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ADVANCES IN SARCOPENIA TREATMENT FOR A HEALTHIER FUTURE

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Abstract

Sarcopenia is a common, costly condition linked to falls, fractures, disability, and death. Initially defined in 1989 as age-related muscle loss, sarcopenia is now recognized as a progressive disorder involving declines in muscle strength, mass, and function, influenced by inactivity, malnutrition, chronic disease, and hormonal changes. Despite its prevalence—affecting 10–27% of people over 60—diagnosis and treatment remain limited due to the lack of consensus. Current research highlights cellular aging, chronic inflammation, oxidative stress, and anabolic resistance as key mechanisms.

Exercise is the cornerstone of treatment. Resistance training improves strength and mass, while aerobic and high-intensity interval training enhance endurance and metabolic health. Combined exercise regimens yield better outcomes than single modalities. Personalized exercise programs considering age and health status are essential.

Nutrition also plays a critical role. Adequate protein intake (1.0–1.5 g/kg/day), leucine supplementation, and balanced energy intake support muscle maintenance. Mediterranean-style diets are encouraged, while excessive protein or restrictive diets are discouraged. Supplements like Omega-3, probiotics, creatine, and vitamin D show promise, but results are mixed.

Pharmacological treatments are under investigation, including hormonal therapies, selective androgen receptor modulators, myostatin inhibitors, and agents targeting the renin-angiotensin system. However, side effects and insufficient evidence limit their use. Stem cell therapies and ghrelin analogs offer future possibilities.

Ultimately, early intervention with exercise, proper nutrition, and a holistic lifestyle approach remains the most effective strategy against sarcopenia.

Keywords: Sarcopenia; Therapeutics; Exercise; Proteins.

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INTRODUCTION

Sarcopenia is a common and costly health problem associated with adverse outcomes including falls, fractures, physical disability, and death. Although sarcopenia was defined in 1989 as the loss of muscle mass associated with age, it has undergone some definitional changes over time. Sarcopenia is not only an age-related condition, but can also result from various factors such as inactivity, malnutrition, chronic diseases, and hormonal changes. Today, in light of the data obtained over time, it is defined as a progressive, generalized muscle disorder due to changes in muscle strength, mass, and function. In 2016, it was tried to emphasize its importance in clinical practice by receiving the ICD diagnosis code M62.84 (1,2).

Depending on the diagnostic criteria, target populations, and regional variations, the global prevalence of sarcopenia in individuals over the age of 60 is estimated to vary between 10% and 27%. According to different study results, higher prevalence rates are also seen. However, despite being so common, neither diagnosis is made nor adequately treated in clinical practice. The biggest reason for this is the lack of international consensus for diagnosis and the existence of confusion (3). Perhaps this uncertainty and confusion contribute to the lack of awareness. Currently, the Global Leadership Initiative in Sarcopenia (GLIS) organization is conducting studies under different working groups, and it is possible that GLIS reports will shed light on this issue in the future (1,3,4)

The exact causes of sarcopenia are complex and not fully understood. A combination of factors such as poor nutrition, physical inactivity, and age-related chronic diseases contribute to the gradual decline in muscle function with age. Common pathophysiological pathways, including low-grade chronic inflammation, mitochondrial dysfunction, oxidative stress, insulin and anabolic resistance, and other hormonal changes, may help explain the onset and progression of this deteriorating condition. Chronic low-grade inflammation in the body inhibits muscle protein synthesis and increases protein catabolism, contributing to the development of sarcopenia. In addition, inflammation is closely linked to oxidative stress and anabolic resistance and exacerbates the loss of muscle mass, strength and function (2,5-8). Although skeletal muscle is known as a locomotor organ associated with falls, physical impairment, disability and mortality, skeletal muscle is actually also a metabolic organ. It is associated with inflammation, fatigue, diabetes, wound healing, respiratory capacity, infection/complication, hospitalization and mortality. Its definition as a metabolic organ is due to the fact that skeletal muscle is related to amino acid, lipid, glucose and bone metabolism (6,9). Therefore, at this point, skeletal muscle plays a key role in all diseases and life.

Different data regarding the diagnosis and mechanism of sarcopenia also complicate the treatment part. Treatment strategies appropriate to the causes and mechanism of sarcopenia continue to be studied. Sarcopenia treatment involves a range of strategies to prevent muscle loss and increase strength and function. This article will discuss various aspects of sarcopenia treatment in light of recent information.

