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Treating Sarcopenia in Older and Oldest Old

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Abstract: The presence of sarcopenia is not only rapidly rising in geriatric clinical practice and research, but is also becoming a significant concept in numerous medical specialties. This rapidly rising concept has encouraged the need to identify methods for treating sarcopenia. Physical activity measures using resistance training exercise, combined with nutritional interventions (protein and amino acid supplementation) have shown to significantly improve muscle mass and strength in older persons. Moreover, resistance training may improve muscle strength and mass by improving protein synthesis in skeletal muscle cells. Aerobic exercise has also shown to hold beneficial impacts on sarcopenia by improving insulin sensitivity. At the moment, the literature indicates that most significant improvement in sarcopenia is based on exercise programs. Thus, this type of intervention should be implemented in a persistent manner over time in elders, with or at risk of muscle loss. At the same time, physical training exercise should include correcting nutritional deficits with supplementation methods. For example, in older sarcopenic patients with adequate renal function, daily protein intake should be increased to >1. 0 grams of protein per kilogram of body weight. In particular, leucine, β-hydroxy β-methylbutyrate (HMB), creatine and some milk-based proteins have been shown to improve skeletal muscle protein balance. In addition, it is also recommended for adjustment of for vitamin D deficiency, if present, considering the crucial role of vitamin D in the skeletal muscle. In this review, we provide evidence regarding the effects of different physical exercise protocols, specific nutritional intervention, and some new metabolic agents (HMB, citrulline malate, ornithine, and others) on clinical outcomes related to sarcopenia in older adults.

Keywords: Aging, sarcopenia, physical exercise, nutritional intervention, medications.

INTRODUCTION

During the aging process, there is a significant loss in spinal motor neurons (MNs) which is mainly as a result of apoptosis, impaired insulin-like growth factor 1 (IGF-1) signaling, increased pro-inflammatory cytokines, especially tumor necrosis factor (TNF)-α, TNF-β, interleukin (IL)-6, as well as high concentrations of oxidative stress end products [1-2]. These physiological changes over the aging process greatly contribute to the progressive decline in skeletal muscle mass and consequently muscle strength (sarcopenia). The most significant decline is observed over the age of 60 years. From a clinical point of view, sarcopenia leads to functional impairment including poor endurance, slower gait speed and reduced mobility [3]. In addition, sarcopenia can predict falls, poor quality of life, disability and mortality [4]. There is now also evidence to propose that lack of muscle strength, or dynapenia, is an important factor in compromised well being in old age [3]. This demands recognition of the concept of muscle quality that is the strength produced per capacity per unit cross-sectional area. An understanding of the influence of aging on skeletal muscle mass requires attention to both the changes in muscle size and the changes in muscle quality. This is particularly important considering the potential effects of treatments suggested, in term of not only muscle mass improvement but also functional and physical performance.

PATHOPHYSIOLOGY OF SARCOPENIA

Sarcopenia is caused by a reduction in the number and atrophy of skeletal muscle fibers [5]. There is a significant loss in both type I and II muscle fibers with a significant decrease in the cross-sectional area of skeletal muscle fibers, which may be due to reduced muscle protein synthesis in old age. These findings indeed, reflect an imbalance between anabolic and catabolic mechanisms accompanying reduced muscle regeneration during advanced aging. Dual energy x-ray absorptiometry of aging muscle also shows increased collagen and fat deposits [6]. Besides the aging process itself, many factors may play a significant role in skeletal muscle decline over aging such as genetic susceptibility, lifestyle, chronic comorbidities and diverse drug treatments [7-9]. Progressive muscle atrophy leads to impaired mechanical muscle performance, especially a non-linear loss of maximum muscle strength. The ability to produce muscular power is significantly reduced compared to muscle strength [10]. An impairment in mechanical muscle function leads to reduced functional performance for daily tasks, including habitual walking, stair climbing and rising from a chair [4]. This explains why sarcopenia can predict negative outcomes related to disability (poor balance, walking speed, falls, and fractures). Another factor that is responsible for the loss in motor performance is the physiological change in the neuromuscular and central nervous system (CNS) that manifests during aging [11].

