Pharmacological therapy of sarcopenia: past, present and future

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Summary

Sarcopenia, defined as the loss of muscle mass and function, has important consequences in terms of increasing frailty, disability, and social and healthcare costs. The diagnosis of sarcopenia should be considered in all patients presenting a decline in physical function, muscle strength and general health conditions.
Given that the progressive reduction of muscle mass and strength occurs also in aging, the switch towards a pathological condition has been established by combining diagnostic cut-offs and risk factors for reduced mobility, poor quality of life, and increased morbidity and mortality.
On the other hand, the introduction of different criteria for the diagnosis of sarcopenia has hindered the development of guidelines for the management of this disorder. The objective of the treatment of muscle wasting is to maintain or improve muscle mass, and both mechanical and metabolic muscle functions.
The management of sarcopenia should be multifactorial and interdisciplinary, including exercise, particularly muscle strengthening training, intake of proteins and vitamin D, and treatment of diseases causing muscle loss. To date there are no drugs that have been specifically approved for the treatment of sarcopenia (or other conditions causing reduced muscle function) although many substances are commonly used for this purpose. Several drugs have been studied to improve muscle mass and function, such as testosterone, estrogens, selective modulators of the androgen receptor (SARMs), ghrelin, anti-cytokines (IL-1, IL-6,TNF-α), and myostatin inhibitors. Identification of novel molecules targeting specific biological pathways whose stimulation or inhibition produces net anabolic effects on skeletal muscle might be a significant step forward for the treatment of muscle disorders.

KEY WORDS: exercise, sarcopenia, physical activity, cachexia, myostatin, SARMs, testosterone, ghrelin.

Introduction

Over the last few decades there has been a significant increase in the number of older people, leading to progressive ageing of the population, along with a higher prevalence of age-related diseases linked to functional decline in several organ systems (1). After the age of 60, skeletal muscle mass declines up to 3% per year, leading to a progressive reduction of functional capacity, which may be at the root of significant limitations in the performance of basic activities of daily living (ADL) (2, 3).
Sarcopenia defines the muscle deconditioning that occurs with aging, characterized by a reduction in muscle mass and strength, and in physical performance leading to disability, decreased health-related quality of life (HRQoL) and increased morbidity and mortality (4).
Rosenberg coined the term "sarcopenia" in 1989 and from that moment it has been a topic of great interest for researchers across different medical specialties; however, a heated debate still exists about several physiopathological and clinical aspects of sarcopenia including a universally accepted definition (5).
The Centers for Disease Control and Prevention (CDC) have recently assigned an ICD-10-CM code ("M62.84") to age-related sarcopenia recognizing it as an independently reportable medical condition (6, 7).
Undoubtedly, a major gap in the knowledge of sarcopenia concerns therapeutic approaches considering that evidences of pharmacological treatments are commonly scarce, mainly due to methodological issues in performing randomized controlled trials (RCTs) including the identification of the primary endpoints.
According to a recent position paper of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), a proper assessment of the person with sarcopenia requires to follow the International Classification of Functioning, Disability and Health (ICF) framework of the World Health Organization (WHO), which is based on the use of a common language for the definition and measurement of functioning and disability as well as providing a scientific basis for understanding changes in outcomes, in order to improve communication among different health-care providers (8). Indeed, this multidisciplinary working group

identified a core set of domains, including the ICF components within the core areas. In particular, the pathophysiologic manifestations of the disease, such as muscle mass, strength and performance impairments were considered as ICF body functions and structures; falls, mobility limitation, ADL disability, and poor HRQoL were included in the activity and participation ICF components, while resource use (direct and indirect costs) was included in the environmental factors. Even if primary endpoints might vary across different studies, this conceptual model could be a viable strategy to identify both a core outcome set of potential endpoints and target population definitions to be addressed in clinical trials for new treatments of muscle wasting conditions, thus enhancing study comparison and the evidence base (8).

However, methodological challenges about the operational definition and what outcome measures to be considered have hampered and delayed the research into promising therapeutic agents for sarcopenia, such as those targeting myostatin signaling and androgen receptor (AR).

The purpose of this narrative review is to provide the latest knowledge in pharmacological options for the management of sarcopenia and other forms of muscle wasting.

