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Current pharmacotherapies for sarcopenia

Abstract

Introduction: Sarcopenia, the age-related loss of skeletal muscle mass and function, is a global health problem that contributes to the development of physical disability, morbidity and mortality in the ageing population. Sarcopenia is now recognised in many countries as a muscle disease with an ICD-10-CM Diagnosis Code for billing care related to this condition, despite no FDA-approved treatments being currently available.

Areas covered: This review highlights the current state of knowledge regarding the biological mechanisms contributing to the age-related loss of muscle mass and function and provides a summary of existing and emerging pharmacotherapies in clinical trials for sarcopenia.

Expert opinion: While understanding of the pathophysiology of sarcopenia has progressed, rigorous preclinical studies that better inform clinical trials are needed to accelerate drug discovery and identify safe and effective treatments. Few drugs have been developed specifically for sarcopenia and many have failed to meet clinically relevant outcomes related to strength and physical performance. The multifactorial complexity of sarcopenia means that different, personalised treatments are more likely to be required than just a single intervention.

Keywords: aging, exercise, myostatin, sarcopenia, selective androgen receptor modulators, testosterone

Article highlights

- Sarcopenia was originally described as an age-related loss of muscle mass, but recent consensus statements indicate sarcopenia being probable when low muscle strength is detected, and a diagnosis confirmed by the presence of low muscle quantity or quality.
- The International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) (M62.84) code for sarcopenia should improve physician awareness for diagnosing sarcopenia and the development of drug pipelines for treating the condition.
- Sarcopenia is a multifactorial condition, with alterations in neuromuscular structure and function, systemic hormone and inflammatory cytokine concentrations, physical activity levels, and nutritional status, all being contributing factors.
- Growth promoting agents (including myostatin inhibitors, testosterone, and selective androgen receptor modulators) can enhance lean mass, but whether this translates to improved muscular strength and physical performance in older adults with sarcopenia remains to be determined.
- Repurposing drugs that exert beneficial effects across a range of age-related biological processes, is one strategy to maximise effects of pharmacotherapies for sarcopenia.
- Given that lifestyle modifications such as resistance exercise training and nutritional formulations are the most widely recognised nonpharmacological approaches for tackling sarcopenia, future clinical trials examining drug-exercise and/or drug-nutrition interactions are warranted.

1. Introduction

Sarcopenia is an important geriatric condition, originally characterised by progressive and generalised age-related loss of skeletal muscle mass [1], and also a loss of muscle strength and physical function. In 2010 the European Working Group on Sarcopenia in Older People (EWGSOP) provided a working definition of sarcopenia based on the presence of both low muscle mass and function [2]. In 2014 the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project (initiated in 2009) reported cut-off points for low muscle mass and weakness using data from nine existing sources of community-dwelling older adults [3]. This evidence-based approach included recommendations for maximal grip strength (<26 kg in men; < 16 kg in women) and appendicular lean mass adjusted for body mass index (<0.789 in men; <0.512 in men) and provided among the first clinically relevant criteria based on a large and diverse population.

The EWGSOP reconvened in 2018 to assess the knowledge gained in the decade since establishing the working definition and provide an updated operational definition of sarcopenia, based on it being a progressive skeletal muscle disorder associated with increased likelihood of adverse outcomes, including falls, fractures, physical disability and mortality. In their revised guidelines, muscle strength as a criterion became more prominent since it better predicted adverse outcomes than muscle mass [4]. The 2018 definition indicated sarcopenia is probable when low muscle strength is detected, and a diagnosis of sarcopenia confirmed by the presence of low muscle quantity or quality. Low physical performance is used to identify the severity of sarcopenia, with the condition considered severe when low muscle strength, low muscle quantity/quality and low physical performance are all detected. These criteria and cut-off points for diagnosis in men and women have been described to facilitate early detection and better treatment [4].

From a public health perspective, sarcopenia has widespread clinical implications and the increasing proportion of older adults in the population means it will impact the lives of the elderly and place increasing demands on healthcare systems [5]. Economic assessments of the impact of

sarcopenia are difficult given that sarcopenia contributes to, or is implicated in, the incidence of many comorbidities, requiring different levels of health care, but health care costs attributed to sarcopenia were estimated to range between USD $11.8 billion and USD$26.2 billion, even two decades ago. Therefore, strategies to reduce the prevalence of sarcopenia or treat it effectively, could lead to billions of dollars in savings [6,7] related to healthcare, in addition to alleviating patient suffering by promoting quality of life through the preservation of functional independence. Sarcopenia is now recognised in many countries as a muscle disease with an ICD-10-CM Diagnosis Code for billing care related to this condition [8]. This was expected to increase physician awareness for diagnosing sarcopenia and for pharma companies to develop compound pipelines for treating the condition.

2. Pathophysiology of sarcopenia

There is extensive literature describing the pathophysiology of sarcopenia, including the cellular and molecular mechanisms responsible for age-related muscle wasting and functional impairment (for a recent comprehensive review on this topic, see [9]). Sarcopenia is a neuromuscular condition with potentially multiple underlying mechanisms and specific and relative contributions that likely differ between individuals. The pathophysiology of sarcopenia is complex given that underlying mechanisms may include multiple (often interrelated) factors responsible for the loss of motor unit patency (i.e. preservation of motor neurons and recruitment of all muscle fibres under their control); motor unit remodelling associated with preferential losses of some motor unit types and reinnervation of previously denervated muscle fibres [10]; neuromuscular junctional (NMJ) integrity affecting neurotransmission but also the signalling pathways implicated in the maintenance of cell size [11]; defects in excitation-contraction coupling, specifically associated with the release and reuptake of Ca^{2+} from the sarcoplasmic reticulum [12-14]; events associated with cross-bridge cycling and the dynamics of force generation [15-17]; and the many signalling and metabolic factors responsible for regulating muscle protein synthesis and degradation that affect the rate and magnitude of muscle atrophy and

potential alterations in metabolism [18]. Such factors could include perturbations in nutritional status, anabolic hormones, genetics, local and/or systemic inflammation, oxidative stress [19,20], existing (or future) diseases and conditions, and physical activity/exercise patterns (Figure 1). Sarcopenia differs mechanistically from other conditions leading to muscle atrophy such as disuse, cachexia, and denervation, and the literature is replete with studies that have examined the contributing mechanisms regulating muscle mass and how different interventions might counteract sarcopenia and preserve muscular function, independence and quality of life [21]. In addition to the studies investigating biological mechanisms, research is ongoing to develop predictive risk models for sarcopenia considering age, sex, and race, and comorbidities [22].

3. Emerging pharmacotherapies for sarcopenia

It is generally accepted that the progressive loss of muscle mass and function with advanced ageing is inevitable and some individuals may be at an increased risk for accelerated sarcopenia development due to genetic, lifestyle and environmental factors. Yet despite this knowledge pharmacotherapies specifically for sarcopenia have not been widely pursued. Non-pharmacological approaches such as resistance exercise and nutritional (protein) supplementation remain the most widely accepted strategies to tackle the symptoms of sarcopenia [23]. However, within the last decade clinical trials have examined whether pharmacotherapies developed for other wasting conditions (like cancer cachexia or muscular dystrophy) may also prevent, attenuate or reverse age-related losses of muscle mass and function. The following section provides an update on emerging pharmacotherapies designed specifically for the treatment of sarcopenia with a focus on clinical trials in phase 2 or higher.

3.1. Growth differentiation factors – Myostatin

Myostatin (growth differentiation factor-8, GDF-8), a member of the transforming growth factor-beta (TGF-β) superfamily, is a secreted protein which functions as a potent negative regulator

of skeletal muscle growth. Myostatin attracted much attention after the discovery that naturally occurring mutations and experimental knockout of the myostatin gene, increases the size and number of skeletal muscle fibres [24,25]. Myostatin binding to activin type II receptors (ActRIIB) on the muscle fibre membrane results in activation of transmembrane activin type I receptor-like kinases, ALK4 or ALK5, which promotes phosphorylation of Smad2 and Smad3, to form a heterotrimeric complex with Smad4 that mediates changes intracellular signalling and gene expression [26]. Smad2/3 signalling can also reduce Akt signalling [27], with implications for the regulation of proteostasis through downstream effectors mTORC1 and FoxO [28]. Myostatin may also potentially regulate skeletal muscle mass through inhibition of myoblast proliferation and myogenic differentiation [29,30]. Blocking myostatin signalling through genetic and pharmacological approaches induces skeletal muscle hypertrophy [31], whereas overexpression or systemic administration causes muscle atrophy [27]. The responsiveness of adult skeletal muscle to myostatin makes it an attractive therapeutic target for stimulating muscle growth and/or preventing muscle wasting with sarcopenia.

