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Review

# Sarcopenic obesity: emerging mechanisms and therapeutic potential

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ABSTRACT

Sarcopenic obesity, or the loss of muscle mass and function associated with excess adiposity, is a largely untreatable medical condition associated with diminished quality of life and increased risk of mortality. To date, it remains somewhat paradoxical and mechanistically undefined as to why a subset of adults with obesity develop muscular decline, an anabolic stimulus generally associated with retention of lean mass. Here, we review evidence surrounding the definition, etiology, and treatment of sarcopenic obesity with an emphasis on emerging regulatory nodes with therapeutic potential. We review the available clinical evidence largely focused on diet, lifestyle, and behavioral interventions to improve quality of life in patients with sarcopenic obesity. Based upon available evidence, relieving consequences of energy burden, such as oxidative stress, myosteatosis, and/or mitochondrial dysfunction, is a promising area for therapeutic development in the treatment and management of sarcopenic obesity.

## 1. Introduction

Adults over the age of 65 represent the most rapidly expanding demographic globally, having increased from 6 % to 9.6 % of the population share from 1990 to 2021 [1]. Aging is associated with a loss of independence exacerbated by mobility, frailty, functional capacity, and cognitive ability. Sarcopenia, or the progressive loss of muscle mass and strength, is the most common disease associated with advancing age, present in >10 % or ~70.3 million individuals globally [2]. Adults over the age of 65 with sarcopenia experience disability, diminished quality of life, and premature risk of death, constituting significant individual and socioeconomic burden.

Obesity, or the progressive and recurrent accumulation of excess body fat, is the most prevalent non-communicable disease in human history, affecting >13 % or ~1 billion individuals globally [3]. Concurrently, there is an unprecedented prevalence of obesity in the elderly, estimated at ~35 % globally with >70 % overweight [4]. In young and middle-aged adults, obesity is generally associated with absolute increases in muscle mass and sustained function, the exception being patients with severe obesity or a BMI $\geq$ 50 kg/m$^2$ [5]. Despite this, obesity shortens longevity and increases cardiovascular morbidity and mortality [6], strengthening the notion that weight management is an essential component of healthy aging.

In the late 20th century, a subset of older adults was identified as having both obesity and sarcopenia, soon thereafter to be termed sarcopenic obesity. Sarcopenic obesity is now broadly accepted as a clinical condition defined by excess adiposity and low skeletal muscle mass and/or function [7]. It is currently estimated that ~11 % of older adults globally have sarcopenic obesity, which dramatically increases after the age of 70 [8]. Sarcopenic obesity is a prognostic factor for disability and survival, dramatically increasing the risk of obesity- and age-related disease [9,10].To date, sarcopenic obesity remains a largely untreatable condition with no targeted medical therapies. Furthermore, mechanisms of disease onset remain elusive. The purpose herein is to review evolving evidence surrounding the diagnosis, etiology, and treatment of sarcopenic obesity. Given the dramatically underserved nature of this patient population and lack of available evidence, we focus largely on emerging pre-clinical therapeutic developments with intention to treat sarcopenic obesity.

## 2. Etiology of sarcopenic obesity

The delineating feature of sarcopenic obesity is the decline in muscle mass and/or function, observed in terms of loss of lean mass, strength, and/or locomotor activity. Muscle contraction, or the ability of skeletal fibers to produce force, is dependent on several factors, the most notable being muscle: (1) size/volume, (2) architecture, (3) quality, and (4) bioenergetic potential. As such, a decline in any one or a combination of

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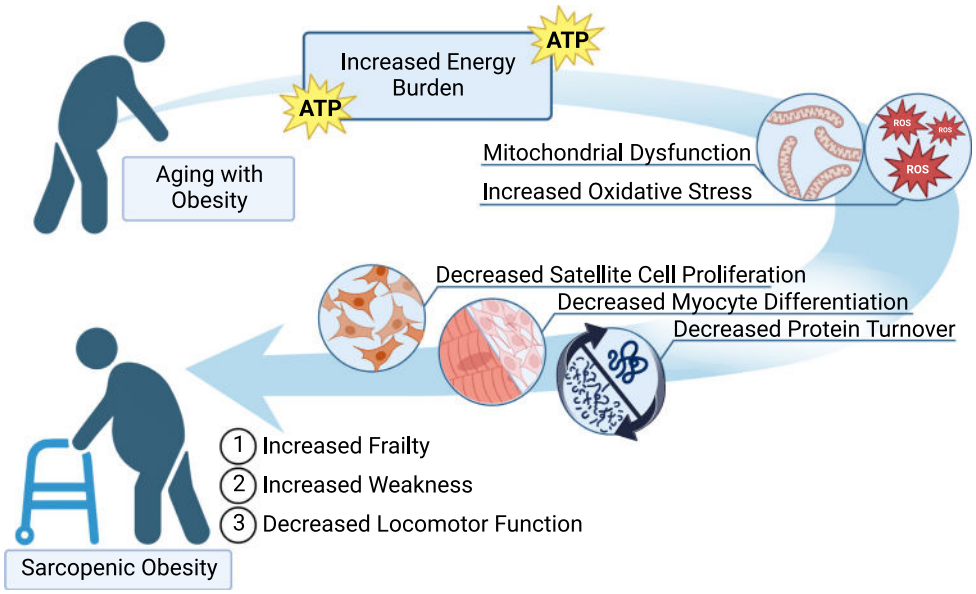


