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Osteosarcopenia
A brief overview of the disease of the future

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Osteosarcopenia is a newly reported syndrome that describes the co-existence of osteoporosis and sarcopenia. Osteosarcopenia causes an increase in morbidity and mortality, and reduces the quality of life, but it is expected to incur billions in annual health care costs over the coming decades. Its etiology is multi-factorial, with a combination of genetic, mechanical, biochemical, and lifestyle factors. Clinicians should screen for osteosarcopenia using imaging methods (e.g., dual-energy X-ray absorptiometry) to quantify muscle and bone mass, and assess muscle strength (e.g., grip strength) and functionality (e.g., gait speed). Lifestyle changes, exercise and nutritional interventions, such as protein supplementation, vitamin D and dietary intake of calcium, have beneficial effects in the prevention and treatment of osteoporosis and sarcopenia. Future studies are needed in order to design treatment guidelines for patients with osteosarcopenia.

Οστεοσαρκοπενία, σύντομη ανασκόπηση της «πάθησης του μέλλοντος»

Περίληψη στο τέλος του άρθρου

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1. INTRODUCTION

As the world's population ages, the prevalence of chronic diseases increases.[1] Musculoskeletal diseases represent a significant health burden in older persons and a major cost to health systems worldwide. Osteoporosis and sarcopenia are two of the most prevalent chronic diseases in older people, with the conditions sharing overlapping risk factors and pathogenesis.[2] Together, these two diseases form a geriatric syndrome known as osteosarcopenia. Both osteoporosis and sarcopenia constitute a high risk for falls, fractures, and further functional decline.[3]

The term osteosarcopenia was first coined by Duque and colleagues to describe a condition in a subset of older persons.[1,2] It is suggested that when individuals experience a concurrent loss of bone mineral density and muscle strength, mass, and function, this should be interpreted as a single diagnosis of osteosarcopenia, which may be preventable and treatable.[1] Osteosarcopenia may occur in 5–37% of community-dwelling adults over the age of 65 years.[4,5] This wide range is driven by variations in population, setting, and the definitions applied.[4] Osteosarcopenia is associated with significantly increased mortality. One recent study of 324 elderly Korean patients with hip fracture showed a 1-year mortality rate of 15.1% in the osteosarcopenic patients, higher than that of patients with osteoporosis (5.1%) or sarcopenia (10.3%) alone.[5,6]

Osteosarcopenia continues to be a topic of controversy as researchers worldwide seek to elucidate whether osteosarcopenia is associated with greater risk of negative outcomes than its component parts.[4] Individuals with osteoporosis and sarcopenia often remain underdetected and undertreated.[1] The absence of a consensus operational definition of sarcopenia, and inaccurate measures of muscle mass, have hampered global progress in the field.[4] Understanding its pathophysiology and diagnosis, and its non-pharmacological and pharmacological management are tasks of great importance.[7] The aim of this review was

to summarize the latest developments in osteosarcopenia.

2. DIAGNOSIS

2.1. Osteoporosis

Osteoporosis is defined as a "systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture".[1,8] The World Health Organization (WHO) developed specific criteria to define osteoporosis in postmenopausal women, based on bone mineral density (BMD).[9] In general, most organizations recommend that all adults aged older than 50 years with a history of fracture undergo BMD screening.[10] The gold standard for diagnosing osteoporosis utilizes BMD measurements, especially in the hip and lumbar spine, with the dual-energy X-ray absorptiometry (DXA) device, or the occurrence of non-traumatic hip or vertebral fractures (tab. 1).[10,11] The widespread clinical use of DXA, particularly applied at the proximal femur and lumbar spine, is based on the many prospective studies that have documented a strong gradient of risk for fracture prediction.[12]

In 2008, the University of Sheffield released a model as a fracture prediction tool, the FRAX® tool.[13] The FRAX tool is used for assessing fracture risk, assisting clinicians to better target individuals for intervention. It can incorporate up to 6 clinical risk factors, any variation in body mass index (BMI), and include or exclude BMD at the femoral neck, entered as either a T-score or a Z-score. FRAX is freely accessible at http://www.shef.ac.uk/FRAX[14] with models currently available for 62 countries (68 models) and in 33 languages.[10,12]

