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Reviews

Current and investigational medications for the treatment of sarcopenia

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ABSTRACT

Sarcopenia, defined as the loss of muscle mass and function, is a widely prevalent and severe condition in older adults. Since 2016, it is recognized as a disease. Strength exercise training and nutritional support are the frontline treatment of sarcopenia, with no drug currently approved for this indication. However, new therapeutic options are emerging. In this review, we evidenced that only very few trials have focused on sarcopenia/sarcopenic patients. Most drug trials were performed in different clinical older populations (e.g., men with hypogonadism, post-menopausal women at risk for osteoporosis), and their efficacy were tested separately on the components of sarcopenia (muscle mass, muscle strength and physical performances). Results from trials testing the effects of Testosterone, Selective Androgen Receptor Modulators (SARMs), Estrogen, Dehydroepiandrosterone (DHEA), Insulin-like Growth Factor-1 (IGF-1), Growth Hormone (GH), GH Secretagogue (GHS), drug targeting Myostatin and Activin receptor pathway, Vitamin D, Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs), or β-blockers, were compiled. Although some drugs have been effective in improving muscle mass and/or strength, this was not translated into clinically relevant improvements on physical performance. Finally, some promising molecules investigated in on-going clinical trials and in preclinical phase were summarized, including apelin and irisin.

1. Introduction

Sarcopenia was recognized as a pathology (ICD-10-CM code M62.84) in September 2016, nearly 30 years after this term was coined and first mentioned by Irwin Rosenberg [1] and after important basic and clinical investigations. Its recognition as a disease involving reduced muscle mass, muscle strength, and low physical performance contributed to raising the awareness on sarcopenia among clinicians [2] and paves the way to the development of potential treatments.

Sarcopenia is a burdensome condition, considered the biological substrate and primary cause of frailty, a syndrome that precedes disability in older adults. Sarcopenia is associated with falls and fractures, mobility disability, and contributes to a reduced quality of life [2]. Therefore, it is possible that a drug treating sarcopenia would contribute to maintain/improve functional levels, ultimately promoting healthy aging as defined by the World Health Organization (WHO) [3], and reducing sarcopenia-related healthcare costs (estimated at £2 billion/year in the UK, for example) [4].

By acting on muscle mass and strength, a treatment for sarcopenia would have the ultimate goal of reducing both mobility disability (or physical performances in a clinically relevant way – see Fig. 1) and the rates of major health events, such as fractures. Reaching this final aim is important for the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) approval. However, sarcopenia drug development is still in its infancy. Current recommendations for the treatment of sarcopenia are mainly limited to the practice of strength exercise and to increased energy food intake with a diet rich in proteins [5]. Although effective, nutritional support and exercise programs are often unattainable in clinical practice, especially in frail, poly-morbid sarcopenic patients [6]. Therefore, the prospect of effective and safe drugs targeting the biological mechanisms of sarcopenia appears as a very attractive therapeutic perspective. In this review, we provided an update of pharmacological treatments tested in humans and discussed current advances in drug development for sarcopenia, including molecules in preclinical phase. Drugs were classified according to their primary mechanism of action (e.g., targeting changes in hormones and muscle metabolism, oxidative stress, etc.). The findings are discussed according to clinical efficacy and safety.

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2. Methods

Although this is not a systematic review, in order to avoid losing important studies on the topic we searched PubMed (on December 25th 2022) for articles published between Jan 1990 (the year following the moment the term sarcopenia was first used) until present. Search terms were: random* AND (sarcopeni*) AND (drug OR pharmaco*). Since the focus of this review is on pharmacological treatments of sarcopenia, trials testing non-pharmacological interventions (e.g., physical activity, nutritional supplementation [e.g., branched chain amino-acid, omega 3, creatine, probiotics, etc.]) were not included. The reference list of relevant articles was scrutinized, as well as the most recent recommendations for sarcopenia treatment from scientific societies. ClinicalTrials.gov (http://www.clinicaltrial.gov) was used for retrieving ongoing pharmacological interventions on sarcopenia under phases 1, 2 or 3.

3. Results and discussion

Overall, very few trials focused on the treatment/prevention of sarcopenia or selected a population of patients with a diagnostic of sarcopenia. Most drugs investigated to date were used to improve one or more components of sarcopenia, i.e., muscle mass, muscle strength or physical performance, in different clinical populations (e.g., men with hypogonadism, post-menopausal women at risk for osteoporosis). Here below we first present the few trials focusing on sarcopenia/sarcopenic patients. Then, we provide a comprehensive overview of the main drugs tested for their effectiveness on at least one component of sarcopenia (Fig. 1). Finally, we summarize the most promising pre-clinical molecules emerging in the field of sarcopenia. The biological mechanisms through which each drug would act on sarcopenia and its components are displayed in Appendix 1 Supplementary data.

4. Trials on sarcopenia/sarcopenic patients

To date, few randomized controlled trials (RCT) have included older adults with sarcopenia (e.g., European Working Group on Sarcopenia in Older People [EWGSOP] or the Asian Working Group for Sarcopenia [AWGS] criteria) to study the effect of a drug on sarcopenia and its components. It should be noted that there is a large diversity of physical tests used to assess muscle strength or physical performances as well as a large diversity of body composition assessment tools (CT scan, computerized tomography scan; DEXA, dual X-ray absorptiometry; BIA, bioelectrical impedance analysis; MRI, magnetic resonance imaging…). The variety of assessment tools leads to a diversified terminology that limits comparison and generalizability of findings and may lead to confusion. For example, although related, terms like lean mass or muscle mass do not designate the same construct and should not be used as synonyms.

One study [7] explored the muscle-related effects of MK-0773, a Selective Androgen Receptor Modulator (SARM), in 170 women aged 65 years and over with sarcopenia and moderate physical dysfunction. This RCT showed that 6 months of MK-0773 resulted in a significant within-group increase on muscle mass (lean body mass (LBM assessed by DEXA) +1.26 kg ± 1.09 and Appendicular Lean Mass (ALM) +0.72 kg ± 0.55), even though the between-group differences were not significant. No differences were found for muscle strength or physical performance between MK-0773 and placebo.

Another RCT investigated the benefits of Perindopril, an Angiotensin Converting Enzyme inhibitor (ACEi), in 145 sarcopenic subjects defined by the EWGSOP criteria [8]. No effect was found on total LBM (as measured by BIA), handgrip strength (HGS), quadriceps strength (dynamometer), Short Physical Performance Battery (SPPB), 6-min walk test, gait speed, or chair rise test at 12 months (see Table 1).

Nine RCT studied the effect of vitamin D supplementation on the

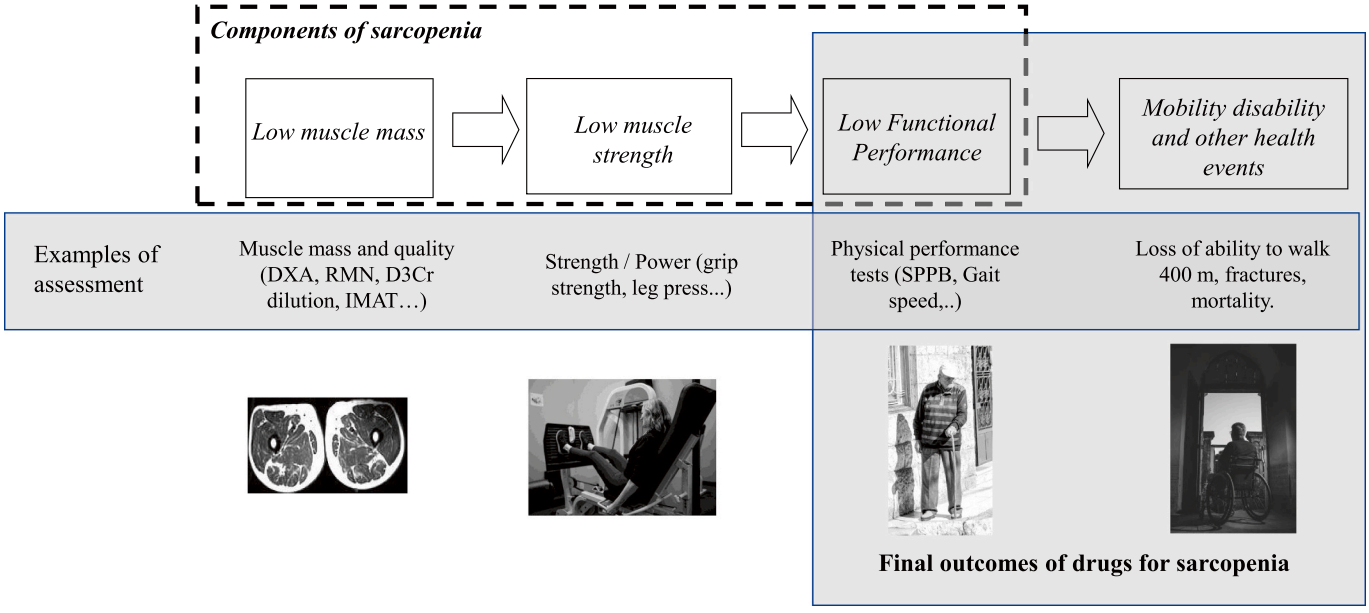

Fig. 1. SARCOPENIA as an indication for medication

Note:

The mobility disability process is, at least in part, the final result of quantitative and qualitative declines in muscle tissue which lead to a loss of muscle function (loss of muscle strength, muscle power, etc.), which beyond a certain threshold, results in a reduction in physical performances (slow gait speed, short physical performance battery, slow chair rise test, slow stair climbing…). At their ultimate stages, the functional limitations result in inability to perform a physical task (mobility disability). Many factors can influence each step of the process (depression, sensory limitation, pain, social factors, etc.) making the demonstration of the effectiveness of a treatment targeting muscle tissue all the more challenging as the objective is downstream. The clinical relevance of a treatment for sarcopenia is evaluated on a clinically significant improvement of physical performances, reduce mobility disability and prevention of their associated major health events (falls, fractures, nursing home admission, death).