Pathophysiology of sarcopenia and heterogeneity of muscle wasting

The best treatment for a disease is the one that acts targeting the key pathogenic mechanisms underlying the disease process. Unfortunately, we still have only partial knowledge of the mechanisms that play a significant role in the genesis of muscle loss in terms of strength and/or function.

Commonly, muscle wasting is defined as the progressive and generalized loss of muscle mass that might occur also independently of aging, in many diseases, including acute (sepsis, burns, trauma) and chronic [chronic obstructive pulmonary disease (COPD), cancer-associated cachexia, diabetes, Cushing syndrome] disorders (9). Age-related muscle wasting, or sarcopenia, is commonly identified as a multifactorial geriatric syndrome, while cachexia represents a metabolic syndrome where inflammation is the key factor associated with an underlying disease and characterized by the loss of muscle mass with or without fat mass loss, so that the prominent clinical feature of cachexia is weight loss in adults.

Although muscle wasting comes from different causes and is frequently a complication of several chronic disorders, sarcopenia and cachexia primarily result from metabolic changes due to common molecular determinants (10, 11). Moreover, these conditions might share many clinical features, including body weight loss, fatigue, muscle atrophy, weakness, and loss of appetite (10, 12). On the other hand, muscle loss can be observed also in patients with autoimmune diseases, such as rheumatoid arthritis (RA), that are often characterized by a cachectic state without body-wide wasting probably due to normal energy balance and preservation of fat mass (13).

At the molecular level, muscle wasting occurring in sarcopenia is triggered by an unbalance between protein synthesis and breakdown in favour of catabolic events mediated by muscle-specific ubiquitin ligases (E3 protein, atrogin1/MAFbx and MuRF1) resulting in loss of muscle mass, decrease of fiber size and myonuclear content, reduction of contraction force and myofibrosis (10, 14). Cachexia is a complex metabolic syndrome characterized by severe muscle atrophy with or without loss of fat. In this condition, muscle wasting is caused mainly by the ubiquitin-proteasome system (UPS)-mediated proteolysis. However, also pro-inflammatory cytokines, such as TNFα, IL-1 and IL-6, seem to lead to muscle loss in cancer-associated cachexia. Moreover, in cancer cachexia, tumor factors induce overexpression of Pax7 thus inhibiting myogenic differentiation of both satellite and non-satellite muscle cells that results in muscle atrophy (15).

In the sarcopenic muscle other pathogenic factors play an important role, including a specific reduction of synthesis of myosin heavy chain (MyHC), whereas actin synthesis is not affected (4, 16). Indeed, MyHC IIa and MyHC IIx mRNA expressions decrease during aging, resulting in a decline of MyHC IIa and IIx proteins by 3% and 1% per decade, respectively (17). Furthermore, attenuation of muscle contractility occurring in older individuals may be explained by many factors, including the reduction in the fraction of myosin heads that bind to actin filament (18), the impaired excitation-contraction coupling due to reduction of maximal release of calcium from the sarcoplasmic reticulum (19), and loss of motor units (20).

In the aging muscle, mitochondrial dysfunction is considered as a key factor for reduced maximal oxygen consumption (21), walking capacity (22), muscle strength and endurance (23). However, mechanisms contributing to mitochondrial involvement remain largely unknown. In this regard, emerging evidence suggests that extrinsic factors, such as the aging milieu and denervation, can depress mitochondrial respiratory function (24).

Infiltration of fat tissue among the muscle fibers may be an additional independent variable for muscle atrophy. Indeed, accumulation of intermuscular adipose tissue (IMAT) is associated with muscle deconditioning and impaired muscle regeneration, and it is not surprisingly that fatty infiltrations occur in many muscle wasting conditions, such as myopathies, COPD, cachexia, and sarcopenia (25). Fatty infiltration could induce the secretion of proinflammatory cytokines that adversely affects the skeletal muscle (26) resulting in reduced protein synthesis. In particular, TNF-α and IL-6 might induce apoptosis of muscle fibers, especially those of type II (27). However, although fatty infiltration is closely linked to inactivity, the molecular players involved in this process are poorly understood.

