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The Impact of Bariatric Surgery on Bone Health: State of the Art and New Recognized Links

Authors
Fernando Mendonça[1, 2], Raquel Soares[2, 3, 4], Davide Carvalho[1, 2, 3], Paula Freitas[1, 2, 3]

Affiliations
1 Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar e Universitário de S. João, Porto, Portugal
2 Faculdade de Medicina da Universidade do Porto, Porto, Portugal
3 Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal
4 Departamento de Biomedicina, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

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Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Fernando Mendonça
Serviço de Endocrinologia
Diabetes e Metabolismo
Centro Hospitalar e Universitário de S. João
Porto
Portugal
Tel.: + 351/915/570 714
fernandomiguel_92@hotmail.com

ABSTRACT

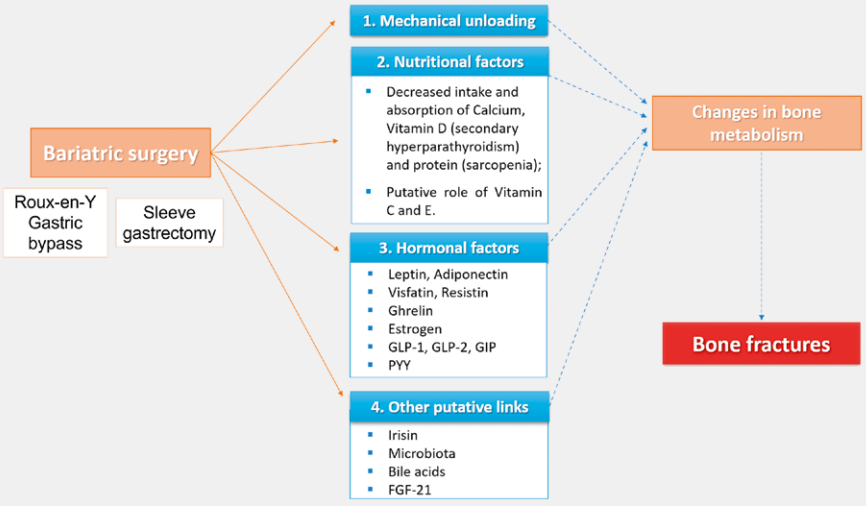
Bariatric surgery (BS) is the most effective therapy for severe obesity, which improves several comorbidities (such as diabetes, hypertension, dyslipidemia, among others) and results in marked weight loss. Despite these consensual beneficial effects, sleeve gastrectomy and Roux-en-Y gastric bypass (the two main bariatric techniques) have also been associated with changes in bone metabolism and progressive bone loss. The objective of this literature review is to examine the impact of bariatric surgery on bone and its main metabolic links, and to analyze the latest findings regarding the risk of fracture among patients submitted to bariatric surgery.

Introduction

Obesity is a preventable global health problem that continues to grow at an alarming rate [1]. According to the World Health Organization, in 2016, almost 2 billion adults were overweight and 650 million were obese [2]. Projected estimates from 2017 show that in 2030, obesity levels could reach huge proportions in some countries, such as the United States, Mexico, and the United Kingdom, where respectively 47, 39, and 35 % of the population is believed to be affected by this chronic disease [3]. These data gain particular relevance after acknowledging that obesity is related with multiple associated conditions, such as type 2 diabetes [4], hypertension [5], dyslipidemia [6], obstructive sleep apnea, cardiovascular disease, cancer, and increased mortality [7–9]. The management of this disease and its associated complications has evolved during the last decade [10], with an increased awareness for the long-term benefits of a more definitive approaches, such as bariatric surgery [11, 12]. These benefits (which include durable weight loss, diabetes remission, and the amelioration of multiple cardiovascular risk factors and other comorbidities) led to a progressive increase in the number of surgeries performed worldwide [13, 14].

Despite these advantages, one possible side effect of surgical procedures is their negative impact on bone health, an important issue that received more attention during the last decade [15, 16]. The mechanisms that are responsible for bone deterioration after bariatric surgery encompass diminished mechanical loading, malabsorption (calcium and vitamin D, among other nutrients) and altered gastrointestinal and adipocyte hormone levels [17].

Accordingly, the objective of this narrative review is to analyses the impact of bariatric surgery on bone metabolism, focusing mainly on the two most performed procedures worldwide [sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB)] (▶ **Fig. 1**). The review then proceeds to present the main players in this intricate relationship and to explore new recognized connections, based on recent data. The main techniques to measure bone mineral density



▶ **Fig. 1** Schematic presentation of the connections between bariatric surgery and bone metabolism. GLP-1: Glucagon-like peptide 1; GLP-2: Glucagon-like peptide 2; GIP: Gastric inhibitory polypeptide; PYY: Peptide YY; FGF-21: Fibroblast growth factor 21.

and predict fracture risk are also discussed, as well as the risk of a fracture occurring after bariatric surgery.

