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Weight Loss-Induced Reduction of Bone Mineral Density in Older Adults with Obesity

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Abstract

Obesity in older adults is a growing public health problem, yet the appropriate treatment remains controversial partly due to evidence that weight loss reduces bone mass and may increase fracture risk. The purpose of this review is to summarize the research to date on the effects of diet-induced weight loss on bone health in obese (body mass index 30 kg/m^2 and above) older (aged 65 years or older) adults. Observational studies have shown that weight loss in this population decreases total hip bone mineral density and increases the risk of frailty fractures (composite of proximal femur, pelvis, and proximal humerus fractures). Randomized controlled trials have largely confirmed these earlier observations but have also shown that exercise, particularly progressive resistance training, can attenuate or even alleviate this bone loss. Further research incorporating outcomes concerning bone quality and mass are needed to identify the optimal exercise and nutritional regimens to counteract the bone loss.

Keywords

older adults; obesity; weight loss; bone; bone mineral density; bone markers; fracture; review

1. The Public Health Problem of Obesity in Older Adults

The number of older adults (≥65 years) in the United States is expected to more than double between 2010 and 2050 from 40.8 million to 88.5 million. Over a third of older adults today are obese (Body Mass Index [BMI] ≥ 30 kg/m^2) and trends suggest that the prevalence of obesity in this rapidly growing age group is increasing as well.[1] For older adults, obesity is not only associated with a number of serious medical conditions, but also exacerbates the age-related decline in physical function causing frailty, decreases quality of life, and increases nursing home admissions.[2] Despite this, there are concerns that weight loss in this obese older population may be harmful due to the loss of bone mass which can lead to an increased risk of fractures.[3;4] In 2013, the AHA/ACC/TOS guidelines for the management of obesity stated “the overall safety of weight loss interventions for patients aged 65 and

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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".[5]

2. Effect of Obesity on Age-related Loss of Bone Mass and Fracture Risk

Bone is constantly undergoing the process of remodeling, which is mediated by the tightly regulated actions of bone forming osteoblasts and bone resorbing osteoclasts. Ninety percent of peak bone mass is typically achieved by age 20 and the potential for increasing bone mass remains while bone formation and resorption are closely matched. Starting around the age of 30 there is a progressive shift towards favoring of bone resorption over bone formation.[6] Cross-sectional studies looking at age-related changes in areal bone mineral density (BMD) as assessed by dual-energy x-ray absorptiometry (DXA) have noted increasing loss of bone mass with age.[7] Volumetric BMD and bone geometry assessed by high resolution peripheral quantitative computed tomography (HRpQCT) in addition to estimated bone strength assessed by finite element analysis (FEA) have also been shown to worsen with age.[8–9] Multiple mechanisms including secondary hyperparathyroidism, decreased physical activity with age, and the accumulation of bone marrow fat associated with aging have been implicated with estrogen deficiency associated with menopause in women being the most well studied.[6;10–12]

The positive association between BMI and BMD at the spine and total hip has been verified in a number of epidemiological studies.[13–15] Obesity is thought to decrease fracture risk primarily by increasing mechanical loading on the bone due to an increase in overall body mass. Obesity may also provide additional site specific benefits to fracture risk beyond increased BMD such as increased adiposity at the thigh providing a "cushioning effect" in the event of a fall onto the hip.[16–17]

Despite these potential benefits, more recent data within the last decade suggest that the BMD in the obese does not correlate well with overall fracture risk.[18–22] Increasing BMI is known to lower reproducibility and may also artificially increase BMD measurement at the spine in obese subjects.[18] Obesity has a site-dependent effect on fracture risk with decreases in hip, pelvic, and wrist fractures, but increases in ankle, upper arm, and humerus fractures.[19] Once corrected for BMD, one meta-analysis found that obesity was associated with an overall increase in osteoporotic fractures (hazard ratio 1.16; 95% confidence interval, 1.09–1.23).[21] Epidemiological studies have also corroborated this finding by noting that the majority of fractures actually occur in this population as well.[22–23]

