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# Therapeutic and Lifestyle Approaches to Obesity in Older Persons

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## Abstract

**Purpose of Review:** Obesity rates worldwide continue to increase and will disproportionately affect older adults due to population aging. This review highlights recent progress pertaining to therapeutic approaches to obesity in older adults.

**Recent Findings:** Caloric restriction (CR) alone improves physical function and quality of life in older adults with obesity but is associated with loss of lean mass and increases fracture risk. Adding progressive resistance training (RT) to CR attenuates loss of muscle and bone mass and increasing protein intake enhances this effect. Adding aerobic endurance training (AT) to CR further improves cardiorespiratory fitness but adding both AT and RT to CR results in the greatest improvement in overall physical function while still preserving lean mass. Future promising therapeutic interventions include testosterone, myostatin inhibitors, and bariatric surgery, but there are few studies specific to obese older adults.

**Summary:** The optimal approach towards obesity in older persons is lifestyle intervention incorporating CR and exercise consisting of AT and RT. Maintenance of adequate protein intake, calcium, and vitamin D is advisable. There is insufficient evidence specific to obese older adults to recommend testosterone or bariatric surgery at this time. Myostatin inhibitors may become a future treatment and clinical trials are ongoing.

### Keywords

obesity; older adults; weight loss; caloric restriction; exercise

## Introduction

The population of older adults (≥65 years) worldwide currently stands at just under 1 billion and is expected to double within the next 30 years. In Europe today, 1 in 4 adults is over the

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age of 65 years; however, this ratio is anticipated to be 1 in 2 by 2050 [1]. Coinciding with the future aging of the population is the ongoing public health epidemic of obesity (Body Mass Index [BMI] ≥ 30 kg/m$^2$), which has already tripled in prevalence globally within the past 40 years [2]. In the United States, which has the highest population of obese individuals today, 41% of older adults are currently obese and trends suggest the rate will continue to increase [3, 4].

Obesity is associated with multiple chronic diseases including hypertension, diabetes, heart disease, stroke, and cancer and has been shown to decrease quality of life and life expectancy. For older adults, obesity synergistically exacerbates the age-related decline in muscle mass and physical function (sarcopenia) causing frailty, an increase in institutionalization rates, and greater health care costs [5]. Despite the inevitability of this looming public health issue, there remains a concerning dearth of knowledge regarding the best therapeutic approaches for managing obesity in older persons [6**], especially for sarcopenic obese individuals who suffer the worst of both conditions [7].

The current review summarizes updates from the most recent literature pertaining to both lifestyle and pharmacological interventions for combating obesity in older persons. We also address the latest evidence surrounding the safety of intentional weight loss interventions in the elderly obese population.

## Caloric Restriction (CR)

Clinically significant weight loss is not only achievable in the obese older adults, but evidence suggests that increasing age is a strong predictor of adherence to lifestyle interventions in both men and women [8, 9]. In multiple randomized controlled trials (RCTs), CR ranging from 500–1000 kilocalorie per day deficits with or without concurrent exercise training is effective at inducing weight loss [6**]. Early evidence also suggests that intervention with a very low calorie diet (intake of as little as 800 kilocalories a day) was tolerated in older adults and resulted in 11.1% decrease in body weight over 12 weeks [10*].

CR alone improves measurable outcomes of physical function and quality of life; however, it has also consistently been shown to decrease lean body mass and bone mineral density (BMD) at the hip assessed by dual-energy x-ray absorptiometry (DXA) [6**]. While CR is the first therapeutic option for the treatment of obesity in the general population, there are concerns that this approach may be harmful in older adults due to associated loss of muscle and bone mass, which can further exacerbate sarcopenia and increase fracture risk [11]. The most recent iteration of the AHA/ACC/TOS guidelines for the management of obesity states “the overall safety of weight loss interventions for patients aged 65 and older remains controversial” and “…there is a need for further research to understand the most appropriate strategies and prescriptions for weight loss for some key populations including older adults” [12].

