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Review Article

SARCOPENIA – CAUSES AND MANAGEMENT

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Abstract. Sarcopenia is an epidemic that has been recognized only recently, presenting a threat to the functional independence and quality of life of the elderly. Sarcopenia is defined as a loss of muscle mass in combination with changes in muscle quality and physical function. Common causes of sarcopenia are the aging process, an imbalance of sex hormones, lack of physical activity or chronic diseases, which is why sarcopenia, apart from the elderly, can also occur in the younger population. Both dimensions of sarcopenia, quantitative, skeletal muscle loss, and qualitative, loss of quality of life and disability, should be considered when creating and designing preventive and therapeutic measures. There are quick and simple tests for the diagnosis of sarcopenia, but they are still not sufficiently recognized and regularly used as part of physiotherapy assessment.

Key words: Sarcopenia, Muscle mass, Muscle streght, Aging

Introduction

Aging is defined as a series of changes in the structure and function of the organs that start after an achieved reproductive maturity of an individual. They manifest in reduced adaptive abilities and time-related deterioration of the physiological functions necessary for survival. Reduction in adaptability to stressful influences from an external or internal environment leads to a series of diseases that are marked as "diseases of old age". The question remains if they are caused by the aging of tissue and organisms as a whole or if aging is the consequence of the stated diseases. In sarcopenia, they first arise in the form of a selective change in the muscular system, but in the end, they cover the skeletal muscular system in its entirety which leads to the loss of muscular mass, functional ability and an incapability of performing basic vital functions individually which leads to the dependence on other people, hospitalization and big material expenses that families and society have to set aside for the ill. The real cause of sarcopenia is still unknown so it is designated as a multi-causal phenomenon of old age.

The term sarcopenia was originally used by Irwin Rosenberg to define the age-related loss of muscle mass [1]. Nowadays, it is thought that sarcopenia represents not only the loss of mass, but, more importantly, the loss of muscles strength and function too. With advancing age, the muscle mass gradually and progressively decreases; in the elderly is twice as low as that in younger persons [2]. Sarcopenia has often been compared to osteoporosis – what is osteoporosis for bones, that is sarcopenia for muscles. It is often accompanied by myosteatosis (intramuscular and intermuscular increase in the amount of connective tissue, especially fat tissue), resulting in a condition defined as sarcopenic obesity [3], which is often associated with an increasing incidence of insulin resistance in the elederly [4].

The loss of skeletal muscle mass in sarcopenia leads to declining physical strength and ability to perform the activities of daily living. Strength and muscle power reduction accompanying the process of sarcopenia is termed dynapenia [5].

Simultaneously, bone tissue density also decreases, stiffness of the joints is increased, and posture of the body is changed (kyphosis). These changes in body composition are the basic cause and factor contributing to physical frailty in the elderly [6,7]. This leads to an increased risk of fractures and injuries, difficult recovery from illnesses, and prolonged hospital treatments, possibly resulting in functional dependency and long-term disability, requiring permanent assistance in daily activities [8,9].

A number of researchers interested in the problem of sarcopenia have attempted to reach a consensus for the definition of sarcopenia, since the loss of muscle mass as a single factor cannot fully explain this condition or syndrome at the present time. The definition of sarcopenia involves the following aspects as well: physical functions (walking speed, for instance), muscle power and finally muscle mass [10]. Some authors consider that the loss of muscle power and mass should be defined separately, i.e. the term sarcopenia should be used for muscle mass reduction due to aging, and dynapenia, which involves muscle power loss due to aging, should be used to describe declining functional activity [11]. The European Working Group for Sarcopenia in the elderly defines sarcopenia as both the loss of muscle mass and loss of function [12]. The arguments supporting this notion involve the fact that various research data have shown that muscle mass maintenance or increase does not prevent age-related muscle power de-

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cline and that muscle weakness is independently associated with physical disability and mortality. Physiological mechanisms underlying age-related muscle weakness are multidimensional and result from a deficiency in neural activation, the reduction of inner muscle ability to generate force and muscle wasting itself [11].

