density is –2.5 standard deviations (SD) T–score. In adults with normal bone mass density the value is –1 SD (T-score), and it is called osteopenia if the bone mass density is between –1 SD and –2.5 SD of T–score. Currently, DXA is the most widely used method for clinical assessment of osteoporosis, due to its wide availability, low cost, and minimal radiation exposure. The table below shows the indications for bone densitometry.[14,31] Trabecular bone score (TBS) is a new imaging technique that quantifies the gray-scale texture of lumbar spine images measured by DXA. An increased TBS then indicates a stronger bone mass density, while a low TBS reflects a low bone mass density, resulting in a higher risk of fracture. However, TBS is not recommended as a diagnostic tool but rather as a complementary measure to other risk assessments such as FRAX and BMD.[31] CT examination is superior to DXA for assessment of the bone compartment. However, currently, CT is only recommended as a complement due to limited costs and higher radiation exposure.[31,33] Currently, osteoporosis screening with MRI is not recommended due to expensive time and costs.[31] Quantitative ultrasound (QUS) with the main parameters used to assess bone tissue with QUS, namely broadband ultrasound attenuation (BUA) and speed of sound (SOS). SOS can better measure cortical bone properties and correlate better with BMD, whereas BUA relies more on trabecular bone characteristics. Patients with lower QUS parameter values have an increased risk of fracture.[31]

Diagnosis of sarcopenia

At this time, there are no standard diagnostic criteria for sarcopenia. Some techniques used to assess muscle mass have limitations. Although CT and MRI are considered the gold standard for the assessment of muscle mass, DXA has become the primary diagnostic measure due to its low radiation and cost and clinical availability. DXA measures fat mass and bone mass to assess appendicular lean mass (ALM) compared with body height (ALM/ht^2). According to some classifications, men who have $ALM/ht^2 < 7.26$ kg/m^2 and women who have < 5.5 kg/m^2 are considered to have lean mass.[15,31] Currently, there is no consensus on the appropriate protocol for assessing muscle mass in relation to strength transducer ultrasound.[31] Although not considered imaging, bioimpedance analysis (BIA) and bioimpedance spectroscopy (BIS) have played an important role in diagnosing sarcopenia when DXA is not available or contraindicated. In the table below can be seen the diagnostic criteria for sarcopenia.[31]

Based on the degree of severity, sarcopenia can be divided into 3 stages, namely the presarcopenia stage which is characterized by a decrease in muscle mass without any interference with strength or physical performance. The sarcopenia stage is characterized by a decrease in muscle mass accompanied by a decrease in muscle strength or a decrease in physical performance. Meanwhile, the severe stage of sarcopenia is characterized by a decrease in muscle mass accompanied by a decrease in muscle strength and physical performance.[15]

Biochemical and hormonal markers of skeletal muscle function and metabolism are targets of basic and clinical research. Serum concentration creatinine kinase (CK) describes muscle mass in which men have a higher concentration than women. In people with osteosarcopenia, serum CK concentrations are expected to be low due to reduced muscle mass. However, pharmacotherapy with statins, fibrates, antiretrovirals, and angiotensin II receptor antagonists can increase serum CK concentrations and thereby mask low serum CK levels.[32] Additionally, myostatin or growth differentiation factor 8 (GDF–8) is expressed in skeletal muscle and inhibits myoblast proliferation. Myostatin measurement can be done by enzyme–linked immunisorbent assay (ELISA) and this test is often performed in patients with various musculoskeletal diseases and increasingly in

osteosarcopenia. Follistatin is also known as activin-binding protein, and is a strong myostatin antagonist. Follistatin appears to stimulate muscle growth by opposing myostatin, which inhibits excessive muscle growth.[32] Furthermore, exercise increases levelsPeroxisome proliferator–activated receptor Gamma coactivator – 1α (PGC–1α), which secretes precursors of irisin Fibronectin type III. Therefore, serum irisin has been proposed as a biomarker for sarcopenia, even with the potential for early screening for sarcopenia.[32]

Management of osteosarcopenia

Management of osteosarcopenia includes pharmacological and non-pharmacological treatments such as nutritional intervention and physical exercise.[26]

Exercise

A meta-analysis explains that exercise reduces the overall risk of fracture by 51% in adults over 45 years. The optimal approach to osteosarcopenia may be targeted at a combined program of resistance training and high speed, practice weight–bearing, balance, and mobility activities.[6,34] Meta-analysis by Silva et al. (2013) showed a 29% reduction in the risk of falls in elderly people who underwent a resistance and balance training program. Likewise, in 2010, the World Health Organization (WHO) published "The Global Recommendations on Physical Activity for Health" which recommends physical activity in geriatrics. The general recommendations for physical activity provided by WHO and ACSM, as in the table below, apply to all healthy older adults regardless of gender, race, ethnicity, or income level.[36]

