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Sarcopenic Obesity – How Do We Treat It?

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Abstract

Purpose of review—The increasing prevalence of sarcopenic obesity in older adults has heightened interest in identifying the most effective treatment. This review highlights recent progress in management with an emphasis on lifestyle interventions and pharmacologic therapy aimed at reversing sarcopenic obesity.

Recent findings—While weight loss and exercise independently reverse sarcopenic obesity, they act synergistically in combination to improve body composition and physical function beyond which is observed with either intervention alone. Optimizing protein intake appears to have beneficial effects on net muscle protein accretion in older adults. Myostatin inhibition is associated with favorable changes in body composition in animal studies, though experience in humans is relatively limited. Testosterone and growth hormone offer improvements in body composition but the benefits must be weighed against potential risks of therapy. GHRH-analog therapy shows promise but further studies are needed in older adults.

Summary—At present, lifestyle interventions incorporating both diet-induced weight loss and regular exercise appear to be the optimal treatment for sarcopenic obesity. Maintenance of adequate protein intake is also advisable. Ongoing studies will determine whether pharmacologic therapy such as myostatin inhibitors or GHRH-analogs have a role in the treatment of sarcopenic obesity.

Keywords

sarcopenic obesity; myostatin inhibitors; exercise; weight loss; elderly; older adults

Introduction

Sarcopenic obesity has been appropriately characterized as a confluence of two epidemics, namely the aging of the population and the obesity epidemic [1]. It is characterized by obesity with decreased muscle mass and function [2], with a prevalence as high as 20% in

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Conflicts of interest
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older populations [3]. Indeed, older adults are particularly susceptible to the adverse effects of excess body fat on physical function because of 1) decreased muscle mass and strength that occurs with aging (sarcopenia) and 2) a need to carry greater body mass due to obesity. This increasingly prevalent phenotype has given rise to a population of older adults at increased risk for disability [2], institutionalization [4], and mortality [5]. While these sequelae are widely recognized as inherent to obesity in older adults, it is now accepted that the combination of obesity with sarcopenia, a change in body composition typical of aging, poses even greater risks for poor health-related outcomes and disability than either obesity or sarcopenia alone ([6–10]. The obvious public health implications in an aging society have underscored the importance of identifying the best approach for management of sarcopenic obesity. Unfortunately, the pathogenesis of sarcopenic obesity is multifactorial, such that the optimal treatment for this disorder is not well understood. Specifically, the excess adiposity owing to this condition has been attributed in part to a positive energy balance associated with aging, the consequence of decreases in all major components of total energy expenditure [11] as well as a reduction in physical activity [12•]. Concurrently, these aspects of aging affect the propensity for development of sarcopenia, which is further exacerbated by other age-related changes such as reduced protein intake [13], increased skeletal muscle fatty infiltration [14], impaired muscle energetics [15], altered skeletal muscle substrate metabolism [16], increased expression of myostatin [17], impaired sensitivity to the anabolic effects of insulin with associated mitochondrial dysfunction [18], and age-related reductions in growth hormone and testosterone secretion [10;17;19•–21]. Accordingly, a multifaceted approach to the management of sarcopenic obesity remains the most promising in terms of reducing the associated health care burden from both a personal and public health perspective. The current review provides a summary of recent advancements in therapies for sarcopenic obesity, encompassing a growing literature pertaining to lifestyle interventions and also pharmacologic therapies currently under investigation.

Lifestyle Interventions

The independent and combined effects of lifestyle interventions on sarcopenic obesity are well-described. We will review evidence pertaining to weight loss, exercise, and nutritional modification.