**Fig. 1.** Working model of sarcopenic obesity. Obesity in the background of aging exacerbates energy imbalance, resulting in excessive mitochondrial fission, declining quality control, and increased oxidative stress. In turn, regenerative functions within skeletal muscle decline, including decreased proliferative potential, myotube maturation, and protein turnover. In result, skeletal muscle function declines, resulting in frailty, decreased force production, and diminished locomotor function.

determinants may result in a decline in muscle function. Furthermore, the sole delineation between sarcopenic obesity and age-related sarcopenia is systemic energy burden. As such, the interaction between sites of lipid storage and force production most likely dictates disease onset and progression, though the cellular and molecular mechanisms remain elusive.

### 2.1. *Endocrine control of muscle function by adipose tissue*

Adipose tissue is the predominant site of fat storage and engages in interorgan crosstalk to coordinate the cellular response to extrinsic lipid signals [11,12]. For example, adipocytes themselves or infiltrating macrophages within adipose tissue produce pro-inflammatory cytokines, such as interleukin-6 (IL-6) and/or tumor necrosis factor alpha (TNF-α), in response to excess free fatty acids which upregulate the systemic inflammatory response [13]. To this end, IL-6 and TNF-α are negatively associated with muscle mass and strength in both men and women with sarcopenic obesity [14,15]. IL-6 mediated activation of STAT3 also independently triggers muscle wasting by stimulating atrophy-related signaling in skeletal muscle [16].

Leptin, an adipokine responsible for regulating energy balance by inhibiting hunger, can also drive myoblast proliferation and prevent premature terminal differentiation of muscle cells [17]. Indeed, ten days of leptin treatment significantly increased hindlimb muscle mass and muscle cross-sectional area in aged mice with a healthy weight [18]. Remarkably, circulating leptin seems to be increased in patients with sarcopenic obesity compared to non-sarcopenic controls, suggesting that the up-regulation of leptin is likely due to resistance to its action, thus blunting the positive effects of leptin in skeletal muscle [19–21]. Adiponectin secreted from adipose tissue also regulates muscle glucose metabolism, fatty acid oxidation, muscle proteolysis, and muscle regeneration during aging [22–26]. Likewise, plasma adiponectin levels are higher in patients with sarcopenic obesity compared to body weight and age-matched controls [27], suggesting that loss of adiponectin sensitivity may contribute to the onset and progression of sarcopenic obesity by stimulating protein degradation in skeletal muscle [28].

Aromatase is an essential enzyme in the estrogen biosynthetic pathway that irreversibly converts testosterone to estradiol [29]. Obesity increases the risk of hypogonadism, and androgen deficiency fuels unfavorable changes in body composition [30]. Consequently, primary or secondary deficiencies in testosterone impairs muscle protein synthesis, myogenic differentiation, and stimulates adipogenesis, subsequently impairing overall muscle function and quality [31].

### 2.2. *Muscular determinants of sarcopenic obesity*

Given the multidimensionality of the disease, it is challenging to find specific molecular signatures in skeletal muscle that may explain why sarcopenic obesity further compromises skeletal muscle mass and function. The accelerated rate of muscle loss observed in sarcopenic obesity is primarily characterized by an a symbiotic relationship between protein synthesis and breakdown [32], resulting in diminished quality, quantity, and/or distribution of muscle fibers. For example, sarcopenia is associated with specific type II muscle fiber atrophy and diminished satellite cell pools [33], which is highlighted in mouse models of sarcopenic obesity [34]. This observation is important in that type II muscle fibers typically have a larger cross-sectional area than type I fibers, in addition to being able to generate force more rapidly, which may be essential for performing activities of daily living [35].

Change in function and/or number of resident stem cells within skeletal muscle may contribute to the onset of sarcopenic obesity. In both human and rodent models, satellite cells are required for the regenerative capacity of skeletal muscle, which may directly exacerbate muscle function and mass [36]. In the context of obesity, the adipose tissue secretome significantly impairs myogenesis, but this effect is restricted to older myoblasts compared to young [37]. Obesity also reduces satellite cell number and proliferative capacity and slows activation [38,39]. Importantly, mitochondria seem to regulate satellite cell function by augmenting organelle division [40], namely fission and fusion [41]. Energy burden in the context of obesity and aging activates mitochondrial fission, which overtime depletes mitochondrial volume and may complicate long-term muscle performance [40,42]. Consistently, restoration of oxidative phosphorylation (OXPHOS) capacity and mitochondrial quality control rescues the regenerative failure of excessive mitochondrial fission in aged satellite cells [43]. In contrast, satellite cells are largely not required to maintain muscle cross-sectional area in aging mice [44]. Taken collectively, these data suggest that mitochondrial morphology and function are tightly interconnected in muscle stem cells and that this connection is critical in the switch between quiescence and the proliferative fate of these cells during tissue repair. Overall, obesity decreases muscle mass and muscle quality [45], and it is suspected that this diminished satellite cell content and proliferative function may be related to impaired mitochondrial dynamics, resulting in the loss of skeletal mass and function.