Measuring the Impact of bariatric surgery on bone mass and fracture risk

Several imagiological and analytical tools have been applied, mainly during the last decade, to understand how obesity and bariatric surgery affects bone metabolism. Most of them used dual-energy X-ray absorptiometry (DXA), which is a quantitative non-invasive technique that is the standard reference method for measuring BMD. DXA is commonly used to diagnosis and monitor osteoporosis, however it can also have other applications, such as in evaluating whole body composition [18]. Despite being extensively used as the main imagery for evaluating bone (even among obese individuals), it does, however, have various limitations. Up until recently, the tables of DXA scanners were only able to support a maximum weight of 136–160 kg, depending on the machine used. Despite the fact that newer models can support heavier weights (up to 205 kg), the problem is that sometimes tables are not wide enough to accommodate some severely obese patients [15]. In addition, the precision of DXA scans declines with higher BMI and excessive fat accumulation around bones, which could lead to unpredictable errors in DXA evaluation of up to 20 %. This fact explains the increased difficulty in obtaining and interpreting measurements from axial sites (lumbar spine, hip) when compared with those from peripheral ones (such as radius or tibia). Other problems that lead to imprecisions include differential positioning of adipose abdominal panniculus and the presence of vertebral fractures, which can also contribute to erroneous BMD values [19]. The accuracy of BMD is also affected by significant weight loss, which is a recurrent problem among this particular population who is submitted to bariatric surgery. This problem seems to be related with an alteration in the distance between X-ray source and the bone, owing to the diminished interposition of fat (which can change the evaluation of bone area, while calculating areal BMD or bone mineral content) [20]. Another handicap of DXA is that it can only measure two different tissues at the same time (for instance, soft tissue and bone) and when it measures body composition, a DXA scan tends to make assumptions about fat/lean tissues ratios to reveal the densities of three different tissues (lean tissue, fat, and bone). These ratios can be flawed in cases of significant weight loss. Finally, different manufacturers of DXA machine (GE-Lunar, Hologic, Norland) employ distinct methods to determinate BMD and adipose tissue proportion, which makes it impossible to compare results obtained from machines with different brands [21].

Bearing in mind the limitations of the use of DXA in obese states, other methods for evaluating have been pursued. One of them is quantitative computed tomography (QCT), which is a three-dimensional technique that quantifies BMD in several sites, such as the hip, spine (axial QCT) [22] or forearm, proximal femur, and tibia (peripheral QCT – pQCT). The strengths of QCT are the ability to separate cortical and trabecular bone, the determination of 3D geometric parameters (such as cross-sectional area, dimensions, cortical thickness, trabecular structure), and enabling the technician to characterize the bone in more detail. This ultimately leads to a better understanding of bone-related anomalies associated with the risk of fracture [23]. This exam can even be recommended for specific groups to maximize the accuracy of the evaluation of bone features, namely: very large or small patients (e. g., those with obesity) and older patients with advanced degenerative disease of the lumbar spine, as well as in cases where high sensitivity is needed (corticosteroid or parathormone treatment). The limitations of QCT include a relatively higher dose of radiation when compared with DXA and a limited number of longitudinal studies have evaluated QCT's ability to predict fractures [24, 25]. A study by Yu

et al. compared the QCT and DXA measurements of 30 patients with morbid obesity who had been submitted to RYGB. This study found that both methods detected a 3 % lower incidence of BMD in the spine, but discordant measurements at the hip, with the detection of a larger decline in total BMD when the patient was evaluated with DXA (9 %), with negligible changes of total BMD at any site of the hip when measured with QCT (despite having a 3.0–4.5 % loss of trabecular bone). The results suggest that one of these two methods is probably affected by the presence of foreign objects, which prompts the need for further research in the area of bone evaluation in obese/bariatric states [26].

The need to prevent bone fractures led the University of Sheffield to launch the fracture risk assessment tool (FRAX) in 2008, which provides country-specific algorithms to predict the 10-year probability of hip and major osteoporotic fracture (spine, hip, proximal humerus, and distal forearm) of a given patient. This tool evaluated seven different clinical risk factors that impact fracture risk, namely: previous fragility fracture, systemic glucocorticoid use, mother/father hip fracture, smoking, excess alcohol consumption, rheumatoid arthritis, and other causes of secondary osteoporosis. When added to age, sex, and BMI, these factors provide a 10-year fracture probability estimate that is independent of BMD [27]. This popular tool, which can be easily accessed through its website [28], includes the option to measure the BMD of femoral neck to refine the results. The FRAX estimate also helps physicians to decide whether to intervene therapeutically, although the various available guidelines differ with regards the treatment of cutoffs.

Another tool that can be incorporated optionally in the FRAX is the trabecular bone score (TBS) [29], which is a textural index that is associated with bone microarchitecture which analyses pixel gray-level variations in the DXA image of the lumbar spine. By so doing, TBS can distinguish differences in the 3-dimensional bone microarchitecture, even in 2-dimensional DXA evaluations with the same BMD levels. One finding that is independent of BMD is the fact that higher TBS values are correlated with stronger bone microstructure, whereas low values are correlated with a worse, fracture-prone microarchitecture [30]. The proposed TBS cutoffs for bone architecture among pos-menopausal women are: >1350 – normal; TBS between 1200 and 1350, which is consistent with partially-deteriorated bone microarchitecture; and TBS<1200 – degraded bone microarchitecture. Limits for other groups of patients (such as male patients) are yet to be defined [31]. One of the main limitations of TBS is its lower accuracy for extreme levels of BMI, which is only being recommended for those patients who have a BMI of between 15–37 kg/m^2 [29]. When considering the BMI requirements for bariatric surgery, it is easy to understand that TBS has a limited range for application in these patients. Despite this fact, recent versions of the software are less impacted by excessive fat interposition, and at least two articles have applied this software among bariatric patients to predict fracture risk [32, 33].

The increase in bone turnover, which occurs in various pathological states (osteoporosis, among others), is associated with a decay of bone microarchitecture and with an increase in fracture risk that is independent of BMD [34]. This fact led to the increased popularity of the markers of bone turnover – biochemical agents evaluated in blood or urine. These products mirror bone metabolic activity and can be categorized as bone formation or bone absorption markers (▶ **Table 1**) [35]. Even among bariatric patients, the most-used markers of bone formation are N-terminal pro-peptide of type 1 collagen (P1NP) and osteocalcin. In turn, the most-used markers of resorption are C-terminal telopeptide of type 1 collagen (CTX-1) and N-terminal telopeptide of type 1 collagen(NTX-1) [19].

