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REVIEW ARTICLE

REASON OF PROGRESSIVE LOSS OF FUNCTION AND FRAILTY IN ELDERLY: SARCOPENIA

ABSTRACT

Sarcopenia is a multi-factorial and complex condition that can be defined as loss of mass, strength, quality, and function in muscles associated with age. While there are still research studies in progress, the primary cause of sarcopenia has not yet been defined. To diagnose sarcopenia, muscle mass, muscle strength, and physical performance should be estimated. However, the lack of diagnostic criteria to identify patients with sarcopenia hinders potential management options. With advances in molecular physiology, potential medicines that can make changes in skeletal muscles are currently being defined. Unfortunately, the molecules in the literature are not of the type that meet our expectations yet, due to their side effects and the lack of evidence, as there is insufficient data on the mechanism, efficacy, and safety of pharmacologic treatments. Resistive exercises and nutritional support prophylaxes are useful in the treatment of sarcopenia; therefore, health professionals have much work to do to plan personal, or when necessary, community- or home-based, exercise programs. Considered one of the geriatric symptoms, sarcopenia is important for both its health and economic consequences. Therefore, in order to bring attention to the diagnosis and treatment of sarcopenia in clinical practice, we deal with its different aspects in this review.

Key Words: Aged; Sarcopenia; Frail Elderly.



DERLEME

YAŞLILARDA PROGRESİF YETİ KAYBI VE KIRILGANLIK NEDENİ: SARKOPENİ

Öz

Kaslarda yaşla ilişkili olarak kitle, güç, kalite ve fonksiyon azalması olarak tanımlanabilen sarkopeni multifaktöryel ve kompleks bir tablodur. Araştırmalar devam etmekte olup, sarkopeniye neden olan primer neden henüz tanımlanamamıştır. Sarkopeni tanısı için; kas kütlesi, kas gücü ve fiziksel performansın değerlendirilmesi gerekmektedir. Sarkopeni olan hastaları belirlemek için tanı kriterlerinin olmaması, potansiyel tedavi seçeneklerini aksatmaktadır. Moleküler fizyoloji alanındaki gelişmelerle birlikte iskelet kasında değişiklik oluşturabilecek potansiyel ilaçlar tanımlanmaya başlamıştır. Ancak literatürdeki moleküller gerek yan etkileri gerekse kanıt eksiklikleri nedeniyle maalesef henüz beklentilerimizi karşılayacak nitelikte değildir. Farmakolojik tedavilerin mekanizması, etkinliği ve güvenliği ile ilgili veriler yetersizdir. Dirençli egzersizler ve nutrisyonel destek önleme ve tedavi açısından faydalı olmaktadır. Bu nedenle kişiye özel, gereğinde toplum bazlı, gereğinde ev egzersiz programları planlanması için sağlık profesyonellerine çok görev düşmektedir. Geriatrik sendromlardan biri olarak da sayılan sarkopeni hem sağlık hem de ekonomik yönüyle önem arz etmektedir. Sarkopeni tanı ve tedavisine klinik pratiğimiz açısından dikkat çekebilemek için, bu derlemede farklı yönleriyle ele alınmaya çalışılacaktır.

Anahtar Sözcükler: Yaşlı; Sarkopeni; Kırılgan Yaşlı.

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INTRODUCTION

Sarcopenia, defined as an undesired loss of muscle mass that occurs with aging, is associated with a loss of muscle strength and functionality, and it appears as a potential predictor of mortality (1). Also considered one of the geriatric symptoms, sarcopenia is important for both its health and economic consequences (2). In order to bring attention to the diagnosis and treatment of sarcopenia in clinical practice, we deal with different aspects of it in this review.

DEFINITION

Sarcopenia is derived from the Greek words “sarx,” meaning “flesh,” and “penia,” meaning “loss” or “poverty.” Although two decades have passed since it was first defined in 1989, both the word itself and the clinical condition defined by it are still controversial (2). While the prevalence of sarcopenia is approximately 25% in those aged under 70 years, it goes up to 40% in those aged 80 years and over. Sarcopenia is seen in one-third of women and two-thirds of men over 60 years of age.

