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Sarcopenic obesity: etiology and lifestyle therapy

M. LOMBARDO[1,2], A. BOARIA[1], G. AULISA[2], E. PADUA[1,3], G. ANNINO[1,3], A. PRATESI[4], M. CAPRIO[1], F. IELLAMO[2,3], A. BELLIA[1,2]

[1]Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Open University, Rome, Italy
[2]Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy
[3]School of Human Movement Science, University of Rome "Tor Vergata" Rome, Italy
[4]Local Health Authority – ULSS n. 2 – Treviso, Italy

Abstract. – OBJECTIVE: Sarcopenic obesity (OS) is a multifactorial condition characterized by the simultaneous presences of sarcopenia and obesity. The prevalence of OS is increasing in adults over 65 years of age; people with OS present greater health risks than people who are only sarcopenic or obese. Therefore, the study of OS and the search for effective treatment are important due to the constant increase of the elderly population.

MATERIALS AND METHODS: This review discusses the etiology and evolutionary mechanisms of OS while exploring its molecular, metabolic, oxidative, inflammatory, hormonal, and nutritional stresses. Studies have tried to unravel the causes related to the onset of sarcopenia, which is responsible for the decrease of muscle mass and strength in elderly subjects. The diagnostic criteria and the methods of evaluation of OS are described in these research studies, although there is no univocal definition for these parameters. The most studied treatments in OS are illustrated and highlight how the physical activity performed through both aerobic and resistance exercises, as well as a correct nutritional treatment, prove to be the most effective interventions in the regression of the pathology and in the improvement of physical function.

RESULTS: New therapies for OS are hypothesized that will open the way to other possible types of intervention in the future.

CONCLUSIONS: The deficiency of muscle mass in obese elderly subjects will be one of the health challenges of the future to reduce the risk of chronic diseases.

Key Words:
Sarcopenia, Muscle strength, Disability, Obesity, Older people.

Introduction

As we age, the human organism is subjected to a slow, gradual decline that leads to the change of biological mechanisms capable of directly influencing the health of the subject; this causes the onset of pathologies typical of aging and senescence. The study of such mechanisms is important to counteract and delay the risk of disabling diseases and promote effective interventions that guarantee a high degree of functional capacity and self-sufficiency. Two conditions that seriously endanger the health of older people are the progressive loss of muscle tissue and obesity. Sarcopenia is a condition defined by the EWGSOP (European Working Group on Sarcopenia in Older People) as a multifactorial syndrome characterized by the progressive and generalized loss of muscle mass, strength, and functional capacity[1]. It represents a natural phenomenon related to aging that can significantly increase the risk of osteoporosis, frailty, mobility, disability, and mortality. It is estimated that approximately 45% of the elderly American population – about 18 million people – are affected by sarcopenia and that the risk of disability is 1.5-4.6-fold greater in elderly people suffering from sarcopenia than older people with unaffected muscle mass[2]. In terms of cost, it is estimated that in the United States in 2004 the expenditure for public health interventions attributable to sarcopenia was around $18.5 billion ($10.8 billion for men, $7.7 billion for women), representing around 1.5% of the total costs of public health interventions.

Etiology and Evolutionary Mechanisms

The mechanisms related to the onset of OS are varied and not fully understood. The fat mass tends to increase up to about 70 years of age and then slowly decrease[3,4]. The considerable inter-individual variations involved in muscle mass loss in elderly subjects suggest that thermogenesis adaptation plays an important role in the energy