According to the physiopathological aspects, in sarcopenia there are typical age-related hormonal changes, such as a decline of androgens levels that have a role in proliferation, myogenic differentiation, and protein metabolism or an overproduction of myostatin with a consequent inhibition of muscle protein synthesis through the AKT-mTOR pathway (28). Therefore, the knowledge of these aspects might be crucial in the identification of targets for the treatment of sarcopenia.

Treatment of sarcopenia

Nutritional/supplemental approaches

Identification of effective interventions to counteract muscle wasting diseases is a major research issue that requires understanding of the molecular mechanisms involved in muscle atrophy and weakness. To date, nutritional approach (i.e. intake of proteins and vitamin D) and exercise, particularly muscle strengthening, are the mainstay of the treatment of sarcopenia.

In order to reduce the risk of developing sarcopenia it is necessary an adequate protein, calcium and vitamin D intake; in particular, protein intake and physical activity have a key role in the anabolic stimulation of muscle protein synthesis (29).

Providing an adequate protein intake is a challenging issue in elderly subjects. In this population, poor dietary protein supply is dependent on several variables, including the anorexia of aging (30), the anabolic resistance (31), the intake pattern throughout the day (32), and the molecular content (33).

The PROT-AGE Study Group recommends an average daily intake of at least 1.0-1.2 g protein/kg, providing an amount of 25-30 g of proteins per meal (breakfast–lunch–dinner), in order to stimulate an adequate muscle anabolic response in older people (34). Pennings et al. suggested that intake of whey protein is more effective in enhancing postprandial protein synthesis in aged muscle, probably due to a more rapid digestion and absorption and a higher leucine content (2.5 g per day) compared with the ingestion of casein (35). Furthermore, branched essential amino acids (EAAs) increase appetite (36) and stimulate muscle protein synthesis (37).

Concerns about safety issues of protein intake in older people are mostly unfounded because only advanced renal disease (estimated GFR <30 mL/min) requires protein restriction to slow the progression of disease (34). According to the consensus statement of the ESCEO, a high-quality protein diet has a key role in promoting wellbeing in elderly (29).

A recent scoping review, the Italian Study Group on Healthy Aging by Nutraceuticals and Dietary Supplements (HANDS), reported that not only the leucine, but also beta-alanine, calcium, creatine, and vitamin D play a key role in maintaining or improving skeletal muscle mass and function during aging (38).

In particular, in older people, beta-alanine supplementation at 3.2 g per day for 12 weeks improves endurance capacity (39), calcium intake (1 g per day for 24 weeks) increases muscle mass and strength when combined with protein and vitamin D administration in the immediate post-exercise (40), creatine supplementation (5 g per day for 12 weeks) combined with resistance exercise (RE) improves both appendicular muscle strength and muscle mass, and leucine intake (2.5 g per day) might be beneficial to stimulate postprandial muscle protein synthesis (29, 41). A separate mention should be dedicated to vitamin D, whose actions in skeletal muscle tissue are receiving growing interest, and its role in muscle wasting diseases has substantial clinical implications, especially about the risk of falls (42).

It is well known that reduced expression of vitamin D receptor (VDR) in several tissues, including skeletal muscle (43), and high prevalence of vitamin D deficiency are common findings in older individuals (44, 45). Vitamin D deficiency prolonged over time results in a reduction of type II fibers, muscle atrophy and weakness (46), that in turn contribute to the onset of inactivity, increased risk of falls and "frailty" (47). However, evidences about vitamin D administration to counteract muscle wasting diseases are controversial. Two systematic review and meta-analysis investigating the effect of vitamin D supplementation on muscle strength, suggested a dose-response relationship reporting a significant effect of cholecalciferol on muscle strength, particularly of quadriceps muscles and in patients with severe vitamin D deficiency (48, 49). Similar findings were reported in a meta-analysis that suggested improvement of muscle strength and balance in older patients receiving a supplementation of vitamin D (800-1,000 IU per day) (50). On the other hand, a previous systematic review suggested that the combination of vitamin D and calcium appears to be more effective than vitamin D or calcium supplementation alone in improving muscle strength, balance and gait speed in older people (51). Moreover, vitamin D supplementation seems to enhance the effectiveness of other interventions, such as RE and nutraceuticals administration, in terms of improvement of skeletal muscle function, as demonstrated recently by Rondanelli et al. (52). In this study, the Authors showed that combined daily dietary intake of whey proteins, EAAs, vitamin D and exercise, were able to significantly increase muscle mass and strength in sarcopenic subjects.

