MANAGEMENT OF ENDOCRINE DISEASE

Bone complications of bariatric surgery: updates on sleeve gastrectomy, fractures, and interventions

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Abstract

Despite well recognized improvements in obesity-related comorbidities, increasing evidence implicates bariatric surgery in the onset of adverse skeletal health outcomes. The purpose of this review is to provide a focused update in three critical areas: (i) emergent data on sleeve gastrectomy and bone loss, (ii) evidence linking bariatric surgery to incident fracture, and (iii) intervention strategies designed to mitigate surgical bone loss. Better understanding of these issues will inform our treatment of skeletal health for patients planning bariatric surgery.

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Introduction

Bariatric surgery results in marked and durable weight loss for adults with severe obesity, and is also recognized as a treatment for type 2 diabetes (1). Despite the myriad benefits of these procedures, increasing evidence implicates bariatric surgery in the onset of adverse skeletal health outcomes. In the past decade, over two dozen review articles have been devoted to the topic of bariatric surgery and bone loss, and as the utilization of bariatric surgery continues to rise (2), new literature is constantly

emerging. In particular, the exponential increase in sleeve gastrectomy (SG) has led to additional evidence about the effects of this popular procedure on the skeleton. Furthermore, new data have been published examining fracture risk by specific bariatric procedure. Finally, interventional studies are beginning to emerge that are exploring strategies to minimize bone loss after bariatric surgery. In this review paper, we aim to provide an update on these clinically important topics.

Invited Author's profile

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Sleeve gastrectomy and bone loss

Sleeve gastrectomy (SG) is a relatively new bariatric procedure, in which the stomach is reduced to about 15% of its original size by surgical removal of a large portion of the body along the greater curvature. While several reviews (3, 4, 5) and meta-analyses (6, 7) have reported on bone loss – particularly at the hip – secondary to Roux-en-Y gastric bypass (RYGB; the historically most utilized and well documented bariatric procedure), less is known about SG. As SG has recently surpassed RYGB as the most popular bariatric procedure, comprising over 60% of all surgeries performed in 2018 (8), better understanding of the skeletal consequence of this specific surgical type has important clinical implications.

Physiologically, compared to procedures with a more pronounced malabsorptive component (i.e. RYGB, biliopancreatic diversion with duodenal switch (BPD-DS)), SG may result in less bone loss. For example,

when comparing SG to RYGB, achieved weight loss is less robust (9), with fewer nutrient deficiencies (10) and less pronounced increases in bone turnover (11, 12, 13). In the past decade, over a dozen studies have reported on change in BMD following SG using DXA (12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24), with primary design features and findings reported in Table 1. Six-, 12-, and 24-month percent change in total hip and lumbar spine BMD are also depicted graphically in Fig. 1. In the ensuing text, studies will be discussed sequentially by duration; however, across all studies and time points, SG appears to be consistently associated with declines in both total hip and femoral neck BMD, while associations at the lumbar spine are inconsistent.

In the first 6 months after SG, four prospective observational studies (14, 15, 25, 26) report a postoperative decline in BMD (approximately 3–7%) (14, 15) at the total hip and femoral neck, which is accompanied by an increase in biomarkers of bone turnover (13). As is seen

Table 1 Studies reporting on regional change in DXA-measured areal bone mineral density (BMD) after sleeve gastrectomy (SG).

