Bariatric Surgery and Bone Loss: Do We Need to Be Concerned?

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Abstract

Despite significant improvement in weight and comorbid conditions, there is growing evidence that bariatric surgery may exert a negative effect on the skeleton. This review has focused on the impact of bariatric surgery on bone health, with the concern that bariatric surgery may increase skeletal fragility and fracture risk by accelerating bone loss. We have highlighted studies evaluating changes in bone metabolism after three commonly performed bariatric procedures including laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass surgery and increasingly popular sleeve gastrectomy. This review has also discussed some of the technical issues faced in measuring bone in obese populations and during dynamic weight loss. There is limited evidence regarding potential mechanisms for the reported observations of increased bone turnover and/or bone loss after bariatric surgery. We have reviewed the evidence surrounding potential factors affecting bone health in bariatric patients such as rapid weight loss per se, nutritional deficiencies, effects of fat-derived adipokines and gut-derived appetite-regulatory hormones. Future prospective long-term cohort studies are needed to define how to quantify bone loss in individuals with obesity, particularly following massive weight loss, and for how long the bone changes continue. These studies will help clarify any negative clinical consequences of these changes, including future fracture risk in this unique group of patients.

Introduction

The prevalence of obesity worldwide has increased significantly in recent decades because of a complex range of environmental and possibly also epigenetic factors. Obesity is associated with increased mortality [1] with reduced life expectancy, especially amongst people affected from young adulthood [2], as well as multiple comorbidities including type 2 diabetes, hyperlipidemia, sleep apnoea, malignancy and decreased quality of life [3].

The medical management of obesity is limited by the variable, limited response to treatment, suboptimal compliance and adverse effects of antiobesity medications. At present, the only effective, long-term treatment for obesity remains bariatric surgery, which results in substantial and sustained weight loss, significant reductions in comorbid conditions, and prolonged longevity [4]. In fact, the utilization of bariatric surgery as a therapeutic approach to morbid obesity has increased two and a half-fold worldwide between 2003 and 2011 [5].

Although many studies have demonstrated the short- and long-term efficacy of bariatric surgery for weight loss, there are limited data regarding any long-term side effects of these procedures. Recently, there has been an increased focus on the impact of bariatric surgery on bone metabolism, with the concern that bariatric surgery may increase skeletal fragility and fracture risk by accelerating bone loss.

The majority of research performed in this area has been cross-sectional and provides little evidence as to the possible mechanisms for any observed abnormalities in bone metabolism with few data documenting longitudinal changes in bone density and bone turnover.

This review will highlight studies examining the impact of obesity surgery on bone metabolism, focussing on the three most commonly performed procedures: laparoscopic adjustable gastric banding (LAGB or gastric banding), sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB), as well as considering effects of biliopancreatic diversion (BPD) on bone. It will then explore potential underlying mechanisms for the reported observations of heightened bone turnover or bone loss after bariatric surgery and potential long-term consequences of bariatric surgery, including the long-term risk of fracture in this population of patients. Before covering these topics, it will first give an overview of the effect of obesity (without bariatric surgery) on bone, as well as more detailed information about the various bariatric surgery procedures, since both of these issues are relevant to understanding the effects of bariatric surgery on bone.

Obesity and Bone

With the increasing prevalence of obesity, one area of research that is beginning to attract greater attention is the effect of obesity on bone. Epidemiological evidence suggests that obesity is correlated with increased bone mass and that increased body weight protects against bone loss [6, 7]. However, despite such evidence of a protective effect of obesity on bone, there is increasing evidence that excess weight due to adiposity may be detrimental to bone and fracture risk.

Osteoporosis and obesity have been shown to coexist, as evident in disorders involving fat redistribution such as type 2 diabetes mellitus, Cushing's disease and drug-induced lipodystrophies [8]. Indeed, in some cohorts, the per cent of total fat mass is strongly and inversely associated with bone mineral density (BMD) [9]. Severe obesity may compromise skeletal health in overweight and obese children who have reduced bone area and bone mass relative to body weight compared with their leaner peers [10]. Obesity is associated with lower serum 25-hydroxyvitamin D and higher serum parathyroid hormone levels than in non-obese individuals [11, 12]. Obesity is also associated with hypogonadotropic hypogonadism in men [13] and higher circulating concentrations of inflammatory cytokines, which are key mediators of osteoclast differentiation through the regulation of RANKL/RANK/OPG pathway [14]. Increased production by visceral fat of adiponectin and pro-inflammatory cytokines may result in adverse effects on bone [15], as demonstrated in obese adolescent and pre-menopausal women [16, 17]. Obese women have lower rates of bone formation, as indicated by circulating type I collagen levels, suggesting that increased body fat suppresses new collagen formation [18].

Recent evidence indicates that the regulation of adipose tissue and bone is closely related [19], since adipocytes and osteoblasts derive from a common mesenchymal stem progenitor. Multiple clinical conditions such as osteoporosis and ageing-related bone loss are associated with an increase in marrow fat, which suggests a conversion of stromal cells to adipocytes rather than osteoblasts [20]. Several studies that examined the function of adipocytes in bone marrow and mesenchymal stem cells isolated from bone marrow of post-menopausal osteoporotic patients found these cells to express more adipose tissue differentiation markers than those from subjects with normal bone mass [21]. Increased bone marrow fat has been found in subjects with morphologic evidence of bone weakness such as endplate depression and compression fractures [22]. Finally, an inverse association was noted between vertebral bone marrow fat and trabecular BMD in pre-menopausal obese women [17], in keeping with the hypothesis that adipose tissue and bone mass may undergo inverse regulation.

Besides associations with osteoporosis, low BMD or lower rates of bone formation, obesity is also associated with fractures, and not only in older people [23], as there are data to show an increased prevalence of forearm fractures amongst obese young adults [24, 25]. Post-menopausal obesity appears to be a risk factor for fracture at specific sites such as the tibia and ankle [25]. In a recent meta-analysis of women with an average age of 63 years, high BMI after adjustment for BMD was associated with a higher risk of non-vertebral and all osteoporotic fractures [26]. Post-menopausal obesity also appears to be a risk factor for low trauma fractures. A study of 799 women with low trauma fracture attending a Fracture Liaison Service in the UK found that 28 % of these women were obese. Despite having fractured, in the majority of these obese women, BMD was normal as defined as a T-score >−1 [25]. A subsequent prospective, multinational study of 60,393 women reported similar rates of low trauma fractures between obese and non-obese post-menopausal women [27]. These findings question the commonly held perception that obesity is protective against osteoporosis or low trauma fractures. Moreover, they raise the possibility that low trauma fractures are occurring in obese women at a higher BMD than usually recognized as a risk for such fractures.

As the prevalence of obesity continues to increase, it is important to recognize that bone quality may be compromised in obesity and that this population of patients contributes significantly to overall fracture burden.

Efficacy of Bariatric Surgery

Bariatric surgery is generally reserved for patients with a BMI greater than 40 kg/m2, or for those with a BMI greater than 35 kg/m2 whose obesity is complicated by one or more major diseases such as type 2 diabetes mellitus or sleep apnoea. There are two major surgical categories: gastric interventions including LAGB, also known as gastric banding, vertical

gastroplasty and sleeve gastrectomy as well as gastrointestinal diversionary procedures such as RYGB and biliopancreatic diversion.

The first surgical treatment procedure for obesity was performed in 1952 by Viktor Henrikson in Gothenburg. This procedure involved resection of a large part of the small bowel, creating weight loss through nutrient malabsorption. Other surgical procedures soon followed. These early surgeries were complicated by a high frequency of adverse events [28].

