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RESEARCH ARTICLE

Effects of Weight Loss on Bone Status after Bariatric Surgery: Association Between Adipokines and Bone Markers

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Abstract
Background The prevalence of overweight and obesity is increasing dramatically worldwide. As a consequence, bariatric surgery for morbid obesity is in constant development. Although bariatric surgery has proven its efficiency at achieving weight loss and correcting comorbidities, it may cause vitamin deficiencies and subsequent complications. The goal of this review is to assess the impact of obesity surgery on bone metabolism and to analyze the underlying mechanisms and relationships with adipokines. Our review focuses on gastric banding, vertical banded gastroplasty, and gastric bypass.
Methods The articles were located via PubMed database, using the key words "bariatric surgery," "weight loss," "bone loss," and "bone metabolism" and published until May 2006.
Results Five main studies were reviewed concerning gastric banding and six concerning Roux-en-Y gastric bypass. An early increase in bone markers (formation and resorption) is constantly found, prevailing on bone resorption, and resulting in early bone loss.
Conclusion According to the few studies available, bone loss frequently occurs after bariatric surgery and particularly in a more pronounced way after gastric bypass, but its clinical significance is still under discussion. In addition, the physiopathology of these changes remains unclear, but could implicate adipokines such as leptin and adiponectin.

Keywords Bariatric surgery · Bone markers · Adipokines

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Introduction

Obesity is a growing problem worldwide, especially morbid obesity. Using international cut-off limits, 66.3% of adults are overweight, 32.2% obese, and 4.8% morbidly obese in the USA [1]. Half of all adults and one in five children in Europe are overweight [2].

Bariatric surgery is the most effective treatment for this pathology, with different techniques including pure restriction surgery (gastric banding, vertical banded gastroplasty [VBG], sleeve gastrectomy) and malabsorption surgery with or without associated restriction (Roux-en-Y gastric bypass [RYGBP], duodenal switch, biliopancreatic diversion, jejunoileal bypass…). It has been shown to be efficient at correcting comorbidities [3] and may be a cost effective alternative treatment in morbid obesity [4, 5].

Among the different types of surgery, RYGBP is known to be associated with malabsorption and particularly with iron, vitamin B12, and folate deficiency [6].

However, it remains uncertain whether a possible negative effect of this surgery on bone metabolism exists, which

may have clinical consequences in terms of increased risks of bone fracture. In this review, we examine the effects of two types of bariatric surgery, pure restriction surgery (i.e., gastric banding and VBG) and malabsorption surgery (i.e., gastric bypass and other malabsorptive surgery), on bone metabolism using available data in the literature.

Leptin [7, 8] is an adipocytes hormone that has a complex anti-osteogenic action, mediating by sympathetic nervous system and the central cocaine- and amphetamine-related transcript (CART) pathway. Adiponectin [9] plays also an important role in the control of bone mass. These physiopathological hypotheses will be discussed, focusing on the role of adipocyte hormones on bone markers after weight loss.

Methods Section

The articles were located via PubMed database, using the key words "bariatric surgery," "weight loss," "bone loss," and "bone metabolism" and published until May 2006, with no other limits for search. We identified nine studies [10–18] concerning malabsorption procedures other than RYGBP, five studies [19–23] concerning gastric banding, and seven [24–29] concerning RYGBP. One study [30] was excluded because of the small number of patients described (three patients who encompassed RYGBP, one who encompassed biliopancreatic diversion).We thereafter reviewed in detail the main studies dealing with gastric banding and with RYGBP, because these are the most common surgical techniques practiced today.

Results

Bone and Pure Restriction Surgery

The principal studies available on adjustable gastric banding (ABG) or VBG are summarized in Table 1 [19–23]. The studies are all observational prospective studies, with sample sizes ranging from 17 to 81 subjects, with or without controls subjects, obese or not obese, and the length of follow-up periods were relatively short, from 12 to 24 months. There are no intervention studies available.

The mean body mass index (BMI) range is from 40 to 46 kg/m^2, with a mean weight loss of 21.4 to 33.4% from preoperative weight. Calcium and vitamin D supplementation are not systematic, and hormonal replacement therapy is rarely prescribed.