References	n (% females)	Duration (months)	Age (years)	Preoperative BMI (kg/m ²)	Weight loss (%)	Percent change in regional BMD at follow-up		
						Total hip	Femoral neck	Lumbar spine
Pluskiewicz <i>et al.</i> (14)	29 (100%)	6	40	43	–28	–5.2*	–7.0*	–1.2*
Adamczyk <i>et al.</i> (15)	25 (0%)	6	45	43	–21	–3.5*	–3.3*	+2.9*
Muschitz <i>et al.</i> (25)	38 (100%)	6	41	46	NR	↓*	NR	↓
Wang <i>et al.</i> (26)	34 (0%)	12	32	41	–24	→	↓	→
Wang <i>et al.</i> (26)	37 (100%)	12	33	38	–26	↓*	↓*	↓
Nogués <i>et al.</i> (16)	8 (100%)	12	50	44	–30	–7.1*	–8.3*	–4.6*
Ruiz-Tovar <i>et al.</i> (17)	42 (93%)	12	44	51	–39	NR	NR	+5.7*
Carrasco <i>et al.</i> (18)	20 (100%)	12	34	37	–31	NR	–3.2	–1.7
Adamczyk <i>et al.</i> (19)	36 (100%)	12	41	42	–27	–5.3*	–6.2*	–1.2
Hsin <i>et al.</i> (20)	40 (68%)	12	30	40	–34	–5.4*	NR	0
Maghrabi <i>et al.</i> (21)	19 (59%)*	12	48*	36*	–25 ^a	–7.6 ^a	NR	–0.7 ^a
Muschitz <i>et al.</i> (25)	37 (100%)	12	41*	46*	NR	↓*	NR	↓*
Tan <i>et al.</i> (22)	12 (67%)	12	36	41	–25	–7.6*	–10.2*	–0.9
Bredella <i>et al.</i> (12)	10 (90%)	12	50	44	–25	–6.8*	–4.9*	–2.8*
Carrasco <i>et al.</i> (27)	19 (100%)	12	34*	37*	–30	NR	↓*	↓
Wang <i>et al.</i> (26)	34 (0%)	12	32	41	–31	↓	↓	↑
Wang <i>et al.</i> (26)	37 (100%)	12	33	38	–31	↓*	↓*	↓
Guerrero-Pérez <i>et al.</i> (23)	15 (66%)	12	49	39	–27	NR	–5.3 ^a	–0.5 ^a
Misra <i>et al.</i> (24)	22 (73%)	12	18	47	–27	–4.7*	–6.9*	–0.3
Ruiz-Tovar <i>et al.</i> (17)	30 (93%)*	24	44*	51*	–41	NR	NR	+7.9*
Muschitz <i>et al.</i> (25)	35 (100%)	24	41*	46*	NR	↓*	NR	↓*
Maghrabi <i>et al.</i> (21)	19 (59%)*	24	48*	36*	–23 ^a	–9.2 ^a	NR	–2.3 ^a
Carrasco <i>et al.</i> (27)	14 (100%)	24	34*	37*	–28	NR	↓	↓

*Statistically significant change compared with baseline (within-group comparison). ^aStatistically significant change from baseline compared with an intensive medical therapy control group (between-group comparison). ^aData were reported as a median rather than a mean. ~Percentage change were not directly reported by the authors and were instead estimated from available values at baseline and follow-up. *Data were available only for the baseline population ($n = 42$ for Ruiz-Tovar *et al.* (17); $n = 54$ for Maghrabi *et al.* (21); $n = 38$ for Muschitz *et al.* (25); $n = 26$ for Carrasco *et al.* (18) and not the presented subset of the population followed over time. If accurate abstraction of percentage change in BMD was not possible (25, 26, 27), the directionality of the BMD change compared to baseline was indicated with an arrow (↑ increased, ↓ decreased, → unchanged). SG, sleeve gastrectomy; Percent change in BMD is shown as group mean, unless otherwise indicated.

Figure 1

Percent change in (A) lumbar spine and (B) total hip bone mineral density (BMD) in the 6, 12, and 24 months following sleeve gastrectomy (SG). *Significant change from baseline ($P < 0.05$). ^Significant change from baseline compared to control group ($P < 0.05$).

in other states of high bone turnover, there is an increase in both indices of bone resorption (e.g. C-terminal telopeptide, CTX) and bone formation (e.g. procollagen type 1 N-terminal propeptide, P1NP; osteocalcin). Short term effects in the spine are contradictory according to the available prospective observational SG data, with one study consisting of all women (14) showing a modest 1.2% decline, and one study of all men (15) showing an increase of 2.9%. By 12 months after SG, bone turnover markers approach their peak values (25), and are accompanied by 4–8% BMD losses in the total hip (12, 16, 19, 20, 21, 22, 24) and a wider range of 3–10% losses in the femoral neck (12, 16, 19, 22, 24, 27). Additionally, a prospective observational study of 38 SG patients reported significant declines in absolute total hip BMD (25). Intriguingly, limited data suggest women are more susceptible to SG-associated hip bone loss than men (26). Changes in lumbar spine BMD at 12 months were inconclusive; the majority of studies present null findings, while studies reporting significant changes were of conflicting directionality (12, 16, 17, 25). Of the four studies that detected a significant 12-month change in spine BMD, two were prospective observational studies (12, 25) including a study of 10 SG participants reported a 2.8% decrease (12). Another prospective pilot trial of participants randomized to SG ($n=8$) or RYGB ($n=7$) reported a 4.6% decrease among the SG participants (16), whereas a retrospective chart review of 42 SG patients that found a 5.7% increase at 12 months (17). This inconsistency in postoperative spine BMD change is also present in the

