Osteosarcopenia and Physical Activity

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Abstract

Osteosarcopenia syndrome has recently been identified as a condition encompassing osteopenia/osteoporosis and sarcopenia. Osteosarcopenia is especially deleterious in older adults. Sarcoopenia and osteoporosis have common risk factors and biological pathways, and are significantly associated with physical disabilities and major threats to the loss of autonomy in life. Genetic, endocrine and mechanical factors as well as inflammatory and nutritional states concurrently affect muscle tissues and bone metabolism. Exercise can affect osteosarcopenia patients through increase in the concentration of anabolic hormones, signaling pathways of mTOR, Wnt-Catenin pathway, down-regulator of inflammation, etc. Studies have shown that a complete exercise program (including aerobic activity, strength, flexibility, and equilibrium exercises) can have a positive effect on osteosarcopenia individuals. In addition, long-term exercises should be carried out in order to create positive effects; otherwise the effects of exercise activities will be eliminated.

INTRODUCTION

Aging is rapidly increasing in the world and so the prevalence of many chronic diseases is raising in the elderly population. Aging is associated with some structural and functional changes, augment disability, weakness, and falling [1]. Contributing factors for physical impairment are a gradual deterioration of the bone (osteoporosis) and a progressive decrease in muscle mass (sarcopenia) [1].

Sarcopenia and osteoporosis are among the major concerns of the World Health Organization. Genes, endocrine glands, and mechanical factors, as well as nutritional and inflammatory conditions affect both muscle and bone tissue. Clinical trials on bones and muscles have shown that bones interact closely with the muscles through local and humoral signaling pathways, in addition to their musculoskeletal function. However, the physiological and pathological mechanisms of their interaction are not completely clear [2].

Osteopenia / Osteoporosis

Osteoporosis is a serious skeletal disorder associated with bone mass loss and structural weakness in bone tissue causing numerous and extensive fractures [3]. Osteoporosis diagnosis is done based on measurement of bone mineral density (BMD) in the lumbar spine and hip by the DEXA machine. According to the World Health Organization, T-score smaller and equal to -2.5 is osteoporosis, T-score between -1 and -2.5 means osteopenia and T-score larger than -1 means healthy. DEXA is known as the gold standard for osteoporosis diagnosis and has a high degree of validity [4,5].

Growth period is the best time to increase the amount of BMD and level by increasing the load due to high speed bone build-up and reconstruction. Bone strength is related to many factors associated with bone tissue size and volume and bone structural network [6].

The two main factors causing osteoporosis are: the peak of the bone mass in adults and the rate of bone mass loss with aging [7]. It has been shown that bone mineral content increases during childhood and reaches its maximum during puberty [8]. A large part of this phenomenon (more than 90%) is achieved by about 17-18 years of age. In boys, bone mass began to increase with a steep slope by about 10 years of age, and much of it is formed during pre-puberty and afterwards, to about 17-18 years of age. In girls, this increase is more gradual and the highest bone mass accumulation occurs in a 4-year period of about 11-15 years [7]. Therefore, different factors at this time will have the greatest impact on the peak of the bone mass. Bone formation is predominant up to 25 years of age and stabilizes until age 35 and then gradually decreases [7].

Sarcopenia

The muscle mass reaches its maximum by approximately 25 years of age, and by the age of 50, there is a 5% decrease in the number of muscle fibers. At the end of second decade of life, the muscle mass begins to decrease, and its rate increases in the fifth decade of life [9]. The annual loss of muscle mass is between 1% and 2% per year, resulting in a 30% reduction in muscle mass by the age of 80. The reduction in muscle strength between the ages of 50 and 60 is 1.5%, followed by 3% [10,11]. Chronic diseases,
drug use, environmental factors, inappropriate nutrition and physical inactivity can increase the rate of muscle mass.

Sarcopenia is a term used primarily to describe the reduction of muscle mass associated with aging [12]. This term represents the level where the musculoskeletal muscle mass or muscle strength decreases from the threshold in which health is affected. The European Union has defined sarcopenia as a gradual and total reduction in muscle mass and strength with the increasing risk of physical disability, reducing physical function and quality of life [13]. Although loss of strength and muscle mass can occur simultaneously, this relationship is not linear [13].

Although there are several definitions of sarcopenia, one common criterion is the use of skeletal muscle mass less than 2 SD of the average skeletal muscle mass of healthy young people. There is also a definition based on the gender: skeletal muscle mass less than 7.26 kg/m² is defined for men and less than 5.45 kg/m² for women. The people under this cut point have significantly larger risk of adverse functional status, such as a higher risk of disability, falls, and fractures [14].

