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REVIEW

The Effects of Obesity and Weight Loss Interventions on Bone Health: A Narrative Review

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Abstract

Purpose of Review This review explores the effects of obesity and weight loss on bone and musculoskeletal health.

Recent Findings Obesity is associated with lower bone turnover, higher bone mineral density (BMD) and reduced risk of hip and wrist fractures, although ankle and lower leg fractures may be more frequent. In contrast, weight loss increases bone turnover, especially bone resorption, reduces BMD, especially at cortical sites, and increases fracture risk, especially at the hip and wrist. Skeletal adverse events depend on the magnitude of weight loss and are more prominent following bariatric surgery. Changes in mechanical loading, loss of muscle mass, hormonal alterations, and nutrient/vitamin deficiencies are implicated. Emerging anti-obesity medications may have a positive effect on bone and partially compensate the negative impact of weight loss. Regular exercise, vitamin D supplementation, adequate calcium and protein intake can mitigate these effects.

Summary Identification of the effects of excess body weight and the benefit-to-risk balance of weight loss interventions on bone health may help improve clinical management of invididuals with obesity and related metabolic disorders.

Keywords Obesity · Bone · Weight · Overweight · Weight Loss · Bone Mineral Density

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Introduction

The increasing prevalence of obesity, and consequently of its associated comorbidities, represents a substantial health challenge, inferring a substantial and increasing economic burden in healthcare systems worldwide [1]. The consequences of obesity include metabolic disorders (type 2 diabetes mellitus, dyslipidemia, metabolic dysfunction-associated steatotic liver disease), hypertension and cardiovascular diseases, increased prevalence of certain cancers, and musculoskeletal disorders, such as osteoarthritis [1]. Regarding bone health, the role of obesity is ambiguous, with decreased fracture risk in some sites while increased in other sites despite sustained BMD values [2, 3]. Besides preventive campaigns launched by organizations, scientific societies and healthcare systems globally, the current management of obesity includes lifestyle modifications (dietary interventions and regular exercise) alone or combined with specific drugs aiming to reduce either appetite and food intake or food absorption, and, in more severe cases, bariatric surgery [4]. However, weight loss despite its beneficial effects in cardiometabolic parameters, is clearly associated

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with adverse effects on bone [5]. This review will summarize current evidence on the skeletal effects of obesity and of weight loss and their effective management.

Obesity and Bone

Relationship between Obesity, Bone Turnover, and Bone Mineral Density

Obesity had traditionally been believed to act protectively against fractures because of higher BMD and shielding by subcutaneous fat against the impact of falls. Importantly, higher BMD in people living with obesity (PwO) is not an artifact of dual-energy X-ray absorptiometry (DXA) measurements, even if the measurement of BMD is sometimes challenging [3].

Compared with the general population, PwO have a higher areal and volumetric BMD at all skeletal sites, and generally better bone microarchitecture parameters and bone strength as evaluated by high-resolution peripheral quantitative computed tomography (HR-pQCT) [6, 7]. Furthermore, while bone size is not modified, PwO have thicker and denser cortices and a higher trabecular number than non-obese adults. Finally, PwO have a greater estimated failure load at the radius and tibia [6, 7]. Bone turnover, as assessed by serum biochemical markers of bone formation and bone resorption, is generally lower in PwO than individuals without obesity [8].

Site-Specific Relationship between Obesity and Fracture

A thorough meta-analysis including 25 prospective cohort studies from different countries confirmed the protective role of high body mass index (BMI) on fragility fractures, including hip fractures [9]. However, the relationship between BMI and fracture risk is complex and mediated by BMD in both men and women. Since BMD is a mediator, it should not be used as a confounding factor in adjusted models [10].

Importantly, the association between obesity and fracture risk is also dependent on the skeletal site considered [8, 9, 11]. Specific fracture sites in PwO have been recorded mainly in studies with female populations [8, 9]. Compared to normal weight or underweight women, hip and wrist fractures are less common in PwO, whereas fractures of the ankle and lower leg are more common, and some studies have also reported an increased risk of proximal humerus fractures [12, 13]. Vertebral fractures have been less well-studied, reports are mostly limited to clinical vertebral fractures, and results are inconclusive, with some studies showing increased while others reduced risk or even no association[5]. In a large population-based cohort study of older men, obesity was associated with an increased frequency of multiple rib fractures and a reduced risk of hip, clinical vertebral, wrist, and pelvic fractures [14]. However, mortality following fractures is not higher and may be lower in PwO than in the normal-weight population [15]. This aligns with the phenomenon known as the "obesity paradox", also described in elderly patients with cardiovascular diseases [16]. It is unclear whether this correlation between obesity and better survival is due methodological or other non-causal factors, or there is a causal relationship.

Risk Factors for Fracture in PwO

In PwO, many fracture risk factors are the same as in the general population. These include a previous history of fracture, early menopause age, presence of comorbidities, reduced physical function, and falls.

Falls

Several studies have demonstrated an increased risk of falls in both men and women with obesity [13, 17, 18]. A meta-analysis of observational studies in adults aged > 60 years reported that the risk of falls was significantly greater in PwO than in persons without obesity (relative risk [RR] 1.16 [95% CI 1.07, 1.26]), and the risk of multiple falls was also significantly increased (RR, 1.18 [95% CI 1.08–1.29]) [18]. Underlying mechanisms that have been considered responsible include sarcopenic obesity, osteoarthritis in the lower limbs, postural instability, poorer protective responses during a fall, and diabetic neuropathy [3] (Fig. 1).

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is common in PwO and may confer an additional fracture risk through its effects on bone material properties and fall risk [19]. Both conditions are characterized by normal/elevated BMD. Interestingly, increased hip fracture risk has consistently been reported in T2DM, despite the protective effect of obesity per se on these fractures [20]. In a large retrospective observational study of older women, comparison of those with T2DM alone or obesity alone suggested that in the absence of obesity, diabetes may be associated with a higher risk of vertebral and hip fractures than obesity alone [21]. In the same study, in the obesity alone group, non-vertebral non-hip fractures predominated [21]. Nevertheless, further studies are required to establish the impact of coexisting T2DM on fracture risk in PwO.

