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REVIEW

Pharmacologic Options for the Treatment of Sarcopenia

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Abstract Sarcopenia is now clinically defined as a loss of muscle mass coupled with functional deterioration (either walking speed or distance **or** grip strength). Based on the FRAX studies suggesting that the questions without bone mineral density can be used to screen for osteoporosis, there is now a valid simple questionnaire to screen for sarcopenia, i.e., the SARC-F. Numerous factors have been implicated in the pathophysiology of sarcopenia. These include genetic factors, mitochondrial defects, decreased anabolic hormones (e.g., testosterone, vitamin D, growth hormone and insulin growth hormone-1), inflammatory cytokine excess, insulin resistance, decreased protein intake and activity, poor blood flow to muscle and deficiency of growth derived factor-11. Over the last decade, there has been a remarkable increase in our understanding of the molecular biology of muscle, resulting in a marked increase in potential future targets for the treatment of sarcopenia. At present, resistance exercise, protein supplementation, and vitamin D have been established as the basic treatment of sarcopenia. High-dose testosterone increases muscle power and function, but has a number of potentially limiting side effects. Other drugs in clinical development include selective androgen receptor molecules, ghrelin agonists, myostatin antibodies, activin IIR antagonists, angiotensin converting enzyme inhibitors, beta antagonists, and fast skeletal muscle troponin activators. As sarcopenia is a major predictor of frailty, hip fracture, disability, and mortality in older persons, the development of drugs to treat it is eagerly awaited.

Keywords Sarcopenia · Muscle loss · Frailty · Muscle function · Low muscle mass

Introduction

Sarcopenia was originally defined as the age-related loss of muscle mass [1]. Subsequently, it became obvious to clinicians that it was muscle quality, rather than muscle mass that determined the function of muscle [2, 3]. This led to the suggestion that it was muscle power (force x velocity) which should be utilized to determine the role of muscle in determining outcomes. It was suggested that this should be termed dynapenia [4]. From this developed the concept of a sarcopenia-disability cascade (Table 1). Each component of this cascade can be separately measured and theoretically would lead to worse outcomes.

However, in 2010, Cruz-Jentoft et al. [5] published the "European Consensus on Definition and Diagnosis of Sarcopenia." They redefined sarcopenia as being muscle loss coupled with a decline in function (either walking speed or grip strength). This definition was validated as having a strong predictive ability of poor outcomes [6–8]. Subsequently, 4 other definitions of sarcopenia, all using gait speed and grip strength, as well as some measurement of low muscle mass have been published [9–12]. Each uses slightly different cut off points and 2 recognized the importance of having different cut offs for different ethnic groups. Woo et al. [13] compared each of these definitions and found that they had slightly different predictive abilities. Of the definitions, the Foundation of NIH (FNIH)

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Table 1 The sarcopenia-disability cascade

Term	Definition	Measurement
Sarcopenia	Loss of muscle mass not due to cachexia or peripheral vascular disease	Dual energy X-ray absorptiometry
		MRI/CT
		Ultrasound
		Bioelectrical impedance
		Midarm muscle circumference
		Calf circumference
Kratopenia	Loss of force i.e., strength	Isometric (dynometry)
		Isotonic
Dynapenia	Loss of power i.e., force × velocity	Walking speed
		Walking distance
		Stair climbing
		Jebsen hand function
Frailty	Physical phenotype (fatigue, resistance, aerobic, illness, loss of weight)	CHS (fried) criteria
		FRAIL questionnaire
		Study of osteoporotic fractures criteria Canadian (Rockwood) criteria
Disability	Loss of activities of daily living (ADLs)	Katz ADLs
		Barthel index
		Functional index measure

The modern definition of sarcopenia is a combination for sarcopenia and dynapenia or kratopenia (grip strength)

Table 2 The SARC-F questionnaire for sarcopenia

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0
		Some = 1
		A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0
		Some = 1
		A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0
		Some = 1
		A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of ten stairs?	None = 0
		Some = 1
		A lot or unable = 2
Falls	How many times have you fallen in the last year?	None = 0
		1–3 falls = 1
		4 or more falls = 2

Scoring: 1–10 total points possible; 0–2 for each component; 0 = best, 10 = worst; 0–3 healthy; ≥ 4 is symptomatic for sarcopenia

sarcopenia criteria using gait speed, but not grip strength, had slightly better predictive value for poor outcomes.

Based on the parallels between osteoporosis and sarcopenia and the finding that the 6 FRAX questions without Bone Mineral Density are highly predictive of fracture risk [14], we developed a simple sarcopenic questionnaire to predict poor muscle function (Table 2) [15]. This questionnaire has been shown to be a valid predictor of poor outcomes similar to that of the FNIH (walking speed) definition in both the United States and Asia [13, 16–18].

