Pharmacological targeting of age-related changes in skeletal muscle tissue

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Abstract
Sarcopenia, the age-related loss of skeletal muscle mass and function, increases the risk of developing chronic diseases in older individuals and is a strong predictor of disability and death. Because of the ongoing demographic transition, age-related muscle weakness is responsible for an alarming and increasing contribution to health care costs in Western countries. Exercise-based interventions are most successful in preventing the decline in skeletal muscle mass and in preserving or ameliorating functional capacities with increasing age. However, other treatment options are still scarce. In this review, we explore currently applied nutritional and pharmacological approaches to mitigate age-related muscle wasting, and discuss potential future therapeutic avenues.
Introduction

Sarcopenia is a geriatric syndrome characterized by the loss of skeletal muscle mass and function that develops gradually during aging [1]. Data from cross-sectional studies indicate that muscle mass and strength reach their peak values between the second and the fourth decade of life and start to decline continuously from the third and fifth decade [1]. Besides neurodegenerative events and mental decline, sarcopenia is the main cause for loss-of-independence, the inability to perform daily tasks and social interactions, frailty and falls, admission to nursing homes, and thus reduced overall quality of life, morbidity and mortality. Muscle aging involves complex qualitative and quantitative changes in the neuromuscular system [2]. However, the etiology of sarcopenia is still poorly understood and it is unknown to what extent the development is an inevitable consequence of aging and/or the result of a combination of additional factors including a decrease in physical activity, nutrient deficiencies and genetic predisposition. Age-related co-morbidities such as cardiovascular diseases, obesity and type 2 diabetes, the decline of hormones [e.g. estrogens, androgens and growth hormone (GH)] as well as age-associated chronic, systemic low-grade inflammation likely also contribute to the development of sarcopenia and may account for inter-individual variations in the age of onset and slope of progression.

Due to the demographic transition, the world’s geriatric population is continuously expanding, resulting in an ever-increasing number of sarcopenic patients, tightly linked to enormous personal, social and financial burdens. To date, exercise and an active life-style are the most effective interventions for preventing the decline in skeletal muscle mass and preserving or even ameliorating functional capacities with increasing age. In fact, a recent systematic meta-analysis of muscle morphology and performance in master athletes suggests that exercise training preserves physical function, muscular strength and body fat levels with increasing age similar to that of young, healthy individuals [3]. However, to overcome issues with compliance, adherence, and, in the case of co-morbidities, exercise intolerance, other approaches would be of high clinical relevance. Unfortunately, efficient pharmacological avenues are still lacking. In this review, we discuss applied and emerging nutritional and pharmacological strategies for the treatment and prevention of sarcopenia with regard to benefits, limitations and open questions.

Age-associated anabolic resistance

In general, skeletal muscle mass is determined by the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB) controlled by an overarching process called proteostasis. Thus, loss of muscle mass often is the result of a negative net protein balance arising from a reduction in MPS and/or increase in MPB. Dietary protein and exercise are two independent stimuli for MPS and act synergistically leading to a net increase of skeletal muscle mass when combined [4]. Aging is
associated with an attenuated response of MPS to both, protein ingestion [5] and exercise [6], a phenomenon known as anabolic resistance. Thus, analogous to the impaired sensitivity to insulin in insulin-resistant patients (e.g. in type 2 diabetes), skeletal muscle becomes less sensitive to essential amino acids and/or training stimuli. A decline in muscular activity, chronic, systemic low-grade inflammation (including that of skeletal muscle) as well as impaired digestion and/or absorption of dietary protein are hypothesized to contribute to this reduced sensitivity. Therefore, exercise, anti-inflammatory interventions and specific dietary modifications may help to overcome age-related anabolic resistance.

**Nutritional Strategies**

For a variety of reasons, under- and malnutrition are often observed in elderly individuals, leading to inadequate caloric and/or deficient marco- and micronutrient intake [7, 8]. Accordingly, dietary interventions are of high interest to mitigate sarcopenia, even though only limited and inconsistent evidence exists, primarily based on cross-sectional studies [9]. Nevertheless, several micro- and macronutrients, including protein, essential amino acids, omega-3 (n-3) polyunsaturated fatty acids (PUFAs) as well as caloric restriction (CR) as dietary intervention have been suggested to exert beneficial effects on sarcopenia and therefore, are discussed in the following sections.

