Effects of weight-loss interventions on bone health in people living with obesity

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Abstract

Strategies to reduce weight in people living with obesity (PwO) include calorie restriction, metabolic and bariatric surgery (MBS), and anti-obesity drugs including glucagon-like peptide-1 receptor agonists (GLP-1Ra), such as liraglutide and semaglutide. Although weight loss in PwO has many health benefits, it can result in increased bone loss and fracture risk. Indeed, the consequences of weight loss interventions are well known: (i) significant weight loss induced by caloric restriction and MBS results in high turnover bone loss and (ii) unlike calorie restriction, PwO experience a substantial deterioration in bone microarchitecture and strength

associated with an increased risk of fracture after MBS, especially malabsorptive procedures. GLP-1 may enhance bone metabolism and improve bone quality, and liraglutide appears to have a positive effect on bone health despite significant weight loss in several rodent models. However, most of the positive effects on bone have been observed at concentrations much higher than those approved for obesity care in humans. The effects of GLP-1Ra on bone health in PwO are still limited; however, significant weight loss induced by GLP-1Ra may also result in accelerated bone turnover and bone loss, and semaglutide could lead to an increased risk of fractures in the at-risk population. The mechanisms responsible for the adverse skeletal effects of MBS are not yet fully understood, and there are insufficient human studies supporting pathophysiological hypotheses. However, data suggest that multiple mechanisms are involved, including nutritional factors, mechanical unloading, hormonal factors, adipokines, and alterations in the gut microbiome. Recommendations for the prevention and treatment of osteoporosis secondary to MBS are now available, and the efficacy of anti-osteoporosis medications in preventing bone loss has been evaluated in two randomized controlled trials. Priorities for future research include the development of effective approaches to reduce fracture risk in PwO following MBS and investigation of the effects of anti-obesity drugs on bone health.

Lay Summary

Weight loss can improve health for people living with obesity, but it may also weaken bones and increase fracture risk. Metabolic and bariatric surgery causes the biggest bone problems, while new weight-loss medicines including GLP-1 receptor agonists may also affect bone health. More research is needed to find safe ways to protect bones while supporting weight loss.

Introduction

The obesity epidemic is recognized as a major public health challenge worldwide. Common health consequences of obesity include cardiovascular disease, type 2 diabetes (T2D), certain types of cancer, and musculoskeletal conditions such as osteoarthritis. Measures to reduce weight are beneficial for many of these comorbidities and may potentially improve health span; however, weight loss can adversely affect bone health. This review considers baseline bone structure and fracture risk in people living with obesity (PwO), and then discusses the skeletal

effects of interventions that promote weight loss, including calorie restriction, metabolic and bariatric surgery (MBS), and glucagon-like peptide-1 receptor agonists (GLP-1Ra).

Obesity and Bone Health

Obesity and fracture risk

Historically, obesity was regarded as a protective factor against fractures; however, mounting evidence has since disproven the simplicity of this notion. This misleading assumption originated from studies that defined obesity based solely on body mass index (BMI), an imperfect measure of clinical obesity and excess adiposity. Meta-analyses of observational studies, predominantly involving postmenopausal women, have revealed that individuals with generalized obesity have a reduced risk of overall fractures, hip and wrist fractures; yet they face an elevated risk of fractures in the humerus and distal lower limbs, such as the tibia and ankle **(1, 2)**. Recent findings underscore the need to consider multiple factors beyond BMI to more accurately capture fracture risk in PwO. These factors encompass body fat distribution and body composition as well as the presence of sarcopenic obesity, obesity-associated comorbidities, traditional risk factors for fracture, and reduced bone mineral density (BMD). Abdominal obesity (i.e. elevated waist circumference) has been linked to an increased risk of fractures in the hip, vertebrae, and distal lower limbs **(3, 4)**. Furthermore, body distribution patterns have been linked to site-specific risk of fragility fractures in elderly US men and women **(5, 6)**. Hence, individuals with a leaner body shape (i.e., in the lowest quartiles of body roundness index and abdominal fat index) and higher arm circumference (reflective of muscle mass) had the lowest risk of vertebral fractures. In contrast, individuals in the lowest quartile of body roundness index and highest quartile of weight-adjusted waist index were at a heightened risk of hip fractures. Among PwO, those with low BMD, pre-existing risk factors for fracture, and a higher frailty index are particularly vulnerable to fractures, including early hip fractures and all-cause mortality **(7-9)**. Additional significant clinical risk factors for fractures in PwO include an increased risk of falls and concomitant T2D **(10, 11) (Figure 1)**.

Impact of obesity on BMD, bone microarchitecture and strength

PwO tend to exhibit higher areal and volumetric BMD across all skeletal regions, along with generally better bone microarchitecture and strength as assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT), compared to those without obesity **(1)**.

Nonetheless, this advantage may not be enough to prevent fractures due to the increased impact of higher body weight during falls. When compared with age-matched normal-weight counterparts, postmenopausal women with obesity have weaker bone parameters after adjusting for individual body weight or fat mass **(12)**. Circulating bone turnover markers (BTMs), including bone formation markers, are typically lower in PwO than in those without **(1)**. On the other hand, visceral obesity has been linked to reduced BMD in the spine and hip for both sexes, and to reduced bone quality and strength at the tissue level in premenopausal women, characterized by lower trabecular bone volume, greater cortical porosity, and decreased bone formation rate **(13, 14)**.

Pathophysiology

The "obesity paradox"—defined as an elevated risk of fractures at specific anatomical sites despite generally favorable BMD and bone microarchitecture parameters—remains incompletely elucidated (reviewed in **(15)**). Numerous studies have demonstrated a positive association between BMI and BMD. The normal or elevated BMD observed at various skeletal sites in PwO is hypothesized to result from increased mechanical loading on weight-bearing bones, potentially with a greater contribution from lean mass than fat mass. Moreover, systemic hormonal influences—including elevated insulin levels, adipose tissue-derived estrogens, and adipokines such as leptin—may exert anabolic effects on the skeleton, although their significance in humans remains uncertain. The combination of increased BMD and greater subcutaneous soft tissue padding, particularly in the hip region, may partly account for the reduced incidence of hip fractures in PwO. Furthermore, altered fall mechanics—such as a propensity for backward or lateral falls rather than forward falls—may contribute to the reduced risk of wrist fractures and a heightened risk of humeral fractures. The increased prevalence of ankle and distal lower limb fractures in PwO may be attributed to a tendency toward excessive inversion and eversion of the ankle and lower leg, compounded by greater body mass.