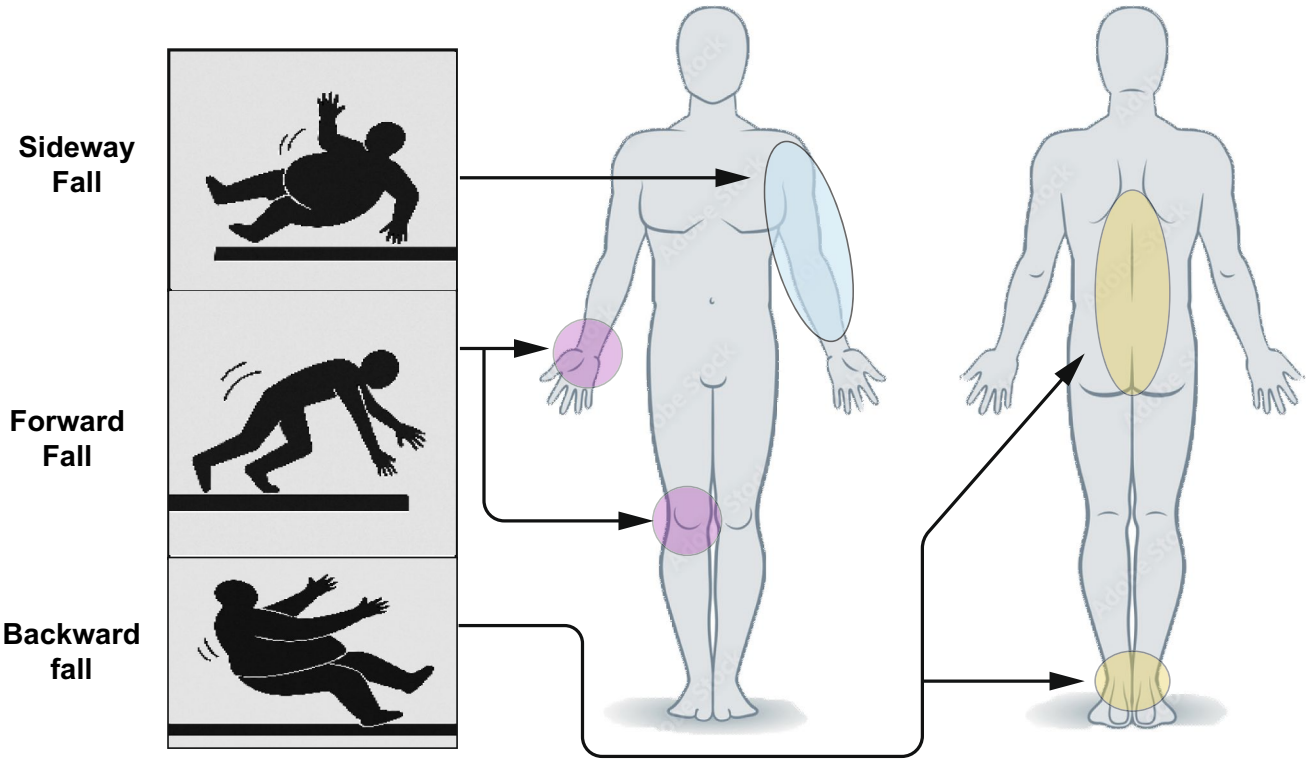

Fig. 1 Fractures and falls in people living with obesity. Obesity can shift the center of gravity, making it harder to maintain balance and potentially increasing the likelihood of a fall. People living with obesity may be more prone to falling backward or sideways, which has been associated with a higher incidence of fractures in the ankles, lower legs, and humerus respectively, —contrasting with wrist and hip fractures that are more common in healthy-weight individuals falling forward

Sarcopenic Obesity

In 2022, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) proposed that sarcopenic obesity should be defined as the coexistence of excess adiposity and low muscle mass/function [22]. The estimated prevalence of sarcopenic obesity varies considerably due to the significant variability in the definition used for both conditions among studies [22]. When muscle strength, instead of muscle mass alone, is evaluated, the estimated prevalence is low, possibly around 10% in older adults, and it increases with age [23]. Finally, sarcopenic obesity has been associated with adverse musculoskeletal outcomes [24]. In a systematic review and meta-analysis, older adults with sarcopenic obesity had a higher risk of falls than individuals with non-sarcopenic obesity (risk ratio: 1.17; 95% CI 1.01, 1.36)(25).

Pathophysiology

The increased fracture risk at specific sites (lower leg/ankle, proximal humerus) despite higher BMD, remains incompletely understood [5, 26]. The higher BMD observed at all skeletal sites in PwO could be attributed to the increased mechanical load applied to the weight-bearing bones (with a possibly greater impact of lean mass than fat mass) [27], and to the positive systemic effect on the skeleton of various hormones, including higher insulin, estrogen production by the adipose tissue, and adipokines (e.g., increased leptin) [5, 26]. Besides BMD, bone microarchitecture parameters and strength are also more favorable [7]. However, the impact forces in a fall are greater in PwO because body weight is greater, whereas the relationship between BMI and BMD is non-linear; the rate of BMD increase is attenuated at very high BMI values. Hence, these “bone advantages” might not compensate for the increased impact forces at play during falls in PwO [28].

Soft tissue padding around the hip region may explain the lower risk of hip fractures in this population [29, 30]. This factor has been highlighted by the reduction in hip fractures observed with the use of energy-absorbing hip pads [31]. The patterns of falls specific to PwO (backward or sideways instead of forward fall) may partly explain the site-dependent association between obesity and fractures [32]. The susceptibility to ankle/distal lower limb fractures in PwO may result from excessive introversion and extroversion of the ankle and lower leg combined with higher body weight [5]. Limited mobility of the lower limbs in PwO may also contribute to the increased risk of falls and the specific pattern of falling. Other factors that may adversely affect

musculoskeletal health in PwO include vitamin D deficiency/insufficiency, given the sequestration of vitamin D in the adipose tissue [33], and hypogonadism in men living with obesity [34] (Fig. 2).

Fat and Bone Interactions in PwO

Obesity and its interaction with bones have been highlighted in this chapter. However, it has been demonstrated that differences in fat distribution are important for bone health. Subcutaneous fat has been briefly mentioned as protective against the impact of falls when located around the hip region (soft tissue padding) [29, 30]. Adipose visceral fat, also called 'central obesity', is out of the scope of this review as its effects on bone health are specific and detrimental [35, 36]. Lastly, data on the role of bone marrow adipose tissue in bone health in PwO are limited, and conflicting results have been reported [37]. Furthermore, adipose tissue is highly active and generates a variety of cytokines and adipokines that possess both pro-inflammatory and anti-inflammatory characteristics, leading to varied impacts on bone cells, influencing both bone resorption and formation.

Summary

Fractures in PwO constitute a substantial public health burden. Their pathogenesis remains to be fully clarified, but an increased risk of falls, sarcopenic obesity, and often comorbid T2DM play a significant role. Evaluating frailty status may help the effort to unravel the complex relationship between obesity and fracture risk [38]. The management of bone health in PwO does not differ substantially from that in the general population [5].