Corresponding Author: Mauro Lombardo, MD; e-mail: mauro.lombardo@uniroma5.it

balance in OS[5-7]. The explanatory model of the mechanisms that favor the onset of sarcopenic obesity is shown in Figure 1. Muscle proteins are constantly subjected to processes of synthesis and degradation. In adults, the adequate intake of proteins in the diet allows protein turnover and the nitrogen balance to be stable. However, from the third decade of life, this relation is slowly and progressively altered, and the processes of muscle protein degradation tend to be greater than those of synthesis. Several studies have reported that muscle protein synthesis in sedentary elderly subjects is reduced by 30% compared to young people and that catabolism is significantly increased. Then, there is a reduction in the diameter and the number of muscle fibers – particularly those of rapid contraction type II compared to the slow type I – which pass from an average of 60% in the young sedentary to 30% after 80 years. There is also a reduced capacity for neuromuscular recruitment and a decrease in motor units (-30%); neuromuscular junctions age, resulting in less precision and efficiency in the contraction phase and irregularities in the conduction of the action potential. The phenomenon progressively leads to a loss of muscle mass, estimated at around 0.5-2% per year. The etiopathogenesis of sarcopenia is primarily due to the alteration of protein metabolism at the level of muscle tissue, in which the proteolytic processes are not accompanied by an adequate level of protein synthesis. The muscle cells tend to progressively lose sensitivity to the anabolic stimuli induced by the essential amino acid leucine and IGF-1; thus, it becomes a condition of anabolic resistance[8]. The loss of muscle mass due to aging decreases the resting basal metabolism (BMR), increasing the likelihood of developing obesity[9-11]. Age-related muscle changes are characterized by a gradual loss of motor neurons, reduction of growth factors, increased pro-inflammatory cytokines, and oxidative stress. The denervated muscle fibers are restored again by the nearby residual motor axons, forming enlarged motor units. Consequently, the physiological loss of spinal motoneurons leads to a decrease in the number and size of muscle fibers. This reduces the mechanical performance of the muscle in terms of strength, power, and speed, which results in reduced functional capacity in carrying out normal activities. The key role of chronic inflammation in the muscular reorganization of the elderly has become increasingly important in recent studies. These findings are supported by analyzing blood values of cytokines; elderly patients have 2-4 times greater amounts of inflammatory cytokines compared to healthy young people.

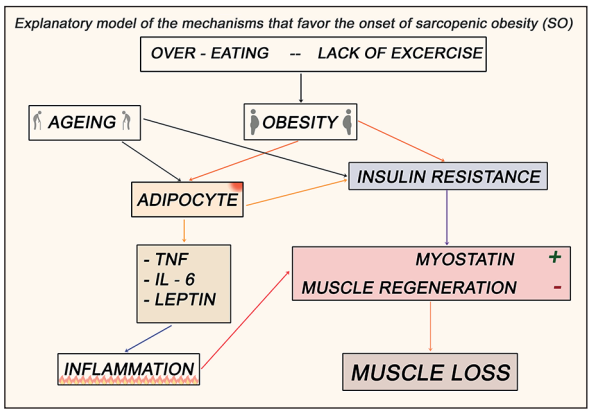

Figure 1. Explanatory model of the mechanisms that favor the onset of sarcopenic obesity.

Oxidative Stress

The term oxidative stress was introduced for the first time in 1989 by Sies[12], who defined it as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense systems. Under physiological conditions, the cell maintains a reducing state thanks to an assortment of enzymes and molecules that counterbalance the production of ROS. If the generation of ROS exceeds the antioxidant capacities of the cell itself – or if the detoxification mechanisms decrease – a new condition is established called oxidative stress. This condition seems to play a role of paramount importance in many diseases; it is often associated with muscle atrophy, cancer, trauma, and other neurodegenerative diseases[13,14].

Inflammation

As people age, an increase in intramuscular fat deposits is observed. This is similar to the condition caused by severe obesity, and it is further associated with lipid deposition in the liver, heart, and pancreas. This increases the risk of lipotoxicity and inflammation, inducing differentiation of progenitor cells that express adipose tissue genes, interfering with muscle protein synthesis, and exacerbating sarcopenia. The regeneration of muscle tissue is also opposed by the slow but progressive development of insulin resistance[15-20]. The decrease in the number of mitochondria and the increase in the production of reactive oxygen species occur in the muscle as a result of the increase in intracellular lipid