**Protein and amino acids**

Besides exercise, protein intake provides the main anabolic stimulus to skeletal muscle. Upon protein ingestion, amino acid levels rise in the blood (hyperaminoacidemia), stimulate MPS and suppress MPB. Basal (i.e. unstimulated) levels of MPS and MPB often do not change with increasing age [10, 11]. In contrast, there is emerging evidence that older individuals show a compromised stimulation of MPS (and maybe also a reduced inhibition of MPB) in response to protein ingestion [5], which may be further exacerbated by physical inactivity and short periods of bedrest [12]. However, this blunted response to dietary protein can partially be overcome with higher amounts of protein per single meal [5]. In particular, protein quality i.e. the content of the amino acid leucine appears to be crucial [13, 14]. Of all amino acids, leucine and its metabolite β-hydroxy-β-methylbutyrate (HMB) [15] have the most potent ability to activate the mammalian target of rapamycin complex 1 (mTORC1), which subsequently phosphorylates the downstream signaling targets ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) that facilitate translation initiation and stimulation of MPS (Figure 1) [16]. The effect of leucine can further be potentiated by co-ingestion of other branched-chain amino acids or the whole spectrum of essential amino acids [17]. Of note, Katsanos et al. [14] observed that the leucine content in a mixture of essential amino acids needed to be higher in older compared to younger men (1.7 g vs. 2.8 g) to stimulate MPS. Therefore,
it has been proposed that older individuals may benefit not only from eating higher amounts of protein, but also from using high quality (i.e. leucine rich) sources and optimally, evenly distribute the intake throughout the day to robustly stimulate MPS in a sustained manner [18]. However, 6% of men and 12% of women aged 70 years or above do not meet the United States’ Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) for protein [18]. Moreover, since the current EAR and RDA for protein intake in elderly adults might be too low [18], the number of people getting insufficient amounts of protein may be underestimated. Nevertheless, the general recommendation of a higher protein intake for elderly adults as an antisarcopenic stimulus is still debated. Recent observational studies indicate that higher protein intake is associated with better preservation of muscle mass and function with aging [18] and results from short-term intervention studies suggest that improving dietary protein quality and quantity may partially reduce the negative effects of short-term physical inactivity on muscle mass [19, 20] and function [19-21]. On the other hand, clinical trials so far have failed to demonstrate the effectiveness of protein supplementation to promote muscle mass and function in elderly adults [22-24] and only a few long-term longitudinal trials assessing the potential protective effect of higher protein intake on muscle mass and function with aging exist [25]. Furthermore, results on the enhancing effect of protein supplementation on resistance training-mediated improvements in muscle mass and strength of older adults have been conflicting [26]. Thus, more long-term intervention trials will have to demonstrate the efficacy of protein intake at different levels and qualities to mediate benefits to the aging population.

Omega-3 polyunsaturated fatty acids

N-3 PUFAs modulate the biophysical properties of cell membranes and are involved in lipid signaling processes. The n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exhibit anti-inflammatory properties [27] and are frequently consumed as fish oil supplements. Besides potential effects on chronic, systemic inflammation, n-3 PUFAs may also sensitize skeletal muscle to the anabolic stimuli of resistance exercise and dietary amino acids [28]. In an 8-week supplementation trial, n-3 PUFAs potentiated MPS and increased mTORC1-p70S6K1 phosphorylation in response to a hyperaminoacidemic-hyperinsulinemic clamp in older adults [28]. Sedentary elderly men and women (60-85 years old) participating in a randomized controlled trial of 6-month fish oil-derived n-3 PUFA supplementation further functionally benefitted from improved average isokinetic power, thigh muscle volume, handgrip strength, and one-repetition maximum [29]. However, despite these positive reports, the exact effects of n-3 PUFA supplementation on skeletal muscle of older individuals remain to be determined. In particular, the time course of EPA and DHA integration in muscle cell walls, as well as the exact dosing have to be evaluated [30]. For example, 3 months of daily supplementation with 1.3 g of n-3 PUFAs was not affecting muscle strength and physical function [31], whereas a similar
6-month treatment was sufficient [29]. Moreover, in a recent trial, a combination of 3 g daily fish oil with exercise training for 3 months enhanced exercise-induced gains in isometric torque and muscle quality (strength per unit muscle area) in female participants but, curiously, not in males [32].