Bone mass and structure are influenced by adaptive mechanisms that are sensitive to their mechanical environment. Muscle contractions induce fluid movement in the bone extracellular matrix, and this fluid shift exerts force on osteocytes and bone lining cells. All of these activities trigger the release of nitric oxide and prostaglandins, which leads to the division and differentiation of osteoprogenitor cells and, consequently, the initiation of new bone production. The effects of mechanical loads produced by physical activity depend on the magnitude, duration, and rate of the applied load. Longer duration with lower amplitude or short duration and high amplitude loads have the same effect on bone formation. In the picture below, you can see how transduction occurs after a mechanical stimulus to the bone.[36]

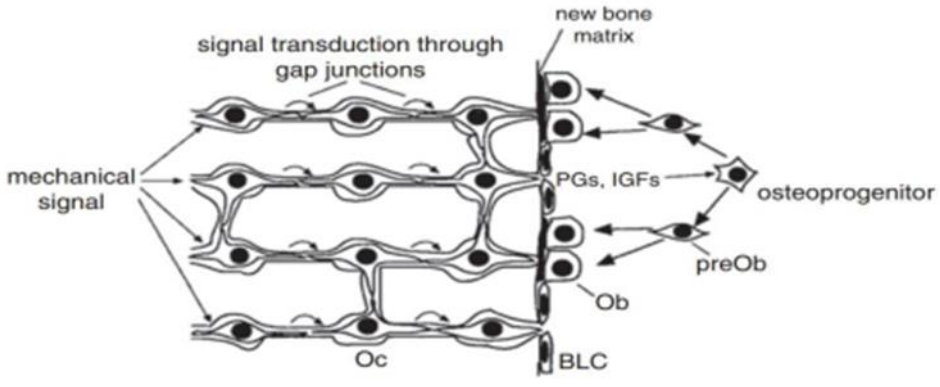

Figure 5. Illustration of signal transduction pathways after mechanical stimulus in bone.[36]

Walking is the simplest physical exercise and the most common choice because of its low risk. However, data on changes in bone mass due to walking activities are still controversial. In general, due to its low impact, most studies investigating the relationship between BMD and walking reported no changes in bone mass.[36]

Aerobic activity has more benefits for bones. Quoted by Vitale et al. (2019) in a 7-month trial, positive effects on spinal BMD from comparing high-intensity to low-intensity walking activities, the low-intensity group showed similar bone loss to controls, while high-intensity walking showed an increase in BMD. It can be assumed that high-intensity walking is very effective in reducing the risk of falls and improving lower extremity function in the elderly.[36] Resistance training is the type of physical activity that is most often and effectively applied to increase bone mass in elderly men or women with osteoporosis. This exercise induces osteogenesis due to increased mechanical stress on the bone. According to Vitale et al. (2019), the results observed in older adults of both sexes who underwent 12 months of intervention showed that total body BMD was not modified in the active group but decreased in the control group at the end of the study.[36] Resistance training for a year at high intensity can increase BMD and dynamic balance abilities in older people, especially in relation to the risk of falls and osteoporotic fractures. According to Troy et al. (2018) The National Osteoporosis Foundation (NOF) and other organizations strongly recommend weight-bearing exercise involving as many muscle groups as possible for the prevention and treatment of osteoporosis. Although moderate to high-intensity exercise is best for increasing BMD, it is important to note that mechanical loading during this type of physical activity, especially in patients with obesity, osteoarthritis, or those with abnormal joint biomechanics, can exacerbate joint degradation or cause a decrease in cartilage thickness. Therefore, in such cases, supervision by doctors and expert trainers is required.[36,37] In a study studying the effects of a combination of aerobic exercise and endurance training compared with a control group in an older female population, after 9 months of training, individuals in the group combined training recorded better spinal and whole body BMD compared to controls. A study cited by Vitale et al. (2019) showed that an 8-month period of combined exercise with moderate-intensity weight-bearing exercise could significantly influence bone adaptation in older individuals. Although other studies have found no effect on bone mass from the program combined training, in general, it appears that this combination exercise is helpful for slowing the decline in bone mass with aging.[36] To date, there is no strong evidence of which protocol is superior to another for sarcopenic patients. Resistance training seems to be more beneficial in replenishing muscle quantity and improving its quality, temporarily endurance training can improve functional abilities, and combined training potentially works on both strength and endurance.[36]

Nutrition

The nutritional approach to osteosarcopenia focuses on vitamin D, calcium, and protein intake. According to Oliveira and Vaz (2015), vitamin D supplementation can have many beneficial effects, such as increasing muscle strength, reducing mortality and risk of falls, and increasing functional capacity. In general, guidelines recommend 800 – 2000 IU/day in older adults, aiming for a serum 25 – hydroxyvitamin D target of at least 50 nmol/liter (20 ng/ml).[24,34,35] Compston et al. (2017) stated although the benefits of calcium in reducing fracture risk are unclear, guidelines recommend adequate calcium intake in patients with osteosarcopenia, with a recommended daily intake of 700 – 1200 mg. A meta-analysis by Daly (2017) showed that combined vitamin D and calcium supplementation safely and effectively reduces fracture risk in older individuals. If calcium intake is below recommended values, supplementation of 500 – 600 mg/day is recommended in older adults. However, there is controversy regarding dietary supplementation with higher calcium doses of >2000 mg/day because it is associated with increased cardiovascular side effects in adults aged >50 years.[18,34]

