



Review Article

Bariatric surgery and skeletal health: A narrative review and position statement for management by the European Calcified Tissue Society (ECTS)

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ABSTRACT

Context: Numerous studies have demonstrated detrimental skeletal consequences following bariatric surgery.

Methods: A working group of the European Calcified Tissue Society (ECTS) performed an updated review of existing literature on changes of bone turnover markers (BTMs), bone mineral density (BMD), and fracture risk following bariatric surgery and provided advice on management based on expert opinion.

Literature review: Based on observational studies, bariatric surgery is associated with a 21–44% higher risk of all fractures. Fracture risk is time-dependent and increases approximately 3 years after bariatric surgery. The bariatric procedures that have a malabsorptive component (including Roux-en-Y Gastric bypass (RYGB) and biliopancreatic diversion (BPD)) have clearly been associated with the highest risk of fracture. The extent of high-turnover bone loss suggests a severe skeletal insult. This is associated with diminished bone strength and compromised microarchitecture. RYGB was the most performed bariatric procedure worldwide until very recently, when sleeve gastrectomy (SG) became more prominent. There is growing evidence that RYGB is associated with greater reduction in BMD, greater increase in BTMs, and higher risk of fractures compared with SG but RCTs on optimal management are still lacking.

Expert opinion: In all patients, it is mandatory to treat vitamin D deficiency, to achieve adequate daily calcium and protein intake and to promote physical activity before and following bariatric surgery. In post-menopausal women and men older than 50 years, osteoporosis treatment would be reasonable in the presence of any of the following criteria: i) history of recent fragility fracture after 40 years of age, ii) BMD T-score ≤ -2 at hip or spine, iii) FRAX score with femoral neck BMD exceeding 20% for the 10-year major osteoporotic fracture probability or exceeding 3% for hip fracture. Zoledronate as first choice should be preferred due to intolerance of oral formulations and malabsorption. Zoledronate should be used with caution due to hypocalcemia risk. It is recommended to ensure adequate 25-OH vitamin D level and calcium supplementation before administering zoledronate.

Conclusions: The bariatric procedures that have a malabsorptive component have been associated with the highest turnover bone loss and risk of fracture. There is a knowledge gap on osteoporosis treatment in patients undergoing bariatric surgery. More research is necessary to direct and support guidelines.

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1. Introduction

According to recent WHO global estimates, more than 1.9 billion adults aged 18 years and older were overweight (Body Mass Index (BMI) 25.0 to <30 kg/m^2) in 2016. Overall, about 13% of the world adult population (650 million), was obese (BMI 30.0 kg/m^2 or higher) (11% of men and 15% of women). The worldwide prevalence of obesity nearly tripled between 1975 and 2016 [1]. Obesity is a major risk factor for cardiovascular diseases, diabetes, sarcopenia, falls and fractures at certain sites, and several malignant diseases [2]. Bariatric surgery is the only intervention resulting in substantial and long-term weight loss in morbid (severe) obesity. Consensual indications for bariatric surgery are BMI ≥ 40 kg/m^2 , BMI ≥ 35 kg/m^2 with type 2 diabetes mellitus (T2DM), or other comorbidities that could be significantly improved after bariatric surgery. Furthermore, the effectiveness of bariatric procedures is based on outcomes such as T2DM remission, resolution of dyslipidemia and hypertension, quality of life improvement, and improved late morbidity [3].

However, numerous studies have demonstrated detrimental skeletal consequences following bariatric surgery, especially with laparoscopic Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD). Bariatric procedures have been found to be associated with rapid bone loss and dramatic increase in bone turnover markers (BTMs), leading to both an early and sustained bone loss [4,5]. Furthermore, this state is associated with reduced bone strength, microarchitecture deterioration and increased risk of fracture over time [6,7]. Pathophysiological hypotheses are multifactorial and mechanisms may involve deficiencies of nutritional factors, mechanical unloading, alterations in gut-derived hormones, and many others. Several reviews have already been published on this issue [8,9], but the field is evolving rapidly, and new data are now available focusing on bone outcomes according to the type of bariatric procedure.

In this review, we aim to provide a broad perspective on the association between bariatric surgery and skeletal outcomes, with an emphasis on observational studies with fracture risk as endpoint and potential mechanisms for skeletal deterioration such as alterations in adipokines and neuroendocrine hormones, and changes in bone marrow adiposity (BMA). We opted for a narrative review instead of a systematic review to incorporate research questions, and to address evolving areas in which there is yet insufficient evidence. We discuss the type of intervention that might prevent high turnover bone loss, and we highlight knowledge gaps. Finally, we propose recommendations on prevention and treatment of osteoporosis following bariatric surgery. Because of restrictions on the length of the manuscript, the reader is referred to three other recent review articles summarizing current bariatric procedures [7–9].

2. Search strategy

Members of the European Calcified Tissue Society (ECTS) Clinical Action Group of the Policy and Consensus Committee, JP, ET, MCZ, and JJB, planned this update. Two independent researchers (JP and ET) reviewed all eligible studies. JP and ET prepared the initial draft, all other named authors - members of the ECTS Clinical Action Group of the Policy and Consensus Committee and the ECTS Board - participated in the interpretation and completion of the manuscript.

A computerized literature search was performed in PubMed (last update: August 18, 2020) using the terms “bariatric surgery”, “sleeve gastrectomy”, “Roux-en-Y gastric bypass”, “fractures”, “bone mineral density”, “bone turnover markers” and “osteoporosis”. The search was not limited by publication data or language. The Medical Subject Heading (MeSH) database was used as a terminological search filter in combination with methodological search filters. Relevant articles were also found in the references of these papers.

3. Fracture risk after bariatric surgery

3.1. Is there an increased risk of fracture after bariatric surgery compared to morbidly obese controls without surgery?

Table 1 shows the associations between bariatric surgery and fractures. All epidemiological studies on retrospective cohorts with regard to fracture risk after bariatric surgery are included [10–19]. Due to the design of these studies (retrospective cohorts), no lifestyle intervention (diet/exercise programs) was performed in morbidly obese control groups (without surgery). In a study conducted by Lalmohamed A. et al. [10], the authors found no increase in (fragility and non-fragility) fracture risk in patients who had undergone bariatric surgery ($n = 2079$; 60% adjustable gastric banding (AGB) procedure) compared with controls (matched for age, sex, year, and BMI), but follow-up time was short (median time 2.2 years). No association was detected between bariatric surgery and all type of fractures (fragility and non-fragility) in another study performed in the UK. However, this study also included many patients undergoing the AGB procedure (47.1%) [11]. In a study conducted by Lu C.W. et al. [12], the authors reported a significant 1.21-fold [1.02–1.43] increase in overall fracture risk (fragility and non-fragility) in the surgical group compared to an obese control group (matched for age, sex, Charlson comorbidity index, diabetes, hypertension, hyperlipidemia, and time elapsed since obesity was diagnosed). Restrictive procedures such as SG, gastropasty and gastrectomy were mainly performed (86%, $n = 1775$). However, they found no evidence of a higher risk of fragility fractures (HR = 1.05, 0.77–1.43). It is noteworthy that this study has been conducted in a cohort of patients younger than those usually at risk for fragility fractures with a mean age (SD) of 31.8 (9.2) years. In a study conducted by Rousseau et al. [13], patients who underwent bariatric surgery ($n = 12,676$), were age and sex matched with obese ($n = 38,028$) and non-obese ($n = 126,760$) controls. Bariatric patients were found to be more prone to fractures compared to the obese control group (RR = 1.38, 1.23–1.55). After surgery, only BPD ($n = 1986$) was clearly associated with a higher risk of fracture (adjusted RR = 1.60, 1.25–2.03) compared with the non-obese group, whereas no comparison was available with the obese control group [13]. In another study, Yu E. et al. [14] compared the risk of non-vertebral fragility fractures (consisting of humerus, wrist, hip, and pelvis fractures) in obese adults after RYGB and AGB procedures ($n = 7516$ for both groups) and found an increased risk of non-vertebral fracture (HR = 1.43, 1.13–1.81) in RYGB patients in comparison to AGB patients. Four other studies were powered to evaluate RYGB-specific fracture risk in large population data sets [16–19]. Using Medicare data, Yu E. et al. found that RYGB ($n = 29,624$) was associated with an increased risk of non-vertebral fractures (including hip, wrist, and pelvis fractures) in comparison to AGB ($n = 12,721$). Moreover, older adults had similar RYGB-associated increases in fracture risk as younger adults [16]. In a Swedish study performed by Axelsson K.F. et al., RYGB in comparison to obese controls ($n = 38,971$ in both groups) was associated with an increased risk of any type of fracture in patients with and without diabetes. Surprisingly, a greater weight loss or inadequate calcium and vitamin D supplementation after surgery were not associated with increased fracture risk [17]. Fashandi AZ et al. also found that patients who underwent bariatric surgery ($n = 3439$), mainly RYGB (~80% of bariatric surgery procedures), are at increased risk of any fracture compared to a propensity-matched control group (6.4 vs. 2.7%, $p = 0.0001$) [18].