Obesity is thought to contribute to an increased risk of fracture via a number of separate mechanisms. Obesity is associated with an increased risk of falls as well as a higher risk of greater activities of daily living disability after fall.[24–25] Increased central adiposity leads to an increased level of systemic inflammation whereby various inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) increase bone resorption and negatively impact multiple markers of bone quality (e.g. higher cortical porosity, decreased trabecular bone volume fraction, and lower trabecular stiffness).[26–28] Obesity and increased adiposity is associated with a decrease in serum 25-hydroxyvitamin D levels.[29–30]

Parathyroid hormone levels have also been shown to correlate with increased adiposity, though it is not clear if this is solely related to secondary hyperparathyroidism from decreased 25-hydroxyvitamin D or if other mechanisms are involved.[31–32]

3. Effect of Weight Loss on Bone Mass and Fracture Risk in Older Adults

Observational studies focusing on the effect of weight loss on bone in older adults have shown that weight loss, both intentional and unintentional, is associated with decreases in BMD at the hip as well as an increase in frailty fractures (a composite of proximal femur, pelvis, and proximal humerus fractures).[33–35] In the Study of Osteoporosis Fractures, older women who had weight loss of at least 5% from baseline had a 35% greater decline total hip BMD per year relative to weight stable women and a two-fold increase in the risk of subsequent hip fracture after an average follow-up duration of 6.6 years.[33] Risk was increased regardless of baseline BMI, even in the overweight and obese population that engaged in voluntary weight loss. Women with involuntary weight loss were at the highest risk of frailty fracture.[34] Similar findings were also found in older men in the Osteoporotic Fractures in Men (MrOS) Study where the adjusted average rate of change in total hip BMD was 0.1%/year in men with weight gain, −0.3%/year in weight stable men versus −1.4%/year in men with weight loss. This trend held even in the obese population undergoing voluntary weight loss, who had an average change in total hip BMD of −1.7%/year.[35]

Randomized controlled trials (RCTs) involving older adults with obesity undergoing voluntary weight loss have provided additional insights.[36–45] Table 1 summarizes the findings of 9 RCTs published between 2000–2017 (identified by literature search of Index Medicus between 2000 and 2017, a search of journals that focus on geriatrics or obesity, and a search of references listed in relevant research and review articles) meeting the following specific inclusion criteria: (1) subjects with a minimum age of ≥60 years and mean age of ≥65 years, (2) subjects with a minimum BMI ≥ 27 kg/m^2 and mean BMI ≥ 30 kg/m^2, (3) a weight loss duration of at least 5 months, and (4) at least one study outcome focusing on BMD outcomes at the hip or the lumbar spine (clinically relevant sites of osteoporotic fractures). One additional study was also included despite not meeting the above criteria since the RCT reported on fracture outcomes data.[45]

RCTs involving older adults with obesity have shown that voluntary weight loss without concomitant exercise training decreases BMD at the total hip.[36;39] These findings are consistent with previously mentioned observational studies as well as meta-analysis of weight loss trials not limited to the aging population.[35;46] In a one year RCT published in 2011 by Shah *et al*, there was a significant decrease in BMD at the total hip in the weight loss group (−2.6%) compared to the weight stable control group (−0.6%).[39] Serum C-terminal telopeptide (CTX) and osteocalcin were also elevated in the weight loss group compared to control. The one year RCT by Chao *et al* (2000) also found a decrease in total hip BMD (−1.4%) and an increase in osteocalcin in the weight loss group; however, no difference was found compared to control since the control group also lost significant total hip BMD.[36] Lack of calcium supplementation may have contributed to this as participants averaged only 800 mg/day of calcium intake based on dietary and medication questionnaires, which is below the daily recommended value by the USPSTF.[47] Vitamin D

levels were also not assessed whereas in most of the other RCTs reviewed, both calcium and vitamin D supplementation was provided to all study participants.[37–44]

All RCTs that have been conducted on the older obese population have found no changes in lumbar spine BMD related to weight loss with or without associated exercise training.[36–39;42–44] These results are consistent with a prior meta-analysis of weight loss trials which have concluded that BMD at the lumbar spine is unaffected by weight loss.[46]