In summary, there is increasing evidence that n-3 PUFAs can act as anabolic enhancers on skeletal muscle of elderly people. The effects of n-3 PUFAs have mainly been attributed to their anti-inflammatory properties, but the fact that n-3 PUFA supplementation regimens seem to have similar anabolic effects also in younger adults [33, 34] may indicate the presence of a more direct effect on skeletal muscle. Thus, further studies are required to elucidate the underlying mechanisms and to prove the efficacy of fish oil supplementation as sarcopenia treatment.

**Caloric restriction**

CR increases lifespan in several species ranging from yeast to mammals and potentially even primates [35]. CR dampens mTORC1 activity [36] based on the reduced abundance of nutrients and insulin, as well as from the activation of the potent mTORC1 inhibitor AMP-dependent protein kinase (AMPK). Metformin, a putative AMPK activator, is currently being tested for sarcopenia [37]. In general though, CR as an anti-sarcopenic intervention seems counterintuitive, since activation of mTORC1 is linked to increased MPS and hypertrophy. However, mTORC1 activity might be pathologically elevated in old muscle, at least in mice [38] and one human cohort [11]. As chronic activation of mTORC1 signaling has been associated with muscle wasting [39], sarcopenic elderly could thus benefit from CR interventions aimed at inhibiting mTORC1 activity. Importantly however, inhibiting mTORC1 signaling with rapamycin also blocks essential amino acid induced stimulation of MPS [40], prevents or blunts the increase of MPS and/or muscle mass following resistance exercise in both rodents [41] and humans [42], but not basal, post-absorptive protein metabolism [43]. The use of dietary or pharmacological means to inhibit mTORC1 activity in old muscle thus remains to be explored. CR however elicits other, non-mTORC1-related potential benefits for sarcopenic patients, e.g. the ability to reduce chronic, systemic low-grade inflammation, as demonstrated in an aging rat model [44]. Furthermore, CR-mediated stimulation of mitochondrial function and oxidative metabolism could contribute to therapeutic effects [45], potentially mediated by sirtuins and the peroxisome proliferator activated receptor γ coactivator 1α (PGC-1α) [46]. Finally, the CR-associated reduction in obesity and other co-morbidities such as cardiovascular pathologies and type 2 diabetes could further alleviate the health of elderly individuals.

**Anti-inflammatory drugs**

A persistent, systemic low-grade inflammation is highly associated with a number of chronic diseases [47, 48]. In skeletal muscle, inflammatory cytokines activate molecular pathways involved in muscle
mass regulation, leading to an imbalance in anabolic and catabolic processes [49]. Aging has also been associated with increased levels of circulating pro-inflammatory markers [50, 51], which negatively correlated with muscle mass and strength in elderly adults [52]. In fact, this state of chronic, systemic low-grade inflammation has been termed “inflammaging” [53]. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce systemic low-grade inflammation at least in part by inhibiting cyclooxygenases (COX-1 and COX-2), the key enzymes of leukotriene and prostaglandin synthesis, mediators of inflammation and pain. Long-term treatment of aged rats with the non-selective COX inhibitor ibuprofen improved inflammatory markers, preserved the anabolic response to food intake and increased muscle mass [54]. Notably however, concomitant administration of ibuprofen with exercise in young rodents impaired skeletal muscle regeneration [55], whereas the potent COX-1-selective NSAID indomethacin boosted inflammatory processes in skeletal muscle and brain [56]. Similarly, high doses of NSAIDs compromise muscle strength and hypertrophic adaptations to resistance exercise in young individuals [57]. In contrast, resistance training combined with daily ibuprofen consumption did either not affect [58, 59] or even increased muscle mass [60] and strength [61] in elderly populations. These findings indicate that the usage of NSAIDs in sarcopenia remains to be explored, but may potentially be relevant in later stages of sarcopenia or in conditions with inflammatory comorbidities [63].

