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Is weight loss harmful for skeletal health in obese older adults?

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Short Title: Weight loss and skeletal health in obese elderly

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1. Abstract

Purpose of review: In view of the existing uncertainty about the implications of intentional weight loss in older obese adults, the present review a) summarizes the available evidence from epidemiological and interventional studies concerning the effects of weight loss through lifestyle modifications on skeletal health parameters in older overweight/obese individuals, b) proposes mechanisms that link weight loss to bone loss in this age group, and c) identifies appropriate animal models. **Main findings and future directions:** Based on prospective epidemiological studies, weight loss is associated with bone loss, impaired bone macro- and microstructure and increased fracture risk in the elderly. Data from interventional studies confirm the negative effects of intentional weight loss achieved by lifestyle modifications on skeletal health outcomes in obese older individuals. These effects appear to be modest following a single weight loss attempt, but may persist in the longer term, and presumably, during subsequent weight loss efforts. Current evidence suggests that resistance exercise coupled with caloric restriction mitigates bone and muscle loss. However, alternative strategies do not exist for older individuals, especially those who are unable or unwilling to exercise. Clinical weight loss studies in obese older individuals and preclinical research in relevant animal models with obesity and osteoporosis are required. These will advance our understanding of the pathophysiology of weight-loss-associated skeletal alterations and provide evidence on how bone loss can be counteracted or prevented.

2. Introduction

The increasing human lifespan and prevalence of obesity have led to a rise in the numbers of elderly obese individuals. In Europe the prevalence of obesity in persons above the age of 65 years was reported to be 20.9% (1) According to data from the National Health and Nutrition Examination Survey 2015-2016, 41.0% of older adults in the USA were obese (2). Obese elderly persons are more likely to experience chronic comorbidities, disability, and a poor quality of life (3). The terms *sarcopenic obesity* and *osteosarcopenic obesity* were developed recently to describe the co-existence of obesity and age-associated changes in body composition. The latter include increased and ectopic deposits of fat, as well as loss of muscle and bone (4, 5). Although obese individuals have a higher bone mineral density (BMD) than non-obese individuals, they also have impaired bone macro- and microstructure and different fall patterns (5, 6). These factors inrease the fracture risk of obese elderly at certain anatomical sites and significantly contribute to the disability and financial toll of musculoskeletal diseases among elderly (5, 6).

Intentional weight loss achieved through lifestyle modifications in obese elderly persons is a controversially discussed subject. Intentional weight loss improves physical function as well as metabolic and cardiovascular outcomes in obese elderly (3, 7). Conversely, observational studies suggest an association between weight loss (whether intentional or unintentional) and higher mortality rates, although this negative effect is not supported by randomized controlled weight loss trials (3, 7). Importantly, weight loss is potentially harmful for musculoskeletal health. The evidence in this age group is, however, limited and conclusions are frequently extrapolated from studies in younger individuals (8, 9).

In the present review, we synthesize the available evidence from epidemiological and interventional studies concerning the effects of weight loss though lifestyle modifications (such as diet or exercise) on skeletal health outcomes, including bone turnover markers, bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA), bone geometry and microarchitecture, estimated bone strength, and fracture risk in overweight/obese individuals aged ≥65 years. We further address mechanical and non-mechanical factors that link weight loss to bone loss in this age group. Finally, given the research avenues arising from matching animal models with clinical scenarios, we identify current or potentially usable age-related animal models for osteoporosis and obesity. We believe that this review will guide the design of future research to explore the pathophysiology and management of skeletal changes attributed to weight reduction in obese elderly.

3. Epidemiological studies

Previous prospective epidemiological studies have shown that weight loss in older adults is associated with a greater loss of BMD at weight-bearing skeletal sites (such as the hip or the lumbar spine) (10-18). Specifically, any weight loss ≥1% per year may significantly increase the risk of hip bone loss at a rate of ≥1% (13). Older adults with weight loss ≥5% over a 4-year period had an approximately two-fold higher rate of bone loss at the hip than those who maintained their weight (11). The impact of weight loss on non-weight bearing skeletal sites (such as the radius or the forearm) is not as clear (11, 19). These sites are less affected by mechanical unloading due to weight loss. Importantly, the associations between weight loss and BMD loss is consistent across BMI categories in older men (18) and women (12, 19). The same is true for intentional or unintentional weight loss (12, 18).