Baumgartner et al. defined sarcopenia as the value that is found by dividing appendicular skeletal muscle mass by height squared in meters (muscle mass index), and which is at or less than two standard deviations (SDs) from a young reference population (3). Janssen et al., on the other hand, defined sarcopenia as the value that is found by dividing whole skeletal muscle mass (kg) by body mass (muscle mass/body mass*100), and which is less than one SD from the weight of a young reference group (4).

In order to put an end to the confusion in the diagnosis of sarcopenia, the European Union Geriatric Medicine Society (EUGMS) set up a working group in 2009, The European Working Group on Sarcopenia in Older People (EWGSOP) (5). The report prepared by this group on the definition and diagnosis of sarcopenia was published in 2010. Sarcopenia was described in this report as a syndrome characterized by a loss of generalized and progressive muscle mass and strength, which can lead to negative results, such as physical insufficiency, low quality of life, and death (5). According to this definition, a decline in both muscle mass and muscle function must be present for a diagnosis of sarcopenia. It was also reported, however, that there could be differences among people depending on the activity levels of individuals and other environmental factors. The International Association of Nutrition and Ageing similarly stressed the importance of

function in their definition. Both of these definitions overlap with the definitions of frailty. The Society of Sarcopenia and Cachexia compromised by suggesting that the condition be called sarcopenia with limited mobility (6,7). Sarcopenia with limited mobility defines a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of two standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group (6).

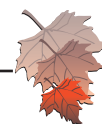
Another definition for sarcopenia was recently introduced by experts working in this field. According to this definition, “Sarcopenia is the age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass. The causes of sarcopenia are multifactorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. While cachexia may be a component of sarcopenia, the two conditions are not the same” (8).

Although it is obvious that sarcopenia is associated with aging, debates still continue as to whether it should be defined as a disease, a syndrome, or a geriatric syndrome (2,8,9).

PATHOPHYSIOLOGY

While there are research studies in progress, the primary cause of sarcopenia has not yet been defined. The currently accepted thought is that sarcopenia is a result of a number of complex, multi-factorial processes. The factors that contribute to sarcopenia are senescence, chronic disease, physical inactivity, and poor food intake. Cachexia may be considered as one etiologic pathway to accelerated sarcopenia (9).

Cachexia has recently been defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle, with or without loss of fat mass. Cachexia is frequently associated with inflammation, insulin resistance, anorexia, and increased breakdown of muscle proteins. Thus, most cachectic individuals are also sarcopenic, but not all sarcopenic individuals are considered cachectic. Sarcopenia is one of the elements of the proposed definition for cachexia. Very recently, a consensus paper expanding this definition of cachexia and identifying relevant issues on how to differentiate cachexia and sarcopenia was published by ESPEN, one of the EWGSOP-endorsing societies (6,7,9,10).



The factors that play a role in the prognosis of sarcopenia include muscle capacity with impaired regeneration (deficit in satellite cell and protein turnover changes), decreased muscle protein synthesis, inadequate protein intake through diet, increase in fat mass, increased oxidative stress, physical inactivity, role of reactive oxygen types, loss of motor neurons, remodeling in motor units and loss in reorganization of neuromuscular compositions, differentiated gene expression, especially reduced sex hormone levels and decreased growth hormone (GH) synthesis, endocrine system disorders (insulin-like growth factor, etc.), and development of a chronic inflammatory condition (11-17). More recently, it has been suggested that alterations within the rennin-angiotensin-aldosterone system might contribute to the development of sarcopenia and the subsequent decline in physical function (18). With aging, a decrease in the levels of GH, testosterone, and insulin growth factor I (IGF-I), and an increase in the serum levels of inflammatory markers (C-reactive protein-CRP and inflammatory cytokines-interleukine-IL-6) occur. Most of these biological markers are correlated with increased disability, mortality, and/or weakness. It has been reported that high levels of IGF-I prevent sarcopenia in men, cytokines such as IL6 and TNF alpha cause lysis in muscles, decreased GH levels promote development of sarcopenia, and increased IL6 and catabolic stimulus affect women more than men in developing sarcopenia. It has been observed that risk of sarcopenia and frailness increased when reduced levels of gonadal hormone and IGF-1 and high peripheral levels of inflammatory mediators and cytokines were combined with a low level of vitamin D (11,19,20). However, the role of either the hypothalamo-pituitary-gonadal/adrenal axis or hormonal dysregulation in the development of sarcopenia cannot be fully explained yet.