deposits. These add to the reduction in proteasomal cellular activity related to aging, as well as causing reduced ubiquitination and autophagy in the protein degradation processes[21-23]. Recently, it has been shown that skeletal muscle tissue produces a variety of molecules called myokines that act in the autocrine, paracrine, and endocrine forms. The most important of these are IL-6, IL-8, IL-15, brain-derived neurotrophic factor (BDNF) and leukemia inhibitory factor (LIF). It was observed in 2000 that the levels of IL-6 increase with exercise; in later studies[24,25], it was noted that IL-6 produced by muscle tissues plays an important role in metabolism, and it acts both locally and in other regions to synergistically increase the availability of energy substrates for muscle contraction. Another myokine whose production tends to increase after exercise is BDNF, an active regulatory protein for the growth and maintenance phase of neuronal activity. Physical activity plays a beneficial role in the delicate balance between myokines. The inflammation worsens both sarcopenia and the accumulation of fat within muscle tissue, creating a vicious cycle that reduces muscle strength and promotes skeletal muscle inactivity. The discovery of myokine provides a plausible biological explanation of the important role of physical exercise on metabolism and anti-inflammatory action.

Hormonal Causes

In women, lower functional levels of estradiol during menopause contributes to the appearance of sarcopenia, which leads to an increase in body weight and fat mass – especially visceral fat – and decreases lean mass. It has been demonstrated that 20% of people over 60 and 50% of those over 80 have hypofunctional levels of testosterone (<275 ng/dl). This is responsible for the reduction of muscle mass and redistribution of visceral fat. The synthesis of GH and IGF-1 also decreases progressively in both sexes as we age. After 30 years, it is estimated to drop 15% every decade[26]. As age increases, cortisol values increase in men. This exposure to glucocorticoids combined with decreased GH levels may contribute to the accumulation of age-dependent visceral fat, which results in the development of inflammation due to the increased synthesis of pro-inflammatory cytokines[27].

Neurological Causes

The degeneration and reduction of the number of spinal motor neurons are only partially compensated by re-innervation and recruitment of a greater number of myofilaments. The loss of neurons is a progressive, irreversible process that increases with age[28]. "Age-related neurodegeneration" can negatively and significantly affect skeletal muscle activity. This chronic neuropathic process – in association with muscular morphological changes – contributes to the reduction in the number of muscle fibers and muscle mass[29].

Functional and Nutritional Causes

As people age, the level of physical activity is reduced, and the ability to stimuli for muscle protein synthesis is active[30,31]. Inactivity increases protein catabolism, reduces the ability to recruit muscle, and facilitates denervation phenomena. These processes lead to a rapid decline in motor skills. From this point of view, the previous physical activity seems to be a protective factor against sarcopenia; it slows its onset and development[32]. Approximately 40% of people over the age of 70 do not take the current RDA regarding the minimum recommended protein intake (0.8 g/kg) each day, not only from a quantitative point of view, but also from a qualitative point of view. The phenomenon is undoubtedly secondary to numerous factors, each of which can exert a variable weight. FAO and WHO have proposed to raise the level of daily protein intake in the elderly to 1.25 g/kg each day, which accounts for the renal function reduction that occurs with advanced age. The increase per kg value can also be explained by the reduction in absorption capacity and metabolic management characteristic of old age. It could be important to consider the lean mass alone for the purposes of calculating the necessary protein intake. It is important to consider that the elderly subject may have subclinical nutritional deficits, particularly vitamins and minerals useful for muscular trophism such as vitamin D. Several reports[33] have shown the positive action of vitamin D on muscular trophism, besides the effects on bones. The effects derived from a pro-inflammatory state associated with the loss of muscle mass and strength promote a vicious cycle, broken only through the application of proper nutritional therapy and the administration of adequate physical activity.

Diagnosis and Evaluation of OS

OS is defined by the sum of the individual definitions of sarcopenia and obesity. The EWGSOP proposed an algorithm for the diagnosis of sarcopenia in older subjects that accounts for the results