▶ **Table 1** Summary of the markers of bone formation and absorption, considering its specific physiological role on bone metabolism.

Bone formation markers		**Bone resorption markers**	
By-products of the synthesis of collagen	▪ Propeptides of type 1 collagen: – C-terminal: P1CP – N-terminal: P1NP	**Collagen degradation products**	▪ Telopeptides of type 1 collagen: – C-terminal: – CTX-1 and CTX-matrix metalloproteinases – N-terminal: NTX-1 ▪ Pyridinium crosslinks: – pyridinoline – deoxypyridonoline ▪ Hydroxyproline
Osteoblastic enzymes	▪ Bone-specific alkaline phosphatase (BSAP) ▪ Total alkaline phosphatase (weaker measure than BSAP – prone to interferences with liver diseases)	**Non-collagenous proteins**	▪ Bone sialoprotein
Matrix proteins	▪ Osteocalcin	**Osteocyte activity markers**	▪ Osteoprotegerin ▪ Receptor activator of nuclear factor kappa-B ligand (RANKL) ▪ Dickkopf-related protein 1
		Osteoclastic enzymes	▪ Cathepsin K ▪ Tartrate-resistant acid phosphatase

Bariatric surgery techniques and its impact on bone

Bariatric surgery has become the most effective option among obese patients to lose weight and for treating some of the related diseases. This surgery is indicated for those individuals with a BMI ≥ 40 kg/m^2, or those with BMI ≥ 35 kg/m^2 and comorbidities such as sleep apnea, dyslipidemia, hypertension, or type 2 diabetes mellitus. However, despite its positive effects, bariatric surgery can be detrimental for bone health, as shown by recent studies [36, 37]. Interestingly, the impact of bariatric surgery on bone appears to differ slightly, according to the surgical technique performed [38]. The two procedures that together account for more than 80 % of the performed bariatric surgeries worldwide are Roux-en-Y gastric bypass (RYGB) and Sleeve gastrectomy (SG). Accordingly, only these two procedures are addressed in this review.

The above-mentioned comorbidities lead to food restriction, malabsorption, and changes in the secretion of several gastrointestinal hormones, which can also impact on bone metabolism [39]. A meta-analysis in 2014, which focused on patients submitted to RYGB revealed a significant decrease in circulating calcium levels and a significant rise in PTH serum levels after surgery. Surprisingly, no difference in serum 25-OH vitamin D was found, although there was also a significant decrease in BMD after RYGB. With regards bone markers, there were significant increases in urinary and serum NTX and in bone-specific alkaline phosphatase (BSAP) [37]. A recent trial on bone marker variation after RYGB found similar results, with increased CTX-1, P1NP and BSAP 2 years after surgery [40]. Another study addressing bariatric type 2 diabetic patients found that there was a significant 280 % increase in osteoblast activity, and a significant decrease in BMD of lumbar spine (− 4.0 %, $p < 0.05$) one year after RYGB [41]. Several studies to date have focused on BMD variation after RYGB, where most of them used DXA measurements and detected a prominent areal Bone Mineral Density (aBMD) decline at the proximal femur during the first year after surgery, with decreases that range from 6 and 11 % [42]. This deterioration at the hip BMD (that is consistent among studies) can be overestimated by DXA, as articles addressing volumetric hip BMD by QCT found smaller declines [43, 44]. On the other hand, DXA assessments of the lumbar spine found that most of the worse aBMD values were after RYGB, albeit not with the same magnitude of the decline in hip aBMD. When considering all the studies addressing spinal BMD, it is evident that there appears to be a decrease in spine bone mass after RYGB which is underestimated by DXA when compared to QCT [42–45]. The appendicular skeleton is also affected, with diminished total and ultradistal radius aBMD detected 12 months after RYGB. The decline of tibial and radial volumetric BMD (vBMD) values is less marked than that observed at spine and hip, however, experiments with HR-QCT suggest that this method may underestimate vBMD variation in states of decreasing adipose mass [45, 46]. With regards the radius, the decrease in trabecular vBMD is responsible for the decline in total vBMD, which occurs due to changes within the cortical or both compartments, just as in the case of the tibia [43, 45, 47]. A recent study followed patients submitted to RYGB for seven years and found that BMD continued to decrease progressively, regardless of the bone site evaluated (hip, spine, radius, and tibia), and even after weight stabilization [48].