Weight loss

Excess adiposity is associated with a state of low-grade chronic inflammation which contributes to the decline in muscle mass and strength observed in older adults with sarcopenic obesity [22]. Moreover, ectopic fat accumulation in skeletal muscle is associated with impaired muscle strength [14], an important determinant of poor health in older age [9]. Intuitively, weight loss therapy would therefore appear an appropriate strategy for reversing sarcopenic obesity. However, weight loss in older adults remains controversial in part due to the associated loss in lean body mass associated with this intervention and concerns for exacerbating sarcopenia [23•]. Nonetheless, it has been demonstrated that weight loss therapy is not only feasible in frail, obese older adults [24], but that older adults may be more compliant with lifestyle interventions and achieve greater weight loss than younger adults [25;26•]. We investigated the effects of a diet-induced reduction in body weight

(~10%) in obese older adults with frailty and found that, while there was some loss in lean body mass associated with this intervention, an even greater reduction in fat mass was observed such that the end result was an improvement in relative sarcopenia (percent body weight as lean body mass) and amelioration of frailty [27••]. As depicted in Figure 1 (MRI images of thigh), an approximate 20% reduction in body weight in this patient resulted in a greater reduction in fat mass than lean mass, leading to improvement of relative sarcopenia and resolution of frailty, as evaluated by the objective physical performance test [28]. Hence, despite a reduction in lean body mass, weight loss appears to be a suitable intervention for the treatment of sarcopenic obesity.

Exercise

Sarcopenic obesity has been attributed in part to an age-related decline in physical activity [12], an observation which has prompted several studies on the effects of exercise on this disorder. Indeed, exercise has been shown to have beneficial effects on multiple aspects of sarcopenic obesity with a resultant increase in muscle protein synthesis [29], reduction in myostatin expression [30•], increase in intramuscular IGF-1 [31], restoration of skeletal muscle sensitivity to the anabolic effects of insulin [32], improvement of nutrient-stimulated vasodilation and nutrient delivery to muscle [33•], enhancement of mitochondrial function [18], and activation of skeletal muscle satellite cells felt to be protective against sarcopenic obesity [34]. Moreover, we have demonstrated that exercise, but not diet-induced weight loss, decreased skeletal muscle inflammatory gene expression in frail, obese older adults [35]. As with weight loss therapy, a regular multicomponent exercise intervention is associated with improvement in sarcopenia with a reduction in fat mass and increase in lean body mass, resulting in reversal of frailty [27]. We suggest an exercise intervention incorporating progressive resistance training (PRT), with three ~90-minute sessions per week consisting of 15 minutes of flexibility, 30 minutes of low-impact aerobic exercise, 30 minutes of high-intensity PRT, and 15 minutes of balance training [36]. PRT has also been studied in Asian Indian subjects, a population inherently prone to sarcopenic obesity with higher relative fat mass and lower relative lean mass than any other ethnic group [37], and was associated with improvements in muscle strength, waist circumference, and multiple metabolic outcomes [38].

Combined weight loss and exercise

The most effective lifestyle intervention for treatment of sarcopenic obesity is one that includes both, diet-induced weight loss and regular exercise. We previously demonstrated that the combination of these interventions acted synergistically to improve sarcopenia and ameliorate frailty more so than either diet or exercise alone [27••]. Further, the reduction in lean body mass associated with weight loss therapy was attenuated, although not prevented, when combined with regular exercise. Muscle strength increased in the combined intervention despite the modest reduction in lean body mass, suggesting an improvement in muscle quality. Figure 2 illustrates this point further by demonstrating that a combined diet and exercise intervention was associated with an increase in relative lean mass and resolution of frailty despite the absolute reduction in lean body mass. These results lend support to the recommendation that lifestyle interventions targeting reversal of sarcopenic obesity incorporate both, diet-induced weight loss and regular exercise.

Nutritional modification

Aging is associated with both, a reduction in dietary protein intake [13] as well as a blunted muscle protein synthesis response to essential amino acid ingestion [39]. Moreover, the recommended dietary allowance for protein intake may not be adequate in older adults [40]. It has been demonstrated in older adults that ingestion of larger amounts of essential amino acids restores the muscle protein synthesis response similarly to that observed in younger adults, suggesting a threshold effect which can be overcome with increased protein intake [41]. Taking this into consideration, it has been suggested that 25–30 grams of high quality protein be ingested per meal in order to prevent sarcopenia in older adults [42]. This recommendation is based on evidence that ingestion of less than 25–30 grams of protein per meal is associated with suboptimal muscle protein synthesis in the elderly [43]. Likewise, ingestion in excess of 30 grams of protein per meal has not been shown to further improve the anabolic response [44]. While sufficient protein intake is paramount to optimizing the muscle protein synthetic response, a diet relatively low in carbohydrates may also be advisable as coingestion of carbohydrates has been shown to exert negative effects on muscle protein turnover in the elderly [45].