DXA, dual-energy X-ray absorptiometry; MRI, Magnetic Resonance Imaging; D3Cr dilution, D3-Creatine Dilution, IMAT, Intra-Muscular Adipose Tissue; SPPB, Short Physical Performance Battery.

Table 1
Summary of randomized controlled trials on Angiotensin Converting Enzyme inhibitor (ACEi) or angiotensin receptor blockers (ARBs) on muscle mass, muscle strength and/or physical performances.

First author, year	Population	Age, years (SD)	Number of participants, treatment/comparator	Follow-up	Effect of ACEi/ ARBs on muscle mass and tissue	Effect of ACEi /ARBs on muscle strength	Effect of ACEi/ARBs on physical performances
LACE study group, 2022 [8]	Participants aged >70 years with sarcopenia, defined as low gait speed and/or low HGS and low muscle mass (EWGSOP, 2010).	78.7 (6.0) perindopril* group 78.8 (6.1) placebo group	145 participants Perindopril* 8 mg/d (n = 73) or Leucine (n = 33) or placebo (n = 39)	12 months	**No effect** on total Lean Body Mass (BIA).	**No effect** on HGS and quadriceps strength (dynamometer)	**No effect** on the SPPB, 6-min walk test, gait speed, chair rise test.
Sjúrðarson, 2022 [106]	Participants aged between 20 and 50 years and healthy.	39 (7.0) years for men and 43 (6.0) for women in Enalapril* group 39 (8.0) years for men and 41 (7.0) for women in placebo group	50 participants Enalapril* (5 mg to 20 mg/d) (n = 25) or or placebo (n = 25) + high-intensity exercise training in both groups	8 weeks	**No increased** of Lean Body Mass (DXA) in ACEi group but significant increased (+3 kg) in exercise training alone group.	**No effect** on rowing ergometer effort	**No effect** on skeletal muscle endurance and VO_2 max.
Pahor, 2019 [105]	Participants aged >70 years with self-reported difficulty walking one-quarter of a mile or climbing a flight of stairs, had a 4 m walking speed at usual pace of <1 m/s but were able to complete the 400 m walk, and had a plasma IL-6 of 2.5–30 pg/mL	77.6 (5.4) years	289 participants Losartan** 50–100 mg/ d only (n = 39) or Fish oil (n = 122) or Combination (n = 26) or Placebo (n = 102)	12 months	NA	NA	**No effect** on the 400-m walking speed and the SPPB.
Sumukadas, 2018 [108]	Participants aged >65 years with at least one fall in the previous year.	78.0 (7.4) years	80 participants Perindopril* 4 mg (n = 40) or Placebo daily (n = 40)	15 weeks	NA	**No effect** on muscle strength (magnetic femoral nerve stimulation)	**No effect** on antero-posterior sway postural sway (force-plate), and the 6-min walk distance.
Heisterberg, 2018 [101]	Men aged >65 years, nonsmokers, with BMI between 19 and 34 with no hypertension or hypotension.	72 (5.0) years in Losartan** alone group 71 (4.0) years in Losartan** + resistance training group 72 (5.0) years in resistance training alone	58 participants Losartan**, 100 mg/day (n = 20) or Losartan** + resistance training (n = 18) or resistance training alone (n = 20)	4 months	**No effect** on quadriceps, vastus lateralis cross-sectional area, (MRI) and type II fiber area No changes induced by ACEi on satellite cell number.	**No effect** on dynamic and isometric quadriceps peak Force (Kin-Com dynamometer)	NA
Curtis, 2016 [109]	Participants with stable COPD in GICOLD stages II to IV, referred for pulmonary rehabilitation and with MRCD score of at least 3 or 2, with functional limitation.	67 (8.0) years	78 participants Enalapril* 10 mg (n = 31) or Placebo (n = 34)	10 weeks	**No effect** on mid-thigh muscle cross-sectional area (CT scan) and fat-free mass (BIA).	**No effect** on quadriceps maximal volitional contraction **Reduced** peak power (cycle ergometry)	NA
Sumukadas, 2014 [110]	Participants aged ≥65 years with a SPPB score ≤ 10.	75.7 (6.8) years	170 participants Perindopril* 4 mg (n = 86) or placebo (n = 84) Both groups received exercise training	20 weeks	NA	**No effect** on quadriceps (handheld dynamometer) or HGS (dynamometer)	**No effect** on 6-min walk distance or SPPB score.
Cesari, 2010 [111]	Participants aged >55 years with at least one indicators of cardiovascular risk: Coronary heart disease/ peripheral vascular disease/ history of stroke/ diabetes with at least one other cardiovascular risk factor.	65.97 (7.41) years	257 participants Fosinopril* (20 to 40 mg/d) (n = 127) or placebo (n = 130)	6 months	NA	**No effect** on HGS (dynamometer)	**No effect** on the SPPB, the 4-meter walking speed, balance, and the chair stand tests.
Bunout, 2009 [112]	Participants aged >70 years, living in the community with stage I hypertension.	75 (4.0) years	120 participants Enalapril* 10 mg/d (n = 60) or Nifedipine 20 mg/ d (n = 60)	9 months	**No effect** on LBM (DEXA).	**No effect** on quadriceps strength (quadriceps table and a digital force transducer) and HGS (dynamometer)	**No effect** on the TUG, the SPPB, endurance (distance that subjects could walk at a constant pace during 12 min).

(*continued on next page*)

Table 1 (*continued*)

First author, year	Population	Age, years (SD)	Number of participants, treatment/comparator	Follow-up	Effect of ACEi/ ARBs on muscle mass and tissue	Effect of ACEi /ARBs on muscle strength	Effect of ACEi/ARBs on physical performances
Sumukadas, 2007 [113]	Participants aged >65 years with self- reported problems with mobility or functional activities of daily living.	78.7 (7.7) years	130 participants Perindopril* 2 to 4 mg/ d (n = 65) or Placebo (n = 65)	20 weeks	NA	NA	**Significantly effect** on 6-min walking distance (mean between-group difference 31.4 m, [CI] 10.8 to 51.9) p = 0.003). **No effect** on the Sit-to-stand time (the time taken to get up from a chair and sit down again 10 times), TUG test and the NEADL scores.
Gerdts, 2006 [114]	Participants aged between 55 and 80 years with electrocardiographic left ventricular hypertrophy.	68 years	51 participants Losartan** 50–100 mg/ d (n = 24) or Atenolol 50–100 mg/d (n = 27)	12 months	NA	NA	**No effect** on VO2max.
Leonetti, 1991 [115]	Participants aged 61 to 79 years with hypertension	66 years.	36 participants Metoprolol 100 mg/d or Captopril* 50 mg/d or hydrochlorothiazide 25 mg/d plus Amiloride 2.5 mg/d or Placebo	2 months	NA	NA	**Exercise endurance was higher** after captopril (541 s) compared to metoprolol (498 s), hydrochlorothiazide amiloride (519 s) or placebo (529 s) (standard bicycle ergometer).