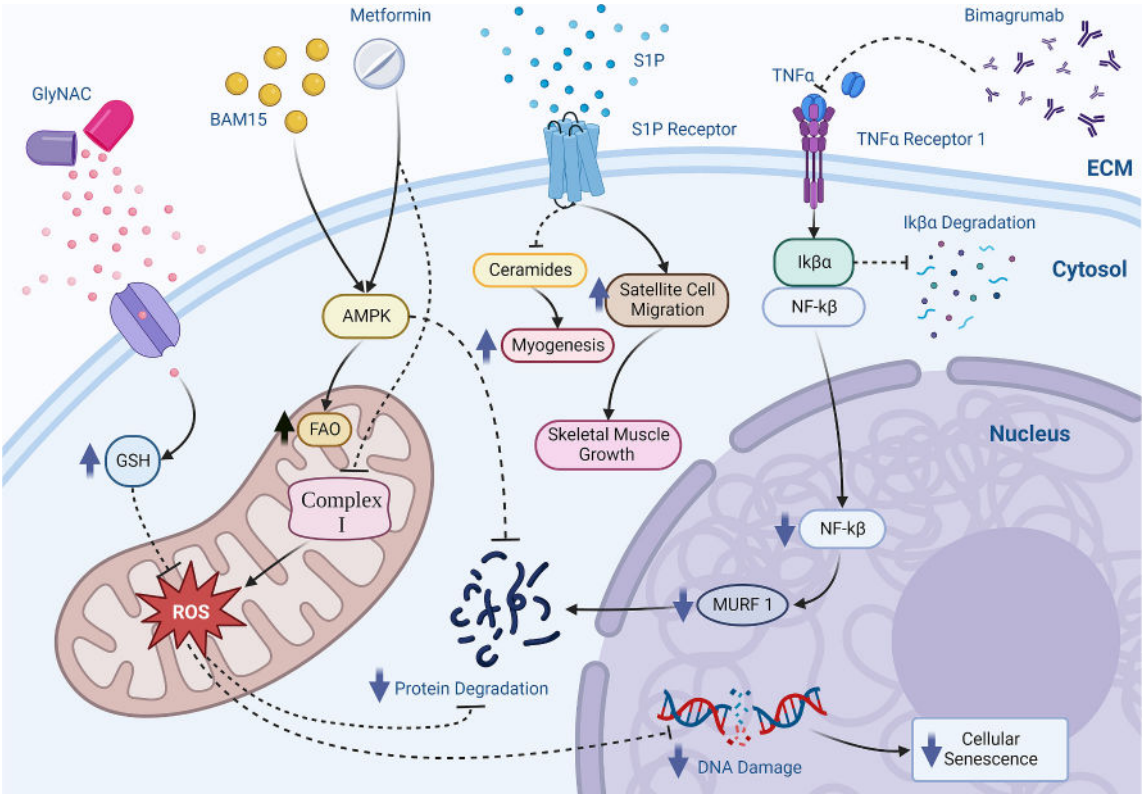


**Fig. 2.** Emerging cellular therapies for sarcopenic obesity.
Pharmacological strategies that enhance muscle function directly by enhancing cellular quality control or indirectly by alleviating energy burden work synergistically to abrogate the physiological consequences of sarcopenic obesity.

Increased intramyocellular lipid (IMCL) content is a common metabolic feature of skeletal muscle with aging and obesity [40,41]. Sarcopenia and obesity amplify one another as muscle loss diminishes the amount of available insulin-responsive tissue, promoting insulin resistance, which, in turn, raises anabolic resistance [46]. There is evidence that a higher IMCL content may play an integral role in the development of muscle resistance to anabolic stimuli and the progression of sarcopenia with aging and muscle atrophy in obesity [47–49]. With advancing age, muscle IMCL accumulation is associated with metabolic abnormalities, reduced strength, poor muscle performance, and mobility [50]. Consistently, reducing IMCL content improves muscle insulin sensitivity insulin in rodents with obesity [51].