available 24-month data, where one prospective study of type 2 diabetes patients randomized to SG, RYGB, or medical therapy found a significant 2.3% decrease in the SG group (21), while the aforementioned retrospective chart review found a significant 7.9% increase (17). The exact reasons for the discrepant BMD results in the spine (relative to the hip) remain unclear, and may be attributed to more region-specific measurement artifact from soft tissue artifact, degenerative joint disease, or vascular calcification (28). Hip data at 24 months are limited, but one available prospective study reported a statistically significant 9.2% reduction in total hip BMD among type 2 diabetes patients randomized to receive SG (21), which provides preliminary evidence that may suggest continued long-term declines in bone density. Finally, a prospective observational study of 38 SG patients documented significant declines in absolute BMD at the spine and the hip over a 2-year period, that was of similar magnitude as observed in RYGB patients, although it should be noted that calcium and vitamin D supplementation were not provided (25). Given that maximum excessive weight loss with SG has been shown to occur 24–36 months postoperatively (29) and that bone turnover markers can remain elevated for several years after SG (25), additional data from well-designed long duration studies are needed to adequately inform postoperative SG clinical care recommendations for skeletal health.

In accordance with individual study findings, a recent meta-analysis investigating changes in BMD after SG (including (12, 14, 15, 16, 18, 20) of the aforementioned studies) reported significant losses at the total hip (pooled mean difference from baseline of -0.06 g/cm²) and femoral neck (-0.05 g/cm²), but no significant change in lumbar spine aBMD (-0.01 g/cm²) at an average of 12 months after SG (30). The authors note that the extent of BMD reduction with SG at all regional sites (total hip, femoral neck, and lumbar spine) appears to be of smaller magnitude than that of a previously published meta-analysis of the RYGB procedure (7). A more recent meta-analysis by Tian and colleagues (including (18, 20, 22, 27) of the aforementioned studies), which directly compared absolute BMD values at 12 months ($n=4$) and 24 months ($n=1$) after SG and RYGB, found no significant difference in postoperative BMD between the surgical groups (31). The authors note, however, the lack of detectable difference in bone loss between surgical types may be due to the small number of studies ($n=5$) and the lack of sufficient long-term data. Another contributing factor may be the reliance of BMD acquisition via DXA, which has limited accuracy

in assessing bone outcomes following surgical weight loss due to changing fat-lean tissue ratios in the region of interest, fan-beam hardening, and other factors (3, 32). Furthermore, DXA cannot distinguish cortical from trabecular bone compartments, nor can it evaluate elements of bone quality. Collectively, it is thought that these limitations of DXA-derived measurements might be confounding the magnitude and direction of BMD changes with surgical weight loss.

Therefore, consideration of additional advanced measures of bone health appear prudent to better characterize changes after SG. Techniques include quantitative CT (QCT) derived volumetric BMD (vBMD), which is less susceptible to obesity and weight loss induced measurement error (33), and high-resolution peripheral quantitative CT (HR-pQCT). To date, three studies have used QCT to measure vBMD after SG (12, 13, 22). One study showed no significant change in six-month lumbar spine vBMD from baseline with SG and found no difference between SG and RYGB (13). Two smaller 12-month studies found statistically significant decreases in the trabecular spine vBMD (−11.2% and approximately −4%) that exceeded the magnitude of the BMD losses detected by DXA at the lumbar spine (−0.9 and −2.8%), and these decreases were not significantly different between SG and RYGB (12, 22). Neither study found significant changes in the total hip nor the femoral neck vBMD after SG. Finally, a very recent study assessed 12-month changes in HR-pQCT derived bone geometry, microarchitecture, vBMD, and mechanical strength in 22 adolescents and young adults with obesity who received SG, as compared with non-surgical controls (24). Detrimental changes in bone quality were observed in the surgical group – including reductions in distal radius trabecular vBMD and distal tibia cortical area/thickness and trabecular number, along with increases in tibia trabecular area and separation – which authors attribute primarily to change in BMI. Interestingly, these changes in bone quality did not appear to compromise overall bone strength estimates, which is possibly due to the observed increase in radial and tibial cortical vBMD. However, it should be noted that increases in cortical vBMD in the context of obesity and weight loss are an unanticipated finding, and may be unique to an adolescent population whose skeleton is still maturing.

In summary, the data available from the last decade suggests that BMD decreases at the axial skeleton after SG, but to a smaller extent than what is observed following RYBG. However, as SG continues to grow in popularity, it is essential that large robustly designed clinical studies

with appropriate non-surgical controls, advanced imaging modalities, and long-term follow-up are prioritized in order to comprehensively assess bone health and elucidate the underlying mechanisms of bone loss with SG compared to other surgical weight loss procedures.