Sarcopenia Treatment

Recent studies show that cellular aging worsens degenerative diseases by affecting skeletal health. Therefore, treatment of aging cells is promising for sarcopenia. Treatment approaches that may be effective on cellular aging include exercise, healthy nutrition, senolytic and senomorph defined treatments. Exercise and nutrition strategies within these treatments may also be effective on preventing cellular aging (5,10,11). Sarcopenia treatment often requires a multidisciplinary approach. It does not seem possible for a one-way approach to be sufficient in such a complex mechanism.

Exercise

Exercises are considered the most important approach in preventing, delaying and treating sarcopenia. Exercise is also one of the most effective interventions to promote healthy aging. Its effect on aging muscles is multifaceted. Exercise has positive effects on inflammation, insulin resistance, microbiota, satellite cell proliferation, myogenesis, nitric oxide-guided vascularization, improvements in mitochondrial bioenergetics and reduced myonuclear apoptosis. In addition, exercises are known to have positive effects on body composition, fall risk, physical performance, quality of life, psychological problems, metabolic syndrome and chronic diseases (10,12,13).

When it comes to sarcopenia, the question of which type of exercise is more effective also comes to the agenda. Different study results on this subject still show the superiority of different exercises.

Resistance exercises have long been prominent as one of the most effective components of exercise therapies in the treatment of sarcopenia. Resistance exercises increase muscle mass and muscle strength and promote neuromuscular plasticity (10,12,13). There are also conflicting results in the literature. However, considering the current literature, it seems important to include resistive exercises in one step of the sarcopenia treatment program (14, 15). It has been reported that low/moderate intensity resistive exercises and low-load exercises increase lean body mass, muscle mass and muscle strength. In resistive exercises, body weight, dumbbells, kettlebells, resistance bands or machines can be used. In addition, marked irregularities in myofiber shape are a hallmark of human skeletal muscle aging and can be reversed by heavy resistance training (16). Resistive exercises are recommended 2-3 times/week, 8-12 repetitions, 1-3 sets, 70-80% 1 repetition maximum (RM) target, with a load starting at 30-40% of 1RM (10,15,17).

Until recent publications, resistive exercises were presented as the most important exercise in sarcopenia treatment. Although Type 2 fibers are important, some researchers have recently stated that aerobic exercises are also very effective (18-21). Aerobic and High Intensity Interval Exercise have positive effects on cardiorespiratory fitness, insulin sensitivity, muscle mass, and muscle function (10). It has been stated that the positive effects on muscle strength and physical functions are particularly striking. Aerobic exercises play a role in improving cardiovascular health as well as increasing muscle endurance. Regular aerobic exercises help increase general physical capacity and provide endurance for long-term use of muscles. Effective aerobic training, characterized by sufficient intensity (70–80% heart rate reserve), duration (30–45 min), and frequency (4–5 days per week), contrasts with resistance training's focus on hypertrophy, offering a high-volume, low-load workout that significantly engages muscles and promotes overall muscle function and growth (10). Recent reviews also indicate that the greatest and most significant muscle gains can be achieved with a multimodal exercise approach. It has been observed that combined exercise treatments are more successful than single exercise treatments (8,22) (Table 1).

Table 1. Components of combined exercise treatments

Resistance exercises Aerobic exercises Endurance exercises	2-3 times/week 20-60 min 1-2 sets 8-10 repetitions
Balance exercises	2-3 times/week
Flexibility exercises	2-3 times/week 10-15 min 15-30 sec stretching
Functional training	2-3 times/week 20-30 min

Exercise programs should be customized according to age, physical condition and health history. Over time, the frequency, intensity and duration of exercises can be increased. Early targeted therapies, including resistance exercise alone or in combination with aerobic exercise or balance training may be required to mitigate the loss of muscle and function that older persons experience during aging (23). Of course, since the main thing will be to prevent sarcopenia, regular physical activity in the early stages and lifelong approaches together with diet strategies will be much more important.

Nutrition

Nutrition plays a critical role in the treatment of sarcopenia. Protein is an essential component for the preservation of muscle mass and muscle recovery. Routine intake of dietary protein directly affects skeletal muscle protein turnover, promotes muscle damage repair, and improves physical activity performance (10,24,25). In older individuals, 1.0-1.5 grams of protein per kilogram of body weight per day is recommended to prevent muscle loss. Both animal- and plant-based proteins can be beneficial, although careful planning may be needed with plant-based diets to ensure sufficient essential amino acid intake. In addition, it is emphasized that daily protein intake should be distributed equally into 3 main meals (0.6 g/kg of high-quality protein per meal) (26). It is also stated that protein intake within the first 30-60 minutes after exercise can increase the positive effect on muscle. The potential of protein supplementation as an effective intervention for managing sarcopenia, particularly in improving muscle mass and strength and muscle function (1,8). However, the benefits of combining it with exercise remain uncertain (27).