Distinct origin make a difference between primary and secondary sarcopenia. Primary sarcopenia is associated with aging alone, while secondary sarcopenia is caused by chronic diseases or reduced mobility. The aforementioned division is difficult to make in everyday practice because older patients often have more comorbidities. Therefore, sarcopenia is ultimately defined as a loss of muscle mass and quality combined with changes in an individual's physical functions.

Changes in body function and muscle quality are closely related to an increase in overall morbidity and mortality. Recognition of sarcopenia as a disease was achieved with the introduction of the ICD-10-CM code (M62.84) by the World Health Organization (WHO). due to its high prevalence and long term bad consequences [13].

Studies have reported that after 30 years of age, muscle mass decreases about 3%-8% per a decade, with the decrease occurring more rapidly after the age of 60 (5% in individuals aged over 65 years, and about 50% in those over 80) [14,15]. Several epidemiological studies, using different measurement methodologies and cut-off values, have attempted to establish the prevalence of sarcopenia [16,17]. Various research data have shown that prevalence rates of sarcopenia in the general population.is between 5 and 40% and that prevalence increases exponentially with inclining age [18-20].

Worldwide the number of people with age-related frailty will double from 321 million in 1990, to 799 million in 2025 [21]. As the result of the expansion of this subpopulation, together with longer life expectancy, the number of the elderly who will become sarcopenic,frail and requiring long-term institutional care, will result in constantly rising health insurance expenses.In general, it seems that 5%-13% of individuals aged 60 to 70 years and 11%-50% of those aged over 80 years have sarcopenia.

Skeletal Muscle Age Related Changes and Sarcopenia

Skeletal muscles consist of different fiber types, but the three main types are recognized: types I, IIa, and IIb. Type I fibers are slow-twitch, fatigue-resistant fibers with a greater oxidative capacity, larger mitochondrial content, and greater capillary density. In contrast, type II muscle fibers are fast-twitch fibers with a high glycolytic capacity. Type II muscle fibers are divided into types IIa, with an intermediate oxidative and glycolytic capacity, and are more fatigue-resistant than type IIb, in which glycolytic activity predominates [22]. Histological human post-mortem studies report a reduction of muscle fibers with aging; from 20 to 80 years of life the number of fibers is reduced by around 50%, with the loss occurring much more rapidly after 60 years. Furthermore, that loss occurs selectively – the loss of fast-twitch type II fibers is greater, compared to slow-twitch type I muscle fibers [23,24]. These morphological changes reflect on muscle function – muscle strength is reduced by 20%-40% in persons aged around 70, compared to those aged 20 years. The loss of muscle strength reaches even 50% in those at and over 90 years of age. A fast-twitch type II muscle fiber is involved in the generation of muscle strength, which is the product of force and velocity of muscle contraction. As the result of this, muscle power declines faster than muscle strength. These finding are clinically relevant, since studies have shown that muscle power is more closely associated with physical performance than muscle strength [25].

Muscle contractions depend on mitochondrial ATP production too. Changes in mitochondrial size, DNA within mitochondria and mitochondrial proteins, directly affect the contraction of an muscle cell. With advancing age, mitochondrial DNA content and protein synthesis are reduced, leading to decline of oxidative capacity and ATP amounts available for muscle contraction, which contributes to muscles reduced aerobic capacity in the elderly [26]. Decreased mitochondrial DNA content, reduced synthesis and activity of its proteins with age are associated with free radical production and oxidative damage to DNA and mitochondrial proteins. All these changes in muscle cells contribute to a general depletion of their metabolic abilities, cutting down the use of oxygen by 30%, which overall represents an important component of the reduction of physical activity and the development of sarcopenia in the elderly [27].