One of the various opinions is that some common pathways between hypoxia and aging could be shared. Another

opinion is that there is a relationship between genetic factors and sarcopenia (21). Although all of these mechanisms have impacts on sarcopenia, it is still difficult to establish the causal relationship of the effects of such mechanisms on muscles.

DIAGNOSIS

The first step in treating sarcopenia is to diagnose it, but the criteria suggested for diagnosing sarcopenia are not in general use yet and frequently go unnoticed in clinical practice. To diagnose sarcopenia, muscle mass, muscle strength, and physical performance should be estimated (5,11,22) (Table 1).

Muscle Mass

- a. Imaging techniques: Three imaging techniques have been used for estimating muscle mass or lean body mass—computed tomography (CT) scan, magnetic resonance imaging (MRI), and dual energy X-ray absorptiometry (DXA). CT and MRI are the gold standards for estimating muscle mass in research, while DXA is the preferred alternative method for research and clinical use. Noninvasive imaging approaches, such as CT, MRI, and positron emission tomography (PET), show promise as clinical tools that might yield important basic information regarding the mechanisms of sarcopenia and the modes of action of multiple interventions (7,23).
- b. Bioimpedance analysis (BIA) estimates the volume of fat and lean body mass. The test itself is inexpensive, easy to use, readily reproducible, and appropriate for both ambulatory and bedridden patients. BIA may be considered as a portable alternative to DXA.

Table 1— Sarcopenia Diagnosis Techniques.

Techniques	Measurements	Comments
Muscle size		
CT scan	Muscle cross-sectional area	Radiation, expensive
MRI scan	Muscle cross-sectional area	Expensive, availability
BIA	Tissue conductivity	Reliability?
Muscle circumferences	Mid-arm and calf circumference	Subcutaneous fat
DXA scan	Total skeletal muscle mass	Reliable, low radiation
Physical performance		
SPPB	Lower extremity function	Validated for elderly



- c. Total body potassium: As skeletal muscle contains >50% of the total body potassium (TBK) pool, TBK is the classic method for estimating skeletal muscle; however, this method is not used in routine practice.
- d. Anthropometric measures: Calculations based on mid-upper arm circumference and skin fold thickness have been used to estimate muscle mass in ambulatory settings. Calf circumference correlates positively with muscle mass; calf circumference <31 cm has been associated with disability. However, age-related changes in fat deposits and loss of skin elasticity contribute to estimation errors in older people. Anthropometric measures are vulnerable to error and are not recommended for routine use in the diagnosis of sarcopenia (5-9).

Muscle Strength

Only a few techniques have been validated for estimating muscle strength.

- a. Handgrip strength: Isometric handgrip strength is strongly related to lower extremity muscle power, knee extension torque, and calf cross-sectional muscle area. Low handgrip strength is a clinical marker of poor mobility and a better predictor of clinical outcome than low muscle mass. A linear relationship has also been found in practice between basal handgrip strength and dependency in daily living activities.
- b. Knee flexion-extension techniques: These can be used for research, but they have limited use in practice because they require special equipment and training. Quadriceps strength was found to be the most useful marker in older people in terms of physical and functional changes (24).
- c. Peak expiratory flow: Peak expiratory flow is determined by the strength of the respiratory muscles in individuals who do not have any lung disease. It is a cheap, easily applied technique with a prognostic value, but there has been limited research on its use in sarcopenia.

Physical Performance

The tests used in estimating physical performance include the short physical performance battery, usual gait speed, timed get up and go test, and stair climb power test.

- a. Short physical performance battery: This test measures balance, gait, strength, and endurance. It is a suggested method for measuring functional results in clinical studies conducted on frail elderly people. Frail elderly syndrome is one of the geriatric syndromes of increased vul-

nerability to stressors due to impairments in multiple interrelated systems. Common signs and symptoms are unintentional weight loss, muscle weakness, fatigue, slow walking speed, and progressive functional decline (25-27). The short physical performance battery is an appropriate test for estimating physical performance, in both clinical practice and research.

