
Effects of obesity treatments on bone mineral density, bone turnover and fracture risk in adults with overweight or obesity

Abstract

Background: New evidence suggests that obesity is deleterious for bone health, and obesity treatments could potentially exacerbate this.

Materials and methods: This narrative review, largely based on recent systematic reviews and meta-analyses, synthesizes the effects on bone of bariatric surgery, weight loss pharmaceuticals and dietary restriction.

Results and conclusions: All three obesity treatments result in statistically significant reductions in hip bone mineral density (BMD) and increases in bone turnover relative to pre-treatment values, with the reductions in hip BMD being strongest for bariatric surgery, notably Roux-en Y gastric bypass (RYGB, 8%–11% of pre-surgical values) and weakest for dietary restriction (1%–1.5% of pre-treatment values). Weight loss pharmaceuticals (orlistat or the glucagon-like peptide-1 receptor agonist, liraglutide) induced no greater changes from pre-treatment values than control, despite greater weight loss. There is suggestive evidence that liraglutide may increase bone mineral content (BMC) – but not BMD – and reduce fracture risk, but more research is required to clarify this. All three obesity treatments have variable effects on spine BMD, probably due to greater measurement error at this site in obesity, suggesting that future research in this field could focus on hip rather than spine BMD. Various mechanisms have been proposed for BMD loss with obesity treatments, notably reduced nutritional intake/absorption and insufficient exercise, and these are potential avenues for protection against bone loss. However, a pressing outstanding question is whether this BMD reduction contributes to increased fracture risk, as has been observed after RYGB, and whether any such increase in fracture risk outweighs the risks of staying obese (unlikely).

Keywords: bariatric surgery; diet reducing; glucagon-like peptide-1 receptor agonists; orlistat; weight loss.

Introduction

There are currently over 2 billion adults in the world with a body mass index (BMI) in the overweight or obese range [1]. This obesity epidemic imposes an enormous burden on individuals and societies by increasing the incidence and severity of health complications and diseases affecting multiple aspects of the body and mind.

Bone is one of very few aspects of health that have been considered to not be adversely affected by obesity. In fact, obesity was even considered to provide protection against osteoporosis [an excessive loss of bone mineral density (BMD) that predisposes to fractures], due to the effect of weight-bearing to increase BMD [2]. However, this stand has been challenged recently, with observations that obesity is associated with deficiencies in nutrients important to bone health such as calcium [3] and vitamin D [4, 5], in addition to perturbations in bone metabolism [5], possible bone loss [6] and higher fracture risk [7]. Indeed, while low BMI (<18.5 kg/m²) is clearly associated with low BMD and a higher risk of fracture, new research shows that the relationship between higher BMIs and fracture risk is non-linear [8]. Now, obesity is no longer considered to be protective against osteoporosis and fracture [9–12]. Obesity per se is increasingly recognized as a state of heightened fracture risk in both men and women [7, 8]. For instance, a study...
involving over 60,000 women from 10 countries revealed an association between BMI ≥ 30 kg/m² and increased risk of ankle and upper leg fractures (with reduced risk of wrist fractures) [7], and a similar correlation was also found in men, albeit only after correction for the increased BMD generally associated with obesity [8], and not without controversy [13]. Interestingly, these fracture sites [7] differ from the fracture sites most commonly seen in osteoporosis, which are the wrist, upper arm, rib, hip and spine [7]. A number of possible contributors to compromised skeletal health in obesity have been proposed, including but not limited to reduced vitamin D bioavailability [9, 14] and an inflammatory state that increases bone turnover [15]. Moreover, individuals with obesity have a heightened risk of mobility impairment [16] and falls [17, 18], due to factors such as poor compensatory stepping responses and postural instability [17] as well as intramuscular fat infiltration which reduces muscle strength [9, 19, 20]. While fat padding surrounding particular bones such as the pelvis and femur lessens the impact of falls [21], it is conceivable that falls in obese individuals might lead to a greater force on other bones due to the laws of physics. Indeed, falls in individuals with obesity are often more serious than in non-obese individuals, resulting in longer hospitalisations [22].

Not only does obesity impose functional risks for bone health, treatments for obesity have now been shown to impair the intake and absorption of nutrients important for bone health, to compromise bone metabolism, to reduce BMD and possibly also increase fracture risk. These effects of obesity treatments – specifically bariatric surgery, weight loss pharmaceuticals and dietary restriction – will be synthesized in the current narrative review, which is largely based on systematic reviews and meta-analyses that have been recently published in this area. By drawing together the effects of these three obesity treatments on bone into a single review, our intention is to crystallize gaps in knowledge that may not be apparent when reflecting on individual treatment modalities, as well as considering the relative risks versus benefits of obesity treatments overall.

Overview of bone physiology

An understanding of general principles of bone physiology is important for appreciation of this review.

Structure of bone

There are two major types of bone tissue; cortical bone (also called compact bone), which is dense and solid, and makes up the characteristic outer hard layer of bones and forms the majority of the long bone structure, and trabecular bone (also called cancellous bone, or spongy bone), which is softer and 'spongier' in appearance, as the name implies, and can be found in the middle of bones such as vertebrae and the long bones [23].

Both cortical and trabecular bone have various types of bone cells interspersed throughout their structures. These include osteoprogenitor cells, osteoblasts, osteocytes and osteoclasts. Osteoprogenitor cells, the precursors to osteoblasts, are found on both the interior and exterior surfaces of bone, and also in association with bone microvasculature [24]. Osteoblasts are responsible for bone formation, as they function to secrete and calcify the bone matrix. Once osteoblasts are enveloped in the mineralized bone matrix, they stop secretion of matrix and are referred to as osteocytes. Osteocytes are the most abundant type of bone cell, and are involved in regulating the balance between bone secretion by osteoblasts and bone resorption by osteoclasts. Osteoclasts arise when mononuclear haemopoietic cells fuse to form larger, multinucleated cells. These cells are located primarily on bone surfaces, where resorption takes place [24, 25].