Gastric banding surgical techniques evolved during the 1970s with the aim of providing a less invasive approach to weight loss. An adjustable band is placed around the upper part of the stomach, restricting the amount of food eaten by patients by mechanisms that are still not entirely clear. Initially, bands with a fixed diameter were used. The first modern adjustable gastric band was invented in 1986 [29], later (1992) applied via a laparoscopic approach. Gastric banding procedures accounted for 18 % of all bariatric procedures worldwide in 2011, but recently their numbers have declined as the sleeve gastrectomy procedure has increased from 0 in 2003 to 27.8 % in 2011 [5].

Sleeve gastrectomy was originally performed as a modification to another bariatric procedure, the duodenal switch, and then later as the first part of a two-stage gastric bypass operation on extremely obese patients for whom the risk of performing gastric bypass surgery was deemed too large. The initial weight loss in these patients was so successful that sleeve gastrectomy began to be investigated as a stand-alone procedure.

In sleeve gastrectomy, a major part of the greater curvature of the stomach is removed, including the complete fundus up to the angle of His, as well as the majority of the corpus and antrum. The pylorus function is left intact, enabling a normal outflow of gastric contents. The full mechanism of action is still not exactly clear, but restriction of food intake through a decrease in gastric volume plays some part. Sleeve gastrectomy also leads to a decrease in gastric acid secretion and a faster gastric emptying rate [30], an effect not observed in gastric banding [31]. Both of these changes would lead to a faster arrival of undigested nutrients in the duodenum, with subsequently increased production of gut hormones that modulate perceptions of hunger and satiety after meals.

Thirty per cent of all bariatric procedures worldwide are now sleeve gastrectomy, and the frequency of this procedure is steadily increasing due to its superior efficacy over gastric banding [5].

Roux-en-Y gastric bypass (RYGB) is a gastrointestinal diversionary procedure that diverts food from a large portion of the stomach and the proximal small intestine into the distal small intestine. It consists of creating a small gastric pouch connected to the small intestine via a Roux-en-Y limb [32]. The length of the Roux-en-Y limb is varied to augment the degree of malabsorption and subsequent weight loss. It was initially believed that RYGB worked solely through malabsorption; however, recent studies have revealed that this surgical technique also alters the secretion of several gut hormones that not only alter hunger and satiety signalling but which also affect energy expenditure [33, 34].

Bariatric surgical procedures promote substantial weight loss that is rarely achieved and even more rarely maintained with nutritional and lifestyle management alone. The efficacy of different types of bariatric surgery varies in terms of weight loss achieved and improvement in obesity-related comorbidities, as will be outlined below.

Weight loss post-bariatric surgery is frequently expressed as per cent loss of excess body weight, the latter being defined as the difference between the pre-operative weight and ideal body weight (i.e. at a BMI of 25 kg/m2).

Gastric banding results in an average loss of 20–30 % of initial body weight [35], equivalent to a loss of 41–54 % of excess body weight [36]. Long-term gastric banding data indicate that the loss of excess (e.g. 47 % of excess) weight can be maintained up to 15 years post-surgery [37]. Sleeve gastrectomy produces an average body weight loss of 20–30 %, equivalent to a loss of 45–64 % of excess body weight [35, 38]. After RYGB, patients lose up to approximately 35 % of their initial weight, equivalent to a loss of 62–75 % of excess body weight, with this loss being maintained at 10–14 years following surgery [36, 39–41].

As well as effects on weight loss and in some cases, even before significant loss of excess body weight, bariatric surgical procedures have been shown to resolve or ameliorate type 2 diabetes mellitus in 57–86 % of cases, hyperlipidemia in approximately 71 % of cases, hypertension in 68 % of cases, and sleep apnoea in 80–85 % of cases, with RYGB having a greater beneficial effect on these comorbidities than other bariatric procedures [36, 42].

Effects of Laparoscopic Adjustable Gastric Banding (Gastric Banding) on Bone

With a paucity of available data, it is currently unclear whether significant effects on bone mass occur following gastric banding. All studies to date have been small with a short follow-up of 24 months or less.

Results at both the spine and hip have been equivocal. A study of pre-menopausal women found an increase of 3.5 % in BMD in the lumbar spine at 12 months post-gastric banding [43], while two other studies reported non-significant increases in lumbar spine BMD of approximately 4.0 % in the first 2 years following gastric banding [44, 45].

Bone loss has been reported in the hip after gastric banding in association with increased bone turnover markers, but to a lesser extent than with RYGB [43–45]. While research in pre-menopausal women suggests that bone loss at the hip site may appear as early as 6 months after gastric banding [43, 44], there are more robust data supporting bone loss at the first year after surgery, by which time the majority of weight loss has occurred. Giusti et al. [43] reported a 2.3 % BMD loss at the hip (femoral neck) at 12 months following gastric banding surgery, and 5.8 % BMD loss at 24 months after the procedure. The bone loss in both publications [43, 44] from this longitudinal study was associated with an early increase in markers of bone resorption (urinary and serum concentrations of type I collagen breakdown products), although an absence of secondary hyperparathyroidism suggested that factors other than lack of calcium and vitamin D were involved in post-surgical bone remodelling.

In contrast to the above studies, a small Swiss pilot study [45] compared the skeletal effects of gastric banding (n = 9) with those of RYGB (n = 4) over 24 months, with matched morbidly obese men and women in the control arm (n = 6). No significant changes from baseline in bone mineral content (BMC) were reported at 24 months in the gastric banding and control groups. However, there was a significant decrease from baseline in BMC in the RYGB group (p = 0.005), which was accompanied by significant increases in bone turnover markers (serum osteocalcin and urinary deoxypyridinoline concentrations).

Effects of Sleeve Gastrectomy on Bone

There are few available data on changes in bone mass or metabolism following sleeve gastrectomy, despite the expansion of this procedure in recent years [46, 47]. To our knowledge, there have been three small studies describing skeletal changes post-sleeve gastrectomy.

One prospective study [48] comparing the effect of sleeve gastrectomy with RYGB on bone mass and remodelling found significant bone mass loss in the lumbar spine and hip at 12 months post-operatively in all surgical patients, relative to baseline values. Bone loss was slightly and non-significantly less pronounced in the spine and femur after sleeve gastrectomy than after RYGB (4.4 vs 4.6 and 5.4 vs 6.3 %, respectively, for the spine and femur). The urine levels of a bone resorption marker, N-terminal telopeptide, were significantly elevated over baseline in both surgical groups, consistent with the reported bone loss.

Another prospective, 6-month study [49] examined BMD changes in 29 obese women with a mean BMI of 43 ± 5 kg/m2 after laparoscopic sleeve gastrectomy and found that their BMD decreased by 1.2 % at the lumbar spine, 7.0 % at the femoral neck and 5.2 % at the total hip. All differences from baseline were significant. In parallel with these BMD declines, the participants' mean body weight and BMI decreased by 28.4 % after 6 months. The loss of BMD at the hip and femoral neck correlated with weight loss (r = 0.48, p < 0.01; r = 0.51, p < 0.01, respectively]. The Pluskiewicz study had several limitations including short follow-up and lack of a control group. Moreover, the study did not include other factors that could either influence or support changes in bone metabolism such as bone turnover markers, calcium intake and vitamin D.

The third study of bone post-gastric sleeve was a retrospective, observational study of 42 morbidly obese patients. The investigators reported an increase in bone density at the spine 2 years post-sleeve gastrectomy [50]. Mean BMD values for spine increased progressively, reaching statistical significance at one and at 2 years. The percentage of BMD increase was 5.7 % at 1 year and 7.9 % at 2 years. BMD changes were not associated with weight loss, but showed a direct correlation with circulating vitamin D and an inverse correlation with circulating parathyroid hormone levels. Hip BMD was not measured. The researchers concluded that an absence of bone loss at the lumbar spine may be related to an effect of parathyroid hormone. Although chronically elevated circulating parathyroid hormone levels have catabolic effects on cortical bone, mild increases in this hormone have anabolic effects on cancellous bone, which predominates at the spine [51]. The increase in lumbar spine bone mineral density was evident in several other bariatric studies in which

post-operative parathyroid hormone levels increased [52–54].