- b. Usual gait speed: In studies, a linear relationship has been found between leg strength and usual walking speed. Walking speed is also related to dependency. The get up and go test, in particular, is considered to be a predictor for results such as serious mobility restriction and mortality. The usual gait speed test is part of the short physical performance battery, but it can also be used alone, in both clinical practice and research.
- c. Timed get up and go test: This is an important test for assessing dynamic balance in particular. It can be used in both geriatric assessment and performance measurement. In this test, the patient starts from a position of sitting on a chair, and is asked to stand up and walk 3 meters and back, and then sit on the chair again; then the completion time is calculated. This test and usual gait speed can be considered the quickest and easiest tests available.
- d. Stair climb power test: This is used more often for research purposes to assess leg power deficits.

The diagnosis of sarcopenia should be based on having low whole body or appendicular fat-free mass in combination with poor physical functioning. Current methods index appendicular fat-free mass to height squared or whole body fat-free mass to height squared. In patients with poor functional capacity, most easily identified using gait speed of than 1 m·s⁻¹, sarcopenia can be diagnosed when lean mass is less than 20% of the values for healthy young adults. Currently, objective cutpoints for sarcopenia in men are made at an appendicular fat lean mass/ ht² (aLM/Ht²) of ≤ 7.23 kg/m², and in women at ≤ 5.67 kg/m² (8).

However, the practical diagnosis of sarcopenia still remains an unsolved problem. Standardized measurements of sarcopenia need to be validated. Although numerous groups of specialists are working on this specific issue, and undoubtedly new data may change this approach, we believe that it is possible to propose a practical approach to manage sarcopenia as a geriatric syndrome. The two easiest clinical tests to start the investigation of suspected sarcopenia might be measurement of walking speed or five time-stands from a chair. If any of these tests are positive (walking speed <0.8 m/s; inability



to stand up from a chair), a BIA might be an inexpensive and easily available method to evaluate the probability of sarcopenia by measuring the ratio between lean body and fat body mass. Further investigations, such as DEXA, might be necessary only in doubtful cases or for research purposes, knowing that the gold standard measures of the ratio of lean/fat body mass are CT and MRI (5-9).

EWGSOP has developed an algorithm to identify individuals with sarcopenia in both clinical practice and clinical research studies (5). According to this algorithm, the first criterion to assess is walking speed in individuals over 65 years of age. If the walking speed is greater than 0.8 m/sec, there is a risk of sarcopenia, and further evaluation is needed, using the handgrip strength test. If the handgrip test result is also low, then a method of measuring muscle strength should be used.

A more recent consensus document defines "sarcopenia with limited mobility" as present in a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-min walk, and who has a lean appendicular mass corrected for height squared of two SDs or more below the mean of healthy persons 20–30 years of age of the same ethnic group. The limitation in mobility should not clearly be a result of otherwise defined specific muscle disease, peripheral vascular disease with intermittent claudication, central or peripheral nervous system disorders, or cachexia. Clinically significant interventions are defined as an increase in the 6-minute walk of at least 50 meters or an increase in walking speed of at least 0.1 m/s (6). However, these criteria remain cumbersome in daily clinical practice, and easily applicable tests, such as handgrip strength testing or one of the biomarkers mentioned above, may help to identify patients in need of a more thorough examination (28).

TREATMENT

With the advances in molecular physiology, potential medicines are now being defined that can make changes in skeletal muscles. Unfortunately, however, the molecules described in the literature are not of the type that meet our expectations yet, due to their side effects and the lack of evidence (22,23,29-31) (Table 2).

Exercise and Physical Activity

Physical inactivity aggravates loss of skeletal muscle. It has been demonstrated that both aerobic and resistance-type exercises decrease the decline in muscle mass and muscle strength that develop with aging (22,30,31). Aerobic exercises (swimming, jogging, and walking) have long been known to be related to cardiovascular fitness and endurance capacity. Although aerobic exercise does not contribute much to muscle hypertrophy, it can increase the cross-sectional area of muscle fibrils. After an aerobic exercise, mitochondrial volume and enzyme activity increase, showing that muscle protein synthesis and muscle quality have improved, regardless of age. Aerobic exercise also decreases body fat (20,32,33). Resistive exercises have a much greater impact on increasing muscle mass and strength and reducing development of sarcopenia. It has been demonstrated that resistive exercises performed even once a week cause recovery in muscle strength (34). Much greater improvements can be secured in both cross-sectional muscle area and muscle strength with more intensive and regular resistive exercises. An apparent increase occurs in skeletal muscle protein synthesis in older people who perform resistive exercises without any increase in total body muscle breakdown. The increase in muscle strength and endurance occurs together with an increase in the dimensions

Table 2— Sarcopenia Treatment Mechanisms.

