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Gastric Bypass Surgery for Morbid Obesity Leads to an Increase in Bone Turnover and a Decrease in Bone Mass

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Little is known about the effects on the skeleton of laparoscopic Roux-en-Y gastric bypass (LRGB) surgery for morbid obesity and subsequent weight loss. We compared 25 patients who had undergone LRGB 11 ± 3 months previously with 30 obese controls matched for age, gender, and menopausal status. Compared with obese controls, patients post LRGB had significantly lower weight (92 ± 16 *vs.* 133 ± 20 kg; $P < 0.001$) and body mass index (31 ± 5 *vs.* 48 ± 7 kg/m^2; $P < 0.001$). Markers of bone turnover were significantly elevated in patients post LRGB compared with controls (urinary *N*-telopeptide cross-linked collagen type 1, 93 ± 38 *vs.* 24 ± 11 nmol bone collagen equivalents per mmol creatinine; and osteocalcin, 11.6 ± 3.4 *vs.* 7.6 ± 3.6 ng/ml; both $P < 0.001$). Fifteen patients were studied prospectively for an average of 9 months after LRGB. They lost 37 ± 9 kg and had a 29 ± 8% fall in body mass index (both $P < 0.001$). Urinary *N*-telopeptide cross-linked collagen type 1 increased by 174 ± 168% at 3 months ($P < 0.01$) and 319 ± 187% at 9 months ($P < 0.01$). Bone mineral density decreased significantly at the total hip (7.8 ± 4.8%; $P < 0.001$), trochanter (9.3 ± 5.7%; $P < 0.001$), and total body (1.6 ± 2.0%; $P < 0.05$), with significant decreases in bone mineral content at these sites.

In summary, within 3 to 9 months after LRGB, morbidly obese patients have an increase in bone resorption associated with a decrease in bone mass. Additional studies are needed to examine these findings over the longer term. (*J Clin Endocrinol Metab* 89: 1061–1065, 2004)

OBESITY IS AN increasing worldwide problem that is associated with significant morbidity and mortality (1). In the United States, at least 15 million people are morbidly obese, defined as a body mass index (BMI) greater than 40 kg/m^2 (2). Weight reduction for morbid obesity reduces mortality and improves comorbid conditions (3). The Roux-en-Y gastric bypass procedure has been shown to produce losses of up to 70% of excess body weight (4). Long-term weight loss with this procedure has been reported to extend out 10–14 yr (5, 6). Because of the reduced major and minor complications with the newer laparoscopic form of Roux-en-Y gastric bypass (LRGB), more patients are opting to undergo this surgery (7). According to the Bariatric Surgical Society, there were an estimated 40,000 operations in 2000 and 75,000 in 2001 (8).

Few data are available regarding the impact of LRGB on skeletal health. It is known that weight loss in healthy patients is associated with bone loss. Minimal losses of bone mass have been reported in a small number of patients undergoing other operations for obesity, such as vertical banded gastroplasty (9) or jejunoileal bypass (10, 11). Osteomalacia and osteopenia have been described frequently after gastrectomy for peptic ulcer or cancer (12–15). To examine the impact of LRGB on the skeleton, we compared patients who had undergone LRGB surgery with patients of similar obesity awaiting the procedure. Furthermore, we prospectively examined short-term skeletal changes in patients before and after LRGB surgery. We postulated that the resultant significant weight loss would be associated with increased bone turnover, changes in bone and mineral metabolism, and loss of bone mass.

Abbreviations: BMC, Bone mineral content; BMD, bone mineral density; BMI, body mass index; BSAP, bone-specific alkaline phosphatase; BUA, broadband ultrasound attenuation; CV, coefficient(s) of variation; DXA, dual-energy x-ray absorptiometry; LRGB, laparoscopic Roux-en-Y gastric bypass; NTx, *N*-telopeptide cross-linked collagen type 1; PA, posteroanterior.

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Patients and Methods

We enrolled 25 men and women who had previously undergone LRGB (at least 6 months before assessment) and 30 morbidly obese men and women on diet control who were awaiting the procedure. A subset of 15 patients who were morbidly obese and subsequently underwent LRGB were followed prospectively and assessed at baseline, at 3 months, and between 6 and 12 months after surgery. All LRGB procedures were performed by a single surgeon (P.R.S.) and included a 15-ml isolated gastric pouch, a stapled end-side gastrojejunostomy, a 75-cm Roux-limb, a 30–50-cm biliopancreatic limb, and a stapled end-side enteroenterostomy. A 150-cm Roux-limb was used in patients with a BMI exceeding 50 kg/m^2. Individuals were excluded if they had diseases or were taking medications known to impact bone and mineral metabolism. All patient visits occurred in the University of Pittsburgh General Clinical Research Center at Montefiore University Hospital (Pittsburgh, PA). Subjects were informed of the nature, risks, and benefits of the study and provided written informed consent before enrolling in the study.