2.2. Sarcopenia

Sarcopenia is a progressive and generalized muscle disease (muscle failure) with an ICD-10-MC diagnosis code that can be used to bill for care in some countries.[15–17]

In 2009, the European Working Group on Sarcopenia in Older People (EWGSOP) was the first to develop an operational definition of sarcopenia,[18] with other working groups providing their own definitions since.[19–21] In 2018, EWGSOP2 updated its definition and diagnostic strategies, using low muscle strength as the primary parameter of sarcopenia. Specifically, sarcopenia is probable when low muscle strength is detected, and the diagnosis is confirmed by the presence of low muscle quantity or quality.

A wide variety of tests and tools is available for measuring sarcopenia parameters in practice and in research (tab. 2).[15,22,23] For muscle mass assessment, DXA is currently the modality of choice.[5,24–26] Bioimpedance analysis (BIA) is a simple, portable and safe technique and it is useful in immobile, bedridden patients. The most common measure for muscle strength is the hand grip hydraulic dynamometer. Finally, the most reliable measure of muscle performance in clinical practice is gait speed, with EWGSOP advising a cut-off for sarcopenia of ≤0.8 m/s.[15,18,26]

Cut-off points for muscle mass, muscle strength and physical performance depend on the measurement technique, and on the availability of reference studies and populations. According to EWGSOP2, probable sarcopenia is defined in patients with reduced hand grip strength (women <16 kg; men <27 kg). The diagnosis of sarcopenia is confirmed by the presence of a low muscle skeletal muscle index (women <5.5 kg/m^2; men <7.0 kg/m^2). When low muscle strength, low muscle quantity/quality and low physical performance are all detected, sarcopenia is considered severe.[15]

Table 2. Assessment tools for measuring parameters of sarcopenia.

Parameter	Tools
Muscle strength	Hang Grip dynamometer, sit to stand test
Muscle mass	DXA, MRI, CT, BIA, ultrasound
Physical performance	Gait speed, 400 cm test, TUG, SPPB

MRI: Magnetic resonance imaging, CT: Computed tomography, DXA: Dual-energy X-ray absorptiometry, BIA: Bioelectrical impedance analysis, SPPB: Short physical performance battery, TUG: Timed-up and go test

Table 1. Descriptive characteristics of bone mass using dual-energy X-ray absorptiometry (DXA).

Bone mass	Descriptive characteristics
Normal	BMD higher than 1 SD below the young adult female reference mean (T-score greater than or equal to -1 SD)
Osteopenia – low bone mass	BMD more than 1 SD below the young female adult mean, but less than 2.5 SD below this value (T-score less than -1 and greater than -2.5 SD)
Osteoporosis	BMD that is 2.5 SD or more below the young female adult mean (T-score less than or equal to -2.5 SD)
Severe osteoporosis (established osteoporosis)	BMD that is 2.5 SD or more below the young female adult mean (T-score ≤-2.5) plus one or more fragility fractures

BMD: Bone mineral density

In addition, EWGSOP2 recommends the use of the SARC-F questionnaire in order to identify individuals at risk for sarcopenia.[15] The SARC-F is a questionnaire that is self-reported by patients as a screen for sarcopenia risk.[27] It includes five items based on the cardinal features or consequences of sarcopenia: Strength, assistance in walking, rising from a chair, climbing stairs, and falls.[28]

3. PATHOPHYSIOLOGY

Many factors can explain the pathophysiology of osteosarcopenia.[29] Evidence suggests that the pathophysiology of osteosarcopenia includes genetic polymorphisms, reduced mechanical loading, and impaired endocrine functioning, as well as altered crosstalk between muscle, bone, and fat cells.[30]

In skeletal tissues, muscle and bone interact mechanically and functionally.[31] Bone and muscle are strongly integrated organs with shared critical functions in structure, strength, and motion.[32,33] The mechanism of concomitant bone and muscle loss with aging is not clear at present. Muscle mass decline with aging appears to occur before bone mass decline with aging.[31] In addition, between skeletal muscle and bone, a complex interplay of mechanical, endocrine, and paracrine signals coordinates their mass and function throughout life.[29]