Several additional mechanisms have been proposed to explain the fracture risk observed in PwO. These include diminished bone turnover rates and increased marrow adiposity, particularly involving saturated lipids, which have been linked to lower BMD at the spine and hip, as well as a greater susceptibility to vertebral fractures **(16)**. Moreover, the lower BMD and impaired bone quality associated with visceral adiposity may reflect the effects of systemic inflammation and oxidative stress—factors known to enhance bone resorption and loss—alongside reduced circulating levels of androgens in men and insulin-like growth factor I (IGF-

I), an hormone involved in maintaining bone remodeling balance by promoting the function and activity of osteoblasts and osteoclasts **(17, 18)**. A recent mendelian-randomization study also revealed a potential causal relationship between metabolic-associated fatty liver disease (MAFLD) and low femoral neck BMD, which may be mediated by BMI **(19)**. Similarly, longstanding T2D, especially in patients with microvascular complications or poorly controlled hyperglycemia, may further deteriorate bone quality and low bone formation in PwO **(20)**. Interestingly, a recent study in male mice fed a high-fat diet (HFD) revealed a novel potential mechanism linking obesity-associated metabolic diseases such as MAFLD and T2D, and skeletal fragility **(21)**. Researchers observed that osteoblast lipid dysfunction may contribute to the reduced bone formation and bone strength in these metabolic conditions, and that enhancing lipolysis specifically in osteoblast progenitor cells (through Plin2 deletion) could offer protection against skeletal fragility induced by a HFD. New evidence also indicates that gut microbiota dysbiosis may contribute to obesity-related skeletal fragility through various mechanisms, including the induction of bone marrow macrophage senescence and the stimulation of grancalcin secretion **(22)**. Finally, a systematic review and meta-analysis showed that older adults with sarcopenic obesity have lower femoral neck BMD and an increased propensity to fall compared with either controls without sarcopenic obesity or those with obesity alone, and an increased risk of non-vertebral fractures compared with older adults with sarcopenia alone **(23)**.

Further studies are needed to better understand the pathophysiology underlying the "obesity paradox". This is particularly relevant given the expanding array of weight-loss interventions, which have implications for bone health in PwO.

Calorie Restriction Induced Bone Loss

Calorie restriction has been the time-honored method for inducing weight loss in humans. However, reduced energy intake can have deleterious effects on lean mass and skeletal integrity. Notwithstanding, reduced calorie intake is still the most frequent, and cost-effective way for treating obesity. Newer approaches, including intermittent fasting, or temporal

restriction of food, have surged in popularity. However, compliance remains relatively poor; thus, the magnitude of weight loss is far less than other strategies such as MBS. Although not yet proven in humans, calorie restriction in rodents and other non-human non-primate models enhances lifespan, providing another incentive to try calorie restriction. Even more promising for humans, calorie restriction for over two years has been shown to improve surrogate markers of health span in a manner similar to gastric bypass **(24,25)**.

It is well established that high-turnover bone loss occurs after calorie restriction. One theory is that the skeleton undergoes "adaptive remodeling" to fit the changes in body composition and weight. However, it is unclear whether this represents a pathophysiological or normal compensatory response to weight loss. The need to delineate the mechanisms of these skeletal changes with calorie restriction, particularly in PwO, is heightened by the introduction of the new anti-obesity medications and recent clinical initiatives to conduct longer and larger dietary restriction trials, which will extend beyond the two years previously reported by the CALERIE study **(24)**.

Obesity, the Skeleton and Calorie Restriction: Confounding Effects

Weight loss studies in PwO have shown higher rates of bone resorption and lower BMD in some, but not all studies **(26)**. In mice, the induction of obesity with a HFD followed by calorie restriction leads to more aggressive bone loss than in normal-weight mice undergoing calorie restriction **(27)**. Interestingly, although HFD induces an inflammatory response in peripheral adipose tissue, there is no evidence of inflammation within the bone marrow of mice or humans despite higher rates of bone resorption **(28,29)**. In fact, there is evidence that a short-term high-calorie diet in humans reduces inflammatory transcriptomic pathways **(29)**. Taken together, evidence from mouse and human studies suggests a complicated picture of obesity-induced skeletal alterations that are overlaid with fundamental changes in bone health after calorie restriction.

Unique Remodeling Changes with Calorie Restriction Induced Bone Loss in Mice

Dietary induced changes in bone mass in PwO are associated with changes in substrate availability **(30)**. However, the overall impact on body composition is conflicted by numerous comorbidities in most PwO. Mice can recapitulate some effects of a high-calorie diet without these confounding factors, and have proven to be a useful model to study skeletal

responsiveness. In regards to the latter, skeletal changes in mice from 30% calorie restriction are associated with two distinct characteristics. First, there is a clear and rapid induction of bone marrow adiposity with bone loss that resembles that occurring after HFD, although the transcriptomic changes are markedly different **(29,31)**. This appears to be due to a skeletal stem cell switch towards adipogenesis and is consistent with the histomorphometric findings of reduced bone formation and lower numbers of osteoblasts **(32-34)**. Second, lower cortical bone mass after calorie restriction, with some intracortical porosity of the endocortical envelope, is a feature of calorie restriction in most mouse models **(35)**. The mechanisms that underlie the effects on cortical bone are not known, although this feature and marrow adiposity are also seen in human aging **(33)**. Studies from the Rosen laboratory have identified adipsin or complement factor D as one of the top adipokines upregulated in the marrow of mice undergoing 30% calorie restriction **(36)**. They also showed that global genetic deletion of adipsin reverses marrow adiposity induced by calorie restriction and at least partially prevents cortical porosity **(36)**. Further studies are needed to confirm these findings with conditional deletion of adipsin and to determine other factors that may be operative during dietary restriction.

Potential Mechanisms of Calorie-Restricted Bone Loss

Cortical bone is particularly vulnerable to bone loss due to calorie restriction, which can lead to a reduced failure load and, ultimately, long bone fractures **(37)**. Under some extreme conditions of calorie restriction, low serum IGF-I has been correlated to lower failure load of the radius and tibia measured by micro-CT **(Figure 2) (38,39)**. However, serum IGF-I measurements are confounded by other factors. First, in humans, unlike in mice, serum IGF-I levels do not decline with calorie restriction but only with low protein intake **(40)**. Hence, in mice, low IGF-I may reflect the severity of dietary deficiency but may be true and unrelated to local changes in skeletal turnover. Second, circulating IGF-I is not a surrogate for tissue IGF-I, particularly in the skeleton. For example, reduced body weight and loss of lean muscle mass could contribute to a reduction in local IGF-I produced at the interface of the muscle and bone on the periosteal surface where appositional growth occurs. Therefore, what comes first, reduced IGF-I or reduced muscle and bone mass leading to lower systemic or local IGF-I, still needs to be answered.