Clearly, further work is required to assess the effect of sleeve gastrectomy on bone mineral density changes after the bariatric surgery. Notably, studies investigating bone mass after bariatric surgery need to investigate multiple sites (i.e. lumbar spine and hip) in order to obtain a clearer understanding of possible effects.

Effects of Roux-en-Y gastric Bypass (RYGB) on Bone

Several studies [45, 52–64] have examined the effects of RYGB for morbid obesity on bone mineral density and/or bone turnover. Further corroborating the observed loss of bone, these studies have shown alterations in urinary or circulating concentrations of bone turnover markers.

In brief, these studies show evidence of an early increase in bone remodelling, as indicated by an increase over baseline values of circulating or urinary concentrations of bone turnover markers including breakdown products of type I collagen (a major organic component of bone matrix that is synthesized primarily in bone) such as serum and urinary N-telopeptide, C-telopeptide, as well as osteocalcin, a non-collagenous protein secreted specifically by osteoblasts. These increments in bone turnover markers over baseline or control values vary widely between studies, ranging between 29 and 319 %. They were observed as early as 3 months after surgery [45, 52, 55] and occurred in spite of patients taking routinely recommended calcium and vitamin D supplements [53–56, 60, 61, 63].

Indices of increased bone turnover have been demonstrated to persist long after the RYGB procedure. A recent study documented elevated serum osteocalcin and serum N-terminal telopeptide concentrations relative to baseline values at 18 months post-RYGB surgery [60], indicating a prolonged increase in bone turnover. This observation is consistent with a previous report describing raised serum osteocalcin levels in patients examined 10 years after RYGB [54].

Despite these demonstrations of increased bone turnover, there are inconsistent findings of changes in bone mass in subjects post-RYGB surgery. Most [45, 52, 55, 58, 64] but not all [53], [54] reports suggest a decline in bone mineral density and bone mineral content during the first year post-surgery. Any decreases in bone mass post-RYGB have been observed predominantly at the hip, further highlighting the need to investigate both hip and spine regions in such research. Further details of these studies will be highlighted below.

Many studies investigating body composition post-RYGB have used whole body dual-energy X-ray absorptiometry (DXA) scanning to assess overall fat, lean and bone mass. While such scans are primarily designed for the clinical assessment of bone mass, they nonetheless give insights into whole body bone mineral content (BMC), which has been reported to be reduced by 3–12 % at 9–24 months after RYGB surgery [52, 53, 55–58, 61].

Prospective studies which assessed changes in BMD up to 3 years [63] after RYGB in men, as well as in women in various menopausal stages, reported the greatest BMD reduction to be in the femoral neck, where the BMD decline was between 9.2 and 10.9 % compared with baseline values [52, 65], and total hip BMD losses ranging from 8 to 10.5 % [58, 63].

The long-term sequelae of RYGB procedures on bone are not known. In particular, it is unclear whether the BMD loss post-bariatric procedures continues, stabilizes or reverses. A strong association between bariatric surgery and osteoporosis is not supported by the literature [66]. Data from 230 patients followed for 3 years after RYGB surgery reported a significant one-year total hip BMD decline of 9.3 % without further BMD loss after the second and third years, suggesting that bone loss may subside after the first post-surgical year [56]. Conversely, a single prospective study of 59 morbidly obese white women aged 46 ± 8 years showed that their bone density continued to decline after the first year after RYGB despite no further significant weight loss. At 12 months post-surgery, patients' BMD decreased at the femoral neck by 10.2 % and by 3.2 % at the lumbar spine, with an additional BMD decline at the femoral neck by 2.7 % and at the lumbar spine by 3.1 % by the third year post-surgery. BMD at both sites remained above the population-average values of women of the same age [67].

From the above studies, it appears that the clearest declines in BMD after RYGB are seen in the hip and femoral neck. However, although some studies showed no significant change in lumbar spine BMD after RYGB surgery [52, 53, 64], several other studies have reported a significant decline in lumbar spine BMD that varied from 3 to 7 % compared with baseline at 9–12 months post-surgery [55, 63, 65], with an additional 3 % decrement in one of the studies at 3 years post-surgery [63].

In obese subjects after bariatric surgery, an important factor influencing bone status is the loss of body weight that has been postulated to result in bone loss through an unloading effect. Indeed, the decrease in bone mineral density observed in adults after RYGB correlated with the amount of lost weight in many studies [45, 52, 58, 62, 64].

Several studies, outlined below, have documented alterations in the calcium–vitamin D–PTH axis, together with changes in bone turnover markers suggesting that changes in this axis may explain some of the observed bone loss post-RYGB surgery.

A prospective study [55] compared bone turnover in 25 patients post-RYGB with that of 30 obese control participants. Compared to controls, significant elevations in bone turnover markers such as serum osteocalcin and urinary N-terminal telopeptide were observed at 3 and 9 months post-operatively, in association with prominent and significant decreases in BMD of the total hip (7.8 ± 4.8 %, $p < 0.001$), trochanter (9.3 ± 5.7 %, $p < 0.001$) and total body (1.6 ± 2.0 %, $p < 0.05$), as well as significantly reduced BMC at all of these sites by 9 months post-surgery. Other assessments of bone and mineral metabolism (i.e. serum concentrations of parathyroid hormone and calcium as well as 24-h urinary calcium excretion) were not different between controls and post-surgical patients. The post-surgical group self-reported significantly higher dietary vitamin D and calcium intakes, suggesting that vitamin and mineral supplementation may protect against secondary hyperparathyroidism after RYGB surgery.

In a recent prospective analysis comparing pre- and post-surgery values, a similar bone mineral density loss of 8 % was reported in the hip of 23 patients investigated at 12 months post-RYGB [52]. In this study, a linear relationship was observed between weight loss and the decline in bone mineral density, which was associated with raised bone turnover markers relative to baseline ($p < 0.01$ for both urinary N-terminal telopeptide and serum osteocalcin). There was evidence of calcium and vitamin D malabsorption with reduced urinary calcium excretion after RYGB, as well as elevated serum concentrations of parathyroid hormone and unchanged serum 25-hydroxyvitamin D concentrations. Self-reported oral vitamin D intake increased by 260 % by 12 months post-surgery. The authors concluded that RYGB-related bone loss is associated with alterations in the calcium–vitamin D–parathyroid hormone axis, through calcium and vitamin D malabsorption and secondary hyperparathyroidism.

In accordance with previously described studies [52, 63], a recent study of 22 women examined 12 months post-RYGB surgery found that their BMD had decreased by an average of 7.26 % in the lumbar spine, by 8.78 % in the femoral neck, and by 8.59 % at total femur, with associated hyperparathyroidism and elevated urinary concentrations of the bone resorption marker urine N-terminal telopeptide (NTx) [65]. This post-operative bone mass loss occurred in spite of a doubling of 25-hydroxy vitamin D intake amongst study patients via monitored use of multivitamin supplement and regular doses of cholecalciferol. The achieved circulating 25-hydroxy vitamin D levels did not change in the post-operative period despite this supervised supplementation [11.7 (9.7 – 18.0) vs 15.7 (10.2-2.7)] pg/dL pre-operatively, $p = 0.327$], suggesting reduced vitamin absorption or assimilation post-RYGB.

Perhaps more troubling than the above reports of RYGB-induced bone loss in adults are reports of the potential effect of bariatric surgery on bone mass in younger subjects. Currently RYGB remains the most commonly performed bariatric surgical procedure for morbidly obese teens in most US centres [68], albeit sleeve gastrectomy has the potential to become the preferred surgical intervention in obese adolescents due to its efficacy and fewer complications including nutritional deficiencies [69]. A retrospective study [59] of 61 adolescents at 2 years post-RYGB surgery reported significant post-operative bone loss, with a 7.4 % decrease in BMC. There was a decline in the *Z* score for BMD from 1.5 to 0.1; however, it still remained within the normal range for gender and age, likely due to the high bone mineral content and density before surgery in this extremely obese population. Longer follow-up is required to determine whether bone loss in this group of young patients continues, stabilizes or reverses.