RCTs have shown that diet-induced weight loss combined with exercise training (lifestyle therapy) will attenuate, but not completely alleviate, the loss of total hip BMD associated with weight loss in older obese patients. In Villareal *et al* (2008), obese subjects undergoing lifestyle intervention had greater loss of total hip BMD compared to control (−2.4% vs +0.1%).[37] The 2011 study by Shah *et al* found that despite achieving similar degrees of weight loss in the diet-only (−9.6%) and diet-exercise (−9.4%) groups, the diet-only group had a significantly greater loss of total hip BMD as compared to the lifestyle intervention group (−2.4% vs −1.1%).[39] Relative to the control group, CTX and osteocalcin increased in the diet group, but remained unchanged in the diet-exercise group. Santanasto *et al* (2011) conducted a 6 month study where older adults with obesity were randomized to either exercise or diet-exercise groups.[38] The diet-exercise group was able to achieve modest weight loss (−5.5%) whereas the exercise group was weight stable (−1.2%). Total hip BMD at 6 months did not significantly differ between groups; however, this may be due to the smaller difference in weight loss between groups (4.3%) seen as most other RCTs saw at least an 8% difference between dieting and weight stable groups.[37;39–45]

Progressive resistance exercise training (RT) is more effective than either aerobic exercise training (AT) or a combination of the two (CT) at attenuating loss of BMD at the total hip. In 2017, Beavers *et al* published the combined results of two separately conducted 5 month RCTs focusing on the differing effects of AT versus RT in conjunction with diet-induced weight loss in overweight and older adults with obesity.[43] After adjusting for multiple factors including age, BMI, and degree of weight loss, the study found that BMD at femoral neck (+1.2%) and total hip (+0.2%) were unchanged in the RT group while BMD at the femoral neck (−0.7%) and total hip (−0.7%) were reduced in the AT group. The question of AT or RT in dieting was further expanded upon in a 6 month RCT published in 2017 by Villareal *et al*.[44] Older adults with obesity were randomized to control or diet-induced weight loss in conjunction with AT, RT, or CT. All exercise groups achieve a similar degree of weight loss (−9%) while weight remained stable in the control group. Loss of BMD at the total hip was greatest in AT (−2.7%), reduced in CT (−1.1%), and stable in RT (−0.6%) and control (+0.2%).

The decrease in total hip BMD associated with weight loss may correspond to an increased risk of frailty fractures in older adults with obesity. In 2017, Johnson *et al* reported on incidence of fractures amongst study participants within the Look AHEAD (Action for Health in Diabetes) trial, where 5,145 volunteers with type 2 diabetes mellitus (DM) between ages 45–76 were randomized to diabetes support and education intervention (DSE) or intensive lifestyle intervention (ILI) with a goal of ≥7% weight loss achieved through diet and increased physical activity.[45] No significant differences were noted in the number of

incident fractures or hip fractures between groups after a median follow-up time of 11.3 years; however, a significant 39% increased risk of frailty fractures was noted in the ILI group when compared to DSE group. This occurred despite previously documented improvements in fitness and physical activity as well as a decreased incidence of self-reported falls in the ILI group compared to the DSE group.[45;48] The finding is also consistent with the initial observations seen in the Study of Osteoporosis Fractures.[33;34]

Older adults with obesity who experience bone loss associated with voluntary weight loss do not see a reciprocal improvement in bone mass with weight regain.[41] In 2013, Waters *et al* published the results of extended follow-up on 16 volunteers who participated in the exercise-diet group of the previously described one year RCT by Shah *et al*.[40] During the initial 12 months of intervention, the volunteers lost significant weight (−11.2%); however, a portion of the initial weight loss was regained such that only a net change of −6.9% from baseline was noted at 30 month follow-up. While an initial loss of BMD at the total hip was noted at 12 months (−1.9%), further losses were noted at 30 months (−4.5%) despite significant weight regain during the period (Figure 1). These findings are consistent with prior findings most notably postmenopausal women.[49–51]

4. Mechanisms for Bone Loss

Inadequate calcium intake is strongly associated with an increased risk of osteoporosis and fracture.[52] Likewise, calcium supplementation has also been shown to reduce the rate of bone loss in osteoporotic patients and decrease fracture risk as well.[53] Correction of vitamin D deficiency is a vital as the primary function of vitamin D in calcium balance is to increase the absorption of calcium in the intestine. Unfortunately, age is associated with a decreased absorption of calcium due to intestinal resistance to calcitriol as well as a reduction in expression of intestinal calcium transporters.[54] Obesity appears to increase intestinal absorption of calcium, though the exact mechanisms are unknown.[55] Further complicating matters, weight loss through caloric restriction itself is associated with decreased intestinal absorption of calcium in a manner independent from the effects of vitamin D.[56] Altogether, these findings suggest that negative alterations in calcium balance during weight loss may play a critical role in bone loss that is even further exacerbated in the older populations attempting to lose weight.