Several pharmacotherapies have been developed to disrupt myostatin signalling in skeletal muscle, including neutralising antibodies to myostatin [32,33], a modified myostatin propeptide to block myostatin [34], and a soluble ActRIIB receptor Fc fusion protein [35-38]. Several studies have shown promising results for muscle mass and function through direct inhibition of myostatin in older adults. Eli Lilly and Company examined the effect of landogrozumab (LY2495655), a fully humanised monoclonal antibody which binds and neutralises myostatin, on lean body mass and physical performance in fall-prone older individuals with muscle weakness (NCT01604408; Completed 2013). In this randomised, phase 2 clinical trial, LY2495655 treatment increased appendicular lean mass and trended to improve some performance-based measures dependent on the generation of muscle power (e.g., stair climbing) [39]. However, functional measures of strength (hand-grip, isometric leg strength) and endurance (6-minute walking distance) were not affected by LY2495655 treatment. While further studies are required to determine the overall functional implications, the initial findings of an

accumulation of lean mass independent of exercise in older frail elders is important for other patient populations where exercise is not feasible.

Regeneron Pharmaceuticals/Sanofi completed recruitment for a randomised, phase 2 study examining the safety and efficacy of a 3-month subcutaneous treatment of trevogrumab (REGN1033/SAR391786) for patients with sarcopenia (NCT01963598; Completed 2015). REGN1033 is a fully human monoclonal antibody that is a specific and potent myostatin antagonist which can increase muscle mass and function in aged mice [40]. Regeneron reported on the efficacy of different REGN1033 doses in 253 patients with sarcopenia at the 8th Cachexia Conference (Society of Sarcopenia, Cachexia and Wasting Disorders) [41]. REGN1033 treatment increased total lean body mass but only tended to improve measures of strength and function. Regeneron also has a phase 1 clinical trial assessing the safety and tolerability of garetosmab (REGN2477) alone and when combined with REGN1033 in healthy postmenopausal women and healthy adult men (NCT02943239; Active, not recruiting). REGN2477 is a fully human monoclonal antibody that inhibits activin A but does not bind other TGF-β family members. While no results of this trial have been published so far, Regeneron have previously found that combined activin A and myostatin inhibition enhanced muscle growth and force production in mice and monkeys [42]. Interestingly, the hypertrophic effects on muscle were similar to those achieved with the soluble form of ActRIIB which blocks numerous TGF-β ligands, but specific blockade of myostatin and activin A avoided adverse effects associated with broad inhibition [42].

Novartis Pharmaceuticals completed a phase 2 study to assess effects of bimagrumab (BYM338) on skeletal muscle mass and function in sarcopenic adults with mobility limitations (NCT01601600; Completed 2013). BYM338 is a human monoclonal antibody that binds to type II activin receptors and prevents ligand-receptor binding to inhibit downstream signalling. The investigators found 16 weeks of treatment increased muscle mass and strength in older adults with sarcopenia and improved mobility in those with slow walking speed [43]. Subsequently, Novartis

completed recruitment for two phase 2 clinical trials to determine the efficacy of repeat dosing with multiple dose levels of BYM338 on patient physical function, skeletal muscle mass and strength (NCT02333331; Completed 2018) and to assess the durability of beneficial effects on physical function in older adults with sarcopenia (NCT02468674; Completed 2018). The results have not yet been reported or published but should provide valuable insight into the therapeutic potential of targeting TGF-β ligands to maintain skeletal muscle mass and function in older adults.

3.2. Testosterone

Sex steroids influence the growth and maintenance of skeletal muscle and a decline in their circulating levels can impact on the maintenance of muscle mass and function. Testosterone has been examined extensively for the prevention of muscle wasting associated with ageing and chronic disease [44,45]. While the anabolic properties of androgens on skeletal muscle mass and morphology have been well documented, the mechanisms by which androgens regulate skeletal muscle metabolism and function have only recently been understood [46]. Classically, the cellular actions of testosterone result from binding to the androgen receptor (AR) within the cytoplasm. This stimulates nuclear translocation and transcription of target genes through direct interactions between ligand-receptor proteins with DNA or with other transcription factors. Non-genomic actions of sex steroids include the activation of signal transduction pathways through perturbations in cyclic nucleotide production, Ca^{2+} fluxes and kinase activation [47]. These genomic and non-genomic actions can have profound effects on myogenic gene expression and skeletal muscle structure and function.

Circulating testosterone levels decrease with advanced age [48-50] and are associated with the loss of muscle mass and strength [51]. Testosterone increases muscle mass through the enlargement of both type I and type II muscle fibres [52], and can interact with mechanical loading to potentiate this growth response [47]. Short-term testosterone treatment increases fractional protein synthesis rate and muscle IGF-1 expression in elderly men [53]. Studies in rodents and cell culture models have

shown that testosterone regulates muscle proteostasis through stimulation of Akt/mTORC1 signalling and suppression of FoxO transcriptional target gene expression after androgen withdrawal [54]. Testosterone may also facilitate muscle growth through decreased myostatin expression, improved regenerative potential of muscle stem cells (satellite cells) and suppressed skeletal muscle oxidative stress and apoptosis [55]. Importantly, testosterone has positive effects on bone mineral density and bone strength [47,56], making it an attractive treatment since sarcopenia and osteoporosis are often evident in older adults.

There is strong evidence that androgens increase muscle mass and strength under physiological and pathological conditions. The Testosterone in Older Men (TOM) Trial determined whether testosterone (administered once daily for 6 months) in older men with low testosterone levels and mobility limitations would increase maximal voluntary muscle strength (NCT00240981; Terminated 2009) [57]. While the trial was stopped before enrolment had completed due to a higher rate of adverse cardiovascular events, testosterone treatment improved muscular strength [58]. Follow-up analysis revealed a significantly greater proportion of men receiving testosterone improved their performance in leg press and chest press movements and stair-climbing power [59]. These benefits were independent of changes in serum concentrations of C-terminal agrin fragment (CAF), a potential biomarker for sarcopenia, indicating testosterone-mediated functional improvements may not have been related to neuromuscular junction stabilisation [60]. More recent data from the Testosterone Trials (TTrials; NCT00799617; Completed 2014) reported that testosterone treatment improved self-reported walking ability and six-minute walk test distance, which was related to baseline gait speed and self-reported mobility limitation [61]. Testosterone treatment did not affect the rate of falls, suggesting that exercise training may be needed to translate testosterone-induced muscle mass and strength gains into functional improvements.

Given the potential adverse effects of testosterone in the elderly [58,62], a question that remains is whether the risk-to-benefit ratio is favourable to recommend high-dose testosterone treatment for

older men. Testosterone treatment has been associated with increased risk of benign prostate hyperplasia, prostate cancer, and adverse cardiovascular events [63]. The conversion of testosterone to dihydrotestosterone by 5α-reductase is primarily responsible for driving prostate growth and the development of benign prostatic hyperplasia [64]. Therefore, a phase 2 randomised clinical trial (NCT00475501; Completed 2012) determined whether a higher-than-replacement dose of testosterone and finasteride, a type II 5α-reductase inhibitor, could safely increase muscle strength in hypogonadal older men [65]. Testosterone enanthate (125 mg/wk.) combined with finasteride (5 mg/d) for 52 weeks significantly increased muscle strength and bone mineral density without causing prostate enlargement [65]. Improvements in muscle strength, fat free mass, and haematocrit with testosterone treatment were not affected by finasteride. These results, and that of others [66-68], demonstrate that testosterone and 5α-reductase inhibitor co-treatment can improve muscle mass, physical performance, and bone mineral density without prostate enlargement in older men.

Another important question that remains is whether the beneficial effects of testosterone on muscle mass and strength can be maintained after treatment withdrawal. A phase 4 clinical trial (NCT00190060; Completed 2008) examined the potential beneficial effects of testosterone treatment on muscle strength and functional capacity in frail elderly men [69]. The authors found testosterone treatment for 6 months increased several clinically relevant outcomes (including lean mass, isometric knee extension torque, and quality of life measures), but these effects were not maintained at 6 months after discontinuation of treatment [69]. While these initials findings suggest short-term improvements may not persist upon androgen withdrawal, studies investigating longer duration and varying dosing strategies are required to determine whether continual treatment is needed to maintain clinically-relevant outcomes in sarcopenic individuals.

Aerobic capacity, measured by peak oxygen uptake ($V\dot{O}_2peak$) during a graded exercise test, is strong predictor of all-cause mortality in men and women [70]. Age-related changes in aerobic capacity may be due in part to reductions in capillary density, mitochondrial content and function,

and/or haemoglobin levels [71]. A recent study from the Testosterone's Effects on Atherosclerosis progression in Aging Men (TEAAM) trial examined effects of long-term testosterone treatment (daily 1% transdermal testosterone gel for 3 years) on aerobic capacity in older men [72]. The authors reported that the mean 3-year decrease in VO_2peak was significantly less in testosterone treated men and was associated with increased haemoglobin concentration [72]. Similar observations have been observed in a subset analysis of the TOM trial (NCT00240981; Completed 2009), examining effects of 6 months testosterone treatment on VO_2peak on aerobic performance in mobility-limited older men [73]. The authors found that testosterone treatment attenuated the age-related decline in VO_2peak and lactate threshold [73]. Collectively, these findings suggest testosterone treatment may be a viable pharmacotherapy to improve both muscle strength and aerobic performance in older individuals, which could have profound effects on overall morbidity and mortality. However, long-term effects of testosterone treatment on disease susceptibility need to be considered.