Note. ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; *, ACEi; **, ARBs; EWGSOP, 2010 European Working Group on Sarcopenia in Older People definition; HGS, handgrip strength; IL-6, Interleukin-6; LBM, Lean Body Mass; SPPB, Short Physical Performance Battery; VO2max, maximal oxygen uptake; GICOLD stages, Global Initiative for Chronic Obstructive Lung Disease stages; MRCD score, Medical Research Council Dyspnea score; NEADL score, Nottingham Extended Activities of Daily Living scores; VO2max, Peak oxygen uptake; TUG, Timed-Up and Go test; BIA, bioelectrical impedance analysis; CT scan, computerized tomography scan; DEXA, dual X-ray absorptiometry; MRI, magnetic resonance imaging; NA, None Applicable.

context of sarcopenia [9]. Although performed in populations of sarcopenic patients defined according with the EWGSOP or the AWGS criteria, all these RCTs provided vitamin D combined with protein supplementation and/or exercise training. Therefore, their design does not allow to isolate the specific effect of vitamin D. Despite undertaking complex statistical approaches in an attempt to disentangle the specific effect of vitamin D, it is difficult to drawn solid conclusions from these trials. Using data from these nine RCT, Cheng et al. meta-analysis reported that, compared to placebo, combining vitamin D supplementation with exercise and protein supplementation increase HGS (mean difference, MD 3.86; 95 % CI, 0.52 to 7.21) and combination of vitamin D and protein could improve chair-stand test (MD −1.32 s; 95 % CI, −1.98 to 0.65). The authors recognize that the effects highlighted in certain combinations of interventions are weak. Moreover, in some RCTs, deficiency in vitamin D was not an eligibility criterion; participants without deficiency have a low probability to benefit from vitamin D supplementation. Greater effects of vitamin D supplementation on muscle have been previously reported in patients with vitamin D deficiency at baseline (<25 nmol/l) [10].

Finally, two RCT tested the benefits of Bimagrumab, a monoclonal antibody that inhibits the action of Myostatin and Activin A [11,12]. In a phase 2 proof-of-concept clinical study, Rooks et al. reported promising results in sarcopenic participant (subjects 65 and older with a 4-m gait speed between 0.4 and 1.0 m/s and a low appendicular skeletal muscle index) on HGS and muscle mass (thigh muscle volume + 4.80 % [± 5.81 %] in the Bimagrumab group vs −1.01 % [±4.43 %] in the placebo group at 24 weeks (MRI); increase in ALM (DEXA) of 4.30 % [0.6 kg] vs no change in the placebo group [−0.2 %] at 16 weeks). Sensitivity analyses performed among the frailest participants (gait speed <0.8 m/s) showed an improvement of physical performance at 16 weeks (walking speed [+0.15 m/s], 6-min walk test [82 m more] in the Bimagrumab group than in the placebo) [11]. However, these results were not confirmed in a recent phase 3 RCT [12] performed among 180 community-living adults with sarcopenia (4-m gait speed ≥0.3 m/s and < 0.8 m/s, and low appendicular skeletal muscle index). Participants were randomized to monthly Bimagrumab 700 mg or placebo for 6 months with adequate diet and home-based exercise. Participants mean (SD) age was 79.1 (5.3) years. Despite a statistically significant increase on LBM (DXA) by 7 % (95%CI, 6 % - 8 %) in the treatment group vs 1 % (95%CI, 0 % - 2 %) in the placebo group (25-week LBM change: 2.02 kg ±1.95 in the Bimagrumab group vs 0.08 ± 1.17 kg in placebo [p < 0.001]), no significant increase in either the SPPB or the 6-min walk test were observed.

Several on-going RCT targeting components of sarcopenia are reported in Clinicaltrials.gov but few recruit sarcopenic patients (Fig. 2). Current evidence is still scarce mainly because patients with sarcopenia have been poorly investigated as a target population in pharmacological trials. See Supplementary materials Tables S4, S5 and S6 on medications in ongoing Phase 2, 3 and 4 Clinical Trials for Sarcopenia identified from Clinicaltrials.gov (as searched on April 12th, 2023). Indications and primary outcomes vary substantially across studies.

5. Trials on sarcopenia components in several clinical populations

5.1. Hormonal drugs

5.1.1. Testosterone

The progressive decline of 1 to 2 % per year in testosterone blood level observed after the age of 30 [13] may be associated with clinical symptoms of hypogonadism among which the decline in muscle mass, strength and physical performance [14]. Testosterone is considered a major determinant of the maintenance of muscle mass and function during aging [15]. However, no study on testosterone supplementation has specifically targeted sarcopenia or sarcopenic patients. Therefore, the efficacy and safety of testosterone supplementation in the context of sarcopenia remain to be determined.

5.1.1.1. Efficacy. Several reviews and meta-analyses of RCT investigating the effect of testosterone on the components of sarcopenia (i.e.,

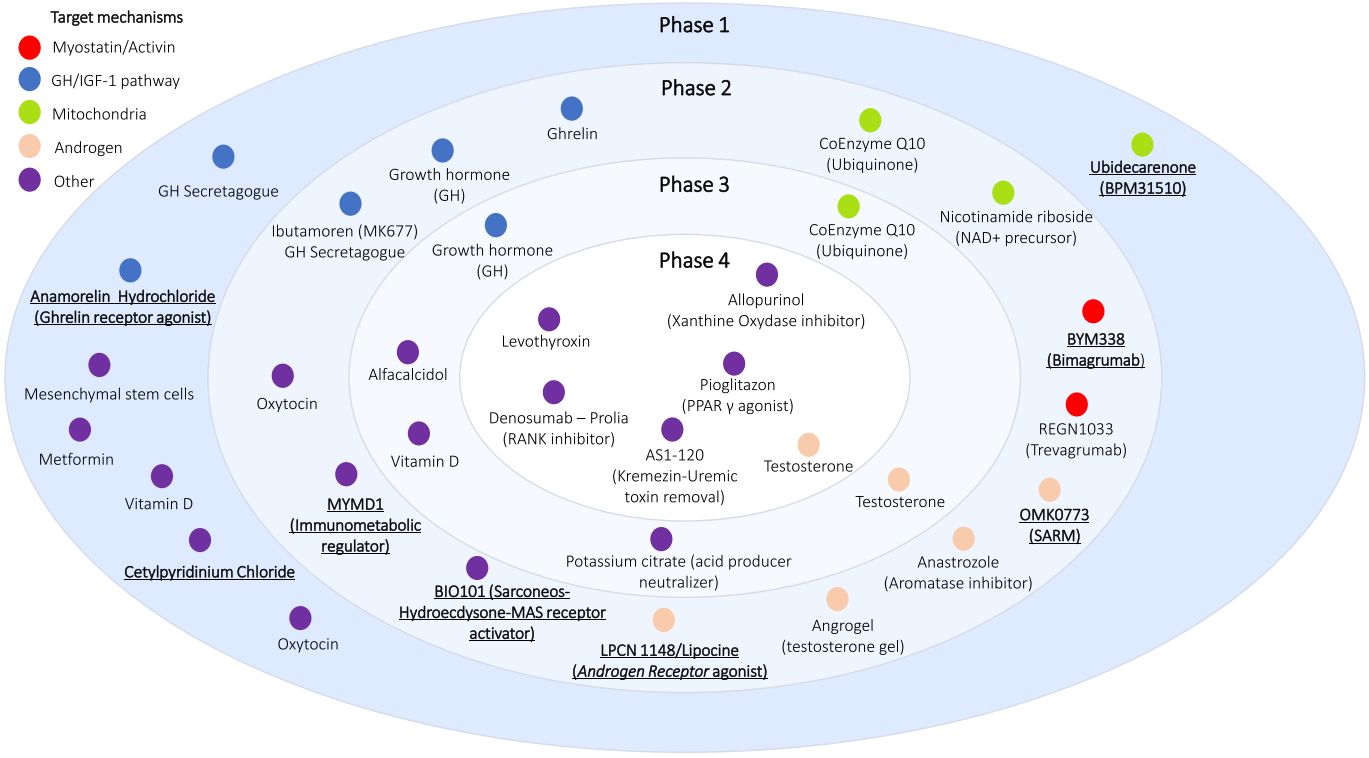

Fig. 2. Clinical trial on sarcopenia reported in the ClinicalTrials.gov database
Note: from *Clinical trial.gov* with "condition or Disease": Sarcopenia and Advance search: Clinical trials (interventional trial)/Older adults (65+)/Early phase 1, phase 1, 2, 3, 4 (February 8th, 2023)
Underlined and bold compounds are investigated in participants with sarcopenia criteria
This research focused on drug and excluded nutritional and behavioral intervention and does not target cachexia.

muscle mass, strength and function) have been published in recent years [16–23]. It should be noted that the design of the multiple trials varies substantially in terms of study population, duration, dose, route of administration, pharmaceutical formulation but also physical tests assessed, resulting in high heterogeneity. This diminishes comparisons across studies and limits the generalizability of the findings.

The meta-analyses by Correa et al. ($n = 17$ studies) and Parahiba et al. ($n = 11$ studies) found that testosterone increases muscle mass and muscle strength in middle-aged/older men. However, the results on physical performances were inconsistent. Whereas Bashin et al. [19], in the most recent recommendations of the Endocrine Society Clinical Practice Guideline, indicate that testosterone treatment in men with hypogonadism increases muscle mass and strength, the Belgian Society of Gerontology and Geriatrics [23] support that the effect of testosterone in men with low serum levels of testosterone (<200–300 ng/dl) is important on muscle mass but it is considered modest or minimal on muscle strength. Most investigations [24–27], including the above-mentioned reviews and meta-analysis, concluded that testosterone benefits on physical performance is unconvincing. For instance, Kenny et al. [28] (5 mg AndroGel 1 % daily during 12 months) and Srinivas-Shankar et al. [25] (50 mg Testogel 1 % daily during 6 months) found no differences between testosterone group and controls on the SPPB, the supine to stand test and the Get Up and Go test [28] or the gait speed, the 6-min walk test, and the physical performance test [25]. Furthermore, when statistically significant, the magnitude of the effect of testosterone on the components of sarcopenia varies across trials and its clinical relevance is arguable [29,30].