Target or Pathways	Potential Beneficial Effect on Muscle
Androgen receptors	Increase muscle mass and strength
Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha	Increase muscle oxidative metabolism
Myostatin	Increase muscle mass and strength
Peroxisome proliferator-activated receptor-delta	Increase type I fibers and oxidative metabolism
Insulin-like growth factor 1	Increase muscle mass and strength
μ-adrenergic receptor	Increase muscle mass
Neuregulins	Increase muscle mass and enhance glucose utilization
Angiotensin-converting enzyme	Improve muscle function and physical performance
Inflammatory cytokines	Decrease catabolic effects

**Table 3—** Sarcopenia Treatment Options.

Intervention	Effect	Comments
Exercise	Increased cardiovascular fitness with increased endurance	Overall beneficial effects
Aerobic	*Increased mitochondrial volume and activity	Motivation to exercise remains low
Resistance	*Increased muscle mass and strength *Increased skeletal muscle protein synthesis and muscle fiber size *Improvement in physical performance	
Nutrition supplement	Variable evidence of increased muscle mass and strength	Good protein intake May reduce natural food intake
Hormone therapy		
Testosterone	*Variable evidence of increased muscle mass and strength	*Masculinization of women, increased risk of prostate cancer in men
Estrogen	*Poor evidence of increased muscle mass, but not function	*Risk of breast cancer
Growth hormone	*Some evidence of increased muscle mass and variable evidence of increased muscle strength	*Side effects including fluid retention, orthostatic hypotension
Vitamin D	Variable evidence of increased muscle strength Reduced number of falls in nursing home residents	Fracture reduction, possible cardiovascular benefits
ACE inhibitors	Some evidence of increased exercise capacity	Cardiovascular benefits Renal function needs monitoring
Creatine	Variable evidence of increased muscle strength and endurance, especially when combined with exercise	Reports of nephritis
New treatments		
Myostatin antagonists	Not sufficient evidence	
PPAR agonist		
AICAR		

of both type 1 and type 2 muscle fibers (30). The increase in muscle strength and size that developed when performing moderate resistive exercises in elderly individuals 65–75 years of age was found to be similar to that of young people (34). It was observed in a meta-analysis that physical function, walking speed, timed get up and go test, and stair climb power improved, and more importantly, a marked effect on muscle strength occurred, in elderly individuals who performed progressive resistance exercise training two or three times a week (34,35). Resistance exercise training appears to be relatively safe to perform, even in participants with multiple comorbidities, and can help in the prevention of falls (30,31). It is recommended that these individuals increase physical activity, and especially, continue with resistive exercise programs, due to their protective and healing effects (36).

Nutritional Support Therapy

Many older people do not consume the required amount of protein in their diets, which results in decreased lean body

mass and increased functional disorders. Recent studies suggest that the proposed 0.8 g/kg/day protein intake is not enough for older people, and that in order to secure an optimal health condition, protein intake should be increased to 1.2–1.3 g/kg/day. A protein intake of 1.5 g/kg/day is especially recommended during inevitable periods of inactivity (29,36). Daily intake of protein should be distributed proportionally among the meals throughout the day (muscle protein synthesis stimulation). Protein synthesis and protein balance improved progressively when protein intake was increased from 0.5 to 1.0, 1.5, and 2 g/kg/day in hospitalized elderly people with malnutrition (27,30). Chronic essential amino acid (EAA) supplements given to healthy older women were also shown to increase muscle protein synthesis and lean body mass (29,36,37). In a study conducted by Rieu et al., it was found that leucine supplementation increased muscle protein synthesis in older men (38).