Most studies have thus shown an increased fracture risk, but it remains unclear whether the increase in fracture risk is further enhanced by bone fragility due to aging since studies have mainly been conducted in younger populations than those usually at risk for fragility fractures.

Table 1

Summary of bariatric surgery retrospective cohort studies by characteristics and fracture results.

Author (year) Location	Participants (n)	Sex (% female)	Age (years); mean (SD)	Baseline BMI (kg/ m ²); mean (SD)	Type of surgery	Follow-up duration; mean or median	Main results (95% confidence interval)
Lalmohammed et al. (2012) UK	BS (2079) Control (10,442)	83.9 85.3	44.6 (11.1) 44.9 (11.2)	43.2 (7.2) 40.8 (6.4)	AGB (60%), RYGB (29%), other	BS: 2.2 Control: 2.3	Adjusted relative risk for any fracture 0.89 (0.60–1.33)
Nakamura et al. (2014) USA	BS No control group	82 N/A	44 (10) N/A	49.0 (8.4) N/A	RYGB, other	BS: 8.9 No Control group	Adjusted relative risk for any fracture 2.3 (1.8–2.8)
Lu et al. (2015) Taiwan	BS (2064) Control (5027)	63.7 64.4	31.8 (9.2) 31.9 (9.9)	N/A N/A	SG, RYGB, other	BS: 4.8 Control: 4.9	Adjusted hazard ratio for any fracture 1.21 (1.01–1.44)
Douglas et al. (2015) UK	BS (3882) Control (3882)	80.5 81.6	45 (11) 45 (11)	44.7 (8.8) 42.1 (6.5)	AGB (47.1%), RYGB (36.6%), SG (15.8%), other	BS: 3.4 Control: 3.4	Hazard ratio Any fracture 1.26 (0.79–2.01)
Rousseau et al. (2016) Canada	BS (12,676) Control (38,028)	72.3 72.3	42.6 (11) 42.7 (11)	N/A N/A	SG, RYGB, other	BS: 4.4 Control: 4.4	Adjusted relative risk for any fracture 1.44 (1.29–1.59)
Yu et al. (2016) USA	RYGB (7516) AGB (7516)	78.9 79.0	43.6 (10.4) 43.5 (10.5)	N/A N/A	RYGB (50%), AGB (50%)	RYGB: 2.3 AGB: 2.3	Adjusted hazard ratio for nonvertebral fractures 1.43 (1.13–1.81)
Axelsson et al. (2018) Sweden	BS (38,971) Control (38,971)	66.1 to 78.9 65.6 to 77.3	40.9 (11.2) 41.0 (11.2)	42.4 (5.5) N/A	RYGB (100%)	BS: 3.1 Control: 3.1	Adjusted hazard ratio for any fracture -Patients with diabetes 1.26 (1.05–1.53) -Patients without diabetes 1.32 (1.18–1.47)
Yu et al. (2019) USA	RYGB (29,624) AGB (12,721)	78.8 77.9	51 (12) 55 (12)	N/A N/A	RYGB, AGB	RYGB: 3.3 AGB: 3.9	Adjusted hazard ratio for nonvertebral fractures 1.73 (1.45–2.08)
Paccou et al. (2020) France	BS (40,992) Control (40,992)	78.4 78.4	49.1 (6.6) 49.1 (6.6)	N/A N/A	SG (45.5%), RYGB (35.4%), other	BS: 6.2 Control: 5.3	Adjusted hazard ratio for major osteoporotic fracture 1.22 (1.08–1.39)
Khalid et al. (2020) USA	RYGB (16,371) SG (16,371) Control (16,371)	74.9 74.9 74.9	N/A N/A N/A	N/A N/A N/A	RYGB (50%) SG (50%)	RYGB: 3 SG: 3 Control: 3	Odds ratio for any fracture -Control vs RYGB 0.95 (0.84–1.07) -Control vs SG 0.53 (0.46–0.62)

Note: BS, bariatric surgery; RYGB, roux-en-Y gastric bypass, AGB, adjustable gastric banding, SG, sleeve gastrectomy.

3.2. Which bariatric procedures are associated with highest and lowest fracture risk?

Among all surgery types, RYGB and SG were most often compared (Table 1). Paccou J. et al. reported a significant 1.22-fold [1.08–1.39] increase in major fragility fracture risk in the surgical group (consisting of humerus, wrist, hip, and vertebral fractures) compared with an obese control group (matched for age, sex, grade of obesity, year of inclusion and Charlson comorbidity index) [19]. Sleeve gastrectomy was the most frequent surgical technique (18,635 (45.5%)), followed by RYGB (14,532 (35.4%)). They observed an increase in risk of fragility fracture for RYGB only (HR = 1.70, 1.46 to 1.98) but not SG or other procedures such as AGB, and vertical banded gastroplasty (VBG) compared with matched controls ($n = 40,992$). Khalid S.I. et al. found no increase in fracture risk in patients who had undergone RYGB ($n = 16,371$) compared with controls (obese patients who were eligible but did not undergo bariatric surgery), but follow-up time was short (3 years) [20]. Patients undergoing SG ($n = 16,371$) were found to have a decreased risk of any fracture in comparison with controls (Odds Ratio = 0.53, 0.46–0.62). A systematic review and Bayesian network meta-analysis comparing the risk of fracture for bariatric procedures was recently published [21]. An average 1.41-fold risk of fracture was identified in the bariatric group compared with the control group and among different surgical procedures, BPD was associated with the highest risk of fracture, followed by RYGB, non-surgical intervention, AGB and SG.

It also remains unclear whether the magnitude of fracture risk is similar with sleeve gastrectomy (SG), which has recently surpassed RYGB as the most popular form of bariatric surgery.

4. Fracture site-specific evaluations

Regarding fracture site-specific analyses, no comparisons between the bariatric surgery group and the obese control group were reported in the study by Rousseau et al. [13]. In the study conducted by Lu C.W. et al. [12], only fractures at unusual sites – including clavicles, scapulae, sternum and feet and toes – reached statistical significance. Using two different USA databases, Yu E et al. found that RYGB patients compared to AGB had a higher risk of fracture at the hip [14,16], and wrist [14,16], which is in line with findings of the French retrospective cohort [19]. Moreover, the Swedish study also supported these findings of pronounced hip and upper-extremity fractures after RYGB, although they reported a paradoxically reduced risk of lower-leg fracture [17]. This fracture site (weight-bearing lower-leg) is commonly associated with obesity and the fracture risk at this site may thus be reduced after weight loss. Interestingly, a higher risk of proximal humeral fractures has also been associated with obesity in some studies [22,23], and fracture risk at this site may thus be reduced after weight loss. In two studies to date, SG was associated with a lower risk of proximal humerus fractures [19,20]. However, the protective effect of SG on proximal humerus fracture risk needs further validation.