The optimal route of administration (intramuscular, transdermal, oral) for testosterone remains a matter of debate. Currently, the effect of the different routes of administration of testosterone on components of sarcopenia has never been investigated. However, in their meta-analysis, Skinner et al. [18] investigated separately the effects of intramuscular and transdermal testosterone supplementation for LBM (from 31 RCT) and muscle strength (17 RCT). Overall, the authors confirm a 3.4 % increase in LBM in testosterone groups and a significant improvement of muscle strength. Interestingly, intramuscular treatment resulted in 3-to-5 times greater improvement of muscle mass or muscle strength compared to transdermal formulation. A larger increase in muscle strength was also found previously by other researchers for injected instead of transdermal or oral administration of testosterone [22]. Although Parahiba et al.'s meta-analysis did not confirm this result [17], Corona et al. [21] reported that LBM did not improve in trials using oral testosterone while transdermal and intramuscular preparations significantly improved LBM, with better results for the latter [21].

In sum, no study investigated the potential benefits of testosterone on sarcopenia. Despite different methodological approaches, all meta-analysis reached similar conclusions: testosterone supplementation is effective for improving muscle mass and muscle strength in older patients with different severity levels of hypogonadism. However, the efficacy of testosterone on physical performance is null or very low.

5.1.1.2. Safety. The caution of current recommendations [5] for testosterone supplementation in the treatment of sarcopenia components is reinforced by the lack of knowledge on the long-term safety of this intervention. Available data from RCT do not reveal major safety concerns, but most studies were not sufficiently powered to allow the identification of potential adverse effects. Although some studies found an increase in cardiovascular events [26,31–34], a recent expert committee concluded that current evidence does not support increased risks of cardiovascular events with testosterone therapy [35]; large RCTs are still needed [36]. Moreover, an important number of epidemiological studies showed that low testosterone concentrations are associated with mortality, coronary artery disease, poor glycemic control, markers of inflammation, and metabolic syndrome [36,37]. Regarding the risk of

prostate cancer, systematic reviews [38] and meta-analysis [19] did not find differences on prostate volume in hypogonadal subjects or on the International Prostate Symptom Score in people treated with testosterone compared to controls. Therefore, the evidence does not support testosterone supplementation as a cause of prostate cancer [39], but the data remain scarce and initial control and monitoring of Prostate Specific Antigen is recommended [19].

5.1.2. Selective androgen receptor modulator (SARM)

SARMs are synthetic androgen modulators. The variability of androgen receptor regulatory proteins from one organ to another [40] allows SARMs under study to have physiological effects specifically targeting skeletal muscle, while avoiding undesirable androgenic effects [41]. SARMs do not bind progesterone receptor or glucocorticoid receptor. This eliminates concerns about the potential adverse effects of testosterone and opens up therapeutic perspectives for sarcopenia in women. Several SARMs, such as 7 α-methyl-19-nortesterone (MENT or Trestolone), Ligandrol or Ostarine (enobosarm) [42] have been investigated but none has been approved under a clinical indication by FDA or EMA.

In a randomized phase 2 study, Dalton et al. showed that 12 weeks of the SARM GTx-024 (enobosarm) in 120 healthy men and women over the age of 60 resulted in an increase in lean body mass (assessed by DEXA) of 1.3 kg as well as an improved performance in the stair climb test [43].

Muscle wasting is a component of sarcopenia often investigated in the context of other pathologies (e.g., cancer, chronic obstructive pulmonary disease [COPD]) [44,45]. A phase 2 RCT in 120 cancer patients showed a significant LBM increase (assessed by DEXA) (but no changes in physical function) in subjects treated for up to 113 days by enobosarm 1 mg (+1.5 kg, −2.1 to 12.6) or 3 mg (+1.0 kg, −4.8 to 11.5) vs. placebo (no change) [45]. Two phase 3 RCT test enobosarm effects for preventing muscle wasting (POWER study 1 and 2) in 641 men or postmenopausal women on chemotherapy for advanced non-small cell lung cancer [46]. The co-primary endpoints (defined in partnership with the FDA) were ≥ 10 % improvement in physical function (stair climb power) and no LBM loss (assessed by DEXA) compared to baseline. Although information available in the Clinicaltrial.gov database suggests that enobosarm improved LBM, the results of these trials have not been published yet. In patients with COPD, the SARM GSK2881078, in combination with a physical activity program, improved maximal quadriceps strength by 5.2 % for men and 7.0 % in women at 90 days, in addition to a 2 kg gain of muscle mass in both sexes [44].

5.1.2.1. Safety. The long-term side effects of SARMs are almost unknown. A decrease on high-density lipoprotein (HDL) blood level calls for caution regarding its use in patients at risk for cardiovascular events. The effects of SARM on circulating testosterone levels as well as on liver function require attention [47].

In sum, although our knowledge of these new molecules is generally very fragmented [48], the results of clinical studies on SARMs are promising, particularly on muscle wasting in patient with severe inflammatory diseases in which muscle mass, by itself, is an independent risk factor for treatment tolerance and survival, such as cancer and COPD.

5.1.3. Estrogens

No RCT has studied the effect of estrogens in sarcopenic patients. However, several studies have evaluated the effects of estrogens on muscle mass, muscle strength or physical performances in the context of osteoporosis in post-menopausal women [49,50], who are much younger than the usual sarcopenic patients. Despite epidemiological and basic research arguments, the benefits of estrogens in preventing loss of muscle mass and strength in postmenopausal women are not confirmed in most RCT, as reported by reviews and meta-analyses [49,50].

In 2019, a meta-analysis investigated the effects of estrogen hormone therapy on LBM (assessed by DXA, or BIA) compiling data from 12 RCTs with a total of 4474 postmenopausal women [50]. This meta-analysis concluded that estrogen did not significantly slow the loss of muscle mass. Indeed, postmenopausal women on estrogen lost 0.06 kg (−0.05 to 0.18) less LBM than those without treatment. The meta-analysis performed by Xu et al. (2020) focused on the effects of estrogen therapy on muscle strength in postmenopausal women [49]. This work compiled data from nine studies, totalizing 2476 subjects. The authors concluded that estrogen had no significant effects on muscle strength, refuting the findings of a previous meta-analysis [51]. In that meta-analysis, Greising et al. compiled data from 23 studies and found a small but significant improvement of 5 % on muscle strength in women on estrogen compared with controls. These meta-analyses suggest that the benefit (if any) of estrogen for sarcopenic women would be modest. It is also possible that relatively young post-menopausal women have functional reserves that are too high to benefit from the intervention. A six months supplementation with isoflavone, a phytoestrogen, in a small RCT involving 18 obese-sarcopenic postmenopausal women, reported a small but significant improvement of ALM (assessed by DXA) [52].

Other drugs with estrogenic properties have been investigated. The few RCTs that evaluated the effect of Tibolone, a synthetic steroid with androgenic, estrogenic and progestin properties, did not report significant improvements on muscle strength, endurance or power [53–55]. The potential cardiovascular side effects of Tibolone rule out therapeutic perspectives in older adults with sarcopenia. A 12-month RCT [56] with 198 healthy women (≥70 years) found a small but significant increase on fat-free mass (assessed by BIA) (0.83 Kg ±2.4 kg versus 0.03 kg ±1.5) and total body water in subjects taking raloxifene, a selective estrogen receptor modulator (SERM), compared to placebo. Muscle strength and muscle power did not change.

5.1.3.1. Safety. The recent meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer [57] and the Million Women Study [58] reported that estrogen therapy is associated with a higher risk of breast cancer. This issue is an important limitation for the relevance of future estrogen treatment in patients with sarcopenia.

5.1.4. Dehydroepiandrosterone (DHEA)

DHEA, a nandrolone precursor, is synthetized in men and women and have the ability to enhance testosterone levels [48,59]. To date, six RCT in older adults (Table 2) have investigated the effects of 50 to 75 mg/day of DHEA provided during 6 to 24 months on muscle mass [27,28,60–63], muscle strength and physical performance [27,28]. Among them, two positive studies suggested that DHEA potentiates the beneficial effects of a physical activity program on muscle functioning [28,61]. DHEA supplementation alone does not seem to lead to gains in muscle mass/volume or strength in older individuals. However, Jankowski et al. [64] performed pooled analysis of three RCT (total of 295 women and 290 men) [27,62,65] and found that DHEA supplementation resulted in a sex-specific effect on body composition with a mild increase of 0.5 kg of fat-free mass only in women. A recent meta-analysis that investigated the muscle-related impact of DHEA supplementation also suggested, based on three RCT, that DHEA treatment resulted in a small but significant improvement on LBM (0.68 kg, 95 %, CI: 0.31–1.05) [59]. Potential long-term benefits of DHEA on physical performances remain unknown.