Neural functional alterations due to apoptosis can be observed at the peripheral level (losses in axons and motor end plates) as well as at the spinal level (loss in MNs). In particular, there is a significant reduction in both the number and width of large myelinated MN axons. Interestingly, it has been demonstrated that partially denervated muscle fibers can be reinnervated by the sprouting of surrounding surviving motor axons or motor end plates, which cause extremely large motor units (MUs) [12]. As previously mentioned, there is also an age-related alteration in neuromuscular function which in turn, leads to deficits in MN frequency firing, muscle agonist activation and antagonist co-activation. All of these factors account not only for the loss in muscle strength, but also for balance and coordination impairment. The formation of large MUs affects fine motor control and force steadiness. Finally, the literature strongly suggests that age-related decline in muscle IGF-1 may also play a significant role in developing sarcopenia [13]. IGF-1 promotes myoblast proliferation and differentiation, as well as in-

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creased production in the skeletal muscle through signaling pathways including phosphatidylinositol 3 (PI3) and MAP kinases along with calcineurin.

NON-PHARMACOLOGICAL TREATMENT

Physical Activity

Sarcopenia can have serious clinical consequences, thus its natural course and identifying safe treatment strategies is a crucial and necessary challenge. Lifestyle interventions including physical activity programs and specific nutritional supplementations are currently considered to hold the strongest and safest impact on improving sarcopenia [14-17]. Since the 1980s, several studies have confirmed that physical exercise is an effective countermeasure against sarcopenia. Regular physical activity has been shown to improve overall life expectancy, reduce the risk for physical disabilities and chronic disease progression by improving the physiological effects related to a sedentary lifestyle [18]. However, the type of physical exercise to be applied in older adults needs to be clearly defined in order to reduce any type of risk associated with physical exercise programs in elders. At the moment, the Institute of Medicine has defined "Physical activity" as all body movements produced through contraction of skeletal muscles [19].

Physical exercise can be distinguished in: 1) baseline activity; 2) leisure-time physical activity; 3) moderate-intensity physical activity; and 4) exercise. Baseline activity is defined as light-intense energy expenditure just above sedentary behavior such as walking slowly, standing and lifting lightweight objects [19]. According to this definition, even though individuals with a baseline physical activity level are above a sedentary lifestyle per se, they are considered inactive. Any type of physical activity above baseline activity is considered health enhancing. Leisure-time physical activity is generally considered aerobic and encompasses all popular leisure activities such as biking, golfing, etc. Moderate-intensity physical activity causes a significant rise in the heart rate and respiration. It requires reaching a moderate level of physical energy related to one's personal aerobic capacity [20]. Examples of moderate-intensity physical activities include brisk walking, dancing and swimming. Indeed, physical activities have clearly shown to be associated with beneficial impacts on comorbidities. Lastly, exercise is considered a physical activity that creates specific adaptations in a given physiological system. Exercise is generally planned, structured and repetitive. It is typically performed to achieve weight loss, improve health and/or physical fitness.

Types of Exercise

There are different forms of exercise: i) aerobic (endurance), ii) resistance (strength) training and iii) combined aerobic and resistance [1]. Other forms of exercise also include stretching and balance exercises. Aerobic exercise is a form of exercise performed over a lengthy time span (>20 minutes) characterized by repeated low-force muscle contractions with a low frequency in muscle fiber activation. Aerobic activity depends primarily on oxygen consumption to meet the energy demands and it enhances body composition, cardio-respiratory fitness and/or cardio-metabolic health. Resistance exercise is a form of exercise over intermittent time intervals (< 2-4 min of total work per muscle group) and is characterized by small high-force muscle contractions working against an applied load that cause high frequency muscle activation. Resistance training involves the use of weight machines, dumbbells, and barbells as resistance sources for improving muscle strength [21]. From a metabolic point of view, resistance training (also defined as strength training) relies on anaerobic metabolism, thus it mostly stimulates glycolytic metabolism and lowers mitochondria density in muscle cells, while aerobic training increases oxidative metabolism and mitochondrial density. In older persons, strength training may hold some advantages for improving neuromuscular function as compared to endurance training by increasing muscle strength and power [21-25]. Aerobic exercise (walking, jogging or biking) has a small impact on improving muscle mass and strength [26]. For example, using cross-sectional data, Klitgaard *et al*., [27] found that in a large sample of elderly men in different exercise training programs, elderly weightlifters maintained better muscle mass and strength as compared to swimmers. Even though the importance of aerobic exercise in cardio-respiratory capacity is widely recognized, its use in older patients with sarcopenia may not hold clear evidence in the presence of chronic comorbidities.