Sarcopenia has multiple causes and, as older persons develop a variety of diseases with increased production of cytokines, it may overlap with cachexia [19]. In this

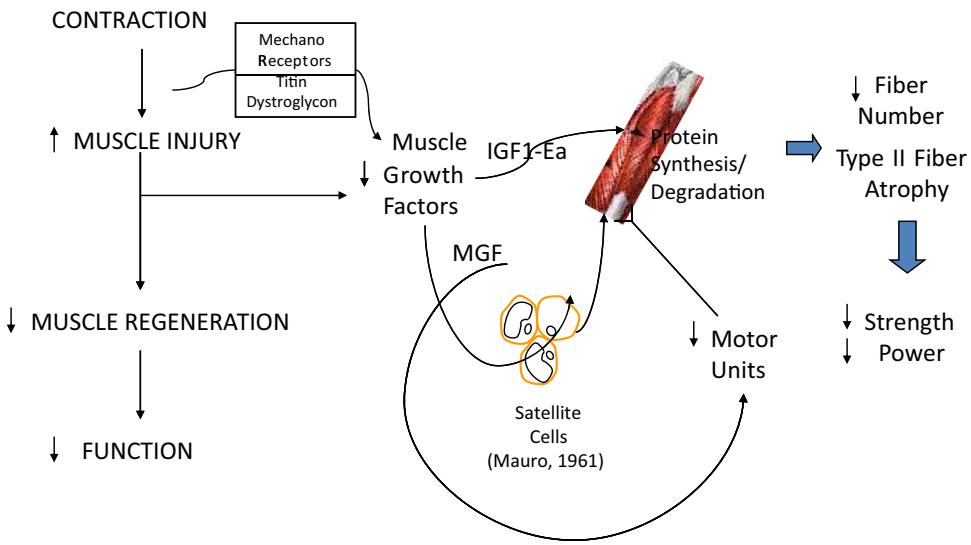

Fig. 1 Aging, exercise, and muscle injury

review, we will first explore the physiological causes of sarcopenia with a special emphasis on potential pharmaceutical targets. We will then review the available and developing treatments for sarcopenia.

The Pathophysiology of Sarcopenia

When muscle contracts this activates mechanoreceptors, i.e., titin and dystroglycan, and causes muscle injury. The mechanoreceptors increase the activity of muscle growth factors (IGF1-Ea and muscle growth factor) which increase muscle protein synthesis and recruit satellite cells and motor units. This leads to muscle regeneration and increased muscle function (Fig. 1). With aging, there is increased muscle injury with a decrease in muscle regeneration and function. This is due to a decrease in muscle growth factors leading to a reduction in the protein synthesis/degradation cycle and the activation of satellite cells and motor units. Anatomically, with aging there is Type II fiber atrophy resulting in decreased muscle mass, strength, and power [20].

Old muscle shows fiber size heterogeneity and fiber grouping with an increase in myosin heavy chain [21]. This differs from cachexia where fiber size variability is not seen. This is similar to the histological changes seen with Amyotrophic Lateral Sclerosis. Sarcopenic patients have a reduction in the motor unit number index (MUNIX) which is intermediate between that seen in healthy older persons and in patients with Amyotropic Lateral Sclerosis [22]. Further evidence of motor neuron degeneration is the increase in C-terminal agrin fragments in about a third of sarcopenic patients [23]. With aging, there is a 25 % loss of motoneurons leading to sprouting of small motor neurons that innervate Type II fibers leading to an eventual loss of type II fibers [24]. Circulating levels of ciliary neurotopic factor (CNTF), which stimulate motor unit formation, decline with aging [25, 26]. Older persons who have the null allele rs1800169 for CNTF have lower grip strength [27]. Axokine, a modified version of CNTF, was tried for weight loss due to its anorectic properties. The trials were suspended when subjects developed antibodies to CNTF.

Myokines

Besides CNTF, skeletal muscle produces a variety of myokines that can modulate muscle growth and repair (Fig. 2) [28–30]. Some of these, such as interleukin-6, may be predominantly produced by adipose tissue infiltrating muscle [31]. A number of these myokines have direct effects on muscle such as IGF-1, IGF binding proteins, myostatin, musclin, leukemia inhibitory factor and CXCL-1. Others such as VEGF-B, IL-8 and Follistatin-like 1 increase angiogenesis in muscles. Proteomics of muscle secretions should lead to the discovery of many more myokines that modulate muscle growth [30].

IL-15 is an inflammatory cytokine produced by muscle that increases contractile protein accumulation and causes myotube hypertrophy [32]. In vivo IL-15 reduces fast muscle fatigue and enhanced oxidative metabolism. Fatigue is an important component of the frailty phenotype that is separate from sarcopenia [33, 34]. IL-15 agonists or stimulants could be useful for the treatment of fatigue in older persons. Fatigue is, in part, related to a loss of muscle. A number of studies are examining the role of IL-15 agonists in advanced cancer (www.clinicaltrials.gov).