Bariatric surgery and fracture risk

Epidemiologic studies published in the past decade provide valuable insight into the impact of various bariatric procedures on fracture risk. Descriptive summary data from controlled observational studies are presented chronologically in Table 2 (34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45). An important distinction that has emerged from the literature is that fracture risk varies by type of bariatric procedure. In two of the earliest accounts from the United Kingdom, bariatric surgery – comprised predominantly of adjustable gastric banding (AGB) – was not associated with increased fracture risk (34, 36). Given the negligible effects of AGB on bone metabolism (46) combined with the relatively short median length of follow-up for these studies (≤ 3 years), these negative results are not overly surprising. Indeed, more recent literature examining procedure-specific outcomes demonstrated that the AGB procedure does not lead to increased fracture risk (38). Conversely, literature focused on metabolic bariatric surgeries (i.e. all bariatric surgical types except AGB, which is purely restrictive) uniformly report a modest, positive association (i.e. 1.3- to 2.3-fold increase in fracture risk (47, 48)); although, upwards of a five-fold increase in fracture risk has been observed at some skeletal sites in at least two studies (35, 42).

In 2018, Zhang and colleagues conducted a meta-analysis of available literature through September 2017 (47), including five high quality observational studies (34, 36, 37, 38, 39) and one small randomized controlled trial (RCT) (21). In analyses encompassing all forms of bariatric surgery, pooled estimates reveal a 29% increased risk of any fracture (RR: 1.29 95% CI: 1.18, 1.42), with increased risk especially seen at non-vertebral (RR: 1.42, 95% CI: 1.08, 1.87) and upper limb (RR: 1.68, 95% CI: 1.15, 2.45) sites. Also noted was a trend for increased fracture risk associated with metabolic vs restrictive procedures (RR: 1.54 95% CI: 0.96, 2.46). Likewise, a subsequent meta-analysis published in 2019 by Ablett *et al.* (48) reported significantly increased fracture risk across observational studies reporting on metabolic, but not restrictive, surgical procedures. Also included were three small trials, providing short term evidence of the association between

Table 2 Abridged summary of controlled observational studies reporting on fractures after bariatric surgery.

References	Groups (% surgical type indicated with mixed procedures)	Females (%)	Age (years)	Follow up (years)	Sample (n)	Fractures (n)	Primary findings			
							HR	RR	SIR	Fracture risk
Lalmohamed <i>et al.</i> (34)	AGB: 60; RYGB: 29 Age, sex, BMI, year, and practice matched controls	84	45	2.2	2079	207		0.9 (0.6, 1.3)		Any fracture
Nakamura <i>et al.</i> (35)	RYGB: 94; VBG: 5; other: <1	82	44	7.7	258	132			2.3 (1.8, 2.5)	Any fracture
Douglas <i>et al.</i> (36)	AGB: 47; RYGB: 37; SG: 16; other: <1 Propensity score matched controls	81	45	3.4	3882	39	1.3 (0.9, 2.0)			Any fracture
Lu <i>et al.</i> (37)	Restrictive: 86; malabsorptive: 14 Propensity score matched controls	64	32	4.9	2064	183	1.2 (1.0, 1.4)			Any fracture
Rousseau <i>et al.</i> (38)	AGB: 42; SG: 28; BPD: 21; RYGB: 9 Age/sex matched obese controls	72	43	4.4	12 676	514		1.4 (1.2, 1.6)		Any fracture
Yu <i>et al.</i> (39)	RYGB Propensity score matched AGB controls	79	44	2.3	7516	163	1.4 (1.1, 1.8)			Non-vertebral fracture
Axelsson <i>et al.</i> (40)	RYGB with diabetes Propensity score matched controls	66	47	3.1	7758	251	1.3 (1.0, 1.5)			Any fracture
Axelsson <i>et al.</i> (40)	RYGB without diabetes Propensity score matched controls	78	39		31 213	768	1.3 (1.2, 1.5)			Any fracture
Fashandi <i>et al.</i> (41)	RYGB: 79; AGB: 11; SG: 8 Propensity score matched controls	81	43	7.6	3439	220				Fracture rate: 6.4% vs 2.7% ($P < 0.0001$)
Javananinen <i>et al.</i> (42)	RYGB Propensity score matched controls	69	48	6.8	253	31	RYGB and SG: 5.6 (1.8, 17.2)			Any fracture

(Continued)

Table 2 (Continued).