Bone and muscle interact closely in both an anatomical and chemical fashion.[57] Mechanical loading of muscle stimulates bone formation by inhibiting osteocyte secretion of sclerostin, which is an inhibitor of the Wnt/Lrp5 signaling pathway vital to osteoblast differentiation.[58] In Shah *et al*, multivariate analysis found that changes in lean body mass was the strongest independent predictor of changes in total hip BMD followed by serum osteocalcin and 1-repetition maximum strength.[39] A follow-up study on the same intervention groups later demonstrated that change in thigh muscle volume assessed by magnetic resonance imaging (MRI) was also an independent predictor of total hip BMD.[40] Limiting muscle loss in the setting of voluntary weight loss will likely play a crucial role in the optimization of treatment of older adults with obesity as failure to do so may simultaneously predispose them to osteoporosis, sarcopenia, and increasing frailty.

Bone mass and bone quality are both adversely affected by increasing inflammation.[26–28] Obesity itself is associated with a chronic state of inflammation and adipose tissue in obese patients is known to express higher levels of TNF-α, IL-6, C-reactive protein (CRP), and leptin. TNF-α and IL-6 are key players in osteoclast differentiation and chronic inflammation leads to increased bone resorption.[59] Visceral adipose tissue (VAT) is particularly pro-inflammatory and increasing VAT has been associated with lower trabecular bone volume, lower bone formation rate, lower stiffness, and higher cortical porosity – all suggesting decreased bone quality.[28] VAT has also been associated with decreasing levels of IGF-1, which is anabolic to the osteoblast.[26] As age is already associated with increasing inflammation, obesity is likely exacerbating the negative effects of inflammation on bone health in older adults with obesity.[60]

5. Measures to Counter Bone Loss

Adequate supplementation of calcium and vitamin D remain at the core of treatment in all aging individuals; however, routine supplementation of calcium may be especially important in the setting of voluntary weight loss.[56] Additionally, the fact that calcium absorption in the intestine is strongly affected by the amount of dietary intake of fat should be taken into consideration when developing nutrition plans and assessing patient food diaries.[55]

Exercise training, particularly RT, provides multiple benefits to bone health in the setting of diet-induced weight loss. Supervised RT has been shown to counteract the expected loss of total hip BMD associated with weight loss in a randomized trial involving older adults with obesity.[44] Increases in mechanical loading suppress osteocyte secretion of sclerostin, which is typically increased in the setting of weight loss but negated by concurrent exercise training.[61] Exercise acutely increases circulating levels of IGF-1, which promotes osteoblast differentiation.[26] Lastly, exercise training improves muscle quality as well as reduces the loss of muscle mass associated with weight loss. Retention of lean body mass through exercise training additionally aids in reducing fracture risk through decreased risk of falls from improved physical function and balance.[51]

Related to the retention of muscle mass associated with exercise is the question of optimal protein intake for the obese older adult undergoing lifestyle therapy. Aging skeletal muscle has a decreased sensitivity and responsiveness to essential amino acids and likely requires a higher protein intake in order to achieve muscle protein synthesis.[62] A review of the effects of protein intake in adults age ≥50 years old suggests that higher protein diets help to preserve lean mass while increasing loss of fat mass during weight loss interventions.[63] One study in overweight and obese postmenopausal women (50–70 years old) reported that increasing protein intake from 60 to 86 grams/day attenuated loss of areal BMD at the hip as well as volumetric BMD of the tibia.[64] The current recommendation by the PROT-AGE study group is to target at least an average daily intake of 1.2 grams of protein per kilogram of body weight each day while undergoing active exercise training barring contraindications such as renal dysfunction; however, the optimal average daily intake is still unknown.[65]

