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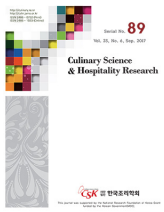

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[Research Notes]

Osteosarcopenic Obesity in Elderly: The Cascade of Bone, Muscle, and Fat in Inflammatory Process

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KEYWORDS

Sarcopenia, ageing, Inflammation, Osteosarcopenic obesity, Nutrients.

ABSTRACT

Conditions related to body composition and aging, such as osteopenic obesity, sarcopenia/ sarcopenic obesity, and the newly termed osteosarcopenic obesity(triad of bone, muscle and adipose tissue impairment), are beginning to gain recognition. Currently, it has begun to attract the attention of scholars from all over the world, however, for this disease, it still needs a more clear understanding and perception. Therefore, this article considered the osteoporosis, muscle depression, and obesity, these diseases as a gate to study the relationship among muscle, bone, and fat. In addition, in the aging process, the formation of IGF-cortisol, testosterone, and estrogen is sensitive. These hormones can not only absorb muscle protein metabolism, but also affect alienation. The decrease in IGF-cortisol in the elderly resulted in increased visceral fat, decreased muscle mass and bone mineral density, and then affected decreased skeletal muscle atrophy and decreased quality. The reduction of skeletal muscle quality and strength and increase body fat affected the adipose tissue to produce inflammatory cytokines, thereby reduced skeletal muscle, promoted cardiovascular disease, metabolic syndrome and insulin resistance in chronic diseases. Almost all chronic inflammatory diseases were associated with bone, muscle and fat. These mechanisms were complex and interrelated. Inflammation reduces bone formation, increases fat and reduces muscle mass. And thus not only had a significant impact on the motor system, but also made the incidence increase of fracture, osteoporosis, fragile syndrome, fall, osteomalacia and other bone disease. This article aimed to start from the interaction between the muscles and bones of the elderly, extended to obesity, muscle deficiency, osteoporosis and other diseases, finally, from a nutritional point of view, to discuss how to treat osteoporosis obesity.

1. INTRODUCTION

Over 30 years of age, the body function of human being developed to decline and muscle before to shrink, meanwhile, adipose tissue also increased. And 35 years old to 70 years old, muscle function will drop 30%. For example, male muscle volume was 30% atrophy, 50% increase in fat mass and the muscles of women's waist, buttocks, thigh, skin also reduced (Moller, Copeland, & Nair, 2007). The reduction of IGF-cortisol in the bulk leaders in the increase of visceral fat and the

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decrease in muscle mass and bone mineral density. The physical changes are important cases of obesity, sarcopenia, and osteoporosis. Studies have shown that over 30 years of age, the amount of skeletal muscle per highway decreased by 6% every 10 years, during the 40～60 years after 20 years old, the reducing of skeletal muscle mass was up to about 40% (Lexell, 1993). Although skeletal muscle atrophy, decreased quality, muscle mass continues to decline, but the muscle receptor patients under the weight of the body is not significant or even increased, therefore, compared with the normal situation, the weight of patients with little muscle loss even increased, the patient has fat muscle characteristics (Grimby & Saltin, 1983).

However, sarcopenia patients with skeletal muscle quality reduction, decreased strength and physical decline not only has a great impact on the motor system, the specific performance is the increase of falls and the incidence of fractures, but also systematically effects on the overall physiological state of the elderly, manifested as prolonged hospitalization, increased incidence of complications and increased mortality, even multiple systems of malignant tumors were significantly higher (Batsis, Mackenzie, Barre, Lopez-Jimenez, & Bartels, 2014; Bijlsma, Meskers, Westendorp, & Maier, 2012). For more than 20 years, large-scale clinical studies on sarcopenia has been reported that to some extent, muscle deficiency to some extent with it is closely associated with fragile syndromes, falls, osteomalacia, osteoporosis and brittle fracture (Scott, Daly, Sanders, & Ebeling, 2015; Grisso et al., 1991; Pereira, Leite, & Paula, 2015; Cedergikn, Cruz-Jentoft, & Maggi, 2013). This article intends to start from the interaction between elderly muscles and bones, extends to obesity, muscle deficiency, osteoporosis and other diseases, and then concludes its control methods.