References	Groups (% surgical type indicated with mixed procedures)	Females (%)	Age (years)	Follow up (years)	Sample (n)	Fractures (n)	Primary findings			
							HR	RR	SIR	Fracture risk
Yu <i>et al.</i> (43)	SG			6.9	142	11				
	Age and sex matched non-surgical weight loss controls			13.3	199	17				
Ahlin <i>et al.</i> (44)	RYGB	79	51	3.5	29 624	491	1.7 (1.5, 2.1)			Non-vertebral fracture
	AGB controls				12 721	167				
Paccou <i>et al.</i> (45)	RYGB: 13; AGB: 19; VBG: 68	71	47	15.1–17.9	2007	352	RYGB: 2.6 (2.0, 3.3); AGB: 2.0 (1.4, 2.8); VBG: 2.2 (1.7, 2.8)			Any fracture
	Obesity and group matched controls			17.6	2040	302				
Paccou <i>et al.</i> (45)	SG: 46; RYGB: 35; AGB: 13; VBG: 6	78	49	5.7	40 992	585	1.2 (1.1, 1.4); RYGB: 1.7 (1.5, 2.0); SG: 0.95 (0.8, 1.1)			MOF
	Age, sex, obesity, year of inclusion, and comorbidity matched controls				40 992	416				

AGB, adjustable gastric band; RYGB, Roux-En-Y gastric bypass; VBG, vertical banded gastroplasty; SG, sleeve gastrectomy; BPD, biliopancreatic diversion. RR, risk ratio; SIR, standardized incidence ratio; HR, hazard ratio; MOF, major osteoporotic fracture.

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bariatric surgery and fractures (21, 49, 50). Although bariatric surgery was associated with marked weight loss (22 kg), no association with fracture was observed. That said, trials were underpowered ($n=13$ fracture events) to adequately determine risk.

Since the publication of these meta-analyses, six additional observational studies (41, 42, 43, 44, 45, 51) have been published. In the first of the observational studies, Fashandi and colleagues observed a two-fold higher fracture risk (6.4% vs 2.7%; $P < 0.01$) among 3439 patients with a history of bariatric surgery (79% RYGB, 11% SG), as compared to non-surgical comorbidity and BMI-matched controls (41). Fractures were reported within 8 years post-surgery, and RYGB was associated with higher fracture risk than SG. A smaller study from Finland (253 RYGB and 142 SG patients) reported a striking five-fold increase in cumulative fracture risk associated with bariatric surgery as compared with a non-surgically treated age and sex matched obese (though not BMI matched) patient group (HR: 5.49 (1.76, 17.15)), with no risk difference between procedures (42). In 2019, Blom-Hogestol *et al.* reported a 15% fragility fracture prevalence among 194 Norwegian RYGB patients with an average age of 50 years who were assessed 10 years post-surgery (51). Although this study lacked a control group, authors noted the fracture rate they observed is higher than what would be expected in an age-comparable general population, and more similar to that of patients taking chronic glucocorticoids. In agreement with several other studies, authors report that fractures did not occur until several years after surgery. In one of the only studies to have a significant proportion of older adults, Yu and colleagues observed a 73% increased risk of non-vertebral fractures among 29,624 RYGB vs 12,721 AGB recipients using Medicare claims data over an average 3.5 years of follow up (43). Site-specific analyses reveal significantly increased hip, wrist, and pelvis fracture among RYGB recipients (HR ranging from 1.5 to 2.8), with similar effects across different age, sex, and racial subgroupings. Finally, the two most recent observational publications provide timely insight into surgery specific fracture risk (44, 45). As with prior publications, authors report modestly increased (HR: 1.2–2.6) fracture risk with bariatric surgery; however, when stratified by surgical type, this association only persisted for RYGB (not AGB, SG, or vertical banded gastroplasty (VBG)). In fact, in the publication by Paccou and colleagues (45) – a large ($n=81,984$) retrospective cohort utilizing data from the French National Inpatient Database – SG was found to be protective against proximal humerus fracture (HR: 0.65 95% CI: 0.45, 0.94). These findings reinforce the

observation that each bariatric procedure carries a unique fracture risk.

One additional RCT of bariatric surgery has also published fracture outcomes (52). As with other trial reports, the Diabetes Surgery Study captured fractures as adverse events within an RCT of surgical weight loss ($n=60$) vs intensive lifestyle intervention ($n=60$). Over the first 2 years of the trial, seven serious falls with five fractures and three serious falls and one fracture were reported among female participants of the RYGB and the lifestyle intervention groups, respectively. While numerically increased, formal statistical comparison between groups was untenable given the small numbers involved.