In addition, it is thought that SG also interferes in the production of multiple gastrointestinal hormones that regulate appetite, such as ghrelin [49]. As this technique is relatively new when compared with RYGB, it is not surprising that the data regarding its effects on the skeleton are still limited. Despite this fact, a recent systematic review and meta-analysis revealed that, after surgery, those patients submitted to SG presented an increase in serum calcium, serum 25-hydroxyvitamin D, and serum phosphate, while showing a decrease in serum Parathormone (PTH) levels. No change in serum alkaline phosphatase was seen after SG. Furthermore, a significant decrease in hip BMD and femoral neck BMD was reported. Interestingly, no changes in lumbar spine BMD were detected after surgery [50]. The authors of this recent review also pronounce on the observation that the magnitude of the reductions of BMD among those submitted to SG appear to be lower than those reported elsewhere for RYGB [37]. It is important to stress that the majority of all the articles included in the analysis had a follow-up period of 12 months, and that only one study presented a follow-up greater than one year (60 months) [50]. A recent observational study followed 48 patients submitted to SG for a period of four years. At year 4, the rates of bone loss were: 8.1 ± 5.5 % for the femur neck, 2.0 ± 7.2 % for the lumbar spine; 7.7 ± 6.4 % for the total hip, and 2.4 ± 5.5 % in for whole body BMI. This study, which also followed 47 individuals submitted to RYGB, concluded that bone loss at four years was comparable between procedures, although SG was associated with less bone deterioration for total hip BMD [51]. Another meta-analysis published in 2020 compared the changes in bone metabolism between SG and RYGB. It found that, among SG patients, the circulating levels of calcium were higher than those from RYGB, whereas those of phosphorus were lower. The alterations in 25-hydroxyvitamin D after SG were also less significant than those detected after RYGB. No differences in BMD were observed between the two groups regardless, of the area evaluated. 8 of the 13 studies included had a follow-up of 12 months, 1 of 6 months, and only 4 presented a follow-up longer than a year [52]. Another recent study addressing postmenopausal women found no significant differences between SG and RYGB in total and regional BMD after surgery. However, despite this fact, there was a clear decrease in the BMD of ribs and spine after surgery in both groups, which suggests that DEXA could have an important role postoperatively among high-risk women [53].

Despite the increasing body of evidence to support the deleterious effects on bones of both SG and RYGB, the currently-available data has several limitations. For instance, most of the studies are small, with an average population of fewer than 30 patients, with short follow-ups. For these reasons, further research is required to clarify not only the impact of SG on bone metabolism, but also the various other differences in outcomes between these two bariatric procedures [54].

Bone fractures and bariatric surgery

The most significant clinical consequence of bariatric surgery on the skeleton is bone fracture – a condition which is associated with increased morbidity and mortality [55]. Considering that bariatric

surgery (and malabsorptive procedures in particular) appears to be associated with increased bone loss, it became crucial to understand whether this resulted in the occurrence of fractures. The first steps were taken to clarify this relationship during the decade of 2010 to 2020 [56].

The first meta-analysis on the subject of bone fracture comprised five studies and it revealed that obese patients who have been submitted to bariatric surgery have a higher risk for all types of fracture when compared with non-surgical control individuals (note: this finding was even more pronounced in non-vertebral sites, such as the upper limbs). In addition, it was also found that subjects submitted to mixed procedures (with a component of restriction and another of malabsorption, such as RYGB) had a tendency to present increased fracture risk in comparison with those who underwent restrictive procedures [57]. Another systematic review consisted of 15 studies and was published the following year, revealing that bariatric surgery patients were associated with a higher risk of fracture when compared with individuals not submitted to surgery (but having a similar baseline weight). This fact was seen most often among those submitted to malabsorptive procedures. Three of these studies found that the fractures reported were mainly located in the lower limbs (involving the tarsal, metatarsal, and phalangeal bones). Interestingly, the meta-analysis of these trials did not exhibit an increased risk of fractures among bariatric surgery patients (contrary to what happened in purely observational studies) [58]. One of the explanations for this difference is the length of the follow-up period. For to be able to accurately evaluate the long-term fracture risk in such patients, it is essential that the length of follow-up periods is sufficiently long enough for fractures to occur. This becomes evident when comparing the results of observational studies which have more than five years follow-up [59–63] with the first observational study, which had a shorter follow-up [64]. The most recent meta-analysis addressing this issue was published at the end of 2020. It included 11 articles and states that, on average, bariatric patients had 1.41 times more fracture risk when compared with the non-surgical control group. Another relevant conclusion was that fracture risk after surgery was site-specific, affecting more the upper limbs, spine, and hip [65], which differs from the previous systematic review [58]. These divergences regarding fracture sites need to be clarified by carrying out with trials with longer follow-up periods (in order to maximize fracture occurrence), although this is an ideal scenario, which is difficult to achieve owing to increased follow-up losses as time progresses [66]. Finally, the risk of fracture associated with bariatric surgery continued to increase, even during the 5th postoperative year, when surgical-induced weigh loss is no longer occurs [65].

In conclusion, all the evidence to date seems to indicate that fracture risk after BS varies according to the procedure, with consistent evidence implicating that RYGB leads to an increased risk of clinically important fractures on one hand, while on the other hand, studies on SG found that the risk of fracture after this type of bariatric surgery is not greater than RYGB and could indeed potentially be even less. Despite these facts, more research is needed on fracture risk after SG. Other pertinent finding is that fracture risk appears to mainly occur two or more years after surgery, and then increases during the following years. Finally, fractures related with BS tend to occur at a much younger age than age-related fractures. Our review thus highlights that fracture risk should be included as another factor for consideration when deciding whether to opt for BS, especially among older patients [56].

Bone loss after bariatric surgery: which factors need to be considered?

The detrimental effects of bariatric surgery on bone metabolism appear to have multiple etiologies which are discussed below in this section (▶ **Table 2**).

Mechanical factors

One of the first mechanisms to be proposed as a link between bone loss and BS was mechanical unloading. For it is known that the skeleton adapts to the mechanical strain, leading to alterations in bone mass and microarchitecture when weight loading changes [67]. After being submitted to BS, body weight decreases up to 30 %, and this lower mechanical load can contribute to reduced bone formation, augmented bone resorption, and decreased BMD [16]. These effects seem to be mediated, at least partially, by the increased secretion by osteocytes of sclerostin – a negative regulator of bone formation [68]. However, mechanical factors cannot be cited as the cause of the continued loss of bone mass, despite weight stabilization [47], or even for altered bone architecture after BS in non-loading-bearing bone sites [61]. This gap can be partially filled by factors which are related to nutritional status.