4.1. Is there a need for long-term assessment of fracture risk after bariatric surgery?

Studies describing bone health five to ten years after bariatric surgery are scarce. It is interesting to note that fracture risk usually starts to increase 3 years postoperatively [14,16,17,19]. In the study by Yu E. et al. [14], non-vertebral fracture risk associated with RYGB manifested >2 years after surgery and increased further in subsequent years, with the highest risk in the fifth year after surgery (HR = 3.91, 1.58–9.64). This augmented fracture risk, gradually escalating in time, has also been demonstrated in other studies [16,17,19]. However, the absolute number of fractures remained relatively low and patients in those studies were relatively young (average age around 43 years), with a mean follow-up time ranging from 2 to 8.2 years and a suboptimal collection of incident fractures. In a recent study [24], 122 patients (77% female, mean (SD) age 50.3 (9.0) years) were evaluated 10 years after a RYGB procedure. During the 10 years of follow-up, the number of patients with at least one fragility fracture was 18 (15%), 7 (11%) premenopausal females or males ≤49 years and 11 (9%) postmenopausal females or males ≥50 years. Lower limb fractures were the most prevalent, followed by rib fractures. The mean (SD) duration from RYGB to first fragility fracture was 8.4 (1.8) years. In addition, at least one moderate [(reduction of vertebral height of >25 to 40%)] to severe (> 40%)] morphometric vertebral fracture was found in 10 patients (8%). In the Swedish Obese Subjects (SOS) study, an ongoing, non-randomized, prospective, controlled intervention study, authors investigated fracture risk for different bariatric surgery procedures in 2007 patients treated with bariatric surgery (13.3% RYGB, 18.7% AGB, and 68.0% VBG) and 2040 control patients [25]. Patients in the control group received usual care at their primary health care centers. The median follow-up time was 17.6 years and the highest incidence rate for first-time fracture was observed in the RYGB group (22.9 per 1000 person-years). The risk of fracture was increased in the RYGB group compared with the control group (adjusted HR = 2.58, 2.02–3.31). In line with previous studies, the increase in fracture risk started 3 years after RYGB. Wrist fractures ($n = 157$) were the most common type of fracture in the whole study population [25]. One limitation of this study is that the most frequent procedure was VBG, which has become a rare procedure and is nowadays considered obsolete.

In summary, there is an increased risk of fracture after bariatric surgery. The bariatric procedures that have a malabsorptive component (including RYGB and BPD) have clearly been associated with the highest risk of fracture. The type of surgery performed is mainly RYGB, and wrist fractures represent the most common type of fracture in epidemiological studies conducted in young populations. An increased risk of hip fractures has also been reported, which is quite unusual in young populations. This increase in fracture risk is usually described starting from the 3rd postoperative year but the long-term risk remains to be determined. In addition, fracture risk associated with SG should be further investigated. Finally, the most important limiting factor in the interpretation of all these studies is the selection of control groups. There is a need to compare lifestyle intervention (diet/exercise programs) versus bariatric surgery in terms of fracture risk. Indeed, an intensive lifestyle intervention resulting in long-term weight loss in overweight/obese adults may be associated with an increased risk of fragility fracture [26].

5. Bone turnover, bone mineral density, and microarchitecture after bariatric surgery

In this section, data derived from human studies with BTMs, bone mass, and microarchitecture outcomes will be summarized. Since RYGB was the most frequently performed bariatric procedure worldwide until very recently, most of the data presented in this section derived from studies evaluating this surgical procedure.

5.1. Bone turnover markers after bariatric surgery

BTMs dramatically increase following bariatric surgery, reflecting a high bone turnover state [4,9]. After RYGB, serum C-terminal cross-linked telopeptide of type I collagen (CTX) elevation has been documented as early as 10 days postoperatively [5], with levels peaking by 6 to 12 months and remaining elevated up to 7 years [4,5,9,27,28]. During the first postoperative years, CTX characteristically increases by 50–300% [9,27,28]. Levels of bone specific alkaline phosphatase were also found to be increased after RYGB, although to a lesser degree (10–25%) compared to CTX [27,28]. Similarly, procollagen type I N-terminal propeptide (PINP), another marker of bone formation, increased also to a lesser extent (20–150%) in comparison to CTX [4,5,9,27,28]. After BPD, increases in CTX of 66% were observed as early as 3 days after BPD while a decrease in osteocalcin of 19% was observed at this timepoint, followed by a higher increase in CTX over osteocalcin at 3 and 12 months [29]. In a group of 37 obese premenopausal women (age: 24–52 y; mean BMI = 43.7 kg/m²) who underwent AGB, CTX increased by 100% during the first 6 months, and then stabilized until 2 years [30].

A few non-randomized clinical trials [31,32], but not all [333], have reported greater increase in serum BTMs (PINP and CTX) after RYGB compared to SG. In a randomized clinical trial, including 92 patients (34 premenopausal women, 31 postmenopausal women, and 27 men), Hofso et al. have documented a greater increase in BTMs one year after RYGB compared to SG (Fig. 1) [34]. The study by Muschitz et al. is the only study reporting similar increases in BTMs after RYGB and SG in 90 premenopausal women [33]. In another non-randomized clinical trial, involving 19 adults (50% women) aged 21–65 years, RYGB was accompanied by increases in BTMs whereas no increase was noted in patients undergoing AGB at 1 year [35].

5.2. Bone mineral density after bariatric surgery

Numerous studies including reviews and meta-analyses on the association of bariatric surgery with bone loss have been published [36,37]. Significant bone loss after RYGB occurred as early as 6 months following surgery in postmenopausal women [6]. At the hip, bone loss was consistently reported following RYGB, and to a larger extent compared to findings at the lumbar spine. Total hip BMD by dual x-ray absorptiometry (DXA) declined by 3–5% at 6 months, and by 6–10.5% at 9–12 months. Femoral neck BMD declined by 5–12% at 12 months. Lumbar spine BMD declined by 4–5% at 12 months [32,34]. Few studies extended beyond 2 years and report, although inconsistently, an additional but more gradual decline of 2–3% at the total hip during the follow-up period [36,37].

We identified 8 studies (from 2013 to 2020) describing areal BMD (aBMD) changes following bariatric surgery, comparing RYGB with SG, at various sites, using DXA. Table 2 shows the aBMD changes following bariatric surgery. A few non-randomized studies have reported greater reductions in BMD at total hip, but not lumbar spine, after RYGB compared to SG [32,38,39]. In contrast, other non-randomized studies have reported no differences between groups at any site [33,40,41]. In two randomized controlled studies of patients with obesity and T2DM, patients who underwent RYGB had a greater reduction in (aBMD) at the total hip [34], femoral neck [34] and lumbar spine [34,42] than patients who underwent SG (Fig. 2). Based on available data, it is not possible to draw conclusions on differences between men, pre- and postmenopausal women. In a study in which 54 subjects (BMI: 36 ± 1 kg/m², age: 48 ± 4y) with T2DM were randomized to intensive medical therapy ($n = 17$), RYGB ($n = 18$), or SG ($n = 19$), bone loss at 2 years was found to be significantly greater in SG and RYGB groups, compared to intensive medical therapy at total hip BMD (−9.2%, −9.5%, and −0.3%). At lumbar spine, significant bone loss was only found in SG group with no change in RYGB and intensive medical therapy (−2.3%, 0.4%, and 0.8%) [43].