It is well known that high-fat diet-induced mitochondrial dysfunction causes muscle IMCL accumulation [52]. Indeed, 3-hydroxyacyl-CoA dehydrogenase (HAD) activity, a key enzyme for mitochondrial fatty acid oxidation, is blunted in patients with sarcopenic obesity [53]. Similarly, mitochondrial respiratory chain complex I and IV activities and the PGC-1α mRNA level are significantly reduced in rats with sarcopenic obesity. PGC-1α regulates mitochondrial energy metabolism and biogenesis and influences carbohydrate and lipid utilization by activating members of the nuclear receptor family [54]. Therefore, targeting mitochondria to enhance fatty acid oxidation may be a plausible and innovative approach to treating sarcopenic obesity. It would reduce IMCL content, thereby improving insulin action and consequently the anabolic response, thus leading to preserved muscle mass (Fig. 1).

## 3. Diagnosis

Sarcopenic obesity is a sub-clinical disease in that there is no universal consensus on diagnostic criteria and implementation in clinical practice. As such, identification and diagnosis rely on the sum of its parts, that being obesity and sarcopenia. Obesity is universally, albeit sub optimally identified by determination of the body mass index (BMI) derived from the mass and height of an individual. Patients with a BMI $\geq 30\ kg/m^2$ meet the diagnostic criteria for obesity and would be treated as such outside of rare circumstances when a patient has unusually high lean mass, for example in some athletic populations. In a research setting, severity of obesity may be further refined according to absolute or age-normalized cut-offs of excess visceral fat mass [55]. Like obesity, sarcopenia was only recently recognized as an independent disease with clear diagnostic criteria [56]. Sarcopenia is now defined as loss of muscle function (dynapenia) and mass, identified clinically by a gait speed <0.8 m/s and low appendicular lean mass [57,58]. Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) issued a joint consensus statement on the definition and diagnostic criteria for sarcopenic obesity [59]. The proposed diagnostic workflow is as follows: (1) screening of patients by high BMI or elevated waist circumference and surrogate parameters for sarcopenia (symptoms, clinical suspicion, and/or questionnaires); (2) diagnosis of patients by testing muscle function followed by body composition analysis; and (3) staging, if positive for sarcopenic obesity, based upon the absence (stage I) or presence (stage II) of attributable clinical complications such as functional disabilities, cardiovascular, and/or respiratory diseases [59]. To date, no international classification of diseases (ICD) code has been designated for sarcopenic obesity, and the working definition/differential diagnosis is constantly evolving. Age is a strong risk factor for the onset and severity of sarcopenic obesity, but the disease is not exclusive to old age [60]. As such, diagnostic consideration is given based upon symptomatic presentation, with age being a component of risk management.

**Table 1**
Clinical investigations with intention to treat sarcopenic obesity.

| Study | Intervention | Sample | Population | Sarcopenic obesity criterion | Result |
|---|---|---|---|---|---|
| Camajani et al. (2022) | VLCKD combined with interval training | 24 | Men and women aged 50–70 years | FM >39–41 % for women and >29–31 % for men; STS > 15 s; SPPB < 8 | Equal reduction of FM and increase in muscle strength for both treatment arms compared to baseline |
| Camajani et al. (2022) | LCD combined with whey and leucine supplementation | 16 | Men and women aged 50–70 years | FM > 38 %; HGS < 16 kg; STS > 15 s; SPPB < 8 | Reduction of FM and increase in muscle strength compared to baseline |
| Wittmann et al. (2016) | WB-EMS or WB-EMS combined with protein supplementation | 75 | Women aged ≥70 years | FM > 35 %; SMI < 5.75 kg/m$^2$ | MetS Z-score reduction in WB-EMS alone compared to control group |
| Kemmler et al. (2016) | WB-EMS or WB-EMS combined with protein supplementation | 75 | Women aged ≥70 years | FM > 35 %; SMI < 5.75 kg/m$^2$ | Improvement in sarcopenia z-score in both treatment arms compared to control group |
| Kemmler et al. (2017) | WB-EMS combined with protein supplementation or isolated protein supplementation | 100 | men aged ≥70 years | FM > 27 %, SMI < 0.789 | Improvement in sarcopenia z-score in both treatment arms compared to control group |
| Liao et al. (2017) | Elastic band RT | 46 | Women aged 60–80 years | FM > 30 %, SMI < 1 SD sex-specific mean | Reduction of FM and improvement in physical capacity relative to control group |
| Liao et al. (2018) | Elastic band RT | 56 | Women aged 60–80 years | FM > 30 %, SMI < 2 SD sex-specific mean | Improvement in in muscle quality and physical function relative to control group |
| Chen et al. (2017) | RT, AT, and CT | 60 | Men and women aged 65–75 | ASM ≤ 32.5 % for men and ≤25.7 % for women | RT, AT, and CT improved ASM relative to control group |
| Nabuco et al. (2019) | Whey protein combined with RT | 26 | Women aged ≥60 years | ASLT < 15.02 kg and FM > 35 % | Increased ALST and decreased FM relative to placebo |
| Espinoza et al. (2021) | Intranasal oxytocin | 21 | Men and women aged ≥60 years | BMI 30–43 kg/m$^2$ and gait speed <1 m/s | Oxytocin increased whole body lean mass compared to placebo |

Abbreviations: VLCKD: very low calorie ketogenic diet, FM: fat mass, SST: sit-to-stand test, SPPB: short physical performance battery, HGS: hanggrip strength, WB-EMS: whole-body electromyostimulation, SMI: skeletal muscle index, MetS Z-score: metabolic syndrome Z-score, SD: standard deviation, RT: resistance training, AT: aerobic training, CT: combined resistance and aerobic training, ASM: appendicular skeletal muscle mass, BMI: body mass index, ASLT: appendicular lean soft tissue.