Supplementation with leucine, the most potent branched-chain amino acid for stimulation of protein synthesis, has also been proposed for the prevention of sarcopenia [46]. Indeed, leucine supplementation in older adults has been associated with enhanced muscle protein synthesis independently of ingestion of other amino acids [47]. While these data are promising with regard to nutritional modification and improvements in muscle protein synthesis, long-term studies are ongoing in older adults to determine whether these interventions are effective in preventing muscle loss in older adults.

Pharmacologic therapy

While lifestyle interventions are a cornerstone of management of sarcopenic obesity, it is appreciated that these measures are not always feasible in all patients, either due to physical limitations or poor adherence. Accordingly, there has been growing interest in pharmacologic therapies for this increasingly prevalent condition. We will specifically review recent advancements in the use of myostatin inhibitors for the prevention of sarcopenia as well as explore the benefits and limitations of other anabolic therapies which have been studied in this context such as testosterone and mediators of the IGF-1 system.

Myostatin inhibitors

The role of myostatin in sarcopenic obesity has received considerable attention in recent years and there is accumulating evidence that its inhibition may result in favorable changes in both adiposity and lean body mass. A member of the TGF-β superfamily of secreted growth factors, myostatin is produced by skeletal muscle and adipose tissue, functioning as a negative regulator of muscle mass [48]. Its clinical relevance has been confirmed in rodent models whereby myostatin infusion has resulted in marked muscle wasting [49]. Moreover, myostatin influences adipocyte differentiation with substantial evidence to suggest myostatin-mediated crosstalk between muscle and adipose tissue [30•]. In this sense, skeletal muscle may be considered an endocrine organ, contributing a role in the regulation

of body composition. Indeed, myostatin has proven to be a biomarker of sarcopenia in the elderly, correlating inversely with muscle mass, with higher levels being observed in frail older adults compared to younger adults [50]. In contrast, observations of myostatin deficiency in nature have shed light on the implications of myostatin inhibition, with exceptional muscularity and scarce adiposity being well-described in myostatin-deficient cattle [51]. Similarly, a homozygous mutation in the myostatin gene has been described in a human child with increased muscle strength and phenotypic features overlapping those described in myostatin-deficient livestock [52]. These observations have given way to experimental models of myostatin deficiency aimed at determining whether myostatin inhibition is a suitable strategy for the treatment of sarcopenic obesity. Data in animal models have been promising with myostatin knockout mice demonstrating favorable changes in adipose tissue [53•], reduced inflammatory markers [54], increased muscle mass [55], and protection against age-related sarcopenia [56]. Further, inhibition of myostatin by the administration of myostatin antibodies or introduction of inhibitory propeptides in mice has been associated with improved muscle mass and function [57–61], increased intramuscular satellite cell function and IGF-1 signaling (55), enhanced thermogenesis [62•], and resistance to obesity [61;62].

While the prospect of myostatin inhibition for the treatment of sarcopenic obesity appears promising based on animal studies, data have been much more limited in humans with past studies focusing primarily on treatment in patients with muscular dystrophy. In one phase I/II trial of a myostatin antibody, no improvement in muscle strength or function was observed in muscular dystrophy patients, although the study was not powered for efficacy [63]. In another study, myostatin inhibition in muscular dystrophy patients was associated with improvements in muscle function at a cellular level; however, there were no quantitative improvements in muscle strength observed [64]. While it is possible that the lack of efficacy beyond the cellular level may have been related to the underlying pathologic process in muscular dystrophy, these results do raise some uncertainty. For instance, similar findings were described in rodent models wherein the absence of myostatin resulted in compromised muscle force production [55] and impaired muscle energetics [65••] despite an increase in muscle mass. Further uncertainties regarding the effects of myostatin inhibition on muscle function stem from observations in individuals with the K153R polymorphism in the myostatin gene, a variant reported to reduce the ability of myostatin to modulate muscle mass and strength [66]. While this variant may contribute to exceptional longevity [67], there are also reports of diminished muscle force in some [68], but not all [69] affected individuals. There are other unanswered questions regarding the long-term cardiovascular safety of myostatin inhibition given the evidence of myocardial expression of myostatin and its role in the development of heart failure [70]. For these reasons, long-term data are needed to elucidate the role myostatin inhibition may have in the prevention or treatment of sarcopenic obesity, with current studies ongoing in healthy adults.