**Osteosarcopenia**

Sarcopenia and osteoporosis have common risk factors and biological pathways, and are significantly associated with physical disabilities and major threats to the loss of autonomy in life [15]. Many elderly, especially those at risk, are at the same time exposed to osteoporosis and sarcopenia, and the risks and complications of these two diseases increase. Combining these two disorders increases the negative health outcomes [10].

Bone and muscle are not only related due to their adjacency, but also chemically and metabolically. In addition, specific pathophysiological findings, such as lipid infiltration and alterations in stem cell differentiation are common in both diseases, thus suggesting that sarcopenia and osteoporosis are related [16].

Bone and muscle are active metabolic tissues that are continuously regulated with harmony of counteracting processes. The protein synthesis of skeletal muscle is balanced by degradation, while bone formation is balanced by reabsorption [17]. An imbalance in the regulation of these tissues can lead to a decrease in BMD or sarcopenia. Both diseases are multifactorial and pathophysiological pathways share different pathophysiological pathways [17].

Apart from age, there are other factors contributing to the development of osteosarcopenia. Genetic polymorphisms of the genes Glycine-N-acyltransferase (GLYAT), methyltransferase-like 21C (METTL21C), myostatin, α-actinin 3, proliferator-activated receptor gamma coactivator 1-α (PGC-1α), and myocyte enhancer factor 2C (MEF-2C) are related to bone and muscle mass [2, 10].

Endocrine gland disorders (mainly diabetes, abnormal thyroid function and low levels of vitamin D, sex steroids, growth hormone and insulin-like growth factor-I), Malnutrition, obesity, and the use of corticosteroids are also associated with osteosarcopenia [2, 10].

Bone and muscle are adaptive, their mass and strength varies in response to applied mechanical loads. In addition, mechanical stimulation is essential for the health of both tissues; therefore, the reduction of physical activity levels may lead to a loss of balance in favor of muscle destruction and bone resorption [10]. Fatty infiltration of muscle and bone, which has been interpreted as a natural phenomenon in the past, is now known to contribute to osteosarcopenia. It is probably due to the negative effect of secretion of inflammatory cytokines by bone marrow and body fat in a known process called lipotoxicity [18]. Studies have shown that sarcopenic and osteopenic patients have high serum levels of inflammatory cytokines, particularly IL-6 (IL-6) and high tumor necrosis factor alpha (TNF-α) associated with systemic and local lipotoxicity [18, 19]. Additionally, there are many indications that there is a close relationship between bone mass and muscle mass. A positive correlation has been recorded between the two tissues where the increase in muscle mass is related to the increase of BMD and vice versa [5, 10, 19].

Common risk factors for osteoporosis and sarcopenia are not the only mechanism that describes bone and muscle mass reduction. Clinical and basic researches have proposed crosstalk between two tissues where the fat plays a major role in this action and reactions. The musculoskeletal unit interacts mechanically and physically but also biochemically via paracrine and endocrine communication [2, 10].

Many paths are involved in this development that can describe the development and progression of osteosarcopenia. However, all effective paths are not fully understood. One of these mechanisms includes Osteocalcin, an osteoblast-derived protein marker of bone formation that stimulates β-cell proliferation and insulin secretion and acts directly on skeletal muscle, correlating with muscle strength [10].

Another intrinsic mechanism of muscle and bone involvement is secretion of the vascular endothelial growth factor (VEGF) by a bone marrow mesenchymal stromal cell stimulating the proliferation of myoblast. The muscle also secretes several endocrine molecules that affect the bone, such as IGF-1, irisin, osteonectin, osteoglycin, fibroblast growth factor-2, IL-6, IL-5, myostatin and matrix metalloproteinase 2 (MMP2) [10, 20].

In addition, hormonal factors found in the bone (FGF21, subcaboxylated osteocalcin, and sclerostin) have some effects on skeletal muscle [21]. There are also common pathways such as GH / IGF-1, sex steroids, and Wnt signaling in the bone-muscle control unit which can be compatible with mechanical stimulation and damage [22].

**Physical activity**

In general, physical activity is necessary to maintain and improve all components of body composition, as well as mental and physiological health of people of all ages. Even low intensity physical activity or normal activities is required to maintain or improve BMD, maintain muscle strength and quality, improve balance and inflammation associated with aging [23, 24].

A comprehensive exercise program for elderly people should include aerobic, strength, flexibility and balance exercises. These four types of exercises are necessary to maintain body composition and health of the elderly. Applying a full exercise
program reduces the risk of falling, improves the ability to function and improves the quality of life in older adults [23, 24].