Nutritional factors

After BS, there is a reduction of the intake of various nutrients which have a crucial role in maintaining bone mass, such as proteins, calcium, and vitamin D. This diminished intake is also aggravated by malabsorption issues which arise after surgery (mainly after RYGB, but also after SG), which thus paves the way for alterations in bone metabolism and for presumably related fractures [19, 21]. These post-surgical nutritional factors can also exacerbate pre-existing alterations in phosphocalcium metabolism (such as vitamin D deficiency), which further contributes to the development of secondary hyperparathyroidism (SHPT) [69]. As a matter of fact, Vitamin D insufficiency has been reported before surgery in up to 80 % of bariatric patients. In addition, several studies had demonstrated that, despite being supplemented, patients presented calcium and vitamin D levels that were usually below or in the lower end of the normal range after surgery [70]. Previous data revealed that patients with stable or increased vitamin D levels had less bone loss at the femoral neck compared to patients whose vitamin D level had declined [71]. Furthermore, patients who were randomized to take a high dose of this vitamin presented less hip bone loss than those who received 800 IU daily [72]. This data supports the hypothesis that maintaining normal vitamin D levels is essential to preserve hip bone after surgery. Another study reported that, despite achieving vitamin D serum levels>30 ng/ml and a calcium intake of 1200 mg/daily, fractional calcium absorption decreased from 33 ± 14 % before BS to 7 ± 4 % in patients after RYGB, leading to a reduction of the absolute amount of calcium absorbed daily (from 392 ± 168 mg to 82 ± 45 mg) [73]. In addition, recent

▶ **Table 2** Effects of various players on bone and its variation in obese states and after bariatric surgery.

Parameter	Overall action on bone	Variation of the plasmatic level		
		Obese vs. lean state	After surgery	
			SG	RYGB
Leptin	It is likely that leptin has an overall positive effect on bone. The bone effects of leptin can be different, according to the area of the skeleton studied [152].	↑[153]	↓[154]	↓[154]
Adiponectin	Has a dual action with opposite outcomes on bone metabolism, which makes its global effect uncertain [155].	↓[153]	↑[156]	↑[156]
Ghrelin	Clinical data presents variable results, with some studies finding a positive association between ghrelin and BMD [109], while others present no significant association [96, 110] or even a deleterious effect on bone [111].	**=/**↓[122]	↓[122]	↓[122]**/may be** ↑ **in the long term**[108]
Resistin/Visfatin	Insufficient data to draw any clear role of these hormones on bone.	↑[153]**/=**[157]	**?**	**?**
Vitamin C	Positive correlation with BMD in multiple bone sites and an association with decreased risk of BMD-independent fractures [76, 77].	↓[158]	**?**	**?**
Vitamin E	Insufficient data. Seems to favor a net increase in bone mass and to promote structural integrity of the skeleton [81].	**?**	**?**	**?**
Vitamin D	Overall positive effects on bone. Prolonged and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults [159].	↓[160]	↑[161] **(but depends on the efficacy of the supplementation)**	↑[161] **(but depends on the efficacy of the supplementation)**
Irisin	Overall positive effects in bone considering the available evidence: low levels correlated with vertebral fractures; higher levels associated with increased BMD/bone strength [128].	↑[162–163]	**?**	**?**
Bile acids	Insufficient data. Positively correlated with BMD and negatively correlated with bone turnover biomarkers reflecting bone absorption in postmenopausal women [140].	↑[164]	↑[139]	↑[139]
FGF-21	Insufficient data, with conflicting results. Some articles show adverse effects on bone while one article on humans states that FGF21 can increase bone mass in women through paracrine mechanisms in the bone-adipose interface [165].	↑[166]	↑**/=**[146]	↑**(post-prandrial)** [167] **/**↓[166]
GLP-1	Directly affects bone cells and regulates bone turnover by increasing formation and decreasing resorption [115].	↓[168]	↑[107, 169]	↑**post-prandrial = fasting** [170]
GLP-2	Inhibits bone resorption with only minimal effects on bone formation. Four months of treatment with GLP-2 increased hip BMD in post-menopausal women [115].	↓[171]	↑[112]	↑[112]
GIP	GIP has a direct effect on regulation on bone metabolism with anabolic effects on osteoblasts and anti-resorptive effects on osteoclasts [115].	**=**[122]	**=(fasting)** [107] ↑**(post-prandrial)** [122]	**?**[172]
PYY	PYY can play a role in bone mass regulation as evident from association studies in populations with altered energy balance (supported mostly from rodent studies) [115].	↓ [122]	=/↑ fasting [122] ↑**postprandrial** [107]	=/↑ fasting ↑ postprandial [122]

=: Stable levels; ↑: Increased levels; ↓: Decreased levels; ?: Findings need clarification; Note that this data is based upon several papers, but many areas are still controversial, and studies have had conflicting results. For that reason, the associations may change in the future depending on the new findings in the area. This table aims to present a summary of the most consistent patterns.