Taken together, these studies show that RYGB surgery induces changes in bone remodelling with consistent increase in bone turnover markers and commonly observed bone loss, particularly at the hip. The clinical significance of the observed biological and radiological changes is unclear.

Effects of Biliopancreatic Diversion (BPD) on Bone

Current evidence suggests that biliopancreatic diversion (BPD) with duodenal switch is the most effective procedure for long-term excess weight loss and reversal of comorbidities [36].

However, the prevalence of this procedure declined worldwide from 4.8 in 2003 to 2.2 % in 2011 [5] due to the associated risk of severe metabolic abnormalities. Reports addressing impact of BPD on bone health are scarce and contradictory. Secondary hyperparathyroidism occurs in up to 70 % of BPD patients due to compromised calcium and vitamin D absorption [70], with the associated long-term increase in bone turnover markers despite rigorous calcium and vitamin D replacement [71]. Subsequently, osteoporosis and osteomalacia may develop, as shown by analysis of bone histology at 4 years post-BPD surgery [72, 73].

In contrast to the above studies suggesting bone loss in response to BPD, bone biopsies from 33 BPD patients examined 4 years after BPD surgery showed no evidence of demineralization, as well as showing an increased bone formation rate and trabecular bone volume [74]. Bone mineral density of the hip of these patients was unchanged, but that of the lumbar spine was decreased by 4 %. One-third of patients in this study developed secondary hyperparathyroidism in spite of monitored calcium and vitamin D supplementation.

Comprehensive long-term studies are required to address lifelong sequelae of this uncommon, irreversible bariatric BPD procedure and to define the optimum nutritional programme required to preserve normal bone mineralization process and prevent the potential development of osteoporosis in these patients.

Bariatric Surgery, Bone and Measurement of Bone Mass in Severe Obesity

It is important to point out that interpretation of the published data about bariatric surgery and skeletal health is limited at this stage due to small sample sizes, inconsistent study measures, varying degrees of bone loss as well as potential difficulties in the accuracy of measurement of bone mass in morbid obesity and during weight loss.

The majority of studies have used areal BMD (aBMD; grams per square centimetre) as the primary outcome for bone health in post-bariatric patients, as determined by DXA. In clinical settings, measurement of aBMD by DXA is accepted as a surrogate marker of bone strength and fracture risk [75, 76]. However, this technology is not designed to measure geometric or strength changes known or thought to occur subsequent to changes in mechanical loading. Furthermore, major changes in fat mass and its distribution may affect the precision of BMD measurement in this group of patients, especially when assessing aBMD [77–82]. Variability in aBMD increases significantly with tissue depths greater than 25 cm, and excess fat around bone can result in overestimation of aBMD in obese subjects [83, 84]. Variation in determination of bone area may potentially result in errors in BMD in obese subjects [77, 85].

Positioning of obese subjects for scanning is more difficult than for lean people [84], and variability in positioning of the fat panniculus affects the accuracy of BMD measurements in the hip area. Overlying abdominal pannus can lead to heterogeneity of soft tissue composition over the scanned region of interest (ROI) and unpredictable changes in aBMD values [86], particularly at the proximal femur.

In addition to these technical limitations in obesity, effects of obesity on DXA-based measurements of BMD also vary according to the measurement technique, including the type of DXA system used, the distribution of body fat, the software used, and scan mode [81]. Different DXA manufacturers (GE-Lunar, Norland and Hologic) differ in their methods of fat and BMD determination, and direct comparisons across manufacturers are not possible.

A recent study by Yu and co-workers [87] quantified bone loss using both DXA and quantitative computed tomography (QCT) in 30 obese individuals who lost weight through RYGB. The two methods found a similar, 3 % decline in spine BMD yet discrepant results at the hip. Analysis of DXA scans identified an up to 9 % decline in total hip BMD, whereas QCT detected a more modest loss (3.0–4.5 %) of trabecular bone and negligible total bone loss at any hip site. Both methods were probably affected by artefact in this study. The DXA resulted in an apparent increase in the area of the bone, while QCT resulted in an apparent decrease in measured bone volume. Weight loss will alter the distance between the hip and the X-ray source in fan beam DXA scanners resulting in errors in estimation of bone size although not BMD. By contrast, applying thresholds to QCT to determine the soft tissue/cortical bone edge might have resulted in an apparent decline in volume consequent to a real decline in BMD. This artefact would result in bone loss being underestimated with QCT [88].

In recent years, peripheral quantitative computed tomography (pQCT) has been used to measure volumetric bone density (vBMD, g/cm3) and mechanically meaningful measures of bone geometry, such as bone cross-sectional area and cortical thickness, measurements for which strength differences are evident between populations such as athletes and non-athletes

or between overweight and healthy weight individuals. Given the planar nature of DXA, pQCT provides a more accurate characterization of bone's three-dimensional structure [89–91]. Yet both DXA-based aBMD outcomes and bone strength indices, obtainable by pQCT technology have been shown to correlate strongly with fracture risk [92].

High-resolution peripheral quantitative computed tomography (HR-pQCT), contrary to DXA, may assess the extent to which cortical and trabecular bone are differentially affected after bariatric surgery. The potential advantage of this method has been highlighted by a recent study, which used HR-pQCT technology to evaluate changes in vBMD and microstructure after RYGB bariatric surgery [64]. This study suggested that RYGB surgery primarily affects the cortical bone and that these cortical changes are associated with increased parathyroid hormone levels in surgical patients. In contrast, bone loss at the hip in this study was primarily associated with weight loss [64]. Further studies are needed to corroborate these findings.

In summary, technological limitations in obese populations may preclude accurate assessments of prospective bone changes with any of the available technologies. Extreme obesity and excess fat introduces errors in all BMD measurements and may result in an erroneous estimation of the actual decreases in bone density following substantial weight reduction [77, 80–82]. Studies evaluating the effects of fat simulation on BMD measurements by DXA have reported under- or overestimation in BMD values, depending on the DXA scanner model and software used [77, 93].

Taken together, these limitations of areal bone mineral density by DXA need to be recognized when exploring models, such as bariatric surgery, where changes occur in the mechanical loading environment. The potentially reduced accuracy of DXA measurements in extreme obese scenario underlines the need to perform duplicate scans, follow subjects for extended periods post-surgery after weight loss has ceased, and consider newer technologies, such as pQCT, to further delineate changes in bone volumetric density, geometry and strength after bariatric surgery.

Moreover, measures of bone mass via DXA or other methods should be supplemented with measures of circulating or urinary concentrations of bone turnover markers, to gain a deeper level of insight into any effects of obesity or weight loss on bone physiology.

Potential Mechanisms of Bone Loss after Bariatric Surgery

The cause of the bone mass loss in obese subjects after weight loss has not been fully elucidated. Several mechanisms may explain the changes in bone metabolism observed after bariatric surgery.

In obese subjects after bariatric surgery, one important factor influencing bone status is probably loss of body weight, resulting in reduced mechanical load on the skeleton. Traditionally, this had been thought to be a major contributor to bone mass loss. However, it has recently been reported in adolescents that weight loss accounted for as little as 14 % of their loss of BMC after bariatric surgery, suggesting a significant contribution of additional factors [59]. Additionally, in another study [94] bone loss was found to be greater in the group who lost less weight, suggesting that factors other than weight loss per se were involved in the loss of bone. Such factors include pre-existing micronutrient deficiency, post-surgical changes in calciotropic hormones as well as changes in gut hormones and hormones derived from adipose tissue. These factors will be discussed in greater detail below.