Increasing muscle tension and balance, reducing falling and reducing bone loss rate, especially in the femoral neck, can be among the beneficial effects of regular activity. Also, the mechanical forces activate various signaling pathways involved in bone formation and the turnover of muscle protein. Studies have shown positive effects of long-term exercises on walking improvement, physical performance parameters, and fall in elderly [25]. However, these effects are dependent on the continuation of exercise by individuals. Research has shown that the effects of exercise on muscle strength and bone density disappear within 6 months after the cessation of regular activity. There is no agreement on the type, duration, and intensity of exercise [26].

Exercise affects the structure of the body by three mechanisms: the direct impact on the bone transmitted by biological receptors to biological signals; its indirect effects by improving muscle mass and strength that stimulate the mechanical secondary receptors; and by altering the levels of the hormones (such as calcitropic hormone, leptin, etc.) and environmental factors [27]. The mechanical load applied by the exercise, the Wnt-Catenin pathway and the pathway for bone morphogenetic proteins play an important role. In addition, the results indicate an increase in osteogenic differentiation and bone formation due to changes in levels of hormones such as parathyroid, estrogen and prostaglandin E2 hormone due to exercise [28].

Studies showed that exercise can increase the concentration of anabolic hormones such as GH / IGF-1 and FSH / LH / estrogen in a wide range of ages [29-31]. Exercise moderate IGF-1 liver production by changing the flow of GH secreted by the pituitary gland. Increasing the amplitude and frequency of GH / IGF-1 production is expressed by the stressful effects of exercises on serum glucose levels. IGF-1 is also topically applied by bone and muscle cells in response to activation of mechanical receptors and expression of IGF-1 in osteocyte and bone epithelium cells within 6 hours of mechanical load. Insulin and IGF-1 are anabolic agents in osteoblasts causing bone growth and development by activating the signaling pathways of AKT and ERK [29, 32].

Sarcopenia is associated with changes in skeletal muscle. These mechanisms can be summarized as metabolic, cellular, vascular, and inflammatory. Metabolic changes are associated with the mammalian target of rapamycin (mTOR) kinase which is a key regulator of cell growth. In the normal muscle, mTOR activation controls the protein synthesis in the muscle, a process that is disturbed in the sarcopenic muscle [33, 34]. In terms of the cellular mechanism, the loss of a number of muscle fibers and atrophy of fibers, especially type II fibers, is the main cause of sarcopenia. In addition, the decrease in myofibrillar protein due to the lack of satellite cell capacity in response to growth factors and cytokines required to stimulate the production of these proteins affects the number of activated satellite cells and muscle fibers [33, 34].

The application of mechanical load activates mTOR, thus stimulating the synthesis of muscle protein. Exercise increases myofibrillar protein by activating satellite cells. In addition, recent evidence suggests that exercises reduce fat infiltration in the muscle. In terms of mitochondrial function, exercise also increases the proliferator activated receptor gamma co-activator 1-alpha and muscle fatty acid binding protein with subsequent activation of mitochondrial genes while optimizing their energy production. Ultimately, the exercise is a down-regulator of inflammation. Reports of clinical studies showed a reduction in C-reactive protein and interleukin 6 levels in frail older people [33, 34].

As mentioned, exercise can stimulate the secretion of anabolic hormones (eg GH, IGF-1, testosterone), and have positive effects on patients with sarcopenia [30, 31, 35, 36]. Regarding the maintenance of muscle mass, recent findings have shown that resistance exercises effectively increase muscle mass and protein synthesis, but the best practice for elderly people is the activity that they are able to do it. In addition, to improve the remodeling bone, applying mechanical load can have a positive effect on myogenesis [23, 31].

Studies have shown that regular weight bearing exercises and muscle-strengthening exercises can have many benefits with a focus on improving agility, strength, standing and balance [37-39]. Performing exercises at least three times a week for at least 20 minutes improves muscle and bone density, increases muscle strength, reduces or delays movement restrictions and prevents falling and fractures in the elderly [38, 39]. However, although these exercises are very effective for the safe treatment of people with osteosarcopenia, patients with multiple disabilities (attacks of impaired nervous system and cardiac dysfunction) may not be able to perform the recommended activities [39].

**CONCLUSIONS**

However, studies to date suggest that osteosarcopenia is a new geriatric syndrome increasing in the elderly. Sarcopenia and osteoporosis have common risk factors and pathways. The metabolic, cellular, vascular, and inflammatory factors, etc., can be cited as some causes of osteosarcopenia, and so far, all effective paths have not been fully understood. Studies have shown that a complete exercise program (including aerobic activity, strength, flexibility, and equilibrium exercises) can have a positive effect on osteosarcopenia individuals by stimulating and altering the secretion of hormones, signaling anabolic pathways and mechanical receptors. In addition, long-term exercises should be carried out in order to create positive effects; otherwise the effects of exercise activities will be eliminated.

**REFERENCES**