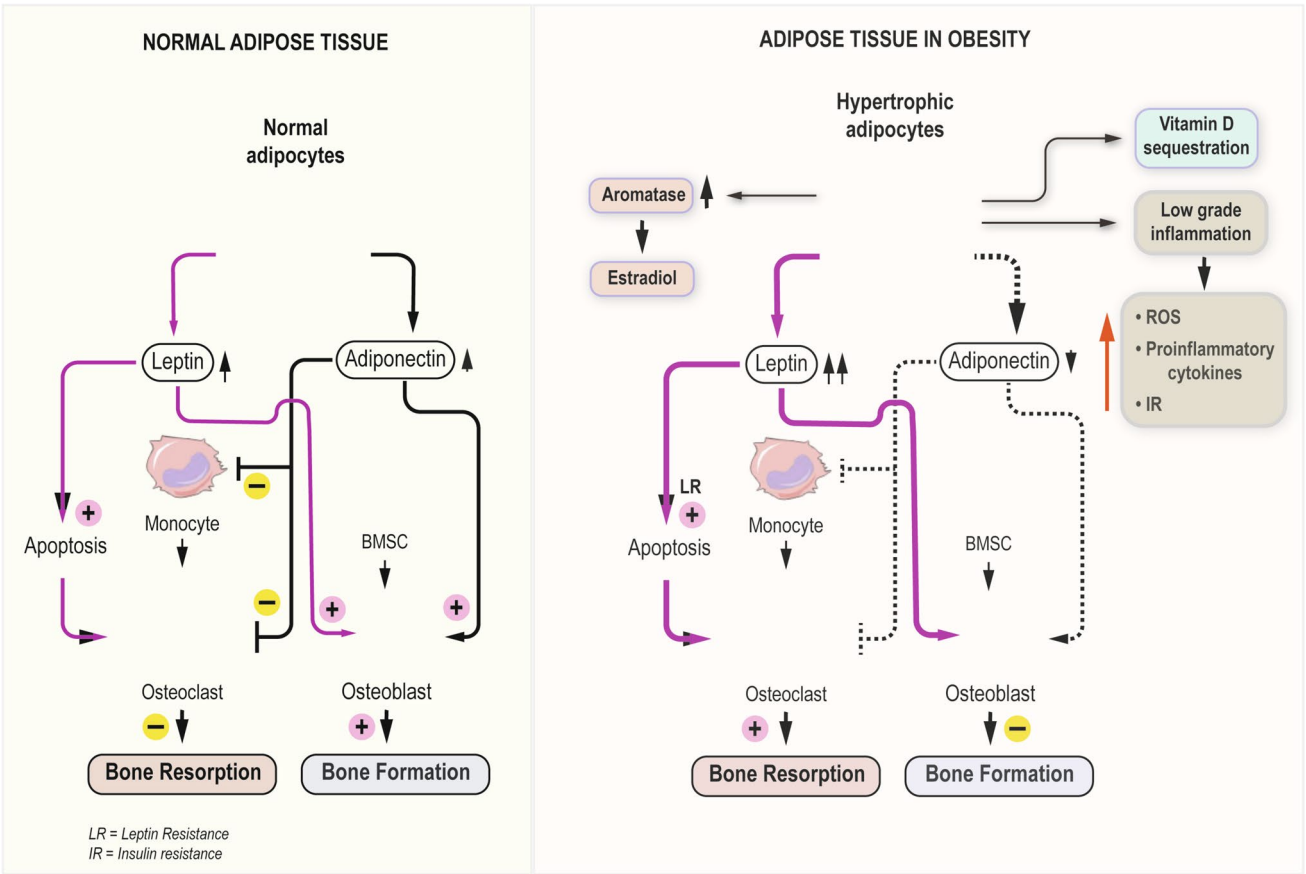

Fig. 2 Pathophysiological interactions between obesity and bone. Adipose tissue acts as an active endocrine organ by secreting adipokines such as leptin and adiponectin, which regulate bone remodeling by modulating osteoblast and osteoclast activity to favor bone formation. In obesity, hypertrophic adipocytes exhibit increased leptin secretion, promoting leptin resistance, and reduced adiponectin production, thereby disrupting normal bone metabolism and favoring bone resorption. Additionally, obese adipose tissue sequesters vitamin D, promotes the release of proinflammatory cytokines and reactive oxygen species, and induces insulin resistance. In addition, increased aromatase activity elevates estrogen levels, leading to hypogonadism in men. ROS, reactive oxygen species; LR, leptin resistance; IR, insulin resistance

Weight Loss and Bone

Effects of Weight Loss on Bone Metabolism

Diet

Existing evidence from interventional studies has shown that weight reduction in PwO through caloric restriction results in increased levels of bone turnover markers (BTMs), especially of bone resorption marker C-terminal telopeptide of type 1 collagen (CTx) as shown in short-term dietary interventions [39–43]. This was corroborated in a systematic review and meta-analysis that reported that interventions lasting 2 or 3 months (but not 6, 12, or 24 months) induced significant increases in serum CTx and osteocalcin (OC), but not procollagen type 1 N-terminal propeptide (P1NP) [44]. Time-restricted eating does not affect CTx or P1NP concentrations as shown in few recent randomized controlled trials (RCTs) [45–47]. Furthermore, caloric restriction has been reported to increase [48] or have a neutral effect on parathyroid hormone (PTH) concentrations [49]. Increases in 25-hydroxyvitamin D (25[OH]D) concentrations have been observed through dietary interventions [48, 50]. RCTs reporting changes in bone metabolism during caloric restriction induced-weight loss are summarized in Table 1.

Drugs

Anti-obesity medications mainly include anorexigens, i.e. molecules that act on the hypothalamus to suppress appetite and food intake. Among them the most featured are the incretin analogs which include the currently widely used glucagon-like peptide 1 receptor agonists (GLP-1RAs: semaglutide, liraglutide) and the dual gastric inhibitory polypeptide receptor (GIPR) and GLP-1R agonist, tirzepatide, along with the emerging double GLP-1 and glucagon receptor (GCGR) agonists (cotadutide, survodutide), and triple GLP-1R, GIPR, and GCGR agonists (retatrutide, mazdutide) [51]. Other compounds under investigation for their anorexigenic efficacy are the long-acting amylin analog cagrilintide, and activin type II receptor (ActRII) antagonists (bimagrumab, garetosmab). Other marketed anti-obesity medications are naltrexone plus bupropion, phentermine plus topiramate, and setmelanotide, which is restricted to use in monogenic or syndromic obesity. Besides anorexigens, orlistat, a lipase inhibitor that prevents food fat absorption from the intestine, has also been used.