Resistance exercise is designed to improve muscle strength and mass. Thus, resistance exercise may hold more specific indications (primary preventive or treatment) for sarcopenia in order to protect against physical functional declines, disability and early all-cause mortality in older adults [28-29]. At the moment, low to moderate intensity physical activity programs on protecting or reducing disability remain unclear. Moderate-intensity resistance training seems to lack the significant impact on lean skeletal muscle mass and reduction in functional decline may manifest only when a high intensity exercise training program is proposed. Fielding *et al.,* [29] showed that a training stimulus of a suitable intensity (70-90% of 1-Repetition Maximum, 1 -RM) produced significant gains in muscle mass and strength in healthy older individuals [29]. Frontera *et al*., [15] (observed an increase in cross-sectional area muscle of the mid-thigh of 11. 4% and muscle strength (>100%) at the end of 12 weeks of high intensity training in older men. These authors also showed that following 12 weeks of progressive resistance training, a group of adult men (aging 60-72 years) had a 2-3 fold increase in 1-RM leg strength, with an 11% increase in muscle mass [16]. Other authors have investigated if these benefits could be found in low to moderate physical activity exercise programs. However, uptile now only a limited number of studies have been able to support this hypothesis. Resistance training in elderly persons has shown to produce significant improvements in muscle strength [15-16, 24, 29]. Even though such improvement is smaller in absolute terms, percentage increases are similar as compared to younger adults. In regards to the specific types of resistance training exercise activities, the use of a standard concentric exercise protocol, which allows for muscle loads of >1-RM, holds greater potential for muscle strength gains.

Physical Activity: Benefits

Improved clinical outcomes obtained from physical activity programs are widely known. Many studies have demonstrated how specific programs of physical activity can improve muscle mass and muscle strength associated with aging and sarcopenia [17-18, 30]. Their final effect indeed, is to reduce the risk of physical disability. In the Established Populations for Epidemiologic Studies of the Elderly (EPESE studies), routine physical activity was associated with a 3 year reduced risk of mortality [31]. In addition, moderate to vigorous leisure-time physical activity has been shown to lower the risk of poor physical functioning and, thus the onset of disability [32]. Using data from a standardized geriatric assessment tool, a moderate physical activity program was an independent prognostic indicator for community-dwelling elders [33]. Similarly, a cohort of older Finnish adults undergoing a high level of everyday physical activity (household chores, walking and gardening) were found to be associated with significantly smaller reductions in knee extension strength and grip strength after five years as compared to older adults in a sedentary lifestyle [34]. The efficacy of physical activity in preventing disability and/or functional worsening has also been found in randomized clinical trials (RCT). RCTs have demonstrated a positive effect of physical activity programs in frail elders. For example, in the FAST study, a randomized trial conducted among 439 community-dwelling older adults with knee osteoarthritis, self-reported physical function was associated with a significant enhancement in objective physical performance, walking speed and balance as compared to those in a health education program group [35].

Longitudinal studies have also indicated that regular physical activity is associated with extended longevity [36-37]. Participating in a physical activity program even late in the life has shown to improve functional autonomy and reduce mortality [37]. Physical exercise encompasses different factors that can stimulate aerobic metabolism, increase muscle strength, power and mass. Aerobic exercise training can significantly decrease resting heart rate, increase VO2 max, improve endothelial and baroreflex function, and reduce the arterial stiffness. Resistance exercise training can improve muscle strength, power and endurance and has shown to improve physical performance tasks related to everyday activities such as walking, standing from a chair and balance. Indeed, the combination of aerobic and resistance training should be considered fundamental for preventing and managing numerous chronic comorbidities often present in sarcopenic elders [32]. Progressive resistance training is considered effective and safe against sarcopenia even in very old geriatric patients. Binder *et al*., studied the effects of resistance training on 91 community-dwelling subjects with frailty syndrome (greater than 78 years of age) in a RCT [38]. These authors observed that after 3 months of supervised progressive resistance training, there were significant improvements in maximal voluntary thigh muscle strength and whole body fat-free mass. Muscle strength enhancements (up to >50% strength gain) usually manifest after 6 weeks of resistance training at a rhythm of 2-3 sessions per week [32]. Therefore, age should not be considered a barrier to the improvements in muscle mass and function following resistance exercise. Specific resistance exercise programs from RCT have proven to be relatively safe even in the presence of comorbidities, and can protect against falls, disability and losses in personal independence [38-39].