Other genetic models of calorie restriction provide further evidence that cortical bone loss may be related to circulating IGF-I. Global deletion of igf1 or igf1r in mice leads to markedly smaller bones with a reduced cortical bone area **(41)**. The Rosen lab has shown that conditional deletion

of liver igf1 in mice, which contributes 75% of total IGF-I to the circulation, leads to reduced cortical bone area and periosteal circumference **(42)**. Furthermore, temporal deletion of IGF-I using tamoxifen to drive an albumin promoter in floxed Igf1 mice leads to a marked reduction in periosteal apposition and smaller bone area. This occurs both in young mice and in animals, even at one year of age, when linear growth has slowed. Finally, to highlight the importance of circulating IGF-1 in appositional growth, we found that mice with a genetic deletion of Igf1 crossed with mice that had transgenic overexpression of Igf1 in the liver resulted in a mouse that had normal cortical bone area and periosteal apposition, suggesting that circulating IGF-I is an important component in regulating cortical bone during substrate deficiency **(43)**.

In healthy non-obese C57BL6J mice, we found that 30% calorie restriction in both young and older mice, led to 20% weight loss and a nearly 50% reduction in circulating IGF-I **(44)**. Importantly, bone loss is more profound in these mice than in normal weight mice **(27)**. Moreover, serum IGF-I correlated with cortical thickness and periosteal circumference in both male and female normal-weight mice, and accounted for up to 70% of the variance in these parameters. More recent studies in the Rosen laboratory have shown that a similar reduction in IGF-I occurs after mice are fed with a HFD and then calorie-restricted. Importantly, trabecular bone mass was preserved in both situations. Histomorphometric analysis revealed that the three bone surfaces (endosteal, endocortical, and periosteal) demonstrated a marked suppression in bone formation and resorption, which differed from human studies showing increased resorption **(33,44)**.

Several marrow adipokines have been associated with changes in skeletal remodeling during calorie restriction in mice. For example, it is known that marrow and circulating adiponectin increase with anorexia nervosa, and in experimental models, this increase is likely due to the enhancement in marrow adiposity **(45)**. Adiponectin is an adipokine that regulates glucose control by inducing insulin sensitivity. Its effect on the skeleton is less clear because of the opposing effects of this adipokine on body composition parameters. Adipsin, as noted above, is another adipokine generated in both peripheral and marrow adipocytes. Adipsin, made by marrow adipocytes and their progenitors, inhibits osteogenic differentiation *in vitro*, and *in vivo* deletion of adipsin from marrow progenitors preserves bone mass and rescues caloric restriction-induced skeletal phenotypes, particularly in cortical bone **(36)**. It is likely that other proteins and adipokines will be isolated from the marrow that regulate skeletal remodeling.

Human Studies of Calorie Restriction

Calorie restriction in PwO is very common, due in part to the obesity epidemic and the promise of a potentially improved health span. However, the skeleton has been less well studied as an off-target tissue affected by reduced calorie intake. Several observational cohort studies and a few longitudinal but smaller and shorter trials have been conducted to examine bone outcomes, primarily in PwO attempting to lose weight with calorie restriction **(46-48)**. Overall, there has been a consistent signal for some degree of bone loss (1-1.5%) in humans with 10% weight loss using Dual Energy X-ray absorptiometry (DXA) measurements. Importantly, different exercise regimens or weighted vests do not fully attenuate bone loss from the femoral neck **(46-48)**. Similar data were noted in the Look Ahead study of T2D, where fracture risk was increased by 39% with calorie restriction and with the separation between control and weight loss subjects beginning at year 3 **(49)**. Notably, most of these fractures occur in the cortical bone. This was also found in the long-term follow-up, although BMD did not further deteriorate over the decade following year 3 **(50)**.

The strongest and longest trial of calorie restriction that included BMD as an outcome was CALERIE, which was performed in the 2000s **(24)**. 218 healthy and normal-weight individuals were randomized to a diet that was 25% calorie-restricted (n=143) or ad libitum (n=75) for 2 years. After 6 months, the calorie restriction group had attained a 19% reduction in caloric intake, but by year 2, calorie intake was only 8% of the baseline values **(24)**. Significant weight loss was achieved at 6 months in the calorie restriction group (-7.3 ± 0.2) compared to the ad libitum group (-0.8 ± 0.3; $p<0.001$). Despite the modest difference at the end of the study, the markers of cardiometabolic fitness and insulin resistance markedly improved. The skeletal changes were measured by DXA and showed significant bone loss from the lumbar spine and total hip of approximately 1% after year 1 in the calorie restriction group, which continued in year 2, without plateauing, even though calorie intake was only reduced by 9%. BTMs showed greater bone resorption and only modest but not significant suppression of bone formation. Serum IGF-I levels did not differ by group; however, at year 2, IGF-1 was significantly lower than at baseline in both groups, reflecting reduced calorie intake.

Effects of Exercise on Calorie-Restriction Induced Bone Loss

There is a significant rationale for attempting to mitigate bone loss during calorie restriction with exercise although current data suggest that any effect is likely to be modest. First, as noted in CALERIE, virtually every clinical trial has demonstrated bone loss from the hip with restriction of calories over a sustained period. In a clinical trial 187 older adults with obesity,

aerobic training did not prevent bone loss from the hip or spine, although resistance training showed a modest attenuation **(51)**. A meta-analyses of 9 trials noted that neither aerobic or resistance exercise could prevent areal BMD loss from the total hip (~ -2%) or spine (-0.5%) during weight loss **(47)**. But, loss of femoral neck areal BMD was attenuated slightly (-0.88%). In contrast, Beavers *et al* in a 12-month randomized clinical trial of older individuals with obesity, neither weighted vest use nor progressive resistance training was able to mitigate weight loss-associated bone loss at the hip **(46)**.