Inhibitors of the renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone (RAA) regulatory circuit controls blood pressure and electrolyte balance. The enzyme renin converts angiotensinogen to angiotensin I, which in turn is cleaved by the angiotensin-converting enzyme (ACE) to the active hormone angiotensin II. The effects of RAA activity on skeletal muscle are significant, but yet still poorly understood. For example, reduced expression of ACE has been associated with a greater anabolic response to training [64]. Inversely, infusion of angiotensin II increases proteolysis and decreases local and systemic insulin-like growth factor 1 (IGF-1) levels [65]. Muscle-specific IGF-1 expression prevents angiotensin II-induced skeletal muscle wasting [66]. Besides their potent effects on cardiovascular and endothelial function, inhibitors of the RAA system could have anti-inflammatory effects by decreasing angiotensin II-induced NF-κB (nuclear factor κB) activation, thereby blocking the production of interleukin 6 (IL-6) and C-reactive protein (CRP) [63]. This effect might complement the improvements in cardiac output, hemodynamic parameters and endothelial function that positively affect muscle metabolism and function [67]. For example, in a cohort of 641 aging women with hypertension, the use of ACE inhibitors was associated with a lower decline in muscle strength and walking speed over a three-year period [68]. The ACE inhibitor perindopril improved six-minute walking distance in a double-blind randomized controlled trial with 130 geriatric patients [69]. In contrast, the ACE inhibitor fosinopril had no significant effect on the inflammatory profile (CRP, IL-6 and PAI-1 levels) [70] or physical performance [71] of adults with
elevated cardiovascular risk. Discrepancies in the outcome might be explained by differences in inflammatory profiles of the participants at baseline [63]. In old mice, the angiotensin receptor type 1 (AT1R) inhibitor losartan prevented immobilization-induced muscle loss [72], improved measures of physical function and decreased IL-6 levels [73]. Whether losartan has similar effects in humans is currently investigated in a clinical trial with older adults [49].

**Myostatin pathway and activin type II receptor function**

Myostatin and its downstream signaling pathways are strong negative regulators of muscle mass. It is unclear whether myostatin and related factors, e.g. GDF11, contribute to the disease etiology of sarcopenia [74, 75]. Blocking myostatin signaling might nevertheless be a promising strategy to increase muscle mass in many wasting contexts, including sarcopenia [49]. In old mice, myostatin knockout results in muscle fiber hypertrophy, increased activation of satellite cells *in vitro* and improvements of muscle regeneration [76, 77]. Disappointingly though, neutralization of the myostatin protein with humanized myostatin antibodies (LY2495655 and REGN1033) only slightly increased appendicular lean body mass and gait speed in sarcopenic elderly, and did not ameliorate grip strength despite the achieved gains in muscle mass [78, 79]. Since the myostatin receptor complex (activin type IIB receptor and activin receptor-like kinase 4 or 5) is activated by multiple ligands, blockage of receptor function might be a more promising approach [80]. Different strategies to reduce activity of this receptor are currently being pursued and clinical trials with myostatin pathway inhibitors are in progress, including in sarcopenic patients [49].

**Testosterone and selective androgen receptor modulators**

Cross-sectional and longitudinal studies in aging men indicate that testosterone levels gradually decrease between the third and the ninth decade of life, with high inter-individual variability [81-84]. This aging-associated reduction in androgen production and/or bioavailability is thought to contribute to muscular atrophy and the development of sarcopenia. Testosterone treatment stimulates muscle protein synthesis and induces muscle fiber hypertrophy in a dose-dependent manner [85] and, therefore, testosterone replacement therapy has been used as treatment strategy for sarcopenia. For example, in hypogonadal pre-frail and frail elderly men, daily dermal testosterone gel application for six months increased serum testosterone levels and preserved muscle thickness [86]. Testosterone also improves muscle strength in women [87]. Even though the effects of testosterone on the balance between MPS and MPB are thought to be predominately mediated by its binding to the androgen receptor (AR) thereby inducing IGF-I transcription and/or interacting with phosphoinositide 3-kinase (PI3K) to activate the PI3K-Akt/protein kinase B (PKB)-mTORC1 pathway, the exact mechanism of testosterone action in skeletal muscle has not been fully elucidated so far [88]. Moreover, despite
promising effects on muscle mass [89] and in some cases also force [90], improved muscle function was not achieved in all trials. Importantly, due to the high number of serious adverse effects (e.g. increased risk of prostate cancer and cardiovascular events, erythrocytosis, behavioral abnormalities, and virilization in women) [91-93], androgen replacement therapies are non-viable treatment options for general prescription if applied in a non-substituting manner. To circumvent the problem of adverse effects that are mostly linked to androgenic and/or non-skeletal muscle tissue-linked effects of androgens, selective androgen receptor modulators (SARMs) that retain anabolic, but lose androgenic properties might be a safer treatment option, even if skeletal muscle-specificity cannot be achieved. For example, the SARM enbosarm elicits a dose-dependent increase in total lean body mass as well as improvements in physical function in both older male and female participants, importantly without an increased risk of adverse effects [94]. Treatment with MK-0773, another SARM, increased lean body mass of sarcopenic elderly women but had no effect on muscle strength [95]. There was no evidence for androgenization induced by MK-0773, but several participants in the treatment group showed elevated transaminase levels. Different SARMS are currently being evaluated in clinical trials [49].