Considering the confirmatory findings from these reports, specific exercise programs are needed for elderly patients. However, the type of exercise program for disease prevention and treatment needs to be clearly defined, especially in frail elders. For example, even though most studies suggest that resistance training can be performed safely in an elderly population, it does not hold indications for use in patients with congestive heart failure because of a potential negative impact on left ventricular function [28]. Stretching and balance exercises are indicated in elderly people at high risk for falls and/or with mobility disability. Positive effects of exercise on physical function may be mediated by a direct effect on muscle strength, cardio-respiratory function and balance [40]. From a physiological point of view, regular exercise improves aerobic capacity of the patient, his muscle strength and endurance. The down-regulation of inflammatory system during physical activity may also play an important role in preventing physical impairment and disability. Regular physical activity programs have shown to lower C-reactive protein (CRP) and IL-6 in both younger adult and elderly population studies [41]. For example, the Lifestyle Interventions and Independence for Elders (LIFE) trial showed that greater physical activity was associated with a significant reduction in pro-inflammatory cytokine, IL-6, in elderly individuals, and this reduction was particularly found in those at a greater risk of disability [42]. In addition, several smaller trials have shown a positive effect of aerobic exercise training on reducing CRP and IL-6 in adults and older persons [43-44]. Therefore, even though the effect of physical activity on reducing pro-inflammatory biomarkers seems obvious, whether this reduction could protect against negative outcomes related to health conditions associated with inflammation was not tested.

Physical Activity: Guidelines

The main modifiable risk factor for sarcopenia is sedentary lifestyle behavior. Sedentary behavior is defined as a range of activities with energy expenditure ≤ 1. 5 times the energy expenditure at rest [45]. In other terms, sedentary behavior (essentially time spent sitting or lying down) increases with advancing age. It has been shown that the effects of a sedentary lifestyle are a loss of muscle mass and muscle strength results in muscle weakness and a vicious cycle begins with a further reduction in activity levels. Sedentary behavior is a risk factor for numerous chronic diseases and mortality among older adults [46-47]. Recommendations for adult and older people include combined endurance and strength exercises, performed on a regular schedule (at least 3 days per week). It is important to underline that individual targets should be analyzed to provide the best type of exercise program necessary, especially in the presence of pre-existing medical conditions.

General Recommendations

Start slowly: Start any type of activity should be initiated using a short time span with low intensity to gradually increase in order to minimize the risk of injury. In addition, if any changes in health status occur, activity plans should be re-evaluated [19].

Warm-Up And Cool Down: These activities are considered of extreme importance before (warm-up) and after physical activity (cool down) especially for older persons. They typically differ from the real training for slower speed or lower intensity. These exercises allow to gradually modify an individual's heart rate and/or breathing. For example, a warm-up with aerobic activity consists of short intervals of low-intensity movements (for example, walking for 5 minutes) [19]. Any type of training program should be individualized according to the presence of pre-existing chronic conditions, fall risk, individual abilities and fitness. Muscle strengthening programs and/or balance training should be considered before aerobic training in older persons with frailty syndrome.

Recommendations For Aerobic Exercise

ACSM/AHA recommendations [20, 48] for aerobic exercise in older adults place a great emphasis on general health promotion. The main suggestions are achieving routine aerobic physical activity and exercise patterns. Older adults are encouraged to perform 30-60 minutes of moderate-intensity physical activity per day (150-300 minutes per week), or at least 20-30 min per day (75-150 min per week) of vigorous intensity. Exercise should be performed at least three days/week. Exercise sessions should last a minimum of 10 minutes for intermittent aerobic activity. Every session should reach at least a total energy expenditure of 150/250 Kcal. Activities such as fast walking, swimming and biking are usually well tolerated in older individuals without frailty.

Recommendations For Resistance Exercise

The current ACSM/AHA guidelines suggest to perform resistance training on two or more non-consecutive days per week, using a single set of 8-10 exercises and at a moderate (5-6 of the rating of perceived exertion out of 10) to vigorous (7-8 of the rating of perceived exertion out of 10) level of effort that allows 8-12 repetitions [20, 48]. Prescription of resistance exercise should include a training period (1-2 times per week) in order to allow older adults to safely learn at low dosage with minimal sets. Following this period, a gradual increase in training dosage allows improvements in strength and mass. Progression in resistance exercise should be done according to the following: i) gradual intensity increase from moderate to vigorous; ii) gradual increase in the number of sets from a single set to as many as three or four sets per muscle group; iii) gradual decrease in the number of repetitions performed with a progressively heavier loading. Lower extremity functioning has shown to be strongly associated with clinical outcomes and mortality, which may be explained by loss in muscle mass and strength. Thus, it is essential to identify a training program with specific focus on improvements of lower extremity mass and strength to enhance overall functional abilities. In regard to flexibility and stretching, the ACSM recommends that flexibility exercises should be performed at least two days per week, ten minutes per day from moderate to intense including exercises involving areas of the neck, shoulder, elbow, wrist, hip, knee and ankle [48].