## 4. Treatment

Current treatment of sarcopenic obesity is focused on improving quality of life via lifestyle intervention and palliative care when patients are immobilized. First line therapy for patients with sarcopenic obesity is exercise focused on enhancing muscle function. Secondary interventions include micronutrient supplementation, dietary/medical/surgical therapy for weight management, and/or hormonal replacement, when applicable [61]. To date, there are no curative and/or targeted therapies for sarcopenic obesity. For patients with mobility, resistance exercise programs are the cornerstone of treatment for notably favorable effects on muscle function and body composition in older adults (Fig. 2).

### 4.1. Lifestyle and medical interventions

In patients with established sarcopenia, exercise programs improve muscle strength and performance in a dose-dependent manner with variable outcomes for muscle mass [62–64]. Resistance, aerobic, and combination training programs reduce body fat and improve muscle function in older men and women in a community dwelling setting with sarcopenic obesity [65]. Notably, resistance exercise training alone was superior for improvements in muscle performance. Elastic resistance training improves physical function while reducing fat mass in older women with sarcopenic obesity [66,67]. Similarly, dietary modification that ensures adequate and/or high protein intake prevents the decline in muscle mass and in some cases, improves muscle function [68,69]. Dietary restriction is the gold-standard first-line treatment for obesity and counteracts, to an extent, the deleterious effects of aging on skeletal muscle function across mammals [70]. However, evidence of safety and efficacy in patients with sarcopenic obesity is sparse. In a recent trial, a very low-calorie diet improved muscle performance in patients with sarcopenic obesity, albeit to the detriment of muscle mass [71]. Patients treated with a very low-calorie diet plus exercise exhibited similar improvements in muscle function with preserved lean mass, indicating that combinatorial therapy is synergistic in disease management. Micronutrients and minerals such as amino acids, vitamin D, selenium, and magnesium may be supplemented into the diet to correct pre-existing deficiencies or to establish supraphysiologic concentrations to elicit a biological response [72]. Whey protein supplementation in combination with exercise improves muscle function in adults with sarcopenic obesity [73]. In males, testosterone replacement therapy may be implemented alone or in combination with diet, exercise, or vitamin supplementation to restore androgen balance [74]. Use in older adults is somewhat limited due to high risk of cardiovascular events [75]. Similarly, in postmenopausal women, estrogen replacement therapy may be used alone or in combination with lifestyle intervention with generally positive outcomes on retention of lean mass in muscle function [76]. Whole-body electromyostimulation (WB-EMS) is an exercise-mimetic approach which replaces contractile force from resistance training by supplying a mild electrical pulse to targeted muscle groups over a given period of time [77]. Advantages of the treatment are time efficiency and accessibility for populations with high frailty. Though WB-EMS favorably improves body composition and muscle function compared to non-interventional controls [78–80], the effect sizes are small and may be ineffective in adults with more severe sarcopenic obesity [81]. More recently, oxytocin therapy has been employed as an exploratory therapy for sarcopenic obesity with the aim of restoring age-relative decline in oxytocin production. Intranasal oxytocin is well-tolerated and improves lean mass in older adults with sarcopenic obesity [82]. However, it remains unclear if intranasal oxytocin improves muscle function and physical ability. A summary of prevailing clinical interventions is displayed in Table 1. Collectively, treatment options are deficient and complicated by the contrasting needs underlying sarcopenia and obesity. For the remainder of the review, we discuss emerging targeted therapies for sarcopenic obesity.

### 4.2. Mitochondrial uncouplers

Mitochondria are rate-limiting organelles that control cellular function by exergonic supply of adenosine triphosphate (ATP), synthesizing macromolecules, regulating protein-metabolite interactions, and cuing cell fate. Aging and obesity are associated with an array of mitochondrial maladaptive processes that trigger organelle dysfunction and oxidative stress, contributing to lipid-induced insulin resistance, muscle atrophy, cellular senescence, and a decline in force production capacity [42,83–85]. Interventions such as calorie restriction enhance mitochondrial fitness by promoting bioenergetic efficiency and maintaining