In sum, only few, small-scale RCT of relatively short duration investigated the effects of DHEA on components of sarcopenia. Sex-specific improvements of DHEA treatment on LBM deserve further investigations in well-powered phase 3 RCT before any solid conclusions can be drawn.

Table 2
Randomized controlled trials that investigate effect of DHEA supplementation on muscle component of sarcopenia in subjects 65+ years.

References	Participants	Dose	Duration	Main results
Percheron et al. 2003 [60]	280 healthy ambulatory and independent men and women aged 60 to 80 years	50 mg/d, orally or placebo	1 year	No positive effect inherent to DHEA treatment was observed either on muscle strength or in muscle cross-sectional areas (CT scan).
Nair et al. 2006 [27]	87 men aged 61.8 to 72.6 years with low levels of DHEAS and testosterone and 57 women aged 65.6 to 71.3 years with low levels of DHEAS	29 men received 75 mg per day DHEA, 27 men received transdermal testosterone patch 5 mg/day, and 31 received placebo 27 women, received DHEA and 30 women received placebo	2 years	No physiologically relevant effects on body composition (DEXA for LBM and CT scan for thigh-muscle area) or physical performance for DHEA or testosterone
Villareal et al. 2006 [61]	56 men and women aged 65 to 78 years from the community	50 mg/day	10 months of DHEA (+weightlifting exercise training during the last 4 months).	DHEA alone did not significantly increase strength or thigh muscle volume (MRI). DHEA therapy potentiated the effect of weightlifting training on muscle strength and muscle volume.
von Mühlen et al. 2008 [62]	225 healthy adults aged 55 to 85 years	50 mg/day	1 year	Not effect on lean body mass (DEXA)
Kenny et al. 2010 [28]	99 women (mean age 76.6 years ±6.0) with low DHEAS levels, low bone mass, and frailty	50 mg/d DHEA (all received calcium and cholecalciferol and participated in 90-min twice-weekly exercise regimens)	6 months	No effect on muscle mass (DEXA) improvement lower extremity strength and in SPPB score
Jankowski et al. 2011 [63]	58 women and 61 men, aged 60 to 88 years, with low serum DHEAS	DHEA 50 mg/day	1 year	No effect on thigh muscle areas (CT scan)

Notes. DHEAS, dehydroepiandrosterone sulfate; SPPB, Short Physical Performance Battery; CT scan, computerized tomography scan; DEXA, dual X-ray absorptiometry; MRI, magnetic resonance imaging.

5.1.5. Insulin-like Growth Factor 1 (IGF-1), Growth Hormone (GH), GH Secretagogue (GHS)

5.1.5.1. Efficacy. The benefits of IGF-1 mimetic, GH or GHS supplementation have never been investigated in sarcopenic patients; their response to these molecules remains unknown. Testing these molecules should constitute the object of future research in the sarcopenia field [66,67].

IGF-1 mimetic, GH (the main hormone stimulating the secretion of IGF-1) or GHS (such as ghrelin) are tested for the treatment, prevention or improvement of muscle functioning in older adults, but also among younger athletes, cachexic patients or subjects with severe neurological diseases, such as spinal and bulbar muscular atrophy [68]. RCT have reported contradictory results on muscle mass, strength and physical performances [68–72]. Regarding IGF-1, contradictory findings are further confused by epidemiological data that did not confirm the association between low IGF-1 levels and low muscle mass and strength or low functional performance in older adults [73], raising doubts on the benefits of this treatment in sarcopenic patients.

To date, a few trials have studied the effect of GH or GHS in older people mainly in the context of hypopituitarism [69–72].

- Treatment with GH

In 1990, Rudman et al. reported an increase of 8.8 % at 6 months in LBM (assessed by total body potassium level) after GH supplementation in healthy subjects, aged 51 to 81 years old, and having a low blood level of IGF-1 (<300ui/l). However, subsequent clinical studies in hypopituitary patients showed that the benefits of GH supplementation on muscle mass did not always translate into improved muscle strength or physical performances [72]. A RCT performed by Papadakis et al. in healthy subjects, aged 70 to 85 years, with low levels of IGF-1, confirmed that GH supplementation for 6 months improves LBM (DEXA) by 4.4 %, without improving muscle strength and endurance parameters. During a follow-up of 5 [70], then 10 years [71], Götherström et al. reported that long-term GH replacement therapy improved knee muscle strength in 24 GH deficient adults (mean age of 65.2 years; range 61–74 years). These results deserve attention and need still to be confirmed in a larger, well-powered RCT. Two systematic reviews and meta-analysis on the effect of GH substitution on muscle functioning in adults with GH deficiency were performed in 2009 [74] and 2010 [75]. Rubeck et al. (2009), synthetizing the data of 15 trials, reported a significant improvement on aerobic exercise capacity and muscle mass [74] while Widdowson and Gibney [75] fails to demonstrate any benefit on muscle strength using data of 9 trials. Major limitations of most investigations in this field are the short duration (often <6 months) and small sample size (often <100 subjects). Furthermore, the comparison with sarcopenic subjects is questionable because these RCT were performed in patients of different ages, with hypopituitarism secondary to pituitary tumor treatments, and associated with other endocrine disorders and not simply older adults with low GH levels due to aging.

In eighteen healthy elderly men (65 to 82 years) without hypopituitarism, but having a baseline GH level about half that observed in young subjects, and practicing a weight training program for 14 weeks, GH supplementation increased the gain of LBM (DEXA) but did not increase muscle strength compared to weight training alone [76]. In young athletes, a recent meta-analysis on GH use didn't demonstrate a favorable effect on either muscle strength or endurance capacities [77].

A meta-analysis of 18 RCT (220 participants, mean age 69 years) having evaluated GH treatment among subjects without specific pathology found a significant increase of 2.1 kg (1.3 to 2.9) in LBM but also a high frequency of adverse effects [78]. The high incidence of side effects (such as arthralgia, gynecomastia, edema, carpal tunnel syndrome and the onset of diabetes mellitus and impaired fasting glucose) has resulted in high drop-out rates in GH clinical trials, generating substantial bias in the studies and raising important concerns about the use of GH in clinical practice.

Taken together, these results raise doubts about a positive benefit/risk balance of GH supplementation in sarcopenic older adults. Although GH supplementation may lead to muscle hypertrophy, its benefits on muscle function have not been demonstrated.

- Treatment with GH secretagogues

Ghrelin mimetic or agonist, such as Anamorelin, stimulate GH secretion with no significant increase in serious adverse events [79]. The increases of LBM (DEXA) by 1.56 kg in patients with non-small cell lung cancer and by 1.89 kg in patients with unresectable colorectal, gastric, or pancreatic cancer has led to Anamorelin approval under the indication of cancer cachexia in Japan in 2020 [79], even though this drug did not prove effective in improving muscle function [80]. Similar findings were obtained in the RCT ($n = 65$ men and women; aged 60–81 years, without cancer, inflammatory or any specific disease) by Nass et al. [81]. Those authors showed that MK-677, an oral ghrelin mimetic, significantly increased GH and IGF-1 levels, comparable to those of healthy young adults, and improved LBM (DXA) (+1.1 kg [0.7 to 1.5]) compared to placebo (−0.5 kg [−1.1 to 0.2]) at 1 year. No changes were observed in several muscle strength and physical performance tests. Body cell mass increased in the MK-677 group compared to placebo, suggesting that muscle mass gain was partly related to increase on intracellular water.

Promising results were reported in subjects aged 65–84 years, at risk of functional decline (slow gait speed, poor handgrip strength, at least one limitation at the SF-36 Health Survey or Instrumental Activities of Daily Living, or to have experienced two or more falls within the past two years) and treated for 1 year with capromorelin, an oral GHS [82]. That work confirmed an LBM gain of 1.4 kg (DEXA) and, contrary to previous findings, observed a significant improvement of functional performances, such as tandem walking, power stair climbs as well as a trend to improve the 6-min walk test and the five-repetition chair rise test, at 12 months. The magnitude of improvement was overall modest. Unlike previous studies involving robust subjects, the improvement in functional performance observed in the study by White et al. is potentially explained by the recruitment of frail subjects. Including healthy subjects in interventional trials expose to a risk of ceiling effect on physical performance tests. Although not performed under the indication of sarcopenia, the results of White et al.'s study suggest that sarcopenic subjects, who are often frail and at-risk for functional decline, could potentially benefit from this therapeutic approach. No serious adverse effects were reported in the clinical trials described above, but a statistically significant increase on fasting blood glucose and a decrease on insulin sensitivity were observed in the treatment group. Confirmatory clinical studies remain to be conducted to determine the safety and benefit of ghrelin mimetic or agonists in older adults, particularly in sarcopenic patients.