Several epidemiological studies indicate negative associations between weight loss, bone microarchitecture and strength in older individuals (20-24). Men with weight loss had lower bone

strength, total body BMD, cortical BMD and thickness (assessed by high resolution peripheral quantitative computed tomography or HR-pQCT) at the distal radius and tibia compared to those with stable weight over a 7-year follow-up (24). These findings remained unchaged after adjustments for age and BMI (24). In a retrospective analysis, recent (6 years) and long-term (40 years) weight loss were associated with a lower cortical BMD and deterioration of the cortical microarchitecture at the tibia (22). Interestingly, total bone area was increased in weight losers compared to weight gainers, with the between-group differences being more pronounced in long-term weight loss (22). Periosteal apposition may represent a compensatory response to maintain bone strength, which, eventually, declines with weight loss (22). Taken together these studies largely support weight-loss-related changes in the microstructure of cortical bone and the loss of bone strength.

Trabecular microarchitecture appears to be affected by weight loss in the elderly, although current evidence on this aspect is less consistent. Weight loss was not associated with altered trabecular parameters in older men followed up for 7 years (24). Compared to those who experienced moderate bone loss or maintained their BMD, men who had accelerated bone loss (≥10% BMD loss from baseline) over a 7-year follow-up period were older, had a lower baseline BMI, greater weight loss, and a compromised trabecular microarchitecture (23). Reductions in trabecular BMD and alterations in trabecular microarchitecture have also been associated with long-term (over 40 years) weight loss (22). These conflicting findings may be at least partially explained by differences in study design, follow-up period, cohort characteristics, and bone assessment methods.

Large epidemiological studies have consistently shown associations between weight loss and a greater risk of fractures in the central part of the body (*e.g.,* hip, spine), the upper limb (*e.g.,* forearm), and the lower limb (*e.g.,* ankle) in older women (12, 25-29). Data concerning older men are scarce, but also suggest that weight loss is a risk factor for hip fracture (30). A limitation of many of these studies is their failure to distinguish between intentional and unintentional weight loss. Unintentional weight loss is frequently associated with comorbidities and poor health, which may affect bone loss, fall patterns, and the risk of fractures in independent ways. Conversely, intentional weight loss may involve practices (such as exercise), which have some bone-sparing effects even among older adults (31). Of the few studies addressing intentional weight loss (12, 28), one showed that both, intentional and unintentional weight loss were associated with an approximately doubled risk of hip fracture in older women (12). These associations were consistent in those with a BMI <25.9kg/m^2 and ≥25.9kg/m^2 (12). Another study revealed different fracture risks by anatomical site, depending on the intention to lose weight (28). An elevated fracture risk has been associated with both, short-term (a few years) (29) and long-term (a few decades) weight loss (25, 26). This raises concerns about the impact of weight loss in old age, as well as, during early and mid-adulthood.

Weight changes have been commonly assessed as the difference between baseline and a single follow-up. However, during this period individuals may experience repeated episodes of weight loss and subsequent weight gain or weight cycling. These weight variations have been associated with negative effects on skeletal health in younger individuals (32, 33). The few available studies in the elderly suggest that weight cycling increases their risk of fracture (34, 35). These findings were closely related to the extent of variability in weight (34) and the number of weight cycling episodes between the ages of 25 and 50 years (35).

4. Interventional studies

This section addresses the findings of interventional studies focused on lifestyle changes resulting in weight loss. The studies evaluated skeletal health outcomes in overweight/obese (BMI≥27 kg/m^2) older persons (mean age per study arm ≥65 years) (Table 2).

Diet-induced weight loss is accompanied by transient increases in bone turnover markers and BMD reductions at clinically important skeletal sites in overweight/obese older individuals. A 12-month randomized controlled trial (RCT) comprised 107 obese and frail older adults (36, 37). The subjects who had been randomized to an energy-deficient diet had a mean weight loss of ~10%. They also experienced synchronous increases in osteocalcin (bone formation) and C-telopeptide of type I collagen or CTX (bone resorption) levels, and decreases in hip BMD at 6 and 12 months compared to baseline (36, 37). Hip structure analysis based on DXA-acquired BMD images revealed decreases in cross-sectional area and cortical thickness, and increases in buckling ratio at the hip in the weight loss group at 12 months (31). Collectively, these changes suggest bone degradation secondary to weight loss achieved by diet rather than a normalization of BMD relative to weight loss. Importantly, the prescribed diet in this arm was characterized by a moderate energy deficit, while providing sufficient quantities of protein, calcium, and vitamin D (36). These data suggest that even well-planned weight loss diets may not suffice to maintain skeletal health in the elderly. Other studies that have included weight loss arms through caloric restrictions alone also suggest hip BMD losses of ~2%, which, however, did not reach statistical significance (38, 39). In contrast to hip BMD, lumbar spine and total body BMD appear to be unaffected by weight loss in this age group (36, 38, 39). It is uncertain whether these findings were actual treatment effects or were flawed by measurement error. In the presence of obesity or during aging, calcifications originating from atherosclerotic lesions within the aorta or osteophytes may artificially mask bone reduction (9). Nevertheless, these findings in obese elderly individuals are consistent with those of a meta-analysis of diet-induced weight loss studies (9). The majority of the studies were conducted in younger adults, and indicated similar skeletal responses to this weight loss approach with age (9).