The mechanical relationship between skeletal muscle and bone has been simplified to muscle contractions serving to load, and bones acting as attachment sites.[32] The traditional view of the prominent mechanical interactions between muscle and bone is emphasized by the "mechanostat" hypothesis.[26] This theory states that muscle imposes mechanical forces on bone, with a certain threshold dictating whether bone is formed or resorbed.[34] Several lines of evidence have shown that low magnitude mechanical signals are anabolic to bone and muscle.[31,34,35]

Since both bone and muscle cells are derived from mesenchymal stem cells, similar genetic factors are considered to influence bone and muscle. Osteoporosis and sarcopenia may be affected by genetic polymorphisms of several genes, including androgen receptor, estrogen receptor, catechol-O-methyltransferase, insulin-like growth factor-1 (IGF-1), vitamin D receptor and low-density-lipoprotein receptor-related protein.[31]

Other possible causal factors of osteosarcopenia are related to endocrine metabolism abnormality, including those involved in diabetes mellitus (DM) and vitamin D metabolism.[32] Vitamin D, the growth hormone (GH)/IGF-1 axis and testosterone are the most important hormones that affect both muscle and bone metabolism. Muscle and bone also secrete certain factors, known as myokines and osteokines, respectively, which aid the communication between muscle and bone. Severe vitamin D deficiency leads to osteomalacia and muscle weakness due to type II muscle fiber atrophy.[29] Vitamin D deficiency is common in the elderly and causes increased risk of falls, sarcopenia and osteoporosis.[29,30]

GH and IGF-1 induce muscle hypertrophy, bone development and the preservation of bone mass. GH deficiency causes reduction in muscle and bone mass and an increase in fat mass.[31]

4. TREATMENT

The treatment for osteosarcopenia includes pharmacological and non-pharmacological interventions.

4.1. Non-pharmacological interventions

Non-pharmacological management of osteoporosis includes adequate intake of calcium, vitamin D and protein, weight-bearing exercise, smoking cessation, limitation of alcohol/caffeine consumption, and fall-prevention techniques.[10,36–39]

The effects of exercise in improving muscle and skeletal system have been well documented.[39–41] Several randomized controlled trials (RCTs) have demonstrated the efficacy of progressive resistance exercise to stimulate osteoblastogenesis and muscle protein synthesis, leading to improvement in bone microarchitecture, muscle mass, strength, and functional capacity in elderly persons with osteoporosis and sarcopenia.[30,42–45] Exercise affects the structure of the body by three mechanisms: (a) Direct impact on the bone transmitted by biological receptors to biological signals; (b) indirect effects, by improving muscle mass and strength that stimulate the mechanical secondary receptors; (c) alteration of the levels of hormones (calciotropic hormone, leptin, etc.) and environmental factors.[46]

The most appropriate type, intensity, duration, and frequency of exercise required to influence osteosarcopenia is not known,[38] but resistance training has a positive effect on bone by improving BMD[47] and on sarcopenia by a direct effect on the muscle.[38,48,49] Resistance training may reduce fat mass and improve BMD.[50] The optimal approach for osteosarcopenia may be targeted multi-modal programs that incorporate traditional and high-velocity progressive resistance training (PRT), weight-bearing impact exercises and challenging balance/mobility activities.[42]

Vitamin D is a fat-soluble vitamin that plays a most important role in calcium and bone metabolism.[33] Vitamin D acts as a mediator in the cross-talk between muscle and bone by affecting myokines such as myostatin, vascular endothelial growth factor (VEGF), IGF-1 and osteoglycin, and osteokines, including sclerostin, osteocalcin and fibroblast growth factor-23 (FGF-23), which have a positive effect on bone and muscle, respectively.[38] The association of vitamin D with osteosarcopenia has not yet been evaluated in a single interventional study, but its therapeutic benefit can be inferred from studies on osteopenia and sarcopenia. Future observational and interventional studies are needed to confirm the exact role of vitamin D in the pathophysiology and treatment of osteosarcopenia.