Height was measured to the nearest 1 cm using a Harpenden stadiometer (Holtain Ltd., Crymych, Dyfed, UK), and weight was measured with a balance-beam scale (Health-o-meter, Sunbeam, Boca Raton, FL). BMI was calculated as weight (kilograms) divided by height (meters^2). We assessed calcium intake with a previously validated food frequency

questionnaire (16). A 24-h urine collection was assessed for total calcium and creatinine. Assessments of bone mineral metabolism included serum calcium, 25-hydroxyvitamin D [nanograms per milliliter; Nichols Advantage RIA, Nichols Institute Diagnostics, San Juan Capistrano, CA; intraassay coefficient(s) of variation (CV), 5.0–6.1%] and intact PTH (picograms per milliliter; Immulite Chemiluminescence Assay, Diagnostic Products Corp., Los Angeles, CA). Biochemical markers of bone formation included serum intact osteocalcin (nanograms per milliliter; Metra Osteocalcin EIA Kit, Quidel Corp., San Diego, CA; intraassay CV, 4.3–8.1%) and bone-specific alkaline phosphatase (BSAP) (nanograms per milliliter; Hybritech, Inc., San Diego, CA; intraassay CV, 5.5%). A second-void fasting urine specimen was collected for a marker of bone resorption, *N*-telopeptide cross-linked collagen type 1 (NTx; nanomoles bone collagen equivalents per millimole creatinine), measured with an enzyme-linked immunosorbent assay (Osteomark, Ostex International, Seattle, WA; intraassay CV, 5–19%). Serum was collected in the nonfasting state for the assay of leptin (HL-81K, Linco Research Inc., St. Charles, MO; intraassay CV, 5%) and total ghrelin (RK-031–30, Phoenix Pharmaceuticals Inc., Belmont, CA; intraassay CV, 9%). Bone mineral density (BMD; grams per centimeter^2) and bone mineral content (BMC; grams) were assessed at the posteroanterior (PA) lumbar spine (L1–L4), hip (femoral neck, trochanter, and total hip), forearm (one-third distal radius, ultradistal, and total radius), and total body by dual-energy x-ray absorptiometry (DXA; QDR-4500A, Hologic, Inc., Bedford, MA). Bone mass of the heel was measured with a QUS-2 Ultrasonometer (Quidel Corp., Mountain View, CA), which measures broadband ultrasound attenuation (BUA; decibels per megahertz). Body composition (total percentage fat mass and total lean mass) was assessed by DXA (QDR-4500A, Hologic, Inc.).

Statistical analysis

Continuous variables were analyzed with a two-sample Student's *t* test for cross-sectional data. Longitudinal data for BMD and BMC were analyzed by paired Student's *t* test and ANOVA with Bonferroni correction. Categorical variables were analyzed by Fisher's exact test. To determine relationships between variables, simple linear regression and stepwise linear regression were performed. Results are shown as mean ± SD. All analyses were carried out with a 95% confidence interval, and a P value < 0.05 was considered significant. All analyses were performed using SAS 8.1 software (SAS Institute Inc., Cary, NC).

Results

Clinical characteristics

Age and gender distributions were similar between patients who had undergone gastric bypass and obese controls (Table 1). Postsurgical patients had LRGB surgery an average of 10.8 ± 2.6 months before enrollment. As expected, patients in this group *vs.* controls had a lower BMI (32 ± 5 *vs.* 48 ± 7 kg/m^2; $P < 0.001$) and weight (92 ± 16 *vs.* 133 ± 20 kg; $P < 0.001$). Serum leptin levels were significantly lower in the patients who had undergone LRGB compared with controls (16.0 ± 12.8 *vs.* 70.4 ± 35.0 ng/ml, respectively; $P < 0.001$). Baseline BMI and weight correlated significantly with serum leptin levels ($r = 0.76$ and 0.65, respectively; $P < 0.001$). Serum ghrelin levels were also significantly lower in patients who had undergone LRGB than in controls (400 ± 106 *vs.* 699 ± 257 pg/ml, respectively; $P < 0.001$).