Testosterone

A predictable decline in testosterone with aging parallels both the loss in lean body mass and the gain in fat mass which lead to sarcopenic obesity [71]. The beneficial effects of testosterone replacement on body composition and muscle strength in hypogonadal men

have been well documented in a recent review [72••]. The current review will focus rather on the effects of testosterone therapy in healthy men on age-related changes in body composition. While most studies have reported favorable changes in fat mass and lean body mass, the data pertaining to muscle strength have been mixed. Hildreth et al recently investigated the effects of 12 months of testosterone therapy or placebo in healthy older adults randomized to progressive resistance training versus no exercise [73••]. In those subjects randomized to exercise, testosterone therapy was associated with improvements in fat mass and fat-free mass; however, no differences were observed in physical function or muscle strength compared to placebo. In contrast, upper body strength improved in the non-exerciser subjects treated with testosterone although no improvements were noted in physical function. Changes in body composition paralleled those observed in the exercisers. Similarly, other studies in healthy older men have reported favorable effects of testosterone therapy on body composition [74;75]. In terms of muscle strength, a 36-month double-blind placebo-controlled trial identified no improvements in knee extension or flexion with testosterone therapy [74]. A 4-week study of the effects of testosterone therapy in 6 healthy older men demonstrated improvements in hamstring and quadriceps strength although there was no control group for comparison [76]. Likewise, Bhasin et al reported a dose-dependent increase in leg press strength in healthy older men after 20 weeks of testosterone therapy which did not differ from the effects observed in a cohort of young men [75]. Importantly, adverse events were observed more frequently with higher doses of testosterone. Thus, evidence suggests that testosterone therapy in healthy older men exerts beneficial effects on body composition which may be protective against sarcopenic obesity; however, there is need for careful monitoring for potential adverse events such as erythrocytosis, growth of subclinical prostate cancer, worsening of obstructive sleep apnea, and fluid retention.. The 2010 Endocrine Society Guidelines suggest treatment in older adults only if clinical and biochemical evidence of hypogonadism are present and after an informed discussion regarding the risks and benefits of therapy [77].

Other therapies

Aging is associated with a progressive decline in growth hormone (GH) secretion and IGF-1 production [72••, which is felt to be responsible in part for the decline in lean body mass and increase in fat mass that contribute to sarcopenic obesity [78]. Thus, GH therapy has been studied as an anti-aging agent and, in healthy older adults, reverses these changes in body composition [79]. Unfortunately, treatment has also been associated with significant adverse events such as arthralgias, edema, and glucose intolerance, and for this reason a systematic review in 2007 concluded that GH should not be used as anti-aging therapy [80]. Thus, more recent studies have employed novel techniques to augment endogenous pulsatile GH with the intention of minimizing the adverse events associated with exogenous GH therapy. The growth hormone secretagogue capromorelin improved body composition and physical function in healthy older adults but was associated with aggravation of glucose homeostasis [81]. On the other hand, Makimura et al recently reported the effects of a GHRH analog which reduced fat mass and increased lean body mass in obese individuals yet was not associated with abnormalities in glucose homeostasis or other adverse events compared to placebo [82••]. The subjects in this study were younger than those included in the capromorelin study. Nonetheless, the results are promising and future studies are needed to

determine whether tesamorelin may be useful for the treatment of sarcopenic obesity in older adults.

The role for androgenic therapies aside from testosterone in improving body composition has also been evaluated. While there are conflicting data pertaining to the use of dehydroepiandrosterone (DHEA) alone on muscle mass and strength, we have demonstrated that DHEA supplementation potentiates the anabolic effects of heavy resistance exercise in older adults [83]. A recent meta-analysis of double blind placebo controlled trials in elderly men showed that DHEA supplementation can induce a small but significant positive effect on body composition, which is dependent on DHEA conversion to androgens or estrogens [84]. The use of anabolic steroids for reversal of the changes in body composition associated with aging has received less attention in recent years. Treatment of elderly men with the synthetic anabolic androgen, oxandrolone, was associated with improvements in lean body mass, fat mass, and muscle strength [85], but significant reductions in high-density lipoprotein (HDL) cholesterol were also observed [86]. Recently, a phase 2 trial in cancer cachexia, suggested that a non-steroidal selective androgen receptor modulator, enobasarm, might lead to improvements in lean body mass without the toxic effects associated with androgens.