The results of theses studies are generally in agreement, despite the heterogeneity of the data measured. The studies found an early increase in bone remodeling, particularly for markers of bone resorption (urinary and serum cross laps). Data on markers of bone formation (measured by the serum osteocalcin) are scarce. A small decrease in serum calcium is inconsistent in the literature, and there are no arguments for secondary hyperparathyroidism and vitamin D deficiency.

Concerning bone mineral density (BMD), a decrease in femoral BMD has been shown in most studies, whereas no differences have been shown at the lumber spine and for total BMD.

Among available studies, there are no data on the effects of VBG or ABG on the risk for fracture.

Bone and Malabsorption Surgery

Concerning malabsorption surgery, it is noteworthy to distinguish techniques such as jejunoileal bypass, biliopancreatic diversion, duodenal switch [10–18] that required a significant deviation of the digestive tract [31] and that resulted in marked malabsorption, with osteomalacia and secondary hyperparathyroidism, from gastric bypass.

Hypovitaminosis D can result in secondary hyperparathyroidism with increased bone turnover (bone formation assessed by measurement of serum osteocalcin, bone resorption by measurement of serum and urinary cross laps) and in a decrease in serum and urinary calcium [32].

Compston et al. [11, 12] found osteomalacia and secondary hyperparathyroidism on histomorphometry on transiliac biopsies in 50% of patients after jejunoileal bypass and 73% with defective mineralization after biliopancreatic bypass in 41 patients analyzed retrospectively 1 to 5 years after surgery.

However, the clinical significance of these anatomopathologic defects remains unclear. In 2002, Marceau et al. [13] observed that there were histological signs of increased bone activity and decreased bone cortical thickness on iliac crest biopsy after biliopancreatic diversion among 33 patients followed for 10 years.

However, no statistical difference in Z nor T scores, markers of bone fracture, were shown in the same patients. Vage et al. [18] found no significant reduction in BMD beyond that which was expected for age, 25 years after jejunoileal bypass.

This suggests that bone has a great adaptability.

Over the past decade, most surgeons favored the RYGBP surgery because of a good efficiency in terms of weight loss with a decrease in side effects [33].

Principal studies concerning gastric bypass are summarized in Table 2 [24–29].

Most studies are retrospective (from 11 months to 10 years after surgery), and some are prospective, with a length of follow-up from 6 months to 6 years. Calcium and vitamin D supplementation are not always specified, nor is the prescription of any hormonal replacement therapy. The number of subjects ranges from 19 to 243.

Table 1 Effects of gastric banding and vertical banded gastroplasty

Surgery	*N*	BMI (kg/m^2)	Type of study	Follow-up (months)	Weight loss (kg)	Ca/Vit D supplement	Results	
							Radiology	Biology
VBG [19]	18 obeses	43	Prospective	24	24 (21.4%)	75 μg/day calciferol	BMD (DEXA)	Ca (mmol/l) 2.32–2.21*
	18 controls	23				?	−3.9%* at Ward's triangle	PAL (UI/l) 77–61*
							−4.8%* at trochanter	Hydroxyprolinury/creat 23–35 at 6 months* NS after 1 year
							NS at lumbar spine	25(OH)D3 (μg/l) 25–30*
ABG [20]}	37 non menopausal women	43.7	Prospective	24	39.1 (33.4%)	?	Total BMC: −3.49%*	25(OH)D3 (μg/l) 18.5–22.7*m24
							Total BMD :NS	PTH (ng/l) 52.8–45.1* m12 NS m24
							L2–L4BMC: +7.99%*	Ca (mmol/l) 2.32–2.25* m24
							L2–L4 BMD:NS	PAL (UI/l) 74.6–59.8* m 24
							Trochanter BMC:NS	Serum telopeptides +100%* m24
							Trochanter BMD: −6.48%*	Urinary telopeptides (ng/l) 132.2–182* m18 NS m24
							Fl neck BMC: −4.8%*	
							Fl neck BMD: −5.79%*	
VBG [21]	16 patients	46.4	Prospective	12	25%* VBG	No	BMD VBG/controls: L1–L4: NS	VBG/controls: Deoxypyridinolinury (nM/Mm) 5.16–8.78*/NS
	65 controls	36			15% controls		Fl neck: 1.18–1.02*/1.11–1.00*	Bone alkaline phosphatase NS
							Trochanter: 1.04–0.93*/1.31–1.19*	Osteocalcin (ng/ml) 5.48–8.35*/ 6.21–6.79*
							Ward's triangle: 0.92–0.79*/1.15–1.04*	Estradiol (pg/ml) 112.27–87.64*/NS
								PTH: NS
ABG [22]	31 non menopausal women	43.6	prospective	12	27.6 (23.3%)	?	NS for Total BMC and BMD. L2–L4 BMC and BMD. Trochanter BMC and BMD. Fl Neck BMC and BMD	Serum telopeptides +100%*
								Urinary telopeptides (μl/l) 136–215*
								Ca: NS
								25(OH)D3: NS
								PTH: NS
								PAL: NS
ABG23	17 patients	40.4	prospective	24	23.4 (21.8%)	No	Total BMD: NS	–