Taken all together, the totality of evidence suggests metabolic bariatric procedures modestly increase fracture risk; however, there are certainly limitations to the currently available evidence base. First, cross-study comparison of the data is difficult given the heterogeneous study populations involved. Furthermore, design characteristics among published studies varied widely, encompassing differences among surgical procedure studied, length of follow-up, control group matching, and adjustment for important confounders, such as BMI. In addition, given the relatively low rate of fracture, most studies were not powered to adequately assess fracture risk by skeletal site, though this appears to be an important consideration. Finally, observational data can only guide clinical practice so far. Data from RCTs provide the highest level of evidence, yet are pragmatically difficult to design (especially when surgical procedures are involved) and power for fracture endpoints. Among the four published clinical trials, for instance, the longest reported follow up was limited to 24 months and fracture data were captured only as adverse events – with less than 20 events reported across all studies. It is exceedingly unlikely that a definitive randomized trial will ever be conducted to discern the effect of bariatric surgery on incident fracture, and therefore synthesis across rigorously performed observational studies provides the most reliable insight on the topic (53).

Thus, after acknowledging these caveats, we draw several conclusions from the available literature. First, fracture risk after bariatric surgery varies based on procedure, with available data implicating metabolic, rather than purely restrictive, procedures in modestly increased fracture risk. In particular, there is consistent evidence across multiple large studies that RYGB increases the risk of clinically important fractures. Although SG has recently surpassed RYGB as the most commonly performed surgical procedure, there is insufficient data

to confidently characterize fracture incidence after SG; however at present, risk appears at least no greater than RYGB, and may potentially be less (41, 42, 45). As more data become available, we strongly recommend that future researchers quantify fracture risk for SG (and other bariatric procedures), separately. Second, fracture risk appears to manifest more than 2 years post-surgery, and increases in subsequent years. Although the exact reason for the delayed onset is challenging to explain, results point to additional mechanisms contributing to fracture risk beyond mechanical unloading. Third, fracture risk after bariatric surgery appears to be site specific, with traditional osteoporotic sites such as hip and forearm typically (though not always (37)) most affected. And finally, although the absolute risk of fracture is modest (39), the average age of fracture onset is much younger than one might expect for age-related fractures. As these cohorts age, and as bariatric procedures are increasingly performed in older adults (54), fracture burden is likely to rise.

Intervening to preserve bone health among bariatric surgery patients

Mechanistic understanding of the etiology of fracture risk associated with bariatric surgery is necessary to properly design and evaluate countermeasure strategies. While this review is not meant to provide a comprehensive overview on the topic, we do include a schematic of potential mechanisms (Fig. 2), and briefly touch upon

Figure 2

Proposed mechanisms underlying surgical weight loss-associated bone loss.

each before considering available intervention data. For a more detailed discussion of potential mechanistic underpinnings of surgical weight loss associated bone loss, we refer the reader to the following papers (55, 56, 57, 58).

It has long been known that mechanical unloading of the skeleton results in the loss of bone mass (59), and therefore it is likely that the large magnitude of weight loss that occurs after bariatric surgery plays a role in surgical bone loss. Several short-term studies have noted correlations between the decline in BMD observed after bariatric surgery and the extent of weight loss and/or lean mass loss (60, 61, 62, 63, 64). That said, long-term studies documenting persistent elevation of biomarkers of bone turnover and continuous reductions in bone density and microarchitecture following weight stabilization indicate that the effects of surgical weight loss on bone extend beyond skeletal unloading (65, 66). In further support of non-mechanical mechanisms, intriguing data from murine models of bariatric surgery show that RYGB results in exaggerated losses of bone structure and strength as compared to weight-adjusted sham-operated controls (67, 68).

Additional proposed mechanisms include nutrient malabsorption – especially calcium, vitamin D, and protein (27, 69, 70, 71) – as well as hormonal alterations, including secondary hyperparathyroidism (due to calcium and/or vitamin D deficiency) and changes in gastrointestinal and/or adipocyte hormones (72). Finally, there is evidence that increased frequency of falling may further contribute to fracture rates. Strikingly, one-third of RYGB patients report two or more falls and one-quarter report balance problems in the 5 years post-surgery (73).