2. SARCOPENIA

Muscle reduction is a natural aging phenomenon that with the increase of age, the muscle mass and muscle strength decrease. Many studies have shown that the physiological changes in the elderly are increasing with age. For example, osteoporosis found 50 years ago, the researchers found that bone density decreased, the incidence of osteoporosis increased. Hence, the reduction in muscle mass, the incidence of muscle reduction increased. Consequently, with time going by, a large number of researchers in the world began to pay attention to muscle reduction. The prevalence rate of 65 years is 5% to 10%, and over 70 years old, the prevalence rate of sarcopenia is more than 40%(Morley, Anker, & Haehling, 2014). At present, there are about 50 million patients with muscle deficiency in the world, and it is estimated that by 2050, the number of patients will reach 500 million (Cruz-Jentoft et al., 2010). Hence, in October 2016, the US Centers for Disease Management classified muscle reduction as a disease. A variety of studies have shown that muscle deficiency and osteoporosis, cardiovascular disease, diabetes, metabolic syndrome, insulin resistance syndrome and other diseases have a complementary relationship (Batsis, Mackenzie, Jones, Lopez-Jimenez, & Bartels, 2016; Han et al., 2014; Urano & Inoue, 2015; Krzymińska et al., 2014). Sarcopenia needs to get more attention.

3. SARCOPENIC OBESITY

Sarcopenia is defined as an old age disease in which skeletal muscle mass and strength decrease with age. Sarcopenic obesity is a combination of "sarcopenia" and "obesity", which is the result of the aging process. With the increase of age, muscle strength and bone mass decline, and then it can be defined as osteopenia which is directly related to the risk of falls and fractures of the elderly. Sarcopenic obesity may have a greater negative impact on the health of the elderly than the single "sarcopenia" or "obesity". Most importantly, sarcopenia can make adipose tissue produce inflammatory cytokines, especially visceral fat to accelerate muscle metabolism, and thus it plays a significant role in the elderly muscle loss. Consequently, the elderly sarcopenic obesity is a major risk factor for chronic diseases, such as osteoporosis, inflammation, type 2 diabetes and cardiovascular disease.

4. OSTEOPOROSIS

Osteoporosis is a skeletal disease characterized by low bone mineral density(BMD) and microarchitectural degradation of bone tissue, increasing the risk of disease associated with fracture (Cummings & Melton, 2002). In a plenty of developing and developed countries, the incidence and mortality of osteoporotic fractures are very high. BMD is an important predictor of osteoporotic's primary marker and fracture risk, and is a complex quantitative trait with a normal distribution in humans. The pathogenesis of osteoporosis has not been very

clear, and it is generally believed that muscle loss, lack of calcium intake, lack of exercise and genetic is important factor in osteoporosis. As one of the most closely related organizations with skeletal morphology and function, muscle is closely related to osteoporosis. Changes in bone mineral density and muscle strength of the age of the law is consistent, which reflects the muscle and bone in the function and shape of the consistency. Therefore, in addition to osteoporosis, the loss of skeletal muscle is also a common disease in the elderly population. This symptom relates to diseases such as sarcopenia, a major skeletal disease characterized by a decrease in muscle mass, resulting in the decrease in bone strength and muscle mass and an increase in the incidence of fractures (Cruz-Jentoft et al., 2010; Chen et al., 2014).