Causes of Sarcopenia

Sarcopenia is a multifactorial individually variable and dependent condition the occurrence and onset of which is still being investigated, as well as the possible therapeutic approaches for its prevention and treatment. The most common causes contributing to the occurrence of sarcopenia are mutually dependent structural and functional changes in the body that occur as a result of aging, as well as various neurological, endocrine, inflammatory and physical activity/inactivity factors. In addition, smoking and poor nutrition, age-related changes in cytokine levels, increased oxidative stress, loss of alpha motor neurons, apoptosis of muscle cells and genetic susceptibility are some of the important risk factors also [28]. But, all authors agree that for the time being we cannot single out the primary or predominant one in its occurrence [22,29].

Neurological factors

Age-associated changes in the neuromuscular system play important role in the onset of sarcopenia. The number of motor neurons and functional motor units in the spinal cord decrease with advancing age [30]. According to the literature data, motor units tend to be preserved until the age of 60; after that, their number decreases dramatically [31]. Human nerve cells (postmitotic) have a life expectancy; reductions in their number depend on their location

in the body, age and presence of a disease [32]. The striated muscles from which a great force is expected, have motor units in which one neuron innervates hundreds, and even over a thousand muscle fibers. A loss of muscle fibers starts with a loss of motor neurons. Morphological changes in the anterior horns of the spinal cord, affecting cell bodies of motor neurons, as well as their axons at the periphery, in the elderly, can be undoubtedly responsible for older age muscular atrophy. Decrease in number of motor neurons with advancing age will result in muscle fiber denervation within a motor unit which leads to atrophy and consequential death of muscle fibers, which ultimately results in muscle wasting [33]. When a motor neuron „dies", the adjacent motor neuron (usually a slow-twitch one) may reinnervate the muscle fibers in question, preventing their atrophy. This process is termed motor unit remodeling. When compared with fast-twitch motor units, slow-twitch units produce a much weaker force, so that remodeling with slow-twitch motor neurons produces less effective motor units. A remodeled slow-twitch motor unit will have coarser movement control and weaker force produced [33,34], which could explain worse balance and declining movement velocity with aging. The speed of denervation of fast-twitch muscle fibers may exceed the speed of reinnervation by slow-twitch motor neurons, which could explain the atrophy of fast-twitch muscle fibers in the elderly. Further, the loss of integrity of the neuromuscular junction (NMJ) can be the principal factor contributing to sarcopenia, and may also involve muscle innervation.

Neuromuscular Junction and Sarcopenia

The NMJ undergoes significant changes with aging. These changes can contribute to reduced muscle strength, coordination, and functional performance in the elderly. Besides the structural alterations in the NMJ like the loss of muscle fibers, fragmentation of the synapse (motor endplate becomes less organized and fragmented, reducing its efficiency), reduction in acetylcholine receptors (the density of receptors on the muscle membrane decreases, impairing signal transmission), other key changes are more functional. They are impaired synaptic function because of the reduced release of acetylcholine from motor neurons and increased synaptic cleft width, which delays neurotransmitter diffusion and signal transmission, reduced energy production in motor neurons and muscle fibers affects NMJ performance due to mitochondrial dysfunction and overall NMJ degeneration because of frequently present chronic low-grade inflammation in the elderly. Consequences of NMJ aging are sarcopenia, reduced muscle power, poor coordination and increased risk of falls [35]. Strategies to preserve NMJ function in the elderly should be exercises like resistance training which promotes motor unit recruitment and reduces muscle loss and aerobic exercise which enhances mitochondrial function and reduces inflammation [36,37]. Besides that, they would be very useful dietary Interventions like adequate protein intake (e.g., leucine-rich proteins) which supports muscle repair and regeneration, supplementation with antioxidant drugs to combat oxidative stress (e.g., vitamins C and E) and Omega-3 fatty acids to reduce inflammation and support neuromuscular health [38]. A new approach to the prevention and treatment of sarcopenia could be based on medical therapies like interventions with growth hormone, IGF-1, or drugs targeting muscle and nerve regeneration. Research is ongoing into possible gene therapy applications and developing exosome-based therapies [39,40,41,42]. However, this modern approach is still in its experimental phase, and further research is needed to optimize the use of gene therapies and exosomes- based drug application in clinical practice [38,43].