Several studies have addressed the combined effects of exercise and caloric restriction on bone health (31, 36, 37, 40-43). In an earlier investigation, older women were offered counseling on diet and physical activity to induce weight loss (40). Weight loss was a significant predictor of total body BMD, but not spine or hip BMD (40). Interestingly, total body and hip BMD declined in the weight loss group, but also in controls (40). The study was not informative about the individual contributions of diet and exercise to weight loss and bone loss, and the participants did not follow a specific exercise program under supervision. However, the data revealed the importance of including a control group with no weight loss, given that aging itself is associated with bone deterioration. Haywood et al., compared the skeletal effects of exercise combined with healthy eating, a hypocaloric diet or a very low-calorie diet (VLCD) (41). Total body BMD was assessed by DXA as the sole skeletal health outcome at baseline and at 12 weeks follow-up. The exercise plus VLCD group experienced greatest weight loss, accompanied by a small, but significant, reduction in total body BMD; no significant changes were observed in the other study arms (41). Additional evidence on the effects of exercise added to weight loss were obtained from two further RCTs (36, 42). In a first small cohort, the effects of a lifestyle intervention consisting of caloric restriction, calcium and vitamin D supplementation, and a combined aerobic and resistance training program were compared to no treatment . The weight loss plus exercise group experienced 2-3% reductions in hip BMD, suggesting that caloric restriction, even when combined with exercise, reduces BMD. The reductions in hip BMD were correlated with elevations in CTX (~100-fold)

and osteocalcin (~60-fold), indicating that the bone loss was mediated by an uncoupling of bone formation from resorption, favoring the latter. BMD was maintained at the lumbar spine, which was suggested to be a bone-protective effect of exercise (42). In a subsequent study by the same group, 107 obese and frail older adults were randomized to no treatment, caloric restriction, exercise without weight loss, or caloric restriction combined with exercise (36). The group that was randomized to caloric restriction combined with exercise experienced less hip bone loss than those who followed caloric restriction alone. Unlike the group subjected to caloric restriction, the combined exercise and caloric restriction group did not experience changes in bone turnover markers or bone structure (cross-sectional area, cortical thickness, and volumetric BMD) at the 1-year follow-up, although trabecular microarchitecture was not assessed (31, 37). These results suggest that a combination of resistance and aerobic training added to a weight loss program can lessen the bone loss induced by weight reduction.

More recent studies have focused on the exercise type that would be most beneficial for weight loss in obese older individuals (39, 44, 45). In a 6-month RCT, Villareal and co-workers compared the effects of weight loss with resistance training, aerobic training or both, in frail and obese older individuals. Despite similar weight loss (~9% from baseline body weight) in all three groups, only the addition of resistance training prevented a weight-loss-induced reduction of hip BMD (44). Beaver et al. investigated the effects of diet-induced weight loss only compared to diet-induced weight loss combined with resistance or aerobic exercise training in 187 obese older adults with cardiovascular disease and/or metabolic syndrome (45). At the 18-month follow-up, total hip BMD was reduced by approximately 2% in all groups, but no between-group differences were reported. (39). Volumetric BMD and cortical thickness estimates at the hip and femoral neck (assessed by CT scans) were significantly declined in all groups, with the most pronounced changes seen in the diet-induced weight loss group (39). In a pooled analysis of the three treatment groups, bone strength estimated with subject-specific finite-element models (based on CT-derived parameters) was reduced by 6.5% at 18 months compared to baseline (46). Although this sub-analysis was not powered to detect between-group differences, finite element models can be used to provide better predictions of bone strength and fracture risk in future weight loss interventions. Taken together, these findings suggest that resistance training exerts bone-sparing effects in weight loss interventions which, however, may not always be captured by BMD assessed by DXA. The discrepant results between the studies may be explained by differences in exercise regimens and the baseline characteristics of the study populations. Frail and obese individuals are possibly more responsive to the effects of exercise training.