Bone turnover

Even in the absence of significant skeletal injuries or disorders, bone is continuously involved in a process of remodeling (bone formation and resorption), which contributes to calcium homeostasis and repairs micro fractures [26]. The volume of bone that is both formed and resorbed during this continuous process at a given time is referred to as bone turnover [27]. Bone formation and resorption are coupled, as bone resorption by osteoclasts is closely followed by osteoblast formation and bone secretion [28]. Therefore, in instances of bone catabolic states, there is an increase in both bone formation and resorption [29].

Analysis of bone

Dual energy X-ray absorptiometry (DXA)

DXA is the standard reference method for measuring BMD, a factor used for the diagnosis of osteoporosis [30]. BMD is dependent on the net balance between bone formation and resorption, however, these changes cannot be detected by DXA scans until substantial bone turnover has taken place, which can take between 6 and 12 months depending on the stimulus [10, 31]. Moreover, the precision...
of DXA scans has been shown to decline with increasing BMI [32], as well as when measuring BMD in people who are not weight-stable (i.e. undergoing dynamic changes in body weight) [33]. These imprecisions are due to several reasons, notably difficulties in positioning patients/participants on the scanning bed, fractures in the vertebrae, which heighten apparent spinal BMD, and artifact errors caused by changing amounts of fat tissue surrounding bones [10, 12, 34]. Indeed, the presence of fat around bone can result in unpredictable errors in DXA bone measurements of up to 20%, as determined by experiments where phantom bone models or lean participants were wrapped with plastic bags containing semi-solid fat [33, 35]. This error may be due in part to artifact effects of soft tissues, as well as to the effect of fat mass and changes in fat mass to alter the distance between the X-ray source and the bone site under investigation [33]. Another technical limitation of DXA is that its dual energy X-ray sources can only measure two tissue types at any one time (e.g. bone and soft tissue). Thus, being a two-compartment model for the determination of body composition, DXA calculations assume certain ratios of fat to lean tissues to determine the density of fat, lean and bone tissues. However, these assumed ratios may be violated in obesity and with weight changes (e.g. after weight loss) [33]. Despite these limitations, DXA is still used and recommended as the principle method for assessing bone mass, even in obesity [10, 31, 36]. Nevertheless, it has been suggested that when conducting and interpreting data from studies that present potential DXA measurement errors (as in the case of obesity treatments), it is crucial that the DXA scanner be calibrated correctly [36], and that other modes of assessing bone mass are used for confirmation.

**Computed tomography (CT)**

Some of the limitations of using DXA to track bone in people with obesity in response to weight loss may be overcome by the use of computed tomography (CT), which has greater sensitivity for detecting changes in bone density [37] and – unlike DXA – is able to provide insights into micro architectural changes in cortical and trabecular bone [23]. However, this technique is not widely available for bone analyses in clinical or research settings, and – when it is available – peripheral sites such as the forearm or foreleg are more amenable to CT scanning than the traditional sites of bone analysis for the assessment of fracture risk (hip and spine) [38]. A further deterrent to the use of CT in serial analyses of human bone is the fact that with current technology, radiation exposure from a CT scan is approximately 10-fold greater than that of a DXA scan [39]. As such, there is limited research that has assessed changes in bone using CT during obesity treatments.

**Markers of bone turnover**

Due to the above limitations of DXA scanning, especially in individuals with obesity and in those undergoing weight flux, as well as the above limitations of CT scanning, biomarkers (or markers) of bone turnover can and should be used as an adjunct to DXA scans when assessing bone health. In our recent systematic review and meta-analysis [34], we noted that markers of bone turnover that have been commonly used include N-terminal propeptide of type I procollagen (P1NP) and osteocalcin for bone formation, and C-terminal telopeptide of type I collagen (CTX) and N-terminal telopeptide of type I collagen (NTX) for bone resorption [40–42]. P1NP and CTX have recently been recommended as the standardized reference markers for bone formation and resorption, respectively [40–42]. Other markers include serum bone-specific alkaline phosphatase (BAP) for bone formation, and the ratio of fasting concentrations of urinary hydroxyproline/creatinine (fU-OHpr/creat) and serum tartrate-resistant acid phosphatase (TRAP5B) for bone resorption, but these are less commonly measured and will not be discussed in further detail here.

The marker of bone formation P1NP is produced by the enzymatic breakdown of type I procollagen, which is secreted by osteoblasts [23]. While P1NP could originate from other sources besides bone, these non-skeletal sources contribute minimally to circulatory fractions, as these tissues have a slower turnover rate than bone [43]. Osteocalcin, an osteoblast-derived cytokine, is another sensitive marker of osteoblast activity, and therefore bone formation [25]. Although it is not now considered a standard reference marker of bone formation, its widespread use in previous studies over many years has contributed to its ongoing use, as a means of comparison of bone turnover in new studies with that reported in previous studies. A recent study spurred potentially further interest in the measurement of serum osteocalcin levels as a marker of bone formation, by showing a significant association between serum osteocalcin concentrations with incident hip fracture risk in older men, whereas there was no significant association between serum P1NP concentrations and hip fracture after adjusting for other relevant risk factors in this population [44]. A potential source of error with osteocalcin, however, is that due to the incorporation of osteocalcin into the bone matrix, it has been suggested...
that osteocalcin fragments may be released even during bone resorption [45–47].

CTX and NTX are formed by osteoclasts from the degradation of type I collagen during bone resorption. One difficulty when assessing these telopeptides as bone resorption markers is their diurnal variability. Sample collection from serum or urine in a fasted state has been shown not only to reduce these variations, but also to increase analyte sensitivity [48].

**Effect of obesity treatments on bone**

A number of clinical trials have investigated BMD and bone turnover in response to obesity treatments, notably bariatric surgery, weight loss pharmaceuticals and dietary restriction. The mass of information available from these clinical trials has recently enabled systematic reviews and meta-analyses to be conducted. Looking at these three obesity treatments together, as opposed to separately as is usually the case, has revealed interesting commonalities that help to inform further research and clinical practice in the field. These findings are summarized in Table 1.