The prevalence of obesity has also increased in recent years. Obesity has become one of the most serious health problems in the world. Obesity and osteoporosis are caused by a variety of high-risk environmental factors, a variety of susceptible gene accumulation effect, for the multi-gene complex genetic disease. Many studies have shown that obesity is positively associated with BMD and has a protective effect on the prevention of osteoporosis and reduces the risk of fracture (Glauber, Vollmer, Nevitt, Ensrud & Orwoll, 1995; Thomas, Burguera, Melton, Atkinson, O'fallon, Riggs, & Khosla, 2001). Both obesity and osteoporosis may share some regulatory factors. In the process of obesity, many hormones related to body weight are associated with changes in bone mass, such as: leptin, estrogen, adiponectin secreted by adipose tissue; gastrointestinal hormone secreted by digestive tract stimulates growth hormone secretion; pancreatic secretion of insulin, pancreas leptin. Hence, we simply summarize the effects of muscle and bone on the pathogenesis of osteoporosis, muscle loss, and obesity.

5. OSTEOSARCOPENIC OBESITY SYNDROME

Diseases which are related to the formation of the body with the problem aging such as osteopenic obesity, sarcopenia / sarcopenic obesity, and the newly termed osteosarcopenic obesity(triad of bonemuscle and adipose tissue impairment), began to be recognized around the world. Recently, American scholars have proposed a new syndrome called osteosarcopenic obesity (OSO), which marks the end result of damage to bone, muscle and adipose tissue during aging. OSO may be due to overweight or obesity chronic inflammation, as well as due to improper diet and bad habits (Ilich, Kelly, Inglis, Panton, Duque, & Ormsbee, 2014). In addition, some chronic diseases such as cancer, diabetes, and other diseases cause endocrine disorders and stem cell lineage damage, leading to physical disorders, at last, may also lead to OSO (Ormsbee, Prado, Ilich, Purcell, Siervo, Folsom, & Panton, 2014). Thus, we can conclude that osteosarcopenic obesity is a disease that is largely affected by the aging population.

In recent years, although the close relationship between bone and muscle has been recognized, the inclusion of fat tissue, either as an overt obesity, as an age-induced redistribution of fat, or as an infiltrated fat into bone and muscle, in bone and muscle damage are beginning to get more attention. In the aging process, bone and muscle mass or strength decreased, while the body fat increased. These changes in body composition are accompanied by increased low-grade mild inflammation and the decline in physical activity, a combination which favors OSO (Thomas et al., 2001).

In addition to the physical changes in bones, muscles and fats, protein assimilation hormones will fall with aging as the growth increases. There are also a decline in insulin-like growth factor-1 (IGF-1) (Rozing et al., 2009) associated with aging, but this may also link to the decline in growth hormone. Moreover, it is recognized that estrogen and testosterone in men and women will decline with the increase of age. With age, inflammation increases, then leading to the transfer of mesenchymal stem cell (MSC) pedigree, which facilitates greater fat formation in bone and muscle as well as in adipose tissue. Ultimately, this deregulation of MSC lineage commitment may contribute to many chronic diseases, including osteoporosis and obesity and subsequent functional decline. Thus, over time, eventually it may lead to osteosarcopenic obesity, for example, sarcopenic obesity is the result of increasing fat mass and fat infiltration into the muscles (the reason may be multifaceted and should include diet and lifestyle, but will depend on the individual) and last, it results in decreased muscle mass and function, and the possible vulnerability increases. Reducing the amount of exercise, muscle mass decline and improper nutrition, and age or combination of inflammation, inducing and accelerating infiltration of fat into the bone lead to osteopenic obesity and when compounded with sarcopenia eventual OSO. However, nutritional therapy can effectively prevent and treat OSO syndrome and it will be briefly described as follows.