Growth hormone and insulin-like growth factor 1

GH is synthetized in the adenohypophysis and affects skeletal muscle indirectly by stimulating IGF-1 release by the liver, which in turn acts on skeletal muscle via the IGF-1-receptor (IGF-1R) and subsequent activation of the PI3K-Akt/PKB-mTORC1 pathway [96]. Accordingly, in mice with a skeletal muscle-specific ablation of the IGF-1R, GH administration does not increase muscle mass [97]. In humans, aging is associated with a decrease in GH secretion and lower levels of circulating IGF-1 [98]. In line, GH replacement therapy increases lean mass in older men with a relative GH-deficiency [99] and daily injection of recombinant GH prevented a decline in muscle cross-sectional area (CSA) during two weeks of single leg immobilization and led to a greater increase of muscle CSA during the following six weeks of rehabilitation training compared to a placebo treated group [100]. Similarly, various forms of human recombinant IGF-1 are being assessed for their therapeutic value in sarcopenia and other muscle wasting diseases [101, 102]. However, while GH and IGF-1 treatment may be beneficial in individuals with relative deficiencies, non-replacement therapy of both hormones might be hampered by severe adverse effects, including cardiovascular complications and glucose intolerance [103].

Vitamin D

The synthesis of the active form of the hormone vitamin D requires skin exposure to sunlight (i.e. UVB light) [104]. Accordingly, older adults are at higher risk of vitamin D deficiency due to limited sun exposure, decreased capacity for cutaneous vitamin D synthesis and reduced intake and/or absorbance of vitamin D from the diet [105]. Even though the main function of vitamin D entails the
regulation of calcium homeostasis and bone metabolism, skeletal muscle tissue also expresses the vitamin D receptor (VDR) [106] and knockout of the VDR results in muscular abnormalities [107]. Moreover, an increasing body of literature suggests a relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and skeletal muscle physiology in elderly adults. Vitamin D deficiency is associated with reduced muscle mass and function, whereas vitamin D treatment seems to improve these parameters [108, 109]. Moreover, VDR expression has been reported to decrease in muscle with age [110] and VDR gene polymorphisms may further modify the risk of sarcopenia, even though the exact contribution of different genotypes has yet to be identified [111].

Given the blunted responsiveness of elderly adults to dietary protein and resistance exercise that often correlates with low levels of vitamin D, it has been suggested that vitamin D supplementation may overcome anabolic resistance. For example, participants with higher 25(OH)D levels and higher dietary protein intake at baseline responded with greater gains in muscle mass to a vitamin D- and leucine-enriched whey protein diet for 13 weeks [112]. Furthermore, a one year vitamin D supplementation together with a HMB-, arginine- and lysine-containing drink resulted in increased fat-free mass in elderly adults without exercise training, but only in those individuals with a 25(OH)D status of ≥30 nmol/ml [113]. Similarly, vitamin D supplementation significantly increased muscle strength in older adults [114] and treating women with low vitamin D levels resulted in 10% increase in muscle fiber size [115]. In fact, resistance exercise and vitamin D supplementation provide reciprocally beneficial effects on strength gains [116] and bone mineral density compared to exercise or vitamin D supplementation alone [116]. Despite these observations, the underlying mechanisms of vitamin D action in skeletal muscle remain enigmatic. Moreover, while the effects of vitamin D supplementation may be more pronounced in individuals with lower levels [109, 117], the optimal dose, route of administration, dosing intervals and treatment duration require further investigations [118]. Finally, a recent analysis showed no benefit of vitamin D supplementation on clinically relevant outcome measures such as fractures, falls or bone mineral density [119].