Protein and energy supplementation might increase muscle strength, even in very old people, in the short term, but a



Cochrane review has found no definite functional benefit of nutritional supplementation (39). Although older people who exercise have increased protein requirements, studies investigating whether nutritional supplementation in combination with resistance training can augment muscle strength gains in older people have yielded inconsistent results (32). Tieland et al. established that dietary supplementation of protein improves physical performance; however, it does not increase skeletal muscle mass in frail elderly people (40). Another recent study by Tieland et al. suggested that prolonged resistance-type exercise training constitutes an effective strategy to improve strength and physical performance in frail elderly people. They concluded that dietary protein supplementation is required to allow muscle mass gain during exercise training in frail elderly people (41).

Because oxidative stress is part of the etiology of sarcopenia, the use of antioxidants becomes a current issue. However, intake of antioxidant substances from foodstuffs in a natural way is recommended. In addition, it is stressed that exercise is important in providing antioxidant activity as well (22,29-32).

Hormonal Therapies

- a. Testosterone: Emerging data suggest that testosterone induces muscle fiber hypertrophy, by acting at multiple steps in the pathways that regulate muscle protein synthesis and breakdown, as well as pluripotent stem cell commitment and differentiation. It is often mentioned for its impact on motor neuron and peripheral neuron regeneration and circadian rhythm. It has been demonstrated that decreasing levels of testosterone with aging is associated with decreasing muscle mass, muscle strength, functional state, and bone density. However, conflicting results have been obtained in studies dealing with replacement of testosterone. Although there was an increase in muscle mass in most of the studies, no increase was observed in muscle strength. In addition, despite a clear beneficial effect of testosterone supplementation on lean body mass and fat mass, evidence of a direct effect of this treatment on disability and physical performance is still lacking. Replacement of testosterone may also lead to undesired results, such as prostate enlargement, fluid retention, gynecomastia, polycythemia, and sleep apnea. A new therapeutic perspective represented by Selective Androgen Receptor Modulators has the same anabolic effect on muscle tissue as testosterone, of treatment obtained by improving the tissue selectivity of this drug, but without the undesirable side effects (22,29-31).
- b. Estrogens and Tibolone: Estrogens and tibolone could have a direct effect on skeletal muscles by binding to estrogen receptors present in human skeletal muscle. Tibolone can probably also act by binding androgenic receptors in skeletal muscle. Furthermore, tibolone and transdermal estrogen therapy effectively restore spontaneous GH episodic release, significantly reducing pulse frequency and significantly increasing pulse amplitude; tibolone has also been shown to increase serum IGF-1 levels directly. Theoretically, tibolone may have another positive effect on muscle strength, because it increases the plasma levels of nitric oxide (NO), and NO mediates satellite cell activation. Although the effect of lack of estrogen in the development of sarcopenia in older women is known, replacement therapy did not show any distinct effects on muscle composition and function. It is not a preferred treatment, due to increased breast cancer and cardiovascular risks (30,31).
- c. Growth hormone: Growth hormone shows its anabolic effect through IGF-1. With aging, there is a decrease in GH, as well as in IGF-1 levels and pulsatile frequency and amplitude. IGF-1 has both hyperplastic and hypertrophic effects on skeletal muscle. Besides stimulating muscle protein synthesis, IGF-1 also suppresses proteolysis, promotes the delivery of amino acids and glucose to myocytes, and stimulates myoblast proliferation and differentiation. Systemic IGF-1 administration increases the rate of skeletal muscle functional recovery after injury, reduces the susceptibility to contraction-induced damage, and improves endurance and contractile function. Mechanisms hypothesized for this effect include the reduction of inflammatory response (e.g., IL6 and IL-1 β) and the severity of cardiomyocyte apoptosis.

Despite numerous studies that assessed the effects of GH administration on muscle mass, strength, and physical performance, this issue is still being debated. In particular, controversial findings have been reported in healthy or moderately frail, non-GH-deficient older adults following GH administration. Although there was an increase in muscle mass in healthy elderly people with no GH deficit, there was no apparent change in muscle strength. Its use in old age sarcopenia is not recommended, as it could lead to undesired results such as fluid retention, gynecomastia, orthostatic hypotension, and carpal tunnel syndrome (30,31,42).
- d. Vitamin D: Vitamin D plays an important role in muscle and bone metabolism. Low levels of vitamin D are associ-



ated with atrophy and sarcopenia, especially in type 2 muscle fibrils. Replacement of vitamin D has been found to improve muscle strength, decrease falls, and prevent fractures. These effects are especially significant in individuals with low vitamin D levels. Replacement of vitamin D has also been shown to reduce markedly the risk of falling in older people. This effect becomes apparent in vitamin D replacement doses of 700–1000 IU/day (43–44). Although it is plausible to associate low levels of vitamin D with a reduction in muscle strength and physical function, the evidence for supplementation has been inconsistent. Safety issues surrounding vitamin D supplementation in older people include increased risk of nephrolithiasis and hypercalcemia.