Other treatments currently in development include inhibitors of transcription factor nuclear factor kappa B (NF-κB) for protection against cancer-related cachexia. Early studies demonstrate favorable effects of NF-κB inhibition on cancer-related cachexia and provide further insight into the pathogenesis of this disorder, offering promise for continued progress in the development of targeted therapies for muscle wasting disorders [87].

Conclusion

The rising prevalence of obesity in older adults coupled with the age-related decline in muscle mass and resulting relative sarcopenia act synergistically to maximize disability, morbidity, and mortality. Given the public health implications, an effective treatment strategy in an aging population is essential. We propose that efforts to treat sarcopenic obesity be based primarily on lifestyle interventions. While there is convincing evidence that weight loss and exercise independently result in reversal of sarcopenic obesity and frailty, an intervention strategy incorporating combined weight loss and exercise has proven to be the most effective treatment for this disorder. We agree with recommendations to ensure adequate high-quality protein intake in older adults. With regard to pharmacologic therapies for sarcopenic obesity, we do not believe that the data as of yet support testosterone therapy in the absence of symptomatic hypogonadism. On the other hand, there is promising, albeit limited data pertaining to the use of myostatin inhibitors and GHRH-analogs for sarcopenic obesity and we will look to future studies with cautious optimism.

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Key points

- The most effective treatment strategy for sarcopenic obesity is one that incorporates both diet-induced weight loss and a regular multicomponent exercise program incorporating progressive resistance training
- In the absence of hypogonadism, current evidence does not justify the use of testosterone therapy for the treatment of sarcopenic obesity.
- Further studies are needed to determine whether there is a role for myostatin inhibitors or GHRH-analogs for the treatment of sarcopenic obesity.