We identified only two studies that addressed the weight maintenance in the longer term (follow-up >1year) (39, 47). In a 30-month follow-up of a one-year weight loss intervention (36), Waters et al. reported progressive hip BMD reductions (47). Similarly, Beavers et al. demonstrated continuous bone loss, despite weight regain in all groups from 18 to 30 months (39). Both studies support unfavorable changes in skeletal health due to long-term weight loss. These studies were subject to reporting bias because they were based on subsets of the initial groups and did not include individuals with no weight loss. Nevertheless, they underpin the need for follow-up studies to evaluate weight management approaches in the elderly and characterize skeletal health outcomes associated with sustained weight loss or multiple weight loss attempts.

5. Mechanisms

We investigated the available evidence on the mechanistic links between weight loss and bone loss in obese older individuals or relevant aged animal models. We also discuss speculative contributors to

bone loss during weight loss which, however, have been poorly investigated in obese elderly under weight loss and require further elucidation. The effects of weight loss on skeletal outcomes during aging are likely multifactorial and may be mediated by i) mechanical unloading, ii) changes in body composition, iii) restriction of important nutrients for bone metabolism and health, iv) alterations in gonadal hormones and endocrine factors that co-regulate energy and bone metabolism, and v) changes in inflammatory factors. These factors appear to affect the balance between bone formation and resorption. This, in turn, mediates changes in the macro- and microstructure of bone as well as bone material, which determine bone strength and, ultimately, the risk of fractures (Fig. 1). They also influence other geriatric outcomes such as physical function or falls, which are known to modify the risk of fracture (37, 44, 48) (Fig. 1.).

Mechanical Unloading

Bone adapts its mass, structure, and strength to the loads applied by muscle contractions as a result of physical activity or gravitational forces (*i.e.,* body weight) (49). Several lines of evidence support mechanical unloading as a mediator of the effects of weight loss on bone. First, diet-induced weight loss consistently results in bone loss at the weight-bearing hip rather than total body (36, 37, 39). Second, changes in muscle mass and strength are correlated with bone changes in the hip in older individuals; these effects are largely explained by the gravitational forces exerted by muscles on bone (37). Third, exercise, and especially resistance training incorporated in weight loss programs can preserve fat-free mass and reduce the negative skeletal effects of weight loss (31, 37). At the molecular level, the skeletal effects of mechanical unloading during diet-induced weight loss are supported by elevations in sclerostin levels (31). Sclerostin is produced by osteocytes, the bone mechanosensors, and acts on bone formation through inhibition of the canonical *Wnt* signaling pathway. The latter regulates osteoblastic differentiation, proliferation, and activity. Despite the significant role of mechanical unloading on bone responses to weight loss, it cannot explain the skeletal changes that occur at non-weight-bearing sites (27-29), or continued bone loss after a weight loss plateau (47).

Body composition

Obese older individuals have been shown to lose fat-free mass during single weight loss interventions, but also during weight cycling (36, 41, 42). In the latter, weight regain is predominantly accompanied by the acquisition of fat mass rather than fat-free mass (50). In addition to the aforementioned mechanical link between muscle and bone, these tissues are connected through bidirectional signaling. The latter involves molecules produced by muscle which act on bone, molecules secreted by bone with action on muscles, and local/systemic endocrine factors that affect bone and muscle (51). Muscle mass also affects skeletal health through its role in physical performance and fall prevention; this emphasizes the need for strategies aimed at the maintenance of muscle mass during weight loss. A recent systematic review of weight loss RCTs in obese elderly person provided a summary of current evidence on the subject. The review showed that caloric restrictions combined with exercise attenuated the reductions in muscle and bone mass seen in diet-only study arms, and resulted in greatest improvements in physical performance (48).

The relationship between bone and adipose tissue during weight loss appears to be particularly strong during aging. For example, in a population-based prospective study in older men, fat loss - and not loss of lean body mass - was strongly associated with hip bone loss in older men who lost weight over two years (16). These results likely reflect the actions of fat mass in modulating bone health above and beyond its effects on skeletal loading. Several endocrine factors that link bone and adipose tissue have

been identified (52); these appear to mediate skeletal responses to weight loss during aging (see below).

The current published literature supports the role of bone marrow adipose tissue in bone and energy metabolism and osteogenesis (53). Marrow adipocytes have a common origin with osteoblasts, both arising from mesenchymal stem cells (MSC). Alterations in the MSC lineage allocation may contribute to the associations between increased marrow adipose tissue and the elevated risk of fracture in osteoporosis, anorexia nervosa, and diabetes (53). Limited animal and human data suggest that marrow fat is reduced during weight loss (54, 55); these reductions may also attenuate bone loss. Given the age-related increase in marrow adipose tissue (56), it would be interesting to explore changes in bone marrow and their contribution to skeletal outcomes during weight loss in obese elderly.