research in pre-menopausal women showed that calcium absorption was impaired after surgery – not only among those submitted to RYGB, but also in those patients undergoing SG (when calcium absorption was significantly reduced from 36.5 ± 2.0 % before SG, to 21.0 ± 2.3 % and 18.8 ± 3.4 % at 12 and 24 months after SG) [74]. This calcium malabsorption is believed to be one on the main reasons for the increased levels of parathormone (PTH) after bariatric surgery that has been described in several studies [16, 37, 71]. Interestingly, some data report that the overall PTH action on bone metabolism could change according to the type of bone (cancellous vs cortical). One study reported that in patients with post-operative increases in PTH levels, lumbar spine BMD remained stable. In addition, other studies where PTH was stable or decreased, showed that BMD decreased, which supports the hypothesis that PTH can have a protective effect on the cancellous bone of the lumbar spine. On the other hand, augmented PTH levels appear to be associated with increased cortical bone loss in the tibia [70, 75]. The true impact of secondary hyperparathyroidism after bariatric surgery on bone metabolism is still a matter of debate nowadays and more studies are needed to clarify this intricate relationship [67]. Another nutritional factor, which could also play a role in bone metabolism after bariatric surgery is vitamin C. It is well known that scurvy (the lack of vitamin C) is characterized by lower values of BMD and bone mineral content. Most research on the impact of vitamin C on bone health in humans has reported a positive correlation with BMD in multiple bone sites and also an association with decreased risk of BMD-independent fractures. The effects of vitamin C include the stimulation of osteoblast maturation and the inhibition of osteoclast activity [76, 77]. Two of the studies carried out on levels of Vitamin C in bariatric patients showed an increased level of this vitamin after RYGB (one and five years after surgery) [78, 79], while another study demonstrated that there was a significant reduction in serum vitamin C levels 24 months after RYGB [80]. The role of this vitamin in bone metabolism after bariatric surgery still needs clarification, as few papers have been published on this issue, and those that have present conflicting results.

Vitamin E – a lipophilic vitamin with antioxidant properties, seems to favor a net increase in bone mass and ensure structural integrity of the skeleton [81]. A review by Lewis et al. found no significant changes to the prevalence of Vitamin E deficiency at 12 months, compared to baseline. Despite this fact, one of the papers included in their review presented a statistically significant decrease in average serum vitamin E levels at six months after BS, and two other papers found a statistically significant decrease in average vitamin E plasmatic levels at 12 months (both compared to baseline) [82]. A more recent systematic review showed that patients undergoing malabsorptive procedures (such as RYGB) are at higher risk of developing vitamin E deficiency, although clinical manifestations of this deficiency are rarely reported [83]. Considering the apparent lower levels of Vitamin E after BS and its bone protective effects, one can hypothesize that this vitamin is another link between BS and its prejudicial effects on bones.

Dietary protein ingestion among bariatric patients after BS tends to be inadequate, which can potentially lead to a decrease in lean body mass, diminished metabolic rates, and physiological damage [84]. A study carried out on a population of 30 women submitted to RYGB revealed that most amino acids increased as early as three months after surgery, which probably reflects muscle catabolism [85]. Recent evidence from a study of 184 patients undergoing SG showed that the proportion of patients with sarcopenia increased one year after surgery (8 % before surgery vs 32 % one year after) [86]. Considering that sarcopenia (reduced muscle mass) is associated with a decrease in BMD and with osteoporosis among human subjects [87, 88], it becomes clear that muscle-bone unit can also play a role in bone metabolism after BS. In addition, other papers have shown that adequate protein intake after BS minimizes muscle and bone loss [32, 89] and raises awareness for the need for a personalized nutritional plan, which can ultimately protect the skeleton of these individuals after surgery, considering patients' metabolic needs.

Hormonal factors

Despite the important role of mechanical and nutritional factors, hormonal changes resulting from anatomical alterations and weight loss also have an impact on bone metabolism after BS. One of the involved hormones is leptin – an adipokine which is released in amounts that are proportional to whole body adipose tissue [90]. Previous data demonstrated that leptin promotes osteoblastogenesis and inhibits osteoclastogenesis through various central and peripheral pathways, and that it also favoring osteoblast differentiation and matrix mineralization [91, 92]. In addition, a decrease in this adipokine after RYGB was inversely correlated with increased levels of markers of bone formation and resorption. The raise of resorption markers was more evident, which indicates an overall effect toward bone loss [93]. This suggests that leptin has a net positive impact on BMD that is then lost – at least partially – as its levels decline after surgery (which is not only observed after RYBG, but also after SG) [94]. Interestingly, impaired leptin signaling in the hypothalamus was found to be a predictor of decreased cortical bone mass and overall BMD or content, albeit with a presumably related increase in trabecular bone formation [95]. Apart from the overall positive effect (supported by a meta-analysis by Biver et al. [96]), there is also evidence that leptin can have a negative impact on bone, due to a central effect through a sympathetic pathway, however further research on this issue is required [92].

Another potential link between BS and bone health is adiponectin – a bone marrow fat-derived hormone which, similar to leptin, does not have a clearly understood role in this relationship. Its serum levels – which are negatively correlated with adipose mass – increase after BS [97]. Circulating adiponectin has been associated with an overall anti-osteogenic effect on bone cells through indirect stimulation of osteoclast formation [98]. Other possible mechanisms that result in bony deleterious effects originate from adiponectin's ability to bind growth factors and decrease plasmatic insulin concentrations, which ultimately counteract the anabolic effects of these hormones on the skeleton [21]. A meta-analysis of 59 papers demonstrated that adiponectin was negatively associated with BMD, independent of peripheral fat mass parameters, menopausal status, and gender [96]. This association was also supported by a prospective study of 42 women 12 months after RYGB [99]. Despite these findings, a correlation between the change in adiponectin and increased plasmatic markers of

bone turnover was not found in another study of 20 patients who had been submitted to RYGB [93].