Nutritional Supplementation

Anorexia of aging, defined as loss of appetite and/or reduction of food intake, can lead to muscle wasting, decreased immunocompetence, depression and an increased rate of disease complications. In particular, a reduction in food intake along with an exercise decline leads to significant losses in muscle mass and strength [49]. Anorexia is strongly associated with a higher risk of quantitative malnutrition due to low-calorie intake. On the other hand, anorexia - especially in the early stage - may be correlated with a high risk of qualitative low intake of single nutrients, in particular, protein and vitamins [49]. It could be hypothesized that this selective malnutrition - for example, in terms of single macro- or micronutrients - is directly correlated with the onset of sarcopenia. Sarcopenia is mainly associated with atrophy of type II skeletal muscle fibers, which are mainly involved in producing strength. Muscle composition and function are regulated by muscle protein turnover rate. A loss in muscle protein synthesis may be due to many factors including an inadequate nutritional intake, a deficit in post-absorptive protein synthesis and due to an erroneous response to nutrients, especially amino acids [50]. It has been shown that physical exercise and oral nutritional supplementation may improve muscle mass through different mechanisms (Fig. **1**).

Amino Acids

Many studies investigated muscle anabolic responses following an oral or intravenous intake of amino acid mixtures in the adult and elderly persons [51-52]. These duties reported, in view of unchanged protein breakdown, a large increase in muscle protein synthesis with an associated reduction in protein turnover rate independently of the type of mixture. These findings suggest that muscle protein anabolism may be increased by a high amino acid disposal, thus underlining the importance related to the quantity of amino acids intake. This finding confirms that low doses of protein intake do not stimulate muscle protein synthesis as compared to higher doses [53], which may also be influenced by an impaired response to insulin [54]. These data indicate that a threshold exists for protein synthesis production. In addition, this threshold increases over the aging process and in the presence of proinflammation. In light of this, many authors have investigated if the dietary protein requirement differs between the young and older adults in order to identify the needed amount of protein intake in elderly persons [55]. These studies demonstrate that the protein requirement is increased in aged individuals, especially during bed rest. Currently, it is suggested to maintain a daily protein intake of 0. 89 g/kg/d and 1. 3-1. 6 g/kg/d in case of bed rest to a maximum of 2. 2 g/Kg/d in order to avoid renal function reduction [56]. Besides the quantity of protein, it seems important to reach the greatest protein availability through the best protein digestion rate which depends on the daily protein feeding pattern and on the quality of proteins (in particular, the content in essential amino acids). With regard to the first concept, it has been shown that an intermittent protein intake pattern may improve protein retention in elderly patients and that this effect persists several days after the end of diet [57]. This persistent effect may be due to the combination of high carbohydrates and low protein meals, which reduces protein breakdown because they induce postprandial hyperinsulinemia. Considering that the ingestion of a large quantity of proteins (90 grams) in a single meal is not able to enhance the anabolic response more than a moderate quantity (30 grams), most experts suggest a daily protein distribution of 30 g at each meal. Furthermore, in order to stimulate muscle protein anabolism, it is important to consume protein mixtures that are rapidly absorbed. Whey proteins have a high and fast absorption as compared to casein, which is considered a "slow" protein. Bovine milk contains a mixture of whey and casein proteins and this combination has been hypothesized to promote both rapid and sustained muscle protein synthesis as well as muscle breakdown reduction. Interestingly, milk ingestion increases muscle protein synthesis [58], especially during resistance exercise training.