redox balance [86]. Interestingly, we and others have found that mitochondrially targeted uncouplers, such as BAM15 and SHC517, reverse adiposity while preserving lean mass to a greater extent than calorie restriction alone [87–89]. Mitochondrial uncouplers enhance electron flow through partial dissipation of the electrochemical gradient requisite for ATP synthesis [90]. This strategy is attractive in the context of healthy aging in that uncouplers enhance energy expenditure independent of appetite and food intake, a key determinant of sarcopenia. More recently, we have demonstrated that restricting bioenergetic efficiency lowers body fat, increases muscle fiber area, and enhances muscle function and locomotion in preclinical models of sarcopenic obesity [34]. Restricting bioenergetic efficiency appears to improve muscle function by enhancing mitochondrial quality control and biogenesis, ensuring that damaged mitochondria are cleared from the network and replaced with properly functioning organelles [34]. Mitochondrial uncoupling may improve muscle function indirectly by alleviating age-related neurodegeneration [91]. To this end, mild mitochondrial uncoupling has been observed to be a protective mechanism against aging by enhancing the functional integrity of active muscle fibers [92]. To date, evidence remains limited to small rodent and in vitro models, and as such further investigation is required to determine therapeutic efficacy in larger mammals. However, structural optimization to improve absorption, distribution, and pharmacokinetic properties of currently available uncoupling agents is required to achieve the requisite potency and efficacy for treatment in humans.

### 4.3. Sphingosine-1-phosphate (S1P) receptor agonists

Sphingosine-1-phosphate (S1P) is a bioactive phospholipid that mediates an array of cellular processes as a downstream product of the sphingomyelin signaling pathway. Extracellular S1P binds to the cell surface receptors, enabling intracellular signal transduction. S1P concentrations are elevated in patients and rodents with obesity, which serves to maintain metabolic homeostasis and restrict tissue inflammation [93,94]. Furthermore, aging suppresses S1P receptor signaling which limits tissue repair [93]. Activation of S1P receptors opposes the action of ceramides which contribute to insulin resistance and inflammation in obesity and aging [95,96]. Ceramide is a lipid intermediary in cellular stress responses and an essential factor of sphingolipid metabolism. Increases in ceramide synthesis through a higher dietary intake of saturated fatty acids (e.g., palmitate) are also correlated with the development of insulin resistance and sarcopenic obesity [97]. Fingolimod (FTY720) is an S1P analog compound that can downregulate S1P receptors (S1PR) or degrade sphingolipids such as ceramide [98]. 4 weeks of FTY720 treatment increased lean mass and strength in mice with obesity, although the anabolic response to muscle contraction was not improved in aged animals [97]. Despite FTY720 therapy decreasing the accumulation of ceramide and other sphingolipids in the skeletal muscle of obese and aged obese animals, inflammatory markers are upregulated after FTY720 therapy even when sphingolipid accumulation is reduced in the muscle of sarcopenic obese animals [97]. So far, FTY720 treatment is efficient in improving muscle insulin resistance and preserving muscle mass and function by targeting S1P only in young mice with obesity but not in mice with sarcopenic obesity [99].

### 4.4. Nuclear factor-κB (NF-κB) inactivation

The nuclear factor κB (NF-κB) is a heterodimeric protein complex that governs aspects of transcription, inflammation, and cell fate through membrane receptors and extracellular signals. Under homeostatic conditions, NF-κB proteins remain sequestered and inactive in the cytoplasmic domain by IκBα [100]. Extracellular signals such as cytokines promote degradation of IκBα, resulting in NF-κB activation and subsequent signal transduction. In the context of aging, NF-κB transcriptional activity is elevated as a function of increased cellular senescence and/or inflammation [101]. Within aged skeletal muscle, the combination of elevated reactive oxygen species (ROS) and inflammation is required for the induction of cytokines such as TNF-α and its downstream target NF-κB [102,103]. Some known downstream targets of NF-κB include myostatin, another member of the transforming growth factor beta superfamily, that together with activin A negatively regulates skeletal muscle mass [104,105]. The activin type II receptor, acting through Smad 2/3, is the major pathway regulating skeletal muscle size [106]. Obesity in the context of aging exacerbates NF-κB activation via skeletal muscle and adipose tissue inflammation [107]. Bimagrumab is a monoclonal antibody that blocks activin II receptors, preventing the activity of myostatin and other negative skeletal muscle regulators that show increased muscle weight and muscle hypertrophy after treatment [108,109]. Given the crosstalk between cytokine pathways and TGF-β signaling, Bimagrumab may also protect muscle mass by inactivating NF-κB, as activin A is a downstream signal of NF-κB in the cytokine release pathway, which causes muscle atrophy [110]. Myostatin is known to signal muscle cells in a pro-oxidant manner by increasing ROS production via NF-κB [111]. In support of this notion, blocking activin A signaling can restore muscle function in pre-clinical models of cachexia [112]. It is broadly accepted that NF-κB mediates muscle wasting induced by TNF-α [113]. TNF-α may also trigger ceramide formation through stimulation of both de novo synthesis pathways consisting of the condensation of palmitoyl-CoA with serine and sphingomyelinase-mediated hydrolysis of membrane sphingomyelin [113]. Thus, it is reasonable to assume that targeting NF-κB may provide a feasible target for treating sarcopenic obesity. Although NF-κB inactivation improves insulin sensitivity associated with ceramide content reduction in aged mice, it is detrimental to muscle health during aging because it changes the expression of genes related to muscle progenitor cell migration, differentiation, and fusion, as well as increasing proteasome activity [114].