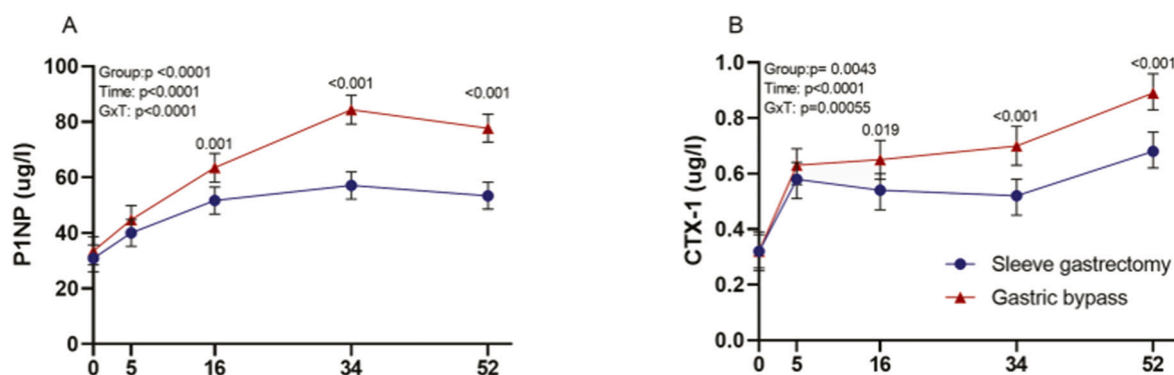


Fig. 1. Bone turnover markers after sleeve gastrectomy (n = 48) and gastric bypass (n = 44) during 1-year follow-up - Adapted from [34]. P-values were derived from linear mixed effects models for repeated measures. Bars indicate 95% confidence intervals. Abbreviations: CTX-1, C-telopeptide of type I collagen; P1NP, procollagen type 1 N-terminal propeptide.

Table 2

Studies reporting on regional change in DXA-measured areal bone mineral density after sleeve gastrectomy and Roux-en-Y gastric bypass.

Author (year) Location	Study design	Participants (n)	Sex	Duration	Total hip (SG vs RYGB)	Fem. neck (SG vs RYGB)	Lumbar spine (SG vs RYGB)
Carrasco (2018) Chile [40]	Non-randomized	26 SG 32 RYGB	26 PreM women 32 PreM women	2 years	N/A	↓ vs. ↓*	↓ vs. ↓*
Bredella (2017) USA [32]	Non-randomized	10 SG 11 RYGB	9 women and 1 man 9 women and 2 men	1 year	↓* vs. ↓* #	↓* vs. ↓* #	↓* vs. ↓*
Muschitz (2015) Austria [33]	Non-randomized	52 SG 38 RYGB	52 PreM women 38 PreM women	2 years	↓* vs. ↓*	N/A	↓* vs. ↓*
Cadart (2020) France [38]	Non-randomized	28 SG 47 RYGB	N/A N/A	4 years	−7.7% vs. −10.9% #	−8.1% vs. −8.6%	−2.0% vs. −2.8%
Villarassa (2013) Spain [41]	Case-control	33 SG 33 RYGB	33 women 33 women	1 year	N/A	↓* vs. ↓*	↓* vs. ↓*
Hsin (2015) Taiwan [39]	Case-control	40 SG 40 RYGB	27 PreM women 13 Men 27 PreM women 13 Men	1 year	−5.4* vs. N/A	N/A	0 vs. N/A
Guerrero-Pérez (2020) Spain [42]	Randomized	15 SG 15 RYGB	4 PreM women 6 PostM women 5 Men 3 PreM women 5 PostM women 7 Men	5 years	N/A	−4.2%* vs. −12.1%*	−3.9%* vs. −11.6%*
Ofso (2021) Norway [34]	Randomized	48 SG 44 RYGB	15 PreM women 15 PostM women 18 Men 19 PreM women 16 PostM women 9 Men	1 year	↓ vs. ↓ #	↓ vs. ↓ #	→ vs. ↓ #

If accurate abstraction of percentage change in BMD was not possible, the directionality of the BMD change compared to baseline was indicated with an arrow (↑ increased, ↓ decreased, → no change). Abbreviations: aBMD, areal bone mineral density; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; N/A: not available. PreM: premenopausal; PostM: postmenopausal.

* Statistically significant change compared with baseline (within-group comparison).

Statistically significant between SG and RYGB.

5.3. Bone microarchitecture after bariatric surgery

Three small studies (N = 25–48) [6,28,29,44,45] evaluated post RYGB changes over 7 years in bone microarchitecture, volumetric bone mineral density (vBMD) in cortical and trabecular compartments and strength, using high resolution peripheral QCT (HR-pQCT). Findings from those studies at 1–7 years post RYGB demonstrated increased cortical porosity, and although not unanimously described, total, trabecular, and cortical vBMD were found to decline significantly at both weight bearing and non-weight bearing skeletal sites [6,28,29,44,45]. Moreover, effects of RYGB on volumetric BMD and microarchitecture appeared to occur early, with a continuing deterioration over time particularly impacting postmenopausal women [6,28,29,44,45]. In a cross-sectional study, 25 RYGB and 25 AGB subjects who underwent bariatric surgery ≥10 years ago were matched

(1:1) with nonsurgical controls based on age, sex, and current BMI [46]. In comparison to controls, RYGB subjects had significantly lower volumetric BMD and substantial deficits in cortical and trabecular microarchitecture both at the distal radius and tibia whereas no differences were observed in volumetric BMD and microarchitecture between subjects who underwent AGB compared to controls [46]. Regarding estimated bone strength, microfinite element analyses revealed a 17% lower failure load at the radius (p = 0.003) and 12% lower failure load at the tibia (p < 0.001) in RYGB as compared with BMI-matched controls (Fig. 3).

In summary, BTMs dramatically increase whereas BMD decreases after bariatric surgery, reflecting both an early and sustained state of high turnover bone loss. Moreover, this is associated with diminished bone strength and microarchitectural deterioration worsening over time. Furthermore, gastric bypass is associated with greater reductions

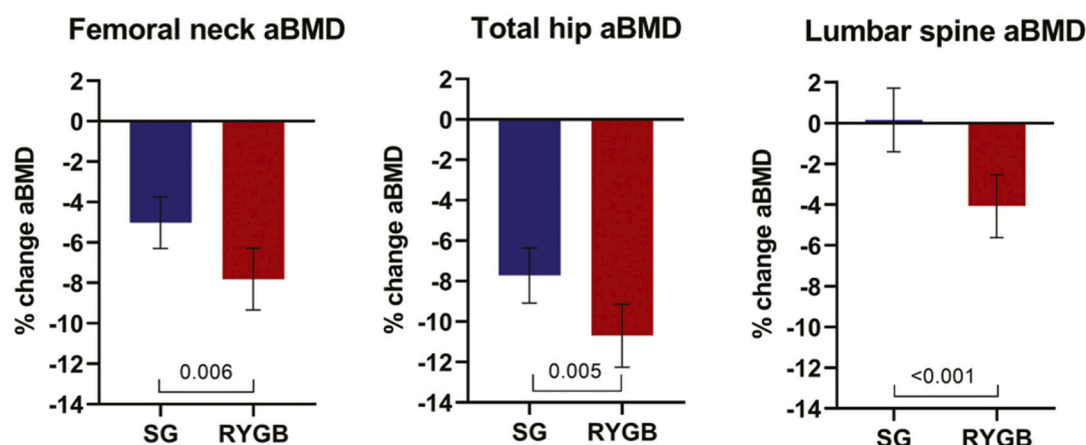


Fig. 2. Mean percent change in areal bone mineral density from baseline to 1 year after sleeve gastrectomy ($n = 48$) and Roux-en-Y gastric bypass ($n = 44$) - Adapted from [34]. Bars indicate 95% confidence intervals. P -values were calculated using independent samples t -test. Abbreviations: SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; aBMD: areal bone mineral density.