3.3. Selective Androgen Receptor Modulators (SARMs)

Given the potential adverse effects of long-term testosterone treatment, alternative approaches with potent anabolic properties specifically in muscle, are attractive strategies to combat muscle wasting conditions. Selective AR modulators (SARMs) are a class of nonsteroidal AR ligands that bind AR and display tissue-selectivity of androgenic signalling [74,75]. The first SARMs were described in 1998 [75,76], and initial preclinical studies in rodents found some SARMs had significant anabolic activity, with only moderate to minimal androgenic activity [77,78]. Importantly, these SARMs demonstrated anabolic activity in muscle and bone, but unlike testosterone and other androgens, these nonsteroidal agents minimised growth of the prostate and other secondary sexual organs [77]. Not surprisingly, there has been significant interest in the clinical development of SARMs for treating muscle wasting conditions, including sarcopenia and frailty.

Only a few studies thus far examined the effects of SARMs in sarcopenic individuals. Merck Sharp & Dohme Corporation completed a phase 2 clinical trial (NCT00529659: Completed 2009) which evaluated the safety, tolerability, and efficacy of MK-0773 (also known as PF-05314882) in women with mobility disability. MK-0773 treatment (50 mg orally twice daily; 6 months) increased lean body mass but did not improve muscular strength or physical performance [79]. MK-0773 was generally safe and well-tolerated, with no evidence of androgenisation. GTx has also completed a phase 2 clinical trial to evaluate enobosarm (GTx-024) in 120 healthy elderly men (>60 years of age) and postmenopausal women. GTx-024 treatment resulted in a dose-dependent increase in total lean body mass and physical function [80]. The treatment was well tolerated, with the incidence of adverse events similar between treatment groups. While not specifically targeted for sarcopenia, a recently completed phase 2 trial (NCT03241342; Completed 2018) evaluated GTx-024 as a potential treatment for stress urinary incontinence in postmenopausal women. Given there are no treatments available for this condition, SARMs may be a strategy to selectively enhancing pelvic floor muscle function without unwanted side-effects of androgen therapies. Preclinical studies have shown that treatment of ovariectomized mice with SARMs improved pelvic muscle mass [81]. The data from this clinical trial should provide insight into the clinical relevance of SARM treatment for other muscle atrophy conditions associated with ageing. The potential for long-term SARM treatment to prevent sarcopenia remains to be studied.

3.4. Anti-inflammatory agents

Ageing is accompanied by chronic low-grade inflammation, which has given rise to the term "inflammageing" [82]. Systemic levels of inflammatory cytokines such as tumour necrosis factor α (TNFα), interleukin 6 (IL-6) and C-reactive protein (CRP) have been associated with the loss of muscle mass, strength and function [83]. Classically, systemic cytokines alter cellular homeostasis by binding to their respective α-receptors which homo- or hetero-dimerize with β-receptors to initiate intracellular

signal transduction. Alternatively, soluble receptors present in circulation may also bind specific cytokines and transduce intracellular signalling through interaction with membrane bound β-receptors in cells that do not express α-receptors. Growing evidence suggest this alternative, non-canonical receptor signalling may mediate the proinflammatory functions of cytokines. Chronically elevated systemic cytokines and muscle inflammatory signalling has been linked to disrupted muscle proteostasis [84,85], muscle stem cell dysfunction [86], apoptosis [87,88], oxidative stress [87], and contractile and mitochondrial function [88,89]. Inflammation may also affect non-muscle cells (e.g., fibroblasts and endothelial cells) within the muscle microenvironment. Therefore, systemic cytokines and muscle inflammatory signalling may be attractive therapeutic targets for sarcopenia.

Considerable progress has been made in the development of pharmacotherapies to counteract chronically elevated cytokines in many inflammatory and disease conditions. These strategies target either the specific cytokine, its receptor, or the downstream intracellular signalling axis. For example, inhibitors targeting IL-6 signalling include monoclonal antibodies directed against IL-6 and IL-6 receptor (e.g., anti-IL-6 monoclonal antibodies), soluble receptors linked to human immunoglobulin IgG1-Fc (e.g., sgp130Fc), and small molecule inhibitors of JAK (e.g., ruxolitinib) [90]. While many of these pharmacotherapies have been evaluated in clinical trials for other chronic diseases (e.g., cancers, inflammatory diseases, obesity), little is known about their potential application for age-related muscle wasting. However, given that many cytokine-related signalling pathways have established roles in myogenesis [91], metabolism [92], and muscle growth and remodelling [93], it is likely that long-term inhibition could negatively affect skeletal muscle mass and function. Furthermore, blocking receptor and downstream intracellular signalling events may also interfere with other cytokines or non-inflammatory pathways, to limit their therapeutic potential.

Another strategy to combat chronic low-grade inflammation is to use non-steroidal anti-inflammatory drugs (NSAIDs); commonly used for the management of inflammation and pain. These drugs exert their actions by blocking the activity of cyclooxygenase (COX), which subsequently

suppresses prostaglandin biosynthesis and inflammatory processes. NSAIDs may delay the onset of sarcopenia and slow the progression of muscle loss [94]. In a randomised double-blind controlled trial short-term NSAID treatment with piroxicam (10 mg daily), a nonselective COX inhibitor, decreased serum IL-6 and chemokine concentrations and improved muscle performance and mobility in geriatric patients hospitalised with acute infection-induced inflammation (ISRCTN58517443; Completed 2006) [95,96]. This group also showed that short-term treatment with the selective COX-2 inhibitor celecoxib improved muscle fatigue resistance elderly patients hospitalised with acute infection-induced inflammation [97]. Despite the overall improvements in muscle function, the therapeutic merit of NSAIDs in these individuals is questionable due to the adverse effects and associated risks. Whether these benefits can be achieved in older individuals without comorbidities remains to be determined. Preclinical studies have provided evidence that long-term NSAID treatment (Ibuprofen, 5 months, 30 mg/kg/d) can decrease plasma IL-6 levels and improve muscle mass in old Wistar rats [98]. These benefits were accompanied by enhanced muscle protein synthesis and decreased proteolytic responses to refeeding [98]. While these initial studies highlight the potential therapeutic merit of NSAID treatment, whether similar benefits can be achieved in sarcopenic individuals remains to be determined. Although anti-inflammatory agents have been used successfully in a variety of conditions, clinical trials are needed to investigate whether short-term cycles of cytokine inhibition can prevent sarcopenia or enhance other therapies such as resistance exercise and nutritional interventions.

3.5. Other potential drug candidates

Drug repurposing may be an alternative approach to prevent sarcopenia. Repurposing drugs that demonstrate multiple benefits across a range of disease states is one potential way to maximise the effects of pharmacotherapies in older, individuals while avoiding potential drug–drug interactions and adverse events. As it relates to sarcopenia, these drugs would may possess pro-anabolic or anti-inflammatory properties that could serve to enhance skeletal muscle mass and function with ageing.

The following section will briefly highlight pharmacotherapies that are being repositioned as potential therapeutics for age-related atrophy and dysfunction.

3.5.1. Angiotensin converting enzyme (ACE) inhibitors

Angiotensin-converting enzyme (ACE) is a core component of the renin-angiotensin system (RAS) where it converts the hormone angiotensin I to angiotensin II. The potent vasoconstrictor angiotensin II can also stimulate the secretion of aldosterone, thereby exerting robust regulatory effects on blood pressure, electrolyte balance, and fluid retention [99]. In addition to blood pressure regulation, emerging evidence suggests these molecules exert pro-inflammatory and pro-fibrotic activities that disrupt cellular homeostasis and function [99,100]. While ACE inhibitors largely promote vasodilation and lower blood pressure, they can also reduce inflammation by suppressing NF-κB activity and ROS-mediate inflammatory processes (reviewed in [101]). Therefore, the secondary effects of ACE inhibitors may be a valuable therapeutic tool for sarcopenia.

ACE inhibitors are mainly prescribed for treating hypertension and congestive heart failure where they reduce hospitalisation and mortality [102]. However, the ACE inhibitor perindopril can improve physical function (six-minute walk) in functionally impaired older adults [103]. Greater muscle strength and larger lower extremity mass has been reported in older people taking ACE inhibitors [104,105]. A phase 4 (NCT01650402; Active, not recruiting) is examining the effects of INtensive versus standard blood pressure lowering to prevent Functional declINe In The Elderly (INFINITY) [106]. This prospective randomized, open-label trial will examine if multiple antihypertensive therapies, ACE inhibitor (lisinopril) and calcium channel blocker (amlodipine), can improve mobility parameters (self-pace walk and stance times) and cognitive function (executive function, processing times) in older patients with elevated 24-hr systolic blood pressure. The trial should improve understanding of intensive blood pressure treatment strategies on functional outcomes

in older persons with hypertension and cerebrovascular disease, which elevated their risk of functional impairment.