of two simple physical tests that can be performed in the outpatient setting: the fast walking test and the hand PTO test (Figure 2). The measurement of the isometric muscle strength of the hand using the handgrip test is highly correlated with the muscular strength of the lower limb, which can be assessed with the flexion-extension exercise of the knees and gastrocnemius muscle[34]. Some authors have identified a linear correlation between the muscle strength measured with the handgrip and the inability to perform some daily tasks[35]. The measure of the step velocity can alone represent a parameter with a high predictive value of functional alteration in the sarcopenic patient[36,37]. It consists of measuring the speed in which a journey of six meters is carried out: if the speed is less than 0.8 m/s, a functional alteration is assumed. Another useful test is the "timed up and go-test" (TUG), which is used for the assessment of dynamic equilibrium and measures the time needed to complete a series of activities related to motor function. The subject is asked to stand up from a chair, walk 3 m, turn around, go back, and sit down again. The patient's balancing function is observed and marked on a five-point scale[38]. If the patient has to balance for 10 s or less, the functionality is considered good, between 11-20 seconds is considered a standard level of function for frail elderly and disabled patients, while a time greater than 20 s indicates that the person needs external assistance. A score equal to or greater than 14 s suggests that the person may be subject to falls. Larger values indicate

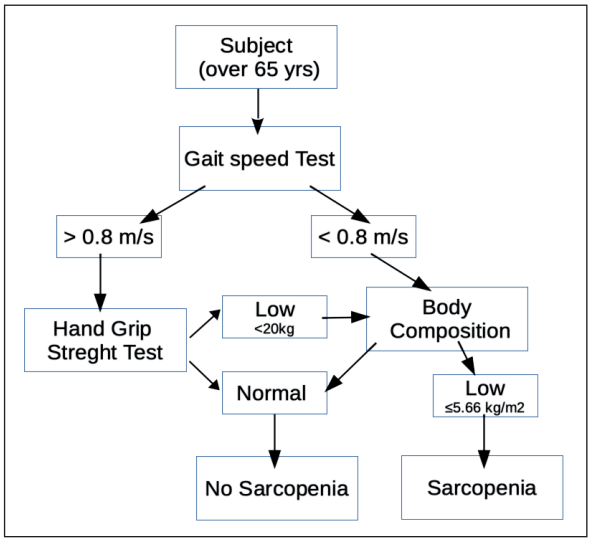

Figure 2. Diagnostic algorithm for sarcopenia.

the disability of the subject. Obesity refers to the excessive accumulation of body fat (WHO) that can increase the risk of disease and mortality. An obese person has a BMI greater than 30 kg/m^2. As with sarcopenia, there is no gold standard for identifying an obese subject. In the current clinical practice, the BMI index, the percentage of body and visceral fat, and the measurement of the patient circumference are often used as indicators of obesity. In many studies, sarcopenia is defined as the relation between the mass of the appendiceal skeleton and height squared (ASM/height^2) or weight (ASM/weight). Some authors have proposed to classify obesity based on the percentage of fat mass of the subject. Among these, WHO in 1995 defines obesity as a condition in which fat mass is ≥ 35% in women and ≥ 25% in men.

Consequences of Sarcopenic Obesity

Hospitalized patients with recognized sarcopenia have a higher mortality rate compared to hospitalized patients without sarcopenia[39]. This same trend holds for patients evaluated after 12 months from admission. Although the etiological causes recognized to date are multiple and not fully clarified, sarcopenia represents a geriatric syndrome that increases the risk of disability, mortality, and hospitalization. Arango- Lopera et al[40] show that in 345 elderly Mexican patients, the rate of mortality correlated to sarcopenia is higher. In the "SIRENTE" study[41], the association between sarcopenia and mortality in eighty years old subjects has been demonstrated, and the negative role that it can take in particularly frail elderly people has also been shown. In another work[42], the measurement of visceral fat and quadriceps muscle area showed greater postural instability for sarcopenic patients. Individuals with OS are at a greater risk for knee osteoarthritis and greater risk of falls than patients with obesity alone[43]. A study[46] that evaluated patients over 6 years revealed that subjects with high BMIs and low handgrip values had a greater risk of developing type 2 diabetes mellitus. Individuals with reduced muscle mass and high waist circumference had a greater risk of developing depression, stress, and worse psychological health than normal-scoring individuals[46]. Finally, one area of particular interest is related to the correlation between OS and cancer, which requires further studies to assess accurately this relation[47].