While a number of studies have reported on the effects of GLP-1RAs on bone, many of them derive from populations with T2DM, a condition characterized by low bone turnover and poor bone material properties but often normal or even increased BMD [52]. In these clinical studies, in contrast to preclinical studies which showed stimulation of bone formation and reduction of bone resorption, the effects of GLP-1RAs on BTMs were heterogenous [5, 53, 54]. Fewer studies reported the effects of GLP-1RAs on BTMs in individuals with overweight or obesity without diabetes [55–58]. In the larger of these studies to date, liraglutide treatment, either alone or combined with exercise, increased CTx and modestly increased P1NP [57]. In general, clinical studies suggest that treatment with GLP-1RAs either does not affect bone turnover or increases both formation and even more resorption, potentially favoring bone loss. However, this could be because of the induced weight loss and not the GLP-1RA used. Furthermore, some of these GLP-1RAs studies followed a period of dietary measures that induced significant weight loss and thus already had a skeletal effect. From the existing limited evidence, it is unclear if one GLP-1RA analog is more bone sparing than the others. Regarding other parameters of bone metabolism, studies suggest no change in serum calcium, phosphate, PTH, or 25OHD levels with GLP-1RAs [56, 59, 60].

Similarly with GLP-1RAs, preclinical evidence with the newer incretin analogs (dual GLP-1R and GIPR, dual GLP-1R and GCGR, and triple GLP-1R, GIPR, and GCGR agonists) and long-acting amylin analogs indicates that they may have a positive effect on bone [61]; however, supporting clinical data are lacking currently. ActRII antagonists, besides weight loss, could also have a muscle and bone sparing effect [54]. Limited clinical data suggest that orlistat does not alter bone turnover [62, 63].

Bariatric Surgery

Bariatric surgery (BS), including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and biliopancreatic diversion (BPD), is a highly effective intervention for severe obesity, resulting in rapid weight loss and substantial improvements in metabolic health. Among these, SG and RYGB are the most commonly performed procedures [64]. However, beyond weight reduction, bariatric procedures exert significant effects on bone metabolism, mediated through complex changes in mechanical loading, hormonal alterations, and nutrient malabsorption. Evidence suggests that bariatric surgery induces a marked and sustained increase in BTMs, reflective of accelerated bone turnover [65]. Indeed, circulating levels of CTx, P1NP, bone-specific alkaline phosphatase (BALP), and OC rise significantly within 3 to 10 days following surgery, peak within 6 to 24 months, and remain elevated even up to 7 years postoperatively [66]. Both SG and RYGB promote this increase, but RYGB exerts a more pronounced effect, particularly on bone resorption. More specifically, RYGB results in greater

Table 1 RCTs reporting changes in bone metabolism during caloric restriction-induced weight loss

Publication	Study Design	Population	Intervention	Control	Outcomes	
					Changes in weight	**Changes in Bone metabolism**
Riedt et al. 2007 [83]	RCT	44 overweight premenopausal women [n = 44; (± SD) age: 38 ± 6.4 y; (BMI): 27.7 ± 2.1 kg/m^2]	Energy restriction [weight loss (WL) groups] with 1) normal (1 g/d) or (n = 17) 2) high (1.8 g/d) calcium intake (n = 14) for 6 months	Weight maintenance at 1 g Ca/d intake (n = 13)	WL groups lost 7.2 ± 3.3% of initial body weight	No ↓ in BMD or ↑ in BTMs with weight loss at normal or high calcium intake
Lucey et al. 2008 [39]	RCT	276 overweight/obese men and women (BMI 27.5–32.5 kg/m^2; age: 20–40 y)	3 dietary groups with seafood vs control: cod (3 × 150 g/wk) (n = 70), salmon (3 × 150 g/wk) (n = 74), and fish-oil capsules (3 g/d) (n = 66) over 8 weeks	Sunflower-oil capsules (3 g/d (n = 66)	Mean weight (± SD) loss in 8 weeks: 5.14 ± 3.0 kg (5.8% ± 3.2% body weight) in the 4 dietary groups combined	↑ uNTx and CTx (P < 0.05) ↓ OC (P < 0.05) Fish or fish-oil consumption had no effect (P > 0.1) on the changes in BTMs induced by weight loss
Redman et al 2008 [81]	RCT	46 healthy, overweight men and women	(1) 25% CR from baseline energy requirements (CR group) (n = 12); (2) 25% energy deficit by a combination of CR and ↑ aerobic exercise (CR + EX group) (n = 12); and (3) low-calorie diet (890 kcal/d; goal, 15% weight loss) followed by weight maintenance (LCD group) (n = 11) over 6 months	Healthy diet (control group) (n = 11)	Mean ± SE body weight ↓ by −1.0% ± 1.1% (control), −10.4% ± 0.9% (CR), −10.0% ± 0.8% (CR + EX), and −13.9% ± 0.7% (LCD)	↑ CTX in all intervention groups (CR, 23% ± 10%; CR + EX, 22% ± 9%; & LCD, 74% ± 16% vs. control, 4% ± 10%) ↓ BLAP in the CR group (−23% ± 10%) but unchanged in the CR + EX, LCD, and control groups no change in total body or hip BMD for any group
Villareal et al. 2008 [79]	RCT	27 obese older adults (18 women, aged 70 ± 5 years; BMI: 39 ± 5 kg/m^2); 17 in diet + exercise and 10 controls	caloric restriction (↓ by ~ 500–750 kcal/d) + exercise (aerobic exercise and strength exercise) over 12 months	Control group	Body weight ↓ by −10 ± 2 vs ↑ + 1 ± 1% in controls, P < 0.001	↓TH BMD by − 2.4 ± 2.5% in treatment group vs 0.1 ± 2.1% in controls
Hinton et al. 2009 [41]	Secondary analysis of RCT	Obese men (n = 49) and women (n = 64) BMI 30–40 kg/m^2, aged 40.8 ± 0.6 y	12 weeks of moderate energy restriction (~1200 kcal/day) followed by 24 weeks on either a low	NA??or recommended dairy weight maintenance diet	Women lost an average of 11.3 ± 0.4% of initial body weight and men lost 13.0 ± 0.6% over 12 weeks	Women: Total body BMD unchanged (0.33 ± 0.20%) after 12 weeks Men: Total body BMD ↑ (1.34 ± 0.28%) after 12 weeks
Rector et al 2009 [40]	RCT	36 overweight or class I obese (BMI 25.0–29.9 and 30.0–34.9 kg/m^2 women; age: 18–35 y)	(i) energy restriction only (n = 11; DIET); (ii) energy restriction plus non-weight-bearing exercise (n = 12, CYCLE); or (iii) energy restriction plus weight-bearing exercise (n = 13, RUN) over 6 weeks	NA	~5% reduction in body weight in 6 weeks: (DIET = 5.2%; CYCLE = 5.0%; RUN = 4.7%)	↑ OC & CTx with weight loss in all 3 groups (p < 0.05) BALP unaltered by the weight-loss interventions
Foster et al. 2010 [80]	Randomized parallel-group trial	307 participants with a mean age of 45.5 y (SD, 9.7 y) and mean BMI of 36.1 kg/m^2 (SD, 3.5 kg/m^2)	Low-carbohydrate diet (n = 153) over 2 years	Low-fat diet (n = 154)	Participants in both groups lost approximately 11% of initial weight at 6 and 12 months, with subsequent weight regain to a 7% weight loss at 2 years	No differences between groups in changes in BMD or body composition over 2 years