Leucine plays a number of roles in the regulation of muscle metabolism, including protein synthesis and conversion, maintenance of glucose homeostasis and provision of nitrogen for muscle alanine and glutamine synthesis. Leucine can reverse the age-related decline of muscle protein synthesis. Meat, fish, eggs, milk, cheese, soy products, nuts such as peanuts and legumes are rich in leucine (8). Total protein intake, with three meals containing 0.6 g/kg of high-quality protein and at least 5 g of leucine per meal, has been recommended. Some studies show that taking 3 g of leucine supplements per day can be effective in increasing muscle mass and strength (28). Positive results have also been obtained with amino acids such as beta-hydroxy-beta-methyl butyrate (HMB) (leucine metabolite), arginine, lysine, glutamine. It has been stated that taking 1-3 g of HMB per day is effective on muscle strength and body composition, but its effect on muscle mass is small. However, interestingly, it has been stated that its positive effects are observed not especially in active individuals but in bed rest (29,30). Therefore, it is clear that more studies are needed on the effects of products to be given as supplements.

Not only adequate protein but also adequate energy intake is important. The benefits of excessively restrictive diets that only include protein intake are debatable. The harms of diets with excessive protein intake, especially animal proteins, are discussed due to the risk of dysbiosis, cardiovascular disease and non-alcoholic liver disease. The Mediterranean diet is seen to be effective on muscle mass and physical performance in terms of its richness of content (17,31). Adequate energy intake is necessary for muscle repair and maintenance. The combination of protein and carbohydrates is especially beneficial for recovery after exercise and increasing muscle mass. This combination increases muscle protein synthesis and supports muscle repair.

Omega 3 is one of the most researched supplements. However, although its beneficial effects are mentioned in many diseases, conflicting results confuse us. The most reliable data in terms of evidence regarding Omega-3 is that it is effective

on inflammation. Long-chain polyunsaturated fatty acids are anti-inflammatory molecules that have a positive effect on the anabolic processes associated with aging and insulin sensitivity. In the treatment of sarcopenia, it is seen that Omega 3 supplementation is effective on lean body mass and skeletal muscle mass, but conflicting results are obtained regarding muscle strength. It is controversial whether it can improve functional results in muscle wasting disorders such as sarcopenia and cancer cachexia. It is also thought to be effective in preventing sarcopenia. However, it is stated that it can be effective on physical performance in use for more than 6 months, and 2 g (400 mg EPA-300 DHA) should be used per day for muscle mass/strength effect. However, there is no clear data on long-term effect, how long and in what dose it should be used. Practically, the nutritional recommendation is to eat fish 4 times a week for Omega 3 (3,32,33).

Research points to gut microbiota dysbiosis, a disturbance in microbial communities within the gut, as a potential key player in the pathogenesis of these age-related conditions. Therefore, the effects of microbiota have begun to be investigated in all diseases. Some studies show that intestinal microflora can also be associated with sarcopenia. With age, intestinal flora diversity and richness decreases, and Actinobacteria and Fusobacteria species decrease. f-Ruminococcaceae; g Faecalibacterium, g-Prevotella, Lachnoclostridium and other genera decrease, g-Bacteroides, Parabacteroides, Shigella increase and a relationship has been reported with sarcopenia. Probiotic oral supplementation (Bifidobacterium and Lactobacillus supplements) enhanced muscle strength, muscle mass, muscle endurance and physical performance and function. Interestingly, the effects of Bifidobacteria on sarcopenia differ between Asian and European individuals. It is stated that Lactobacillus Rocheand- Lactobacillus galaei provides a decrease in pro-inflammatory cytokines. Therefore, this issue seems to be a subject that needs to be investigated in different populations with different probiotics and different doses. However, it is more important to keep the intestinal microbiota healthy with healthy foods in general, to provide flora diversity and to increase physical activity (34-36).

Unfortunately, there are conflicting results regarding the effects of nutritional support treatment-supplements on muscle strength and muscle mass. Recently, the concept of nutritional rehabilitation has started to be used frequently. In this context, the importance of nutritional screening is actually emphasized. It is emphasized that a holistic approach can be beneficial by including healthy components of nutrition and supporting it with regular exercise. As a result, the following is basically recommended for nutrition; the focus is on natural intake of less processed foods, the Mediterranean diet, age- and person-specific treatment, and a healthy diet throughout life (17,31,37).