Nutrient restriction

Macro- and micronutrient deficiencies are common among elderly individuals, due to altered lifestyle or metabolism. These may be exacerbated by energy-deficient diets, which frequently lack key nutrients for skeletal health including protein, vitamin D, and calcium. Energy and nutrient restriction are suggested to exert synergistic effects on bone (57-59), although these effects are less well understood in adults aged ≥65 years. Nevertheless, the provision of protein, calcium, and/or vitamin D in sufficient quantities cannot maintain bone health during weight loss efforts in the elderly (36, 41, 42). This suggests that higher doses of these nutrients or other combined strategies might be needed to mitigate the undesirable weight-loss-induced effects on the skeletal system.

Endocrine factors

The contribution of endocrine factors such as estrogens, insulin-like-growth-factor-1 (IGF-1), leptin, and adiponectin to bone loss observed after weight loss has been detailed elsewhere (8). Hereby, we summarize the key findings in older obese individuals. Although reductions in estradiol levels have been reported in obese older women and men during weight loss, possibly due to the reduction of fat mass, these were not correlated with bone loss. Thus, estradiol probably exerts indirect rather than direct effects on bone responses to weight loss (37, 42, 56). IGF-1 reductions have been inconsistently reported in older adults under energy or protein restriction (37, 42). However, it is unclear whether the absence of changes reflects true effects of the intervention or whether IGF-1 reductions are masked by increases in its binding proteins (60). A reduction in leptin, an adipokine significantly involved in the regulation of energy metabolism and with established central and peripheral effects on bone (56), is a consistent finding among obese elderly weight losers (37, 42). In contrast, the role of adiponectin, another adipokine with potential action on bone (61), in skeletal changes in obese elderly under weight loss remains poorly understood.

Inflammation

Chronic inflammation plays an important role in bone loss by affecting the generation and/or function of osteoblasts and osteoclasts either directly or indirectly (62). Inflammation also contributes to sarcopenia by accelerating protein degradation and slowing down protein synthesis in the muscle (56). It is widely accepted that aging, obesity and exercise are characterized by chronic low-grade inflammation, and weight loss reduces inflammatory markers (63-65). However, the effects of weight loss and exercise on inflammatory molecules and processes in relation to skeletal health outcomes in older obese individuals require further elucidation. Besides, a complex interplay exists between bone

and inflammatory factors derived from muscle, adipose tissue, brain, the immune system and host-gut microbiota interactions, which might be further modified by weight loss and exercise during aging (66).

Animal studies

Animal studies complement and extend research in humans by allowing a detailed examination of caloric restriction, exercise, or nutrient manipulation under standardized conditions, and by addressing mechanistic aspects. One of the strengths of animal studies is the existence of similarities in age-related bone loss and obesity among animals and humans. Further advantages of animal studies include the accurate control of diet and exercise, the employment of many study arms, and the ability to analyze changes at different levels (67-69). These advantages are contrasted by a significant diversity among different animal models. The use of animal models requires knowledge of the respective bone anatomy, physiology, energy homeostasis, and the differences between these parameters in animals and humans (67-69). Despite the differences, meticulously designed experimental studies in animals, accompanied by critical data interpretation, have great potential to enhance our knowledge in this area.

Surprisingly, we found no previous study on the effects of caloric restriction on skeletal health in obese aged animals, underpinning a significant literature gap in this age group. Current evidence is derived from research in lean aged animals (57, 70-74) or obese mature animals (75-78), which cannot be extrapolated to obese aged animals. As such, we hereby present available animal models that capture age-related bone loss and obesity. We also propose potentially relevant models, which, however, require validation prior to their use in future weight loss interventions.

Excellent reviews have described animal models of senile osteoporosis (67, 79) and obesity (68, 80); however, models including both phenotypes are scarce (81). A simple and useful model may be the application of a diet-induced obesity (DIO) paradigm in young, mature or aged animals. In the DIO paradigm, animals are provided *ad libitum* access to energy-dense diets, and the progression of obesity and its metabolic consequences are monitored (76, 81). Indeed, 12-month-old C57BL/6J female mice fed a high-fat diet for 6 months experienced increases in body weight, total body and fat mass, but also reduced BMD at multiple skeletal sites (81). Despite its validity and relevance to human obesity, the DIO paradigm is influenced by animal characteristics (*e.g.,* strain, sex, age) and dietary composition, which have been reviewed in the past (80) and should be considered in future experimental designs. Alternatively, genetically modified obese animal models like the obese Zucker rats and the leptin-deficient (ob/ob) obese mice, which are shown to exhibit bone phenotypes resembling osteoporosis, can be used as relevant models (77, 82, 83).