**Effect of bariatric surgery on bone**

Bariatric surgery is an increasingly prevalent treatment option for obesity with demonstrated short and long term efficacy for weight loss and in reducing obesity-associated co-morbidities [49]. The three most commonly performed bariatric surgeries are Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (gastric banding), and sleeve gastrectomy [50]. In RYGB, the stomach is stapled to create a small pouch, which reduces the amount of food that can be consumed. This small pouch is then directly attached to the small intestine, which effectively bypasses the rest of the stomach and the upper part of the small intestine, thus considerably reducing the surface area available for absorption of nutrients [50]. Patients undergoing RYGB typically lose 35% of their initial body weight, which corresponds to a loss of 62%–75% of excess body weight [51]. Gastric banding involves an adjustable band being placed around the stomach, thereby allowing only small amounts of food to be consumed at a time. It typically results in a loss of between 20% and 30% of initial body weight [52], which is equivalent to a loss of 41%–54% of excess body weight [49]. Sleeve gastrectomy is a newer but increasingly common procedure in which over 80% of the stomach is removed, resulting in nutrients rapidly passing through the stomach and altering gut hormones and metabolism [50, 52]. It can produce body weight losses of between 20% and 30% of initial body weight, which is equivalent to a 45%–64% of excess body weight [10, 52].

Despite the successful weight loss outcomes of bariatric surgery for patients with obesity, detrimental effects on bone have been reported [10, 53]. BMD has been found to be significantly decreased post bariatric surgery, with differing results between surgery types [10, 54–56]. Most available information about the effects of bariatric surgery on bone comes from studies on RYGB. It appears to have a greater detrimental effect on bone than gastric banding or sleeve gastrectomy – not only in terms of reducing BMD, at least at the hip, but also in terms of increasing the risk of osteoporotic fractures [10, 50, 55–58]. Hip BMD has been shown to decrease by 8%–11% from pre-surgical values in the first 12 months after RYGB [10, 50, 56, 59, 60]. A systematic review and meta-analysis of 12 trials (three randomized controlled trials and nine quasi experimental trials) showed that reductions in hip BMD after RYGB or another less common bariatric procedure, biliopancreatic diversion, were significantly greater than the reductions induced by gastric banding or sleeve gastrectomy, when measured 12 months post surgery [56]. The change from pre-surgical values in hip BMD in the RYGB group (nine trials involving RYGB and one trial involving biliopancreatic diversion) was −0.12 g/cm², and in the other surgical group (one trial involving gastric banding and two trials involving sleeve gastrectomy) it was −0.04 g/cm² [56]. These findings for sleeve gastrectomy are in keeping with a trial of shorter duration in 29 women, which was not included in the above-mentioned systematic review and meta-analysis [61]. Indeed, at 6 months post sleeve gastrectomy, BMD losses relative to pre-surgery values were observed at the hip (−0.059 ± 0.030 g/cm² or −5.2%) and femoral neck (−0.072 ± 0.046 g/cm² or −70%), with a slight but significant decrease at the lumbar spine [61].

One disadvantage of studies that investigate pre-versus post-surgical BMD is that they do not control for changes in BMD that would have occurred over time in the absence of any intervention. Addressing this limitation, a systematic review and meta-analysis published in 2015 investigated 10 studies that compared BMD between a non-surgical control group (n = 261) with participants that had bariatric surgery (n = 241), with DXA scans being conducted at 10 months to 10 years post-surgery [55]. There were seven studies involving RYGB, one study involving a mixture of RYGB and another bariatric procedure, namely vertical banded gastroplasty, one study on vertical banded gastroplasty alone, and one study with
Table 1: Summary of effects of obesity treatments on hip and spine bone mineral density (BMD), markers of bone turnover and fracture risk.

<table>
<thead>
<tr>
<th>Obesity treatment</th>
<th>6-24 months after commencement of treatment</th>
<th>Bone turnover</th>
<th>Fracture risk</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>Spine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bariatric surgery</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RYGB</td>
<td>–0.12 g/cm² (–6% to –11%)</td>
<td>Mixed data – no change of significant change in either direction</td>
<td>Long-term durability of effect on BMD unknown – mixed findings</td>
<td></td>
</tr>
<tr>
<td>Sleeve gastrectomy</td>
<td>–0.04 g/cm² (-10% to –11%)</td>
<td>Increased</td>
<td>Suggested increase (stronger with RYGB than with sleeve gastrectomy or other surgery types)</td>
<td></td>
</tr>
<tr>
<td>Weight loss pharmaceuticals</td>
<td>–0.06 to –0.08 g/cm²</td>
<td>No change</td>
<td>NA</td>
<td>No differences from placebo control despite greater weight loss</td>
</tr>
<tr>
<td>Orlistat</td>
<td>–0.01 g/cm²</td>
<td>Increased</td>
<td>NA</td>
<td>Suggested increase (stronger with RYGB than with sleeve gastrectomy or other surgery types)</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>–0.03 g/cm² (for arm, not hip)</td>
<td>No change</td>
<td>NA</td>
<td>Suggested decrease with no effect on resorption</td>
</tr>
<tr>
<td>Exenatide</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Effects attenuated by multinutritional and certain exercises</td>
</tr>
<tr>
<td>Dietary restriction</td>
<td>–0.001 to –0.007 g/cm² (–1% to –1.5%)</td>
<td>Suggested promotion of bone formation with no effect on resorption</td>
<td>NA</td>
<td>Effects attenuated by multinutritional and certain exercises</td>
</tr>
</tbody>
</table>

BMD, Bone mineral density; NA, data not available in this review; RYGB, Roux-en-Y gastric bypass. Orlistat has not been approved for the treatment of obesity, but has shown weight loss properties in clinical trials. Please see text for references.
an unspecified bariatric surgical type. This meta-analysis showed significantly lower BMD at the femoral neck in the surgical than in the non-surgical control group, but only by −0.005 g/cm², with no difference between operated and non-operated groups in lumbar spine BMD [55]. This finding of reduced BMD at the hip but not the spine after bariatric surgery is in keeping with observations that although gastric banding has been shown to significantly reduce hip BMD [56], it is associated with a small, but significant, increase relative to pre-surgical values in lumbar spine BMD at 12 [62] and 24 months [57] after surgery.