Leucine

Leucine, a branched chain amino acid, is an essential amino acid and modulates muscle metabolism. Leucine stimulates muscle anabolism through the mammalian target of rapamycin (mTOR) which is a regulator of leucine effects on mRNA translation needed for skeletal muscle protein synthesis. Leucine also interacts with proteolytic mechanisms by attenuating skeletal muscle breakdown. Katsanos *et al*. [59] compared the effects of a single dose of branched chain amino acid with different amount of leucine on postprandial protein synthesis in elderly subjects. These authors found that subjects supplemented with higher dose had a significantly higher protein synthesis as compared to the subjects supplemented with lower doses. These data suggested that leucine supplementation could be an effective approach for treating sarcopenia, but further studies are still required needed. Recently, there is increasing interest on the impact of other amino acids or their metabolites on muscle protein synthesis, such as HMB, citrulline malate, ornithine alpha - ketoglutarate.

Beta Hydroxy Beta Methylbutyrate (HMB)

HMB is an amino acid metabolite, which modulates protein degradation through the inhibition of caspase-8, a protein implicated in cellular apoptosis. HMB has also been shown to directly upregulate protein synthesis by activating the mTOR signaling pathway and promote muscle tissue response to endogenous growth hormones such as IGF-1 [60]. It has been demonstrated that HMB alone or in combination with other amino acids, increased protein rates by approximately 20% [61]. Such increase was associated with improved muscle mass and strength, as well as physical performance at 3 grams per day. These data suggest that HMB represents a safe and useful oral nutritional supplement for elderly sarcopenic patients.

Citrulline Malate

Citrulline malate supplementation, a combination of an amino acid implicated in urea cycle and a tricarboxylic acid that increments arginine levels. Arginine produces nitric oxide which, in turn, controls many skeletal muscle physiological functions, such as mitochondriogenesis, muscle repair through satellite cell activation, contractile functions, glucose uptake and oxidation [62]. Recently, study was conducted to assess the benefits of citrulline malate supplementation in high intensity anaerobic performance (flat barbell bench press), which showed a significant improvement in physical performance (increased number of repetitions) in the citrulline malate group compared with placebo [62]. Even though these findings are encouraging for oral supplementation with citrulline malate in improving physical performance, additional studies in older frail persons are needed.

Ornithine Alpha-Ketoglutarate

Ornithine alpha-ketoglutarate (OAK), a precursor of amino acids such as glutamine and arginine, could represent an effective nutritional supplement in sarcopenia because OAK stimulates insulin secretion. A recent study testing the impact of OAK supplementation in malnourished elderly participants found positive effects on weight and body mass index [63]. Further studies are needed to assess potential effects on elderly without nutritional problems.

Essential Fatty Acids

The role of essential fatty acids (omega- 3 and omega- 6) in muscle metabolism has been recently reported. In particular omega-6 fatty acids, such as linoleic acid found in corn and sunflower oils, may promote the development of sarcopenia because they are the precursor for eicosanoids [64]. Recent studies have demonstrated

that a high ratio of omega-6/omega-3 can cause higher levels of IL-6, which interferes with IGF-1 mediated processes by blocking the protein p70s60k phosphorylation necessary for protein synthesis activation [65]. On the contrary, omega-3 fatty acids including linolenic acid and its metabolic products, such as eicosapentaenoic acid and docosahexaenic acid found in fish oil, promote muscle anabolism. In a recent study conducted in 3000 older adults, higher consumptions of fish oil were found to be associated with stronger grip strength [66].

Vitamin D

Vitamin D deficiency is a very common condition among older adults caused by reduced sunshine exposure, decreased kidney absorption and a reduced expression of Vitamin D receptors. Vitamin D is considered to play a pivotal role both in bone and skeletal muscle metabolism. In muscle tissue, vitamin D modulates: i) gene expression of IGF-1 factor-binding protein-3, ii) calcium channels of muscle membrane fibers, and iii) holds a neurotrophic effect on nerve conduction [67]. Vitamin D deficiency is associated with muscle atrophy, reduced muscular strength and power, impaired balance and consequent increased risk of recurrent falls and fractures [68]. Many studies have explored the effects of vitamin D supplementation on muscle mass and function. Sato *et al*., [69] investigated the impact of a period of vitamin D prolonged supplementation of 1000 UI (3-6 months) and found that such a supplementation was associated with an increase in the size of type II muscle fibers. Interestingly, other authors have also shown beneficial effects of vitamin D supplementation on muscle strength and falls [70-71]. Therefore, vitamin D supplementation should be considered an effective approach toward preventing and treating sarcopenia in older persons. Currently, there are strong recommendations to measure vitamin D plasma levels in elderly people, especially nursing home residents, and to begin daily oral supplementation (700-1000 UI) in patients with levels < 40nmol/l [72]. Considering the strong role played by both vitamin D and physical activity in muscle mass and strength, their use in combination may represent an ideal strategy for treating sarcopenia.