Treatment of Sarcopenic Obesity

Sedentary lifestyles pose a much greater threat to health than aging. The role of movement and

the adoption of healthy nutritional habits are widely recognized by the scientific community for the promotion of well-being and the prevention of chronic degenerative diseases. A sedentary lifestyle and malnutrition – understood to be the intake of food in excess or of poor nutritional quality – are frequently associated with the spread of serious pathologies, which are often improperly defined as "pathologies of well-being". The latter represents the highest percentage of all diseases affecting the population of economically prosperous societies. They significantly compromise the quality of life and cause an increase in social costs due to their insidious development and the many complications that arise over time. The prolonged sedentary state causes a loss of tone and tropism of skeletal muscles, which causes a general loss of efficiency and work capacity over time and leads to the onset of sarcopenia and obesity. The most rational approach to slow down the course of sarcopenia and improve body composition involves the combination of a regular program of physical activity and adequate nutrition.

The Importance of Physical Activity

The ideal intervention to treat OS includes adequate – predominantly restrictive –nutritional therapy, regular physical activity through aerobic exercises against resistance, and the promotion of an active lifestyle. There are few clinical trials available today that have focused attention solely on OS. Villareal et al[48] suggest that a combination of weight loss and exercise provides greater improvement in physical function than either intervention alone. An additional study reports that a loss of fat mass combined with aerobic and resistance exercise is the most effective tool to improve health conditions in obese adults aged > 65 years[49]. Chen et al[50] divided subjects with OS into 4 groups: 3 to different physical exercises (aerobic, resistance, and a combination of aerobics and resistance), while the fourth abstained from performing the motor activity. The result was that the group subjected to resistance exercises showed a greater increase in strength. Several guidelines[51-54] recommend older people to do 150 min per week of physical activity, with at least two sessions dedicated to the development of motor strength. Aerobic training improves cardiorespiratory capacity and reduces the risk of mortality[55,56]; even minimal resistance exercises can affect muscle mass and strength[57,58]. Another research reports that weight loss combined with aerobic and resistance exercises are effective methods that increase functional capacity in obese adults > 65 years of age. In the Canadian Longitudinal Study, which involved 904 elderly men and women with an average age of 74, the mechanisms linking sarcopenic obesity and physical activity were investigated. They showed that obesity appears to contribute more than sarcopenia to a low level of physical performance. A study conducted on 160 obese elderly people was subjected to the same diet treatment, then divided into 3 groups to which aerobic exercises, strength exercises, and combined aerobic and strength exercises were apportioned. The best results were obtained from the group that carried out combined strength and aerobic exercises[59]. Despite the scientifically proven benefits, strength training in the elderly is still poorly practiced, and only a few specialized centers follow the official sarcopenia treatment guidelines Individualized physical activity has been previously demonstrated to effectively counteract the loss of muscle mass[60]; this training acts specifically on type II muscle fibers and produces anabolic adaptation responses that are unachievable with aerobic workouts[61]. Another therapeutic option could be the whole body vibration that has been demonstrated to improve body composition, insulin-resistance, glucose regulation and adiponectin levels to a greater extent compared with diet alone[62].

Nutrition

The most effective nutritional therapy in the patient with OS involves a reduction in body weight and an improvement of muscle mass. The caloric restriction and the adequate intake of proteins with diet seems to provide concrete and reliable results. The caloric deficit occurring with a restrictive diet could negatively affect muscle protein synthesis by increasing the proteolytic mechanisms, and thus cause a further loss of muscle mass[63] and cardiovascular disorders[64]. Increasing the daily consumption of proteins, instead, will stimulate protein synthesis. A group of obese subjects undergoing a restrictive caloric regimen of 500-750 kcal or less per day, with an intake of at least 1 g/kg of protein and undergoing different physical exercises 3 times a week, showed a marked improvement in physical performance[65]. Other studies[66,67] in subjects with OS show that aerobic and resistance exercises help preserve muscle mass when combined with a weight-loss program. An increase in muscle mass and a reduction in visceral fat have