While the above-mentioned cross-sectional study investigated patients versus non-surgical controls at up to 10 years post surgery, few prospective studies have reported on BMD relative to pre-surgical values at time points >12 months post bariatric surgery. However, one prospective study in 59 women who underwent RYGB found that femoral neck BMD decreased by a further 3% between 12 and 36 months post surgery, after an initial 10% decline in the first 12 months post surgery [63]. These decreases in hip BMD were more marked in post-menopausal than in pre-menopausal women, albeit all hip BMD values at 36 months post-surgery remained higher than corresponding values in women of the same age from the general population [63], likely due to the effect of elevated BMI to increase BMD [64]. Conversely, another study found a decrease in total hip BMD of 9% between pre-surgical values and 12 months post RYGB or biliopancreatic diversion, but there were no further significant declines in total hip BMD between 12 and 24 months or 24 and 36 months post surgery [65]. In keeping with these latter findings, subgroup analysis in the above-mentioned 2015 meta-analysis that compared RYGB and other bariatric surgery types with non-operated controls, showed that studies with a time point of ≥24 months post surgery demonstrated no difference in femoral neck or lumbar spine BMD between operated and non-operated groups [55]. This could indicate that the effect of bariatric surgery to reduce BMD may be transient, but further work is required to clarify this possibility.

Lower BMD is linked to a greater risk of fracture, and a significant association between bariatric surgery and fracture has been reported [66, 67]. In a 12-year cohort study involving 2064 patients who underwent any of 10 types of bariatric surgery between 2001 and 2009, compared to 5027 matched controls, those that underwent bariatric surgery showed a non-significant 1.41-fold increased fracture risk at 12–24 months post surgery compared to matched controls (95% confidence interval: 0.99–2.05) [66]. At the end of the 12-year study period, however, there was a significant 1.21-fold increased fracture risk (1.02–1.42) in the operated compared to the non-operated group [66]. Interestingly, the increased fracture risk was only seen in sites that are not typically targets of osteoporotic fractures, namely the clavicle/scapula/sternum and feet/toes – and not in the common osteoporotic fracture sites of the wrist, upper arm, rib, hip or spine – with the reason for this being unknown [66]. In subgroup analysis, this association between bariatric surgery and increased fracture risk was found to be stronger with RYGB surgery than with sleeve gastrectomy or other surgery types [66]. In keeping with these findings, a population-based, historical cohort study of the medical records of 258 patients that had bariatric surgery between 1985 and 2004 found that these patients, over 94% of which had RYGB, carried a higher fracture risk than that of the general population, with an odds ratio of 2.3 (1.8–2.8) [67]. This risk was higher for fractures not only at the traditional osteoporotic sites of the hip, wrist, spine and upper arm, but also at non-osteoporotic sites such as the foot, leg or hand [67]. These two studies [66, 67] are in contrast to a population-based, retrospective cohort study on 2079 surgical patients, which found no evidence of association between bariatric surgery and fracture [68]. However, this could be due to the fact that in this latter cohort study, over 60% of the surgical population had undergone gastric banding rather than RYGB [68].

In keeping with loss of BMD, elevated serum concentrations of bone formation and resorption markers, namely osteocalcin [69, 70] and NTX [70], have been reported after RYGB surgery relative to presurgery values. Increases in bone turnover markers have also been observed in response to gastric banding and sleeve gastrectomy [10]. A meta-analysis of 10 studies involving a total of 344 patients confirmed that whilst total body, femoral neck, lumbar spine and pelvic BMD were significantly decreased post-surgery, serum or urinary concentrations of NTX were significantly elevated [54]. This meta-analysis noted interesting differences in serum concentrations of nutrients that are important for the maintenance of bone mass, namely calcium and vitamin D. That is, serum calcium concentrations were significantly reduced post-bariatric surgery, although no difference could be found in serum concentrations of vitamin D [54]. A prospective study of 73 patients who were followed for 18 months post-bariatric surgery found that urinary NTX concentrations increased significantly by 3 months and remained significantly higher for the duration of the study period, whilst serum calcium concentrations remained stable [53]. This lack of effect of bariatric surgery on serum calcium levels could be due...
to aggressive calcium supplementation pre- and post-surgery, however serum vitamin D levels increased by 3 months post-surgery and then decreased to insufficient levels of < 30 ng/mL by 18 months post-surgery, despite vitamin D supplementation [53]. A similarly less than desirable level of serum vitamin D was also reported in a 12-month prospective longitudinal study on 23 men and women who underwent RYGB surgery [60]. This study reported that despite vitamin D intake increasing from an average of 658 IU/day at baseline to 1698 IU/day at 12 months, 87% of patients had insufficient serum levels of vitamin D at 12 months (≤30 ng/mL) [60]. It has been suggested that current post-surgery supplementation recommendations of 1200–2000 mg calcium daily and 1000 IU vitamin D daily [71] may be insufficient for bariatric patients post-operatively [54]. In summary, bone turnover appears to increase after bariatric surgery, and there is a need for vigilance for nutritional deficiencies both pre- and post-surgery [60].

A recent report [72] has highlighted the possibility that the substantial reductions in BMD seen after RYGB may be due to artifacts of DXA scanning in the context of large weight losses in people with morbid obesity. For instance, DXA scans revealed significant reductions in hip BMD at 12 months after RYGB, in comparison to pre-surgical values and non-surgical controls, but CT scans detected no such decrease in hip BMD [72]. These findings cast doubt over the existence or magnitude of BMD reductions in response to bariatric surgery, and potentially also in response to other obesity treatments. However, a more recent study with CT detected adverse effects of RYGB on BMD, microarchitecture and estimated strength at 12 months after surgery, at least in the tibia, which is a weight-bearing bone (only tibia and radius were assessed by CT, not hip or spine) [73]. Moreover, an adverse effect of RYGB on bone can be deduced by observations of concurrent increases in circulating concentrations of bone turnover markers such as P1NP and CTX in the aforementioned CT study [72] and in other studies [54, 69, 70], and by the evidence of increased fracture risk following bariatric surgery that has been reported in some [66, 67] but not all [68] studies.

Despite the link between bariatric surgery and potentially adverse changes in bone, many factors need to be taken into account, including the risk of obesity itself, when deciding on surgery. As the number of bariatric surgical operations increase, notably in younger patients, it is important that these factors are fully understood, particularly the potential effect of bariatric surgery on long-term fracture risk [11].