Current understanding suggested a direct effect of vitamin D on muscle function to explain association of hypovitaminosis D and increased risk of falls and fractures in the elderly (53).

According to a re-analysis of the data of the trials included in the meta-analysis performed by Bischoff-Ferrari et al. in 2009, high doses of vitamin D (700-1,000 IU/day) reduced the risk of falls by 34% in the elderly (54). Similar findings were reported by Pfeifer et al. that used a daily combined supplementation of calcium and vitamin D at a dose of 1,000 mg + 800 IU to obtain a 27% reduction in the risk of a first fall after 12 months and 39% after 20 months of treatment (55).

In 2014, the American Geriatrics Society recommended a daily vitamin D intake of 1,000-4,000 IU combined with daily calcium intake from 500 to 1,200 mg for older individuals, particularly for those with comorbidities and with a higher risk of falls (56). Interestingly, a recent paper suggested that optimal 25(OH)D concentrations should be higher than 40 ng/ml to improve muscle function and that a vitamin D supplementation of at least 2,000 IU/day is required to reach these serum concentrations (57). Another viable option to enhance muscle function might be calcifediol that demonstrated to increase knee extension strength and muscle performance, and to provide a higher and faster increase in serum 25(OH)D compared with the native form (58). Moreover, daily calcifediol (20 µg) is more potent in improving vitamin D status, gait speed and balance compared with cholecalciferol at 6 months of treatment (59).

However, a high dose or intermittent vitamin D administration seems to be ineffective or harmful. Indeed, Glendenning et al. demonstrated that older women receiving 150,000 IU of cholecalciferol every 3 months up to 9 months, did not report statistically significant differences in terms of physical performance compared to placebo group (60). Furthermore, vitamin D dosage higher than 500,000 IU should be avoided, because of risk of adverse events, such as increased risk of falls and fracture (61).

Up to date, the current consensus of experts suggests a multimodal approach, including nutritional intervention, physical exercise, and pharmacological therapy in the treatment of muscle wasting. Indeed, a recent systematic review and meta-analysis confirmed that the combination of exercise and nutritional intervention is the only EBM-based therapeutic option for sarcopenia in older people (62).

Hormonal approaches

Androgens

A promising therapeutic strategy for muscle wasting conditions relies on the development of androgens as anabolic agents. However, several regulatory issues have hindered the use of testosterone (T) for this purpose, despite its ef-

fects on skeletal muscle, including hypertrophy of both type I and II muscle fibers (63), increase of myonuclear and satellite cell number (64), differentiation of mesenchymal multipotent cells into the myogenic lineage and inhibition of their adipogenic differentiation (65).

Androgens act in various non-reproductive tissues, including skeletal muscle, leading to changes in proliferation, myogenic differentiation, and protein metabolism, both in young as well as in older men (28). Moreover, anabolic effects of androgens are partly due to a crosstalk with other molecules such as Akt, myostatin, IGF-1, and Notch, and to non-genomic mechanisms that lead to increased calcium uptake in muscle cells (28). In recent years, T use has increased among elderly men for the treatment of late-onset hypogonadism (66). This condition is often characterized by low serum T (≤300 ng/dl) associated to fatigue and loss of muscle mass (67). Testosterone administration is able to counteract muscle atrophy and to a lesser degree muscle weakness with some benefits in functional outcomes, in a dose-dependent manner, independent of therapeutic exercise, both in young as well as in older men, particularly in androgen deficient elderly (68). However, patients receiving T supplementation require a careful evaluation of potential side effects, such as increased cardiovascular and prostate cancer risk, and peripheral edema, that hinder this approach in elderly individuals (69).

Recently, the TOM (Testosterone in Older Men With Sarcopenia) Study has been terminated and the results will be published soon. The study aimed to evaluate if T replacement in older men with low T levels could improve muscle strength, physical performance, and a sense of wellbeing, reducing the fatigue (70).