6. Conclusions and Future Directions

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.[1] Arising from concerns regarding loss of bone mass and an increased risk of frailty fractures associated with both voluntary and involuntary weight loss in the elderly, at present time, there remains no consensus regarding the overall net benefit of diet-induced weight loss in older adults with obesity.[5;33] While obesity was once considered protective of bone health, evidence now suggests obesity has a much more complex relationship with bone and is actually associated with an increased risk of ankle, upper arm, and humerus fractures.[22] Diet-induced weight loss in older adults results in significant loss of total hip BMD, but not lumbar spine BMD.[36–39] This loss of BMD does indeed appear to correspond to an increased risk of frailty fractures.[45] Concurrent exercise training attenuates the loss of BMD associated with weight loss and progressive resistance training appears to be particularly effective at attenuating or even alleviating bone loss.[39–40;43–44]

Further research is needed to determine the optimal exercise regimen to best offset the loss of bone mass associated with weight loss while also taking into consideration the additional benefits that other exercise modalities have on comorbidities common the older adults with obesity. In addition, there remain significant gaps in the literature surrounding the optimal daily intake of protein in the specific population of older adults.

Substantial research is also needed to address the effects of lifestyle intervention on bone quality. Prior studies have heavily relied on areal BMD assessment by DXA which is well known to have decreased reproducibility with higher BMI subjects and cannot assess markers of bone quality.[18] Newer imaging modalities including HRpQCT of the distal radius and tibia provides both volumetric BMD as well as multiple markers of bone quality.[66] FEA of images obtained via HRpQCT of the distal radius and tibia, MRI of the hip, and/or CT of the lumbar spine can estimate bone strength while taking into account both bone density and quality.[67] Microindentation testing can directly measure the material properties of bone, an important component of bone quality.[68] Furthermore, currently the Look AHEAD trial is the only study providing incident fracture data and additional trials assessing fracture risk are needed.[45]

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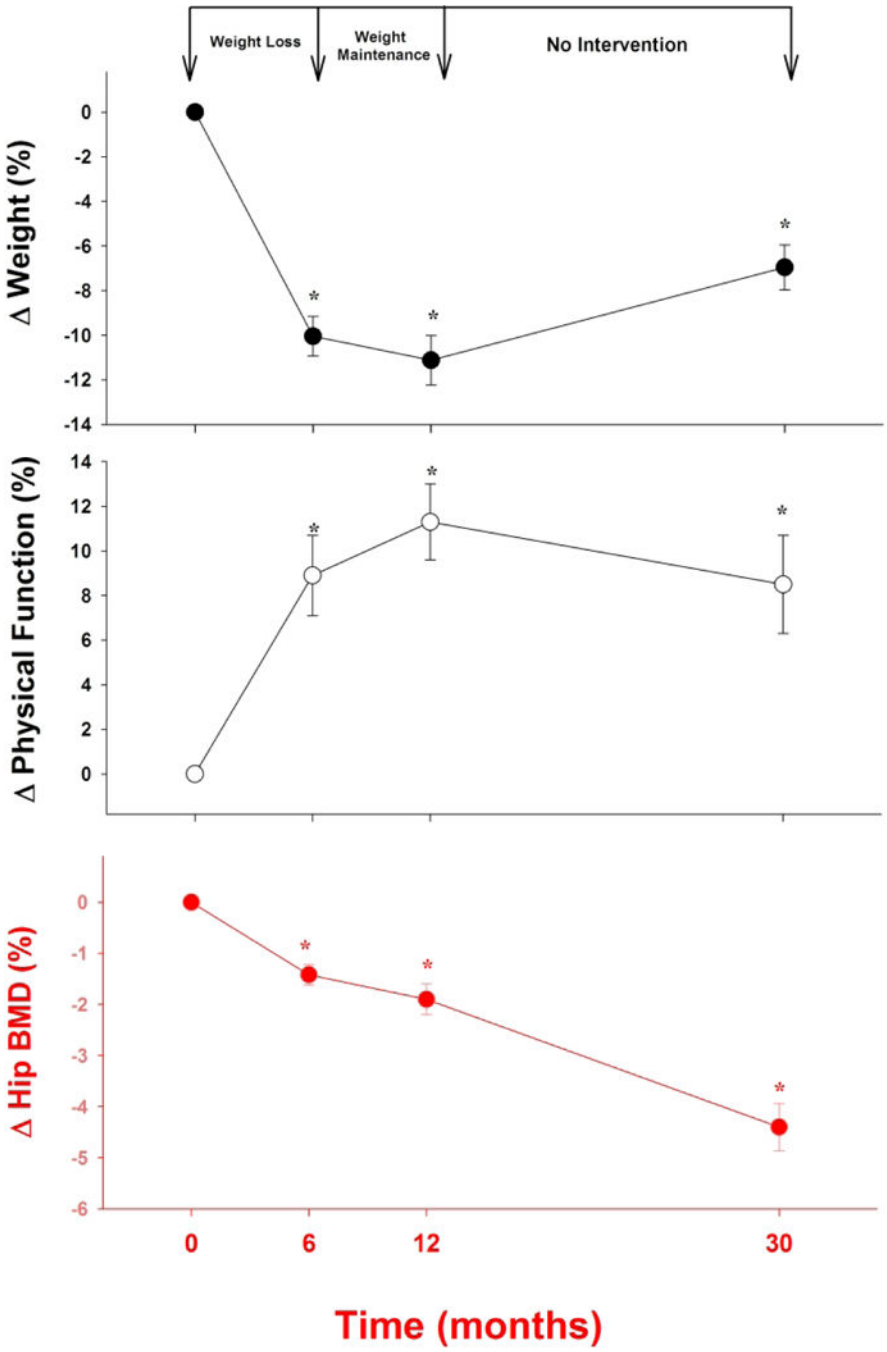