Effect of weight loss pharmaceuticals on bone

International [74, 75] and national [76] organizations recommend that pharmacotherapy be considered for the treatment of obesity, as an adjunct to lifestyle changes, for people with a BMI ≥30 kg/m², or BMI ≥27 kg/m² with at least one comorbid medical condition such as hypertension, dyslipidemia, type 2 diabetes mellitus (TZDM) or obstructive sleep apnea. In terms of available pharmacotherapy, orlistat, liraglutide and naltrexone+bupropion are currently approved as weight loss medications by the European Medicines Agency in Europe, while orlistat, liraglutide, naltrexone+bupropion, phentermine+topiramate and lorcaserin have current approval by the Food and Drug Administration in the USA [77]. In Australia, the Therapeutic Goods Administration has approved orlistat and more recently liraglutide for the long-term treatment of obesity, while phentermine is available as a short-term obesity treatment of up to 3 months. No literature was found on the effects of naltrexone+bupropion, phentermine, phentermine+topiramate and lorcaserin on bone. Therefore, this review will focus on the pharmacological agents orlistat and liraglutide [a glucagon-like peptide-1 (GLP-1) receptor agonist], as well as another GLP-1 receptor agonist, exenatide, and their association with bone health.

Orlistat

Orlistat is a potent and selective inhibitor of gastrointestinal lipase, reducing intestinal fat absorption by up to 30%, resulting in a loss of body weight over and above that of placebo when combined with a well balanced, mildly energy-restricted diet [78]. It is approved for long-term therapy and is available by prescription and over the counter in 120 mg and 60 mg strengths, respectively.

A single clinical trial suggests that orlistat is not associated with any loss of BMD or bone mineral content (BMC) over and above the effect of placebo and associated weight loss [79]. This 12-month, prospective, randomized, placebo-controlled trial of orlistat treatment (120 mg, 3 times a day) in 30 obese participants with a mean age of 41±11 years, showed that mean forearm BMD decreased significantly by 0.01 g/cm² from pre-treatment values to 12 months in the orlistat group, with no difference in treatment effect between the orlistat and placebo groups. The changes in lumbar spine and total body BMD from pre-treatment to 12 months were not significant in either group. Significant weight losses of 11.2±7.5 kg (mean ± SD) and 8.1±7.5 kg were measured in the orlistat and placebo...
The GLP-1 receptor agonists, namely liraglutide and exenatide, were developed and approved for the treatment of T2DM due to their glycaemic control properties. Liraglutide has also been approved for weight management at a higher dose (3 mg/day) than that used to treat T2DM (1.8 mg/day). Exenatide has not been approved for the treatment of obesity, however, has shown weight loss properties in clinical trials [82, 83].

A recent meta-analysis reported that liraglutide treatment, at doses typically used to treat T2DM, is associated with a significantly reduced risk of bone fracture at any site, while exenatide treatment is associated with an elevated risk [84]. This meta-analysis included 16 randomized controlled trials with a total of 11,206 participants (mean age ranging from 45.9 to 59.5 years). Participants with pre-existing osteoporosis were excluded. The overall risk of bone fracture was not influenced by GLP-1 receptor agonists (liraglutide and exenatide combined), with an odds ratio of 1.05 (95% confidence interval 0.59–1.87), when compared with other drugs or placebo. This is a similar finding to another meta-analysis published a year earlier, of seven randomized controlled trials specifically involving people with T2DM, which found that treatment with GLP-1 receptor agonists did not modify the risk of fractures [85]. However, when considered separately, the eight randomized controlled trials of liraglutide treatment were collectively associated with a significantly reduced risk of bone fracture compared with placebo or other active drugs [odds ratio 0.38 (0.17–0.87)] [84]. It should be noted that in two of these eight trials, exenatide was the comparator. Although the trend remained even after these two trials were removed from the analysis, the difference in risk was no longer statistically significant (odds ratio 0.49 [0.19–1.22]). In contrast to liraglutide, there was a significantly greater risk of bone fracture in the exenatide treatment group compared to the comparator group, with an odds ratio of 2.09 (1.03–4.21) [84]. Excluding the two studies with liraglutide as the comparator still resulted in an elevated odds ratio of 1.71 (0.80–3.67).

A number of limitations are worth noting in this meta-analysis [84], including the overall lack of available data on the impact of GLP-1 receptor agonists on bone turnover. In addition, the studies included were not designed to assess the risk of fracture and only 43 fractures were reported in total, mostly as serious adverse events. As such, there may have been a number of unreported fracture incidents. Moreover, the length of most trials were not long enough to adequately assess the risk of fracture. The studies included were between 12 and 104 weeks in duration, with 11 out of 16 trials being 26 weeks in duration or less. Also, concomitant medications such as statins, corticosteroids and estrogens were not routinely reported in all studies involved in the meta-analysis, and may have influenced bone strength and the resultant risk of fracture.
Despite these limitations, another study provides some degree of support for the positive findings of the effect of liraglutide on fracture risk [86]. In this study, 37 non-diabetic, obese women, aged 46 ± 2 years, completed an 8-week meal replacement weight loss program and were then randomized into a liraglutide group (1.2 mg/day, which is less than half the dose of liraglutide used for weight management, n = 18) or a control (not placebo) group (n = 19). Both groups followed a weight maintenance program for the duration of the 52-week pharmaceutical treatment phase. There were no differences in weight loss or weight maintenance between groups. Pelvic BMD decreased significantly from baseline (after weight loss) to the end of the 52-week weight maintenance period in both the liraglutide group (−0.03 ± 0.01 g/cm², p < 0.01) and the control group (−0.02 ± 0.008 g/cm², p < 0.05), with no significant difference in treatment effect between the two groups. There was no significant change in total body or arm-leg BMC in either group. While the gold standard for measuring bone mass is via localized scans of specific bones such as the hip or spine, rather than the whole body scans used for this study, and while bone mass is most commonly reported in density units, the authors of this study noted that although the liraglutide group showed small, non-significant decreases in pelvic, total body and arm-leg BMC as a result of the 52-week weight maintenance phase, the control group showed a significant loss of BMC at all three locations.