One of the major concerns about persistent bone loss is whether there is also a greater risk of fractures, with calorie restriction. One of the longest follow ups of a clinical trial of diet and exercise was Look AHEAD, an intensive lifestyle intervention to improve cardiovascular outcome in Type 2 Diabetes Mellitus. At four years, long term intentional weight loss was associated with greater bone loss at the hip in men but not in women **(52)**. However, there was an increased risk of frailty fractures in the entire group with intensive lifestyle changes versus those with conventional interventions. Notable at year eight and twelve, persistently lower hip aBMD was noted in males in the intensive treated group **(50)**.

Taken together the totality of evidence, suggests that aerobic or resistance exercise alone does not prevent bone loss in young or older individuals with calorie restriction. Hip bone loss is particularly concerning since it might increase the risk for fractures with prolonged dietary restriction. Future long-term trials are needed to determine if exercise could attenuate femoral neck bone loss and prevent hip fractures.

Effects of Metabolic and Bariatric Surgery on Bone

Epidemiology of Metabolic and Bariatric Surgery

Metabolic and bariatric surgery encompasses a variety of surgical procedures designed not only to induce significant and sustained weight loss but also to improve or resolve metabolic conditions such as T2D, cardiovascular disease, and dyslipidemia. The most commonly performed procedures worldwide are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). These surgical procedures induce weight loss through a combination of restriction, malabsorption, and alteration of hormonal mechanisms. Both procedures result in substantial and durable weight loss, typically averaging 25-35% of total body weight, and remission or improvement of T2D in up to 80% of cases **(53)**.

The uptake of MBS has increased steadily over the past two decades. In the United States alone, over 270,000 bariatric procedures were performed in 2023, with SG accounting for the majority (~60%) and RYGB comprising ~25% of cases **(54)**. Although some bariatric centers have recently reported a decline in MBS procedural volume with the advent of newer anti-obesity medications **(55)**, the vast scale of the obesity epidemic ensures that both surgical and pharmacologic therapies will remain important tools for managing obesity. Furthermore, guidelines have expanded the clinical indications for MBS to include individuals with a BMI ≥35 kg/m², or ≥30 kg/m² with obesity-related comorbidities **(56)**. While the benefits of MBS in reducing cardiovascular disease, T2D, and mortality are well documented, concerns regarding its long-term effects on bone health have emerged.

Impact of MBS on BMD and bone turnover

Significant BMD declines are observed after RYGB and, to a lesser extent, SG. Reductions in BMD begin within 6-12 months of surgery and studies demonstrate progressive bone loss and accelerated bone turnover lasting for many years post-operatively **(57,58)**, exceeding skeletal changes typically observed with diet-induced weight loss. In a 7-year longitudinal study of RYGB, patients exhibited cumulative bone loss of 8% at the spine and 17% at the total hip **(59)**. A meta-analysis of 22 observational studies found consistent declines in femoral BMD within the first year of SG, although short-term changes in lumbar spine BMD were not significant **(60)**. The mechanistic underpinnings of greater bone loss at the femur as compared to the spine are unknown, although this pattern is observed in most MBS studies. Three randomized controlled trials have directly compared bone outcomes after SG versus RYGB in adults with T2D, and have confirmed significant femoral bone loss after both procedures, which is of generally smaller magnitude after SG than RYGB **(61-63)**.

Notably, BMD declines after MBS are seen even with optimized calcium and vitamin D supplementation, and exceed what is expected based on weight loss alone. Postmenopausal women appear to be particularly susceptible to bone loss after MBS **(64,65)**. Bone resorption markers increase within the first 2 weeks of RYGB, and remain higher than weight-matched controls even >10 years after surgery **(66,67)**. SG also leads to high turnover bone loss, albeit to a lesser degree than RYGB. Furthermore, HR-pQCT has revealed substantial microarchitectural deterioration after both RYGB and SG **(58, 65)**. Increases in cortical porosity, reductions in trabecular number, and loss of plate-like trabeculae have been documented, with resulting declines in estimated bone strength.

Other forms of MBS have variable impact on bone density, with procedures involving a greater degree of malabsorption leading to larger bone loss. For example, biliopancreatic diversion with duodenal switch (BPD-DS) involves bypass of a larger portion of the small intestine and thus induces greater malabsorption than procedures such as RYGB. Ten-year outcomes from the ASGARD randomized controlled trial demonstrated lower spine and femoral neck BMD among adults randomized to BPD-DS as compared to RYGB **(68)**. In contrast, comparative studies suggest that adjustable gastric banding (AGB), a purely restrictive procedure, has substantially less impact on bone turnover and BMD than either RYGB or SG **(69-71)**.

Impact of MBS on fractures

It is important to understand the clinical consequences of the high-turnover bone loss associated with MBS. PwO tend to have high BMD and therefore bone loss after MBS does not often lead to osteoporotic bone density. Nevertheless, numerous studies and meta-analyses have demonstrated that MBS is associated with increased risk of fractures, although risk varies by procedure type **(72,73)**. On one end of the spectrum, procedures with significant malabsorptive components such as RYGB and BPD-DS greatly increase fracture risk, whereas purely restrictive procedures, such as AGB, do not increase fracture risk as compared to non-surgical obese controls **(74-76)**.

RYGB has the strongest evidence base for increasing fracture risk. Large database epidemiologic studies have reported a 30–80% higher risk of nonvertebral and major osteoporotic fractures in RYGB patients compared with either non-surgical obese controls or patients undergoing AGB **(75,77-79)**. In these studies, risk was increased the most for hip fractures, with estimates ranging from 2-fold to 5-fold higher after RYGB as compared to controls. Fracture risk became apparent approximately 2 years postoperatively, with a continued rise up to 10 years.

Only a few studies have examined fracture risk after SG, and these have shown conflicting results. A study using data from the French National Database found that fracture risk after SG was similar to non-surgical controls with obesity (HR 0.95, 95% CI 0.79–1.14) **(75)**. Another study utilizing Medicare data found that SG decreased risk of fractures compared to non-surgical controls (OR, 0.53; 95% CI 0.46-0.62), although this study was limited by short follow-up time (<2 years) after surgery **(80)**. In contrast, two recent studies reported an increased risk of incident fracture after SG, including one study conducted in a VA population (HR 1.48, 95%

CI 1.31-1.67) and another in a Danish national cohort (HR 1.43, 95% 0.97-2.12) **(81,82)**. Despite these conflicting results, studies have consistently demonstrated that SG leads to lower fracture risk than RYGB when compared head-to-head; this disparate fracture risk may stem from differences in gastrointestinal and metabolic signaling after these distinct procedures **(83)**. Ultimately, given that SG now ranks as the most commonly performed MBS procedure, it is imperative that additional studies are conducted to clarify the long-term impact of SG on fracture risk.