Reduced delivery of essential nutrients, including calcium and vitamin D, may be a consequence of diversionary bariatric procedures such as RYGB, as well as of the energy restriction that follows all successful bariatric operations. Pre-existing alterations in calcium homeostasis [95] and vitamin D deficiency, which are common in obese patients [96, 97], may further contribute to the development of secondary hyperparathyroidism, which has been documented in many [52, 53, 98] but not all studies of bariatric surgery [55, 60]. Such deficiencies could conceivably lead to metabolic and skeletal abnormalities including fractures. Vitamin D insufficiency as defined by mean 25-hydroxy vitamin D level of < 50 or 75 nmol/l has been reported pre-operatively in up to 80 % of bariatric patients [99], with many patients having suboptimal 25-hydroxy vitamin D up to 10 years post-operatively [100]. A review of 14 reports representing data from 1,566 patients found only a single study [101] of 30 patients which reported a mean 25-hydroxy vitamin D > 80 nmol/l. [99]. This study did not report the assay method that was used for vitamin D measurement, making their data difficult to evaluate.

The majority of reported studies on bariatric surgery have not found any significant

increase in vitamin D status above baseline despite vitamin D supplementation [52, 57, 101]. In some studies, although the circulating 25-hydroxy vitamin D levels increased significantly, it did not increase to optimal levels [102, 103]. Suboptimal vitamin D would be consistent with a consequent unresolved hyperparathyroidism, demonstrated in up to 40 % of bariatric patients [102]. Secondary hyperparathyroidism has been demonstrated in up to half of patients two years after RYGB surgery [104]. A more recent study of 22 women (mean BMI 44 kg/m2; mean age 45 years) who underwent RYGB (n = 14) and restrictive procedures (n = 8) reported a substantial increase in circulating parathyroid hormone levels, by 23 ± 8 % (p < 0.02). Two study subjects (1 RYGB and 1 gastric banding patient) developed secondary hyperparathyroidism, which occurred in spite of their pre-operative 25OHD levels being within the normal range, monitored calcium and vitamin D supplementation and stable post-operative serum 25OHD. These findings suggest post-operative depletion in vitamin D and calcium secondary to a varying combination of reduced intake, malabsorption and enhanced storage of vitamin D by adipose tissue [105, 106] that remains well above normal despite adipose tissue loss induced by RYGB surgery.

Serious metabolic bone disorders such as osteomalacia have been estimated to occur in ~2.5 % of patients following gastric bypass in the United States [107]. The osteomalacia and marrow fibrosis which were documented in bone biopsies of five RYGB patients considerably improved after therapy with pharmacologic doses of ergocalciferol (100,000 IU daily) and calcium carbonate (1–2.5 g daily) [108], highlighting the need for prospective long-term studies to determine the appropriate vitamin D supplementation required to prevent osteomalacia in such patients.

Vertical sleeve gastrectomy can also lead to post-operative vitamin D deficiency. In a single study of 60 gastric sleeve patients, 39 % had evidence of vitamin D deficiency at up to 12 months post-surgery despite daily multivitamin supplementation [109]. Restrictive procedures like gastric banding also point to vitamin D deficiency being common up to 2 years after the surgery [110].

Notwithstanding the studies outlined above, the precise impact of micronutrient and vitamin deficiencies on bone health in post-RYGB patients has not been well documented, partly due to lack of standardized guidelines for the nutritional care and assessment of these individuals. Studies have used different post-operative calcium and vitamin D dietary and supplementation protocols. Prescribed supplements have varied in dose and, although sufficient for a general population, may not be sufficient in bariatric surgery patients. Lack of rigorous post-operative follow-up, and varying recommended dosages of calcium and vitamin D supplements across studies, might also have contributed to differences in estimated bone loss. To our knowledge only two studies [52, 64], which reported evidence of calcium and vitamin D malabsorption after RYGB surgery, monitored vitamin D and calcium compliance through standardized questionnaires of intake from food sources and supplements.

Although the American Society for Metabolic and Bariatric Surgery recommends high levels of Ca (1.5–2 g/day) and vitamin D intake (3,000 IU/day) following bariatric surgery [111], exact levels associated with beneficial outcomes are not known due to the lack of randomized controlled trials. Studies suggest that serum 25-hydroxyvitamin D concentrations ≥80 nmol/l optimize calcium absorption and suppresses parathyroid hormone secretion; however—as seen in the above studies—monitored vitamin D supplementation did not mitigate vitamin D insufficiency and observed reductions in BMD [112].

Besides deficiencies in micronutrients, notably calcium and vitamin D as noted above, the more radical bariatric surgical procedure of BPD may lead to macronutrient deficiency, namely protein malnutrition [113]. Protein-calorie malnutrition is recognized by signs such as hypoalbuminemia, oedema, anaemia and hair loss. Hypoalbuminemia has been demonstrated in 3.4–18.0 % of patients post-BPD and duodenal switch [113, 114].

Protein deficiency could conceivably contribute to the bone loss that has been reported in some [72, 73] but not all [74] studies of patients post-PBD surgery. The positive effects of protein intake on bone have been established in several epidemiological and clinical studies [115], but the relationship is not strictly linear because some studies have linked excessive protein intake with hypercalciuria and an increased risk of fracture [116]. In a prospective study of healthy, pre-menopausal women, a low-protein intake of 0.7 g/kg body weight was associated with an increase in bone resorption marker of urinary collagen type 1 cross-linked telopeptide NTX compared with a diet containing 1.0 g/kg of protein [117]. Studies indicate that inadequate dietary protein may lead to low calcium absorption and the development of secondary hyperparathyroidism with an increased risk of osteoporotic

fractures [118]. In the National Health and Nutrition Examination Survey (NHANES I) study, hip fractures were associated with low energy intake, low serum albumin levels and low muscle strength consistent with protein deficiency [119]. A higher-protein weight loss diet may preserve bone mass during caloric restriction by attenuation of decreased circulating concentrations of insulin-like growth factor 1 or calcium absorption [120].

The Endocrine Society guidelines suggest that bariatric patients should ingest 60–120 g of protein daily [121]. A systematic review of protein and bone health concluded that diets containing protein at a level of 1.0–1.5 g/kg body weight are optimal for bone health [122]. A similar level of protein intake is also considered optimum for appetite control and weight management in non-bariatric patients [123]; thus, there are likely to be multiple benefits from this recommendation. However, such a protein intake can be difficult for obese and morbidly obese patients to achieve on calorie restricted eating plans without rigorous attention to dietary choices, let alone for patients with reduced gastric capacity. Thus, prevention of protein malnutrition in bariatric patients requires that patients work with dieticians to help ensure they meet their dietary requirements.

While studies to date have not enabled definitive dissection of the relative contribution of changes in nutrient status and/or weight loss to changes in bone after bariatric surgery, other studies point to novel potential mechanisms of the change emanating from other potential mechanisms, such as the adipose tissue–gut–brain axis.

A serious question to be examined is whether hormonal responses to bariatric surgery contribute to bone loss. Dietary energy restriction (without bariatric surgery) has been shown to induce neuroendocrine changes that would be expected to accelerate bone loss [124]. Such changes include reduced circulating concentrations of thyroid hormones, sex hormones and insulin-like growth factor-1 alongside increases in circulating cortisol levels [125]. There is also a growing body of literature showing that bariatric surgery alters the secretion of hormones from adipose tissue (notably the adipokines leptin and adiponectin), bone-derived factors such as the osteokine osteocalcin and sclerostin, as well as from the gastrointestinal tract (notably the appetite-regulating gut hormones PYY, GLP-1 and ghrelin), all of which have been shown to have significant effects on bone homeostasis in recent studies. The majority of these data demonstrating involvement of these hormones on bone come from a series of elegant gene knockout studies in rodents [126–128]. Current knowledge of the extent of their involvement in any bariatric surgery-induced bone loss and the mechanisms underlying such effects is limited.