These concerns were reinforced in recently published data from the Look AHEAD (Action for Health in Diabetes) trial, which is the first RCT to show an increased risk of frailty fractures with CR in obese older adults [13**]. A significant 39% increase in frailty fractures was noted in the group receiving intensive lifestyle intervention (ILI) compared to the weight-neutral group receiving standard of care after a median follow-up time of 11.3 years. This increase in frailty fractures occurred despite previously documented improvements in physical fitness in the ILI group and highlights the potential risks of weight loss in the older population.

## Exercise Training

Exercise incorporating aspects of both aerobic endurance training (AT) and progressive resistance training (RT) does not result in significant weight loss in the absence of CR, but it does exert positive effects on body composition, improve physical function, increase strength, and positively affect quality of life in aging adults with obesity [6**]. A recent study showed that even older adults with class 2+ obesity (BMI ≥ 35 $kg/m^2$) can safely perform moderate intensity physical activity and benefit in terms of mobility [14*]. While CR and exercise both individually improve physical function and quality of life, CR with concurrent exercise training yields better results than either modality alone [15]. Furthermore, the addition of exercise to CR has been shown to attenuate, though not completely alleviate, loss of muscle mass and BMD.

Recent studies have also focused on the effects of specific exercise modalities – RT and AT. An 18-month RCT studying the effect of CR, CR+RT, or CR+AT on body composition in 249 obese older adults found that addition of either exercise regimen to CR resulted in greater loss of total body mass; however, CR+RT preserved fat-free mass more than CR+AT [16*]. These conclusions are supported by data from two separate 5-month RCTs in overweight and obese older adults comparing the effect of CR+RT or CR+AT on BMD suggesting that RT attenuates loss of hip BMD during CR but AT does not [17]. While these findings suggest that RT in particular is crucial in mitigating the negative effects of CR on fat-free mass, the beneficial effects of AT in the setting of CR have also been highlighted recently. A 20-week RCT studying cardiorespiratory fitness, fatigue, and disability in 180 obese older men and women undergoing AT alone, with moderate (−250 kcal/d) CR, or with intensive (−600 kcal/d) CR found that the addition of moderate or intensive CR to AT equally improve peak oxygen consumption compared to AT alone [18*].

We recently reported the results of a 6-month RCT involving 160 obese older men and women with the aim to directly compare the effects of AT, RT, or combined training (CT) added to matched CR-induced weight loss (Figure 1) [19*]. Physical function assessed by the modified Physical Performance Test (PPT) improved more in CT compared to AT or RT. Peak oxygen consumption improved equally in AT and CT, which was greater than the improvement seen in RT. Decreases in lean body mass and hip BMD were noted in all intervention groups but was less in RT and CT compared to AT. Muscle strength increased equally in RT and CT, while it was only maintained in AT. Dynamic balance assessed by the obstacle course completion time and gait speed improved more in CT compared to AT or RT. These findings indicate additive effects of RT and AT on physical function without interference effect from concurrent training in these obese older adults [20, 21].

The current evidence suggests that obese older adults undertaking CR should participate in both AT and RT, which is consistent with the most recent physical activity recommendations by the American Heart Association and American College of Sports Medicine for overall health in the general population [22]. Local community weight loss programs incorporating exercise can be very successful in this population and significantly improves mobility [23**]. We anticipate that these interventions will become increasingly easy to adapt to in community fitness centers and sports clubs as many nations are now adopting more policies to promote health-enhancing physical activity in an effort to combat rising obesity rates [24].

## Calcium and Vitamin D Supplementation

The American Geriatrics Society currently recommends 1,000 international units (IU) of vitamin $D_3$ per day in addition to calcium supplementation in all non-institutionalized older adults [25]. We agree with this recommendation and emphasize that in obese older adults actively undergoing CR, supplementation of calcium, up to 1,200 mg daily, and vitamin $D_3$ is crucial to minimize the associated loss of BMD. The majority of RCTs involving clinically significant weight loss in obese older adults have employed routine supplementation in their study protocols [6**, 15-19*].