Parameters of skeletal health

After surgery, patients were encouraged by their surgeon and primary care physician to increase total daily calcium to over 1200 mg daily and vitamin D intake to 400–800 IU daily (Table 1). Consequently, the dietary calcium and vitamin D intake levels were significantly higher in the postsurgical group. However, there were no statistically significant differences in serum PTH, 25-hydroxyvitamin D, or 24-h urinary calcium levels between the two groups (Table 1).

TABLE 1. Clinical characteristics

	Gastric bypass patients	Obese controls
N	25	30
Age (yr)	51 ± 8	49 ± 10
Men [% (n)]	36 (9)	20 (6)
Premenopausal women [% (n)]	24 (6)	30 (9)
Postmenopausal women [% (n)]	40 (10)	50 (15)
Height (cm)	171 ± 8	166 ± 7[a]
Weight (kg)	92 ± 16	133 ± 20[c]
BMI (kg/m^2)	32 ± 5	48 ± 7[c]
Serum leptin (ng/ml)	16.0 ± 12.8	70.4 ± 35.0[c]
Serum ghrelin (pg/ml)	400 ± 106	699 ± 257[c]
Dietary calcium (mg/d)	1784 ± 715	1020 ± 472[c]
Dietary vitamin D (IU/d)	693 ± 396	411 ± 252[b]
Serum calcium (mg/dl)	9.1 ± 0.4	9.1 ± 0.4
Serum albumin (g/dl)	3.9 ± 0.3	3.8 ± 0.3
Serum PTH (pg/ml)	67 ± 26	67 ± 38
Serum 25-hydroxyvitamin D (ng/ml)	22 ± 7	17 ± 7
24-h urinary calcium (mg)	160 ± 94	188 ± 104

Results represent mean ± SD.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

TABLE 2. Biochemical markers of bone turnover and bone mass

	Gastric bypass patients	Obese controls
Biochemical markers		
Urinary NTx (nM BCE/mmol Cr)	93 ± 38	24 ± 11[c]
Serum osteocalcin (ng/ml)	11.6 ± 3.4	7.6 ± 3.6[c]
Serum BSAP (ng/ml)	26.1 ± 7.1	24.1 ± 12.0
BMD (g/cm^2)		
Total radius	0.659 ± 0.064	0.626 ± 0.063[a]
Ultradistal radius	0.517 ± 0.064	0.504 ± 0.068
One-third distal radius	0.765 ± 0.073	0.713 ± 0.684[b]
Calcaneal broadband ultrasound attenuation (dB/mHz)	88.7 ± 12.6	96.4 ± 19.1

Results represent mean ± SD. BCE, Bone collagen equivalent; Cr, creatinine.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

Urinary NTx, a marker of bone resorption, was 288% higher in the gastric bypass group; and osteocalcin, a marker of bone formation, was 53% higher in this group ($P < 0.001$ for both) (Table 2). There were no between-group differences in DXA of the ultradistal radius or ultrasound of the calcaneus. However, BMDs of the total radius and one-third distal radius were slightly greater in the postsurgical group *vs.* the obese control group.

Longitudinal study

We followed 15 patients (12 women and 3 men) prospectively before, 3 months after, and an average of 9 months after LRGB surgery. On average, these patients lost 37.3 ± 9.3 kg in weight and had a 27 ± 8% decrease in BMI over 6 months (both $P < 0.001$). Percentage total body fat mass decreased by an average of 21%, and percentage lean mass increased by 15% (both $P < 0.001$). Serum ghrelin decreased by a mean of

53% at 3 months ($P < 0.05$) and 26% at the final visits ($P = 0.10$).

Dietary calcium increased 72 ± 122% and 106 ± 181% at 3 and 9 months, respectively (both *P* nonsignificant). Dietary vitamin D increased significantly by 124 ± 126% and 129 ± 145% at 3 and 9 months, respectively ($P < 0.05$). Serum vitamin D and PTH remained stable. However, 24-h urinary calcium decreased significantly by 41% after 3 months ($P < 0.05$) with a similar trend after 9 months (Table 3).

Biochemical markers of bone turnover are presented in Fig. 1. Urinary NTx increased significantly by a mean of 174 ± 168% at 3 months ($P < 0.01$) and 319 ± 187% at 9 months ($P < 0.001$). Serum osteocalcin increased by a mean of 20 ± 37% at 3 months and 24 ± 50% at 9 months (both *P* nonsignificant). Serum BSAP remained stable ($P > 0.05$).