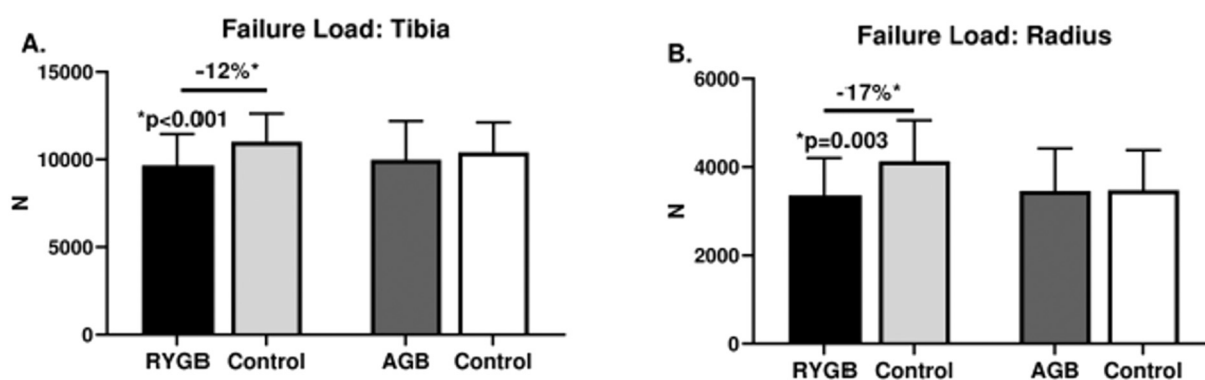


Fig. 3. Mean $\pm$ Standard Deviation of estimated failure load at the radius and tibia in the RYGB, AGB, and matched control groups - Adapted from [46]. Estimated failure load at the distal radius (A) and tibia (B) in the RYGB (black bars) vs matched control group (light gray bars), and in the AGB (dark gray bars) vs control group (white bars).

* P -value <0.05 for comparison between RYGB and controls. Percent difference between surgical and controls groups are shown for significant values.

Table 3

Overview of potential mechanisms for postoperative skeletal changes.

Factor	Effect on bone	Change in factor after bariatric surgery [references]	Anticipated effect of such a change on bone [references]
Vitamin D deficiency/calcium absorption impairment	BMD loss/upregulation of bone turnover	Aggravation of vitamin D & calcium malabsorption/secondary hyperparathyroidism [54–56]	Aggravation of BMD loss/upregulation of bone turnover [56]
PYY	Negative correlation between PYY and BMD	Increase [64]	BMD loss [64]
GIP	Increase in bone formation (animal studies)	Decrease [66]	BMD loss (lack of studies)
GLP-1	Putative osteogenic effect	Increase [68,69]	No major role on BMD loss and upregulation of bone turnover [42,70]
Ghrelin	Putative osteogenic effect	Increase/ decrease or no change [40,74,75]	No major role on BMD loss and upregulation of bone turnover [64]
Adiponectin	Putative negative effect on bone	Increase [40,79–81]	BMD loss [76–78]
Visfatin	Unclear effect on bone	Increase/decrease or no change [81,87,88]	Unclear effect (lack of studies)
Leptin	Putative osteogenic effect	Decrease [68,81]	Upregulation of bone turnover [95]
Mechanical unloading	BMD loss/upregulation of bone turnover	Potentialiation of mechanical unloading [59,60]	Aggravation of BMD loss/upregulation of bone turnover [59,60]
Loss of muscle mass	BMD loss	Potentialiation of muscle mass loss [96–98]	BMD loss/deterioration of microarchitecture [33,45,99]
Increase in BMA	BMD loss	Increase/decrease or no change [32,102,103]	Unclear effect (lack of studies)

Abbreviations: BMD, bone mineral density; GIP, glucose-dependent insulinotropic polypeptide; GLP-1; glucagon-like peptide type 1; PYY, Peptide YY; BMA, Bone marrow adiposity.

in aBMD and a greater increase in BTMs compared to SG while limited evidence suggests maintenance of volumetric BMD and micro-architecture after AGB.

6. Potential mechanisms for postoperative skeletal changes

The negative effects of bariatric surgery on bone metabolism are multifactorial and mechanisms may involve deficiency of nutritional factors, mechanical unloading, alterations in gut-derived hormones, adipokines, neuroendocrine hormones, and changes in body composition and BMA [9]. The potential mechanisms are summarized in Table 3.

6.1. Usual suspects: nutritional factors and mechanical unloading

Vitamin D deficiency is common in the obese population [47] and may be due to insufficient intake of foods and supplements rich in vitamin D [48], limited sunlight exposure [49], lower hepatic synthesis [50], or decreased bioavailability secondary to sequestration or volumetric dilution of this fat-soluble hormone in large fat reservoirs [51]. If not addressed through adequate supplementation, vitamin D deficiency may be aggravated after bariatric surgery and especially after procedures with a malabsorptive component such as RYGB and BPD because of delayed mixing of ingested nutrients with bile acids and pancreatic enzymes.

Calcium absorption mainly takes place in the duodenum and jejunum; as a result, malabsorptive procedures also result in marked calcium absorption impairment [52], which can even persist despite optimized vitamin D status [53]. Thus, although some studies do not report significant changes in vitamin D or parathyroid hormone status post-operatively [32,33], others identify secondary hyperparathyroidism as a common occurrence after bariatric surgery [54–56], highlighting the need for individualized repletion regimens in this population.

With regard to protein homeostasis, the early postoperative phase after RYGB is characterized by an increase in serum levels of most amino acids, possibly because of muscle catabolism [57], while adequate protein intake (1–1.2 g/Kg/day) has been shown to mitigate muscle and bone loss [58].

The skeleton adapts to mechanical strain and loading is a prerequisite for maintenance of bone mass and microarchitecture. Bariatric surgery and ensuing weight loss thus result in the relative unloading of the skeleton. Most studies have reported a strong association between the amount of weight loss and the extent of postoperative bone loss [59,60]. One mechanistic study documented increases in sclerostin levels after bariatric surgery, which correlated with BTMs increases and a BMD decrease [33]. However, BMD declines have also been described at non-weight bearing skeletal sites, such as the radius, after bariatric surgery [28]. Thus, mechanical unloading appears to be a contributing but is not the sole causative factor of post-operative skeletal impairments.

6.2. Alterations in gut-derived hormones

The multifaceted hormonal changes and interactions after bariatric surgery and their putative implications in postoperative bone loss have been covered in detail in other reviews [9,4] and will only be summarized here. Peptide YY (PYY) is produced by the enteroendocrine L-cells of the terminal ileum and colon and has an anorexigenic effect [61]. Lower concentrations of PYY have been reported in obese individuals [62], while in female patients with anorexia nervosa, high levels of PYY correlated positively with low levels of BTMs [63]. PYY levels increase after RYGB surgery and correlate with an uncoupling of bone turnover favoring resorption as well as with BMD loss [64]. Another gut-derived hormone which affects bone metabolism is glucose-dependent insulinotropic polypeptide (GIP). Obese subjects display elevated GIP levels [65]. Whereas most human studies have shown a decrease in GIP post-

malabsorptive bariatric surgery [66], studies evaluating post-operative changes in GIP in association with changes in BMD or BTMs are lacking. In addition to GIP, glucagon-like peptide type 1 (GLP-1) plays a pivotal role in the pathogenesis of diabetes mellitus [67]. GLP-1 has been found to be consistently elevated in response to RYGB [68,69]. However, a 26-week treatment of liraglutide, a GLP-1 receptor agonist, did not affect bone resorption and preserved hip BMD despite weight loss in patients with T2D [70]. Moreover, a recent randomized clinical trial suggested that GLP-1 changes do not play a major role in the deleterious effects of RYGB on bone [42], confirming a previous study which did not report any associations between changes in GLP-1 levels and BTMs outcomes [35]. Ghrelin affects bone metabolism primarily through its stimulatory effect on growth hormone. Given the osteoanabolic effect of growth hormone on bone, ghrelin is also expected to exert positive effects on bone homeostasis. However, data on the association of ghrelin with BMD and BTMs have been conflicting so far [71–73]. Moreover, ghrelin levels have been shown to either be profusely suppressed or unchanged or even increased after bariatric surgery [40,74,75]. Kim et al. failed to identify significant associations between changes in ghrelin levels and BMD in obese subjects undergoing RYGB [64].