Mechanisms of skeletal changes after MBS

Skeletal changes after MBS arise through a multifactorial set of mechanisms that extend beyond simple mechanical unloading of the skeleton. Although the rapid and substantial weight loss following surgery reduces skeletal loading, thus contributing to BMD decreases, long-term data reveal persistent elevations in bone turnover markers and progressive degradation of bone microarchitecture even after weight stabilization, implicating additional biological pathways **(59,67)**. Animal models support the contribution of weight-independent mechanisms, demonstrating exaggerated bone loss following RYGB as compared to calorie-restricted weight-matched controls **(84)**. Nutrient malabsorption, particularly of calcium and vitamin D, plays a critical role after both RYGB and SG, and can lead to secondary hyperparathyroidism in the absence of appropriate supplementation **(85-87)**. In addition, protein malabsorption in combination with substantial loss of lean mass after MBS may contribute to increased fall risk to further elevate fracture risk in this population **(88,89)**. Moreover, post-surgical alterations in gut-derived and adipose-derived hormones, including changes in adiponectin, PYY, leptin, estradiol, and the gut microbiome have been implicated in dysregulated bone remodeling **(90)**. Preclinical studies have also provided critical mechanistic insights into the importance of other factors such as IGFBP-2, G-CSF, and FGF-15 on skeletal metabolism after MBS procedures **(91-93)**. Future research is required to understand the complex interplay of factors that contribute to skeletal changes after MBS.

Clinical management of skeletal health after MBS

Clinical management of MBS patients should prioritize prevention, early detection, and treatment of potential skeletal complications **(55,94)**. Principles of management include lifelong supplementation to achieve daily calcium intake of 1200-1500 mg (calcium citrate preferred over other supplements) and daily vitamin D intake of ~3,000 IU. Starting doses need

to be adjusted to ensure serum 25(OH)D is at target (≥30 ng/ml) with normal PTH and 24-hour urine calcium levels. However, it is unknown how many patients achieve this target with daily vitamin D intake of ~3,000 IU. Higher doses are needed for BPD-DS.

MBS leads to malabsorption of fat-soluble vitamins (including vitamin D and vitamin K) and zinc; however, the impact of vitamin K on bone health is somewhat controversial, and the connection between zinc and bone is not clear. Magnesium deficiency is not typically observed after RYGB or SG. No data have shown improved bone outcomes with the supplementation of these particular vitamins and minerals.

Randomized trials have shown that aggressive vitamin D supplementation and structured exercise interventions are important components of post-surgical management and may partially mitigate bone loss after MBS, although these interventions do not fully attenuate total hip BMD decline (**Figure 3**) **(95-98)**. These exercise interventions involved supervised aerobic and strength training on 3-5 days/week, with increased adherence generally leading to improved BMD preservation.

For older patients with osteoporotic risk factors who are planning MBS, pharmacologic treatment can also be effective. As MBS induces a high bone turnover state, pharmacologic trials have focused on antiresorptive strategies. In a pilot randomized trial of 24 adults undergoing SG, monthly oral risedronate was found to preserve lumbar spine BMD and partially prevent femoral bone loss **(99)**. A recently published randomized trial of 59 participants reported that pre-operative zoledronic acid successfully preserved bone loss at the lumbar spine and femoral neck at 1 year after RYGB and SG **(100)**. Reductions in total hip BMD were less in the zoledronic acid group as compared to untreated controls, although both groups experienced declines (-4% vs -8%, $p<0.002$). Surprisingly, carboxy-terminal type I collagen (CTX) markers were not fully suppressed by bisphosphonates in either of these trials, with 1-year levels 65-85% above preoperative baseline in the bisphosphonate-treated arm **(99,100)**. These results speak to the intensely high bone turnover state induced by MBS. Finally, a randomized trial of denosumab in 36 postmenopausal women and men aged >50 years undergoing RYGB or SG was recently presented **(101)**. In this trial, denosumab fully prevented vertebral and femoral bone loss in the 19 months after MBS (**Figure 3**).

Of note, there was no significant hypocalcemia reported within these small trials, all of which involved adjunct calcium and vitamin D supplementation. However, there have been clinical

case reports of marked hypocalcemia after antiresorptive treatment in MBS patients who were nonadherent to calcium and vitamin D supplementation **(102,103)**, which emphasizes the importance of adequate nutritional counseling for post-MBS patients. To date, no studies of anabolic treatments in bariatric surgery have been reported.

Effects of GLP-1 Receptor Agonists on bone health

Incretin hormones

GLP-1 is an incretin hormone secreted by enteroendocrine L cells located in the distal small intestine and colon when nutrients are consumed. Additionally, it is produced by certain neuronal cells in the brainstem. GLP-1 originating from the gut has a very short circulating half-life of only 1–2 min, owing to its rapid inactivation by the enzyme dipeptidylpeptidase-4 (DPP-4) and subsequent clearance through the kidneys **(104,105)**. GLP-1 exerts its effects through the GLP-1 receptor, which is found in various tissues, including the brain, pancreas, stomach, heart, kidneys, and adipose tissues. Incretin hormones, such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are involved in several functions such as regulating glucose levels, delaying gastric emptying, and reducing food intake **(106,107)**.

GLP-1 Receptor Agonists for weight management

Medications like liraglutide 3.0 mg daily (Saxenda; Novo Nordisk) and semaglutide 2.4 mg weekly (Wegovy; Novo Nordisk), which are GLP-1Ra, have been approved by drug regulatory authorities in several countries for prolonged weight management in PwO **(Table 1)**. These medications resulted in a significant mean weight reduction of 10-15% **(105,106)**. Tirzepatide, which has also been approved for weight management, is a single-molecule agonist of receptors for both GLP-1 and GIP. Tirzepatide' s efficacy in obesity treatment showed a mean weight reduction of greater than 20% with pharmacotherapy for the first time **(110)**. Although GLP-1 might enhance bone metabolism and quality, the impact of these single- and double-agonist anti-obesity drugs on bone health remains unexplored **(108)**.