5.1.6. *Myostatin inhibitor and activin receptor pathway*

5.1.6.1. Efficacy. Several approaches to inhibit myostatin/activin A pathways have been tested, such as neutralizing myostatin or activin A antibodies [83], peptide inhibitors such as follistatin (an endogenous inhibitor), or soluble forms of ActRIIB receptors acting as decoys [84].

The benefit of LY2495655, a humanized recombinant immunoglobulin antibody targeting myostatin, has been studied in two RCT [85,86]. In a phase 2 RCT with 99 older adults who have fallen in the past year, Becker et al. [85] investigated the benefit of monthly subcutaneous injections of 315 mg LY or placebo during 20 weeks on ALM (DEXA). Authors found a significant improvement of ALM (0.43 kg, 95 % CI 0.19–0.66) in the treatment group compared to placebo. Interestingly, several physical performance tests involving strength and power (e.g., stair climbing time, chair rise with arms, fast gait speed) improved significantly. In another phase 2 RCT, Woodhouse et al. [86] investigated the efficacy of 12-week of LY in 400 patients, aged ≥50 years, and undergoing elective total hip arthroplasty. A significant increase of ALM (DEXA) was observed at weeks 8 and 16 but did not meet the primary outcome (i.e., ≥2.5 % increase on ALM).

Regarding Bimagrumab, its direct action on the ActRIIA and ActRIIB receptors allows an increase in muscle mass greater than that observed by inhibiting only myostatin [87]. However, the initial positive results on ALM and physical performances obtained in a phase 2 RCT with sarcopenic patients [11] were not confirmed in the phase 3 study [12]. An increase on LBM (DEXA) but no benefit on physical performance have also been reported in a Phase 2a/b with 250 participants aged 60 years or older who have undergone internal hip surgery for a proximal femoral fracture. In that phase 2a/b trial, participants were randomized to Bimagrumab 70 mg, or Bimagrumab 210 mg, or Bimagrumab 700 mg or placebo, every 4 weeks for 24 weeks. A significant increase on LBM of 1.9 kg (SD 1.7) and 2.8 kg (SD 2.2) were observed in Bimagrumab 210 mg and Bimagrumab 700 mg, respectively [88]. No enhancement of physical performance assessed by the gait speed and the SPPB was observed compared to placebo.

In a phase 1 clinical trial, patients receiving androgen suppression therapy for prostate cancer (at risk of muscle wasting) treated with antimyostatin peptibody (AMG 745) showed a 2.2 % (±0.8 % SE, $p < 0.008$) increase of LBM at 29 days [89]. This benefit was still present one month after the end of the treatment in the intervention group compared to the placebo group. Intra-quadricipital injection of follistatin (ACE-083) in postmenopausal women also resulted in increased muscle volume.

5.1.6.2. Safety. In all these clinical trials, no serious safety issues were reported. These trials suggest that additional studies are needed to confirm the potential benefit of myostatin inhibitors in sarcopenic patients.

5.1.7. *Vitamin D*

The potential effects of vitamin D on sarcopenia is not yet well-established despite intense research in recent years. No <7 meta-analyses (see Table 3) on vitamin D effects on muscle health have been published between 2020 and 2022 [9,89–94]. To the best of our knowledge, no study to date has examined the isolated effect of vitamin D on the muscle health of subjects with sarcopenia [9].

5.1.7.1. Efficacy. Although low vitamin D blood levels were found to be associated with functional decline or muscle fatigue in observational studies [95–97], RCTs have reported conflicting results regarding the effects of vitamin D supplementation on muscle health. Indeed, among the 7 recent meta-analysis above-mentioned, four concluded to no benefits on muscle mass [9,89,90,93], four to no effect on muscle strength [89,90,93,94], three to improvement of muscle strength [9,91,92] and one to significant negative effects on knee flexion strength [89]. Four concluded to no effect on physical performances [9,90,91,94], one on improvement of physical performances [92] and two to worsening effects [89,93] on physical performances (Table 3).

More recently, the Do-Health study, a large phase 3 RCT performed among 2157 healthy adults aged ≥70 yrs. without major comorbidities and having high functioning (median SPPB score of 11), found no effect of vitamin D alone or in combination with other interventions (omega-3 supplementation, strength exercise or both) on physical performance after 3 years [97].

The efficacy of vitamin D on the components of sarcopenia (muscle mass, strength and physical performance) was investigated in non-sarcopenic, heterogeneous populations (e.g., from community-dwellers to nursing home residents) and often in combination with various interventions, such as exercise or nutritional supplementation (e.g., protein, calcium). The variability of doses and formulations of vitamin D and the different interventions' length render it difficult to draw solid conclusions. To date, data from the literature suggest that vitamin D has no or little effect on muscle mass, muscle strength or physical performance. It is important to highlight these findings were obtained mainly among healthy older adults and cannot be generalized to older adults with sarcopenia. In sarcopenic patients, with low baseline vitamin D blood level, sufficient doses, and treatment duration of vitamin D supplementation might theoretically result in greater improvement [94].

Table 3
Summary of 7 meta-analysis performed between 2020 and 2022 investigating the effect of vitamin D on muscle mass, muscle strength and/or physical performances.

References	Selected studies	Number of RCT	Effect on muscle mass	Effect on muscle Strength	Effect on physical performance
Abshirini al. 2022 [94]	RCTs investigating vitamin D supplementation (with or without calcium) on muscle strength and mobility outcomes in postmenopausal women	29 RCT (n = 6485)	NA	**No significant effect** on HGS (n = 4570) (MD: 0.656 kg, 95 % CI = 0.037 to 1.350, P = 0.06) Significant improvement of HGS (MD: 1.137 kg, 95 % CI = 0.215 to 2.059, P = 0.016) with dosages >1000 IU daily, a treatment duration of 3 months and subjects with baseline vitamin D < 30 ng mL^{-1}	**No effect** on TUG (n = 1852)
Barbagallo et al. 2022 [92]	RCTs investigating calcifediol (25-hydroxyvitamin D) on physical performance or muscle strength	7 RCT (n = 269)	NA	**Significant improvement** of the HGS (n = 446) (SMD: 0.532 CI = 0.305 to 0.758 p < 0.0001) and leg extension strength (n = 318) (SMD: 0.641; 0.346 to 0.935 p < 0.0001 No effect on Leg flexion strength (n = 92)	**Significantly improved** of gait speed (n = 52) (SMD: 2.5; 1.768 to 3.232 p < 0.0001) No effect on chair rise time (n = 72), and TUG (n = 124), and SPPB (n = 278)
Cheng et al. 2021 [9]	RCTs investigating vitamin D supplements in **patients with sarcopenia** No trial provided patients with only vitamin D. *Vitamin D was always combined with protein and/or exercise.*	9 RCTs (n = 1420)	Vitamin D alone or combined with protein supplementation or exercise **could increase** lower-limb mass (no statistical significance).	Combining vitamin D supplementation with exercise and protein supplementation **increase HGS** (WMD, 3.86; 95 % CI, 0.52–7.21).	Combination of vitamin D and protein **could improve** chair-stand test (WMD, −1.32; −1.98 to−0.65). Vitamin D supplementation, alone or combined with exercise and protein supplementation, showed a **trend of beneficial effect gait speed** (no statistical significance).
Zhang et al. 2022 [91]	RCTs investigating vitamin D supplements in postmenopausal women	19 RCTs (n = 5240)	NA	**Significant Improvement** of HGS (n = 4229) (+ 0.876 kg; 0.180 to 1.571) (specially for subjects >60 years old, without calcium supplementation, and baseline vitamin D level was >75 nmol/L (30 ng/ml).	**Insignificant improvement** of the TUG (decrease time of 0.044 s (−0.979 to 0.892).
Prokopidis et al. 2022 [93]	RCTs investigating Vitamin D supplementation on components of sarcopenia in older (>50 years) adults	10 RCTs (n = 893)	**No effect** on ALM (n = 207)	**No effect** on HGS (n = 1065)	**Significant worsening** of the SPPB (n = 444) (MD: −0.23; −0.40 to −0.06; p = 0.007) No effect on TUG (n = 800)
Bislev et al. 2022 [90]	RCTs investigating effects of moderate to high doses of vitamin D3 (cholecalciferol) on muscle health in obesity, hyperparathyroidism, Graves' disease, or secondary hyperparathyroidism	4 RCTs (n = 260)	**No effect** on Weight (n = 260), Total lean mass (n = 233), ALMI (n = 233)	**No effect** on HGS (n = 255), Elbow extension, (n = 256), Elbow flexion (n = 253), Knee extension 90° (254), Knee flexion 90° (n = 253), Knee extension 60° (n = 255), Knee flexion 60° (n = 250)	**No effect** on TUG (n = 252), Chair rising test (n = 249)
Bislev et al. 2021 [89]	RCTs investigating vitamin D supplementation with or without calcium on physical performance, muscle strength, and lean mass.	54 RCTs (n = 8747)	**No effect** on total lean mass (n = 1201)	**No effect** on HGS (n = 5946), Elbow extension (n = 235), Elbow flexion (n = 636), Knee extension (n = 1624. **Significant lower** maximum knee flexion strength (n = 765) (MD = −0.33 (−6.63 to −0.03; p = 0.05)	**Significant worsening** at the TUG (n = 5223) (MD = 0.15; 0.03 to 0.26; p = 0.01) **Tendency toward worsening** of SPPB (n = 856) (MD = −0.18 (−0.37 to 0.01; p = 0.06) No effect on Chair rising test (n = 3112) or 6-min walking test (n = 796)

Note. NA, None Applicable; RCTs, Randomized Controlled Trials; SMD, Standard Mean difference; MD, Mean Difference; WMD, Weighted Mean Difference; CI, Confidence Interval; ALM, Appendicular Lean Mass; ALMI, Appendicular Lean Mass Index = ALM/weight^2; BMI, Body Mass Index; TUG, Timed Up and Go test, SPPB, Short Physical Performance Battery; HGS, Handgrip Strength.