Endocrine factors

In addition to muscle-related changes, the changes in endocrine function or response to hormonal stimuli with advancing age may also be responsible for the development or exacerbation of sarcopenia [34]. This means that changing levels of various hormones may contribute to muscle wasting. There has been an increasing body of evidence associating the etiology and pathogenesis of sarcopenia with the age-related drop in the production of testosterone, estrogen, growth hormone, insulin, and dihydroepiandrosterone [28].

It is well known fact that in the elderly the levels of anabolic hormones decrease, while the levels of catabolic ones increase. The primary and most powerful anabolic steroid is testosterone; in andropause, testosterone levels tend to drop; in contrast to a rapid drop of estradiol in menopause, testosteron concentrations decrease gradually with advancing age, at a rate of around 1% a year after 30 years of life [45]. The results therefore show that andropause may be a factor in the development of sarcopenia. In women, testosterone levels drop very rapidly between 20 and 45 years of age [46]. The mechanisms through which testosterone affects muscle tissue are increased protein synthesis, increased intramuscular ribonucleic acid (mRNA), IGF-1 concentration, and reduced concentration of inhibitory IGF-binding protein 4. In accordance with this it is supposed that lower testosterone levels may lead to reduced synthesis of muscle proteins resulting in muscle wasting [47]. All of the above suggest stimulation of the intramuscular IGF-1 system during the application of testosterone. Gentili et al. proposed that intramuscular application of 200 mg of testosterone in older men could affect the GH/IGF-1 axis, leading to increased mass, basal secretion and 24-hour rhythmic production of growth hormone (GH), as well as an increased serum level of IGF-1 [48]. Increased testosterone levels in the elderly up to the level of circulating testosterone present in young men has led to muscle mass increases but without corresponding increases in functional strength [49].

The effect of estrogens on muscle tissue in women can be mediated by their positive modulatory effect on the GH/IGF-l. Although estrogen has a direct anabolic action on muscle tissue, its effects may be mediated by conversion into testosteron as well. Both estrogen and testosterone inhibit the production of catabolic cytokines,

such as interleukins (IL-1 and IL-6), which suggests that the loss of these gonadal hormones with advancing age may exert direct and indirect catabolic effects on muscle tissue. Whether the effect of menopause on muscles is the consequence of hormonal changes and/or lifestyle changes remains to be established. The data is scarce as to the effects of estrogen replacement therapy on muscle mass and strength in women in menopause. The benefits of estrogen replacement to muscle health and function in the elderly could assist in offsetting age related loss of muscle mass and function and delay age related morbidity and their use for overall health benefits in aging females should continue to be evaluated [50].

In contrast to other hormones, growth hormone (GH) does not exert its action via a target gland; instead, it directly affects all the tissues in the body [22]. It increases the number of cells, number of mitoses and specific differentiation of certain cell types (such as bone growth cells and early muscle cells). In addition to its general effects on growth, GH has numerous special metabolic actions; in short, this hormone increases protein content in the body, expends the reserves of fat, and preserves carbohydrates. The action of GH on the utilization of fat, together with its anabolic effect on proteins, leads to an increase in overall muscle mass. Aging is accompanied by the loss of somatotropic cells of the adenohypophysis, more intensively in women than in men. Correlation study between morphometric parameters of somatotropic cells and myocytes of m. psoas during aging showed that the decrease in the number of somatotropic cells of the adenohypophys is approximately the same extent in both men and women, becomes significant only after the age of 70 [22]. The decrease in the number and functional deficit of somatotropic cells is followed by the loss of type II muscle fibers, which is more pronounced in female individuals and becomes significant after the age of 70. In addition, the loss of type II muscle fibers is accompanied by continuous and approximately the same intensity of type I and type II muscle fiber atrophy in both males and females. The identical dynamics of age-related changes in somatotropic cells, followed by age-related changes in type I and especially type II muscle fibers, as well as the existence of a moderate to strong correlation between the morphometric parameters of somatotropic cells of the adenohypophysis and the corresponding morphometric parameters of type I and type II muscle fibers indicate the involvement of age-related changes in somatotropic cells in the development of muscle mass loss, i.e. sarcopenia in otherwise healthy old individuals. During normal aging not only the serum levels of GH decrease. Moreover, the GH/IGF-1 axis demonstrates a gradual decline. The process is known as somatopause and is associated with harmful changes in body composition, i.e. with lean body mass reduction, increased adiposity, and decline of muscle mass and strength [22].