Dehydroepiandrosterone (DHEA), a steroid that can be transformed into sex hormones, might improve muscle strength and performance in older patients when combined with exercise and vitamin D supplementation (71); however no recommendation can be provided to sustain its use for the treatment of sarcopenia.

Concerns about safety profile of T led to the development of promising androgen analogues, such as selective androgen receptor modulators (SARMs), that are preferentially anabolic and that spare the prostate (72).

In 2013, Basaria et al. investigated the safety, tolerability, pharmacokinetics, and effects of ligandrol (LGD-4033), a non-steroidal oral SARM, on muscle mass, muscle strength, stair-climbing power, and sex hormones in healthy individuals. In this 3-week phase I study, 76 healthy young men were randomized to placebo or 0.1, 0.3, or 1 mg LGD-4033 daily (73). Ligandrol administration demonstrated to be well tolerated without change in prostate-specific antigen and increased lean body mass (LBM) and leg press strength in a dose dependent manner during a short period.

More recently, Dubois et al. elucidated the mechanism of action of another nonsteroidal SARM, enobosarm (GTx-024), suggesting both direct, mediated by activation of AR in satellite cells, and indirect effects, via non-muscle AR pathways mediated by muscle fibroblasts, of this drug that should be useful for the prevention of muscle wasting in different clinical conditions (74).

In a phase II placebo-controlled study, enobosarm increased LBM and improved physical function in patients with cancer-associated cachexia *vs* placebo (75). Furthermore, preliminary data of phase III studies (POWER1 and 2) including stage III or IV lung cancer patients with muscle wasting receiving enobosarm are encouraging in terms of muscle anabolic response whereas the findings about its efficacy on handgrip strength (HGS) and muscle power improvements are controversial (76).

In a randomized, double-blind, parallel-arm, placebo-controlled, multicenter, 6-month phase IIA study, Papanicolaou et al. investigated the efficacy and safety of MK0773 (TFM-4AS-1) 50 mg b.i.d in female with sarcopenia (77), reporting significant increase of serum IGF-1 as well as appendicular LBM in patients receiving MK0773 *vs* placebo. However, the study terminated because of an increased risk of failure.

Estrogens

In soleus muscle of ovariectomized rat, estrogens showed to increase relative number of myofibers expressing total (Pax7), activated (MyoD), and proliferating (BrdU) satellite cell markers following downhill running, suggesting a potential protection against post-exercise muscle damage and inflammation (78). On the other hand, weak evidence about the role of estrogens or selective estrogen receptor modulators (SERMs) on muscle mass growth and maintenance is available, although many individuals, either males or females, showed estrogen deficiency later in life (79) and some studies suggest that hormone replacement therapy (HRT) and exercise might play a role in enhancing gait speed and vertical jump height in post-menopausal women (80, 81).

Moreover, the deregulation of the apoptosis that affects satellite cells, as a result of imbalance of sex hormones in older people, might induce sarcopenia. In the future, second messenger inhibitors that counteract apoptotic processes could be useful in minimizing the loss of satellite cells, although it is still unknown how different apoptotic pathways are involved in the development of sarcopenia (82).

Therefore, the role of estrogen deficiency as risk factor for sarcopenia is uncertain, as its effect on muscle mass growth and maintenance is still weak (83).

Growth hormone

In an experimental model, the growth hormone (GH) supplementation modulates mitochondrial biogenesis, reducing age-related oxidative damage, inducing antioxidant enzymes in skeletal muscle, and enhancing muscle protein synthesis, thus acting as an hypertrophic agent (84). In a previous study Rudman et al. (85) showed that GH increased muscle mass also in older individuals. However, available evidence does not suggest any benefits of GH administration in terms of muscle function in elderly (86). Furthermore, GH supplementation showed an unfavorable benefit/risk balance, producing several adverse effects, such as soft tissue edema, hyperglycemia, musculoskeletal pain, and gynecomastia (87).

Ghrelin

In the last decade, improved understanding of multifactorial pathogenesis of muscle wasting conditions has driven research on novel agents addressing different and multimodal targets, such as systemic inflammation and appetite stimulation (88).