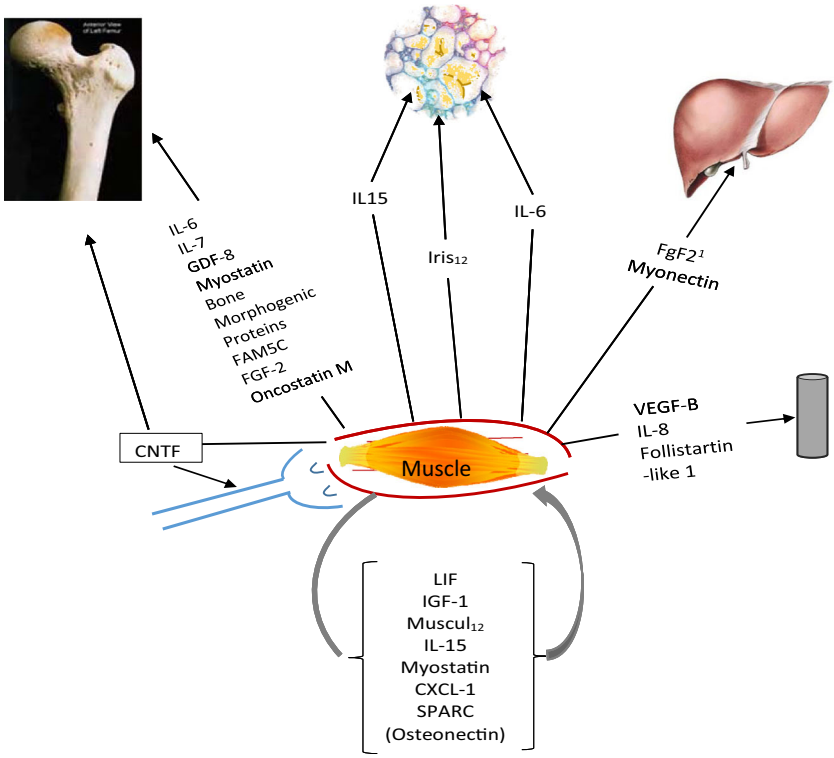

Fig. 2 Myokines and their target sites. *SPARC* secreted protein acidic and rich in cysteine, *IL* interleukin, *GDF* growth differentiation factor, *FGF* fibroblast growth factor, *BMP* bone morphogenetic protein, *LIF* leukemia inhibitory factor, *CXCL-1* chemokine ligand 1, *VEGF-B* Vascular endothelial growth factor, *CNTF* ciliary neurotrophic-derived factor

Genetics

Genes play a role in 65 % of the muscle mass and 50–80 % of muscle strength in older persons [35]. Studies on genes and muscle mass and strength have been rudimentary, with a number of results being controversial [36]. Angiotensin converting enzyme alleles have been shown to play a role in efficiency of muscle contraction. The alpha-actin 3 is responsible for anchoring the actin filaments to the 2-disk in fast twitch fibers. An ACTN3 gene deficiency is associated with reduced power and with endurance activity in men [37, 38]. Bradykinin increases muscle blood flow and the B_2R gene associated with high function is more frequent in endurance athletes. Other genes associated with muscle strength include CNTF, IL-15, collagen type, insulin growth factor II, myostatin, the vitamin D receptor, and the androgen CAG receptor. In older persons, expression of genes for insulin growth factor-1, myostatin, matrix metalloproteinase-2, ciliary neurotrophic factor, and myostatin correlated most optimally with training-induced strength gains [39]. Variants in the activin receptor 1B play an important role in human muscle strength [40]. Perilipin 2 is a protein associated with lipid droplets. Perilipin 2 is higher in older persons and is related to a decline in muscle strength and proteins associated with muscle atrophy, viz MURF1, and atrogin [41]. This suggests that expression of perilipin 2 may play a role in the development of obese sarcopenia [42, 43].

Mitochondria

The peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) regulates mitochondrial biogenesis and function and regulates muscle fiber adaptation to exercise [44]. There is a reduction of PGC-1α gene expression in old animals and older persons [45]. This reduction results in a low-grade inflammatory reaction with increased levels of IL-6 and TNFα. PGC-1α activity decreases functional loss of mitochondrial enzymes in old animals and protects muscle from damage [46]. Biochemically, PGC-1α inhibits FOXO and NFkB and thus decreases autophagy and the ubiquitin–proteasome systems. PGC-1α promotes mitochondrial biogenesis and fusion, thus maintaining ATP levels and reducing AMPK. Excess expression of PGC-1α damages heart and muscle. It has been suggested that increasing PGC-1α levels in sarcopenic tissue to physiological levels may be a key therapeutic approach to treating muscle wasting.