VBG Vertical banded gastroplasty, *PTH* parathormone, *ABG* adjustable gastric banding, *Fl neck* femoral neck, *BMC* bone mineral content, *BMD* bone mineral density, *Ca* calcium, *PAL* phosphatase alcaline, *NS* no significant change.
*$p<0.05$.

Table 2 Effects of gastric bypass

Surgery	*N*	BMI	Type of study	Follow-up (months)	Weight loss (kg)	Ca/Vit D supplement	Results	
							Radiology	Biology
RYGBP [24]	25 patients	31	Retrospective 11 months after surgery			1.2 g Ca and 400–800 UI vit D per day	BMD total radius 0.659 RYGBP vs 0.626 controls*	Urinary NTX +288% RYGBP* vs controls
	30 controls	48	Prospective				BMD Lumbar spine −3.3%* Femoral neck −5.1%* Total hip −7.8%* Total body −1.6%*	Osteocalcin +53% RYGBP vs controls*
							BMC −5.6 %* at hip −5.6%* at trochanter, −3.0%* for total body	Urinary NTX + 174% at m3* + 319% at m9*
	15 patients	48		9	37 (29%)			Osteocalcin NS PTH, Ca, urinary Ca NS
RYGBP [25]	44 patients	33	Retrospective 3 years after surgery		−31%		Lumbar BMD and BMC NS in pre MP women MP women lumbar BMD 1.29 RYGBP/1.17 controls*	
	65 controls	33					Lumbar BMC 57.2 RYGBP/50.0 controls* Fl neck BMC 3.5 RYGBP/4.8 controls*	
	13 patients with low BMD	34	Prospective with intervention (Ca supplement)	6		1.2 g Ca and 8 μg Vit D per day	Lumbar BMD and BMC NS RYGBP/controls	PTH(pg/ml)RYGBP/controls 10.2–9.1/3.4*–3.2* 25(OH)D NS
	13 controls	33						Pyridinolinuria (nmol/mmol) 52.4–46.0/20.9*–21.4* Deoxypyridinolinuria (nmol/mmol) 14.4–12.3/6.0*–6.9* Osteocalcin NS
RYGBP or BPD [26]	233 (7 BPD and 226 RYGBP)	50.5	Prospective	48	?	0.5 g Ca + multivitamin 3/day	15 osteopenia pre op 3 new osteopenia at y1 No osteoporosis	Ca NS
							Fore arm BMD −0.55%* at y1 −3.62%* at y2 −1.83%* at y3	
							Radius BMD +1.85%* at y1, NS after	PTH NS
							Hip BMD −9.27%* at y1, NS after	25 (OH)Vit D NS
							Lumbar BMD	

Table 2 (continued)