The Leucine and ACE inhibitors in sarcopenia (LACE trial) is a multicentre, randomised controlled trial (EudraCT# 2014-003455-61; Active) that will evaluate the efficacy of leucine and perindopril (ACE inhibitor) on physical function (Short Physical Performance Battery score) in male and female patients aged 70 years and older with sarcopenia [107]. The trial will measure an array of clinically-relevant and functionally important parameters (e.g., blood pressure, physical activity/diet, blood biomarkers) to better understand mechanisms of disease progression and responses to treatments. This clinical trial represents a comprehensive assessment of ACE inhibition on muscle mass and function specifically in people with sarcopenia and should improve understanding of the therapeutic potential in this target population.

The ACE inhibitors Combined with Exercise for Seniors - Pilot study (ACES-P) (NCT01891513; Completed 2017) will compare the efficacy of first-line antihypertensive drugs (perindopril, losartan, and hydrochlorothiazide) to improve functional status in hypertensive seniors when combined with chronic exercise. Initial findings on the feasibility, safety and protocol integrity have been published [108]. The authors reported that the 24-week multimodal intervention to improve physical function in functionally impaired older adults was feasible and safe [108]. Unfortunately, due to the low number of participants enrolled, changes in physical performance, clinical metabolic profiles, and systemic biomarkers (e.g., inflammation, oxidative stress) cannot be determined at this time.

3.5.2. Angiotensin II receptor antagonists

Angiotensin II receptor antagonists are commonly used for treating hypertension and heart failure in older adults and are generally well-tolerated. Like ACE inhibitors, these drugs may reduce inflammation, oxidative stress and muscle dysfunction [109,110]. A phase 2 trial (NCT02676466;

Completed 2018), the ENabling Reduction of low-Grade Inflammation in SEniors (ENRGISE) Pilot study, examined the efficacy of two potential anti-inflammatory interventions, angiotensin II receptor antagonist (50-100 mg/d) and omega-3 supplementation (1400-2800 mg/d), to preserve walking ability in older adults with mobility impairment. However, neither losartan nor fish oil supplementation for 12 months altered plasma IL-6 or 400-meter walking speed in older adults with low-grade inflammation and mobility limitations [111]. These findings contrast with previous observations in patients undergoing cardiac surgery [112] and older mice [113]. Another phase 2 (NCT01989793; Completed 2016) will determine whether losartan treatment (25-100 mg, 24 weeks) can prevent reductions in strength associated with ageing. While no results have been published yet, beneficial effects of losartan treatment have been reported in a preclinical model of sarcopenia, with improved muscle remodelling and function after injury in old mice [114]. While not discussed in the clinical trial design or measured in the preclinical study, it will be of interest to determine whether potential changes in function are related to an improved inflammatory profile. Interestingly, angiotensin II receptor blockade did not enhance the hypertrophic growth response or improvements in strength after resistance training in elderly men [115]. The therapeutic potential of angiotensin II receptor antagonists alone and in combination with nonpharmacological approaches for sarcopenia remain to be studied.

3.5.3. Angiotensin-(1-7) receptor agonists

In addition to the "classical" RAS axis, the "alternative" axis involves the conversion of angiotensin I to angiotensin-(1-7) (Ang-(1-7)) by ACE-2, by which Ang-(1-7) activates the G protein-coupled receptor Mas receptor (MasR) to initiate intracellular signalling. This alternative axis is involved in many physiologic and pathophysiological processes across various cell types and disease conditions, however most notably for counteracting the detrimental effects of the classical RAS formed by ACE/Ang II/Ang II type 1 (AT1) receptor [116]. We have recently shown that AVE 0991, a nonpeptide MasR agonist, improved locomotor activity and attenuated muscle wasting in tumour

bearing mice [117]. A randomised, phase 2 trial (NCT03452488; Recruiting) will determine the safety and efficacy of BIO101 administered orally (6 months, 350 and 700 mg/d) in older men and women suffering from age-related sarcopenia (including sarcopenic obesity) aged ≥65 years and at risk of mobility disability (SARA-INT trial). While no results have been published at this time, the sponsoring company Biophytis has presented preliminary data at several international conferences demonstrating anabolic and metabolic properties of BIO101 in skeletal muscle cells in vitro and in vivo [118,119]. This clinical trial provide insight into the therapeutic potential of ACE-2/Ang-(1-7)/MasR axis in sarcopenia development.

3.5.4. Metformin

The biguanide metformin is the most widely prescribed antihyperglycemic agent for type 2 diabetes but can also modulate a number of biological processes involved in the pathophysiology of sarcopenia [120]. Metformin primarily exerts beneficial metabolic effects in skeletal muscle through the activation of adenosine monophosphate activated protein kinase (AMPK) [121], which has established roles in the regulation of glucose uptake and fatty acid oxidation, protein metabolism, autophagy and mitochondrial function [122]. Metformin also demonstrates anti-inflammatory, antioxidant, anticancer, cardio-protective properties [123], which makes it an attractive therapeutic to combat ageing, sarcopenia and frailty. A randomised, double-blind, placebo-controlled trial (NCT02308228; Active, not recruiting) is currently evaluating the effects of metformin on muscle size, strength, and physical function when combined with a progressive resistance training program in men and women 65 years and older. Preliminary analyses reported in the study design protocol demonstrate that 10-weeks metformin treatment increased M2 macrophage abundance and decreased IL-1β gene expression in muscle of insulin resistance individuals [124]. The authors hypothesis that metformin treatment will improve the resistance training response in healthy older adults by modifying the muscle microenvironment (e.g., lower inflammation, increase AMPK activity). Interestingly, a randomised

phase 2 trial (NCT02552355; Completed 2017) found that metformin treatment impaired metabolic and mitochondrial adaptations to 12-weeks of aerobic exercise training in older adults free of chronic disease [125]. Similar observations have been reported in prediabetic men and women. Metformin and exercise (aerobic and resistance) training independently improved whole-body insulin sensitivity, however there was no additive effect [126]. Future clinical trials are warranted to determine if these initial findings translate across all metabolic agents and exercise modalities in older adults with and without disease.

4. Conclusion

To date, few pharmacotherapies for sarcopenia have been pursued beyond phase 2 trials (Table 1). Growth promoting agents (including myostatin inhibitors, testosterone, and SARMs) have potential to enhance lean mass in older individuals, but the translation of these benefits to clinically relevant improvements in muscular strength and physical performance requires further evaluation. It is likely that enhancing neuromuscular performance through neural stimulation or exercise may be needed to realise functional adaptations. Systemic inflammatory cytokines have been implicated in muscle wasting, poor physical performance, and metabolic dysfunction across multiple diseases and conditions. While ageing is often linked with chronic low-grade systemic inflammation, clinical trials are needed to investigate whether inhibiting broad or specific inflammatory cytokines has therapeutic potential for sarcopenia. Given the paradoxical role of inflammatory cytokines in health and disease it is likely that intermittent cycles of inhibition/activation may be needed to maintain muscle mass and function during ageing. There is growing interest for the repurposing of drugs to combat sarcopenia. Several drug candidates (e.g., BIO101, Metformin) have demonstrated positive effects on anabolic and metabolic processes within skeletal muscle. These pharmacotherapies should not only improve muscle mass and function but possibly delay key hallmarks of ageing across multiple tissues and biological

processes. Studies are warranted to determine whether these benefits can be achieved throughout all of life's stages where comorbidities may exist.

5. Expert Opinion

According to the 2018 consensus statement, sarcopenia is described as probable when low muscle strength is detected, and a diagnosis confirmed by the presence of low muscle quantity or quality. Low physical performance identifies the severity of sarcopenia, and the condition considered severe when low muscle strength, low muscle quantity/quality and low physical performance are all detected. Debate and many (not-so-helpful) publications regarding nuances around specific definitions and sub-classifications have restricted progress in accepting, understanding and treating sarcopenia. These discussions have arisen since it has been difficult to establish effective diagnostic criteria for low muscle mass and weakness. While significant progress has been made in our understanding of the pathophysiology of sarcopenia, better understanding the biological processes of sarcopenia is critical for identify objective measures that are feasible, sensitive to change, and can demonstrate clinically relevant improvements. It will be imperative that future clinical trials utilise primary outcome measurements that governmental agencies such as the FDA and/or the European Medicines Agency (EMA) will favour.