Despite limitations in the methods used to determine the above-mentioned changes in bone mass, changes in bone turnover markers observed in this study also supported a favorable effect of liraglutide [86]. Indeed, there were significant, 11%–16% increases in plasma concentrations of the bone formation markers P1NP and osteocalcin during liraglutide treatment, in contrast to non-significant changes in the control group. There was a significant decrease in plasma vitamin D concentrations in the control group, in contrast to a non-significant decrease in the liraglutide group. There was no significant change in the plasma concentrations of the bone resorption marker CTX in either group [86]. These findings for P1NP/osteocalcin and CTX, markers of bone formation and resorption, respectively, suggest that the beneficial effect of liraglutide may be to promote bone formation rather than the prevention of bone resorption.

In contrast to these seemingly positive effects of GLP-1 receptor agonists on bone metabolism, no positive effects were observed in a population-based medical record-linked cohort study. This study included a total of 216,816 individuals with T2DM, 8354 of which were current, recent or past users of a GLP-1 receptor agonist, with a median use of 1.7 years and median follow-up of 5.1 years [87]. Median follow-up of patients with no exposure to GLP-1 receptor agonists was 3.6 years. Overall, this class of drug showed no effect on osteoporotic bone fracture risk. In addition, stratification by GLP-1 receptor agonist type used (liraglutide or exenatide), revealed no decrease or increase in the risk of fracture.

Although there is a lack of data on the impact of GLP-1 receptor agonists on bone metabolism, the current literature concurs that this and other pharmacotherapy for weight loss do not negatively impact bone integrity beyond the effect of placebo and associated weight loss, and that there is no associated increased risk of fracture. Further research is needed however to confirm these findings, and the extent of any potential beneficial effects that liraglutide may have on bone.

**Effects of dietary restriction on bone**

As seen above, treatments for obesity, particularly bariatric surgery, have been associated with bone loss. Given that dietary restriction is the first treatment choice for obesity, and is also an essential component of surgical and pharmacological obesity treatments, studies investigating whether diet-induced weight loss is also associated with bone loss have emerged.

Similarly to bariatric surgery studies, a recent meta-analysis found a significant reduction in hip BMD after diet-induced weight loss interventions of 6–24 (but not 3) months in duration [34]. These reductions in total hip BMD were between 0.010 and 0.015 g/cm², which corresponds to an approximate change of 1%–1.5% from pre-treatment values [34]. While statistically significant, these diet-induced reductions in hip BMD are considerably less than those associated with bariatric surgery (RYGB specifically), which showed a decline of 8%–11% from pre-surgical values in the first 12 months post surgery [10, 50, 56, 59, 60]. In accordance with the high variability of results, the lumbar spine showed no significant change in BMD with diet-induced weight loss [34]. Total body BMD decreased with diet-induced weight loss in both pre- and post-menopausal women, but was only significant in post-menopausal groups [34]. Serum concentrations of osteocalcin, but not P1NP, both of which are markers of bone formation, increased significantly from baseline during 3-month weight loss interventions, however no effect was found in interventions with a longer duration [34]. Similarly, serum concentrations of the bone resorption markers, CTX and NTX, increased significantly after dietary weight loss interventions of 2 or 3 months.
in duration [34]. Given that the serum concentrations of these bone turnover markers increased transiently prior to the decrease in total hip BMD observed after interventions of 6 months or longer, these findings indicate that dietary restriction-induced weight loss results in a real, albeit small and statistically significant, decline in total hip BMD [34].

In addition to dietary restriction for the purposes of weight loss, another dietary intervention that has been linked with bone loss is long-term energy restriction, often referred to as calorie restriction, as a means of potentially increasing longevity and slowing biological aging [88]. A randomized controlled trial in 218 non-obese younger adults (aged 20–50 years), randomized to either 24 months of energy restriction or ad libitum intake, found that total adult BMD declined significantly compared to pre-treatment values at 24 months in the restricted compared to the ad libitum group (–0.017 ± 0.002 vs. 0.001 ± 0.003 g/cm²) [89]. This reduction in hip BMD in the energy-restricted group correlated with weight loss [89]. Serum concentrations of the bone formation marker PINP did not change at 6 months, while that of BAP significantly decreased relative to pre-treatment at 12 months and remained suppressed at 24 months in the energy-restricted as compared to the ad libitum group [89]. This lack of change or reduction in bone formation markers was coupled with significant increases over pre-treatment values in serum concentrations of the bone resorption markers CTX and TRAP5B at 6 and 12 months in the energy-restricted compared to the ad libitum group [89], indicating an uncoupling of the bone turnover process which likely contributed to the loss of BMD in this cohort of younger adults [89].

In contrast to this finding of hip BMD loss with long-term energy restriction in younger adults, diet-induced weight loss in younger adults – unlike in older adults – has not been associated with similar decreases in BMD despite weight losses of 7%–10% from baseline [90–92]. Higher muscle mass and the hormonal profile of younger adults are thought to protect against the negative skeletal effects of diet-induced weight loss [93]. The aforementioned negative effects of long-term energy restriction versus ad libitum intake could thus be attributed to the lower fat free mass of the non-obese younger adults studied in that trial, compared to the higher fat free mass of individuals with overweight or obesity [89]. However, the impact of this small but significant decrease in hip BMD with long-term energy restriction in non-obese adults on fracture risk, as assessed using the World Health Organization fracture risk assessment tool, appears small [89].

It appears unlikely that a single dietary weight loss intervention would lead to an overall negative impact on bone as compared to the metabolic advantages that weight loss confers to a person with overweight or obesity. There is speculation that bone loss in response to diet-induced weight loss is a normal adaptation to a lighter body [93], akin to the finding that significant reductions in fat free mass are also a normal adaptation to weight loss in adults with overweight or obesity [94]. Furthermore, it has been suggested that while BMD may decline due to diet-induced weight loss, bone quality – as assessed by high resolution magnetic resonance imaging of trabecular bone microarchitecture – does not [95]. However, very rarely in obesity is a single weight loss attempt the end point of dietary interventions in an effort to lose weight [12, 34]. Usually, multiple attempts at weight loss and periods of dietary restriction are followed by regain, over many years [12, 34]. Moreover, studies have shown that BMD lost from the hip or lumbar spine over 6 months of diet-induced weight loss was not recovered during weight regain when measured at the 12- and 18-month time points [96, 97]. Due to these results suggesting that diet-induced bone loss is not recovered during weight regain, there is a risk that weight cycling – weight loss followed by regain, occurring 1 or more times – may place people who undergo repeated attempts to lose weight via dietary restriction at an increased risk of adverse effects on bone, particularly those at higher risk of bone loss such as inactive and older women [12, 34]. This finding has been suggested in a large population-based study of 20,745 females and males over 15 years of age [98]. Females who reported their largest weight loss as being 11 kg or more, or who recalled having dieted over 11 times over their life, had an adjusted hazard ratio of 1.48 (95% confidence interval: 1.13–1.94) and 1.73 (1.11–2.68) for osteoporotic fractures, respectively [98].