Mitochondrial dysfunction plays a major role in the pathogenesis of aging [47, 48]. Mitochondria control the production of cellular energy, free radical signaling, and can activate apoptotic pathways. The importance of bioenergetics in the development of sarcopenia is demonstrated by the correlation of ATP synthesis/oxygen consumption and walking speed in older persons [49]. Walking speed is a key component of the modern definitions of sarcopenia. In addition, with aging, there is often increased

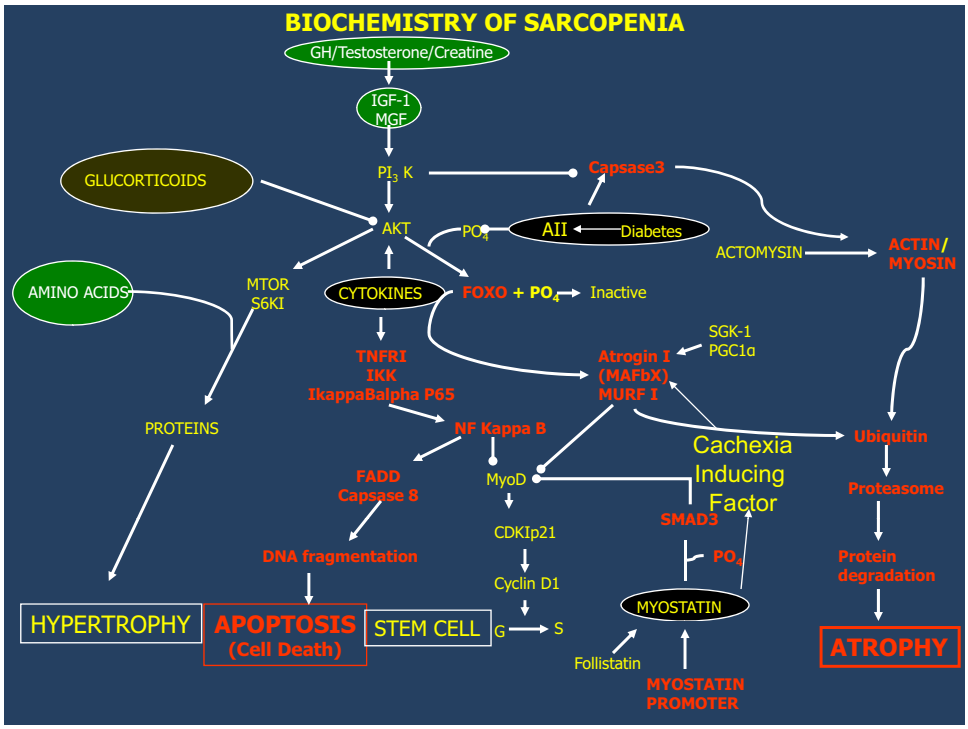

Fig. 3 An overview of biochemical regulation of muscle

fusion leading to giant mitochondria which are difficult to remove from cells and function poorly. Older mitochondria tend to lose their outer membrane increasing their propensity to apoptosis [50]. This is related to a decrease in $CisD_2$ gene expression in older humans. Transgenic mice with $CisD_2$ have enhanced longevity and improved muscle quality [51]. Finally, the decline in PGC1α levels with aging leads to translocation of BAX to the mitochondrial membrane with activation of the mitochondrial membrane pore and loss of cytochrome C. This results in mitochondrial apoptosis.

For all of the above reasons, targeting muscle mitochondria appears to be a reasonable approach to the therapeutics of sarcopenia. However, this is not that simple. Antioxidants tend to over reduce free radicals leading to loss of their necessary functions, e.g., nitric oxide effects on blood flow. Coenzyme Q10, a lipid soluble benzoquinone with a side chain of 10 isoprenoid units, freely diffuses across the inner mitochondrial membrane and couples electron flow to proton movement. It is also a membrane stabilizer but is a potent free radical scavenger. Mitoquinones are antioxidants targeted to accumulate in mitochondria. To date they have not been shown to be clinically useful. Another approach would be to develop substances that could replace the loss of CisD2. Substances that theoretically enhance nuclear/mitochondrial protein interactions include sirtuins (e.g., reservatol) and polyphenols. These have not yet been shown to have major effects on muscle function. Metformin enhances nitric oxide function and may prevent BAX translocation to the mitochondrial membrane. All of these approaches need to be further explored as possible therapeutic approaches to sarcopenia.

Vascular

Another component of the development of sarcopenia with aging is the reduction in blood flow to muscles [52, 53]. With aging, there is a decrease in endothelium-dependent vasodilation, due in part to decreased nitric oxide bioavailability [54]. These changes together with reduced lineal density of the perfused capillaries [55] lead to decreased microvascular oxygenation of muscles [55].