### 4.5. AMP-activated protein kinase (AMPK) agonists

The AMP-activated protein kinase (AMPK) is a conserved sensor of cellular energy status which is activated in response to a wide variety of mitochondrial stressors in order to restore homeostasis of the adenine nucleotide pool. In response to declining ATP or an increase in the AMP: ATP ratio, AMPK is activated to facilitate substrate catabolism and enhance oxidative phosphorylation [115]. In addition to energy sensing, AMPK also serves as a signaling molecule to regulate mitochondrial function and ward against oxidative stress [116]. Liver kinase B1 (LKB1) and protein kinase A (PKA) are both major upstream regulators of AMPK and have been shown to stimulate mitochondrial biogenesis and increase antioxidant capacity, and thus may represent a reasonable approach for improving mitochondrial function and mitigating oxidative stress in sarcopenic obesity [117,118]. Resveratrol, a polyphenol in many plant species, exerts many health benefits, including anti-oxidative, anti-inflammatory, and anti-catabolic effects [119]. Interestingly, the PKA/LKB1/AMPK pathway is activated by resveratrol and attenuates muscle wasting and loss of muscle function by enhancing mitochondrial dynamics, decreasing mitochondrial phenotype abnormalities, and increasing the antioxidant capacity in a rat model of sarcopenic obesity [119]. The 5,7-dimethoxyflavone, a flavone found in Kaempferia parviflora, is studied in the context of aging due to its anti-diabetic, anti-obesity, and anti-inflammatory properties [120,121], and is also a promising treatment for attenuating sarcopenic obesity. Aged mice with obesity provided with 5,7-dimethoxyflavone for eight weeks showed a significant increase in muscle function and mass through stimulation of mitochondrial biogenesis and protein synthesis, as well as attenuation of proteolysis [122]. AICAR is an AMP analogue that pharmacologically stimulates AMPK, both in vitro and in vivo. AICAR improves a number of age-related functions including cognition, motor coordination, cellular senescence, and inflammation [123–125]. It has also been shown to prevent lipid-induced insulin resistance and restore metabolic function in diet-induced models of obesity [126]. Chronic

**Table 2**
Preclinical investigations with intention to treat sarcopenic obesity.

| Study | Intervention | Action | Model | Result |
|---|---|---|---|---|
| Dantas et al. (2021) | BAM15 | Mitochondrial Uncoupler | Aged C57BL/6J mice with obesity | Improved muscle function and size and reduction in body fat |
| Rivas et al. (2019) | FTY720 | S1P analog | Young and aged C57BL/6J mice with obesity | Reduction of FM and increase in muscle strength in young but not old mice |
| Huang et al. (2019) | Resveratrol | AMPK activation | Young and aged Sprague-Dwaley rats with obesity | Prevents muscle atrophy and loss of function |
| Kim et al. (2020) | 5,7-Dimethoxyflavone | mTOR activation | Young and aged C57BL/6J mice with obesity | Improved muscle function and mass |
| Lyu et al. (2022) | Metformin | Non-specific | Aged C57BL/6J mice with obesity | Prevents sarcopenic obesity and reduces muscle fat |
| Nguyen et al. (2013) | GlyNAC | Glutathione activation | Young and aged C57BL/6J mice with sarcopenia | Reduction of FM and insulin resistance |

Abbreviations: FM: fat mass, S1P: sphingosine-1-phosphate, mTOR: mammalian target of rapamycin, AMPK: AMP-activated protein kinase, GlyNAC: glycine and n-Acetylcysteine.