Preclinical models

Research involving GLP-1R knockout (KO) mouse models and *in vitro* bone cell studies has indicated that GLP-1Ra could be advantageous for bone health, even when weight loss is pharmacologically induced **(111,112)**. Liraglutide appears to positively influence bone metabolism in preclinical models. In ovariectomy (OVX)-induced osteoporosis in rat and mouse models, liraglutide is administered at doses ranging from ~80 to ~530 nmol/kg/day. At these doses, liraglutide caused weight loss in the rat models. However, despite significant weight loss, liraglutide-treated animals displayed increased bone mass, trabecular number, and cortical thickness in the appendicular and axial skeletons, with a marked improvement in bone formation parameters **(113,114)**. It is also worth noting that these effects of liraglutide in OVX animals occurred relatively quickly, with positive outcomes observed after just four weeks of treatment, consistent with the *in vitro* data. In OVX rats, administration of semaglutide at ~21 and 43 µg/kg/day resulted in body weight loss in the animals, but also in improvements in BMD at the axial and appendicular skeleton associated with a reduction in BTMs **(113,114)**. However, none of the above studies investigated whether bone biomechanics and resistance to fracture improved following the administration of GLP-1Ra.

In type 2 diabetes mice models, administration of semaglutide at the dose regimen of ~90 µg/kg/day failed to evidence significant weight loss but more importantly, led to alteration of cortical bone microarchitecture, represented by lower cortical thickness, and ultimately to a significant decrease in bone strength **(111)**. On the other hand, administration of tirzepatide at a dose of 70 nmol/kg/day, resulted in a significant weight loss associated with shorter femur compared to saline-treated diabetic mice, but no evident alterations of bone microarchitecture or strength **(111).**

Although the therapeutic dose of liraglutide appeared to enhance bone material properties, the most significant improvements in BMD and microarchitecture were noted at doses much higher than those used for weight loss in PwO **(113)**.

Human studies

Two randomized controlled trials assessed the effects of GLP-1Ra on bone metabolism during the weight loss phase using standard BMD measurement sites **(115,116)**.

Researchers have investigated the impact of semaglutide on bone health in adults at an elevated fracture risk, but without T2D **(115)**. The study involved 64 participants, predominantly female

(86%), with a mean age of 63 years and a BMI ranging from 21 to 39 kg/m². Subjects were randomly assigned to receive either semaglutide (1.0 mg or the highest-tolerated dose) or a placebo weekly for 52 weeks. Semaglutide treatment resulted in a significant average weight reduction of 9.4% ($P < 0.001$), whereas no change was observed in the placebo group. Although serum PINP levels remained similar between the groups from baseline to week 52, the semaglutide group exhibited a 54.8% greater increase in CTX levels than the placebo group. Semaglutide administration decreased BMD by 2.1% in the lumbar spine ($P = 0.01$), 2.6% in the total hip ($P = 0.001$), and 1.5% in the tibial volumetric BMD ($P = 0.003$). The effects of semaglutide, including weight loss, slight BMD loss, and increased CTX, resembled those observed with calorie restriction. However, the study design did not allow for the assessment of the effects of semaglutide on bone metabolism, independent of weight loss, as the control group did not experience comparable weight reduction.

A secondary analysis of an RCT examined the changes in BMD at clinically significant sites following an 8-week low-calorie diet (800 kcal/day) for weight loss, followed by a year-long treatment with liraglutide (3.0 mg daily), exercise alone (a supervised and progressive resistance training program), a combination of both treatments (liraglutide + exercise), or a placebo **(116)**. A total of 195 participants (mean [SD] age, 42.8 [11.9] years; 124 females [64%]; mean [SD] BMI, 37.0 [2.9]) completed the low-calorie diet and were then randomly assigned to the exercise group (n=48), liraglutide group (n=49), combination group (n=49), or placebo group (n=49). None of the participants were on osteoporosis medications and no fractures were reported in any group. Following a weight loss of approximately 14% induced by the low-calorie diet in the entire cohort, the placebo group regained weight, the exercise and liraglutide groups sustained weight loss, and the combination group lost additional weight. As anticipated, the low-calorie diet led to an increase in CTX (+27%) and PINP (+7%) levels, indicating that increased bone turnover favors bone resorption. After calorie restriction, CTX levels continued to increase further between week 8 and 26 in all four groups, especially in the combination group owing to further weight loss; however, these levels decreased during the final phase of the intervention from week 26 to week 52 across all four groups. By week 52, PINP levels had returned to their initial values in all groups. Throughout the study (from week −8 (before low-calorie diet) to week 52), a slight reduction in BMD was noted in all four groups at the lumbar spine and total hip. However, unlike the combination of exercise and liraglutide, liraglutide alone resulted in a decrease in hip (mean change, −0.013 g/cm²; 95% CI, −0.024 to −0.002 g/cm²; $P = 0.02$) and lumbar spine BMD (mean change, −0.019 g/cm²; 95% CI, −0.034

to 0.002 g/cm²; P = 0.02) compared to placebo. Therefore, after weight loss, incorporating exercise with liraglutide helps mitigate BMD loss at the hip and lumbar spine, similar to the pattern observed when weight loss from calorie restriction alone is combined with exercise.

Several factors may contribute to the apparent discrepancy between the favorable skeletal effects observed in animal models and the more neutral or even negative effects reported in PwO. One key aspect is the difference in serum concentrations, since most of the positive findings in rodents were obtained at doses much higher than those approved for obesity care in humans. In addition, other factors may play a role, including the limitations of animal models in fully recapitulating human bone physiology, as well as the possibility of publication bias.

Semaglutide could lead to an increased risk of fractures

Regarding fracture events, the safety profile of semaglutide versus placebo in the STEP1 study has not been published **(109)**. In this RCT, 1961 adults (female, 74.1%, mean age of 46 years) with a BMI of ≥30 (≥27 in persons with at least one weight-related coexisting condition) who did not have T2D were enrolled and randomly assigned, in a 2:1 ratio, to 68 weeks of treatment with semaglutide (2.4 mg per week) or placebo, plus lifestyle intervention. For the first time, fracture rates were reported without any imbalance between the two groups: patients receiving semaglutide compared to those receiving placebo: 5.0% (65/1306) versus 4.7% (31/655) (p-value non-significant) **(Table 2)**.