While diet-induced weight loss is associated with small but significant losses of BMD, lifestyle factors – notably exercise and nutrition – are likely to attenuate any potential long-term deleterious effects. These factors will be discussed in greater detail in the next section.

Given that obesity is a major health concern that confers risk in many areas of health, and given the metabolic advantages of weight loss, it appears that a single weight loss intervention via dietary restriction with a view to weight maintenance holds little risk to bone health, as compared to the known adverse health consequences of remaining obese [34]. Thus, clinicians should continue to recommend dietary restriction for weight loss, with a view to long term weight maintenance, for clients with overweight or obesity, with the addition of weight-bearing exercise and adequate dietary intake of nutrients, notably calcium and protein, for the reasons outlined below.
Possible mechanisms of bone loss induced by obesity treatments

A number of mechanisms have been proposed for the loss of BMD during obesity treatments, and some of these — to be discussed here — represent potential points of lifestyle intervention to prevent adverse effects on bone.

A major contributing factor common to all modalities of obesity treatment seems to be the reduction in mechanical loading on bone as a consequence of weight loss [12], which stimulates the secretion by osteocytes of sclerostin, a protein that inhibits bone formation [99]. This mechanism could explain the observation that bariatric surgeries induce greater bone losses than other obesity treatments, as summarized in Table 1, because they also induce greater weight loss. In keeping with the notion of mechanical unloading contributing to bone loss with obesity treatments, loss of hip BMD was found to be strongly and significantly correlated with loss of body weight in 23 participants at 12 months post-RYGB [60], as well as in 218 non-obese participants after 24 months of dietary restriction [89]. If mechanical unloading contributes to bone loss, possibly and at least partially via changes in sclerostin secretion, then weight-bearing exercises (which includes resistance training and high impact weight bearing exercises such as running, jogging, skipping and dancing) might be expected to overcome this effect. Meta-analyses conclusively report that weight-bearing exercises — notably resistance training combined with high impact weight bearing exercise — significantly preserve BMD compared to other forms of exercise, including jogging mixed with walking or stair climbing or agility exercises, in pre- or post-menopausal women [100–102]. In one of these meta-analyses, resistance training combined with high impact weight bearing exercises was found to be better at enhancing BMD in postmenopausal women than resistance training alone [101]. Moreover exercise, particularly weight-bearing exercise, has been shown to reduce BMD losses during dietary restriction [93, 103]. In addition, exercise-induced weight loss without dietary restriction does not appear to induce the significant decreases in BMD that have been observed with weight loss induced by dietary restriction alone [104]. Interestingly, sclerostin levels have been found to increase in people with overweight or obesity who are prescribed dietary restriction without specific addition, or supervision, of physical activity [99, 105, 106]. Moreover, a weight loss diet, when combined with both aerobic and resistance training, prevented the increase in circulating sclerostin levels otherwise associated with dietary restriction, consolidating a possible role of sclerostin in mediating effects of mechanical unloading and weight-bearing exercises on bone [106].

Another factor that could conceivably contribute to BMD losses with obesity treatments — and which, like weight bearing, holds potential for intervention via lifestyle changes — is reduced intake and/or absorption of nutrients that help to maintain bone mass, notably protein, calcium and possibly also vitamin D. This is particularly true of bariatric surgery, where not only is dietary intake reduced, but malabsorption in the gastrointestinal tract can further exacerbate nutritional deficiencies [107]. In keeping with a role of nutrient depletion in promoting bone loss, BMD loss with obesity treatments can be significantly attenuated or prevented by ensuring adequate dietary (or supplemental) intake of calcium, protein and — in the bariatric surgery population — potentially also vitamin D [12, 93]. A randomized controlled trial showed that in young adults, preserving normal dietary levels of calcium during moderate energy restriction, with or without exercise, helped to conserve hip and total body BMD during weight loss [91]. Similarly, in a randomized controlled trial in overweight pre-menopausal women, both adequate as well as high calcium intakes were shown to attenuate BMD loss during weight loss [90]. In addition, randomized controlled trials have found that higher protein diets (~86 g/day or 24% of energy intake) confer protection against significant bone loss and may decrease bone turnover during diet-induced weight loss [12, 37, 93, 108]. The benefits of vitamin D supplementation to preserve hip BMD during dietary restriction-induced weight loss have recently been called into question, with the observation that it did not attenuate hip BMD loss in a randomized placebo-controlled trial involving 218 post-menopausal women with vitamin D insufficiency [109]. This may be related to the fact that in addition to vitamin D supplementation, women in that trial also underwent an aerobic exercise program that was partly supervised by an exercise physiologist [109], which may have also reduced BMD loss [100–102]. Taken together, these findings imply that ensuring that calcium and protein intake are optimal, as well as that of vitamin D in people undergoing bariatric surgery, and including weight-bearing exercise, could be useful strategies to help mitigate any loss of BMD during obesity treatments.

There are many other mechanisms besides reduced weight bearing and nutritional status that are hypothesized to contribute to bone loss during obesity treatments. These include alterations in hypothalamic neuropeptide expression in response to energy deficit, notably an increase in that of neuropeptide Y [23], alterations in circulating concentrations of gut-derived appetite-regulating
hormones, notably peptide YY and GLP-1 [10, 11], reductions in active levels of other hormones such as sex hormones and insulin-like growth factor [110], and – in the bariatric population – changes in vitamin D and parathyroid hormone status (not strongly supported by the literature) or adipokines [33, 111]. These potential pathways are not discussed in detail here, because they are not as readily amenable to intervention via lifestyle factors as are mechanical unloading and nutritional deficiencies, and the reader is referred to the reviews cited in this paragraph for further information.