Surgery	*N*	BMI	Type of study	Follow-up (months)	Weight loss (kg)	Ca/Vit D supplement	Results	
							Radiology	Biology
RYGBP [27]	243 (41 with long-limb RYGBP, 202 with short-limb RYGBP)	60.6 49.1	Prospective	3.1 years for short-limb RYGBP, 5.7 years for long limb RYGBP	?	?	−4.53%* at y1, NS after –	Ca NS Vitamin D progressive decrease* PTH progressive increase* vit D lower and PTH higher for long-limb RYGBP 88.9 % of high PTH* for the 36 patients with low Vit D 58.0% of high PTH* for the 207 patients with normal Vit D
RYGBP or ABG [29]	19 (4 RYGBP, 9 ABG, 6 controls)	42.7 41.0 41.2	Prospective	24	?	1 g Ca and 800 UI Vit D per day	BMC NS ABG and controls 2.968–2.621* RYGBP BMD NS ABG and controls 1.26–1.22* RYGBP Bone area NS ABG and controls 2.349–2.147* RYGBP	PTH NS Deoxypyridinolinuria Increase* by m3 in RYGBP vs ABG and controls Serum osteocalcin Increase* by m6 in RYGBP vs ABG and controls
RYGBP [28]	33 (26 RYGBP, 7 controls)		Retrospective 10 years after surgery	?	?	?	BMD Increased* at lumbar spine Femoral neck 0.90 vs 1.03*	Ca (mEq/l) 4.3 vs 4.6* PAL (UI/L) 121 vs 37.3* Osteocalcin (μg/ml) 12.6 vs 9.5* 1.25 (OH) vit D NS 25 (OH) Vit D (pg/ml) 24.3 vs 35.9*

ABG Adjustable gastric banding, *RYGBP* Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *MP* menopause, *Fl neck* femoral neck, *BMC* bone mineral content, *BMD* bone mineral density, *PTH* parathormone, *Ca* calcium, *PAL* phosphatase alcaline, *NS* no significant change.
*$p<0.05$.

The mean BMI ranges from 31 to 33 in retrospective studies and from 43 to 60 in prospective studies. Weight loss data are not reported in many of these studies.

However, these studies show evidences of an early increase in bone remodeling. In a recent study, von Mach et al. [29] found a significant increase in deoxypyridinolinuria after 3 months of follow-up and in osteocalcin after 6 months in RYGBP versus ABG and obese controls. Coates et al. [24] found a 288% increase in urinary cross laps and a 53% increase in osteocalcin in gastric bypass 11 months after surgery compared to obese controls. On the other hand, Goode et al. [25] found a significant increase in urinary cross laps but not in osteocalcin, which was not corrected after 6 months of vitamin D and calcium supplementation.

Second, there are data suggesting that secondary hyperparathyroidism occurs after gastric bypass: Goode et al. [25] found a normal but elevated serum parathyroid hormone (PTH) (10.2 pg/ml versus 3.4 pg/ml) in RYGBP patients at 3 years compared to obese controls, and this difference persisted after 6 months of calcium and vitamin D supplementation. Johnson et al. [27] demonstrated a progressive decrease in vitamin D and a progressive increase in PTH in 243 patients who were followed for 3.1 to 5.7 years after gastric bypass. Fifty-eight percent of patients with normal vitamin D levels had a high serum PTH. This biological pattern was more pronounced among the 41 patients with a longer limb bypass (more than 1 m long). Contrary to what was found in these two studies [25, 27], others [24, 26, 28, 29] did not mention secondary hyperparathyroidism or a decrease in serum calcium among their study population.

Finally, there is a decrease in BMD, predominantly located at the hip and seems to be peak in the first year after surgery [27]. Goode et al. [25] suggested that postmenopausal women may be more likely to have a decrease in BMD than non-menopausal women. However, the risk of fracture has never been directly studied.

Discussion

In summary, the present review has found evidence for increased in bone turnover after surgery for morbid obesity, especially after procedures resulting in malabsorption. Increased bone turnover seems to appear early after surgery, with peak turnover occurring in the first year. The clinical significance of these changes has not been fully studied.