6. THE RELATIONSHIP BETWEEN MUSCLE AND BONE

Aging and various pathological conditions affect muscle and bone. In recent years, many evidences suggest that lean body mass is positively correlated with bone mass, leading to the reduction of the risk of fracture. Genetics, endocrine and mechanical factors affect muscle and bone. In contrast to the links from muscle to bone, the effect of bones on the muscles may exist. Bone marrow MSCs support bone formation and bone resorption in bone tissue. A recent study showed that bone marrow MSCs were stimulated by muscle endothelial growth factor (VEGF) into marrow MSCs (Sassoli et al., 2012), whereby bone MSCs affect muscle cells. IGF-I, MGF, myostatin, VEGF and hepatocyte growth factor (HGF) may be an important metabolic factor that regulates muscle mass, both of which are produced in bone cells. Bone cells are very abundant in bone tissue and are thought to be endocrine cells that affect different organs, such as the kidneys and parathyroid glands. A recent study has shown that mechanically loaded MLO-Y4 osteocytes produce various factors such as IGF-I, MGF, VEGF and HGF. In addition, bone cells produce factors such as Wnt3a and prostaglandin E2 (PGE2) that support musclegenesis and muscle function (Gorski et al., 2013). Studied that bone cells usually secrete BMPs through skeletal muscle to inhibit skeletal muscle growth and differentiation. Thus, bone cells may affect muscle mass through a variety of factors.

The study of the relationship between bones and muscles is particularly important for the prevention and treatment of future sarcopenia and osteoporosis. Sarcopenia is related to osteoporosis independently and dependently (Miyakoshi, Hongo, Mizutani, & Shimada, 2013).

7. HORMONE DYSFUNCTION IN BODY COMPOSITION CHANGES

The study found that vitamin D, the growth hormone / insulin-like growth factor I axis and testosterone are physiologically and pathologically important as endocrine factors (Cooper et al., 2012). These findings suggest that there is an interaction between muscle and bone, which may be important for understanding the physiological and pathophysiology of muscle deficiency and osteoporosis.

Higher body mass index (BMI) is related to higher BMD and reduced fracture risk. This mechanism may be due to higher body mass caused by increased strain on the bones, thus making the bone damaged. In the large prospective study of postmenopausal women, the risk of hip fractures was found to decrease as body activity decreased. In addition, in a cross-sectional study in the United Kingdom, male obese patients are more prone to fractures in the ankle and upper arms than female, suggesting that higher bone density in obesity has no protective effect on fractures, which may be associated with physical habits, and the effects of obesity on bones (Ong, Sahota, Tan, & Marshall, 2014).

Several studies have shown that higher muscle mass is associated with increased bone mineral density in postmenopausal women and reduces the risk of fracture (Kaji, 2013). Estrogen plays a role in inhibiting calcium leaching from the bones, women after menopause estrogen deficiency led to the occurrence of lumbar syndrome, osteoporosis and other symptoms, at the same time, 5～10% of women in their early menopause will have this symptom. Therefore, calcium plays a crucial role in muscle contraction, and hypocalcemia induced muscle spasms. These findings suggest that there may be a possibility of interaction between postmenopausal muscle and skeletal metabolism in women (Kaji, 2013). In another study, six years of tracing the changes in body composition of French women (Sornay-Rendu, Karras-Guillibert, Munoz, Claustrat, & Chapurlat, 2012) found that LBM and fat mass did not change in premenopausal and postmenopausal women. However, LBM and bone mass decreased, but the fat of postmenopausal women increased. Therefore, age is the most important determinant factor for the changes in body composition, although menopausal status is only an important determinant of bone mass changes. In men, testosterone is important in the physiology of various organs and tissues. Serum testosterone concentration gradually decreased to one of the aging process. This aging process is accompanied by the reduction in muscle mass and strength, the reduction in body hair and changes in skin, and a decrease in bone mineral content leading to osteoporosis (Tsujimura, 2013).

8. BODY COMPOSITION RELATED INFLAMMATORY DISEASE IN AGING

As the aging occurs, the accumulation of adipose tissue is accompanied by the decrease in muscle and bone strength. In the bone, adipocyte (AC) details in the marrow cavities of long bones and is known to increase with estrogen deficiency,

mechanical unloading, and exposure to glucocorticoids. The factors leading to accumulation of intra and intermuscular fat (myosteatosis) are less well understood, but the recent evidence indicates that increases in intramuscular fat are associated with disuse, altered leptin signaling, sex steroid deficiency, and glucocorticoid treatment, factors that are also implicated in bone marrow adipogenesis. Importantly, with the accumulation of lipids in skeletal muscle and muscle cells, the accumulation of AC is associated with the loss of muscle strength, the decreased insulin sensitivity, and the increase in mortality in the elderly.