Dehydroepiandrosterone (DHEA-prasterone) and dehydroepiandrosterone sulfate (DHEAS) are the precursors of adrenal sex steroids, and their levels decline markedly with advancing age. Supplementation with DHEA prasterone leads to increased serum DHEAS, reaching the levels encountered in younger persons. Direct biological activity of adrenal androgens (androstenedione, DHEA and DHEAS) is minimal since they function primarily as precursors for peripheral conversion into active androgen hormones testosterone and dihydrotestosterone [22].

Inflammation

It is well known that muscle tissue reacts to cytokines, inflammation mediators and that some of them have a catabolic effect, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and myostatin. Others have an anabolic effect, such as interleukin-15 (IL-15) and insulin-like growth factor (IGF-1). But, skeletal muscle has recently been identified as an endocrine organ too. Muscle-derived cytokines, named myokine peptides can be expressed, produced and released by muscle cells to perform autocrine, paracrine or endocrine actions. These peptides mediate crosstalk between muscle and other tissues, mainly adipose tissue, liver and bone. Their effects include regulation of systemic inflammation, immune function, energy metabolism, insulin sensitivity, cell growth, myogenesis, and osteogenesis, and therefore have an undoubted effect on all aspects of sarcopenia [51]. Contraction plays a key role in the regulation of myokine production. For example, cellular production of IL-6 was a significant predictor of sarcopenia in women, but not in men. It was shown that IL-6 production was a significant predictor of mortality. High IGF-1 concentrations compared to low ones, were associated with a smaller loss of lean mass in men, although this was not the case in women. Greater losses of lean mass were also associated with increased mortality rates, which stressed the importance of sarcopenia as a factor contributing to the quantity and quality of life of the elderly [52,53].

Physical Inactivity and Activity

Another factor which leads to sarcopenia, maybe the most conspicuous one, is physical inactivity. It is well known that a sedentary lifestyle and short-term muscular inactivity markedly reduce muscle mass and strength, even in young persons, and the typical examples are long stays in bed and zero gravity conditions. Physical exercise (muscle contraction) leads to a release of muscle growth factors: insulin growth factor (IGF-E) and mechano growth factor (MGF), activating satellite cells and protein synthesis and leading to muscle regeneration [54]. At the cellular level, specific age-related changes involve a reduced number of muscle cells, reductions of time and force of muscle contraction, reduction of sarcoplasmatic reticulum volume and calcium pumping capacity [55].

Impact of Nutrition

An adequate intake of nutrients is key to the maintenance of muscle mass. Reduced food intake with aging, accordingly, may play a role in the development of sarcopenia. It

seems that the two most important factors in the development of sarcopenia are vitamin D and protein deficiencies. It has been proven that deficiency or insufficiency in vitamin D is positively correlated with the risk of several diseases including sarcopenia, cardiovascular diseases, obesity, and cancer. Remelli et al. reviewed the biological, clinical and epidemiological evidence supporting the association between vitamin D and an increased risk of sarcopenia in older people [56].