Moreover, defining optimal treatment modalities (dose, mode of administration, and duration) of vitamin D supplementation to improve muscle health remains to be studied. Additional research is needed on this specific population.

5.1.7.2. Safety. A Cochrane review [98] indicates vitamin D is well tolerated even in very old people. No effect on mortality was observed. Compared to placebo subjects, supplemented participants had however an increased risk of developing hypercalcemia (RR 2.28, 95 % CI 1.57 to 3.31), usually mild (2.6 to 2.8 mmol/L). Such a risk is higher when using 1,25-dihydroxycholecalciferol (calcitriol), the active form of vitamin D. A slight increase in gastrointestinal symptoms, mainly for the combination of calcium and vitamin D (RR 1.05, 95 % CI 1.01 to 1.09) and a small but significant increase in kidney disease (RR 1.16, 95 % CI 1.02 to 1.33) were reported.

5.1.8. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs)

Angiotensin converting enzyme inhibitors (ACEi) inhibit the production of angiotensin II, the main effector of the renin-angiotensin system (RAS), while angiotensin receptor blockers (ARBs) block the effect of angiotensin II on the AT1 receptor. These two hypotensive molecules may be ultimately associated to muscle health through different mechanisms (e.g., increased proteolysis, decreased protein synthesis, inflammation and fibrosis, increased exercise-induced

myostatin inhibition) [99–102].

Observational studies in older subjects found better physical performances in individuals treated with ACEi/ARBs, compared to people not taking these drugs [103,104]. However, RCT provided mixed results on the effects of ACEi or ARBs on muscle mass, muscle strength, and physical performance (Table 1). Findings from recent RCT [8,105,106] and meta-analysis do not support the use of ACEi or ARBs to improve muscle function in older people [107].

Therefore, currently available data do not support the use of ACEi or ARBs to improve muscle function and fight against sarcopenia in older people.

5.1.9. β-adrenoceptor antagonist

β-blockers have demonstrated their benefit in a variety of cardiovascular conditions including hypertension, angina, post-acute myocardial infarction or heart failure by reducing catecholamine stimulation. However, β-blockers also result in bradycardia, reduced endurance capacity, attenuation of muscle adaptive mechanisms to exercise, poor mitochondrial bioenergetics and protein synthesis [108–110].

On the other hand, peripheral β2 receptor agonist such as salbutamol, a drug commonly prescribed for COPD and asthma was shown to increase protein turnover rates in skeletal muscle with a positive net protein synthesis balance in young men ($n = 12$) engaged in an exercise program [111]. In competitive sports, the benefit of salbutamol observed in athletes' performance has resulted in restriction of salbutamol use [112] and included of salbutamol in the prohibited list of the World Anti-Doping Agency (WADA) since 2004. Despite potential therapeutic benefits for muscle wasting, salbutamol or other highly β2-selective agonists (e.g., formoterol, clenbuterol) [113,114] have never been investigated in sarcopenic patients. On the other hand, espindolol (Carvedilol), a non-specific blocker of the β-1 and β-2 adrenergic receptors having moreover an Intrinsic Sympathomimetic Activity (ISA) on the β-2 adrenergic receptors have been tested in the context of cachexia. The rational is that espindolol reduces the catabolic mechanisms by blocking the β-1 adrenergic receptors but also that espindolol induce an anabolic effect by stimulating the β-2 adrenergic receptors [115]. Then, espindolol present promising effects in the context of cachexia [2,116,117]. The RCT ACT ONE ($n = 87$ patients with cachexia due to non-small cell lung cancer and colorectal cancer) demonstrated that espindolol therapy for 16 weeks resulted in weight gain (+0.54 kg/4w in espindolol compared to −0.21 kg/4w in placebo), with a significant increase in LBM (DEXA) [116,117]. More recently, the large COPERNICUS trial ($n = 2289$ patients with severe chronic heart failure) found carvedilol improved weight (+1.2 ± 0.2 kg compared to −0.1 ± 0.2 kg in placebo) and reduced the risk of death compared to placebo [117]. These works with "old" and new drugs open up promising prospects for the treatment of muscle wasting in the context of cachexia, that will need to be confirmed by additional phase 3 studies as well as in sarcopenic patients without cachexia.

6. Recommendations for the pharmacological treatment/prevention of sarcopenia

The evidence for the use of drugs to treat or prevent sarcopenia is still too scarce. Until ongoing trials, in particular well-powered phase 3 RCT, confirm drug effectiveness in the context of sarcopenia, the unique recommendation to fight against this condition is through multidomain lifestyle interventions, in particular, exercise training (emphasizing muscle strength and power exercises) and nutrition (diets rich in proteins). Currently, no drug is approved and no drug should be prescribed under the indication of sarcopenia, including testosterone treatment [5] in the absence of clear hypogonadism symptoms. Regarding testosterone, based on the scientific evidence available to date, the decline in motor function alone should not constitute a therapeutic indication for its supplementation. Therefore, testosterone testing should not be performed in routine for patients with sarcopenia. Currently, testosterone remains an indication only in subjects with an identified cause of hypogonadism [118] since it improves muscle mass and strength in hypogonadal patient [19,119–122]. Although current available evidence does not support that vitamin D supplementation has beneficial effect on muscle health, vitamin D is safe and can have benefits in other organs and overall health [123]. Checking vitamin D levels and supplementing sarcopenic subjects with a deficiency [124] is advisable.

7. The future of drug treatment for sarcopenia: molecules in preclinical phase

Advances in the systematic knowledge of the fundamental drivers of biological aging and the interplay between biological aging and the biology of chronic diseases have contributed to the birth of the concept of Geroscience. The Geroscience field aims to reduce the onset and severity of age-related conditions by targeting the biological mechanisms of aging that are shared by several diseases and geriatric syndromes. By developing new therapeutic approaches, called Gerotherapeutics, capable of modulating the molecular, cellular or genetic mechanisms of aging, Geroscience makes it possible to designing innovative clinical trials against sarcopenia. For example, the TAME (Targeting Aging with MEtformin) project aims to demonstrate that by targeting the multiple mechanisms of aging (senescence, proteostasis, mitochondrial dysfunction, epigenetics, inflammation, etc.), metformin reduces the occurrence of pathologies associated with aging including sarcopenia [125,126]. Metformin and many promising molecules, such as exerkines (Interleukine-6, TNF-a, Interleukin-15, Fibroblast Growth Factor 21, Irisin, Apelin and others) [127] (or senolytic (dasatinib and quercetin, ruxolitinib and others), are currently investigated in preclinical research to prevent the loss of muscle mass/strength and physical performance [128]. Exerkines are mainly secreted by skeletal muscle fibers and have autocrine, paracrine and endocrine effect and have been recently revealed by studying the consequences of muscle contraction, such as during and after exercise [129].