Insulin is an important factor in skeletal muscle synthesis of metabolic factors, and muscle ACs which can reduce insulin sensitivity can impair skeletal muscle normal protein synthesis (Rivas et al., 2016). Therefore, skeletal muscle fat infiltration of insulin sensitivity is reduced by a way that fat infiltration can directly affect muscle mass and muscle strength. At the same time, it also can resist to movement and body vibration and prevent skeletal muscle fat infiltration, and then improve muscle strength. To prevent myosteatosis can improve muscle function and reduce the risk of falls in the elderly and lastly, may affect the incidence of bone fractures. Fatty infiltration of skeletal muscle is also common rotator cuff muscle injury and is a major factor that limits functional recovery (Gumucio et al., 2014). Some studies have shown that fat infiltration and muscle atrophy after rotator cuff repair are difficult to reverse (Gerber, Schneeberger, Hoppeler & Meyer, 2007; Gladstone, Bishop, Lo, & Flatow, 2007). Hyperlipidemia and Type 2 diabetes are independent risk factors for rotator cuff injury (Lin et al., 2015). These risk factors will not only increase the prevalence of rotator cuff injury, but also increase the fat infiltration of injured rotator cuff muscles.

In addition, growth Hormone(GH) / IGF-I axis and testosterone are the most important hormones that affect both muscle and bone. Estrogen, glucocorticoids, thyroid hormones, insulin, leptin and adiponectin can also regulate muscle / bone relationships.

Other major factors may affect the negative effects of muscle and bones, including nutritional status, physical activity, atherosclerosis, hormones and inflammatory cytokines(Cooper et al., 2012), which in turn lead to sarcopenia, Osteoporosis, metabolic syndrome, diabetes, cardiovascular disease, inflammation and so on. For example, diabetes is an important cause for osteoporosis. Although the severity of osteopenia and bone fragility are known in type 1 diabetes, many recent studies have shown the increase in the prevalence of fracture in type 2 diabetes, as well as through decreased bone mass and muscle loss(Butner et al., 2012). Thus, weight control and exercise therapy as well as diabetes medication can regulate the interaction between muscle and bone. Although weight control can reduce the amount of muscle and bone mass in diabetic patients, a one-year lifestyle intervention for type 2 diabetes mellitus has been found to reduce weight gain and a modest increase in hip bone bone, thereby improving bone fitness and glycemic control(Schwartz et al., 2012). Therefore, we should pay attention to the loss of muscle quality of diet treatment to treat patients with diabetes. Several studies have shown that endurance training(strength training) may have unique benefits for the treatment of type 2 diabetes by treating neurological and skeletal dysfunction caused by abnormal metabolic diabetes mellitus(Wood & O'Neill, 2012).

Finally, obesity and osteoporosis are associated with increased oxidative stress and proinflammatory cytokines. Proinflammatory cytokines, including TNF-α, IL-1 and IL-6, are key regulators of osteoclast differentiation and bone resorption. The increase in chronic inflammation and proinflammatory cytokines can increase bone resorption and bone loss in patients with periodontitis, pancreatitis, inflammatory bowel disease and rheumatoid arthritis. It has been demonstrated that elevated proinflammatory cytokines are the main medium for bone loss or osteoporosis. The acceleration of postmenopausal bone loss is associated with the increase in proinflammatory cytokines, which enhances osteoclast activity by modulating the RANKL / RANK / OPG pathway. A significant increase in the prevalence of osteoarthritis in obese patients can be seen from another point that chronic inflammatory responses affect bone metabolism (Anandacoomarasamy, Caterson, Sambrook, Fransen & March, 2008). Adipocytes secreted by cytokines have been shown to have unique anti- apoptotic, anti-inflammatory and anti-oxidative effects.