The effects of the other two adipokines – visfatin and resistin – in this context are largely unknown. In the case of visfatin, no association between BMD and its circulating levels has been found in the metadata or in other cohort-independent studies [100]. Previous data in non-bariatric patients revealed that resistin was a significant determinant of lumbar spine BMD among middle-aged men [101], and that high serum resistin levels were found to be independent contributors to low BMD in postmenopausal women [102]. Further research is required to clarify whether these adipokines play a role in bone metabolism after BS. Another possible connection between BS and bone loss is estrogen – a sex hormone that can be produced in adipose tissue due to the conversion of testosterone into estradiol under the control of the aromatase enzyme. This is the main process of estrogen generation in both men and postmenopausal women. After BS, levels of estradiol were diminished in both men and women with the expected weight loss and adipose tissue reduction [103]. Considering that estrogen acts to promote bone formation and suppress bone absorption [104, 105], the reduction of its levels after BS could be another explanation for metabolic bone changes after surgery.

In turn, the role of ghrelin in BS is still not very clear. This hormone – which is produced in the gastric antrum and fundus – is thought to be an important player in the long-term maintenance of energy stores as it stimulates appetite and decreases energy expenditure [106]. A meta-analysis of 28 studies by McCarty et al. revealed that fasting serum ghrelin levels decreased after SG [107], while another by Xu et al. of 16 papers showed that levels of ghrelin decreased in the short term ($\leq$ 3 months), and increased in the long term (> 3 months) after RYGB [108]. While studies in animals suggest an overall anabolic effect of this hormone on bone, clinical data presents variable results, with some studies finding a positive association between ghrelin and BMD [109], while others present no significant association [96, 110], or even a damaging effect on bone [111]. Accordingly, the impact of ghrelin on bone after BS remains still remains to be determined [21]. The glucagon-like peptides GLP-1 and GLP-2 – which are produced by intestinal L cells in response to food intake – are two hormones whose postprandial circulating levels are increased after RYGB and SG [112, 113]. Similar to teduglutide, GLP2 receptor agonists are used in the treatment of short bowel disorders, as they increase both the bowel surface area and absorption [114]. The few papers to date on the effects of GLP-2 on human bone in vivo have showed that GLP-2 inhibits bone resorption (measured as CTX), with only slight effects on bone formation (measured as P1NP or osteocalcin). Research carried out on post-menopausal women found conflicting results, with one study demonstrating that four months of GLP-2 treatment increased hip BMD [115], while another found no association between GLP-2 activity and osteoporosis [116]. In turn, studies in humans concluded that GLP-1 has benefic effects on bone metabolism, probably through augmented bone formation. No effect on serum CTX concentration was seen [117]. One of these investigations was conducted in weight reduced women with obesity (after diet induced weight loss) and found that treatment with a long-acting GLP-1 receptor agonist increased bone formation by 16 % and prevented bone loss after weight loss following a low-calorie diet [118]. This fact gains even more relevance when we consider that GLP-1 receptor agonists are therapeutic options not only before but also after bariatric surgery [119]. Studies in rats also support the positive impact of GLP-1 on bone strength and quality, which sheds some light on the presumed role of this incretin in protection against bone loss [115, 117]. Despite these facts, recent evidence from the meta-analysis shows that treatment with GLP-1 receptor agonists does not alter the risk of bone fracture, when compared with treatment with other antidiabetic drugs among patients with type 2 diabetes [120].

The gastric inhibitory peptide (GIP) – which is produced by the k-cells in the proximal small intestine after food ingestion – is a hormone with apparently positive effects on bone [67]. Evidence from studies in humans show that GIP reduces CTX independently of insulin, and that a loss-of-function of GIP receptor is associated with decreased BMD, together with an increased risk of fracture. Studies in vitro found that GIP also inhibits osteoclast formation and resorption, while it reduces osteoblast cell death [115]. One interesting article from Torekov et al. also found an association between a functional GIP receptor polymorphism Glu354Gln (rs1800437) and BMD and fracture risk, suggesting the involvement of GIP in the regulation of bone mineral density [121]. Considering several studies have found that the fasting and postprandial levels of this hormone decreased after RYGB, GIP could be another connection in the complex influence of BS on bone. Interestingly, GIP levels after SG were stable, or even increased – which raises several unanswered questions about this issue [122].

Another gut hormone is Peptide YY (PYY) – a regulator of food intake that is secreted by the enteroendocrine L cells of the distal gastrointestinal tract. It is known that postprandial PYY levels are increased after RYGB and SG, although it remains unclear whether the same happens during fasting [21, 122]. Studies of the impact of GIP on bone in humans found an inverse relationship between plasmatic GIP and BMD in populations with weight loss ($\uparrow$ PYY and $\downarrow$ BMD among patients with anorexia nervosa or submitted to RYGB). There is also evidence for the direct effect of PYY on osteoblast and osteoclast activity, with a negative association between PYY and osteoclast activity. In addition, mice without PYY receptors presented an increase in bone mass and strength, although more research is required to clarify the existent controversies regarding the effects of PYY on bone [115].

Acknowledged factors for future lines of research

During the last decade, the impact of microbiota in multiple aspects of metabolic health of the human host has been established with ample evidence [123]. It is known that microbiota are profoundly affected by BS, with an increase of Bacteroides and Proteobacteria, and a decrease in Firmicutes post-operatively in most studies [124]. It is only now that the first steps are being taken to study the influence of microbiota on bone and its related diseases [125, 126]. Interestingly, it is known that several members of the Proteobacteria (augmented after BS) are associated with osteoporosis [125]. Despite this fact, the only paper that to our knowledge exits which addresses the relationship between microbiota and BMD found that gut microbiota presents little relevance for BMD

[127]. Considering the lack of information regarding the impact of changes microbiota after BS on bone, it is still too early to state whether gut bacteria have a clear role in this issue.