The most important function of vitamin D is in the regulation of Ca^{2+} concentration in the circulating blood. But, other than Ca^{2+} homeostasis, vitamin D has significant effects on skeletal muscle in other ways [57]. One of them is the impact on mitochondria and regulation of the expression of the target genes by binding to the nuclear vitamin D receptor; in that way, it participates in numerous physiological processes. Mitochondrial dysfunction results in mild but chronic inflammation due to increased production of reactive oxygen species, leading to qualitative/quantitative deterioration of skeletal muscle, which is thought to be one of the major causes of sarcopenia onset [58]. Hence, vitamin D may have beneficial effects on skeletal muscle by regulating mitochondrial function. Vitamin D has been reported to reduce intramuscular lipid accumulation in elderly individuals too. Sarcopenic patients often become obese (sarcopenic obesity) as a result of the negative correlation that exists between serum vitamin D concentration and body fat mass and reduced its inhibitory effect on the differentiation of preadipocytes, hence obesity becomes probable [59,60].

Studies of different populations have shown that vitamin D deficiency is highly prevalent in the elderly [61]. Maintenance of the muscle mass, in the presence of vitamin D deficiency, seems to require adequate protein intake in the elderly. Aging was shown to be associated with progressively reduced food intake, which predisposed to protein-energy malnutrition leading to the wasting of muscle tissue. Epidemiological studies show that intake of proteins is proportional to muscle mass preservation. The data dealing with nitrogen balance have indicated that the protein intake in the range of 1.0-1.3 g/kg a day is needed to offset the typically lower energy intake and disturbed insulin response in older adults. Consequent studies demonstrated that not only global protein intake was significant in that regard, but also the protein content per a meal. It was shown that aging was associated with skeletal muscle inability to react to lower doses (about 7.5 g) of essential amino acids, while higher doses (10-15 g) could stimulate muscle protein synthesis similarly as in the young. Higher leucine proportions in a mixture of essential amino acids can reverse the weaker response of muscle proteins in the elderly. Nutritional supplementation consisting only of amino acids or proteins can be beneficial in muscle growth promotion by stimulating muscle protein synthesis and increasing the total daily intake of calories, but further studies are necessary to validate that [62].

Gut Microbiota and Sarcopenia

In the last decade, attention has been focused on the possible role of the gut microbiota on the development of sarcopenia. It is well known that the human gastrointestinal tract harbours a complex and dynamic population of microorganisms including bacteria, viruses, fungi, and other microbes, the gut microbiota, which play a crucial role in maintaining health and supporting various physiological processes [63,64].

Gut microbiota performs very important functions such as participation in metabolism (digestion and nutrient absorption, impact on energy balance and fat storage regulation, assistance in water and mineral balance, bioactive compounds activation), regulation of host immunity through maintenance of gut barrier integrity (thus preventing harmful substances from entering the bloodstream) [38]. Intestinal bacteria play a crucial role in maintaining immune and metabolic homeostasis and protecting against pathogens. Altered gut bacterial composition marked as microbiota dysbiosis can affect almost all aspects of the host leading to dysregulation of body functions, host immune response, induction of chronic inflammation and development and progression of diseases in the elderly.

The gut microbiota evolves through life, from infancy to old age. However, the microbiota profiles in the elderly are often not optimal. It is now confirmed that age related changes in gut microbiota composition, often marked by a reduction in beneficial bacteria and an increase in pro-inflammatory microbes, contribute to the onset of sarcopenia and frailty [65,66].

The human gut microbiota impacts muscle health indirectly by influencing nutrient absorption, overall metabolism and chronic inflammation that are common in the elderly.

Therefore, diet is considered as one of the main drivers in shaping the gut microbiota across the life time. Dietary measures, particularly the use of a range of fibers (prebiotics), may be the best way of maintaining a healthy gut microbiota population. Strategies such as ingestion of live beneficial bacteria (probiotics) may also assist in maintaining health, improving muscle function and reducing the risk of frailty in old age, but further research is needed to confirm their effectiveness in targeting muscle loss [38].