In conclusion, it can be shown that obesity may affect bone metabolism by producing adipocytokines.

9. NUTRITION AND EXERCISE FOR BONE-MUSCLE FUNCTIONAL REPAIR

Nutrition is an important factor in the health of the elderly, affecting the health and aging process of the elderly. The prevalence of malnutrition has increased rapidly in the elderly population, and associated with declining human functional status, impaired muscle function, decreased bone quality, im-

mune dysfunction, anemia, cognitive impairment, poor wound healing, slow recovery of surgery, hospitalization high rate of death(Flegal, Carroll, Ogden, & Johnson, 2002). Elderly people often reduce appetite and energy consumption, coupled with decreased biological and physiological functions, such as lean body weight reduction, changes in cytokines and hormones, fluid electrolyte regulation changes, leanding to the reduciton of muscle and bone quality in elderly (Flegal, Carroll, Ogden & Johnson, 2002). In Western countries, many elderly have the problem of over-weight (using Standard BMI Criteria) and the prevalence is rapidly increasing. In 2000, 65% of US citizens over 65 years of age had BMI $\geq$ 25 (Flegal, Carroll, Ogden & Johnson, 2002), and the prevalence of obesity in the United States (BMI 30) increased by 36% from 1991 to 2000 (Mokdad et al., 2001). The relative risk of death in the elderly with high BMI is not as great as that of young people, but is similar to the risk of mortality from diabetes, hypertension and cardiovascular diseases. Older people with high BMI also suffer from symptomatic osteoarthritis, osteoporosis, sarcopenia and bladder problems, as well as sleep apnea and other respiratory problems. So weight loss is safe and beneficial for obese older people, but they are supposed to exercise with caution. The way for the elderly to lose weight is the same as young people (Chapman, 2008). It is better to diet and exercise programs to maintain the quality of muscle weight loss, because single dieting easily lead to muscle and fat loss, and the elderly with age increasing, the quality of skeletal muscle has been declining. Calcium and vitaminD supplements have been shown to reduce the incidence of hip fractures (Chapuy et al., 1992). Micronutrients should be supplemented in patients who have proven to be deficient. High quality protein foods have also shown to increase the energy and protein needs of critically ill patients (Bourdel-Marchasson et al., 2000). This is enough to improve clinical and functional outcomes and reduce the prevalence.

10. PROTEIN

The decline of skeletal muscle quality and strength will make the elderly mortality, morbidity and quality of life decrease. Adequate protein intake is crucial for the improvement of the old muscle and bone function. Some of the controversy over protein intake in the elderly, compared with the lower protein intake requirements, protein intake with a higher amount for the elderly will be better for their physical health (Bauer et al., 2013). There is also new data showing that the optimal health of the elderly depends on maintaining muscle mass, which requires more than the minimum amount of protein uptake (Tang et al., 2014). The body's largest protein unit is skeletal muscle, which makes up about 80% of the cell mass and 30% of whole body protein turnover in lean young adults (Short & Nair, 2000). Each cell contains a protein that has functional and structural properties. In addition, there is a small amount of body protein that can be used to provide energy during starvation. Aging is associated with a gradual decline in resting metabolic rate (RMR), with a decrease of 1% to 2% per decade after the age of 20 (Montero-Fernandez & Serra-Rexach, 2013). This reduction in RMR is closely linked with the decrease in whole body fat-free mass, which is composed of metabolically-activ tissues and organs (Manini, 2010). More than 50% of the body weight of young people is lean muscle, but the lean muscle of people who are 75-80 years old is aging to 25% (Short & Nair, 2000). Loss of muscle mass is usually associated with the increase in fat mass. The greatest loss of muscle mass is seen in the lower limb muscle groups, with the cross-sectional area of the vastus lateralis being reduced by as much as 40% between the age of 20 and 80 years (Evans & Lexell,1995).