been noted in a group of elderly women with OS who carried out resistance exercises[68]. A nutrition-based approach to the patient with OS can prevent a calorie reduction of 500-1000 kcal/day, a weight loss of about 0.5 kg per week, and about 8-10% of their total weight by approximately 6 months, to be followed with a maintenance diet[69]. To date, no specific nutritional protocols are available for OS. The formulations remain highly individualized, *ad hoc* quantities of nutrients are modulated in most diets. It is known that amino acids – among which are branched-chain amino acids (BCAA) – are necessary for the maintenance of muscle health in the elderly[70]. Approximately 300-600 g of muscle protein are degraded daily and re-synthesized every 24 h, with a complete renewal of the entire amount of protein every 3-4 months. Food intake stimulates a degree of protein muscle synthesis, resulting in a positive protein balance. After eating a protein-containing meal, the degree of protein synthesis remains elevated for more than 5 h with a peak of 2-3 h after intake[71]. It has been shown that a dose of approximately 15-20 g of protein in adults is sufficient to stimulate the maximum degree of protein muscle synthesis. This effect is also detected by administering a dose greater than 35 g[72]. To maintain and recover muscle, seniors need to take greater protein in their diet than young people do. Older people should take an average daily protein intake of 1-1.2 g/kg each day. The threshold for an anabolic protein meal and amino-acid intake should be higher in elderly than in young people, i.e., 20-30 g of protein per meal containing about 2.5-2.8 g of leucine. Most elderly subjects with an acute or chronic disease need an increase in protein intake from 1.2-1.5 g/kg per day. Subjects with a critical illness or severe malnutrition can reach 2 g/kg per day. Elderly subjects with severe renal insufficiency who are not on dialysis are an exception. The list of essential amino acids is identical for the young and for the elderly. The intake of fast absorption proteins can represent an advantage over slow absorption proteins. In the elderly subject, a breakdown of the protein requirement divided over several meals during the day is insufficient to determine a plasma peak of amino acids capable of inducing protein synthesis in muscle tissue that has significantly reduced its sensitivity to this stimulus. A senior subject must have at least 30 g of protein per meal to have protein anabolism (Figure 3). In this way, we obtain an increase in protein synthesis and a reduction in proteolysis, thanks to the significant increase in the plasma amino acid concentration[73]. It has been suggested that leucine – an essential amino acid belonging to the branched category – is essential for maintaining healthy muscular and hepatic tissue (as well as valine and isoleucine), whose average requirement should be 40 mg/kg/day. The main sources of leucine come from chicken, fish, ricotta, lentils, sesame, and peanuts. Although sarcopenia is a multifactorial pathology, amino acids and particularly leucine may play a decisive role in attenuating age-related effects related to loss of muscle mass and strength. Numerous researches have shown that essential amino acids (EAAs) are able to stimulate muscle protein synthesis and to counteract the natural resistance to the anabolic stimulus of the elderly subject. The intake of approximately 3-4 g of leucine (≈ 0.045-0.06 g/ideal kg) during meals seems to have a significant stimulatory effect on muscle protein synthesis. In rare cases, it is not possible to meet these needs with food. Therefore, leucine can be taken with dietary supplements.

Vitamin D

Several studies[74,75] have shown that low levels of serum 25-hydroxyvitamin D levels are related

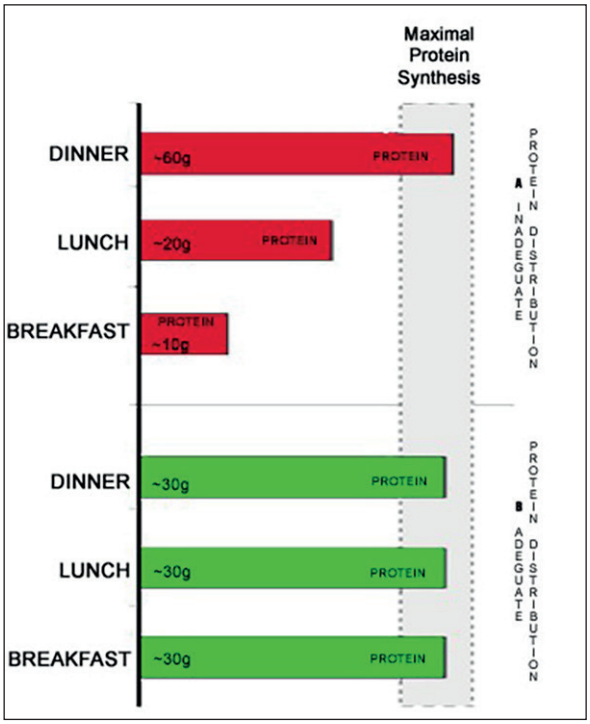

Figure 3. Meal requirements for protein to optimize metabolic roles of amino acids in sarcopenic obesity.