Epidemiology and Management of Sarcopenia

Nowadays, there is no effective and safe therapy which would be able to prevent or replace the lost muscle mass. The standard of management of sarcopenia is either nutritional supplements and appetite stimulants or physical exercise aimed to maintain or increase muscle strength. Despite these therapeutic options, many of the elderly are still losing muscle strength and function and are consequently exposed to the risk of unfavorable outcomes of their physical frailty. Anabolic steroids are sometimes prescribed,

but their contribution is limited due to their poor effectiveness and the occurrence of adverse effects. New therapeutic modalities aimed to prevent and treat sarcopenia can be divided into three categories: intake and absorption of nutrients, targeting skeletal muscles and endocrine strategies.

Improvement of absorption of nutrients represents a first-line treatment of sarcopenia, nevertheless with a modest effectiveness. Some significant advances have been made with skeletal muscle therapeutical targeting, e.g. with myostatin [67]. Endocrine modalities have also been investigated in the treatment of sarcopenia; such an approach would involve selective androgen receptor modulators (SERMs) and growth hormone secretagogues [46,68]. Growth hormone replacement in deficient individuals is able to improve muscle mass, but it is not clear whether such a replacement would be effective in sarcopenic individuals as well.

Some recent studies suggested that the using supraphysiological doses of testosteron in older men could significantly improve the strength of lower extremities and lean muscle mass. Although high dose testosteron results in considerable strength gains, potential risks may nevertheless outweight the beneficial effects. The risks associated with the therapy involve aggessive behavior, thrombosis, sleep apnea, peripheral edema, gynecomastia and an increased risk of prostate cancer [69]. Testosteron replacement up to the medium levels within the normal range results in significant increases of muscle mass, strength, muscle protein synthesis and bone density. However, testosterone treatment has not been recommended for sarcopenia as yet [54]. Also, theoretically, administration of GH in the elderly would improve body composition (increase muscle mass, decrease fat mass, and bone demineralization rate), but there are reports that GH supplementation does not lead to increases in strength, functional capacity, or beneficial metabolic changes [70,71]. The side effects of such a therapy are significant and rather frequent, the most commonly reported being carpal tunnel syndrome, edemas, arthralgia, glucose intolerance, insulin resistence, diabetes and cardiovascular risks. Similarly as with testosterone, growth hormone replacement is not currently recommended as a treatment of sarcopenia due to potentially very serious side effects mentioned above [72]. To define the risk/benefit ratio of such a therapy so that it can be recommended, more long-term studies should be undertaken.

The administration of vitamin D may improve muscle strength and muscle mass and may be useful for the prevention and therapeutic intervention of sarcopenia. Due to the significant impact of Vitamin D on skeletal muscles, the necessary daily doses for the intake of vitamin D in order to prevent sarcopenia and other diseases were determined [60]. The recommended quantities are: 15 µg/day (600 IU) for people under 70 years old; 20 µg/day (800 IU) for those 71 years and older. According to the International Osteoporosis Foundation, dietary vitamin D intake from 20 to 25 µg/day (800 to 1000 IU/day) is required to prevent both falls and bone fractures in the elderly.

It is assumed that for the elderly, in order to preserve their muscle mass, at least 1.2 g/kg protein is needed per day [73]. Also, leucine-enriched combination of essential amino acids increases protein synthesis more than other protein forms; they accomplish this by activating muscle targets of the rapamycin mechanism, a key anabolic regulator [74]. Proteins act in synergy with physical exercise topreserve and enlarge the muscle mass. It is well known that muscle strength can be improved by training, even in the elderly [75].