Because the skeletal effects of bariatric surgery are multifactorial, a multidisciplinary clinical management approach is recommended (5, 74). Patients should be counseled that calcium (1200–1500 mg/day) and vitamin D (2000–3000 IU/day) supplementation will be a lifelong requirement, and providers should perform serial biomarker assessment of both micronutrients. Along with calcium and vitamin D, adequate protein intake (60–75 g/day) and regular weight-bearing exercise are also recommended to maintain lean mass. Finally, pre-operative bone density measurements should be performed on high risk patients (e.g. postmenopausal women, prior fragility fracture, family history of osteoporosis), and some guidelines suggest that all patients be monitored via DXA in the first 2 years post-surgery (74). While prudent, recommendations are largely based on low-quality evidence and expert opinion, with

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little guidance from RCTs. Below we summarize available intervention data among bariatric surgery patients that report on bone-related endpoints, and draw on examples from related fields – such as lifestyle-based weight loss interventions in older adults, and interventions designed to mitigate hypogravity-induced bone loss in astronauts and gastrectomy-induced bone loss in cancer patients – when appropriate.

Diet and exercise interventions have been proposed to minimize bone loss secondary to bariatric surgery, as they have proven effective in scenarios of caloric restriction. Specifically, RCT data show that calcium, vitamin D, and protein supplementation minimize (but do not fully prevent) non-surgical weight loss associated bone loss in older adults (75, 76, 77, 78). Within the bariatric surgery population, a RCT found that aggressive postoperative supplementation with vitamin D (50 000 IU weekly plus 800 IU daily) and calcium (1500 mg daily) prevented secondary hyperparathyroidism and attenuated bone loss in gastric bypass patients; however, it was not sufficient to ameliorate all bone loss (79). An independent effect of protein supplementation on skeletal outcomes post-bariatric surgery has not yet been evaluated. Nevertheless, protein supplementation does appear to preserve lean mass after bariatric surgery (80) which, given its prominent role as a mechanical stimulus for bone growth and in the maintenance of physical function, might be expected to confer bone density benefit.

A 2-year multimodal intervention strategy, combining vitamin D, calcium, and protein supplementation (28 000 IU cholecalciferol/week for 8 weeks before bariatric surgery, 16 000 IU/week and 1000 mg calcium monocaltrate/day after surgery, and daily BMI-adjusted protein supplementation ranging from 35–60 g/day) with an individualized exercise program (Nordic walking 45 min/day for 3 days/week plus strength training 30 min/day for 2 days/week), revealed positive effects on several bone outcome measures among RYGB and SG patients (81). Specifically, smaller increases in CTX (82.6% vs 158.3%) and a normalization of intact parathyroid hormone (iPTH) levels were observed in participants assigned to multimodal intervention ($n=110$) vs control ($n=110$). Declines in aBMD (total hip: -3.9% vs -9.9% ; lumbar spine: -1.2% vs -7.9%), trabecular bone score (TBS: -3.4% vs -10.5%), and lean mass (-3.5% vs -12.4%) were also lessened in the combined intervention group relative to control, though significant losses over baseline still occurred.

The effects of exercise on bone loss post-gastric bypass has been further assessed in two recent Brazilian trials (82, 83). The first non-randomized quasi-experimental study

by Campanha-Versiani *et al.* (82) details the influence of a 12-month weight-bearing and aerobic exercise program on total body and regional aBMD, body composition and muscle strength, and biomarkers of bone turnover among 37 RYGB patients (18 assigned postoperatively to exercise; 19 assigned postoperatively to maintain their usual physical activities (i.e. control conditions)). Exercise subjects performed 36 weeks of twice weekly supervised resistance (60 min of eight muscle building exercises with one to three sets of 10–12 repetitions) and aerobic (25 min of treadmill walking at 70–80% HR_{max}) exercises, and all subjects received dietary counseling and supplementation to ensure adequate calcium, vitamin D, and protein intake. In per protocol analyses, supervised exercise among subjects with >95% compliance attenuated lumbar spine (-1.7% vs -6.9% ; $P=0.01$) and hip BMD (-2.7% vs 7.4% ; $P < 0.01$) loss, while improving overall muscular strength as compared to controls. However, in contrast to the multimodal intervention described above (81), bone turnover markers increased similarly in both the exercise and control groups. The main limitation of this study is the high dropout rate (40% in the intervention group) coupled with the lack of randomization of study subjects. Subsequently, Murai and colleagues (83) randomized 70 RYGB female patients to a 6-month combined progressive, structured, one-on-one supervised aerobic and resistance training program (consisting of 3 days/week moderate intensity treadmill walking (30–60 min/day) and three sets of 10–12 repetitions of seven upper/lower body exercises) vs standard of care. As with the study by Campanha-Versiani (82), all subjects were advised to consume the recommended amounts of calcium (1200–1500 mg/day), vitamin D (3000 IU/day), and protein (≥ 60 g/day). Compared with standard care, exercise mitigated – but did not fully prevent – loss of aBMD at the total hip (-5.0% vs -7.3%), as well as cortical vBMD at the distal radius (0.3% vs -1.8%) as assessed by HR-pQCT. Exercise also attenuated increases in CTX, P1NP, and sclerostin levels, although 25-hydroxyvitamin D (25(OH)D), calcium, iPTH, phosphorus, and magnesium were not affected. The consistent hip bone-sparing treatment effect across the aforementioned lifestyle-based trials is showcased in Fig. 3.