Protein Synthesis

At a basic level, protein synthesis and/or degradation are controlled by activation of the insulin or IGF-1 receptor (Fig. 3). This activates the phosphoinositide 3-kinase (PI3K)-AKT—mammalian target of rapamycin (mTOR) signaling pathway [56]. Increased mTOR, which is also stimulated by essential aminoacids, leads to increased protein synthesis. Both AKT and PGC1α block FOXO activity, thus decreasing the transcription of atrogenes. These include the muscle-specific ligases viz. muscle-specific RING-finger 1 (MURF1 or TRIM63) and atrogin 1. Atrogin 1 degrades proteins that enhance protein synthesis. MURF-1 and ubiquitin tripartite motif containing

protein 32 (TRIM32) directly control myofibril breakdown. MURF1 attacks the myosin binding protein and the myosin light chain eventually leading to destruction of the thick myosin filament. TRIM32 destroys desmin and then the Z-band and eventually the thin actin filament. At the same time TRIM32 directly inhibits PI3 K-AKT activity resulting in increased proteolysis. Myofibrils constitute the vast majority of muscle protein and their destruction leads to loss of muscle function [57, 58]. There is an increase in protein destruction and ubiquination in sarcopenia. Obviously, inhibitors of TRIM32 and/or MURF1 represent attractive therapeutic targets for treating sarcopenia.

MicroRNAs

MicroRNAs (miRNA) are small molecules which regulate posttranscriptional gene function by silencing RNA. They are cleaved in the nucleus by Drosha and then exported into the cytoplasm, where they are processed by DICER and combined with AGO to form RNA-induced silencing complexes. These then repress translation of mRNAs. Satellite cells decline with aging [59]. miRNAs play a central role in satellite cell quiescence [60]. The miRNAs (miR-1, miR-208, and MiR486) regulate satellite cell renewal by modulating Pax7. Decreased skeletal muscle miRNA expression in older persons is associated with a decrease in the function of the IGF-1/PI_sK/AKT pathway [61]. Exercise modulates the response of a number of muscle-specific miRNAs. There is evidence that miRNAs are sensitive to a variety of drugs such as mu opioids [62] and drugs for Parkinson's disease [63]. There appears to be tremendous potential to treat sarcopenia by modulating miRNAs. As more is known about the role of miRNAs in modulating muscle growth, it will also become possible to modulate specific RNAs by mimicking the positive patterns with phosphorothiolated antisenses.

Electrical stimulation of both thighs for 9 weeks improved timed up and go test, walking speed and 5 time chair rise [64]. This training led to an increase in diameter and percent of fast fibers. There was a stimulation of IGF-1 isoforms with a reduction of MuRF-1 and atrogin-1 leading to a reduction in proteolysis. Electrical stimulation also produces an increase of satellite cells. Electrical stimulation increased miR-29 which would decrease fibrotic infiltration of muscle. Overall, this study strongly supports the concept of electrical muscle stimulation for treatment of sarcopenia.

Parabiosis

Studies with parabiotic mice have shown that the combination of a young and an old mouse leads to rejuvenation in the muscle of the older mouse [65]. This was due to an increase in Notch signaling leading to an increase in satellite cells. The humoral agent responsible for this appears, in a large part, to be growth differentiation factor 11 (GDF11) [66]. Sinha et al. [67] have demonstrated that testosterone plays a permissive role in muscle mass and fiber cross-sectional area in parabiotic mice. These data suggest a role for GDF11 in treatment of sarcopenia.

Hibernating animals maintain their muscle structure during winter, raising the question of whether a circulating factor, in addition to shivering thermogenesis, is responsible for the protection of muscle during hibernation. The extensor digitorum longus muscle of the rat, when incubated with serum obtained from hibernating bears had a 40 % decrease in proteolysis, associated with a decline in cathepsin B and ubiquitin [68]. During hibernation, there is an increase in PGC-1α, which is associated with a decrease in FOXO and MURF-1 [69]. Serum- and glucocorticoid-inducible kinase 1 (SGK1) has been shown to downregulate proteolysis, autophagy and increase protein synthesis in hibernating animals [70]. This bypasses the classical AKT-FOXO pathway. SGK-1 may represent an important therapeutic target to prevent atrophy-induced muscle loss.

Table 3 provides a list of potential targets for future drug development. Figure 4 gives an overview of the major factors so far demonstrated to be a component of the pathophysiology of sarcopenia. Many of these already have drugs available or under development. These and their physiological rationale will be discussed in the next section.

Management of Sarcopenia

The primary treatment of sarcopenia is resistance exercise [71–73]. As was shown by the LIFE study, aerobic exercise can also decrease functional decline in lower limb muscles [74]. Exercise has also been shown to be an important therapeutic approach to reversing frailty [75]. There is evidence to support that excess protein [1–1.2 g (kj day)] may also enhance muscle mass and, to a lesser extent, function [76–80]. This is particularly true for leucine enriched essential amino acids (whey protein) [81]. Essential amino acid supplementation prevents muscle mass loss due to bed rest [82]. A recent multicenter study has shown that whey protein together with vitamin D increased both muscle mass and stair climb [83]. There is some evidence for synergistic effects of exercise and protein to enhance muscle function [84–86]. Vitamin D supplementation increases muscle strength without increasing muscle mass or power [87]. Vitamin D is more effective in older persons and those with low vitamin D levels. It also decreases falls in persons who are vitamin D deficient [88].