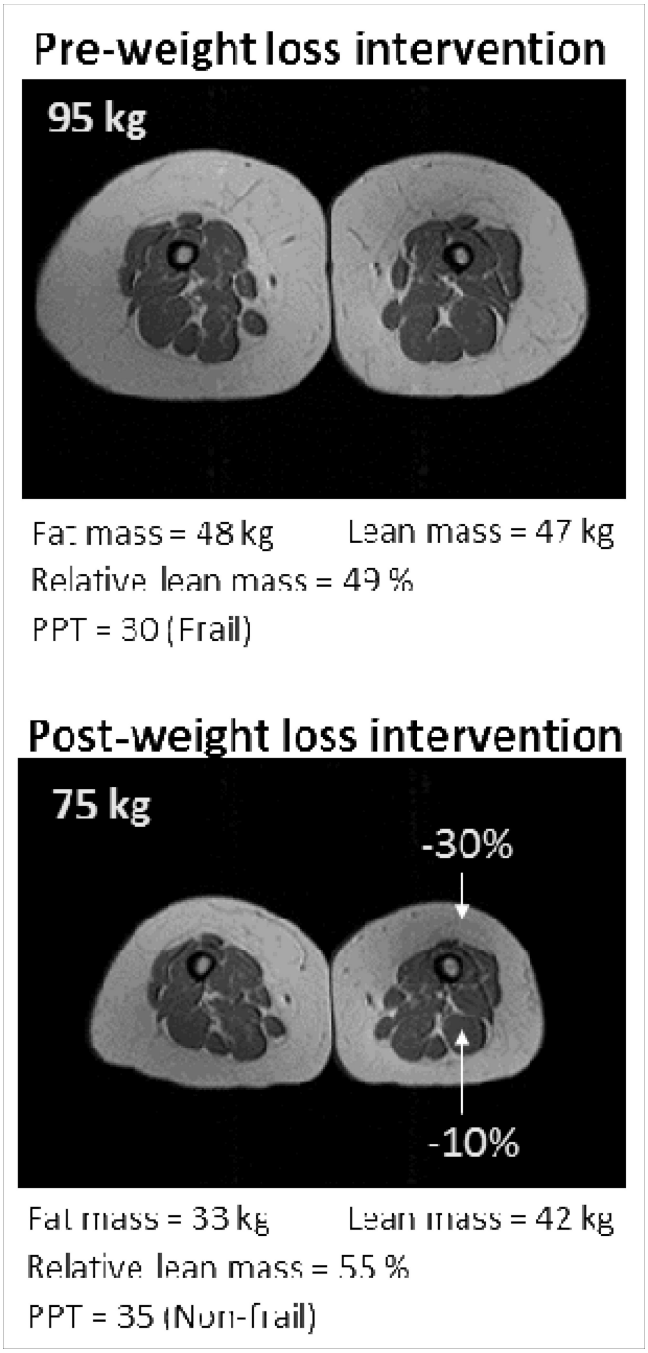

Figure 1. Changes in body composition after weight loss therapy in a frail obese older adult
Physical performance test (PPT) score 0–36 with higher scores indicating better performance (<32 indicates frailty)

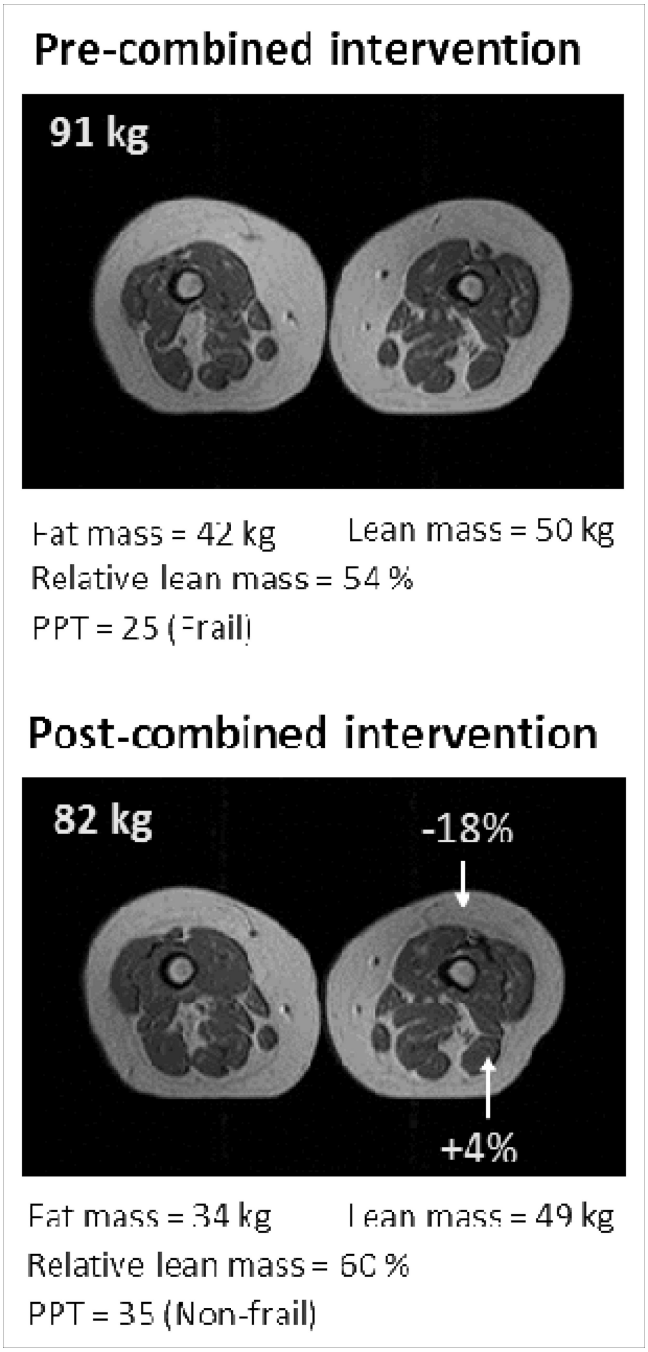

Figure 2. Changes in body composition after combined (exercise plus weight loss) intervention in a frail obese older adult

Physical performance test (PPT) score 0–36 with higher scores indicating better performance (<32 indicates frailty)