Protein intake affects the quality of the elderly's muscles and bone quality. So the elderly to supplement the protein is also necessary. Factors affecting protein demand are the following factors: metabolic needs (with large inter- and intra-individual variation), growth / net tissue deposition and dietary effects. 1. Under constant energy consumption, the increase of energy intake will improve nitrogen balance. This may be due to the ability to inhibit amino acid hydrolysis and oxidation of the hormone reaction (insulin). Excessive dietary energy can lead to the increase of secretion of adipose tissue, so there is a need to increase protein requirements. 2. Inadequate diets may affect the nutritional value of dietary protein, and larger nutrient intake (supplements) can increase the demand for protein metabolism, which requires more nutrients. 3. Metabolic stress caused by systemic inflammatory response, specific immune responses to infection, and other environmental factors, including smoking (Petersen et al., 2007) and large intake of alcohol (Volpi et al., 1998). Therefore, come to the conclusion, the elderly should have the appropriate protein intake.

American scientists recommend that all older people consume 0.8 grams a day, keeping the same level as young

people. In a recent survey (2013), the International Panel of Experts, after assessing evidence, suggested that people over 65 years of age are supposed to have an average daily intake of 1.0～1.2 g/kg of protein per day, or even higher intake (Bauer et al., 2013). More and more studies have shown that the current recommended dietary intake for older people at about 0.8 g/kg/day is not sufficient to optimize muscle mass retention, strength and function (Volpi et al., 2012; Evans, Boccardi, & Paolisso, 2013). Consequently, the protein intake has a significant role in the lives of the elderly.

11. VITAMIN D

Vitamin D has a variety of effects on skeletal muscle and muscle cells. Vitamin D deficiency is common in the elderly. The use of 25-hydroxyvitamin D (25[OH]D) levels in serum measurements is considered as an initial diagnostic criteria for patients with vitamin D deficiency (Holick et al., 2011). In this standard, vitamin D deficiency is defined as 25 (OH)D below 20 ng/mL (50 nmol/L). A recent systematic review showed that the average increase in serum 25 (OH)D concentration was 0.78 ng/mL (1.95nmol/L) per microgram of vitamin D3 supplement per day in the absence of concomitant use of calcium supplements (Autier, Gandini, & Mullie, 2012). In fractures, the use of prescribed calcium plus vitamin D or vitamin D supplements and anti-osteoporosis drugs seems to result in reduced mortality in patients, although vitamin D alone seems to have no effect in the elderly (Nurmi, Sund, Juntunen, & Lüthje, 2011; Rejnmark et al., 2012). However, human skeletal muscle has a receptor for 1,25(OH)D, and vitamin D receptor genotype variations affected BMD and muscle strength. Changes in muscle fibers and muscle differentiation- related genes such as myogenic factor 5 (Myf-5), myogenin and transcription factor 3（TCF 3） occur independently of calcium metabolism in mice with vitamin D receptor deficiency. In mice with vitamin D deficiency, changes in muscle fibers and muscle differentiation-related genes such as Myf-5, myogenin and TCF3 are more independent of calcium metabolism. While severe osteopenia and muscular dystrophy were observed in patients with vitamin D deficiency cartilage lesions. The results of existing studies have shown that low levels of 25 (OH) D osteoporosis in patients with type 2 diabetes are in the high incidence of muscle atrophy. Vitamin D supplements for patients with vitamin D deficiency can reduce their risk of death, and the risk of reduction is directly related to fractures, due to the effect of vitamin D deficiency on bones and the impact on muscle. However, intermittent high doses of vitamin D(oral cholecalciferol at 150,000 IU every 3 months) intake of older menopausal women is valid for prevention them from fall, fractures and muscle strength (Glendenning et al., 2012).Marantes and other studies have shown that (Marantes et al., 2011), low 25(OH)D or high parathyroid hormone (PTH) has no significant effect on adult muscle loss or muscle weakness. This study suggests the age-dependent differences between vitamin D state and sarcopenia. In the presence of osteoporosis in the survey, vitamin D levels were significantly insufficient, moderate intake of vitamin D supplements, has been proven to play a useful role in the prevention of fractures (Reid, Bolland, & Grey, 2014). Over the past few years, the role of vitamin D in skeletal muscle has solved more and more muscular and skeletal problems. Therefore, the vitamin D supplement is essential.