Pharmacological Treatments

With the developments in the field of molecular physiology, potential drugs that can cause changes in skeletal muscle have begun to be identified. However, unfortunately, the molecules in the literature are not yet in a quality that will meet our expectations due to both their side effects and lack of evidence. Potential molecules that can affect any step of muscle metabolism continue to be studied. As a result of the studies conducted, the popularity of some molecules has decreased over time. Here, an attempt has been made to present molecules that are more emphasized (Table 2).

Positive effects of creatine supplements on muscle aging, bone and fat mass, muscle and bone strength and physical performance have been shown. However, while these effects are observed in healthy individuals, the fact that the same effect is not obtained in sarcopenic elderly, immobilization

Table 2. Present molecules

Creatine supplements	Recommended dosage is 3-5 grams/day.
Vitamin D	Older adults looking to maintain skeletal muscle mass and function should avoid vitamin D insufficiency (<50 nmol/L) and deficiency (<25–30 nmol/L).
Estrogen	It's usage is not recommended primarily.
Testosterone	It is the therapeutic option particularly in older men with low testosterone levels (< 200–300 ng/dl).
Insulin-like Growth Factor 1	Not recommended due to potential side effects.
Growth hormone	Not recommended due to potential side effects.
Myostatin pathway inhibitors	More clinical studies are needed.
ACE inhibitors	Studies are ongoing.
Ghrelin	Data on safety are insufficient.
Mesenchymal stem cells	May promote muscle regeneration, but more research is needed.

and chronic disease conditions creates a question mark in terms of treatment. It is recommended that it should be taken in 3-5 grams per day and supported by resistance exercises (38).

Hormonal treatments have always been popular due to their effects on the pathophysiology of sarcopenia. It can help increase muscle mass, but should be used with caution due to its side effects.

Vitamin D receptor is expressed in muscle tissue, albeit in low concentrations, and the expression of this receptor decreases with aging. Vitamin D has important roles in calcium-mediated muscle functions such as contractility, mitochondrial function, and insulin sensitivity by regulating calcium and phosphate absorption. In addition, it regulates genes involved in calcium and phosphate homeostasis. In fact, it has been suggested that vitamin D and its receptors support cellular/molecular mechanisms involved in myogenesis. In addition, vitamin D acts as a mediator in the interaction between muscle and bone tissue through its effects on myokines (myostatin, vascular endothelial growth factor, osteoglycin) and osteokines (sclerostin, osteocalcin, fibroblast growth factor). Vitamin D deficiency negatively affects skeletal muscle and causes a decrease in muscle strength (39,40). The effect of vitamin D supplementation on muscle mass has been shown in experimental models (41). There are studies indicating that it has a slight effect or no effect on muscle strength. There is also a decrease in the risk of falling. There are studies indicating that vitamin D can be potentiated by using it together with protein, leucine, whey protein, probiotics and exercise (13,40). It has been stated that vitamin D and protein combination therapy has no effect on muscle mass and performance, but provides improvement in muscle strength. It has been stated that vitamin D supplementation does not contribute to handgrip strength, timed up and walk test, muscle strength, physical performance and ALM (42). If there is a vitamin D deficiency at the last point, it is recommended to detect and treat it.

Estrogen has a direct effect on the muscle by binding to skeletal muscle estrogen receptors. Although the evidence regarding its effectiveness in the treatment of sarcopenia is insufficient and contradictory, its use is not recommended primarily due to the side effects of estrogen. However, although there have been hopes with selective estrogen receptor modulators, there is no reliable data proven to date (43).

Testosterone supplements are the most frequently used drugs for enhancing muscle

mass and promoting muscle-protein anabolism. Testosterone is the therapeutic option particularly in older men with low testosterone levels (< 200–300 ng/dl). It is stated that it has positive effects on muscle mass and strength. It is also mentioned that testosterone has positive effects on life expectancy. However, testosterone therapy in elderly men is known to pose potential risks such as sleep apnea, erythrocytosis, thrombotic complications, cardiovascular side effects, and prostate cancer. There are also conflicting results regarding side effects. However, it can be said that testosterone therapy is promising. According to our current knowledge, what is really important is the detection and treatment of deficiency (44). Selective androgen receptor modulators can be considered as a new alternative because they provide the same anabolic effect and have fewer side effects. Selective androgen receptor modulators, while working similarly to anabolic steroids, provide a more targeted effect on muscle tissue and aim to avoid side effects on other organs. These substances bind to androgen receptors to stimulate muscle growth, resulting in increased muscle mass. However, long-term safety and efficacy have not yet been tested in clinical trials (3,45-47).