Fig. 1.

Long-Term Weight Loss with Bone Mineral Density Loss in Obese Older Adults. *p<0.05 compared to baseline (adapted from Waters et al *J Nutr Health Aging* 17:3–17; 2013)

Table 1:

Summary of Intervention Studies Examining the Effect of Weight Loss on Bone Mineral Density and Metabolism in Older adults with obesity

Reference	Study Design & Interventions	Sample	Summary of Bone Related Outcomes
Chao *et al.* (2000)	RCT: 12 months; 2 groups: C vs WL; Ca/Vitamin D supplemented	n=67 women; Age ≥60; BMI ≥27.3	Weight (−4.3% WL vs −1.1% C †); L2-L4 BMD (+0.9 ± 4.1% WL vs −0.7 ± 4.1% C); Femoral Neck BMD (−1.4 ± 3.0% WL vs −0.8 ± 2.9% C). Markers: No differences between groups, but both groups had significant rises in OC.
Villareal *et al.* (2008)	RCT: 12 months; 2 groups: C vs WL +Ex; Ca/Vitamin D supplemented	n=27 sedentary women and men with mild to moderate frailty; Age ≥65; BMI ≥30	Weight (−10% WL+Ex vs +1% C †); L1-L4 BMD (+0.9 ± 3.1% WL+Ex vs +1.3 ± 5.8% C); Total Hip BMD (−2.4 ± 2.5% WL+Ex vs +0.1 ± 2.1% C *); Trochanter BMD (−3.3 ± 3.1 WL+Ex vs +0.2 ± 3.3% C *); Intertrochanter BMD (−2.7 ± 3.0% WL+Ex vs +0.3 ± 2.7% C *). Markers: OC and CTX increased from baseline at 6 and 12 months in WL+Ex, but were only significantly different from control at 6 months.
Santanasto *et al.* (2011)	RCT: 6 months; 2 groups: Ex vs WL +Ex; Ca/Vitamin D supplemented	n=36 sedentary women and men; Age ≥60; BMI ≥28	Weight (−5.5% WL+Ex vs −1.2% Ex †); Total Hip BMD (−0.2 ± 3.4% WL+Ex vs +0.5 ± 1.5% Ex)
Shah *et al.* (2011)	RCT: 12 months; 4 groups: C vs Ex vs WL vs WL+Ex; Ca/Vitamin D supplemented	n=107 sedentary men and women with mild to moderate frailty; Age ≥65; BMI ≥30	Weight (−9.6% WL and −9.4% WL+Ex vs −0.2% C †); L1-L4 BMD (+1.1 ± 3.0% WL vs +0.8 ± 2.8% WL+Ex vs +0.4 ± 2.8% C); Total Hip BMD (−2.6 ± 2.5% WL vs −1.1 ± 2.6% WL+Ex †); Femoral Neck BMD (−2.3 ± 2.5% WL vs −0.9 ± 4.8% WL+Ex vs −0.1 ± 3.1% C); Trochanter BMD (−2.3 ± 2.5% WL vs −1.1 ± 2.6% WL+Ex vs −0.4 ± 2.3% C). Markers: OC & CTX increased in WL, decreased in Ex, and stable in WL+Ex, C †.
Armamento-Villareal *et al.* (2012)	See Shah *et al.* (2011)	See Shah *et al.* (2011)	Weight (See Shah et al. [2011]). Serum Sclerostin levels significantly increased from baseline in the WL group at 6 and 12 months but was unchanged in Ex, WL+Ex, and C groups.