Aged animals mimic the natural course of musculoskeletal loss and fat accumulation/redistribution seen with aging in humans. To provide some examples, aged C57BL/6J mice present with low BMD and impaired bone quality (84, 85), but also reduced lean mass and increased fat mass (86). Similarly, aged Sprague–Dawley rats have severe abnormalities in trabecular bone and imbalanced bone turnover favoring bone resorption (87). Furthermore, progressive increases in body fat percentage and body fat to lean mass ratio have been reported in Sprague–Dawley rats monitored from the age of 8 to 24 months (88). As such, aged animals may serve as useful models of age-associated bone loss in the presence of overweight/mild obesity.

Dietary manipulations and characterization of the body composition of animals with senile osteoporosis may provide new alleys of investigation. The same is true for the determination of

skeletal features in established animal models of obesity. For instance, senescence-accelerated mouse (SAM)-P lines are featured by an accelerated aging phenotype and a short lifespan (89). The SAM-P6 mice have been established as a model of senile osteoporosis: they exhibit low peak bone mass due to low bone formation and are prone to spontaneous fractures (90). Nevertheless, these mice have not been used in diet-induced weight loss interventions.

Finally, the use of larger animal models such as dogs, sheep and pigs might be promising for future research because they offer significant advantages compared to smaller animals (79). These include their greater phenotypical similarities to humans and the possibility to collect larger blood volumes over time for biochemical analyses. Nevertheless, their use in age-related research is hampered by their long life span, high costs, handling, housing requirements, and ethical implications.

6. Conclusions

The effects of intentional weight loss in obese older individuals is of clinical significance, because this population is susceptible to poor musculoskeletal health even prior to weight reduction. Prospective studies suggest that weight loss is associated with bone loss, impaired bone microstructure, and a higher risk of fractures in elderly. However, these associations often reflect the negative impact of unintentional weight loss in underweight older individuals rather than the effects of intentional weight loss in their obese counterparts. Interventional studies support the worsening of musculoskeletal health outcomes. Nevertheless, these effects appear to be relatively small following a single weight loss attempt and their contribution to the risk of fractures is unknown. The limited body of data from weight maintenance studies is a cause of concern. These show that bone loss persists during this phase. Given the long-term implications of intentional weight loss or repeated weight reduction efforts, strategies to attenuate the harmful effects of weight loss on bone are clinically relevant, but remain understudied in this group. The most compelling evidence for such strategies is derived from studies that combined caloric restriction with resistance training. Some older individuals cannot or do not wish to perform exercise training. Thus, future work should be focused on alternative approaches that may counteract, if not prevent, bone loss during active weight loss and weight maintenance. Simultaneously, the assessment of other geriatric outcomes and biochemical markers could provide mechanistic links between weight loss and bone loss. To this end, the use of relevant animal models serves as a unique opportunity to understand the pathophysiology of weight-loss-associated bone alterations, as well as develop and test potential counteracting strategies for obese elderly.

8. Statements

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8.2. Statement of Ethics

The authors have no ethical conflicts to disclose.

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MP, KKS, TS, and PP participated in the study conception and design. MP drafted the paper. All authors reviewed and approved the final manuscript.