Table 3 Potential future targets for drug development to treat sarcopenia

Target	Function
1. TRIM 32 inhibitors	Inhibits destruction of desmin, the 2-band, thin actin filaments, and proteolysis
2. Ciliary Neurotrophic Factor agonist	Enhance motor neuron endplate function
3. Myokines activators and inhibitors	Modulate muscle function
4. PGC1α agonist	Mitochondrial biogenesis
5. CisD protein replacement	Improves outer permeability membrane of mitochondria
6. Sirtuins/reservatol/polyphenols	Enhance nuclear/mitochondrial protein interaction
7. Biguanides	Increase nitric oxide function and inhibit BAX translocation to mitochondrial membrane
8. Nitric oxide (Isorbide dinitrite)	Enhance muscle blood flow
9. MicroRNAs (miR-1, miR-29, miR208, and miR486) modulators	Modulate satellite cell quiescence
10. RNA antisense	Modulate RNA function
11. Growth differentiation factor (GDF11)	Satellite cell rejuvenation
12. Serum- and glucocorticoid-inducible kinase 1 (SGK1)	Reduces proteolysis and autophagy and enhances protein synthesis

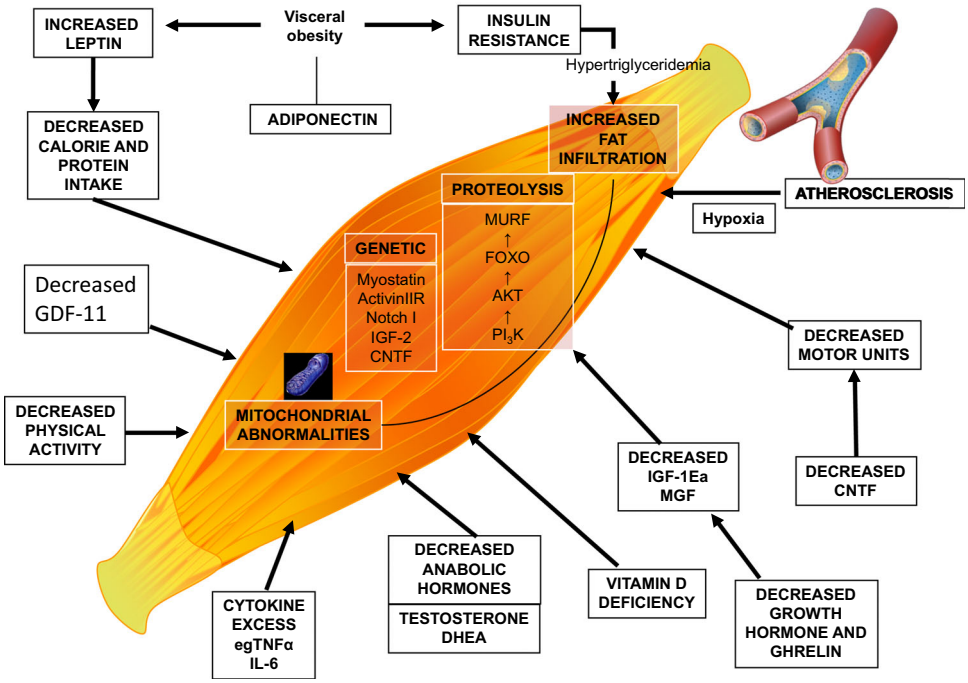

Fig. 4 Factors involved in the Pathophysiology of Sarcopenia. *GDF* growth differentiation factor, *IGF* insulin growth factor; *MGF* mechanogrowth factor, *DHEA* dehydroepiandrosterone, *CNTF* ciliary neurotrophic factor, *IL-6* interleukin 6, *TNFα* tumor necrosis factor α

At present, no drugs have been shown to be clinically more therapeutically effective.

Testosterone

Testosterone levels decline at the rate of 1 % per year from 30 years of age [89, 90]. This decline in testosterone is associated with a decline in muscle mass and strength [91]. Since the original studies showing that testosterone increased muscle strength in older persons [92–94], numerous studies have shown that in low doses testosterone increased muscle mass and decreases fat mass [95] and in higher doses increased both muscle and power [96]. In frail older persons [97–99] and in persons with heart failure [100–103] testosterone increased both strength and walking distance. Testosterone improves muscle strength in women as well as in men [104]. In frail older persons,

testosterone in combination with a protein supplement decreased hospitalization [105].

In lower doses, testosterone increases protein synthesis resulting in an increase in muscle mass [106, 107]. In high doses, testosterone activates satellite cell recruitment and reduces adipose stem cells [108]. Testosterone effects on muscle cells bypass the WNT system and activate β-catenin [109]. This leads to increased myogenesis and cell cycling and decreased adipogenesis.