Table 1 (continued)

Publication	Study Design	Population	Intervention	Control	Outcomes	
					Changes in weight	**Changes in Bone metabolism**
Shah et al 2011 [102]	RCT	107 obese older adults, (aged 70 ± 4 years; BMI: 37.2 ± 4.5 kg/m^2); Control (C), n = 27; Diet (D), n = 26; Exercise (E), n = 26; Diet + exercise (DE), n = 28	Caloric restriction (reduced by ~ 500–750 kcal/d) for D and DE ± supervised aerobic exercise for E and DE over 12 months	No intervention in C	Body weight decreased by: − 9.6% in D, − 9.4% in DE, − 1% in E and − 0.2% in C (between-group P < .001)	↓ TH BMD by − 1.1% in DE and − 2.6% in D and ↑TH BMD by + 1.5% in E (between-group P < .001); ↑ CTX and OC in D and ↓ in E (between-group *P* < .001); no change in CTX and OC in DE
Sukumar et al. 2011 [87]	RCT	47 postmenopausal women (58.0 ± 4.4 years; BMI of 32.1 ± 4.6 kg/m^2)	Individual caloric restriction of about 500 to 600 kcal deficit per day) and higher protein intake higher (HP, 24%, n = 26) over 1 year	Individual caloric restriction of about 500 to 600 kcal deficit per day) and normal protein intake (NP, 18%, n = 21)	Significant loss of 11.7% ± 10.1% of fat mass and 2.7% ± 4.0% of lean mass during the intervention with no difference between groups	In the NP vs. the HP group ↓ BMD at the ultradistal radius (–3.3% ± 4.2% vs. –0.9% ± 3.2%), LS (–1.4% ± 3.6% vs. 0.2% ± 3.4%), & TH (–1.2% ± 1.8% vs. –0.4% ± 1.3%)
Josse et al. 2012 [42]	RCT	90 premenopausal women (aged 28 ± 1 years, BMI: 31.5 ± 0.6 kg/m^2); adequate protein and low dairy (APLD), n = 30; adequate protein and medium dairy (APMD), n = 30; high protein and high dairy (HPHD), n = 30	Caloric restriction (reduced by ~ 500 kcal/d) + daily exercise (aerobic exercise and PRT) with varied intakes of protein and dairy foods over 4 months	NA	Weight loss: < 10% at 4 months (- 4.3 ± 0.7kg)	Greater increase in CTX in APLD; greater increase in P1NP in APMD and HPHD
Tang et al. 2013 [86]	RCT	88 obese individuals (n = 43 male, BMI 31 ± 0.7; n = 45 female, 31 ± 0.6)	Energy deficit diet (750 kcal/d less than energy needs) with high protein intake 1.4 g protein·kg-1·d-1 (HP, 22 men, 22 women) over 12 weeks	Energy deficit diet (750 kcal/d less than energy needs) with normal protein intake 0.8 g protein·kg-1·d-1 (NP, 21 men, 23 women)	Significant weight loss in all participants more pronounced in the NP group independent of gender (− 10.1 ± 0.6 vs. − 8.6 ± 0.4 kg; protein-by-time P < 0.05)	BMD ↓ over time in women but not men (− 0.011 ± 0.003 vs. − 0.003 ± 0.002 g/cm2, gender by-time interaction P < 0.01), independent of diet
Brinkworth et al. 2016 [43]	RCT	65 obese adults (aged 51.3 ± 7.1 y, BMI: 33.4 ± 4.0 kg/m^2) on Very-low-carbohydrate (LC) diet: n = 32; and Higher carbohydrate, low-fat (LF) diet: n = 33	caloric restriction (~ 1450–1650 kcal/d]) over 12 months	NA	Weight loss was similar in both groups (LC: −14.5 ± 9.8 kg, LF: −11.7 ± 7.3 kg; P = 0.26	total body BMD ↓ (LC: 1.26 ± 0.10 to 1.22 ± 0.09g/cm^2, LF: 1.26 ± 0.09 to 1.23 ± 0.08 g/m^2; P < 0.001); ↑ CTX (LC: 319.3 ± 142.6 to 396.5 ± 172.0 ng/L, LF: 276.3 ± 100.6 to 365.9 ± 154.2 ng/L; P < 0.001)

Table 1 (continued)

Publication	Study Design	Population	Intervention	Control	Outcomes	
					Changes in weight	**Changes in Bone metabolism**
Villareal et al. 2016 [49]	Multi-center RCT	218 non-obese (BMI:25.1 ± 1.7 kg/m^2), younger (age:37.9 ± 7.2 y) adults	25% caloric restriction (CR group; n = 143) over 2 years	ad libitum (AL group; n = 75)	Body weight change at 24 months in CR group: − 7.5 ± 0.4 kg (< 0.001)	BMD changes in CR vs. AL group at 24 months: LS (− 0.013 ± 0.003 vs. 0.007 ± 0.004 g/cm^2; p < 0.001), TH (− 0.017 ± 0.002 vs. 0.001 ± 0.003 g/cm^2; p < 0.001) From BTMs only BALP differed between CR & AL groups (− 1.5 ± 0.4 vs. 0.9 ± 0.6 U/L; p = 0.001)
Arma-mento-Villareal et al. 2019 [90]	RCT	160 obese older adults (36% women, aged 70 ± 5 years, BMI 36.2 ± 5.1 kg/m^2); Resistance group (R), n = 40; Aerobic group (A), n = 40; Combination group (R + A), n = 40; Control group (C), n = 40	intensive lifestyle interventions = caloric restriction (↓ by ~ 500–750 kcal/d) + exercise over 6 months	No intervention in C	9% decrease in body weight in all groups A, R and R + A	BMD ↓ by − 0.7% in R, − 1.1% in R + A and − 2.6% in A; Greater ↑ in CTX, P1NP and OC in A vs R and R + A
Ilich et al. 2019 [85]	RCT	135 overweight/obese (BMI: 31.5 ± 5.1 kg/m^2) early-postmenopausal women (age: 55.8 ± 4.3 y)	Energy-restricted weight loss diet + 1) low-fat dairy foods (D; 4–5 servings/day) or 2) Ca + vitamin D supplements (S) over 6 months	Energy-restricted weight loss diet + placebo pills (C)	Weight loss of ~ 4% in all groups	No BMD change in 6 months in any group Urinary CTx ↑ in C group and ↓ in S group, no change in D group
Seimon et al. 2019 [88]	RCT	101 postmenopausal women (age: 58.0 [4.2] years; mean [SD] BMI, 34.4 kg/m^2)	Severe (65%−75%) energy restriction over 4 months	Moderate (25%−35%) energy restriction over 12 months	Severe group ↓ more weight vs moderate group at 12 months (effect size, − 6.6 kg; 95%CI, − 8.2 to − 5.1 kg)	↓ TH BMD (effect size, − 0.017 g/cm^2; 95%CI, − 0.029 to − 0.005 g/cm^2) greater at the severe group at 12 months
Weaver et al. 2019 [84]	RCT	96 obese older adults (aged 70.3 ± 3.7 y, 74% women, BMI 35.4 ± 3.3 kg/m^2)	Hypocaloric, nutritionally complete, higher-protein meal plan targeting ≥ 1.0 g protein · kg body weight–1 · d–1 [weight-loss (WL) group; (n = 47) over 6 months	Weight-stability (WS) group targeting 0.8 g protein · kg body weight–1 · d–1, (n = 49)	Significant weight loss in the WL group (6.6 ± 0.4 kg; 8.6% ± 0.4% of baseline weight)	6-mo regional BMD estimates similar to the WS group (all p > 0.05)
Lobene et al 2021 [45]	Sec-ondary analysis of an RCT with a paral-lel arm design	20 overweight and obese adults aged 18–65 y (BMI ≥ 25 kg/m^2	TRE (AL 8-h eating window) over 12 weeks (n = 11)	Non TRE (n = 9)	Significant weight loss (− 3.7% ± 0.5) in TRE group vs. pre-intervention and vs. Non TRE (p < 0.05)	Both groups: ↓ P1NP (p = 0.04) Greater ↓ in P1NP in the Non TRE group (p = 0.07) BMC ↑ in the TRE group vs. ↓ in the Non-TRE group