In summary, recent studies of gut-derived hormones have highlighted the increase of PYY seen after RYGB surgery as a cause of bone loss, while the role of GIP and GLP-1 remains more obscure. Further rigorous studies are needed to elucidate the relative contribution of each of these hormones. Moreover, fasting vs. postprandial measurements may also need to be taken into account.

6.3. Alterations in estrogen levels, adipokines, neuroendocrine hormones, and sclerostin

Obesity is associated with hyperestrogenism, while free and total estradiol levels are significantly decreased after bariatric surgery in both female and male patients, highlighting a link between waning estrogen levels and an upregulation of bone turnover. Since adiponectin levels inversely correlate to fat mass, and numerous studies have evaluated the relationship between fat and bone mass, the potential contribution of adiponectin to this relationship has been investigated. In human observational studies, adiponectin was found to be negatively associated with BMD [76–78], suggesting it might be a negative regulator of bone metabolism. However, results of in vitro and animal studies are not entirely congruent, partly due to differences between experimental settings and partly due to the complex nature of adiponectin signaling. Regarding adiponectin levels post-bariatric surgery, studies have shown an increase in its levels [40,79–81]. Thus, the consistent and persistent [82] increase of circulating adiponectin levels after bariatric surgery could contribute to the well-described post-operative negative skeletal effects. Visfatin serum levels are increased in obese patients and correlate with indices of insulin resistance [83]. The relationship between visfatin and BMD has been extensively studied and yielded controversial findings. No association between BMD and visfatin circulating levels was observed in several cohort-studies [84,85] as well as in a meta-analysis [71] and a multivariable regression analysis [86]. Serum visfatin levels after bariatric surgery have been either reported to increase [87], decrease [88], or remain unchanged [81]. Clearly there is a dichotomy between anabolic and catabolic effects of visfatin on bone, and further research is needed to determine whether this adipokine is implicated in skeletal health after bariatric surgery. Leptin is a peptide primarily secreted by adipocytes which circulates at levels proportional to fat stores and regulates appetite and energy expenditure. Although increased leptin levels characterize obese individuals, they fail to effectively suppress appetite in these subjects because of an underlying resistance to the hormone [89]. In addition to its metabolic effects, leptin plays an important role in bone physiology [90]. Findings from in vitro studies indicate that leptin could positively influence bone density by increasing bone formation and reducing bone resorption [90].

However, animal studies have yielded contradictory results which underscores the direct anabolic effects of leptin on bone, but also its multiple indirect actions, via the hypothalamus, pituitary gland, and sympathetic nervous system as well as via changes in body weight [90]. Similarly, human studies assessing leptin's effects on bone homeostasis have not been consistent. Some studies have described positive associations between leptin and BMD [77,84,85,91,92], while others have found no associations [76,78]. Recently lower leptin levels were reported as a significant independent risk factor for incident long-bone fractures [93], while plasma leptin levels were shown to be inversely associated with cortical thickness, suggesting that hyperleptinemia might contribute to cortical porosity in patients with T2DM [94]. Since leptin circulates in proportion to body fat mass, as expected a decrease in leptin levels has been reported after bariatric surgery [68,81]. Recently, persistently suppressed leptin levels were reported up to seven years post-bariatric surgery and this correlated with increased BTMs [95]. Sclerostin is a major inhibitor of the osteogenic Wnt signaling pathway, thus impeding bone formation. Although some studies did not report changes in sclerostin levels after bariatric procedures [29], others have found a significant increase in post-operative levels of sclerostin [4,8,33]. Of note, a number of studies have identified that exercise mitigated the surgery-induced increase in sclerostin [8,9,33], which may represent a mechanism underlying the protective effect of exercise on bone mass.

In summary, increased adiponectin and sclerostin, and decreased leptin concentrations might be key factors for skeletal insult following bariatric surgery. Further rigorous studies are needed to elucidate the relative contribution of each of these parameters. Variable assays have been used to measure these parameters, and this may have led to inconstant results.

6.4. Changes in body composition and bone marrow adiposity

Bariatric surgery results in loss of muscle mass [96,97], even if the relative loss of fat mass is greater than that of muscle [98]. The most prominent loss of muscle mass occurs during the first 6 postoperative months [98] and a link between muscle mass decrease and impairment of bone health is widely acknowledged. Several studies have described correlations between reductions in lean mass and declines in bone mass as measured by DXA [33,99] and deterioration of microarchitecture assessed by HR-pQCT [45].

Bone marrow adiposity (BMA) is paradoxically increased in caloric restriction and weight loss as has been described in anorexic patients [100]. Moreover, increased BMA is associated with lower BMD, rapid bone loss and vertebral fractures [101]. As such, should an increase in BMA occur after bariatric surgery, this could constitute a mechanism for postoperative negative skeletal effects. A study of 21 patients having undergone RYGB or SG did not confirm an increase in BMA [31]. Conversely, Bredella MA et al. described higher content of BMA in patients after SG but not in patients after RYGB [32]. Moreover, Kim TY et al. showed that after RYGB, BMA even decreased in diabetic patients [102]. A recent elegant study evaluated biopsy-measured BMA fraction preoperatively and after RYGB [103]. Higher BMA was associated with lower BMD and poorer glycemic control in obese subjects, while after RYGB, a significant decrease in BMA was observed. The reduction in BMA was similar between participants with and without T2DM but appeared sex specific [103]. Thus, further studies with a larger number of participants are needed to delineate whether different bariatric procedures differentially influence BMA and whether this effect results in impaired or improved bone homeostasis. From a mechanistical point of view, rapid loss of BMA and expansion of myeloid cellularity especially with regard to circulating neutrophils was reported in a mouse model of SG, thus highlighting the fact that circulating granulocyte-colony stimulating factor (G-CSF) could be a potential contributor to bone homeostasis post-bariatric surgery [104]. Of note, G-CSF has been previously shown to decrease bone formation [105] and increase bone resorption

[106] in preclinical models.

In summary, data available on BMA changes following bariatric surgery are lacking or unclear.

7. Literature review and recommendations for prevention and treatment of skeletal fragility following bariatric surgery based on expert opinion

7.1. Limitations of available data

Little is known about the effects of lifestyle or drug interventions to prevent high turnover bone loss and no data to date are available on fracture outcome. However, there is little doubt that after all bariatric procedures, sufficient calcium, vitamin D, and protein intake and adequate physical activity are needed to counteract negative effects on bone and muscle.