## Protein Intake

The Institute of Medicine recommended daily allowance (RDA) of protein intake is 0.8 g/kg/d for all adults regardless of age, but many experts and national organizations currently advocate for a daily protein intake of 1.2 g/kg/d or even higher in older adults based on prior evidence suggesting that skeletal muscle in the elderly has a blunted anabolic response to dietary protein [26]. A well-designed 6-month RCT in men with moderate limitations in physical function found no improvement in lean body mass, muscle strength, or physical function when daily protein intake was increased from 0.8 to 1.3 g/kg/d [27**]. A 10-week study found that older adults undertaking CR for obesity saw no improvement in fat-free mass with higher protein intake or with RT; however, the combination of both high protein intake and RT did lead to improved fat-free mass [28**]. These recent trials suggest that the RDA for protein intake of 0.8 g/kg/d is adequate for older adults in most situations, and ~1.2 g/kg/d of protein intake may be beneficial in the setting of CR+RT in obese older adults.

## Testosterone

Both total and free testosterone levels fall with increasing age in men in a pattern that parallels the gradual loss lean mass and increase in adiposity also seen in aging [29]. Comorbidities including obesity are known to accelerate this age-related decline. Based on these observations, testosterone replacement may be a therapeutic option to reverse the negative trends in body composition in aging men [30]. A series of 7 coordinated RCTs involving 788 hypogonadal older men (63% with BMI $\geq 30$ kg/m$^2$) who received testosterone gel or placebo for a year was completed to clarify the potential benefits [31*]. The trial authors recently reviewed their conclusions which found that volunteers on testosterone were noted to have small improvements in walking distance and markedly increased volumetric bone density and estimated strength relative to volunteers taking placebo.

Testosterone has recently been shown to protect against loss of lean mass during weight loss in hypogonadal obese middle-aged men (aged 50 years or older) undergoing CR. A 56-week trial found that testosterone administration during weight loss led to a reduction in loss of lean mass and an increase in fat loss despite similar overall weight loss compared to placebo [32]. Unfortunately, the favorable changes in body composition seen at the conclusion were no longer apparent over a year after discontinuation of testosterone [33**]. While still a promising future therapy, further research is needed to clarify the benefits and risks of testosterone in obese older adults during weight loss therapy.

## Bariatric Surgery

A survey suggests that almost 600,000 bariatric surgery procedures were conducted worldwide in 2014 with sleeve gastrectomy (SG) (45.9%) and Roux-en-Y gastric bypass (RYGB) (39.6%) being the most popular procedures [34]. Both SG and RYGB are effective in older adults at inducing significant weight loss and reducing obesity-associated comorbidities [35]. RYGB appears to be particularly effective at inducing weight loss in older adults compared to SG [36*]; however, older individuals undergoing RYGB have been noted to have an increased risk of nearly all perioperative complications associated with laparoscopic bariatric surgery and longer hospital stays [37]. Despite these findings, older bariatric patients still have a reduced rate of hospitalization following surgery and no difference in 30-day morality rates [38*].

Additional concerns regarding bariatric surgery center around the loss of lean body mass and BMD associated with the profound weight loss following the surgery, which would be particularly detrimental in older adults. In middle-aged adults, one study found minimal loss of lean body mass 5 years after bariatric surgery despite significant overall weight loss [39]. On the other hand, patients undergoing RYGB were noted to have ongoing declines in estimated bone strength at the radius and tibia even after weight stabilization [40*]. Furthermore, a retrospective analysis found RYGB was not only associated with an increased risk of falls and fractures that increased with time, but these risks also had no association with weight lost or calcium and vitamin D supplementation [41**]. Given these findings, extreme caution should be exercised before promoting weight loss surgery in older adults until further research can clarify the potential risks and benefits.