Table 1 (continued)

Publication	Study Design	Population	Intervention	Control	Outcomes	
					Changes in weight	**Changes in Bone metabolism**
Razny et al. 2021 [47]	RCT	64 middle aged Overweight/Obese individuals (55% women, aged 41.0 ± 9.9 y) in Isocaloric diet with n-3 PUFA, n = 13; Isocaloric diet with placebo, n = 14; Low-calorie diet with n-3 PUFA, n = 23; Low-calorie diet with placebo, n = 14	caloric restriction (1200 kcal/d for women and 1500 kcal/d for men) ± n-3 PUFA (1.8 g/day) for 3 months		weight loss by 7% in low-calorie diet, independently of n-3 PUFA supplementation	No change in CTX in isocaloric diet. ↑ in CTX in caloric restriction diets independent of n-3 PUFAs supplementation (0.37 ± 0.17 vs 0.31 ± 0.12 ng/mL, $p < 0.001$)
Papageorgiou et al. 2023 [46]	Secondary analysis of an open-label 6-month RCT	42 participants (76% women), age (median) 47 y, BMI (median) 27.8 kg/m^2	TRE (AL eating within 12 h) over 6 months (n = 23)	SDA (n = 19)	Slight median weight loss of 0.6 kg for both intervention arms pooled together	Among weight loss responders (≥ 0.6 kg weight loss): ↓ CTx after TRE but ↑ after SDA (between-group differences $p = 0.041$ P1NP: no difference between groups ↓ BMC after SDA ($p = 0.028$) but unchanged after TRE ($p = 0.31$)

* Including reduced calorie consumption and increased physical activity designed to achieve and maintain ≥ 7% weight loss

Abbreviations: AL: ad libitum; BALP: Bone alkaline phosphatase; BMC: Bone mineral content; BMD: Bone mineral density; BMI: Body mass index; BTMs: bone turnover markers; CR: caloric restriction; CTx: C-terminal telopeptide of type I collagen; ILI, intensive lifestyle intervention; LS: lumbar spine; OC: osteocalcin; P1NP: N-terminal propeptide of type I collagen; RCT: randomized controlled-trial; SDA: Standard dietary advice; TBS: trabecular bone score; TH: total hip; TRE: Time-restricted eating; uNTx: urinary N-telopeptides of type I collagen; n-3 PUFA: Omega-3 polyunsaturated fatty acid

increases in CTx, P1NP, and tartrate-resistant acid phosphatase isoform 5b (TRAcP5b), BALP and PTH than SG [67]. Especially for CTx, its levels may rise by 50% to 300% following RYGB [65]. This pattern suggests a dominant bone resorption profile post-RYGB, with relatively less bone formation activity. These findings are corroborated by randomized trials and meta-analyses. One RCT [68] demonstrated approximately 100% greater increases in CTx and P1NP at one year post-RYGB compared to SG, further highlighting the differential skeletal responses to these procedures. BALP tends to exhibit more moderate fluctuations, its levels typically peaking within the first postoperative year and showing more pronounced changes following RYGB than SG [67, 69]. These findings are supported by other longitudinal studies [70, 71], confirming also the gradual decline in BTMs, between 12 and 24 months. However, during follow-up, BTMs may remain above baseline, indicating partially sustained increase in bone remodeling activity [71]. This persistent turnover could potentially lead to reduced bone mass and increased fracture risk over time.

Although BPD is performed less frequently due to its higher risk of complications, it is nonetheless associated with substantial alterations in bone metabolism. The skeletal response to BPD is characterized by an early and robust increase in bone resorption, as evidenced by marked elevations in CTx shortly after surgery. In contrast, markers of bone formation, such as OC, initially decrease, suggesting a transient suppression or lag in osteoblastic activity. However, this decline is followed by a progressive rise over time, indicating a delayed anabolic response that may partially offset the heightened resorption observed in the early postoperative period [71]. This pattern reflects the greater metabolic and nutritional impact of procedures with a malabsorptive component, such as RYGB and BPD, which appear to exert a more pronounced effect on bone remodeling dynamics than solely restrictive techniques.

In contrast to the above, a meta-analysis concluded that there were similar changes in CTx, P1NP, calcium, and 25OHD between RYGB and SG, while OC and PTH levels were significantly less elevated in SG [72]. However, this meta-analysis included studies with substantial heterogeneity and its findings should therefore be interpreted with caution. These data suggest that RYGB may impose a greater strain on calcium–vitamin D–PTH homeostasis, potentially due to its larger malabsorptive component. Other evidence supports an increase in PTH levels from 12 to 24 months, likely reflecting a compensatory response to subtle negative calcium balance [67, 71]. These biochemical patterns highlight the complex interplay between bone turnover and mineral homeostasis following BS. In summary, BS leads

to an overall increase in bone turnover, with bone resorption exceeding bone formation. These alterations are more pronounced following RYGB compared to SG, likely due to greater malabsorption and amount of weight lost. Notably, BTMs do not appear to return to preoperative levels over time, suggesting a sustained impact on bone metabolism [73].