While testosterone as a therapeutic agent has been utilized since the 1940s, there is a fear that it will produce excessive side effects [110]. A meta-analysis of the controlled studies of testosterone in older males found no increase in mortality [111]. Whether or not it increases cardiovascular events, and particularly in the first 3 months after administration, remains controversial [112, 113]. Persons with diabetes mellitus have accelerated sarcopenia [114–116], and a recent study in diabetics found a decrease in mortality in diabetics receiving testosterone [117]. Nevertheless, this fear of negative effects from testosterone has driven the exploration for selective androgen receptor modulators (SARMs) which may be, theoretically, safer. At present, of the drugs developed and being developed for sarcopenia, testosterone remains the most efficacious and safest. In view of the fact that testosterone also increases bone mineral density and bone strength [118, 119] and osteoporosis often co-exists with sarcopenia (osteosarcopenia), it would seem that more clinical attention should be paid to the potential role of testosterone for treating sarcopenia. Two major trials are presently underway and these may help determine the place of testosterone in the management of sarcopenia, osteoporosis, and frailty (The Testosterone Trial in Older Men—www.clinicaltrials.gov and the T4DM trial—www.t4dm.org.au).

Anabolic Steroids/Selective Androgen Receptor Modulators (SARMs)

Nandrolone is an injectable anabolic steroid. It increased fiber area and muscle mass, but there is no evidence that it increased strength [120–122]. In three studies of persons with hip fracture, it had a nonstatistical improvement in functional status [123].

MK0773 (TFM-4AS-1) is a 4-aza steroidal drug that has androgen gene selectivity. In females, it increased IGF-1 as well as stair climbing power and gait speed [124]. This study was terminated because of an increased signal for cardiac failure. In women with sarcopenia, it increased muscle mass, bilateral leg press, and stair climbing power but not gait speed (www.clinicaltrials.gov). The study in males was reported at the 90th Endocrine Society in 2008. It showed anabolic effects of MK0773.

SARMs are androgen receptor ligands that band to the androgen receptor with differing sensitivity compared to testosterone [125]. Steroidal SARMs were first developed in the 1940s. More recently, a number of nonsteroidal SARMs have been developed [126].

LGD-4033 is a nonsteroidal, orally active SARM. The phase I trial showed an increase in muscle mass, but no effect on fat mass in a 21-day trial [127]. BMS-564929 is also in phase I trials.

In a 12-week study, enobosarm increased total lean mass and stair climb [128]. In female patients with cancer, enobosarm increased lean mass compared to baseline, but not significantly compared to placebo [129]. In 2 phase 3 trials, it maintained body mass and improved stair climb in one of the 2 trials in patients with cancer [130].

Overall, these studies of SARMs have shown no advantage over testosterone.

Growth Hormone/Insulin Growth Factor-1

Rudman et al. [131] originally showed that growth hormone increased lean body mass in older men. The excitement created by their original data was dampened by finding that a growth hormone treatment for a year led to a variety of side effects such as carpal tunnel syndrome and gynecomastia [132]. Subsequently, growth hormone has been shown to increase muscle mass but not muscle strength in older persons [133]. A combination of growth hormone and testosterone increased muscle mass at 8 weeks and 1 repetition maximum strength only by week 17 [134]. Growth hormone, which produces its effects through the release of liver-derived IGF-1, also increased nitrogen retention [135]. Adverse effects include joint and muscle pain, edema, carpal tunnel syndrome, and hyperglycemia [136].

There are marked reductions of circulating IGF-1 with aging [137]. Both low and high levels of IGF-1 are associated with increased risk of cardiovascular disease. Similarly, there is limited evidence that circulating IGF-1 is associated with muscle power. A single small study of IGF-1 in older persons found an increase in side effects viz. orthostatic hypotension, gynecomastia, myositis, and edema [138].

Ghrelin

Ghrelin is produced from the fundus of the stomach. It increases food intake and growth hormone. These effects of ghrelin are due to the hypothalamic release of nitric oxide [139]. Ghrelin increased food intake and produced muscle mass gain in persons with cancer [140, 141]. The ghrelin agonist, anamorelin, increased food intake, and muscle mass, but not strength in persons with cancer cachexia

[142, 143]. Macimorelin is another ghrelin agonist under development.

Capromorelin, a ghrelin receptor agonist, was tested in older sarcopenic individuals [144]. It increased lean mass, tandem walk, and stair climb at the end of treatment for a year. MK-0677, which also activates the ghrelin receptor to increase growth hormone, was studied for 24 weeks in persons with hip fracture [145]. Over this period, it increased ability to stair climb and also decreased falls. The treatment was associated with an increase in heart failure.

Overall, while ghrelin agonists will increase food intake and muscle mass, it is unlikely that they will produce a significant effect on function in persons with sarcopenia.

Myostatin and Activin II Receptor Inhibitors

Myostatin or growth differentiation factor-8 is produced in skeletal muscle and prevents muscle growth and satellite cell production [146]. Myostatin activates the Activin IIR receptor to increase SMAD (Fig. 3). Lack of myostatin in animals leads to "double muscled" cows (Belgian Blue and Piedmontese). Heterozygote deletion of myostatin in whippets leads to an increase in running ability, while homozygotes are more muscular but not as good runners. A homozygote muscle deletion of myostatin in a young boy resulted in an increase in muscle mass [147].