The SELECT study enrolled 17,604 individuals aged ≥ 45 years with existing cardiovascular disease, no T2D, and BMI exceeding 27 kg/m² **(117) (Table 1)**. Only 27.7% and 7.8% of the enrolled patients were women or ≥ 75 years of age, respectively. Semaglutide was shown to reduce the rates of major adverse cardiovascular events by 20% among persons with a history of atherosclerotic cardiovascular disease and obesity, or in persons who were overweight and had one or more weight-related complications. In 2025, crucial safety data on semaglutide were disclosed **(118)**. Notably, the cardiovascular outcomes study conducted in adults (SELECT study) revealed a higher incidence of hip and pelvic fractures among female patients receiving semaglutide than among those receiving placebo: 1.0% (24/2448) versus 0.2% (5/2424). Similarly, in participants aged ≥ 75 years, the fracture rates were 2.4% (17/703) for semaglutide and 0.6% (4/663) for the placebo. The longer duration of follow-up (mean follow-up period of 39.8 ± 9.4 months), larger number of participants included, older age, and higher prevalence of cardiovascular comorbidities may explain why an increased fracture risk was observed.

Emerging anti-obesity drugs in development

Many new agents are currently under development for the treatment of obesity **(119,120)**. Most of these are based on replicating (or inhibiting) the action of one or more gut-derived hormones including GLP-1, GIP, amylin, and glucagon. Early phase clinical trials have reported unprecedented weight loss and glycemic improvements with several of these agents, approaching the results achievable with bariatric surgery, at least in the short term. However, to date, there are very limited or no preclinical or clinical data available regarding their bone effects.

Conclusions

Although recent data have deepened our understanding of the complex relationships between different fat distribution patterns, sarcopenia, and obesity-associated comorbidities affecting bone health in PwO, further preclinical and clinical research is required to develop personalized strategies aimed at enhancing bone and muscle health in this population.

There is a need for further research to assess the effects of anti-obesity medications on bone metabolism and fracture-related outcomes. In particular, data are needed on optimal strategies for calcium and vitamin D supplementation, exercise, other nutrients such as magnesium, and the use of osteoporotic treatments in patients undergoing different weight loss interventions. Unlike preclinical studies, current evidence suggests that the impact of GLP-1Ra on BMD and bone turnover resembles that of calorie restriction, including modest BMD loss and increased CTX **(115,116)**, but more robust clinical data are needed to guide individualized treatment. Further research is also needed to specifically evaluate the impact of GLP-1Ra on muscle strength and to determine the most effective strategies to preserve muscle mass during treatment.

Existing studies provide robust evidence that MBS, particularly RYGB, leads to significant alterations in bone metabolism, BMD, and fracture risk. It is important to recognize that the profile of adverse skeletal effects is unique to each MBS procedure via a multifactorial pathophysiology involving mechanical unloading, nutrient deficiencies, and hormonal changes. These findings underscore the importance of bone health monitoring and intervention in

patients receiving MBS **(56)**. Ongoing research is needed to delineate the relative contributions of specific pathways and to develop strategies to mitigate skeletal complications.

Author contribution statement

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All authors read and approved the final version of the manuscript.

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Tables and figures

Table 1 Available anti-obesity drugs (phase 3 trials)

Author (year)	**Participants (n)**	**Sex (% female)**	**Age (years); mean (SD)**	**Baseline BMI (kg/m²); baseline weight (kg) mean (SD)**	**Medication**	**Follow-up duration; mean or median**	**Main results Weight loss**
Pi-Sunyer et al. (2015) **SCALE**	Liraglutide (n=2487) Placebo (n=1244)	78.5%	45.1±12.0 years	38.3±6.4 kg/m² 106.2±21.4 kg	Liraglutide 3.0 mg per day BMI >30 kg/m² or >27 kg/m² with comorbidities	56-week trial	Liraglutide: 8.4 kg Placebo: 2.8 kg Liraglutide: 8.0% Placebo: 2.6%
Wilding et al. (2021) **STEP 1**	Semaglutide (n=1306) Placebo (n=655)	74.1%	46±13 years	37.8±6.7 kg/m² 105.4±22.1 kg	Semaglutide 2.4 mg per week BMI >30 kg/m² or >27 kg/m² with Comorbidities	68-week trial	Semaglutide: 15.3 kg Placebo 2.6 kg Semaglutide: 14.9% Placebo: 2.4%
Jastreboff et al. (2022) **SURMOUNT 1**	Tirzepatide (n=1896) -5 mg (n=630) -10mg (n=636) -15mg (n=630) Placebo (n=643)	67.5%	44.9±12.5 years	38.0±6.8 kg/m² 104.8±22.1 kg	Tirzepatide 5 to 15 mg per week BMI >30 kg/m² or >27 kg/m² with Comorbidities	72-week trial	Tirzepatide: -5 mg: 16.1 kg -10 mg: 22.2 kg -15 mg: 23.6 kg Placebo: 2.4 kg Tirzepatide: -5 mg: 15.0% -10 mg: 19.5% -15 mg: 20.9% Placebo: 3.1%
Lincoff et al. (2023) **SELECT**	Semaglutide (n=8803) Placebo (n=8801)	27.8%	61.6±8.9 years	33.3±5.0 kg/m² 96.5±17.5 kg	Semaglutide 2.4 mg per week Age >45 years BMI >27 kg/m² with preexisting	39.8±9.4 months	From randomization to week 104 Semaglutide: 9.4% Placebo: 0.9%

					cardiovascular disease		

Note: BMI=body mass index; SD=standard deviation

Table 2 Safety profile of semaglutide versus placebo in the STEP1 study: fracture events

Characteristics	Semaglutide 2.4 mg N= 1306	Placebo N=655	Total N=1961
- Wrist/forearm	11 (0.8)	6 (1.0)	17 (0.9)
- Radius/ulna/hand/upper limb	13 (1.0)	5 (0.8)	18 (0.9)
- Humerus	3 (0.2)	0	3 (0.2)
- Vertebrae	5 (0.4)	0	5 (0.3)
- Hip/femur	0	2 (0.3)	2 (0.1)
- Pelvis	0	0	0
- Ankle/leg/lower limb	22 (1.5)	9 (1.5)	31 (1.5)
- Foot	6 (0.5)	7 (1.1)	13 (0.7)
- Rib	2 (0.2)	2 (0.3)	4 (0.2)
- Clavicle	3 (0.2)	0	3 (0.2)
Total	65 (5.0)	31 (4.7)	96 (4.9)