Effects of Weight Loss on Bone Mass

Diet

Of the studies that have investigated changes in bone mass in response to diet-induced weight loss in overweight or PwO, the results have been highly variable, with increases [74, 75], decreases [48, 76–79], and no change [80–85] in bone mass being reported. In addition, gender specific BMD changes [86] and site-specific BMD changes [87] have been reported under caloric restriction, while a greater severity of energy restriction also induces a more pronounced loss in bone mass [88]. An older systematic review and meta-analysis of randomized controlled trials, pilot studies, and cohort studies reported that dietary weight-loss interventions were associated with a small but statistically significant reduction in total hip (TH) BMD but not at the lumbar spine (LS) for interventions with durations of 6,12, or 24 months, although this meta-analysis was limited by widely varying types of dietary interventions and lack of a control group in the majority of the studies included [44]. The more consistent bone loss at the hip region compared to LS could be due to degenerative changes of the LS affecting DXA results at this site or due to the different distributions between cortical and trabecular bone at these sites [5]. A recent meta-analysis specifically investigating the effects of time-restricted eating in bone mass based on 7 RCTs did not show a significant reduction in total body BMD [89]. In general, the inconsistency of data regarding bone loss as part of dietary interventions might be due the smaller magnitude of weight loss that accompanies these measures. Of note, it has been reported that weight loss amounting to 7–10% of an individual's baseline weight is necessary in order for bone effects to become apparent [90, 91].

Physical Activity

Research from both epidemiological studies and clinical trials has consistently shown that regular physical activity positively affects bone health and body composition [92, 93]. Exercise plays a key role in building optimal bone mass during youth and slowing bone loss with age, particularly in individuals with lower body fat [94]. The effectiveness of exercise largely depends on its nature. High-impact and resistance training are especially efficacious in boosting BMD, and thus strengthening bones and lowering the risk of fractures [95]. A large body of research supports these benefits, showing consistent and positive outcomes from such training [96].

In contrast, there is limited and inconsistent evidence regarding how aerobic and combined exercise programs affect bone health in PwO. Physical activity can influence bone health through mechanical loading, improving both BMD and bone structure. Additionally, it contributes to an improvement of body composition by increasing muscle mass and reducing fat [96].

Despite these known benefits, the interaction between obesity and exercise effects on bone remains poorly understood [97]. Most research to date has focused on individuals with normal weight, making it uncertain whether these results can be applied to populations with overweight or obesity. While different exercise types—such as aerobic and resistance training—have been tested in PwO to assess their effects on bone, the findings have been varied and inconclusive [97].

Evidence from separate meta-analyses and a systematic review [98–101] indicates that physical training has a limited effect on whole-body BMD (WB BMD) in individuals with overweight or obesity in whom diet or anti-obesity medication are not provided [98, 99]. Specifically, in males, little to no effect was observed on WB BMD, femoral neck (FN) BMD, or LS BMD with exercise(99) alone.

These findings suggest that the osteogenic benefits of exercise may be diminished by the weight loss it often induces. However, physical activity still appears to offer a protective role by potentially offsetting the negative impact of weight loss on BMD in this population. Overall, the results support the use of physical activity as a means to promote weight loss while helping to preserve bone mass in overweight or obese individuals [102].

However, current evidence remains insufficient to recommend any specific type of exercise for improving bone health in obese individuals [98]. Further research is required to better understand how different forms of physical activity influence BMD in this group of subjects.

Drugs

Data from preclinical studies with GLP-1RAs, mainly obtained with exenatide and liraglutide, have shown improved BMD, trabecular and cortical volume, bone microstructure and mechanical properties [103–105]. However, again, findings from clinical studies are inconsistent [5, 53, 54]. No change [55, 106] or slight reduction [57, 60] of BMD has been reported in most of them, an effect that could, at least partly, be due to the degree of weight loss.

Interestingly, in non-diabetic individuals with obesity, liraglutide treatment resulted in BMD losses at both the LS and the hip while the combination of liraglutide with exercise preserved BMD despite the considerable weight loss [57].

Parameters of bone quality and quantity besides BMD have also been investigated. Bone mineral content (BMC) did not change with liraglutide treatment [55], neither did volumetric BMD (vBMD) and bone microstructure [106]. Similarly, semaglutide treatment did not affect trabecular BMD at the first lumbar vertebra evaluated by CT scan [107], or radial vBMD evaluated by HR-pQCT (although it decreased tibial vBMD) [58] or bone material strength index (BMSi) evaluated by microindentation [58]. Finally, GLP-1RA treatment (dulaglutide or semaglutide) increased trabecular bone score (TBS) [60]. All these findings contrast the reduction of BMD in some studies with GLP-1RA described above and imply that this small BMD decrease along with the preserved bone material properties is presumably not able to affect fracture risk [108].

Limited preclinical evidence from the emerging other classes of incretin analogs has suggested increased BMD and bone strength [109, 110] but there are no data from human studies. ActRII antagonists may increase bone mass along with muscle mass [54]. Indeed, in a recent study in mice, bimagrumab increased trabecular and to a lesser degree cortical bone [111], but again no data in humans are available at present. Orlistat did not change BMD or BMC compared to placebo in a small RCT [63].

Collectively, based on the currently available evidence limited by short-term follow-up data, anti-obesity medications do not appear to induce a clinically significant change in bone mass. It seems likely that combination of these medications with exercise, and perhaps with ActRII antagonists, will mitigate or even prevent any weight loss-induced adverse bone effects, but this still needs to be proven.

Bariatric Surgery

Early case reports have described fragility fractures following jejunoileal bypass despite vitamin D supplementation, suggesting that surgery-induced malabsorption could affect bone metabolism [65] Numerous clinical studies and meta-analyses have since confirmed that BMD decreases significantly within the first year post-surgery, especially at weight-bearing skeletal sites such as the TH and FN [65, 112, 113].