The approach most commonly used to combat sarcopenia is the progressive resistance training, involving using muscles to resist some type of external force, which is gradually increased with growing muscle strength. However, studies show that resistance training has considerable beneficial effects on muscle strength in older adults, with a small to moderate impact on physical performance [76]. Recently, various studies have suggested that in contrast to muscle force, muscle power (generation of muscle work per unit of time) is more strongly associated with physical performance [77]. Therefore, muscle power training in the elderly has attracted much attention in recent years. The core element of a power training is that the concentric part of resistance training (lifting or pushing) should be completed as quickly as possible, while the eccentric part (lowering) has to be completed in about 2-3 seconds [78,79]. The studies published so far that have dealt with the comparison of effects with resistance training and with power training do not have consistent results [77,80,81]. Despite its ineffectiveness in increasing muscle mass, strength and function, resistance training exercises may represent a more complicated intervention (requiring equipment, adequate facilities, supervision) and is not indicated in some conditions common in the elderly (such as hypertension and brain stroke).

It is also believed that resistance training can be used to counteract these muscular changes – these exercises increase myofibrillar muscle protein synthesis in both young and older adults. A progressive training with resistance exercises also induces muscle hypertrophy and increases strength in older and physically weak adults. Regular physical activity has a beneficial effect at the level of inflammation, as has been reported in a number of studies [75]. Higher levels of physical activity were associated with lower serum concentrations of several inflammation markers, including C-reactive protein (CRP), IL-6 and fibrinogen, as well as with lower white blood cell counts [82,83]. Together with the effect of de-training, these facts were able to explain the harmful effect of physical inactivity on muscles through the collapse of protein synthesis in the cell induced by inflammation [84].

In some studies, it has been shown that aerobic exercises can improve oxygen volume (VO_{2max}), mitochondrial density and activity, insulin sensitivity and energy expenditure in both the young and the elderly. Although aerobic exercises do not induce evident muscle hypertrophy, some studies have demonstrated that high intensity aerobic training could induce a degree of hypertrophy, as

suggested by an increased lower leg circumference, increased muscle fiber area and satellite cells activation. The characteristic body structure of marathon runners (typical aerobic athletes) casts doubts on anabolic effectiveness of aerobic exercises [85]. It is important to stress that muscles in these athletes, although not hypertrophic, do not lack power and strength, as is the case with sarcopenic adults. In fact, muscle mass is not the only muscle function determinant, and aerobic training can have significant beneficial effects on neuromuscular adaptations and, consequently, muscle quality, especially in those who have led a sedentary lifestyle and have been sarcopenic before the intervention with physical training. It was shown that muscle quality could be significantly improved with resistance (strength) training in the elderly and in the young in whom muscle wasting occurred. Both strength training and aerobic exercise can be very beneficial in the fight against sarcopenia and accompanying metabolic changes in the muscle tissue [86].

It can be concluded that therapeutic options for the prevention and treatment of sarcopenia are still being in their investigation phase; future studies are expected to establish the effectiveness of these therapies in reversing the course of sarcopenia and to find out whether the improvements in body composition and physical performance would translate into favorable outcomes in the ever increasing elderly population.

Conclusion

Sarcopenia is defined as an unwilling loss of muscle mass, strength and function which leads to the physical incapabilitiesof the elderly. Sarcopenia is a multi-causal, that is, multifactorial desease which occurrence is still being examined, as well as possible therapeutic approaches in its prevention and treatment. The most common causes which lead to sarcopenia are: changes in the structural function with aging, changes in the metabolic and biochemical factors with aging, neural, inflammatory factors and physical activity/inactivity. The most common approach in the fight against sarcopenia is progressive resistance exercise, which implies that the participants physically resist some external force that increases with their increasing strength. The improvement of absorption of nutrients is the first line therapy treatment of sarcopenia, but it has very limited effectiveness. Significant progress is being made by focusing on the skeletal muscles, for example with myostatin. Endocrine possibilities are also present in the treatment of sacropenia. The endocrine approach includes selective androgen receptors and growth hormone secretagogues.

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