A major milestone was achieved in 2016 with the recognition of sarcopenia as a disease entity. The ICD-10-CM (M62.84) code for sarcopenia should ideally improve awareness for diagnosing sarcopenia and assist drug development specifically for this condition. Sarcopenia and frailty are major global health problems likely to escalate as the number and proportion of older adults continues to increase worldwide. Therapeutic strategies to address age-related changes in skeletal muscle mass and strength will help frail elders maintain and/or improve their health and quality of life. This is not a trivial problem since sarcopenia is multifactorial in its aetiology, with potential contributions from

alterations in neuromuscular parameters, hormones and inflammatory markers, lifestyle choices and nutritional status. These biological processes serve as therapeutic targets to treat sarcopenia.

Investment in rigorous preclinical evaluations of safe and effective drugs for muscle wasting and weakness is essential before recommending strategies for clinical testing and application to sarcopenia. The use of comprehensive functional and metabolic assessments will enhance the translation of findings to more accurately identify effective treatments for sarcopenia. There is accumulating evidence that a direct relationship between muscle mass, strength and function is not as clear in older individuals as originally assumed [3]. This may be partially explained by age-related changes in muscle metabolism. Therefore, combining whole-body and muscle metabolic measures with performance-based outcomes may identify pharmacotherapies that improve contractile and metabolic independent of mass, which could favourably improve systemic health. Selecting treatments that only improve mass and function may ignore potential co-therapies that could elicit numerous health benefits related to the biology of ageing.

Physical activity and nutritional status are potent regulators of muscle metabolism and phenotype. It is generally accepted that maintaining adequate physical activity levels and caloric intake positively influence healthy ageing. Given the inter-individual variability and the potential contribution of these factors to sarcopenia development, the use of reliable and direct objective measures is critical to assessing the impact of pharmacotherapies on overall quantity and quality of life. Gold standard methods such as doubly labelled water to measure free energy expenditure in free-living conditions should be preferred over self-reported estimates of physical activity and energy intake. Moreover, measures that encompass a combination of movement activities (e.g., sedentary, active, sleep) will provide valuable feedback on how treatments influence behaviour change and whether they ultimately impact health outcomes. Wearable devices and mobile applications are technologies that could provide more robust data acquisition for these parameters. While there have been significant advances in this area from a public health standpoint, standardised procedures for the

use and reporting will be required to reduce variability between trials and provide clinically meaningful data. Currently, lifestyle modifications such as resistance exercise training and nutritional interventions (e.g., protein and amino acids) remain the most widely recognised nonpharmacological approaches for sarcopenia. Clinical trials examining drug-exercise and/or drug-nutrition interactions are warranted, since multiple strategies will be needed to effectively treat age-related muscle wasting and weakness.

References

1. Lynch GS. Sarcopenia–age-related muscle wasting and weakness: mechanisms and treatments. Springer; 2011.
2. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
3. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69(5):547-58.
4. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.
5. Lynch GS. Update on emerging drugs for sarcopenia - age-related muscle wasting. Expert Opin Emerg Drugs. 2008;13(4):655-73. **(•• For historical context, this paper provides an update on emerging therapies and novel approaches for sarcopenia during 2005 - 2008.)**
6. Del Signore S, Roubenoff R. Physical frailty and sarcopenia (PF&S): a point of view from the industry. Aging Clin Exp Res. 2017;29(1):69-74.
7. Janssen I, Shepard DS, Katzmarzyk PT, et al. The healthcare costs of sarcopenia in the United States. J Am Geriatr Soc. 2004;52(1):80-5.
8. Cao L, Morley JE. Sarcopenia Is Recognized as an Independent Condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) Code. J Am Med Dir Assoc. 2016;17(8):675-7.
9. Larsson L, Degens H, Li M, et al. Sarcopenia: Aging-Related Loss of Muscle Mass and Function. Physiol Rev. 2019;99(1):427-511. (• **This paper provides an extensive update on the mechanisms of aging-related loss of muscle mass and function.)**
10. Piasecki M, Ireland A, Piasecki J, et al. Failure to expand the motor unit size to compensate for declining motor unit numbers distinguishes sarcopenic from non-sarcopenic older men. J Physiol. 2018;596(9):1627-1637.
11. Tintignac LA, Brenner HR, Ruegg MA. Mechanisms Regulating Neuromuscular Junction Development and Function and Causes of Muscle Wasting. Physiol Rev. 2015;95(3):809-52.
12. Gaboardi AJ, Kressler J, Snow TK, et al. Aging impairs regulation of ryanodine receptors from extensor digitorum longus but not soleus muscles. Muscle Nerve. 2018;57(6):1022-1025.
13. Michelucci A, Garcia-Castaneda M, Boncompagni S, et al. Role of STIM1/ORAI1-mediated store-operated Ca(2+) entry in skeletal muscle physiology and disease. Cell Calcium. 2018;76:101-115.
14. Pietrangelo L, D'Incecco A, Ainbinder A, et al. Age-dependent uncoupling of mitochondria from Ca2(+) release units in skeletal muscle. Oncotarget. 2015;6(34):35358-71.
15. Claflin DR, Larkin LM, Cederna PS, et al. Effects of high- and low-velocity resistance training on the contractile properties of skeletal muscle fibers from young and older humans. J Appl Physiol (1985). 2011;111(4):1021-30.
16. Li M, Ogilvie H, Ochala J, et al. Aberrant post-translational modifications compromise human myosin motor function in old age. Aging Cell. 2015;14(2):228-35.
17. Trappe S, Williamson D, Godard M, et al. Effect of resistance training on single muscle fiber contractile function in older men. J Appl Physiol (1985). 2000;89(1):143-52.
18. Sandri M, Barberi L, Bijlsma AY, et al. Signalling pathways regulating muscle mass in ageing skeletal muscle: the role of the IGF1-Akt-mTOR-FoxO pathway. Biogerontology. 2013;14(3):303-23.
19. Baumann CW, Kwak D, Liu HM, et al. Age-induced oxidative stress: how does it influence skeletal muscle quantity and quality? J Appl Physiol (1985). 2016;121(5):1047-1052.

20. Qaisar R, Bhaskaran S, Premkumar P, et al. Oxidative stress-induced dysregulation of excitation-contraction coupling contributes to muscle weakness. J Cachexia Sarcopenia Muscle. 2018;9(5):1003-1017.
21. Wilkinson DJ, Piasecki M, Atherton PJ. The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. Ageing Res Rev. 2018;47:123-132.
22. Cawthon PM, Travison TG, Manini TM, et al. Establishing the Link Between Lean Mass and Grip Strength Cut-points With Mobility Disability and Other Health Outcomes: Proceedings of the Sarcopenia Definition and Outcomes Consortium Conference. J Gerontol A Biol Sci Med Sci. 2019.
23. Hardee JP, Carson JA. Understanding Sarcopenia Development: A Role for Healthy Behaviors. Am J Lifestyle Med. 2017;11(1):17-20.
24. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature. 1997;387(6628):83-90.
25. Grobet L, Martin LJ, Poncelet D, et al. A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle. Nat Genet. 1997;17(1):71-4.
26. Sartori R, Gregorevic P, Sandri M. TGFbeta and BMP signaling in skeletal muscle: potential significance for muscle-related disease. Trends Endocrinol Metab. 2014;25(9):464-71.
27. Amirouche A, Durieux AC, Banzet S, et al. Down-regulation of Akt/mammalian target of rapamycin signaling pathway in response to myostatin overexpression in skeletal muscle. Endocrinology. 2009;150(1):286-94.
28. Chen JL, Colgan TD, Walton KL, et al. The TGF-beta Signalling Network in Muscle Development, Adaptation and Disease. Adv Exp Med Biol. 2016;900:97-131.
29. Thomas M, Langley B, Berry C, et al. Myostatin, a negative regulator of muscle growth, functions by inhibiting myoblast proliferation. J Biol Chem. 2000;275(51):40235-43.
30. Rios R, Carneiro I, Arce VM, et al. Myostatin is an inhibitor of myogenic differentiation. Am J Physiol Cell Physiol. 2002;282(5):C993-9.
31. Lee SJ, Huynh TV, Lee YS, et al. Role of satellite cells versus myofibers in muscle hypertrophy induced by inhibition of the myostatin/activin signaling pathway. Proc Natl Acad Sci U S A. 2012;109(35):E2353-60.
32. Whittemore LA, Song K, Li X, et al. Inhibition of myostatin in adult mice increases skeletal muscle mass and strength. Biochem Biophys Res Commun. 2003;300(4):965-71.
33. Murphy KT, Koopman R, Naim T, et al. Antibody-directed myostatin inhibition in 21-mo-old mice reveals novel roles for myostatin signaling in skeletal muscle structure and function. FASEB J. 2010;24(11):4433-42.
34. Bogdanovich S, Perkins KJ, Krag TO, et al. Myostatin propeptide-mediated amelioration of dystrophic pathophysiology. FASEB J. 2005;19(6):543-9.
35. Lee SJ, Reed LA, Davies MV, et al. Regulation of muscle growth by multiple ligands signaling through activin type II receptors. Proc Natl Acad Sci U S A. 2005;102(50):18117-22.
36. Goncalves MD, Pistilli EE, Balduzzi A, et al. Akt deficiency attenuates muscle size and function but not the response to ActRIIB inhibition. PLoS One. 2010;5(9):e12707.
37. Zhou X, Wang JL, Lu J, et al. Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. Cell. 2010;142(4):531-43.
38. Attie KM, Borgstein NG, Yang Y, et al. A single ascending-dose study of muscle regulator ACE-031 in healthy volunteers. Muscle Nerve. 2013;47(3):416-23.
39. Becker C, Lord SR, Studenski SA, et al. Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial. Lancet Diabetes Endocrinol. 2015;3(12):948-57. **(•• This phase 2 clinical trial found LY2495655 treatment increased**

appendicular lean mass but only trended to improve some performance-based measures.)