During the past few years, the relation between irisin and bone has been often in the spotlight [128–130]. Irisin is a molecule that is produced and released by myocytes, which appears to have an overall positive effect in bone metabolism. The available evidence shows that low levels of irisin are associated with vertebral fragility fractures among post-menopausal women, and that levels of irisin are correlated positively with BMD among geriatric men [128, 131]. It is also known that this molecule is associated positively with BMD and bone strength in athletes, and research carried out on children described a positive association between serum irisin and bone status in healthy children [128]. These benefic effects could be explained, at least in part, by the stimulating effect of irisin on osteoblast proliferation and differentiation [132]. Intriguingly, evidence also exists that treatment with irisin increases sclerostin production by osteocytes (leading to bone resorption) and that the deletion of FNDC5 (precursor of irisin) prevents ovariectomy-induced trabecular bone loss [133]. Another article which supports these findings concluded that irisin directly stimulates both osteoclastogenesis and bone resorption in vivo and in vitro [134]. With regards the levels of irisin after SG, it was found that irisin levels increased after six months [135], while another study found no change in its levels after surgery [136]. A third study stated that circulating irisin levels decreased after SG and RYGB in comparison to the baseline [137]. Similar to SG, post-RYGB irisin levels also present conflicting results in several papers [67]. Accordingly, the impact of irisin on bone still needs enlightenment, and this issue represents a promising area of research among bariatric patients.

Bile acids (BA) are another player that has gained increasing attention over the decade of 2010 to 2020 [138]. Accumulating evidence has shown that levels of total fasting and postprandial plasma BA increase after SG and RYGB and it is thought that these changes contribute to improved lipid and glucose homeostasis, insulin sensitivity, and energy expenditure after BS [139]. BA also seem to have a metabolic effect on bone, with a study in postmenopausal women revealing that total serum BA was positively correlated with BMD, and negatively correlated with bone turnover biomarkers of bone resorption [140]. In addition, studies in mice found that the activation of the FXR BA receptor significantly promoted osteoblastic differentiation and that FXR agonists suppressed osteoclast differentiation from bone marrow macrophages. A histological study of mice lumbar spine also demonstrated that FXR deficiency impaired bone formation rate, as well as trabecular bone volume and thickness [141]. Interestingly, different types of BA can have differing effects on bone. Ursodeoxycholic acid inhibits apoptosis and increases survival and differentiation of human osteoblasts, thus neutralizing the detrimental effects of lithocholic acid in these processes [142]. The effects of BA on bone among patients submitted to BS are still not known, and this could be another interesting line of future research.

FGF-21 is a hormone that is produced in the liver and adipocytes, which is positively associated with poor metabolic health, being related with obesity, diabetes, mitochondrial diseases, and ageing. It is also known that FGF-21 has several musculoskeletal effects and that it is involved in muscle atrophy, bone loss and reduced BMD [143]. One of the few studies addressing FGF-21 levels after BS showed a significant increase in fasting FGF21, especially one month after surgery [144], while other stated that there was a 63 % reduction in FGF-21 levels six months after SG [145]. A paper from Khan et al. reported that fasting and 120-minute postprandial FGF21 levels at one month were increased, although these levels returned to baseline values three months after SG [146]. In turn, Gómez-Ambrosi et al. found that FGF21 levels were reduced one year after SG-induced weight loss, but not after RYGB [147]. Therefore, the limited evidence regarding FGF-21 and its impact on bone after BS presents new opportunities for research in bariatric patients.

Other possible interesting line of research is the effect of diet-induced weight loss effects on bone mass. A recent systematic review and meta-analysis of clinical trials found that, in patients with overweight and obesity not submitted to bariatric surgery, a single diet-induced weight-loss intervention leads to a small decrease in total hip BMD (with decreases of 0.010 to 0.015 g/cm^2), but not in lumbar spine BMD (in which was not observed any statistically significant effect of diet-induced weight loss, the same happening with whole body BMD) [148]. A subsequent paper, addressing this issue among older adults with obesity, stated that several prospective observational and interventional studies confirm the negative effects on skeletal health outcomes of intentional weight loss achieved by lifestyle changes. These effects seem to be modest but persistent in the long term [149]. So, it would be interesting to know if different long-term dietary patterns after bariatric surgery can modulate bone metabolism and these effects on bone mass.

Bariatric surgery is also an option for several patients with heterozygous mutations of genes related with genetic obesity (such as MC4R, POMC, PCSK1, SIM1, or PTEN) [150]. Patients with mutations in MC4R gene had higher BMD than matched control participants, underlining a probable influence of genes in these relationship between obesity and bone metabolism (that can, in theory, be also a factor to consider after bariatric surgery) [151].

Conclusion

The impact of bariatric surgery on bone is field of research that has seen a significant breakthrough over the last decade of 2010 to 2020. Several factors that have an impact of bariatric surgery on bone health have been identified, however, how they interact to regulate bone metabolism after metabolic surgery is still largely unknown. For this reason, we believe that this area of research will progress positively and advances the frontier of knowledge over the next decade. Understanding these relationships is crucial to avoid bone loss and to decrease fracture risk after BS and raises awareness of this problem and can possibly lead to improving therapeutical options.

Conflict of Interest

The authors declare that they have no conflict of interest.

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