Calcium could also have a role in treatment of osteosarcopenia.[38] It is well-documented as an important bone mineral, and its importance in muscle function is suggested by its role in calcium-induced muscle contraction and calcium-induced calcium release from the sarcoplasmic reticulum.[38,50]

Given the association between protein and bone and muscle strength, protein supplements are proposed in patients with osteosarcopenia.[38] RCTs examining the effect of protein supplementation (above the recommended daily amount 0.8 g/kg/day), in conjunction with resistance exercise intervention, have demonstrated augmentation in muscle and bone mass, muscle strength, balance, and functional capacity.[43,50,51] The recommended dietary intake of protein is 0.8 grams per kg of body weight per day (g/kg/day) for healthy populations, irrespective of age or sex.[52]

Another novel therapeutic target is the prevention of fat infiltration, which is a common feature observed in osteoporosis and sarcopenia.[38] A decrease in marrow and intrafiber fat in bone and muscle, respectively, would be expected to have a beneficial effect on their mass and function.[53]

4.2. Pharmacological intervention

The treatment of osteosarcopenia with pharmacological agents is a new area of investigation. Although the benefits of anti-osteoporosis medications are well established in older adults with osteoporosis, appropriate medication for sarcopenia is under development and not available to patients.[53,54] No agents for treatment of sarcopenia have yet been approved by any food and drug administration, which may reflect the novelty of sarcopenia.[38]

Pharmacological treatment for osteoporosis, including bisphosphonates (alendronate, risedronate and zoledronic acid), RANKL antagonists (denosumab) and bone anabolics (teriparatide), have shown their efficacy in improving bone density.[10] The therapeutic effects of some compounds on osteoporosis may have an effect on muscle and bone mass and, therefore, could be useful in the treatment of osteosarcopenia. Denosumb, testosterone, GH and antimyostatin bodies may also be useful for patients with osteosarcopenia. Future research should be directed toward pharmacological agents, investigating their effects on both muscles and bones.[38]

5. CONCLUSIONS

Osteosarcopenia, the presence of osteopenia/osteoporosis and sarcopenia, is an emerging geriatric giant, which poses a serious global health burden.[30] Treatment approaches include exercise, improved nutrition and pharmacotherapy. Collaboration among health authorities, clinicians and researchers will bring progress in understanding the pathophysiology, and in devising therapeutic interventions for osteosarcopenia. Future high quality studies are required, to bring benefits to millions of patients worldwide.

ΠΕΡΙΛΗΨΗ

Οστεοσαρκοπενία, σύντομη ανασκόπηση της «πάθησης του μέλλοντος»

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Η οστεοσαρκοπενία είναι ένα νέο σύνδρομο, το οποίο περιγράφει τη συνύπαρξη της οστεοπόρωσης και της σαρκοπενίας. Η οστεοσαρκοπενία προκαλεί ανικανότητα, αυξημένη θνησιμότητα, μειωμένη ποιότητα ζωής και αναμένεται να δημιουργήσει τεράστιο οικονομικό κόστος στις υπηρεσίες υγείας, τις επόμενες δεκαετίες. Η αιτιολογία είναι πολυπαραγοντική, περιλαμβάνοντας παράγοντες γενετικούς, μηχανικούς και σχετιζόμενους με τους τρόπους ζωής.

Οι ιατροί πρέπει να αξιολογούν την οστεοσαρκοπενία με απεικονιστικά μέσα (π.χ. με απορροφησιομετρία ακτίνων Χ διπλής ενέργειας) για την ποσοτικοποίηση της μυϊκής και της οστικής μάζας, αλλά πρέπει επίσης να αξιολογούν τη μυϊκή δύναμη (π.χ. με δυναμόμετρο λαβής) και τη λειτουργικότητα (π.χ. με ταχύτητα βάδισης). Οι αλλαγές στον τρόπο ζωής, η άσκηση και οι διατροφικές παρεμβάσεις έχουν θεραπευτικά οφέλη στην πρόληψη και στη θεραπεία της οστεοπόρωσης και της σαρκοπενίας. Μελλοντικές μελέτες απαιτούνται για τη σχεδίαση κατευθυντήριων θεραπευτικών οδηγιών για τους ασθενείς με οστεοσαρκοπενία.

Λέξεις ευρετηρίου: Θεραπεία, Οστεοπόρωση, Οστεοσαρκοπενία, Πρόληψη, Σαρκοπενία

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