Ghrelin is a peptide produced by stomach cells that enhances GH secretion and regulates energy homeostasis by stimulating food intake and promoting fat storage via a GH-independent mechanism (89). This hormone ("hunger hormone") has also anti-inflammatory and pro-anabolic proper-

ties that could lead to the development of interesting treatment strategies for the management of sarcopenia. Therefore, it is not surprisingly that ghrelin and low-molecular-weight agonists of the ghrelin receptor are considered attractive candidates for the treatment of muscle wasting.

Preclinical and clinical studies reported significant effects of this hormone in regulating loss of skeletal muscle mass in chronic diseases, such as cancer, COPD, CKD, CHF, by different mechanisms, including enhanced mitochondrial-oxidative capacity and PKB phosphorylation, upregulation of GH-STAT5-IGF-1 axis in atrophied muscles, downregulation of proteolytic systems (activated-NFκB, muscle RING finger-1, and atrogin), and reduced expression of inflammatory molecules (CRP, TNFα, IL1β, IL6) (90, 91).

Anamorelin, a selective and highly specific ghrelin-receptor agonist, has longer half-life than ghrelin and is an orally available option for the treatment of cancer-related cachexia (92). Preclinical data suggest significant stimulatory activity on appetite, increased body weight, and stimulatory effect on GH secretion of this novel molecule. Phase 2 trials involving patients with cancer cachexia receiving oral anamorelin *vs* placebo over 12 weeks showed increased appendicular lean mass (ALM) and HRQoL without significant improvement of HGS (93). In two phase III trials (ROMANA 1 and 2) (94) on patients with advanced lung cancer, anamorelin 100 mg given orally once daily *vs* placebo confirmed its efficacy in increasing body weight, particularly LBM. Moreover, Authors reported improved appetite and similar overall survival along with no evidence of tumor growth stimulation. On the other hand, hyperglycemia, diabetes, and nausea were the most common adverse effects (5.3%, 2.1%, and 3.8%, respectively), that could be in part explained by the mechanism of action of ghrelin, which regulates glucose metabolism through different pathways (94, 95).

Anti-cytokines approaches

Muscle wasting is associated with an inflammatory milieu due to increased release of cytokines. Several targeted treatments (i.e. biological therapies), currently used to manage patients affected by chronic diseases, seem to counteract also muscle loss in these populations. In particular, monoclonal antibodies directed against proinflammatory cytokines, have demonstrated their effectiveness in preventing muscle wasting related to chronic diseases, such as inflammatory bowel diseases (IBDs) and cancer. Intravenous infusion of infliximab, an anti-TNFα monoclonal antibody, reversed sarcopenia in patients with Crohn's diseases, thus increasing muscle volume and strength in lower limbs, and decreasing serum IL-6 levels in 25 weeks (96).

IL-6 is a key mediator of inflammatory and immunologic responses in many chronic diseases (97) that regulates energy homeostasis and tissue metabolism, thus inducing marked cachectic changes in cancer experimental models (98). Current strategies inhibiting IL-6 functions have been investigated in both experimental and clinical studies (99). It was recently demonstrated that tocilizumab, an anti-IL-6 receptor antibody, can reduce anorexia and increase both weight and lower limb skeletal muscle mass in murine model of cancer cachexia (chemotherapy-resistant metastatic lung cancer), without affecting tumor growth (100). Also therapies targeting IL-1 seem to be promising options to inhibit pleiotropic actions of pathological inflammation, including muscle wasting. In particular, a phase 1 study on patients with advanced cancer cachexia showed that intravenously administration of MABp1, an anti-IL-1α human monoclonal antibody, significantly increased LBM with limited side effects after 8 weeks (101).

A recent review on possible therapeutic targets for sarcopenia suggested that emerging molecular approaches targeting myokines showed the most promising muscle anabolic effects (102). Indeed, a negative modulation of myostatin/ActRIIB signaling leads to muscle hypertrophy and increases strength and physical performance both in animals and in humans, along with an increased survival without promoting cancer proliferation in an experimental model of cachexia (103).