The extent of BMD loss appears to vary according to the surgical procedure. Mixed restrictive-malabsorptive techniques, particularly RYGB, have been consistently associated with greater reductions in BMD compared to purely restrictive methods like SG [65, 112]. A large body of evidence confirms that BMD loss is more evident at the TH (up to − 11% at 12 months), followed by the FN and the LS and a more pronounced decrease in BMD has been reported in patients over 40 years of age, post-menopausal women, or with longer postoperative follow-up [112]. Although BMD loss tends to subside after the initial rapid weight loss phase, deterioration continues beyond year one, indicating mechanisms beyond mere mechanical unloading [65]. These include nutrient malabsorption, hormonal alterations, and modifications in body composition [65]. Long-term studies further confirm the sustained impact of bariatric surgery on BMD. Over an average follow-up of 9.3 years, individuals who underwent RYGB or SG exhibited significantly lower areal BMD at the TH, FN, and radius compared to non-surgical controls, with no difference between RYGB and SG groups [114]. Notably, the magnitude of initial weight loss was not associated with BMD outcomes, reinforcing the notion that bone alterations are not solely weight-dependent [114]. In a meta-analysis, RYGB negatively impacted bone quality and resulted in significant vBMD reductions at all evaluated cortical and trabecular sites. Time since surgery correlated with progressive vBMD decline at all sites except TH. Additionally, using QCT and HR-pQCT as a reference, DXA tended to underestimate LS and overestimate TH bone loss postoperatively [115]. Moreover, one study assessed the applicability of the TBS in PwO before and after SG. The findings indicate that increased abdominal adiposity may interfere with image acquisition due to greater soft tissue thickness, potentially resulting in artifactual reductions in baseline TBS values. Consequently, the authors concluded that TBS should be interpreted with caution in PwO and elevated waist circumference. Moreover, the study demonstrated that following SG, bone quality—as evaluated by TBS— was compromised in up to 25% of patients [114].

Effects of Weight Loss on Bone Histomorphometry

Research on bone loss in PwO during weight loss typically uses noninvasive methods like DXA and biochemical markers rather than histomorphometry, which, despite its detailed insight into bone microarchitecture, is restricted to clinical studies in populations with obesity due to ethical and procedural concerns [44, 116].

In a preclinical model of dietary-restriction induced weight loss, histomorphometric assessments of the tibial shafts and long bones demonstrated an enlargement of the marrow cavity and cortical thinning compared to weight-stable or higher BMI counterparts [117], reflecting bone's sensitivity to nutritional changes.

In the Framingham Offspring Cohort clinical study (including 769 women, 595 men; mean age 70 ± 8 years), HR-pQCT scans revealed that both short-term (~ 5% over 6 years) and long-term (~ 10% over 40 years) weight loss in

older adults was linked to reduced peripheral BMD, compromised microarchitecture, and reduced bone strength, especially in the tibia. These associations were more pronounced in women and for long-term weight loss, emphasizing how mechanical unloading in weight loss may heighten skeletal fragility [118].

Effects of Weight Loss on Bone Fragility

Several studies have specifically examined fracture incidence following weight reduction interventions, particularly in postmenopausal women and bariatric surgery populations.

In a retrospective cohort study using Swedish national databases, the authors investigated fracture risk after RYGB in 38,971 morbidly obese subjects with and without T2DM for a median follow-up time of 3 years. The study demonstrated a significant increase in any fracture accounting for up to 26% and 32% for patients with and without T2DM, respectively. Fracture incidence increased progressively over time following bariatric surgery and persisted even after patients stabilized at their post-surgical reduced weight. This elevated risk was independent of the amount of weight lost or the use of calcium and vitamin D supplementation [119].

Similar results were obtained, by a nested case–control study examining fracture patterns in severely obese patients after bariatric surgery. The study included 12,676 patients who underwent either of the following 4 types of bariatric surgery (gastric banding; SG; RYGB; biliopancreatic diversion) and were age and sex matched with 38,028 obese and 126,760 non-obese controls [120]. After a mean follow-up of 4.4 years adjusted fracture risk was significantly higher in the bariatric group compared with the obese (relative risk:1.38; 95%CI 1.23–1.55) and the non-obese groups (relative risk: 1.44; 95%CI 1.29—1.59) [120]. Regarding the fracture site, the risk of upper limb and clinical spine fracture almost doubled and the risk of pelvic, hip, or femur fractures increased 2.5-fold after surgery. However, when adjusted for multiple confounders, including comorbidities and duration of follow up, only BPD-DS was clearly associated with an increased fracture risk (adjusted relative risk: 1.60; 95%CI:1.25 −2.03).

Data from studies employing weight loss interventions to improve glycemic control in invididuals with obesity and T2DM, also highlighted the association of increased fracture risk followed by significant weight losses [121, 122].

Post-hoc analyses from the Look AHEAD Randomized Clinical Trial demonstrated that intensive lifestyle intervention leading to significant weight loss (6.0% over a median intervention period of 9.6 years) increased the risk of a frailty fracture (a composite of the first occurrence of a hip, pelvis, upper arm or shoulder fracture), by 39% compared to Diabetes Support and Education group that was associated with lower weight loss (3.5%) [121, 122].

Collectively, data from clinical studies suggest that the metabolic benefits of weight loss in PwO may be counterbalanced by an increased incidence of fragility fractures, particularly in vulnerable populations such as postmenopausal women or patients undergoing drastic weight loss following bariatric surgery.

Conclusion

Evidence suggests that PwO have lower bone turnover, higher BMD values and better bone microarchitecture and strength compared to normal-weight individuals. Furthermore, a reduced risk of hip and wrist fractures has been reported, while, in contrast, ankle and lower leg fractures, and perhaps humerus fractures, seem to be more frequent despite the higher BMD, again when compared to normal-weight individuals. The higher incidence and the different pattern of falls, coexistent T2DM, hormonal and cytokine changes, and sarcopenia are considered to confer to this paradox. Regarding the risk of vertebral fractures, results are inconclusive. Mortality does not seem to increase after a fracture in PwO.

In contrast, weight loss, regardless of whether it is achieved with diet, anti-obesity medications, or bariatric surgery, is characterized by an increase in bone turnover, and predominantly in bone resorption which results in a reduction of BMD [123]. This reduction is more prominent at the cortical bone rich sites, as the hip, compared to the predominantly trabecular bone sites, such as the LS. Fracture risk is increased, mostly at the hip and wrist following bariatric surgery and at the sites of major osteoporotic fractures following caloric restriction. Importantly, this increase in the risk of fracture is observed around 3 years following the intervention. Concurrent changes in mechanical loading, loss of muscle mass, hormonal alterations, and nutrient/vitamin deficiencies are considered contributing factors. Skeletal adverse effects depend on the magnitude of weight loss and become evident after a loss of at least 7–10% of body weight. Skeletal effects are more prominent with RYGB compared to SG.

General measures that should be implemented to mitigate the unfavorable skeletal effects of weight loss include systematic resistance training, vitamin D supplementation, adequate calcium and protein intake, and smoking cessation. The needs for calcium and vitamin D supplementation depend on the intervention, being considerably higher after bariatric surgery, especially RYGB [73]. In individuals with low BMD or other risk factors predisposing to increased fragility, bone-specific treatments could also be considered. Given the increase in bone turnover rate with weight loss, antiresorptive medications (e.g., alendronate, risedronate) should be used as first line treatment.

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Declarations

Competing interests The authors declare no competing interests.

Human/animal studies informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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