For the purpose of this review, we will focus on the appetite-regulating hormones originating from the gut, namely peptide YY (PYY), GLP1 and ghrelin, as well as the adipokines leptin and adiponectin, the osteokine osteocalcin, as well as sclerostin.

Peptide YY

PYY belongs to a polypeptide family that also includes neuropeptide Y (NPY) and pancreatic polypeptide (PP). PYY is recognized as a critical regulator of food intake and energy homeostasis. PYY is released from enteroendocrine L cells lining the distal gastrointestinal tract in response to a meal [129, 130]. Circulating PYY is lowest in the fasting state and rises postprandially to suppress appetite. Obese subjects have been reported to have significantly reduced circulating fasting and postprandial levels of PYY [131].

Postprandial PYY levels have been shown to increase in response to RYGB [132] and sleeve gastrectomy [133], while it remains unclear whether gastric banding has any comparable effects on fasting or postprandial circulating PYY levels [134].

Recently, an inverse relationship between elevated PYY and both body weight and bone loss has been modelled in mice. Transgenic overexpression of PYY in mice was protective against diet and genetically induced obesity and demonstrated strong, negative effects on bone, resulting in decreased bone formation and increased resorption, with opposite effects in PYY null mice [135]. In contrast, a study of an independently generated PYY knockout mouse line reported an osteopenic phenotype, with reductions in vertebral cancellous bone mass and bone strength [136]. The differences observed between these PYY knockout mouse studies might have occurred due to problems with developing genetically altered PYY levels in these animals, as PYY overexpression has teratogenic effect on embryonic neurogenesis [137].

In humans, several reports point towards an association between elevated PYY and low BMD, with PYY being negatively correlated with bone mass in people with normal weight and with anorexia nervosa. Consistent with a negative effect of PYY on body weight and bone

mass, circulating PYY concentrations are markedly elevated in anorexia nervosa [138], a condition well known to be associated with low BMD [139]. Indeed, Utz et al. [139] demonstrated that PYY levels were significantly negatively correlated with metabolic and skeletal indices. Russell [140] demonstrated PYY to be negatively associated with lumbar BMD Z scores and a marker of bone formation, serum type 1 procollagen C-terminal/N-terminal (PINP) in adolescent female athletes both with and without amenorrhoea. Moreover, in lean pre-menopausal women, circulating PYY levels were significantly and negatively correlated with total body and hip bone mass, with PYY contributing to 9 % of the variance in BMD of the hip [141]. A single clinical study to date has correlated raised postprandial PYY levels with bone mineral density loss in bariatric surgery patients (Brzozowska MM, Endocrine Reviews 2013: FP09).

Future work with formal, standardized protocols is needed to elicit exact contributions of these neuroendocrine changes to accelerated bone loss in patients who undergo obesity procedures.

GLP1

GLP1 is a key incretin that, along with PYY, is released from the lower intestinal endocrine L cells in response to ingested nutrients [142]. GLP-1 exerts glucoregulatory actions by stimulating insulin secretion, slowing gastric emptying and attenuating glucose-dependent glucagon secretion [143]. As with PYY, it has been suggested that increased postprandial GLP-1 levels may contribute to inducing a signal of satiety within the hypothalamus and promoting weight loss [144]. Several studies have shown that the secretion of GLP-1 is considerably attenuated in type 2 diabetes [145] and in obesity [146], although contradictory findings have also been reported [147].

Relatively few studies have examined changes in GLP-1 concentrations in obese patients after bariatric procedures. Patients who underwent gastric banding showed either a reduction or no post-surgical change in fasting GLP-1 levels [148–150]. Furthermore, three studies that measured the postprandial GLP-1 levels after a meal at up to 12 months post-gastric banding did not find any significant difference compared to values measured pre-operatively [150–152]. Similarly for sleeve gastrectomy, fasting GLP-1 levels pre-operatively and 3 months post-operatively were similar; however, the postprandial area under the curve and peak levels of GLP-1 increased as early as the first post-operative week [153, 154]. Post-surgical increases in postprandial GLP-1 have been documented following RYGB [150, 155]. Augmented levels of GLP-1 may account for the antidiabetic effect of the RYGB procedure, which has been reported before any major weight loss has occurred [33, 155, 156]. Thus, these data suggest that postprandial—albeit not fasting—circulating levels of GLP-1 may be augmented after bariatric procedures, at least sleeve gastrectomy and RYGB.

Although osteoblasts express the GLP-1 receptor (GLP-1R), the main action of the GLP-1/GLP-1R pathway in bone physiology and bone quality is largely unknown. The influence of GLP-1 on bone regulation has been predominantly studied in rodents. GLP-1 receptor knockout mice have cortical osteopenia and bone fragility, as determined by DXA, as well as increased osteoclastic numbers and bone resorption activity as determined by bone histomorphometry [157]. Rats treated with GLP-1 for 3 days via subcutaneously implanted osmotic pumps displayed elevated expression of osteoblastic genes in bone tissue without any change in plasma glucose and insulin after treatment [158]. In this study, these effects were true for wild-type mice as well as in rat models with glucose intolerance.

The results from these studies point to an insulin-independent anabolic effect of GLP-1 on bone and suggest that GLP-1 could be a useful therapeutic agent for improving the deficient bone formation and bone structure associated with glucose intolerance [158]. However, information about the role of GLP-1 in this regard is scanty and has not been investigated in human studies.

Ghrelin

Ghrelin is a potent appetite-stimulating hormone, synthesized in the gastric antrum and fundus [159]. The circulating concentrations of ghrelin increase under preprandial and fasting conditions, and this change likely contributes to the drive to eat after periods without food [160].

Reports of circulating ghrelin levels after bariatric surgery vary, with either no change or increases in fasting plasma ghrelin relative to baseline after gastric banding [148, 161]. By contrast, a reduction in fasting plasma ghrelin relative to baseline levels was found in one

study up to 5 years after sleeve gastrectomy [162]. Inconsistent post-surgical changes in circulating ghrelin levels have been found after RYGB, with studies demonstrating a reduction [163, 164], no change [165, 166] or increased ghrelin levels versus baseline [167, 168].

In addition to effects on energy homeostasis, ghrelin may play a role in the regulation of bone metabolism through its effects on growth hormone via binding to the growth hormone secretagogue receptor, and as a consequence, an increase in insulin-like growth factor-1 secretion [169]. Ghrelin may also have a role in bone metabolism independent of the growth hormone axis, as osteoblasts have been reported to directly respond to ghrelin with increased proliferation and differentiation [170]. Furthermore, ghrelin was shown to increase BMD in rodents independent of growth hormone signalling [171].

While animal studies suggest a predominantly anabolic effect of ghrelin on bone, clinical findings are not yet clear. In one study, there was no significant association between ghrelin and BMD [172]. Conversely, another study of pre-, peri- and post-menopausal women found a significant positive correlation between ghrelin, oestradiol and BMD at the spine, hip and radius in all subjects [173]. Overnight ghrelin secretion has been found to be positively and significantly related to BMD in healthy adolescent women [174], but no consistent relationship was seen between fasting ghrelin levels and BMD in older men and women [175].

In summary, although both human and animal studies point to ghrelin emerging as a potentially positive regulator of bone, it remains yet to be determined whether ghrelin contributes to changes in bone metabolism in response to bariatric surgery.

Adiponectin

Adiponectin is an adipose tissue regulatory protein that is produced by fat cells and inhibits fat cell synthesis [176]. Serum adiponectin levels are suppressed in obese subjects [177]. Adiponectin levels are negatively correlated with fat mass, with a low expression in adipose tissue in obese mice and humans [178, 179], and they increase with weight loss [180].

Circulating adiponectin has been shown to have antiosteogenic effects on bone cells due to indirect induction of formation of bone-resorbing osteoclasts via stimulation of receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibition of osteoprotegerin production by osteoblasts [181]. Further evidence for potential antiosteogenic actions of adiponectin comes from observations of its ability to bind some growth factors [182] and to reduce circulating insulin concentrations [183]. This would tend to oppose any anabolic effects of insulin on bone and other tissues.