Expert opinion

In summary, all obesity treatments under review in this work – bariatric surgery, weight loss pharmaceuticals and dietary restriction alone – have been shown to result in statistically significant decreases in BMD of the hip, as well as statistically significant increases in bone turnover, as indicated by perturbations in circulating or urinary concentrations of bone turnover markers. The loss of hip BMD relative to pre-treatment values is greatest for bariatric surgery – notably RYGB for which most research in this field has been conducted (8%–11% of pre-surgery values) – and is least for dietary restriction alone (1%–1.5% of pre-intervention values), with weight loss pharmaceuticals (orlistat or the GLP-1 receptor agonist liraglutide) inducing no greater loss in hip BMD than that induced by the control condition of the same dietary restriction with or without placebo. This finding of similar hip BMD losses in both groups despite generally greater weight losses in the groups taking active agents suggests a potential protective effect of these weight loss pharmaceuticals on bone. Indeed, a limited amount of research has suggested that the GLP-1 receptor agonist liraglutide may actually increase BMC (but not BMD) and decrease fracture risk relative to control, but more research is warranted to assess this.

An interesting observation to arise from considering these three different obesity treatments together is that unlike their clear effects to reduce hip BMD, none of them had any clear unidirectional effect on spine BMD. A possible interpretation for this is that obesity treatments affect the weight-bearing site of the hip more readily than they affect the spine, but an alternate explanation is that the spine is more prone to measurement error via DXA than the hip. DXA scans of the spine, in particular the lumbar region (L1–L5), often pick up calcification from other sources besides healthy vertebrae, and this increases apparent BMD readings [112, 113]. Such calcification can originate from atherosclerotic lesions within the aorta, or from osteophytes (protrusions of bone tissue that form in response to joint damage from conditions such as in arthritis), masking underlying changes in bone mass due to age, disease, or other factors [112–114]. As such, ongoing research in this field could benefit from a preferential focus on hip over spine DXA. This could help in situations where the time available for DXA scans is limiting, where radiation exposure needs to be minimized (e.g. when assessing minors or when multiple DXA scans are being undertaken over a relatively short time frame), or when participants have features on their spine that make it difficult to assess changes in BMD due to various interventions (e.g. atherosclerosis or arthritis).

While the meta-analyses synthesized here show a clear effect of obesity treatments to reduce hip BMD, it is not known whether this is a maladaptive change, or whether it simply represents normalization of BMD relative to reduced body mass, akin to the finding that a certain loss of percent fat-free mass is to be expected in response to reduced BMI [94]. It is also not known whether the observed reductions in hip BMD persist or worsen years after completion of the intervention, as suggested in some [63] but not all [55] of a limited number of studies that assessed bone at >12 months after bariatric surgery. This question is currently under investigation in the context of dietary restriction in two long-term (36-month) clinical trials from our team [115, 116]. Most importantly, it is not known whether or not this reduced BMD contributes to a greater fracture risk, as has been suggested by some [66, 67] but not all [68] studies post-bariatric surgery, particularly RYGB, and how any potential increase in fracture risk compares to the risk of not treating obesity. While reduced BMD is certainly an indicator of increased fracture risk, it is not a perfect predictor, and a reduction in BMD per se is not necessarily a path to disease.

In light of these outstanding questions, and in light of the known benefits of losing 3%–15% or more of body weight on multiple aspects of health [117], any concerns about potential effects of obesity treatments on bone health should not deter against treating overweight or obesity. However, and also in light of these outstanding questions, it is prudent to implement strategies that are likely to mitigate bone loss during obesity treatments, particularly in those at higher risk of bone loss such as older adults. These include emphasizing the importance of consuming nutrient-rich foods in favor of nutrient-poor foods with a high energy density, with possible supplementation, thereby helping to ensure adequate intake of nutrients – notably protein, calcium and possibly also...
vitamin D – as well as emphasis of the importance of exercise, all of which have been shown to help maintain BMD during weight loss.

Outlook

In 5–10 years from the time of writing this review, we speculate that this field will have evolved (or should evolve) by combining data sets from multiple clinical trials in order to determine whether the presently observed reductions in hip BMD in response to obesity treatments represent benign normalization of bone mass to the reduced body weight, or the onset of potentially pathological processes. In addition, we propose the importance of long-term prospective studies – 36 months and longer – to determine whether reductions in hip BMD with obesity treatments are reversible, with or without weight regain, and (using data linkage with medical records, for example) whether fracture risk is elevated by obesity treatments relative to untreated overweight or obesity. We also propose that systematic reviews and meta-analyses be conducted on the many trials that have investigated interventions aimed at reducing bone loss during obesity treatments, so that the best evidence-based interventions can be implemented now, to protect against eventual adverse effects of obesity treatments on bone, particularly in those at higher risk of bone loss.

Highlights

- Obesity appears to compromise bone mass and may increase fracture risk.
- Recent meta-analyses show that obesity treatments (surgical, pharmacological and dietary) reduce BMD of the hip, with no clear effect on the spine, perhaps due to greater measurement artifact in the spine.
- Ongoing research in this area could be streamlined by focusing on hip in favor of spine BMD measurements.
- As hip BMD is a major determinant of osteoporotic fracture risk, reduced hip BMD could conceivably increase the risk of fractures with obesity treatments.
- RYGB has been suggested to increase osteoporotic fracture risk.
- It is unknown if a single obesity intervention involving dietary restriction, with or without weight loss pharmaceuticals, increases the risk of fracture, but any such increase is likely to be small relative to the cardio metabolic and other health benefits of loss of excess weight.
- There is little information as to whether BMD losses during obesity treatments are recovered post-treatment, but focusing on weight maintenance after obesity treatment would be prudent for bone health.
- Lifestyle interventions that have been suggested to reduce BMD loss with obesity treatments are increased dietary intake of protein, calcium and potentially also vitamin D, as well as increasing physical activity, notably weight-bearing exercise.
- Meta-analyses would help to determine the best evidence-based interventions against potential adverse effects on bone health with obesity treatments.

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