40. Latres E, Pangilinan J, Miloscio L, et al. Myostatin blockade with a fully human monoclonal antibody induces muscle hypertrophy and reverses muscle atrophy in young and aged mice. Skelet Muscle. 2015;5:34.
41. Ebner N, von Haehling S. Unlocking the wasting enigma: Highlights from the 8th Cachexia Conference. J Cachexia Sarcopenia Muscle. 2016;7(1):90-4.
42. Latres E, Mastaitis J, Fury W, et al. Activin A more prominently regulates muscle mass in primates than does GDF8. Nat Commun. 2017;8:15153.
43. Rooks D, Praestgaard J, Hariry S, et al. Treatment of Sarcopenia with Bimagrumab: Results from a Phase II, Randomized, Controlled, Proof-of-Concept Study. J Am Geriatr Soc. 2017;65(9):1988-1995. **(• This phase 2 trial found BYM388 treatment increased muscle mass and strength in older adults with sarcopenia and improved mobility in those with slow walking speed)**
44. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. J Am Geriatr Soc. 2003;51(1):101-15; discussion 115.
45. Saad F, Rohrig G, von Haehling S, et al. Testosterone Deficiency and Testosterone Treatment in Older Men. Gerontology. 2017;63(2):144-156.
46. Morley JE. Hormones and Sarcopenia. Curr Pharm Des. 2017;23(30):4484-4492.
47. Carson JA, Manolagas SC. Effects of sex steroids on bones and muscles: Similarities, parallels, and putative interactions in health and disease. Bone. 2015;80:67-78.
48. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001;86(2):724-31.
49. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87(2):589-98.
50. Morley JE, Kaiser FE, Perry HM, 3rd, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism. 1997;46(4):410-3.
51. Baumgartner RN, Waters DL, Gallagher D, et al. Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev. 1999;107(2):123-36.
52. Sinha-Hikim I, Artaza J, Woodhouse L, et al. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. Am J Physiol Endocrinol Metab. 2002;283(1):E154-64.
53. Urban RJ, Bodenburg YH, Gilkison C, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol. 1995;269(5 Pt 1):E820-6.
54. White JP, Gao S, Puppa MJ, et al. Testosterone regulation of Akt/mTORC1/FoxO3a signaling in skeletal muscle. Mol Cell Endocrinol. 2013;365(2):174-86.
55. Kovacheva EL, Hikim AP, Shen R, et al. Testosterone supplementation reverses sarcopenia in aging through regulation of myostatin, c-Jun NH2-terminal kinase, Notch, and Akt signaling pathways. Endocrinology. 2010;151(2):628-38.
56. Irwig MS. Bone health in hypogonadal men. Curr Opin Urol. 2014;24(6):608-13.
57. LeBrasseur NK, Lajevardi N, Miciek R, et al. Effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations (The TOM Trial): design and methods. Contemp Clin Trials. 2009;30(2):133-40. **(•• This phase 4 trial found that testosterone increase maximal voluntary muscle strength in older men with low testosterone levels and mobility limitations, but the trial was terminated due to a higher rate of adverse cardiovascular events.)**

58. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;363(2):109-22.
59. Travison TG, Basaria S, Storer TW, et al. Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. J Gerontol A Biol Sci Med Sci. 2011;66(10):1090-9.
60. Gagliano-Juca T, Storer TW, Pencina KM, et al. Testosterone does not affect agrin cleavage in mobility-limited older men despite improvement in physical function. Andrology. 2018;6(1):29-36.
61. Bhasin S, Ellenberg SS, Storer TW, et al. Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials. Lancet Diabetes Endocrinol. 2018;6(11):879-890. **(• This phase 3 trial found that testosterone therapy improved self-reported walking ability and six-minute walk test distance but did not affect the rate of falls in elderly men with low testosterone.)**
62. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci. 2005;60(11):1451-7.
63. Grech A, Breck J, Heidelbaugh J. Adverse effects of testosterone replacement therapy: an update on the evidence and controversy. Ther Adv Drug Saf. 2014;5(5):190-200.
64. Steers WD. 5alpha-reductase activity in the prostate. Urology. 2001;58(6 Suppl 1):17-24; discussion 24.
65. Borst SE, Yarrow JF, Conover CF, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. Am J Physiol Endocrinol Metab. 2014;306(4):E433-42.
66. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab. 2004;89(2):503-10.
67. Bhasin S, Travison TG, Storer TW, et al. Effect of testosterone supplementation with and without a dual 5alpha-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. JAMA. 2012;307(9):931-9.
68. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab. 2005;90(3):1502-10.
69. O'Connell MD, Roberts SA, Srinivas-Shankar U, et al. Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men? J Clin Endocrinol Metab. 2011;96(2):454-8.
70. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., et al. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA. 1989;262(17):2395-401.
71. Cartee GD, Hepple RT, Bamman MM, et al. Exercise Promotes Healthy Aging of Skeletal Muscle. Cell Metab. 2016;23(6):1034-1047.
72. Traustadottir T, Harman SM, Tsitouras P, et al. Long-Term Testosterone Supplementation in Older Men Attenuates Age-Related Decline in Aerobic Capacity. J Clin Endocrinol Metab. 2018;103(8):2861-2869.
73. Storer TW, Bhasin S, Travison TG, et al. Testosterone Attenuates Age-Related Fall in Aerobic Function in Mobility Limited Older Men With Low Testosterone. J Clin Endocrinol Metab. 2016;101(6):2562-9.
74. Bhasin S, Calof OM, Storer TW, et al. Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab. 2006;2(3):146-59.

75. Dalton JT, Mukherjee A, Zhu Z, et al. Discovery of nonsteroidal androgens. Biochem Biophys Res Commun. 1998;244(1):1-4.
76. Edwards JP, West SJ, Pooley CL, et al. New nonsteroidal androgen receptor modulators based on 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g] quinolinone. Bioorg Med Chem Lett. 1998;8(7):745-50.
77. Gao W, Reiser PJ, Coss CC, et al. Selective androgen receptor modulator treatment improves muscle strength and body composition and prevents bone loss in orchidectomized rats. Endocrinology. 2005;146(11):4887-97.
78. Yin D, Gao W, Kearbey JD, et al. Pharmacodynamics of selective androgen receptor modulators. J Pharmacol Exp Ther. 2003;304(3):1334-40.
79. Papanicolaou DA, Ather SN, Zhu H, et al. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging. 2013;17(6):533-43. **(•• MK-0773 treatment increased lean body mass but did not improve muscular strength or physical performance.)**
80. Dalton JT, Barnette KG, Bohl CE, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle. 2011;2(3):153-161. **(• This phase 2 clinical trial found GTx-024 treatment resulted in a dose-dependent increase in total lean body mass and physical function.)**
81. Ponnusamy S, Sullivan RD, Thiyagarajan T, et al. Tissue Selective Androgen Receptor Modulators (SARMs) Increase Pelvic Floor Muscle Mass in Ovariectomized Mice. J Cell Biochem. 2017;118(3):640-646.
82. Franceschi C, Garagnani P, Parini P, et al. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14(10):576-590.
83. Wang J, Leung KS, Chow SK, et al. Inflammation and age-associated skeletal muscle deterioration (sarcopaenia). J Orthop Translat. 2017;10:94-101.
84. Toth MJ, Matthews DE, Tracy RP, et al. Age-related differences in skeletal muscle protein synthesis: relation to markers of immune activation. Am J Physiol Endocrinol Metab. 2005;288(5):E883-91.
85. Hardee JP, Fix DK, Wang X, et al. Systemic IL-6 regulation of eccentric contraction-induced muscle protein synthesis. Am J Physiol Cell Physiol. 2018;315(1):C91-C103.
86. Blau HM, Cosgrove BD, Ho AT. The central role of muscle stem cells in regenerative failure with aging. Nat Med. 2015;21(8):854-62.
87. Zhou J, Liu B, Liang C, et al. Cytokine Signaling in Skeletal Muscle Wasting. Trends Endocrinol Metab. 2016;27(5):335-347.
88. Marzetti E, Calvani R, Cesari M, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. Int J Biochem Cell Biol. 2013;45(10):2288-301.
89. Reid MB, Li YP. Cytokines and oxidative signalling in skeletal muscle. Acta Physiol Scand. 2001;171(3):225-32.
90. Garbers C, Heink S, Korn T, et al. Interleukin-6: designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov. 2018;17(6):395-412.
91. Costamagna D, Costelli P, Sampaolesi M, et al. Role of Inflammation in Muscle Homeostasis and Myogenesis. Mediators Inflamm. 2015;2015:805172.
92. Pal M, Febbraio MA, Whitham M. From cytokine to myokine: the emerging role of interleukin-6 in metabolic regulation. Immunol Cell Biol. 2014;92(4):331-9.
93. Serrano AL, Baeza-Raja B, Perdiguero E, et al. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. Cell Metab. 2008;7(1):33-44.