Waters *et al.* (2013)	Follow-up of WL+Ex from Shah *et al.* (2011) at 6, 12, and 30 months; Ca/Vitamin D supplemented	See Shah *et al.* (2011)	Weight (−9.9% at 6 months, −11.2% at 12 months, −6.9% at 30 months); L1−L4 BMD no significant changes; Total Hip BMD (−1.4 ± 2.5% at 6 months, −1.9 ± 2.5% at 12 months, −4.5 ± 2.4% at 30 months)
Beavers *et al.* (2017)	Two 5 month RCTs; 2 groups: WL +AT vs WL+RT; Ca/Vitamin D supplemented	n=123 sedentary men and women; Age ≥65; BMI ≥27	Weight (−8.2% WL+AT vs −5.7% WL+RT); L1−L4 BMD (+1.0 ± 0.5% WL+AT vs +1.2 ± 0.5% WL +RT); Total Hip BMD (−0.7 ± 0.2% WL+AT vs +0.3 ± 0.2% WL+RT *); Femoral Neck BMD (−0.7 ± 0.6% WL+AT vs +1.2 ± 0.6% WL+RT *)
Villareal *et al.* (2017)	RCT: 6 months; 4 groups: C vs WL +AT vs WL+RT vs WL+CT; Ca/ Vitamin D supplemented	n=160 sedentary men and women with mild to moderate frailty; Age ≥65; BMI ≥30	Weight (−9.3% WL+AT and −8.4% WL+RT and −8.6% WL+CT vs −0.9% C †); L1-L4 BMD (+0.2 ± 3.4% WL+AT vs +0.7 ± 3.4% WL+RT vs +0.7 ± 2.7% WL+CT vs +0.9 ± 3.4% C); Total Hip BMD (−2.7 ± 2.5% WL+AT vs −0.6 ± 2.5% WL+RT *) Total Hip BMD (−2.7 ± 2.5% WL+AT vs +0.2 ± 2.5% C †)
Kelleher *et al.* (2017)	RCT: 22 weeks; 2 groups: WL vs WL +Vest	n=37 sedentary men and women; Age ≥65; BMI ≥30	Weight (−12% WL vs −11% WL+Vest); L1-L4 BMD (+2.0 ± 4.5% WL vs +1.2 ± 2.7% WL+Vest); Total Hip BMD (−1.9 ± 2.1% WL vs −0.6 ± 2.2% WL+Vest); Femoral Neck BMD (− 1.2 ± 3.7% WL vs −1.5 ± 3.6% WL+Vest); Markers: No significant differences between groups.

* $p<0.05$ for the comparison between stated groups

† $p<0.001$ for the comparison between stated groups

C = control group

WL = weight loss only group

WL+Ex = weight loss plus exercise training group

WL+AT = weight loss plus aerobic training group

WL+RT = weight loss plus progressive resistance training group

WL+CT = weight loss plus combined training group

WL+Vest = weight loss plus weighted vest group

RCT = randomized controlled trial

BMI = body mass index (in units of kg/m^2)

BMD = bone mineral density

NTX = N-terminal telopeptide

BSAP = bone specific alkaline phosphatase

OC = osteocalcin

CTX = C-terminal telopeptide

P1NP = N-terminal propeptide of type 1 collagen