Bimagrumab (BYM338), a human monoclonal Ab anti-ActRII, able to bind ActRIIB 200-times more than ActRIIA, showed significant skeletal muscle growth *in vivo*, and greater hypertrophy compared to myostatin propeptide, which acts blocking myostatin only (104). The combination of BYM338 and glucocorticoids is able to both prevent skeletal muscle wasting and increase the recovery from muscle atrophy thus maintaining muscle function (104). In particular, a single dose of bimagrumab (30 mg/kg), increased LBM and volume of the thigh muscles *vs* placebo, with a favorable safety profile (the most common adverse events were muscle spasms and flu-like syndrome) in patients with sporadic inclusion body myositis (sIBM) (105). A recent randomized, double-blind, placebo-controlled study showed that a treatment with intravenous infusion of bimagrumab (30 mg/kg) over 16 weeks increased muscle mass and strength in community-living older people with sarcopenia and improved mobility in participants with slow walking speed (106). Moreover, it was shown that a single dose of bimagrumab 30 mg/kg i.v. might safely accelerate the recovery of thigh muscle volume and reversal of accumulated IMAT, following 2 weeks in a joint-immobilizing cast (107).

A multicentre, phase II trial on the humanized monoclonal anti-myostatin antibody LY2495655 (LY) in older adults with sarcopenia who recently reported falls, showed that patients treated with LY experienced a significant increase in appendicular LBM and muscle function (stair climbing time, chair rise with arms, and fast gait speed) compared with placebo at 24 weeks, suggesting its potential ability to reduce the risk of falls or physical dependency in older fallers (108).

Future approaches

MicroRNAs (miRs)-mediated regulation of several events such as cell proliferation, differentiation and death, DNA repair, oxidative stress response, protein expression in pathological states, is an exciting new area of research also for muscle diseases. These molecules are key components of gene regulation underlying the skeletal muscle phenotype. Once released into the extracellular environment, free or included into extracellular vesicles (EVs), miRs may convey functional information to distant sites. In particular, EVs containing miR-21 seem to be involved in cancer-related muscle wasting (109, 110). However, defining the role of miRs in skeletal muscle adaptation to different stimuli, including aging process and exercise, is very challenging.

It has recently been suggested that even *angiotensin-converting enzyme (ACE) inhibitors* could have beneficial effects on muscle, increasing the number of mitochondria and serum IGF-1 (111), but further studies are needed to better understand the effects of these molecules on skeletal muscle.

The *urocortin 2 (Ucn2)* is a peptide, commonly expressed in the central nervous system and other tissues, recently considered as a potential therapeutic option for sarcopenia, because of its relationship with muscle wasting, insulin resistance, obesity, and diabetes (112). Considering that glucose is an important energy source for skeletal muscle, the insulin resistance could have systemic effects for this tissue (113). Therefore, it might be taken advantage of molecules like Ucn2 in order to obtain an insulin-associated accretion of muscle mass (114).

Another therapeutic option might be the *ursolic acid* that increases muscle mass by inhibiting skeletal muscle gene expression related to atrophy, according to Kunkel et al. that showed how it could reduce the atrogin-1 and MuRF1 mRNA levels in mice. Moreover, a chronic treatment with ursolic acid induced even a muscle hypertrophy (115).

Recently, it was proposed the use of *5-aminolevulinic acid (ALA)*, a mitochondria-activating substance, which is synthesized from glycine and succinyl-CoA by the action of ALA synthase, in the management of sarcopenia. Fujii et al. showed that ALA significantly activated muscle mitochondria, increased muscle mass (with an associated increase in the content of branched-chain amino acids, such as isoleucine, leucine and valine, that stimulate muscle protein synthesis), and improved muscle strength, endurance and glucose tolerance in mice (116). Therefore, the activation of muscle mitochondria by ALA could give a contribution in the treatment of sarcopenia not only improving muscle mass and performance but also increasing the glucose tolerance.

It has been recently hypothesized a role of the satellite cells, the skeletal muscle stem cells, in the muscle fiber hypertrophy and, on the other hand, a correlation between an age-related decline of these cells and sarcopenia (117). However, to date, the satellite cell function as a target in the treatment of sarcopenia is still controversial (118).

Conclusions

Several therapeutic options targeting muscle wasting have been proposed in the last decades. However, the combined approach of exercise and dietary supplements remains the mainstay of both prevention and treatment for sarcopenia. Further studies are urgently needed, particularly aimed to clarify the current understanding about the disconnection between muscle mass and strength and the controversial findings of clinical trials.

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