## Myostatin Inhibitors

Produced in skeletal muscle and adipose tissue, myostatin (also known as Growth and Differentiation Factor 8 or GD8) is a part of the transforming growth factor beta superfamily of secreted growth factors which has been shown to act as a negative regulator of muscle growth [42**]. Myostatin levels are known to be elevated in atrophied skeletal muscle in both animals and humans. Significant skeletal muscle hypertrophy and hyperplasia has been shown to occur in loss-of-function mutations in myostatin in cases involving humans and a variety of animals including cattle, mice, and dogs. Similar findings were also shown in mouse skeletal muscle overexpressing the myostatin inhibitor follistatin and in cases involving inactivating mutations in the primary myostatin receptor activin receptor IIB (ActRIIB) [43]. These findings suggest that myostatin inhibition may be a potent therapeutic option in a range of muscle wasting conditions including sarcopenic obesity and muscle loss associated with weight loss.

Significant progress continues to be made in showing the potency of myostatin inhibition in animal models. Recent reports have found that myostatin inhibition increases lean mass and muscle strength in mouse models of muscular dystrophy [44] and Huntington's disease [45] while preventing muscle atrophy and improving physical function post-stroke [46] and after anterior cruciate ligament repair [47]. A number of myostatin inhibitors have already progressed to early phase clinical trials and exert their potential effects by blocking the interaction between mature myostatin and its receptors. This is accomplished through use of antibodies, ligand traps, or by overexpressing the natural myostatin inhibitor follistatin [48].

Thus far, published reports involving intervention studies in humans have been early phase I and II trials in patients with muscular dystrophy [49*], sarcopenia [50], after elective orthopedic surgery [51], and in healthy individuals [52, 53]. In general these studies have found the pharmacological intervention to be well tolerated; however, results have been mixed. A study involving a monoclonal antibody targeting myostatin led to increases in appendicular lean mass, decreases in fat mass, and improved gait speed in sarcopenic individuals with a recent history of falls [50]. Others have failed to show improvement over placebo [49*, 51-52].

## Conclusion

In the older adult population, the prevalence of obesity is anticipated to grow substantially in the coming years due to an increase in the aging population and in the prevalence of obesity itself. Given the public health implications, an effective treatment strategy is essential. We propose that the primary treatment of obesity in older adults should remain centered around lifestyle interventions incorporating CR and an exercise regimen consisting of both AT and RT. CR in the absence of exercise training or other measures to attenuate anticipated loss of lean mass and BMD should be avoided. We agree with recommendations to ensure adequate calcium and vitamin D supplementation as well as high-quality protein intake in the setting of CR. While therapies such as testosterone and bariatric surgery are already available today, we do not believe that there is sufficient evidence specific to older adults to recommend these options at this time. There may be a potential future role for myostatin inhibitors in the treatment of sarcopenic obesity and muscle loss associated with weight loss and clinical trials are ongoing.

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**Key Points**

- The foundation of obesity management in older adults is lifestyle intervention incorporating caloric restriction-induced weight loss with physical activity consisting of aerobic endurance training and progressive resistance training.
- Adequate vitamin D and calcium supplementation in addition to a daily protein intake of ~1.2 grams per kilogram of body weight is recommended in the setting of lifestyle intervention to maximally preserve muscle mass and bone mineral density during caloric restriction.
- Caloric restriction alone is associated with loss of muscle and bone mass which can exacerbate sarcopenia and increase the risk of fractures in obese older adults.
- Further investigation is required before recommending other therapies for obesity in older adults such as bariatric surgery, testosterone, and myostatin inhibitors.