Clinical studies support the data that adiponectin may have antiosteogenic effects on the skeleton. In a recent meta-analysis of 59 studies which examined the influence of adipokines and ghrelin on bone mineral density and fracture risk in healthy men and women, adiponectin was found to be negatively associated with BMD independently of gender, menopausal status and fat mass parameters [172]. A single, prospective study of 42 women who were investigated at 12 months after gastric bypass [58] documented a significant and positive correlation between circulating adiponectin levels and the reduction in BMD relative to baseline ($r = 0.35$; $p < 0.05$). The described effect was unrelated to baseline parameters of body weight or body composition, or to the gastric bypass-induced changes in these parameters. In another study, although adiponectin significantly increased at 6 months post-RYGB, there was no correlation between change in adiponectin and increase in serum markers of bone turnover [60]. In summary although adiponectin increase induced by weight loss seems to favour bone loss, further studies are required to delineate the impact of increased adiponectin on bone–adipose axis post-bariatric surgery.

Leptin

Leptin is a cytokine-like hormone secreted by adipocytes [184]. One of the major determinants of leptin secretion is fat mass, with circulating leptin levels increasing with increasing fat mass [185]. Leptin plays a central role in the regulation of food intake and energy balance as it inhibits appetite and favours energy expenditure [186]. Several studies have shown that serum leptin concentration decreases after the massive weight reduction induced by bariatric surgery. These studies point to strong correlations between changes in serum leptin concentration with changes in BMI [187–189] as well as fat mass, serum insulin concentrations, and the insulin resistance index [189].

Besides metabolic effects, leptin has also been purported to be a regulator of bone mass via direct effects on bone cells as well as via indirect effects involving the hypothalamus [190].

Leptin has a direct anabolic effect on bone as it stimulates bone formation by driving the differentiation of bone marrow stem cells into the osteoblastic (bone forming) cell lineage, while simultaneously inhibiting the differentiation of osteoclasts (bone-resorbing cells) [191, 192]. This effect has been reported in leptin-deficient animals [193–195]. For instance, peripherally administered leptin had a stimulatory effect on bone mass in leptin-deficient *ob/ob* mice [193].

In contrast to the anabolic effects of leptin acting directly on bone, leptin has been reported to have centrally mediated antiosteogenic actions through at least two separate central nervous system mechanisms including activation of both sympathetic and cocaine amphetamine regulated transcript (CART)-responsive neurons. Leptin has also been reported to promote bone loss by inhibiting osteoblast proliferation and promoting receptor activator of RANKL expression [196]. The central antiosteogenic effect of leptin was first revealed as an increased trabecular bone mass observed in leptin-deficient *ob/ob* mice and leptin receptor-deficient *db/db* mice. Moreover, hypothalamic leptin administration reduced trabecular bone mass in leptin-deficient and wild-type mice [190]. However, more recent work shows that the antiosteogenic actions of leptin are limited to trabecular bone, with leptin-deficient *ob/ob* mice exhibiting decreases in cortical bone mass [197] in conjunction with consistently elevated trabecular bone mass [198].

Conflicting data exist for human studies investigating effects of leptin administration in low leptin states (i.e. congenital leptin deficiency, lipodystrophy and hypothalamic amenorrhoea), where varying effects on bone have been reported, ranging from net bone formation to no change at all [199–202]. However, the following studies shed some light on the possible role of leptin in the regulation of bone in humans.

In a recent meta-analysis of 59 studies, leptin was positively associated with BMD, especially in post-menopausal women, where the pooled correlation coefficient varied from 0.18 to 0.33 [172]. Moreover, in this study, high levels of leptin were predictive of lower risk of vertebral and hip fractures, independent of body weight [172].

Emerging clinical evidence is consistent with the possibility that the post-surgical reduction in circulating leptin levels could contribute to any associated bone catabolism. A reduction in circulating leptin levels consistently observed after bariatric surgery would lead to a reduction in the direct stimulatory effects of leptin on bone cells. For instance, a prospective study of 20 individuals [60] examined serum concentrations of bone turnover markers as well as leptin at 6 and 18 months after RYGB surgery. In this study, the increase in serum N-terminal telopeptide NTX relative to baseline levels correlated significantly with the corresponding decrease in serum leptin levels ($r = 0.45$; $p = 0.04$) as well as the reduction in BMI ($r = 0.58$; $p = 0.009$) and the increase in serum 25-hydroxy vitamin D ($r = 0.43$; $p = 0.05$). In multiple regression analysis, however, only the reduction in circulating leptin levels was a significant predictor of the increase in N-terminal telopeptide (NTX) ($p = 0.016$), suggesting that the RYGB-induced decrease in leptin may be causally related to increased bone turnover.

Osteocalcin

The skeleton has recently emerged as an endocrine organ, with bone cells—osteoblasts and osteoclasts—secreting a variety of proteins, called osteokines. Osteokines not only influence bone homeostasis, they also have an impact on energy and glucose homeostasis [203–207]. The crosstalk between the skeleton and adipose tissue thus constitutes a homeostatic feedback system, with adipokines and osteokines linking these tissues in an active adipose–bone axis.

One important osteokine is osteocalcin. Osteocalcin is a non-collagenous protein marker of osteoblastic activity thought to play a role in bone mineralization and calcium homeostasis [205]. The role of osteocalcin in bone is not entirely understood. Previous studies noted an antianabolic action of osteocalcin with a mild increase in bone mass and greater cortical bone formation in the osteocalcin null mice [208].

Recent reports have identified a crucial role for osteocalcin in energy metabolism by enhancing insulin secretion, insulin sensitivity and energy expenditure [209]. While osteocalcin can exist in two forms, gamma-carboxylated (GLA) and undercarboxylated (GLU), only the undercarboxylated form of this molecule appears to function as a hormone in murine studies. Osteocalcin knock-out mice have increased fat mass and decreased insulin sensitivity [210], while treatment of wild-type mice with undercarboxylated osteocalcin leads to decreased fat mass and improved glucose handling [206].

The above data from murine models suggest that glucose homeostasis is controlled by osteocalcin production and the preponderance of evidence points to this pathway being present in humans, although the carboxylated GLA form of osteocalcin may be more important in humans. The evidence of a relationship between the circulating levels of osteocalcin and development of dyslipidemia, metabolic syndrome, insulin resistance and diabetes mellitus in humans has been growing rapidly with observational data [211–214]. Interestingly, markers of bone turnover including osteocalcin are lower in diabetic patients than in normal individuals and interventions which improve glycemic control have been associated with an increase in serum osteocalcin [215–217]. Additional studies with larger cohorts and longer follow-up are needed to determine whether the increase in osteocalcin following weight loss reflects a change in bone formation, glucose homeostasis or both. However, these studies suggest that alterations in bone turnover and with it osteocalcin levels would impact energy and glucose homeostasis. As such, the increase in turnover following some bariatric surgeries would act to improve fat mass loss and glycaemic control.

Sclerostin

Sclerostin, the product of the sclerosteosis (SOST) gene, is an osteocyte secreted negative regulator of bone formation. Sclerostin blocks Wnt/beta-catenin signalling in cells of the osteoblastic lineage through the low-density lipoprotein receptor-related protein Lrp5/Lrp6 receptor [218]. The contrasting effects of SOST knockout [219] and transgenic overexpression [220] on bone in mice provides compelling evidence that sclerostin secretion by osteocytes can control bone mass by antagonizing the effects of WNT to induce osteoblastogenesis, stimulate pre-osteoblast replication and inhibit osteoblast apoptosis [220–222]. As such, sclerostin secretion by osteocytes in the adult skeleton appears to suppress bone formation and promote bone resorption [223, 224]. Further evidence for this effect of sclerostin is provided in the human disorders of Van Buchem's disease [225] and sclerosteosis [226], which exhibit loss of sclerostin expression and pathologically high bone mass.