Longitudinal data for BMD and BMC are shown in Fig. 2 (n = 12). After 9 months, there was a significant reduction in BMD at the PA spine (3.3 ± 2.6%; $P < 0.01$), femoral neck (5.1 ± 7.1%; $P < 0.01$), total hip (7.8 ± 4.8%; $P < 0.001$), trochanter (9.3 ± 5.7%; $P < 0.001$), and total body (1.6 ± 2.0%; $P < 0.05$). There was no significant change in BMD at the radius or calcaneal BUA. BMC decreased significantly after 9 months at the total hip (5.6 ± 6.1%; $P < 0.01$), trochanter (5.6 ± 7.5%; $P < 0.05$), and total body (3.0 ± 2.5%; $P < 0.01$), with a similar trend at the femoral neck. Bone area and BMC at baseline and 9 months were significantly correlated at the total hip ($r = 0.89$ and 0.77, respectively; both $P < 0.01$) and total body ($r = 0.83$ and 0.82, respectively; both $P < 0.01$) when transformed to natural logarithms and analyzed according to the suggestion of Prentice *et al.* (17). The change in spine BMD was positively associated with the change in lean body mass ($r = 0.67$; $P < 0.05$).

Discussion

We observed that patients who had undergone LRGB surgery an average of 11 months earlier had a significant increase in markers of bone turnover, characterized by increases in bone formation and resorption. This increase was confirmed in our longitudinal study, which suggested that bone resorption increased as early as 3 months after LRGB.

TABLE 3. Obese patients at baseline, 3, and 9 months after LRGB

	Baseline	3 Months	9 Months
Weight (kg)	131 ± 20	114 ± 20[b]	95 ± 21[b]
BMI (kg/m^2)	48 ± 6	42 ± 7[b]	34 ± 6[b]
Body fat (%)	42.8 ± 7.4		35.2 ± 6.3[b]
Lean mass (%)	52.1 ± 5.7		62.0 ± 6.0[b]
Dietary calcium (mg/d)	1087 ± 441	1485 ± 651	1714 ± 825
Dietary vitamin D (IU/d)	389 ± 217	621 ± 133[a]	659 ± 361[a]
Serum calcium (mg/dl)	9.1 ± 0.4	9.1 ± 0.4	9.1 ± 0.3
Serum albumin (g/dl)	3.8 ± 0.3	3.8 ± 0.2[a]	3.7 ± 0.3
Serum PTH (pg/ml)	69 ± 42	61 ± 21	59 ± 30
Serum 25-hydroxyvitamin D (ng/ml)	19.2 ± 6.9	25.0 ± 10.1	22.1 ± 11.7
24-h urinary calcium (mg)	227 ± 106	160 ± 94[a]	157 ± 98
Urinary creatinine (g/liter)	1.6 ± 0.7	2.0 ± 0.8	1.4 ± 0.8
Serum ghrelin (pg/ml)	686 ± 216	337 ± 143[a]	463 ± 198

Results represent mean ± SD.
[a] $P < 0.05$ compared with baseline
[b] $P < 0.001$ compared with baseline.