Taken together, these limited data are in general agreement with the broader literature conferring skeletal protection of certain exercises – directly, by building and maintaining the muscle-bone unit (84) and/or indirectly, via lowered fall risk (85). Osteogenic exercises include ground reaction and/or muscle forces, such as progressive impact or resistance training (86);

Figure 3

Percent change in total hip aBMD after bariatric surgery with and without lifestyle-based intervention.

and unsurprisingly, interventions found to confer the most skeletal protection during non-surgical weight loss include one of these components (87, 88). A recent narrative review summarizing available literature on physical activity and skeletal health provides a description of a basic progressive resistance training program that might be used to improve bone strength (89). Of course, the presumed benefit of exercise is contingent on actual performance; and, although postsurgical increases in physical function (90) and activity behaviors (91) are noted among bariatric surgery patients, the majority fail to meet national physical activity guidelines (92). Indeed, adherence was a major limitation in all of the structured exercise interventions discussed previously, and speaks to the need to consider alternative therapies to combat bone loss in this population.

No published study, to our knowledge, has assessed pharmacotherapeutic interventions in the context of bariatric surgery associated bone loss; however, several lines of reasoning suggest that antiresorptive osteoporosis medications – such as bisphosphonates or denosumab – may be effective. First, surgery-induced weight loss is inherently catabolic to the skeleton (3, 7), with high-turnover bone loss occurring in both cortical and trabecular regions (11, 61, 66, 93) and ultimately increases fracture risk (as previously discussed). Second, clinical studies in postmenopausal osteoporotic women have repeatedly confirmed the efficacy of bisphosphonates in attenuating bone resorption (94), preserving trabecular and cortical structure (95), and ultimately reducing the risk of osteoporotic fracture (96). Third, we reason by analogy as studies from related fields suggest that bisphosphonate use can prove effective at minimizing bone loss in astronauts (97) as well as cancer patients undergoing gastrectomy (98). Clinical practice guidelines currently support the consideration of antiresorptive agents (including bisphosphonates or denosumab) in bariatric surgery patients with

osteoporosis (provided that concerns about absorption, potential for anastomotic ulceration, and calcium/vitamin D insufficiency/hypocalcemia risk are obviated), though this recommendation is largely driven by expert opinion in the absence of data (74). It may also be possible that anabolic agents, and/or mixed anabolic/antiresorptive agents have utility in preserving bone among high risk patients receiving bariatric surgery. Pilot trials examining the safety and feasibility of osteoporosis medications to prophylactically mitigate surgical weight loss associated bone loss are underway (NCT04087096, NCT03424239, and NCT03411902) with definitive data poised to significantly impact clinical care.

Conclusion

In sum, despite well recognized improvements in obesity-related comorbidities, increasing evidence implicates bariatric surgery in the onset of adverse skeletal health outcomes. SG, which has recently become the most commonly performed bariatric surgery, is accompanied by roughly 3–7% bone loss at the axial skeleton in the 6–24 months following surgery. The decline in BMD, while significant, is smaller in magnitude than what has been described after RYGB. Observational data uniformly report a 1.3- to 2.3-fold increase in fracture risk following bariatric surgery; although, risk does appear to vary by surgical type, with the most robust increase seen after RYGB. More information regarding SG-associated fracture risk is needed. Finally, a multifactorial clinical management approach is currently recommended for bone loss secondary to bariatric surgery, including regular BMD assessments; consumption of adequate dietary calcium, vitamin D, and protein; and performance of regular weight-bearing exercise. Although largely driven by expert opinion, limited RCT data do support the efficacy of lifestyle-based countermeasures to minimize –

but not fully prevent – surgical bone loss. Trials designed to optimize adherence to and treatment effects of lifestyle-based intervention strategies, along with those identifying other countermeasure therapies (including pharmacologic approaches), are needed to guide practitioners on how to best manage the serious, common, and costly skeletal consequences of bariatric surgery.

Declaration of interest

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Author contribution statement

K M B and K A G drafted the paper in consultation with E W Y, who critically revised the manuscript. All authors reviewed and approved the final version of this manuscript.

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