AICAR treatment has been shown to reduce muscle wasting and improve muscle function in a mouse model of spinal muscular atrophy [127]. More recently, AICAR was found to exert AMPK-independent effects such as increasing fatty acid oxidation and suppression of gluconeogenesis [128]. However, little to no beneficial effects have been observed in early phase clinical trials due to poor oral availability and efficacy observed above the maximum tolerated dosing [128]. Metformin, the most prevalent antihyperglycemic medication worldwide, activates AMPK by augmenting the cellular adenine nucleotide pool, which contributes to its glucose lowering effects including suppression of gluconeogenesis and intestinal glucose absorption [129]. Metformin attenuates weight gain and results in modest weight reduction over long term administration in humans by restricting food intake and enhancing peripheral insulin sensitivity [130,131]. More recently, metformin has been shown to prevent sarcopenic obesity in mice by protecting muscle function [132]. However, the effect was partially lost with long-term administration of a high-fat diet. The ability of metformin to improve metabolic function has been tied to several upstream triggers of AMPK, including partial inhibition of mitochondrial complex I, alteration of cellular redox balance, and energy charge [133]. Furthermore, AMPK-stimulated energy stress increases mitochondrial biogenesis and mitochondrial protein synthesis and decreases ROS, which is also associated with improved muscle function and insulin sensitivity in skeletal muscle [134,135]. Furthermore, metformin has been shown to preserve skeletal muscle satellite cells, prevent satellite cell senescence induced by lipid overload, and enhance myogenesis [136]. In contrast, metformin blunts the bioenergetic and hypertrophic responses to exercise training in older adults, suggesting a non-synergistic interaction with lifestyle intervention [137,138]. Further, long-term metformin administration may induce muscle atrophy via activation of myostatin, a negative regulator of muscle hypertrophy [139,140]. Metformin has also been connected to muscle atrophy via upregulation of atrogenes, such as *MuRF1* and *MAFbx32*, as well as over-activation of the ubiquitin-proteasome activity system [141]. However, these findings are incongruent with other reports suggesting that metformin enhances redox balance that could prevent the muscle breakdown, likely limiting mitochondrial-complex I linked hydrogen peroxide production [142,143]. Indeed, metformin treatment for 4 weeks reduces the potential for succinate and fatty-acid-supported mitochondrial ROS emission in skeletal muscle without any effect on respiratory control [143]. Collectively, metformin-stimulated AMPK activation favorability influences cellular function which, in the absence of other interventions, improves muscle tone. However, further research is required to establish whether metformin can treat sarcopenic obesity.

### 4.6. Glutathione (GSH) agonists

An uninterrupted supply of energy is necessary to sustain cellular function. Mitochondria act in coordination with nutrient sensors to provide cellular energy. However, leakage of electrons, as mitochondria engage in energy transfer results in ROS production, and if leakage is excessive this can cause damage to the organelles [144]. Oxidative stress and mitochondrial dysfunction are toxic to cellular function, which is further amplified by deficiencies in endogenous antioxidant glutathione activity (GSH) [145,146]. ROS-induced oxidative stress is associated with genomic damage, which can regulate pathological gene expression programs that attenuate muscle stem cells' regenerative potential with advancing age, thus causing cellular senescence [147,148]. To this end, senescent cells, independent of but as observed in aging, produce an inflammatory environment which arrests stem cell proliferation and muscle regeneration, ultimately impairing muscle function [148,149]. Antioxidants may protect mitochondria from ROS, and GSH is an abundant endogenous intracellular antioxidant tripeptide composed of glycine, cysteine, and glutamic acid, ultimately preventing ROS-induced genomic damage [150]. GSH plays an essential role in protecting cells against oxidative stress and is required for optimal mitochondrial fatty-acid oxidation [145]. Compared to young individuals with normal BMI, older adults with obesity have ~66 % lower GSH concentrations in skeletal muscle. Glycine and n-Acetylcysteine (GlyNAC) supplementation is promising in mice [145] and early phase clinical trials for sarcopenic obesity [151], with robust improvements in muscle function and attenuation of mitochondrial dysfunction in skeletal muscle primarily driven by limiting oxidative stress [151]. GlyNAC treatment has been shown to improve gait speed, handgrip strength, and exercise capacity measured by a rapid 6-minute walk test [152]. Since GSH is required for the maintenance of lipid homeostasis in skeletal muscle, aberrant GSH function triggers the onset of insulin resistance and muscle dysfunction as observed in sarcopenic obesity [145,153]. However, stopping GlyNAC resulted in the reversal of the accrued benefits in both muscle function and mitochondrial-fatty-acid oxidation [150,152]. Thus, correcting GSH deficiency with GlyNAC supplementation represents another promising approach for treating sarcopenic obesity. An overview of preclinical models for sarcopenic obesity treatment is provided in Table 2.

## 5. Conclusions

Sarcopenic obesity is a multidimensional disease with limited treatment options. Systemic energy burden established by obesity in the context of aging serves as the pathophysiological driver of disease, exacerbating the rate of muscle loss. To this end, relieving energy burden and enhancing muscle function are requisite components to successful therapeutic intervention. Drugs that target processes related to energy transduction and nutrient deposition appear to have therapeutic value, however, further investigation is required to determine efficacy and tolerability in humans.

### 5.1. Limitations

At current, the body of clinical evidence is not definitive or

generalizable and lacks consistency in defining sarcopenic obesity as a disease state. In pre-clinical models, treatment utility is confounded by the type of controls used in the study (i.e. obesity without sarcopenia in the context of aging). Further research is direly needed to understand the causes and consequences of sarcopenic of obesity as a discretely defined disease.

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## CRediT authorship contribution statement

**Christopher L. Axelrod:** Conceptualization, Writing – original draft, Visualization, Project administration. **Wagner S. Dantas:** Conceptualization, Writing – original draft. **John P. Kirwan:** Conceptualization, Writing – review & editing, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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