12. EXERCISE

Skeletal muscle with endocrine function is the endocrine organ, and this discovery is not only generally accepted, but also attracts more and more public attention. Skeletal muscle synthesis, secreted cytokines and active peptides are called myokines. A large number of epidemiological studies have shown that less active lifestyle can induce the occurrence of multiple metabolic diseases, at the same time, researchers have called these diseases "the disease of physical inactivity", in which muscle factor synthesis and secretion disorders are considered to be one of mechanisms for inducing metabolic disorders (Pedersen, 2009). Exercise can promote muscle contraction, stimulate the expression of a variety of muscle factors, which not only acts on the skeletal muscle itself, regulates skeletal muscle sugar, fat and protein utilization, but also through the blood circulation, reaches the periphery, plays the role of cross talker in skeletal muscle and liver, fat, heart and brain, and then adjust the overall metabolism (Pedersen & Febbraio, 2012). Irisin was a new muscle factor reported by Spiegelman Lab in the "Nature" magazine at the beginning of 2012. The discoverer was named after the Greek mythology, the rainbow goddess Iris, and metaphor like Iris, as a messenger of skeletal muscle, Transmission of skeletal muscle signals, and communication between skeletal muscle and peripheral tissue (Boström et al., 2012). It is a proteolytic

enzyme cleavage of a type III fibronectin that contains fibron-ctin type III domain-containing protein 5 (FNDC5) after the formation of a secreted polypeptide fragment. Exercise can up - regulate the mRNA expression and the level of irisin in skeletal muscle FNDC5. Irisin can promote adipocyte uncoupling protein1 (UCP1) expression, induce fat droplet formation, increase mitochondrial density, increase fat consumption of adipocytes, and cause fat cells to brown fat cell phenotype changes, thereby inhibit the occurrence of obesity and insulin resistance, osteoporosis, sarcopenia, diabetes and other chronic diseases. As a newly discovered muscle factor, irisin expression regulation, biological function and its role in the disease are also urgently to be discovered and explored.

Studies in osteoporotic murine models should shed further light on the potential exercise-mimetic action of Irisin in inhibiting or restoring bone loss (Colaianni & Grano , 2015). Thus, extending these findings for human patients can be encouraged to use Irisin to prevent and treat osteosarcopenic obesity.

13. CONCLUSIONS

OSO is a new clinical syndrome characterized by low bone mass, decreased muscle mass and individual obesity. Although the diagnosis of etiology and pathogenesis and OSO is now obscure, OSO has a negative impact on the lives of the aging population and is a major public health problem. The clinical outcome of OSO is not only to increase the risk of fracture, insulin resistance, and studies have shown that obesity, sarcopenia, osteoporosis, and other chronic diseases are closely related. Especially in South Korea, the growth rate of the elderly than expected; therefore, OSO interest is also increasing rapidly.

This review illustrates that multiple processes are involved in inflammation associated bone, muscle loss, and fat gain. These mechanisms seem to interact in complex ways and often affect each other. The understanding of these mechanisms and how to regulate these mechanisms in a therapeutic environment may be a way to improve OSO.

In view of these results, it seems necessary to promote prevention strategies based on physical activity and a balanced diet to enhance aging, especially vitamin D and protein intake, both of which have been largely demonstrated. At present OSO research is still in the exploratory stage, therefore, in-depth study of OSO has a significant impact on the development of related medical fields.

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