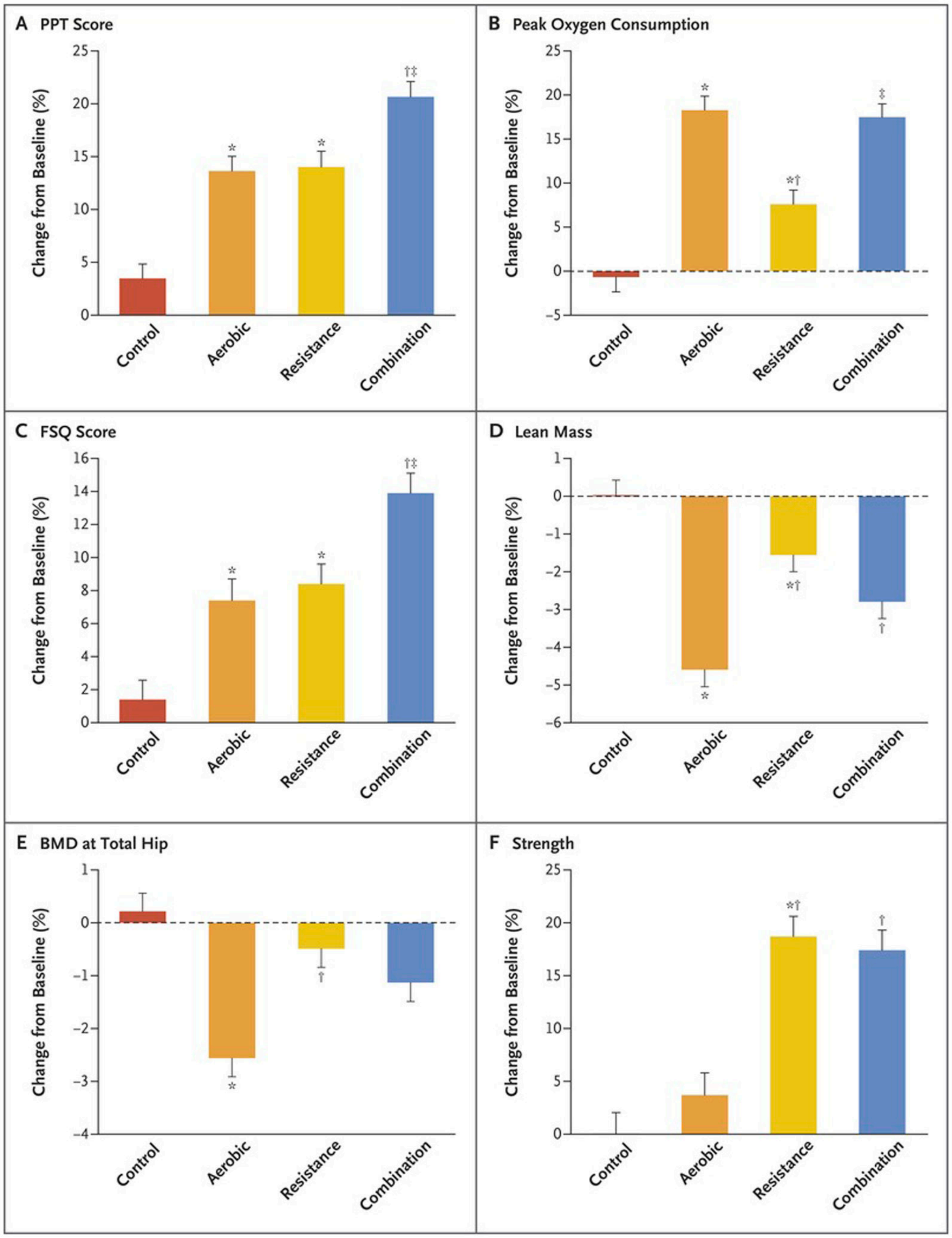


**Figure 1. Mean Percentage Changes in Physical Function, Lean Mass, and BMD at the Total Hip during the Interventions.**

Measures of physical function included the Physical Performance Test (PPT; scores range from 0 to 36, with higher scores indicating better functional status), peak oxygen consumption, Functional Status Questionnaire (FSQ; scores range from 0 to 36, with higher scores indicating better functional status), and strength (measured as total one-repetition maximum [i.e., the total of the maximum weight a participant can lift, in one attempt, in the biceps curl, bench press, seated row, knee extension, knee flexion, and leg press]). Scores on the PPT were used as an objective measure of frailty (primary outcome), and scores on the

FSQ were used as a subjective measure of frailty. The asterisk indicates $P<0.05$ for the comparison with the control group, the dagger $P<0.05$ for the comparison with the aerobic group, and the double dagger $P<0.05$ for the comparison with the resistance group. Percentage changes are presented as least-squares–adjusted means; T bars indicate standard errors. BMD denotes bone mineral density. From [*N Engl J Med*, Villareal DT et al, Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults, Volume 376(20), 1943–1955] 