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Table 1: Glossary

Term	Definition/comment
Bone turnover markers	Surrogate markers of bone turnover, categorized into markers of bone formation or bone resorption. They reflect early dynamic bone changes as opposed to static measures of bone structure. Increases in bone turnover markers suggest bone degradation or temporary measures to repair damage. C-telopeptide of type I collagen (β-CTX) and procollagen type 1 N-terminal propeptide (P1NP) are the current reference standards for bone resorption and formation, respectively.
Bone mineral density (BMD)	Bone mineral content per total area assessed by dual-energy X-ray absorptiometry (DXA).
Dual-energy X-ray absorptiometry (DXA)	A 2D imaging technique currently used as the gold standard to assess BMD. It has good precision and repeatability, but is not informative about bone microstructure.
Hip structural analysis	This type of analysis is applied to DXA images in order to estimate parameters of bone structure at the proximal femur such as cross-sectional area, section modulus (estimate of resistance to bending), and buckling ratio (estimate of resistance to compression).
Volumetric BMD	Bone mineral content per total volume. It can be assessed by imaging techniques including micro computed tomography (μCT) and high-resolution peripheral computed tomography (HR-pQCT).
Bone microstructure	Structural characteristics of cortical and trabecular bone compartments. This can be assessed by imaging techniques including μCT and HR-pQCT. Bone volume fraction, trabecular number, thickness, and separation are common variables used to characterize trabecular bone. Common variables used to characterize cortical bone include cross-sectional area, cortical bone area, cortical bone area fraction and cortical thickness.
Bone strength	The ability of a bone to resist fracture. Recent study designs have been increasingly focused on bone strength, which is estimated using finite element analysis modeling.
Finite element analysis	Mathematical models constructed to provide estimates of bone strength parameters, such as stiffness and failure load. These are commonly based on parameters acquired from μCT or HR-pQCT imaging.
Micro computed tomography (μCT)	A high-resolution 3D imaging technique used to evaluate cortical and trabecular bone microstructure in animal and human samples.
High-resolution peripheral computed tomography (HR-pQCT)	A high-resolution 3D imaging technique used to evaluate volumetric BMD, bone geometry and cortical and trabecular bone microstructure at distal skeletal sites (distal radius and tibia) in humans.
Histomorphometry	A quantitative technique used to study the rate of bone formation and resorption and bone structure on histological sections and bone biopsies.
Fracture risk	The ultimate clinical endpoint in bone research.
Senile osteoporosis	Type of osteoporosis that is associated with aging, typically present in men and women beyond the age of 70 years. It is differentiated from osteoporosis due to other factors, including diseases or drugs.
Intentional weight loss	For this review, intentional weight loss is defined as purposeful efforts to reduce body weight through lifestyle modifications such as diet, exercise, or both. Intentional weight loss may also be achieved through pharmacological approaches or bariatric surgery, which are beyond the scope of this review.
Unintentional weight loss	Involuntary weight reduction caused by several factors including illness, age-related reduction in appetite, and chronic drug use (as a side-effect).
Very low calorie diet (VLCD)	A dietary prescription of ≤800 kcal/day. It is commonly based on partial or full meal replacement with commercial products. VLCDs allow dieters to focus on weight loss over short time periods compared to longer periods required when mild caloric restrictions are prescribed. VLCDs require medical supervision and careful planning, as they may lead to protein malnutrition and micronutrient deficiencies.
Diet-induced weight loss	Weight loss achieved though diet and specifically caloric restriction.
Aged animals	Appropriate animal model to mimic natural age-related physiological changes in humans. For example, laboratory mice have a life span of 2-3 years and reach skeletal maturity at 4-8 months of age, followed by age-associated bone loss and pronounced changes in body composition.
Diet-induced obesity (DIO) paradigm	An animal model used to study the most common cause of obesity. Animals are provided ad libitum access to energy-dense diets, and the progression of obesity and its metabolic consequences are monitored.

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Table 2. Interventional studies that explored the effects of weight loss through lifestyle modification on skeletal health outcomes in obese older adults