**Ghrelin**

The gastrointestinal peptide hormone ghrelin has originally been discovered as an endogenous ligand for the growth hormone secretagogue receptor 1a that has the ability to stimulate GH release [120]. Subsequent studies revealed a broad spectrum of additional physiological functions of ghrelin, including the regulation of feeding behavior by stimulating appetite and food intake as well as the promotion of anti-inflammatory processes [121]. Ghrelin treatment has accordingly been suggested to counteract muscle wasting in sarcopenia in several different ways. First, given that elderly people often lose appetite, ghrelin may increase food intake, helping these individuals to meet adequate energy and nutrient goals to maintain their muscle mass. Accordingly, in studies on cancer patients suffering
from cachexia, synthetic ghrelin receptor agonists increased food intake and muscle mass [49]. However, other functional parameters, such as grip strength, could not be ameliorated by ghrelin treatment. Second, ghrelin-stimulated GH release and the subsequent increase of hepatic IGF-1 production might help to enhance or restore IGF-1 signaling in sarcopenic elderly. Capromorelin, a ghrelin receptor agonist, elevated GH and IGF-1 levels and improved lean mass, tandem walk and stair climbing after one year of treatment in older adults with mild functional limitations [122]. In a one-year randomized double-blind placebo-controlled crossover trial with healthy elderly adults, the ghrelin receptor agonist ibutamoren (MK-677) restored GH and IGF-1 to levels observed in young adults [123]. However, reliable functional endpoints could not be assessed due to the short duration and low sample size of the study. In a later trial, MK-677 was given to people recovering from a hip fracture for a period of 24 weeks. Participants showed higher IGF-1 levels and mild improvements in stair climbing and gait speed but unfortunately, the trial had to be stopped early because of adverse effects [124]. Third, numerous animal studies suggest anti-inflammatory properties of ghrelin and ghrelin receptor agonists [121]. However, human trials demonstrating reduced inflammation with ghrelin treatment have yet to be conducted. Taken together, even though ghrelin may exert beneficial effects on sarcopenia by restoring food intake and increasing muscle mass, the applicability is limited as effects on functional endpoints are modest and clinical trials with long-term follow-ups to evaluate the risk of adverse effects are lacking.

Conclusions and future perspectives

To date, pharmacological therapies for sarcopenia remain elusive, either because clinical trials revealed little efficacy or unacceptable adverse effects. However, treatment options for muscle wasting disorders have expanded dramatically in recent years and a number of new compounds and approaches are currently being evaluated in patients [49]. Several of these are of potential interest for the prevention and treatment of sarcopenia, at least if certain limitations can be overcome. For example, besides the ongoing debate whether aging represents a disease or a natural, physiological process [125], the design of clinical trials for sarcopenia is not trivial: age of participants, length of the trial or the definition of soft and hard endpoints are only some of the open questions that have to be addressed. Nevertheless, besides the phase II and III compounds, other pharmacological and nutritional agents are currently in the experimental stage, and might enter clinical testing in the future, potentially expanding the repertoire of drugs for muscle wasting and sarcopenia [45, 49, 126]. Finally, multi-pronged approaches using combinations of pharmacological and nutritional interventions might result in a positive outcome for sarcopenia. Until then, exercise remains the primary and most efficient intervention to prevent and mitigate sarcopenia, in particular when combined with adequate dietary approaches and skin exposure to sunlight. Of note, while resistance exercise confers the main benefits
on muscle mass and strength, endurance training can further help to increase muscular sensitivity to
anabolic stimuli and by promoting tissue vascularization, cardiovascular and metabolic benefits. Accordingly, a combination of both types of exercise most likely contributes most to an optimized
health span [48, 127, 128]. It thus should be the interest of all stake-holders, including patients, insurance companies and governments, to implement broad incentives for an active life-style to overcome the problems with adherence and compliance.
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Figure Legend

Figure 1. Schematic overview on the nutritional and pharmacological targets and the related signaling pathways to control muscle protein biosynthesis (marked in light blue) and breakdown (marked in orange) in sarcopenia. Abbreviations: ACE, angiotensin-converting enzyme; ActRIIB, activin type IIB receptor; ALK4/5, activin receptor-like kinase 4 or 5; AMPK, AMP-dependent protein kinase, Ang I/II, angiotensin I or II; AT1R, angiotensin receptor type 1; AR, androgen receptor; COX-1/2, cyclooxygenase 1 or 2; FoxO, forhkead box O; GH, growth hormone; IGF-1, insulin-like growth factor 1; Insulin-R, insulin receptor; IGF-1R, IGF-1 receptor; mTORC1, mammalian target of rapamycin complex 1; NF-κB, nuclear factor κB; n-3 PUFAs, omega-3 poly unsaturated fatty acids; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; SARMs, selective androgen receptor modulators; S6K1, ribosomal protein S6 kinase 1; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1.
Caloric restriction

Dietary protein

Leucine

n-3 PUFAs

Fish oil

Exercise

Drugs

Inflammation

UVB