to lower muscle strength, greater body instability, falls, and disability in older men and women. A significant association was also observed between the vitamin D receptor genotypes with quadriceps strength[76]. In more vitamin D supplementation reports[77,78] in elderly subjects with vitamin deficiency, an improvement in the physical function of the geometric extension of the knee compared to the same group was noted after treatment with placebo. As muscle mass and functionality decline with aging, there is a reduction in the expression of vitamin D receptors (VDRs) at the level of skeletal muscle[79]. Previous study[80] has linked some VDR polymorphisms to the reduction of muscle mass and function in the elderly, suggesting that vitamin D plays an important role in the development and in the progression of sarcopenia. Studies[81,82] conducted to evaluate the effectiveness of vitamin D supplementation on functional abilities are partially contradictory. Some reports have not shown that vitamin D intake has improved physical performance. Conversely, a work conducted in 122 elderly subjects with low levels of vitamin D, has shown significant benefit from vitamin D supplementation. In particular, Dhesi et al[83] in 2002 showed in a group of subjects with an average age of 77 years the daily supplementation of 600 IU of ergocalciferol results in a 3% improvement in physical performance, as assessed by the Aggregate Functional Performance Time (AFPT). In control group, physical performance fell by 9%. Regarding postural stability – a factor correlated with vitamin D levels – research has shown an improvement of 13% in vitamin D group, while a control group experienced a 3% decline in postural stability. However, it did not demonstrate any improvement in muscular force[84-87].

Conclusions

The developments related to OS are reflected in the demographic increase in elderly population. The basic evidence on the most effective therapies could lead to a marked improvement in the functional capacity of the subjects and reduce the risk of disability and mortality. A major limitation in research today is the lack of univocity on the diagnostic definition of OS, which does not allow researchers to clearly frame that segment of the population most exposed to risk, compared to patients with sarcopenia or obesity alone. The number of people over sixty in the world is bound to rise over the coming decades, with a predicted increase from 841 million in 2013 to 2 billion in 2050. In addition to these data, it is estimated that in 2047, the elderly will have surpassed the number of children. This explains the importance of scientific research for OS and the pathologies of adulthood. Based on this dramatic prediction, attention and efforts must be focused on studying the most suitable interventions and preventative therapies. Otherwise, there will be heavy repercussions in terms of social costs to ensure assistance services to an increasing number of subjects unable to carry out normal daily activities with sufficient autonomy. OS is a relatively new concept in the panorama of age-related diseases. There is currently no single definition of the pathology; however, evidence suggests a close correlation to the onset of cardiovascular disease and mortality. Although many questions remain unresolved today, it is important to note that OS can be prevented and treated by adopting a healthy lifestyle. The ideal approach is based on the targeted intervention to both slow down the course of sarcopenia and promotes a decrease in adipose mass. The beneficial potential of physical activity, expressed through strength and resistance exercises, on OS is widely documented. Benefits obtained from aerobic exercises and strength exercises are shown at the level of muscle mass, muscle strength, muscular capacity, and mitochondrial activity. However, the best results were obtained by coupling adequate nutritional treatment with regular physical activity. The adequate intake of proteins high in essential amino acids promotes protein synthesis and muscle health, effectively counteracting the onset of sarcopenia. In the case of malnutrition, a supplementation with BCAA-based supplements, leucine, vitamin D, and β-HMB might help to improve and reduce the effects of sarcopenia. For the future, it will be fundamental to deepen the current knowledge of pathology, define standardized protocols for both the diagnosis and the clinical course. It will be equally important to develop fast and simple body composition measurement techniques, which can be included in the daily geriatric screening activity; this will enable the evaluation and identification of an appropriate and effective intervention. Finally, it will be important to continue to improve general public health prevention strategies, while developing specific food education programs, interventions, and regular exercise practice.

Conflict of Interest
The authors declare that they have no conflict of interest. This research received no specific grant from any funding agency in the public, commercial or not for-profit sectors.

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