94. Landi F, Marzetti E, Liperoti R, et al. Nonsteroidal anti-inflammatory drug (NSAID) use and sarcopenia in older people: results from the ilSIRENTE study. J Am Med Dir Assoc. 2013;14(8):626 e9-13.
95. Beyer I, Bautmans I, Njemini R, et al. Effects on muscle performance of NSAID treatment with piroxicam versus placebo in geriatric patients with acute infection-induced inflammation. A double blind randomized controlled trial. BMC Musculoskelet Disord. 2011;12:292.
96. Beyer I, Njemini R, Bautmans I, et al. Immunomodulatory effect of NSAID in geriatric patients with acute infection: effects of piroxicam on chemokine/cytokine secretion patterns and levels of heat shock proteins. A double-blind randomized controlled trial. (ISRCTN58517443). Cell Stress Chaperones. 2012;17(2):255-65.
97. Mets T, Bautmans I, Njemini R, et al. The influence of celecoxib on muscle fatigue resistance and mobility in elderly patients with inflammation. Am J Geriatr Pharmacother. 2004;2(4):230-8.
98. Rieu I, Magne H, Savary-Auzeloux I, et al. Reduction of low grade inflammation restores blunting of postprandial muscle anabolism and limits sarcopenia in old rats. J Physiol. 2009;587(Pt 22):5483-92.
99. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med. 2010;2(7):247-57.
100. Gilbert KC, Brown NJ. Aldosterone and inflammation. Curr Opin Endocrinol Diabetes Obes. 2010;17(3):199-204.
101. Di Raimondo D, Tuttolomondo A, Butta C, et al. Effects of ACE-inhibitors and angiotensin receptor blockers on inflammation. Curr Pharm Des. 2012;18(28):4385-413.
102. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995;273(18):1450-6.
103. Sumukadas D, Witham MD, Struthers AD, et al. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. CMAJ. 2007;177(8):867-74.
104. Onder G, Penninx BW, Balkrishnan R, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet. 2002;359(9310):926-30.
105. Di Bari M, van de Poll-Franse LV, Onder G, et al. Antihypertensive medications and differences in muscle mass in older persons: the Health, Aging and Body Composition Study. J Am Geriatr Soc. 2004;52(6):961-6.
106. White WB, Marfatia R, Schmidt J, et al. INtensive versus standard ambulatory blood pressure lowering to prevent functional DeclINe in the ElderlY (INFINITY). Am Heart J. 2013;165(3):258-265 e1.
107. Band MM, Sumukadas D, Struthers AD, et al. Leucine and ACE inhibitors as therapies for sarcopenia (LACE trial): study protocol for a randomised controlled trial. Trials. 2018;19(1):6.
108. Baptista LC, Jaeger BC, Anton SD, et al. Multimodal Intervention to Improve Functional Status in Hypertensive Older Adults: A Pilot Randomized Controlled Trial. J Clin Med. 2019;8(2).
109. Delafontaine P, Yoshida T. The Renin-Angiotensin System and the Biology of Skeletal Muscle: Mechanisms of Muscle Wasting in Chronic Disease States. Trans Am Clin Climatol Assoc. 2016;127:245-258.
110. Kwon OS, Smuder AJ, Wiggs MP, et al. AT1 receptor blocker losartan protects against mechanical ventilation-induced diaphragmatic dysfunction. J Appl Physiol (1985). 2015;119(10):1033-41.

111. Pahor M, Anton SD, Beavers DP, et al. Effect of losartan and fish oil on plasma IL-6 and mobility in older persons. The ENRGISE Pilot randomized clinical trial. J Gerontol A Biol Sci Med Sci. 2018.
112. Trevelyan J, Brull DJ, Needham EW, et al. Effect of enalapril and losartan on cytokines in patients with stable angina pectoris awaiting coronary artery bypass grafting and their interaction with polymorphisms in the interleukin-6 gene. Am J Cardiol. 2004;94(5):564-9.
113. Lin CH, Yang H, Xue QL, et al. Losartan improves measures of activity, inflammation, and oxidative stress in older mice. Exp Gerontol. 2014;58:174-8.
114. Burks TN, Andres-Mateos E, Marx R, et al. Losartan restores skeletal muscle remodeling and protects against disuse atrophy in sarcopenia. Sci Transl Med. 2011;3(82):82ra37.
115. Heisterberg MF, Andersen JL, Schjerling P, et al. Losartan has no additive effect on the response to heavy-resistance exercise in human elderly skeletal muscle. J Appl Physiol (1985). 2018;125(5):1536-1554.
116. Passos-Silva DG, Verano-Braga T, Santos RA. Angiotensin-(1-7): beyond the cardio-renal actions. Clin Sci (Lond). 2013;124(7):443-56.
117. Murphy KT, Hossain MI, Swiderski K, et al. Mas receptor activation slows tumor growth and attenuates muscle wasting in cancer. Cancer Res. 2018.
118. 8th International Conference on Frailty and Sarcopenia Research (ICFSR), March 1-3, 2018, Miami, USA, Symposia, Conference, Oral communications. J Frailty Aging. 2018;7(1):61-91.
119. Abstracts of the 9th International Conference on Cachexia, Sarcopenia and Muscle Wasting, Berlin, Germany, 10–11 December 2016 (part 1). Journal of Cachexia, Sarcopenia and Muscle. 2016;7(5):626-662.
120. Barzilai N, Crandall JP, Kritchevsky SB, et al. Metformin as a Tool to Target Aging. Cell Metab. 2016;23(6):1060-1065.
121. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001;108(8):1167-74.
122. Kjobsted R, Hingst JR, Fentz J, et al. AMPK in skeletal muscle function and metabolism. FASEB J. 2018;32(4):1741-1777.
123. Kanigur Sultuybek G, Soydas T, Yenmis G. NF-kappaB as the mediator of metformin's effect on ageing and ageing-related diseases. Clin Exp Pharmacol Physiol. 2019.
124. Long DE, Peck BD, Martz JL, et al. Metformin to Augment Strength Training Effective Response in Seniors (MASTERS): study protocol for a randomized controlled trial. Trials. 2017;18(1):192.
125. Konopka AR, Laurin JL, Schoenberg HM, et al. Metformin inhibits mitochondrial adaptations to aerobic exercise training in older adults. Aging Cell. 2019;18(1):e12880.
126. Malin SK, Gerber R, Chipkin SR, et al. Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. Diabetes Care. 2012;35(1):131-6.

Table 1. Emerging pharmacotherapies for sarcopenia: age-related muscle wasting.

Drug	Company / Sponsor	Target	Phase	Study Purpose	Status	NCT / Ref
REGN1033 (SAR391786)	Regeneron Pharmaceuticals	Myostatin	2	Examine the safety and efficacy of 3 months subcutaneous REGN1033 (SAR391786) treatment	Completed; no results reported.	NCT01963598
Bimagrumab (BYM338)	Novartis Pharmaceuticals	ActRIIB	2	Determine effects of BYM338 on skeletal muscle volume, mass, and strength and patient function (gait speed) in non-demented elderly adults with sarcopenia and mobility limitations	Completed; Increased muscle mass and strength.	NCT01601600 Ref: [43]
Bimagrumab (BYM338)	Novartis Pharmaceuticals	ActRIIB	2	Determine the efficacy of repeat dosing with multiple dose levels of bimagrumab on patient physical function, skeletal muscle mass and strength in older adults with sarcopenia.	Recruiting.	NCT02333331
Bimagrumab (BYM338)	Novartis Pharmaceuticals	ActRIIB	2	A 24-week off drug extension parallel group study assessing durability of effect on skeletal muscle strength and function after a 6-month double-blind placebo-controlled study evaluating bimagrumab in older adults with sarcopenia.	Recruiting.	NCT02468674
MK-0773	Merck Sharp & Dohme Corp.	Androgen receptor	2	Evaluate the safety, tolerability, and efficacy of MK-0773 in women with sarcopenia.	Completed; Increase lean body mass but did not improve strength or function. Improved strength and physical function in placebo group, attributed in part, to protein and vitamin D supplementation.	NCT00529659 Ref: [79]
Testosterone enanthate, Androgel 1%, Medrol	The University of Texas Medical Branch, Galveston	Androgen Receptor	4	Assess the ability of short-term testosterone injection and gel application to alter anabolic and inflammatory responses in older men.	Completed; no results reported.	NCT00957801