Insulin-like Growth Factor 1 (IGF) and growth hormone treatments can stimulate muscle growth, but are not recommended due to potential side effects (e.g., increased risk of diabetes, cancer development, increased mortality). More research is needed on the long-term effects of these treatments (3).

Myostatin pathway inhibitors, including myostatin-neutralizing antibodies and activin receptor blockers, hold promise in early trials, but their effectiveness compared with that of exercise alone remains unclear (1). This treatment may be a promising option, especially in older individuals with muscle loss such as sarcopenia. Myostatin inhibitors are being tested in a laboratory setting to increase muscle mass and strength (6). More clinical studies are needed to evaluate whether these treatment methods are effective in humans. Bimagrumab and Landogrozumab are promising as potential drugs in sarcopenic obesity. Bimagrumab is effective on body composition, with little effect on muscle strength and physical performance, and a decrease in fat mass and an improvement in muscle mass have been observed. Bimagrumab (BYM-338), a drug that inhibits ACVR2B, a receptor for ligands like myostatin and activins, has been approved by the FDA for sporadic inclusion body myositis (sIBM). However, it has shown limitations in clinical studies related to sarcopenia. Molecules such as Garetosmab, PINTA-745, Ramatercept and Trevogrumab are also under investigation. Although myostatin and activin II receptor inhibitors are generally well tolerated, further studies are needed to reduce side effects (3,6,23,44,48).

Although there are data on ACE inhibitors increasing IGF-1 levels and mitochondria, it seems insufficient to reflect on clinical practice. As the anabolic and protective role of non-classical RAS, its anabolic effects on skeletal muscle have created excitement for a new agent in the treatment of sarcopenia. However, there is a need for further studies on this molecule as well. The MARS activator BIO 101 molecule is in Phase 3 study and appears to be the most potential drug (3,49,50).

Ghrelin exhibits positive effects on muscle protein synthesis by activating the PI3K/Akt/mTOR pathway, anti-inflammatory effects, and mitochondria. Ghrelin analogs have been reported to increase appetite, weight, and LBM in catabolic states such as cancer cachexia, but data on safety are insufficient (1). Amarolein, a ghrelin analog, is also promising in osteosarcopenia (1,3,51).

Mesenchymal stem cells (MSCs) are cells that can differentiate into muscle tissue-specific cells and promote muscle repair. Injecting these cells into the body can reverse muscle loss and improve muscle

function. There are clinical studies investigating MSCs as a potential treatment for sarcopenia. This treatment may promote muscle regeneration, but more research is needed to determine whether it is effective in humans. In addition, miRNAs are claimed to be potential biomarkers and targets of gene therapy for sarcopenia (1).

When the target of sarcopenia treatment is considered as mitochondria, the prominent treatment options in this regard are; exercise, mitoQ (mitochondria targeted coenzyme Q10); 20 mg/day, Urolithin A; 500-1000 mg/day, Eicosapentaenoic a (EPA), docosahexaenoic acid (DHA), Glycine and N acetyl cysteine; 100 mg/kg/day, NAD; 250-2000 mg/day (52).

Experimental treatment options for sarcopenia offer significant promise in treating muscle loss. Myostatin inhibitors, SARMs, growth hormone and IGF-1 supplements, microbiome manipulation, and stem cell therapies are the focus of research in this area. However, many of these treatments are still in the experimental phase and long-term safety and efficacy data are needed. In the future, these innovative treatment methods are expected to play an important role in treating sarcopenia and improving the quality of life of older adults.

When we look at the literature, we see that electrical stimulation and whole body vibration treatments have positive effects on muscles. It is thought that electrical stimulation treatment can prevent muscle mass loss and increase muscle mass/muscle strength. However, current data are not clear in terms of its effects on muscle strength and muscle function and therefore sarcopenia in the long term (10).

CONCLUSION

Sarcopenia, which can be defined as muscle loss and functional deterioration with age, is a serious health problem faced by the elderly population. Treatment can be done by using a number of different approaches such as exercise, nutrition, and pharmacological interventions. A multidisciplinary treatment plan can be effective in reducing the effects of sarcopenia and improving quality of life. Healthcare professionals play a critical role in managing this process by recommending personalized treatment and lifestyle changes to help individuals reduce their risk of sarcopenia. Exercises and effective nutrition, in which protein-amino acids play a key role, are effective in the prevention and treatment of sarcopenia (16).

In conclusion, there have been no significant advancements in the treatment of this major health issue among the elderly.

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