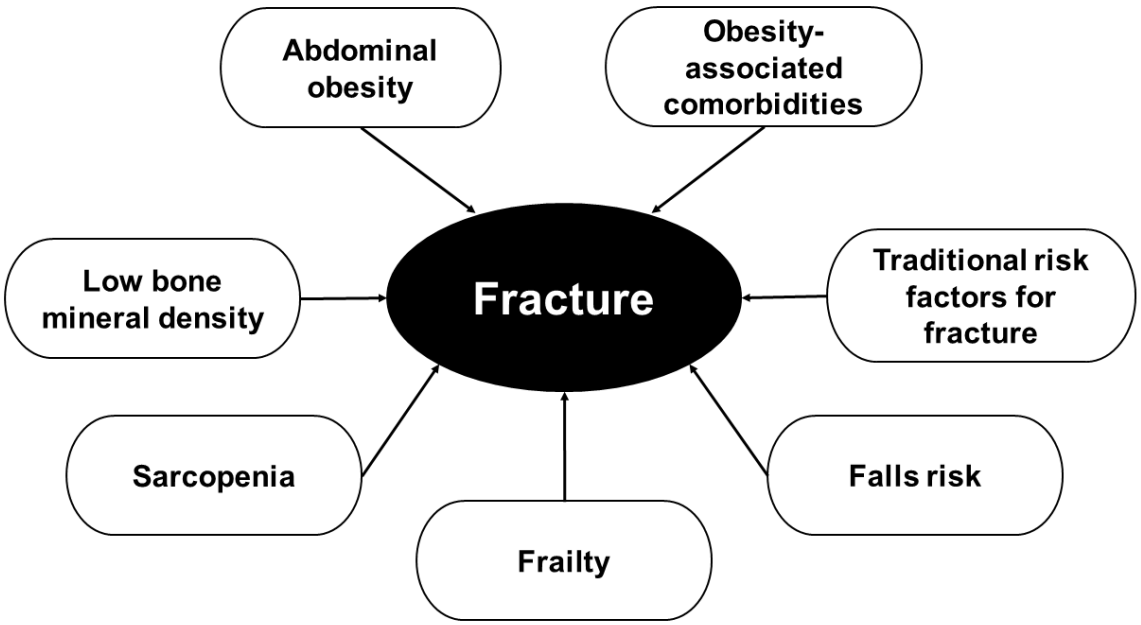
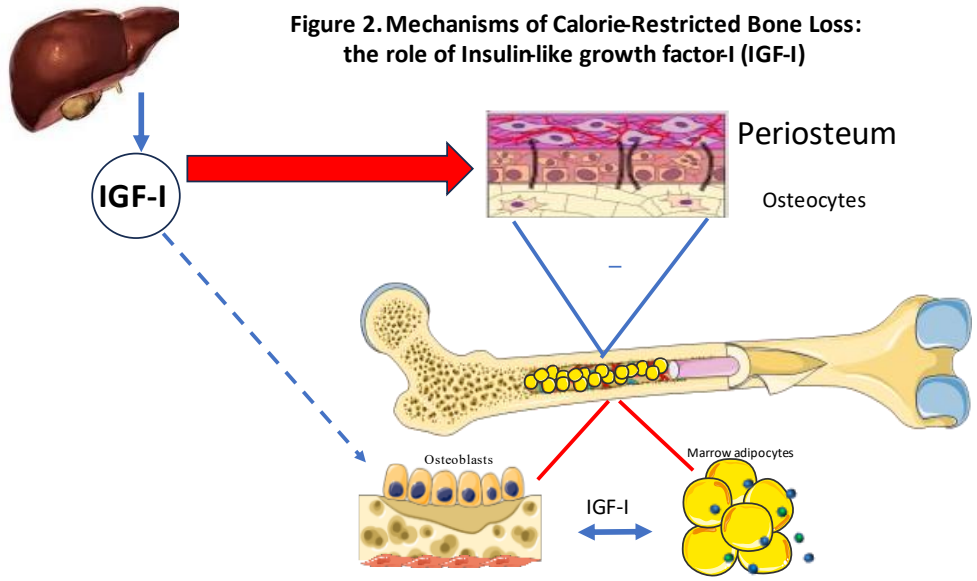


Figure 1 Risk factors for fracture in people living with obesity



Circulating Insulin-like growth factor-I (IGF-I) is predominantly due to hepatic release. Serum levels are related to cortical bone parameters and periosteal circumference in mice and in some disorders such as anorexia nervosa. However IGF-I is also produced by osteoblasts and adipocytes in the bone marrow niche such that both local and systemic IGF-I can impact trabecular bone microarchitecture

Figure 2 Mechanisms of Calorie-Restricted Bone Loss: the role of Insulin-like growth factor-I (IGF-I)

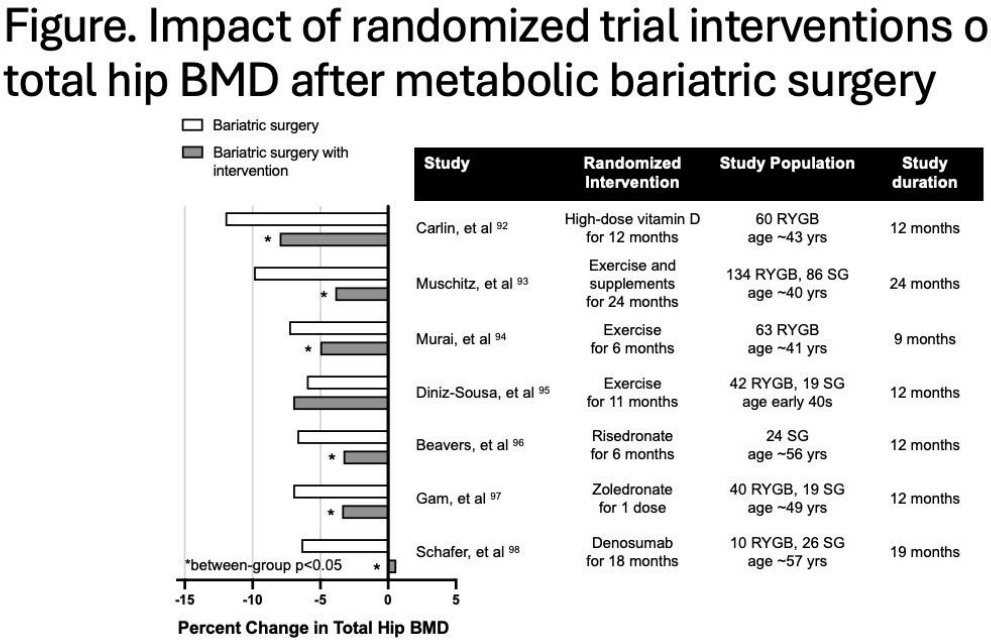


Figure 3 Impact of randomized trial interventions on total hip bone mineral density after metabolic and bariatric surgery