Mechanical loading of bone plays a key role in determining bone mass, strength and size [227, 228]. The exact nature of mechanosensing in bone is not fully elucidated, but points towards sclerostin being a mediator of the bone response to mechanical force. This concept was supported by studies of SOST knockout mice that proved to be resistant to bone loss in the hindlimb unloading model as well as in increases in sclerostin levels in experimental models of skeletal unloading [229, 230].

Recent human studies also support a role of sclerostin in mediating bone responses to mechanical unloading. Post-menopausal women long term immobilized by stroke exhibited significantly higher serum sclerostin levels relative to age- and gender-matched community controls as well as lower bone density as assessed by quantitative ultrasound measurements of the calcaneus [231]. These raised sclerostin levels were associated with increased circulating concentrations of the bone resorption marker, measured by carboxy-terminal telopeptide of type I collagen. These observations of hypersclerostinemia being associated with reduced bone formation in immobilized patients highlight the potential role of sclerostin in osteoporosis resulting from mechanical unloading and disuse in humans.

Recent research indicates that increases in circulating sclerostin levels may contribute to the bone loss associated with weight loss in humans, at least that which is induced by lifestyle interventions [232]. A study of obese (BMI ≥ 30 kg/m2) older (≥65 years) adults who were randomly assigned to a 1-year programme of diet, exercise, combined diet plus exercise or a control group examined the role of mechanical stress in modulating sclerostin levels. The significant weight loss (−9.6 ± 1.2 % of initial body weight) observed in the diet group was associated with significantly increased serum sclerostin levels over baseline values at 6 and 12 months. Additionally, raised sclerostin levels correlated with adverse changes in hip geometry parameters for this group of patients. In contrast, participants who were randomized to the diet plus exercise intervention showed similar weight loss (−9.4 ± 0.8 % of initial body weight) to that observed in the diet-only group with no increase in circulating sclerostin levels and preserved bone quality as assessed by hip geometry parameters. Taken together, these results suggest that sclerostin may partially mediate bone loss and deterioration in bone structure in obese patients undergoing voluntary weight loss [232].

In the light of the above findings, additional studies are warranted to delineate the possible role of sclerostin in bone loss associated with massive changes in weight loss and hence mechanical loading as a result of bariatric surgery. As sclerostin suppression is at least partially responsible for the anabolic action of mechanical loading, pharmacological modulation of sclerostin in osteocytes may provide a possible novel therapeutic approach

directed at preventing bone loss after bariatric surgery. Recently, phase II trials of sclerostin antibody therapy have been published, demonstrating very promising results [233].

Fractures and Bariatric Surgery

Bone loss after bariatric surgery would be particularly important if it results in an increase in fracture risk.

Two recent papers have provided new insight into this issue. Nakamura et al. [234] examined the risk of fracture in patients who underwent predominantly RYGB. The participants aged 44 ± 10 years, 80 % of them were female, and their mean BMI was 49 ± 8 kg/m2 were followed up over 7.7 years. The fracture rate of patients who underwent surgery was compared with that of the general population, matched for age and sex. This study found that bariatric surgery was associated with a 2.3-fold increased relative risk of any fracture (95 % CI 1.8–2.8), including sites considered osteoporotic (that is, hip, spine, humerus and wrist), although most fractures were of the hand, leg and foot. Interestingly, the increase in fractures was observed early after surgery, but over half of the subsequent fractures did not occur until 5 years following bariatric surgery. Moreover, a prior fracture was not predictive of a fracture after surgery in this cohort. These findings suggest that obese patients may have different determinants of fracture than the general population, in which a prior fracture strongly predicts the likelihood of experiencing a subsequent fracture.

These results differ from a retrospective UK study that found no significantly increased risk of fracture relative to controls in patients at a mean of 2.2 years after bariatric surgery. However, the study did demonstrate a trend towards an increased fracture risk 3–5 years post-bariatric surgery in patients who had a greater surgery-induced decrease in BMI [235].

The different outcomes of these two studies most likely arise from significant differences in their study designs. In the UK study, the majority of participants underwent gastric banding, with only 29 % of patients undergoing RYGB. The gastric bypass subjects described by Nakamura et al in the USA were heavier than those in the UK study, and they achieved more marked weight loss. The UK investigators matched their patients and controls for age, sex and weight, whereas the US study compared the fracture rate in participants with that of general population matched for age and sex (but not weight). Matching control groups to pre-surgery weight or BMI would have elucidated any bariatric surgery-induced differences over and above weight itself, but the US comparisons to the general population would not exclude obesity itself as a factor in the increased fracture risk observed.

Thus, further studies are urgently required to determine whether or not bariatric surgery is associated with an increased fracture risk, as such a finding would have important clinical implications for the increasing number of people undergoing bariatric surgery for the management of obesity.

The precise reasons behind the suspected increase in fracture risk in bariatric patients are not fully elucidated. The previously discussed study which used HR-pQCT technology to evaluate volumetric BMD (vBMD) of the distal radius and tibia in RYGB patients at 12 months post-surgery [64] indicated that these patients experienced not only cortical bone loss but also reduced proximal and distal cortical load shares, indicative of decreased cortical bone strength. Changes in bone microarchitecture in these study patients were associated with increased parathyroid hormone levels, which occurred despite patients taking recommended calcium and vitamin D supplements. The researchers concluded that the decrease in the cortical strength after bariatric surgery may be associated with an increased future fracture risk for RYGB patients, particularly in those with secondary hyperparathyroidism and more significant weight loss [64]. However, this remains to be verified.

Summary and Conclusions

Bariatric surgery remains the most effective treatment of severely obese patients. However, the potential long-term effects of bariatric surgical procedures on other outcomes including bone health in this unique group of people are only partially understood.

Despite significant improvement in weight and comorbid conditions, there is a growing concern that bariatric surgery may exert a negative effect on the skeleton by accelerating bone loss, thereby increasing bone fragility [236]. Studies to date suggest that the more invasive procedures such as RYGB, when compared with gastric banding, induce a greater weight reduction as well as bone loss that preferentially affects the hip. In extreme cases, the impact of RYGB on skeletal health could be significant and, if not monitored, lead to severe metabolic disturbances including osteomalacia. However, what is perhaps more of a

concern is the potential risk to bone health associated with the increasingly popular bariatric procedure of sleeve gastrectomy, which is steadily replacing gastric banding. This procedure appears to result in similar bone losses to that induced by RYGB, but long-term data are lacking.

The specific mechanisms responsible for the skeletal effects of bariatric surgery have not been fully elucidated and need to be further defined. However, perturbations in a number of gut- and adipocyte-derived hormones including PYY, GLP-1, ghrelin, adiponectin and leptin post-bariatric surgery may have effects on bone which appear to be predominantly negative. In addition, there is a lack of standardized post-operative calcium, vitamin D and protein dietary and supplementation protocols for these patients. Further research is required to determine optimum doses of nutritional supplements, which are likely to be different in obese bariatric patients due to underlying and surgery-induced differences in nutrient absorption and assimilation.

While much has been learned from DXA-based research, this technology is not without technical limitations in obese populations and during dynamic weight loss. These uncertainties need to be recognized and further explored and defined and studied in conjunction with other technologies such as pQCT that can assess site-specific bone structure, bone geometry and estimates of bone strength, albeit with their own limitations.

Finally, prospective cohort studies that assess bone changes for several years after bariatric procedures, at more than one site, and together with bone turnover markers and carefully measured hormonal parameters, should provide a higher level of evidence for change in bone density. These studies will help clarify any negative clinical consequences of these changes, including future fracture risk in this group of patients.

Disclosures

Conflict of interest Malgorzata Monika Brzozowska, Amanda Sainsbury, John A. Eisman, Paul A. Baldock, and Jacqueline R. Center declare that they have no conflict of interest.

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

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