In humans, creatine, together with resistance exercise, results in an amplification of the normal decrease in myostatin with resistance training alone [148]. Creatine produces a small increase in strength in persons with muscular dystrophy [149]. Myostatin monoclonal antibodies increase muscle mass in mice [150]. In humans with muscular dystrophy, a myostatin antibody (MYO-029) enhanced muscle mass [151]. Muscle fiber diameter increased in the 10 mg/kg dose. Side effects included urticaria and aseptic meningitis at high doses. Another myostatin antibody (AMG 745) increased lean body mass and decreased fat after 28 days in persons on androgen deprivation therapy for prostate cancer [152]. Diarrhea, confusion, and fatigue were more common in the persons receiving active drug. LY2495655 increased muscle volume and handgrip strength in persons with advanced cancer (www.clinicaltrials.gov). REGN1033 (GDF8 antibody) has reported promising effects on muscle at the sarcopenia meeting in Barcelona.

An activin II receptor ligand trap (ACE-011) increased bone mass and strength in monkeys [153]. ACE-031 in 48 postmenopausal women increased lean mass and thigh muscle volume after a single dose [154]. Another ligand trap ACE-083 is also under development. Side effects including telangiectasia, epistaxis, and changes in gonadotrophin levels resulted in the company stopping the development of these compounds.

Table 4 Approaches currently available or being developed to treat sarcopenia

Modality	Effect	Side effects
Resistance exercise	Increase muscle mass, strength, and power	Potential for falls; muscle injuries
Protein (essential amino acids)	Increase muscle mass; synergy with exercise to increase muscle strength and power	Minimal increased creatinine levels
Testosterone	Increase muscle mass, strength, power, and function	Fluid retention; increased hematocrit; short term worsening of sleep apnea; effects on prostate cancer; possible increase in cardiovascular events
Selective androgen receptor modulators (SARMS)	Increase muscle mass; small increase in power	Increased cardiac failure
Growth hormone	Increase nitrogen retention; increase muscle mass	Arthralgia; muscle pain; edema; carpal tunnel syndrome; hyperglycemia
Ghrelin agonists	Increased muscle mass and appetite	Fatigue; atrial fibrillation; dyspnea
Myostatin antibodies	Increased lean body mass and handgrip	Urticaria; aseptic meningitis; diarrhea; confusion; fatigue
Activin 11R antagonists	Increase thigh muscle volume, muscle mass, and 6-min walk distance	Acne; involuntary muscle contractions
Angiotensin converting enzyme inhibitor (perindopril)	Increased distance walked; decreased hip fracture	Hypotension; hyperkalemia; muscle cramps; numbness
Espindolol (B_1/B_2 adrenergic receptor antagonist)	Maintains muscle mass; increased hand grip strength	?
Fast skeletal muscle troponin activators (Tirasemtiv)	Improves muscle function	?

Inclusion body myositis is a rare autoimmune disorder. It occurs in persons 50 years and older. Its hallmark is amyloid inclusion bodies. Bimagramab is an activin receptor inhibitor. In persons with inclusion body myositis, bimagramab increased thigh muscle volume, lean muscle mass, and 6-min walking distance [155].

Espindolol (Mixed Agonist/Antagonist B1,B2, B3 Activity)

Espindolol is the S-enantiomer of pindolol. It increases muscle mass and decreases fat mass in older animals [156]. A phase II trial showed an increase in muscle mass and a decrease in fat mass [157]: It also increased handrip strength.

Angiotensin Converting Enzyme Inhibitor (Perindopril)

Perindopril has been shown to increase distance walked in older persons with left ventricular systolic dysfunction [158]. It also improved 6-min walking distance in older persons with functional impairment [159]. There was, however, no enhancement in persons undergoing exercise training [160]. In addition, in the HYVET study perindopril decreased hip fracture [161].

Fast Skeletal Troponin Activitors (Terasemtiv)

There are drugs which amplify motor neuron input, resulting in improved muscle power and muscle fatigability. Terasemtiv slowed the rate of decline in muscle strength [162]. In persons with peripheral vascular disease, terasemtiv increased work done in a bilateral heel raising test (www.cytokinetics.com/ck2017357).

Conclusion

Sarcopenia (loss of muscle mass and muscle function) is a strong predictor of frailty, disability, and mortality in older persons. At present resistance exercise is the primary treatment for sarcopenia. Supplementation with essential amino acids, creatine, and vitamin D may enhance the effect of resistance exercise. The effects of testosterone on muscle include increased muscle power and function. At present, the side effects of testosterone, though minimal in placebo controlled trials, remain a possible limitation to its use. No other drugs under development have been shown to be more potent than testosterone. All the drugs under development have their own set of side-effects and will clearly be more expensive than resistance exercise or injectable testosterone (Table 4). There are numerous potential targets for enhancing muscle function, and the development of new drugs for sarcopenia represents a potentially exciting clinical area.

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