7.1.1. Non-pharmaceutical treatments

A beneficial impact on lumbar spine and total hip aBMD and muscle mass has been reported with co-supplementation of vitamin D, calcium, and protein combined with aerobic exercise [107]. The aerobic exercise program started 2 weeks after surgery: Nordic walking for a minimum of 45 min at least 3 times/week, as well as strength exercise program for 30 min at least 2 times/week [107]. In a recent randomized controlled trial, exercise mitigated bone loss at the femoral neck, total hip, and distal radius in women with severe obesity after RYGB, which was accompanied by a decrease in BTMs [108]. In addition, exercise training attenuated bone loss of cortical vBMD at the distal radius, but no other differences were observed regarding bone microarchitecture parameters [108]. In this trial, post-surgery exercise training, thrice weekly, included strengthening exercises for major muscle groups and aerobic exercise (30 to 60 min) on a treadmill [108]. Another study suggests that an exercise program is an effective strategy to improve aBMD at lumbar spine in post-bariatric surgery patients [109]. In this study, post-surgery exercise-training program on 3 weekly nonconsecutive days lasting 75 min each included high impact, balance and resistance exercises [109].

7.1.2. Pharmaceutical treatments

While there are very few studies to date that have investigated the effect of osteoporosis treatment, there are several ongoing studies (NCT04279392, NCT03411902) aiming to assess the effect of bisphosphonates on changes in hip and lumbar spine aBMD by DXA following different types of bariatric surgery. The use of inhibitors of bone resorption such as bisphosphonates is logical given the high-turnover bone loss state after bariatric surgery. Liu et al. performed an open-label pilot 24-week study in a small series of 4 postmenopausal women (versus 10 historical controls) to examine the preliminary safety and efficacy of zoledronate (ZOL) to suppress BTMs and prevent declines in BMD (by DXA and QCT) after RYGB surgery. At 24 weeks, a single dose of ZOL prior to RYGB appeared to transiently mitigate but not fully prevent an elevated bone turnover. Moreover, ZOL may preserve trabecular vBMD at the spine (by QCT), but was apparently not sufficient to prevent bone loss at the hip (by DXA) [110]. Swafford et al. recently published the study design of a randomized controlled trial of risendronate after SG [111]. Results of this study are pending [111]. Data on the use of denosumab to prevent bone loss after bariatric surgery are even more limited. There is an ongoing study on denosumab to prevent high-turnover bone loss after RYGB or SG (NCT04087096). Denosumab will be given at months 1, 7 and 13 after surgery followed by a single infusion of ZOL at month 19.

7.2. Current recommendations

The ASMBS (American Society for Metabolic and Bariatric Surgery) published a first position statement in 2015 [112], which has been updated in 2021 [113].

As recommended by the National Osteoporosis Foundation (NOF), a baseline DXA scan is now suggested for 1) all women aged 65+ and men aged 70+, 2) in postmenopausal women and men above age 50–69, based on the risk factor profile, and 3) in men aged 50+ who have had an adult age fracture. Whatever their age, DXA after bariatric surgery in patients who have had RYGB or BPD may be indicated to monitor for osteoporosis at baseline and at about 2 years.

7.3. Recommended strategies based on expert opinions (Fig. 4)

7.3.1. All patients

Mandatory measures preceding and following bariatric surgery include treatment of vitamin D deficiency, optimization of total daily calcium and protein intakes (diet and/or supplements) as well as increase of physical activity (including aerobic and strength exercise program). Vitamin D supplementation is recommended in all patients with 25-OH vitamin D values below 20 ng/mL, and in an individualized manner for values between 21 and 30 ng/mL. Regarding calcium and vitamin D supplements, higher doses than those currently recommended (e.g. calcium: 1200–1500 mg/day and vitamin D: 400–800 U/day) are often necessary. Calcium citrate is preferable to calcium carbonate, due to better absorption and bioavailability in the absence or reduction of gastric acid [114]. Smoking cessation and a decrease of excessive alcohol use should be encouraged.

7.3.2. Post-menopausal women and men ≥ 50 years

We believe that patients at higher fracture risk such as post-menopausal women and men older than 50 years should be assessed for the existence of osteoporosis and past fragility fractures and, if indicated, treated before bariatric surgery. In the absence of a baseline evaluation, fracture risk should be assessed at any time following bariatric surgery. The evaluation should include clinical risk factors including a fracture history, DXA testing of the lumbar spine and hip, spine radiographs or vertebral fracture assessment, measurement of

BTMs, and biochemical analyses to identify secondary causes of osteoporosis. We do not recommend DXA testing of the forearm in very obese patients (over the weight limit for DXA table). Measurement of 24-h urinary calcium may be of value to adjust calcium supplementation in the presence of secondary hyperparathyroidism and serum 25-OH vitamin D level at target. The TBS software and Fracture Risk Assessment Tool (FRAX) have not been validated in this population and need further evaluation to ascertain whether they can accurately predict fracture risk in patients undergoing bariatric surgery. However, we believe that determination of the FRAX score, adjusted or non-adjusted by TBS, may be useful and a FRAX score (with femoral neck BMD) exceeding 20% for the 10-year major osteoporotic fracture probability or exceeding 3% for hip fracture should be considered for therapeutic intervention. The use of HR-pQCT has yielded important information about effects of bariatric surgery on individual bone compartments; however, HR-pQCT is not approved for clinical use, so even at centers that have HR-pQCT, it cannot be implemented currently as a clinical tool in bariatric surgery patients. In post-menopausal women and men older than 50 years, osteoporosis treatment would be reasonable in the presence of any of the following criteria: (Fig. 4):

- History of recent* low energy fracture (vertebral and nonvertebral) after 40 years of age
- T-score $\leq -2^{**}$ at the lumbar spine and/or femur
- FRAX score with femoral neck BMD exceeding 20% for the 10-year major osteoporotic fracture probability or exceeding 3% for hip fracture

* In the last 2 years.

** Most studies have shown that people with obesity have higher BMD compared with subjects with normal weight [115]. Treatment should be considered at more favorable BMD values in obese than in non-obese patients, as BMD may underestimate the risk of fracture in this population. Thus, a BMD intervention threshold at T-score -2.0 at