The physiopathology of bone loss after bariatric surgery remains unclear. Several papers showed that obesity is associated with increased bone load at weight-bearing sites [34–36]. The reduction in body weight may decrease the bone load and help to explain the decrease in BMD, especially at the location of the hip.

Calcium and vitamin D malabsorption may also contribute to the increase in bone remodeling. However, deficiencies are rarely noted. Vitamin D levels are also frequently decreased in obesity, even before surgery, because of its liposolubility (the vitamin is stored in adipose tissue) [37]. Some authors suggest that a specific malabsorption of calcium, independent of vitamin D, could appear after malabsorption surgery [12]. The low prevalence of vitamin deficiencies suggests that the guts have a remarkable adaptability after surgery.

Hypoestrogenism may explain the susceptibility of menopausal women to bone loss after bypass surgery: Estradiol has been found decreased after bariatric surgery [21, 38], maybe because of the decrease in aromatase (a hormone synthesized by adipocytes, which transforms androgens in estrogens). However, there are frequent irregularities in menstruation in obese patients, before and early after bariatric surgery [39], and as a result of these problems, sex hormones are rarely studied, and therefore, conclusions about the relation between obesity surgery and sex hormones cannot be determined.

Finally, two adipocyte hormones are likely to be involved in bone changes.

First, leptin is synthesized by adipocytes, and its serum level is positively correlated with fat mass. Leptin plays a major role in food intake and energy expenditure, and its anti-osteogenic function has been recently demonstrated. In leptin-deficient ob/ob mice, bone mass is increased and at a level higher than could be explained by only weight gain. This is because of a central control of bone remodeling by leptin, which is mediated by the sympathic nervous system; the beta 2 adrenergic receptor located on the osteoblasts stimulates osteoclast differentiation via the receptor activator of NFKb (RANK)–RANK ligand pathway [7, 40]. Leptin has a complex effect on bone loss because its also inhibits osteoclast differentiation by the CART pathway [41], but its final action is anti-osteogenic. The loss of fat mass resulting in the decrease in leptin levels and the loss of bone mass after weight loss could be because of the decrease in leptin resistance, which is observed in obese subjects.

Second, adiponectin is another adipokine, whose level is decreased in obesity. It has anti-inflammatory, anti-atherogenic actions [42]. It has been demonstrated that serum adiponectin was inversely correlated with BMD [9]. Weight loss could therefore increase serum adiponectin and consequently its anti-osteogenic action, which seems to be mediated via the RANK–RANK ligand pathway [43, 44].

Several limits are to be mentioned when interpreting results from the available studies in the literature.

First, the reliability of dual-energy X-ray absorptiometry (DEXA) measurements in obese patients has not been fully assessed. Van Loan et al. [45] suggested that differences in BMD found after weight loss may be explained by a variation in DEXA reliability. Tothill et al. [46, 47] found that the changes observed in BMD could be explained by the effects of changes in fat mass despite no real changes observed in bone mineral content.

Second, bone loss occurs after weight loss independently of the way used to lose weight [48–50] (diet, pharmacotherapy, physical activity, etc.). The effect of surgery itself on bone loss independently of weight loss is thus difficult to determine.

Third, BMD still remains higher than in non-obese controls when weight loss is achieved after bariatric surgery [19]. Despite the lack of available studies, it is possible to hypothesize that the risk of fracture remains lower in obese patients after bariatric surgery than in non-obese patients, because BMD is known to be strongly correlated with risk of fracture [51, 52].

Finally, available studies are heterogeneous in terms of bone remodeling markers used (serum or urinary telopeptides, osteocalcin, PTH, serum calcium, vitamin D…) as well as methodology (heterogeneous body composition change assessment criteria, control group, duration of follow-up, etc.). The clinical significance of the observed radiological and biological changes is unclear.

Conclusion

Bariatric surgery results in an early increase in bone turnover, especially after gastric bypass. This consequently results in a decrease in BMD, which is more pronounced at the hip and in postmenopausal women.

However, the clinical significance of these changes in terms of risk for fracture has not been thoroughly studied to our knowledge. Neither has been the interest of systematic calcium and vitamin D supplementation on bone loss.

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