References	Participants/ Study duration/Follow-up	Intervention arms	Age (years)	BMI (kg/m²)	Weight change (kg[a] or %[b])	Main findings
Chao et al., 2000 (40)	Obese postmenopausal women D: 1 year, FU: 6 months, 1 year	No treatment control: C (n=40)	66±6	30.8±2.6	-0.8±0.7[a]	Whole body and femoral neck BMD, but not lumbar spine BMD, declined in both groups.
		Weight loss (health education): WL (n=27)	66±5	30.9±3.1	-3.5±0.9[a]	
Daly et al., 2005 (43)	Older adults with type 2 diabetes D: weight loss for 6 months and weight maintenance till 1 year FU: 6 months, 1 year	Weight loss (diet): WL (n=13)	67±5	32.5±3.8	(0-6mon) -3.3±2.0[a]	Total BMD did not change in the WL+RT group after 6 months, but was decreased in the WL group. Despite weight regain from 6 to 12 months, total body and regional BMD did not change in WL+RT group, whereas total body BMD decreased with WL.
		Weight loss (diet)+ resistance training: WL+RT (n=16)	68±5	31.5±3.4	(0-6mon) -2.7±3.4[a]	
Villareal et al., 2008 (42)	Frail older adults D: 1 year, FU: 1 year	No treatment control: C (n=10)	71±5	39.0±5.0	1.2±1.3[b]	The WL+E group had greater decreases in total hip trochanter and intertrochanter BMD compared to C.
		Weight loss (diet)+ exercise: WL+E (n=17)	69±5	38.5±5.3	-10.1±2.0[b]	
Villareal et al., 2011 (36)	Frail older adults D: weight loss for 6 months and weight maintenance till 1 year FU: 6 months, 1 year	Control (health education): C (n=27)	69±4	37.3±4.7	−0.1±3.5[b]	Total hip BMD decreased to a lesser extent in the WL+E group compared to the WL group, whereas it increased in the E group.
		Weight loss (diet): WL (n=26)	70±4	37.2±4.5	−9.7±5.4[b]	
		Exercise: E (n=26)	70±4	36.9±5.4	−0.5±3.6[b]	
		Weight loss (diet)+ exercise: WL+E (n=28)	70±4	37.2±5.4	−8.6±3.8[b]	
Armamento-Villareal et al., 2012 (31)	Please consult Villareal et al., 2011, for the characteristics of participants and the intervention					Decreases in cross-sectional area, cortical thickness, and BMD, and increases in buckling ratio at all investigated sites occurred with WL, but not with WL+E.
Beavers et al., 2017 (45)	Sedentary, older adults D: 5 months, FU: 5 months	Weight loss (diet)+ aerobic training: WL+AT (n=60)	69±3	34.7±3.7	-8.2 (7.2-9.3)[b]	Total hip and femoral neck BMD were unchanged in the WL+RT group, and modestly decreased in the WL+AT group. Lumbar spine BMD was increased above baseline in both WL+RT and WL+AT.
		Weight loss (diet)+ resistance training: WL+RT (n=63)	70±4	30.4±2.2	-5.7 (4.6-6.7)[b]	
Haywood et al., 2017 (41)	Older adults D: 12 weeks, FU: 12 weeks	Exercise: E (n=36)	70 (65-85)	40 (32-57)	-3.7 (2.5, 4.8)[b]	There was a small but significant decrease in total body BMD in the E-VLCD group, but no significant changes were reported in the other groups.
		Exercise+ hypocaloric diet: E+WL (n=40)			-5.1 (4, 6.2)[b]	
		Exercise+ very low calorie diet: E-VLCD (n=41)			-11.1 (9.7, 12.5)[b]	
Kelleher et al., 2017 (38)	Older adults D: 22 weeks, FU: 22 weeks	Weight loss (diet): WL (n=17)	70±3	35.3±3.0	-11.2±4.4[a]	No significant differences between groups in BMD at the total hip, femoral neck or lumbar spine. A trend towards a greater percentage reduction in total hip BMD in WL.
		Weight loss (diet)+ vest: WL+V (n=20)	70±3	35.3±2.8	-11.0±6.3[a]	
Villareal et al., 2017 (44)	Sedentary, frail older adults D: 6 months, FU: 6 months	Control (health education): C (n=40)	70±5	36.7±5.0	−0.9±0.5[a]	BMD at the total hip did not change significantly in the WL+RT group, whereas it decreased in the WL+AT group and the WL+RT+AT group. Lumbar spine and whole body BMD did not change significantly in any of the study groups.
		Weight loss (diet)+ aerobic training: WL+AT (n=40)	70±4	35.9±4.4	−9.0±0.6[a]	
		Weight loss (diet)+ resistance training: WL+RT (n=40)	70±5	36.7±5.8	−8.5±0.5[a]	
		Weight loss (diet)+ aerobic+ resistance training: WL+RT+AT (n=40)	70±5	35.8±4.5	−8.5±0.5[a]	
Beavers et al., 2018 (39)	Older participants with cardiovascular disease and/or metabolic syndrome D: 18 months, FU: 18 and 30 months	Weight loss (diet): WL (n=67)	66±5	35.0±4.1	-5.7 (-7.9, -3.8)[a]	At 18 months, hip BMD was reduced by 2% in all groups. Despite weight regain from 18 to 30 months, hip BMD continued to decline (WL+RT<WL). Lumbar spine BMD increased in the WL and WL+RT groups, compared to the WL+AT group.
		Weight loss (diet) +aerobic training: WL+AT (n=67)	67±5	33.9±3.5	-9.9 (-11.8, -7.9)[a]	
		Weight loss (diet) +resistance training: WL+RT (n=60)	67±5	34.6±3.5	-10.1 (-12.0, -8.2)[a]	
Schoell et al., 2018 (46)	Older participants with cardiovascular disease and/or metabolic syndrome	WL, WL+RT and WL+AT considered as one group that experienced weight loss (see arms for Beavers et al., 2018)	66±4	34.0±3.5	-9.5 (-12.7, -6.2)[a]	Estimated bone strength decreased with weight loss. After adjustments, there were no significant

	D: 18 months, FU: 18 months					correlations between weight change and change in volumetric BMD, cortical thickness, or bone strength.

D: Duration, FU: Follow-up, BMI: Body mass index. Data are presented as mean±SD or mean (95% confidence interval). [a]refers to BMI change expressed in kg, [b]refers to BMI change expressed in %.

Figure Legends

Fig. 1. Proposed mechanisms underlying bone loss during intentional weight loss in obese older adults.

Fig. 2. Advantages and disadvantages of small (e.g., mice and rats) and large (e.g., dogs, sheep and pigs) animal models and proposed models in age-related osteoporosis and obesity research.