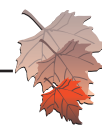
Other Treatments

- a. ACE inhibitors: ACE inhibitors are thought to have positive effects on skeletal muscle function through various mechanisms. These include improvement in endothelial function, muscle fibril type effect, nutritional effect, improvement in endothelial functions and muscle glucose uptake, metabolic effect (IGF-1), changes in body composition, neurohormonal and anti-inflammatory effects (IL-6, TNF alpha, angiotensin, TGF-beta), and regulation of skeletal muscle blood flow through regulation of angiogenesis. Although positive effects have been observed in a limited number of prospective studies, larger scale studies are needed to investigate the effects of ACE inhibitors on sarcopenia (23,29–31,45). Although data on the mechanism exist, in a randomized controlled study no differences were found between enalapril and nifedipine with respect to their effects on muscle performance (46). Therefore, it is too early to make conclusive judgments on the efficacy of ACE inhibitors.
- b. Statins: Statin-group drugs are said to have effects on skeletal muscle through vascular and anti-inflammatory mechanisms. Statins might affect muscle mass and function, retarding the deleterious effects of atherosclerosis on the blood vessels of skeletal muscle, ensuring better perfusion, and therefore, preventing muscle wasting and reducing muscle weakness and/or fatigue. Indeed, statins increase production of nitric oxide in the endothelium, which has local vasodilatory properties, in addition to antithrombotic, antiproliferative, and leucocyte adhesion inhibiting effects. In older persons, higher inflammatory marker levels are strong independent predictors of sarcopenia, probably through accelerated muscle catabo-

lism. Therefore, the evidence that the use of statins reduces inflammation, together with the recognition of inflammation as a major determinant of muscle mass and function, appears to provide a rationale for hypothesizing a direct effect of statins on sarcopenia (30,31,47,48). Further studies are needed to demonstrate the beneficial effects of statins on sarcopenia.

- c. Creatine: Creatine is thought to be effective in the treatment of sarcopenia due to its anabolic and antioxidant effects. It may increase the expression of myogenic transcription factors and facilitate the upregulation of muscle-specific genes such as myogenin and MRF-4, thereby facilitating an increase in muscle mass and strength. Creatine exerts a significant antioxidant activity in living cells, via a mechanism that depends on direct scavenging of reactive oxygen (in particular, hydroxyl radical) and nitrogen species. Its neuroprotective effect is also being investigated. Because its mechanism is not fully understood, long-term studies are needed to demonstrate its safety and effect on renal, hepatic, cardiac, and muscle functions. The effect of creatine is said to be more obvious when used together with resistive exercises, but it is not recommended routinely for sarcopenia treatment, due to controversial results. However, creatine supplementation could increase the risk of interstitial nephritis, highlighting the need for particular caution about its use in older people (30,31,49,50).
- d. Potential new agents: These agents include myostatin antagonists (follistatin), PPAR- γ agonists, and AICAR (5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside); however, there is an inadequate number of studies related to the clinical use of these agents (29,32,33) (Table 3).

In conclusion, the primary goal of therapy in the elderly is to improve quality of life and to reduce the use of health care services and mortality rates; therefore, the factors affecting quality of life should be kept in mind in daily clinical practice (51). Sarcopenia in older people has come to be increasingly significant in terms of public health, due to physical, functional, and financial reasons. The lack of diagnostic criteria to identify patients with sarcopenia hinders potential management options. The primary point that has to be emphasized is that satisfactory success has not yet been achieved in its treatment, as sarcopenia presents as a complex condition and often goes unnoticed in clinical practice. Data on the mechanisms, efficacy, and safety of pharmacological treatments are insufficient. However, resistive exercises and nutritional sup-



port are useful for prevention and treatment. Therefore, health professionals have much work to do to plan personal, or when necessary, community- or home-based exercise programs.

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