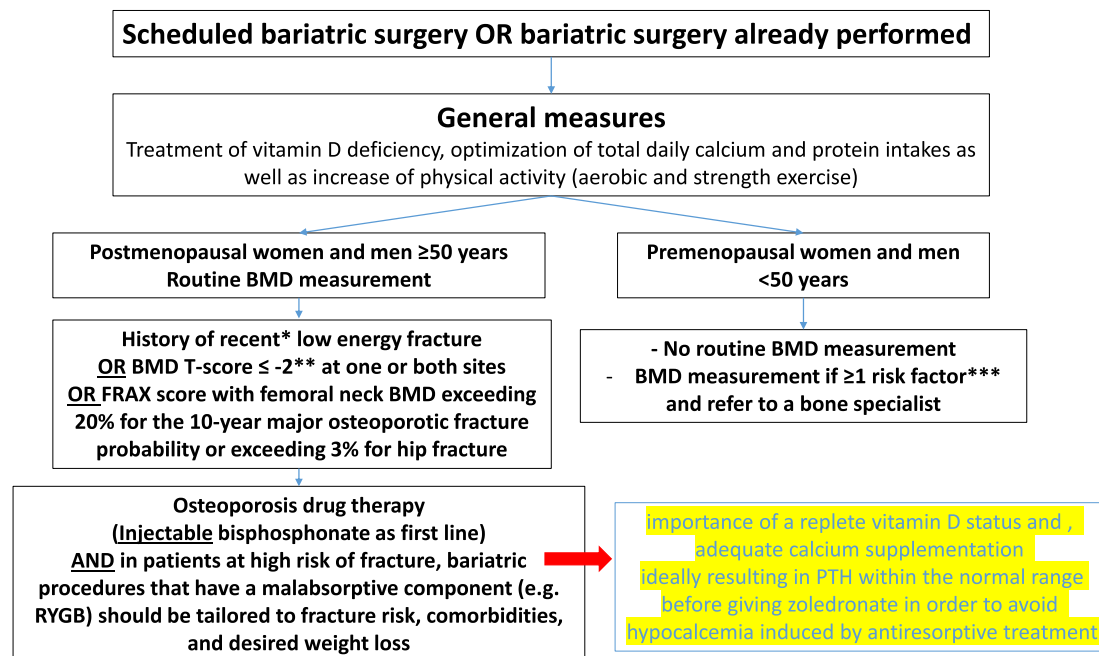


Fig. 4. * In the last 2 years

** A BMD intervention threshold at T-score -2.0 at spine or hip would be reasonable

*** history of low energy fracture after 40 years of age, Asthma or COPD, heart attack, angina, stroke or TIA, Chronic liver disease, Chronic Kidney disease (stage 4 or 5), Parkinson's disease, Rheumatoid arthritis or SLE, Malabsorption (e.g. Crohn's disease, ulcerative colitis, celiac disease), Endocrine problems (e.g. thyrotoxicosis, Hyperparathyroidism, Cushing's syndrome), epilepsy or taking anticonvulsants, history of hip fracture in the patient's mother or father, currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5 mg daily or more.

spine or hip would be reasonable or annual bone loss on treatment is confirmed to exceed 5% [32,34]. We recognize a knowledge gap to support this recommendation but this intervention threshold at T-score – 2.0 has also been validated in several conditions also characterized by a rapid bone loss and a decreased bone quality such as cancer treatment-induced bone loss [116] and bone fragility in diabetes [117].

7.3.3. Proposed therapy

Injectable bisphosphonates (zoledronate as first choice) should be preferred due to intolerance of oral formulations and malabsorption, and denosumab as second choice (contraindication or intolerance for bisphosphonates) because this treatment carries several risks, especially risk of rebound effect on treatment discontinuation.

We recommend to ensure adequate serum 25-OH vitamin D level and calcium supplementation before administering zoledronate or denosumab in order to avoid antiresorptive-induced hypocalcemia [118–120].

Moreover, in patients at high risk of fracture, surgical intervention such as RYGB should be tailored to fracture risk, comorbidities, and desired weight loss.

Patients who are not eligible for osteoporosis treatment should be offered the general measures described above and undergo follow-up including fracture risk assessment and BMD measurement every 1 year, although this interval may be adjusted based on BMD values obtained at baseline and during the follow-up.

7.3.4. Pre-menopausal women and men <50 years

In pre-menopausal women and men younger than 50 years of age, the fracture risk is lower and routine BMD measurement should not be performed unless other clinical risk factors are present (Fig. 4). We believe that BMD measurement should be performed in patients with at least 1 risk factor such as established history of low energy fracture after 40 years of age, and patients should be referred to a bone specialist to determine whether an osteoporosis treatment should be given.

8. Future research related to bariatric surgery and skeletal health

Observational studies with long-term follow-up of skeletal health for patients after bariatric surgery are necessary since the long-term fracture risk remains to be determined. The long-term risk of fracture associated with SG, RYGB, and other bariatric procedures, versus severely obese controls with dietary weight loss interventions should be further explored. In particular, the fracture risk should be evaluated in populations such as postmenopausal women and men older than 50 years. Thus, ancillary skeletal health studies to randomized controlled trials of surgical and/or non-surgical weight loss approaches are desired. Since bariatric surgery is associated with improvements or remission of diabetes, the long-term risk of fracture should be further explored with a comparison between patients with or without remission of diabetes.

More data describing changes in BMD at various sites using DXA and BTMs following bariatric surgery, comparing RYGB with SG, are needed to validate preliminary findings on the most deleterious effect of RYGB. Evidence on microarchitecture deterioration and diminished bone strength following bariatric surgery derived from HR-pQCT studies evaluating RYGB, but not SG. There is a need to assess the impact of SG on bone microarchitecture using HR-pQCT.

Preclinical and clinical studies are needed to elucidate factors associated with skeletal changes beyond the usual suspects since those changes continue even after weight loss plateaus, weight stabilizes, and appropriate nutritional intake associated with training exercise is implemented. Little is known about potential factors associated with high turnover bone loss and increased fracture risk after bariatric surgery. In particular, the roles of adipokines, body composition and BMA should be further assessed. Moreover, the relationship between long-term proton pump inhibitors (PPI) use and fracture needs to be better evaluated because there is frequently an increased need for PPI after

bariatric surgery [121,122].

There is a knowledge gap on screening and management strategies for osteoporosis in patients undergoing bariatric surgery. More research is necessary to direct and support guidelines. Additional research is necessary to determine the best clinical use of DXA, vertebral fracture assessment, BTMs, before and/or after bariatric surgery, in all subjects. We also need to evaluate other tools such as FRAX and trabecular bone score (TBS) in this specific population.

Randomized clinical trials of pharmaceutical and non-pharmaceutical treatments with bone outcomes such as bone strength and/or BMD (areal and volumetric) are warranted. Randomized clinical trials with fracture endpoints would be costly, long lasting, and perhaps impractical but they would provide the best guidance for fracture prevention. Co-supplementation of vitamin D, calcium, and protein combined with exercise counteract partially high turnover bone loss, but the separate effects of these interventions remain to be determined as well as effects of pharmaceutical treatment for osteoporosis. Furthermore, anabolic drugs such as teriparatide and romosozumab should be evaluated in patients undergoing bariatric surgery.

9. Conclusions

The field of skeletal health following bariatric surgery is evolving rapidly. This narrative review summarizes our current knowledge on bone outcomes after bariatric surgery, and potential mechanisms. Observational studies suggest a 21–44% increase in fracture risk following bariatric surgery, especially for wrist and hip fractures. Fracture risk is time dependent and increases approximately 2–3 years after bariatric surgery, and the long-term risk remains partially unknown. The surgical procedure most often performed in recent years is SG and the magnitude of fracture risk associated appears to be lower compared to bariatric procedures that have a malabsorptive component such as RYGB and BPD. Numerous studies demonstrate that BTMs dramatically increase as early as 10 days whereas BMD decreases as early as 6 months after bariatric surgery, reflecting both an early and sustained state of high turnover leading to bone loss associated with microarchitectural alterations worsening over time. Moreover, a greater reduction in aBMD and greater increase in BTMs have been reported with RYGB and BPD compared to SG with data lacking on bone strength and microarchitecture. Regarding AGB, this procedure was not associated with an increased risk of fracture or BTMs levels. Moreover, limited evidence suggests maintenance of volumetric BMD and microarchitecture after AGB. The usual suspects are nutritional factors and mechanical unloading but there is a myriad of factors potentially implicated such as gut-derived hormones, adipokines, and changes in body composition and BMA. However, conflicting results and a knowledge gap do not allow for definitive conclusions. Other questions remain on whom and how to screen, and when to treat. We believe that clinicians should focus their attention on patients at high fracture risk such as postmenopausal women and men older than 50 years. Before and after bariatric surgery, DXA should be used to measure BMD and risk factors for osteoporosis should be assessed. Injectable bisphosphonates (zoledronate as first choice), together with appropriate vitamin D and calcium supplements, should be preferred due to intolerance of oral formulations and malabsorption, and in patients at high risk of fracture, surgical intervention such as RYGB should be tailored to fracture risk, comorbidities, and desired weight loss.

Declaration of competing interest

Pr. Paccou received research funding from MSD and honoraria for lectures from Amgen, UCB, Sandoz, Novartis and Eli Lilly.

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Dr. Pepe has nothing to disclose.

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Pr. Zillikens declares having received honoraria in the past for lectures or advice from Alexion, Amgen, Eli Lilly, Kyowa Kirin, Shire and UCB, unrelated to the current work.

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