7.1. Interleukine-6 (IL-6) and Tumor necrosis factor-α (TNF-α)

Chronic inflammation is a crucial determinant of sarcopenia. Interleukine-6 (IL-6) is one of the most importantly studied exerkines [130]. This proinflammatory cytokine is produced by skeletal muscle during contraction according to the intensity and the duration of exercise. Interestingly, it has been shown that IL-6 deficient mice are resistant to exercise highlighting the crucial role of this cytokine and more broadly of inflammation in exercise-induced myogenesis [131]. However, in different age-dependent and independent models of loss of muscle mass, the elevated level of IL-6 seems to act deleteriously on muscle physiology [132,133]. Consequently, several studies focused on strategies able to limit or neutralize IL-6 production or its consequences. In this context, IL-6 antibody attenuates the dystrophic phenotype, severe muscle degeneration, inflammation, as well as accumulation of non-functional fat and fibrotic tissues in Duchenne myopathy [134]. In addition, pharmacological inhibition of IL-6 activity in mdx male mice inhibits anti-inflammatory responses and improvement in muscle repair [135]. In aging mice, inhibition of TNF-α (another proinflammatory cytokine involved in cachexia), by Etanercept also prevented atrophy and loss of type II fibers [136]. In rheumatoid arthritis, IL-6 and TNF-α are mediators of joint inflammation and contribute to cachexia observed in these patients. Several treatments such as monoclonal antibodies targeting TNF-α (infiximab, adalimumab, certolizumab and golimumab) and IL-6 (tocilizumab and sarilumab), or the soluble TNF-α receptor (etanercept), as well as inhibitor of T cell o-stimulation (abatacept), monoclonal antibodies for CD20 B cell depletion (rituximab) or even inhibitors of the Janus family tyrosine kinase (tofacitinib, baricitinib, upadacitinib and filgotinib) targeting these pro-inflammatory molecules have demonstrated their clinical interest and are now available for

limiting the severity of joint manifestations. By limiting muscle catabolic mechanisms, these drugs could also limit the loss of muscle mass/strength that contribute to functional limitation. Although these treatments reduce the severity of the joint complications, a recent systematic review with meta-analysis of nine randomized studies did not demonstrate a significant improvement in muscle mass [137]. In sensitivity analysis focused on the small number of subjects treated with anti-IL-6 and anti-TNF-α, a statistical trend for gain in lean mass was observed. Currently, whether blockage of IL-6 or TNF-α could be helpful to prevent sarcopenia in the context of rheumatoid arthritis or other chronic inflammatory diseases remains unknown. Further studies are needed in this topic.

7.2. Interleukin-15 (IL-15)

IL-15 is a cytokine that may accumulate in the muscles as a result of repetitive exercise. In vitro, IL-15 mRNA expression is upregulated during myofiber differentiation process and pharmacological or genetic IL-15 supplementation promotes myoblast differentiation in mdx mice [138]. IL-15 administration enhances diaphragm function with increased muscle fiber size [138]. However, contrasting results have shown that IL-15 treatment may induce muscle atrophy in skeletal muscles in young and aged rats [139]. The identified IL-15 mechanisms of action reside essentially in metabolic improvement by activating AMPK and glucose uptake in skeletal muscle. This leads to an increase of fat oxidation, energy expenditure and running endurance in transgenic mice. IL-15 effects need still to be tested and clarified in the context of sarcopenia.

7.3. Fibroblast Growth Factor 21 (FGF21)

The secretion of FGF21 is dysregulated in aged mice. FGF21 works as an endocrinal hormone-like, signaling molecules locally in metabolism. By activating phosphatidylinositol 3-kinase (PI3K)/serine-threonine protein kinase AKT, signaling transducer and activator of transcription (STAT) and mitogen activation protein kinase (MAPK), FGF21 may act autocrinally on skeletal muscle. Indeed, muscle-specific Akt transgenic mice exhibited skeletal muscle fiber hypertrophy with increasing FGF21 expression in the muscle and in plasma [140]. In addition, FGF21 expression is linked with different age-related muscle features such as decrease of autophagy or mitochondria alteration [141]. All these results suggest that FGF21 may be potentially involved in sarcopenia associated mechanisms at least regarding energy-related aspects. Interestingly, high FGF21 in plasma is associated with an increase in primary sarcopenia in different human cohorts whereas genetic overexpression of the hormone is associated with loss of muscle mass through autophagy overactivation.

7.4. Irisin

Irisin is a cleaved form of Fibronectin type III domain-containing protein 5 (FNDC5). Exercise-induced increase in the level of irisin in the blood is controversial but different studies reported an increase in FNDC5 mRNA expression upon exercise in rodent models and humans [142]. Furthermore, a decrease of blood irisin in postmenopausal women with sarcopenia was associated with low quadriceps cross-sectional area [143]. As proposed for FGF21, the effects of irisin on skeletal muscle physiology mainly reside on metabolism since C2C12 exposure to irisin leads to overexpression of mitochondrial-specific transcription factors, such as PGC-1α and mitochondrial transcription factor A [144]. Others reported that irisin induced skeletal muscle hypertrophy due to activation of satellite cells and enhanced protein synthesis. In addition, irisin injection rescues loss of skeletal muscle mass following denervation by enhancing satellite cell activation and reducing protein degradation [145]. These data suggest that irisin has pro-myogenic effects in mice. Further studies are needed to reveal the biological effects of human irisin and the underlying mechanism in human skeletal muscles.

7.5. Apelin

Apelin is a small peptide retrieved into bloodstream under different isoforms: 13, 17 and 36 amino acids. It has recently been shown that apelin, after binding the APJ receptor, may activate AMPK-dependent pathways leading to mitochondriogenesis in skeletal muscles of mice [146,147]. In aged mice and sarcopenic humans, basal and exercise-induced plasma apelin is decreased suggesting a role of the peptide in the field of muscle and aging [148]. Interestingly, mice deficient for apelin or for APJ receptor displayed an increase of muscle wasting comparable of that observed during aging. Moreover, recombinant apelin systemic treatment and muscle specific genic overexpression of apelin both lead to an increase of muscle mass and function in aged mice. Apelin would act through different pathways including AMPK and akt respectively activating metabolism and protein turn-over in skeletal muscle during aging. Moreover, APJ is present on satellite cells and its activation in aged mice results in an increase of proliferation of these cells alongside a better regenerative process after cardiotoxin-induced muscle regeneration [148]. Altogether, these results clearly show that apelin should be considered as a major target in sarcopenia, combined or not with exercise. Clinical trials with apelin analogs must be performed in the future to validate this potential.

7.6. Senolytic drugs

Among the mechanisms of aging, the accumulation of senescent cells in the tissues and the release of Senescence-Associated Secretory Phenotype (SASP, inflammatory cytokines, chemokines, matrix remodeling proteins, and growth factors that have deleterious local and systemic effects on organs including muscle tissue) may contribute to chronic inflammation and to the emergence of numerous chronic diseases [149]. Therefore, targeting senescent cells with senolytic agents (such as dasatinib and quercetin or ruxolitinib a Janus kinase inhibitor) has become an important area of research. Our knowledge remains limited on the involvement of senescent cells in the occurrence of sarcopenia [150] and there are currently no studies in humans supporting the destruction of senescent cells (or SASPs) in skeletal muscle to improve muscle mass or function. The improvement in glucose metabolism and insulin resistance in pre-clinical studies using senolytics has been demonstrated in mice and suggests that senolytics might limit the changes in body composition during aging (gain in fat mass and loss of lean mass) [151]. In aged mice, administration of dasatinib and quercetin reduced fat mass but improvement in skeletal muscle tissue mass was not found [152]. In previous works carried out on aged and irradiated mice to cause focal DNA lesions, treatment with dasatinib and quercetin improved physical performance and was associated with biological decrease of biomarkers of senescence [153]. Other preclinical data suggest that the physical endurance as well as the grip strength of mice improve under senolytics [34]. However, the mediation of these favorable effects of senolytics by better muscle health remains to be demonstrated. Clinical trials in older adults are yet to be conducted.

8. Bacterial products under investigation

The study on animal models of aging, suggest that the intestinal microbiota could be involved in the occurrence of sarcopenia probably by influencing the systemic availability of amino acids and by mechanisms of low-grade inflammation [154]. New discoveries on bacterial quorum sensing peptides such as iAM373, produced by *E. faecalis*, recently identified as a potential novel inducer of sarcopenia in animals but also in humans [155] open new therapeutic perspectives in the field of sarcopenia.

9. Conclusion

The current data from therapeutic trials highlight that improvements in muscle mass and/or strength do not necessarily result in improvements in functional performance, which remains the ultimate objective of sarcopenia treatments. Approaches targeting either loss of muscle mass or strength may be insufficient to improve function due to the multifactorial nature of sarcopenia. The causes of sarcopenia are multiple (including the different biological mechanism of aging) and present high inter-individual variability. This makes it challenging of demonstrating the efficacy of sarcopenia treatments on clinically meaningful physical performance. The efficacy of treatments for sarcopenia may require a personalized approach, in particular, combinations of pharmacological and non-pharmacological interventions (e.g., physical activity, nutritional supplementation [e.g., branched chain amino-acid such as leucine, citrulline, and other amino-acids, omega 3, creatine, β-Hydroxy-β-Methylbutyrate, probiotics). Targeting biological mechanisms of aging, as preconized by the growing scientific field of Geroscience, may constitute an interesting strategy to prevent/treat sarcopenia and should attract further attention in future research.

Contribution

YR wrote the first draft of the manuscript and the revised drafts. YR, CD, BV and PdSB wrote the revised drafts and, contribute to the intellectual content of the manuscript. All authors had final responsibility for the decision to submit for publication.

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Declaration of competing interest

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Appendices. Supplementary data

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