Testosterone enanthate, Finasteride	Endo Pharmaceuticals, Merck Sharp & Dohme Corp.	Androgen Receptor	2	Determine if a higher-than-replacement dose of testosterone and finasteride can be combined to safely increase muscle strength in older men with low blood concentration of testosterone.	Completed; Testosterone combined with finasteride increased muscle strength and bone mineral density and reduces body fat without prostate enlargement.	NCT00475501 Ref: [65]
Transdermal Testosterone and/or Monthly Vitamin D	Besins Healthcare	Androgen Receptor	3	Examine the individual and combined effect of transdermal testosterone and/or Vitamin D in reducing falls risk and improve function in pre-frail hypogonadal senior men.	Recruiting.	NCT02419105
Androgel, Anastrozole	National Institute on Aging (NIA)	Androgen Receptor; Aromatase inhibitor	2	Determine if anastrozole is as effective as testosterone gel in improving bone and muscle strength, hormone levels, and brain function in men over 65 years of age.	Completed; Gait/balance assessment not reported	NCT00104572
Sustanon 250, Zoladex (Gonadotropin releasing hormone analogue)	University of Nottingham	Androgen Receptor; LHRH receptor	3	Evaluate the effect of increased testosterone levels in older males and decreased testosterone levels in young males on muscle protein synthesis.	Recruiting.	NCT03054168
Metformin	Albert Einstein College of Medicine, Inc.	Glucose metabolism	4	Examine effects of metformin on the biology of aging in humans.	Completed; no results reported.	NCT02432287

Metformin	University of New Mexico	Glucose metabolism	3	Investigate the effects of short duration metformin treatment on a surrogate marker of cellular senescence and autophagy among adult patients with prediabetes.	Recruiting.	NCT03309007
Metformin	The University of Texas Health Science Center at San Antonio	Glucose metabolism	2	Test metformin as a novel intervention for prevention of frailty.	Recruiting.	NCT02570672
Metformin	VA Office of Research and Development, Oregon Health and Science University	Glucose metabolism	2	Determine if metformin can prevent the loss in muscle mass and physical performance and to examine changes in muscle histologic characteristics associated with metformin treatment in older adults with prediabetes.	Active; not recruiting.	NCT01804049
Allopurinol	University of Dundee	Xanthine oxidase inhibitor	4	Determine if allopurinol improves physical function and muscle energetics in patients with primary sarcopenia.	Completed; no results reported.	NCT01550107
BIO101 (Sarconeos)	Biophytis	Mas Receptor	2	Evaluate the clinical benefits, safety and tolerability of BIO101 administered orally for 6 months to older patients, and community dwelling men and women aged ≥65 years, suffering from age-related sarcopenia (including sarcopenic obesity), and at risk of mobility disability.	Recruiting.	NCT03452488

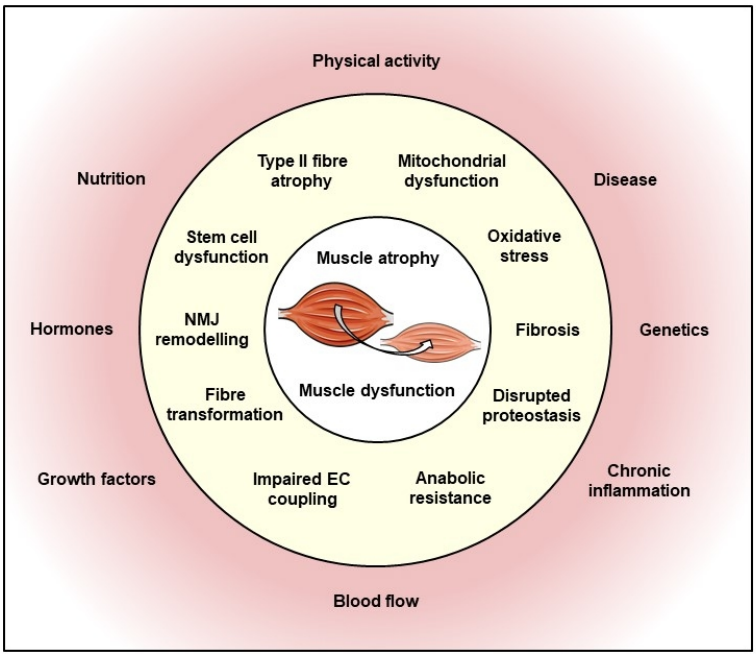
Losartan	Johns Hopkins University, National Institute on Aging (NIA)	AT1 receptor blocker	2	Determine if losartan can prevent the decrease in strength associated with ageing.	Completed; no results reported.	NCT01989793
Losartan	Abbott, National Institute on Aging (NIA)	AT1 receptor blocker	2	Test the ability of anti-inflammatory interventions to prevent major mobility disability by improving or preserving walking ability.	Completed; no results reported	NCT02676466
Losartan, Perindopril, HCTZ	University of Alabama at Birmingham, University of Colorado, Denver	AT1 receptor blocker	2	Determine if choice of antihypertensive medication influences changes in functional status and other cardiovascular risk factors among older persons with hypertension when combined with physical exercise.	Recruiting.	NCT03295734
Lisinopril, Amlodipine	UConn Health, National Institute on Aging (NIA)	ACE inhibitor, Calcium antagonist	4	Evaluate different high blood pressure treatments for controlling decline in mobility and cognition in an ageing population.	Active; not recruiting	NCT01650402
Alfacalcidol	Indonesia University	Vitamin D analogue	3	Determine the effect of alfacalcidol on the upper-body muscle strength in Indonesian elderly women aged 60 years or older with low handgrip strength.	Completed; no results reported	NCT02327091

Data are presented for clinical trials in phase 2 development and higher, as available from *Clinicaltrials.gov*. Abbreviations: NCT, National Clinical Trial; Ref, Reference; AR, androgen receptor; LHRH, luteinizing-hormone releasing hormone; AMPK, AMP-activated protein kinase; GR, glucocorticoid receptor; AT1, angiotensin II type 1; HCTZ, Hydrochlorothiazide; ACE, Angiotensin converting enzyme.

Figure Legends

Figure 1. Pathophysiology of sarcopenia. The underlying pathophysiology of sarcopenia is complex and multifactorial and addressing its different symptoms will likely require more than a single treatment. Sarcopenia is often described as a neuromuscular syndrome since age-related changes occur to both the neural aspects of innervation and the preservation of motor units, as well as effects directly on muscle fibres. Skeletal muscle mass is maintained by a coordinated balance between protein synthesis and protein degradation, termed protein turnover. Muscle mass and phenotype are responsive to both systemic factors and the local environment. Factors described in the outer ring are those that can directly influence mechanisms outlined in the inner ring that are ultimately responsible for muscle atrophy and dysfunction. Perturbations in systemic factors such as inflammatory cytokines and hormones can disrupt skeletal muscle energy metabolism and proteostasis. Nutritional status can have profound effects on mass regulation. Older adults are at an increased risk for nutritional insufficiency and are recommended to consume more protein than the current Recommended Dietary Allowance, perhaps confounded by an age-related decreased response to feeding and/or nutrients, termed anabolic resistance. Ageing is associated with reduced vascular function and blood flow, which can affect delivery and uptake of oxygen, hormones, nutrients and amino acids to muscle. Circulating levels of (anabolic) hormones and growth factors decrease with age. Muscle phenotype can be influenced by genetic and lifestyle factors, and the interactions between them. Physical activity levels influence whole-body and muscle health during ageing, with regular resistance exercise training being an effective intervention to help attenuate age-related changes in muscle mass and strength. The inner ring describes some of the mechanisms responsible for structural, metabolic and functional consequences of sarcopenia. These include: 1) the preferential loss and atrophy of type II (fast) muscle fibres and the remodelling of motor units that can shift overall fibre proportions towards a slower

phenotype; 2) alterations in muscle proteostasis leading to fibre atrophy and possible degeneration induced by oxidative stress and mitochondrial dysfunction leading to metabolic impairments; 3) alterations at the neuromuscular junction (NMJ) that potentially compromises neurotransmission; 4) changes in excitation-contraction coupling including mechanisms regulating the release and reuptake of Ca^{2+} by the sarcoplasmic reticulum, alterations in the number of participating cross-bridges, the force generated per cross-bridge, altered rates of cross-bridge attachment and detachment; and 5) an anabolic resistance to nutritional intake, particularly protein. These contributing mechanisms can also compromise muscle function without the loss of muscle mass; a condition described as 'dynapenia'. Figure was made with Servier Medical Art (https://smart.servier.com/).



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