DRUG TREATMENTS

Angiotensin-Converting-Enzyme inhibitors (ACE inhibitors)

There is a strong evidence that ACE-inhibitors have positive direct effects on muscle composition and function. For example, their use in patients with congestive heart failure promoted the shift from type I to type II muscle fibers [73]. ACE inhibitors also hold an anti-inflammatory effect, as seen by lower levels of IL-6 and TNF-α plasma concentrations during treatment [74]. Furthermore, ACE-inhibitors can modulate the GH/IGF-1 pathway, which reduces angiotensin-II induced muscle loss [75]. The effects of ACE-inhibitors on muscle performance measures have been tested by various studies. Di Bari *et al.,* [76] conducted a study in over 2000 older persons and found that muscle mass was preserved in those using ACE-inhibitors. Another report demonstrated a significant improvement in physical performance measures (including the 6-minute walking test) in older patients using ACE-inhibitors compared to placebo [77]. In conclusion, ACE-inhibitors seem to represent a promising approach in order to reduce muscle loss but further evidence is required.

Statins

There is substantial literature that statins may hold a positive effect on skeletal muscle and physical performance. Statins may improve muscle weakness and fatigue by improving endothelial function through nitric oxide release, thus preventing muscle wasting [78]. Statins may also prevent sarcopenia by reducing inflammation. Indeed there is evidence of cholesterol-independent actions, namely "pleiotropic effects" of statin use on endothelial function including anti-oxidation and anti-inflammatory effects, modulation of immune activation and atherosclerotic plaque stabilization, decreased platelet activation, cytokine-mediated vascular smooth muscle cell proliferation [79]. In any case, it is important to underline that statin use has been associated with adverse effects on skeletal muscle mass [80]. These effects may be related to lower aerobic exercise tolerance caused by impaired mitochondrial function, decreased mitochondrial content and apoptotic pathways. In a longitudinal study performed in community-dwelling older adults, treatment with statins was associated with greater decline in strength and increases the risk of falls [81]. Therefore, statin use in sarcopenia older persons seems to remain limited.

Testosterone

It is widely known that testosterone levels gradually decline in aging men and such decline has been observed to be associated with losses in muscle mass, strength and function. Basic research confirms that testosterone administration prevents sarcopenia in hypogonadic men. The anabolic effects of testosterone include reducing protein breakdown [82] and increasing size of both types I and II fibers. Testosterone also holds positive effects on motor neurons by promoting nerve regeneration following traumatic damage. A recent study tested the effects of testosterone administration in frail older men and found a significant increase in lean muscle mass, strength and physical performance measures [83]. Unfortunately, use of testosterone in clinical practice is limited due to common side effects, such as prostate cancer, increased cardiovascular events, peripheral edema, gynecomastia, polycythemia and sleep apnea. Recent evidence suggests the use of testosterone in men with low serum testosterone levels to improve muscle strength [84].

Dehydroepiandrosterone (DHEA)

Studies have found variable results regarding the effects of DHEA supplementation on muscle mass and function in older adults. For example, some investigations conducted in aged men and women found that DHEA supplementation increased bone density, testosterone and estradiol levels, but it did not affect muscle size, strength, or function [85]. Improvements in strength and function may require a combination of DHEA and exercise, although this result was not observed in all studies. A recent review by Baker *et al*., [86] showed that the benefits of DHEA on muscle strength and physical function in older adults remain uncertain. Significant impact of DHEA on physical function or performance measures was not observed. Even though DHEA supplementation has shown to improve bone mineral density and sex hormone levels, it has not shown to significantly impact markers of sarcopenia (mass and strength).

Ghrelin

Ghrelin is a gastric peptide hormone in response to fasting and it regulates the sensation of hunger through melanocortin receptor antagonism. It stimulates the release of GH through the activation of GH secretagogue receptor. Ghrelin concentrations have been reported to be related with muscle mass [87], but very few studies had been conducted in older people. Therefore, it is not currently a valid option for sarcopenia prevention or treatment in older persons.

Creatine

The use of creatine has been recently proposed for the prevention and treatment of sarcopenia [88]. Even though there is evidence for the impact of creatine supplementation on sarcopenia in middle-aged and older adults, there are conflicting results. For example, improved muscle mass and strength in older adults were found in those using creatine supplementation in combination with resistance training [89]. However, another recent report did not find any enhancements with creatine supplementation on mass, total body mass, or upper extremity strength [90]. Based on these conflicting results, creatine supplementation is not recommended for treating sarcopenia in older adults [91].