According to Fatima et al. (2019), there is an association between protein and sarcopenia, where a low protein diet of <0.45g/kg/day in elderly people aged 65 years is associated with muscle atrophy and

moderate or high protein consumption of around 1.1g/kg/day in adults being 70–79 years old was associated with less muscle loss. Additionally, high protein intake >1.0g/kg/day has been associated with better lower extremity physical performance when compared with protein intake <0.8g/kg/day in the elderly.[1,40]

Additionally, there is evidence from Daly (2017) showing a decreased protein anabolic response in older people, further exacerbating the problem of inadequate intake. Thus, a higher protein intake of around 1.0–1.2 g/kg/day is recommended in the elderly, with at least 20–25 g of high-quality protein at each meal and after exercise. Protein whey, namely protein that is quickly digested and absorbed, contains abundant levels of leucine, which is the main stimulator mammalian target of rapamycin complex 1 (mTORC1) in skeletal muscle and is the most potent dietary strategy to increase muscle protein synthesis. However, increasing protein intake is more effective when vitamin D levels are within the optimal range. Another option is the metabolite leucine – hydroxy – methylbutyrate, which is also effective in stimulating muscle protein synthesis and reducing muscle catabolism, although randomized controlled trials (RCTs) are needed to demonstrate its effectiveness in osteosarcopenic individuals.[6,34]

Pharmacotherapy

Bisphosphonate therapy for osteoporosis (alendronate, risedronate, and zoledronate) remains the first-line treatment. This drug works through a signaling pathway that induces osteoclast apoptosis, thereby reducing bone resorption and increasing bone mineral density. Bisphosphonates are indicated in patients who cannot receive hormonal therapy or have osteoporosis in men. In the table below you can see the types and doses of bisphosphonates for the treatment of osteoporosis.[41] Next, there is raloxifene which is an anti-estrogen that has estrogen-like effects on bones and lipids, but does not stimulate the endometrium and breasts. The mechanism of this drug is thought to involve transforming growth factor – Beta3 (TGF-β3) produced by osteoblasts, which functions to inhibit osteoclast differentiation and bone mass loss. The recommended dose for the treatment of osteoporosis is 60 mg/day. Hormonal replacement therapy is given to postmenopausal women with conjugated estrogens 0.3125–1.25 mg/day, combined with medroxyprogesterone acetate 2.5–10 mg/day daily.[41] The other main pharmacological therapy for osteoporosis is denosumab, which is an activator receptor activator of nuclear factor κB Ligand (RANKL) inhibitor that inhibits osteoclastogenesis, and the anabolic agent teriparatide, which is a recombinant parathyroid hormone (PTH). Patients recommended for antiresorptive or anabolic treatment of osteoporosis, according to National Osteoporosis Foundation (NOF), are adults with minimal pelvic trauma or back fracture with a T–score <2.5 in dual-energy X–Ray absorptiometry (DXA) or 10-year risk of fracture based on FRAX 3% in the hip or 20% for other osteoporotic fractures. Before treatment, it is recommended that patients have a vitamin D status >50 nmol/L and be counseled about the risks and potential side effects of the treatment agent.[6,17] Several new therapies are being developed, such as selective androgen receptor modulators, agents in the activin signaling pathway, myostatin neutralizing antibodies/propeptides, recombinant follistatin, follistatin derivatives, and soluble activin receptors (SAR), as well as recombinant growth hormone, growth hormone secretagogue, and testosterone therapy.[35,40] Surgery is performed if osteoporosis sufferers experience fractures. Surgical therapy in osteoporotic patients must pay attention to the following principles, namely, in elderly patients, surgical treatment should be carried out immediately if necessary, surgical treatment aims at stable fixation, calcium intake must still be considered, and treatment with previous drugs must be continued. Treatment evaluation is carried out by bone densitometry examination after 1–2 years. Treatment is said to be successful if within 1 year there is no increase or decrease in bone mass density because the bone resorption process has been suppressed. Biochemical markers may also be performed after 3–4 months of

treatment for treatment evaluation.[41]

2. Conclusion

Healthy aging depends on the ability to maintain the reserve capacity of various physiological systems. Osteosarcopenia is a combination of low bone mass density and damage to the microarchitecture of bone tissue with loss of muscle mass, strength, and function that increases the tendency to fall. The diagnosis of osteosarcopenia is based on the diagnosis of osteoporosis and sarcopenia. Management of osteosarcopenia is carried out holistically, including management of osteoporosis and sarcopenia both non-pharmacologically and pharmacologically.

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