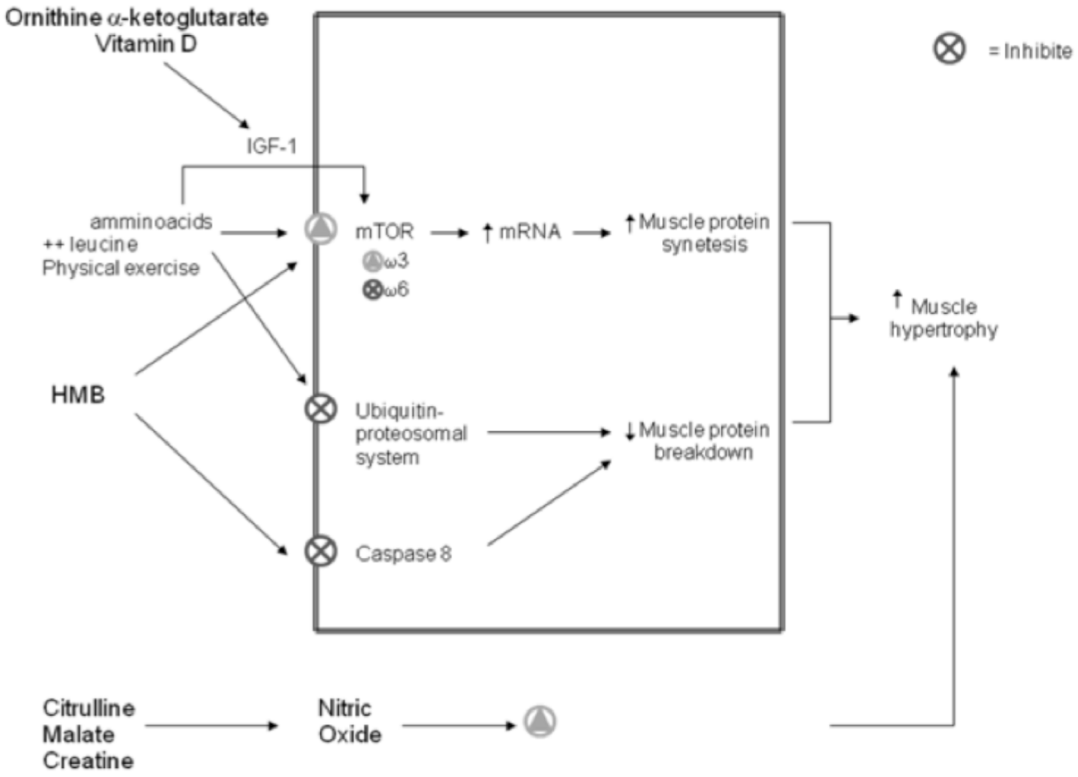

Fig. (1). Potential pathways related to nutritional interventions and specific drugs that may influence cellular events implicated in the regulation of muscle mass mTOR: mammalian target of rapamycin HMB: β-hydroxy β-methylbutyrate.

Selective Androgen Receptor Modulators

Synthetic androgen modulators such as Selective Androgen Receptor Modulators (SARMs) are potential alternatives to testosterone treatment. SARMs have the same anabolic effect on muscle tissue as testosterone, but they do not have the same side effects because of their improved tissue selectivity [92-93]. The first trials testing SARMs for physical performance outcomes have shown promising results. Treatment with Enobosarm has been associated with increases in lean body mass and stair climbing ability, without virilizing effects, in healthy older men and women and in patients with cancer cachexia [94]. However, another trial testing 6 month treatment with MK-0773 was found to be associated with increases in lean body mass, but not in muscle strength or physical performance in older women with sarcopenia and mobility limitations [95]. Another trial testing SARM, LGD-4033, showed increased lean body mass without affecting PSA levels in healthy young men [96]. As suggested by these initial trials, these agents may offer an important potential for future clinical indications in sarcopenia.

CONCLUSION

Combination of a specific physical exercise protocol and an adequate intake of amino acids may represent the best strategy to prevent and treat sarcopenia in older persons. Furthermore, even though several promising pharmacological approaches are currently under investigation, there are not any uses they are not yet available for treating sarcopenia in older frail persons in the clinical practice.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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