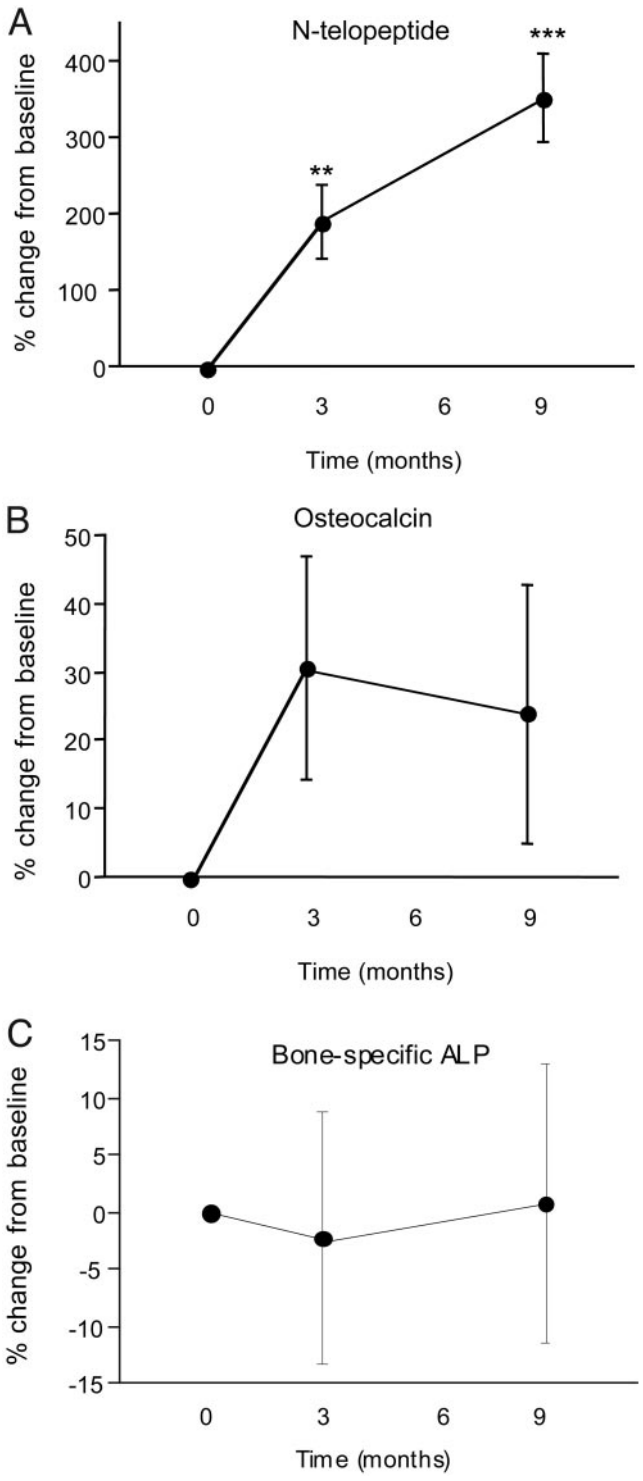

FIG. 1. Percentage change in urinary NTx (A), serum osteocalcin (B), and serum bone-specific alkaline phosphatase (ALP) (C) after LRGB surgery. Data represent mean ± SE. **, $P < 0.01$ compared with baseline; ***, $P < 0.001$ compared with baseline.

Other assessments of bone and mineral metabolism (*i.e.* serum PTH, serum calcium, 24-h urinary calcium) were not different between controls and postsurgical patients, despite the significantly higher self-reported dietary calcium and vitamin D intakes in the postsurgical group. However, serum

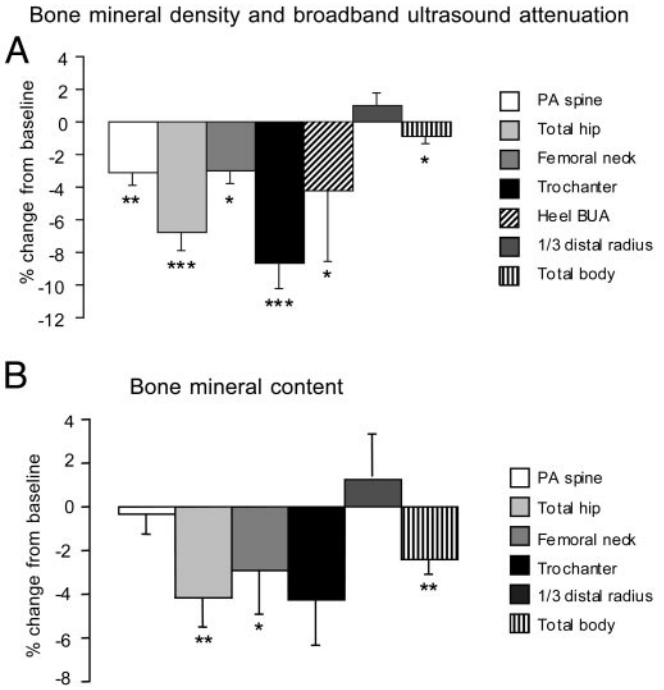

FIG. 2. Percentage change in BMD and BUA (A) and BMC (B) 9 months after LRGB surgery. Data represent mean ± SE. *, $P < 0.05$ compared with baseline; **, $P < 0.01$ compared with baseline; ***, $P < 0.001$ compared with baseline.

25-hydroxyvitamin D levels were low in both patient groups, consistent with previous observations in obesity (18). In the longitudinal investigation, after an average of 9 months, BMD decreased significantly at the total hip, trochanter, and total body. Radial BMD and calcaneal BUA remained stable. Urinary NTx increased significantly at 3 and 9 months. Altogether, these results suggest that there is an increase in bone resorption beginning as early as 3 months after LRGB that results in significant loss of bone mineral, predominantly at the hip.

Previous studies have examined BMD and bone mineral metabolism after surgery in patients with morbid obesity. Marceau *et al.* (19) examined 33 patients at 4 and 10 yr after biliopancreatic diversion. They reported that there were few changes in bone mass in these patients. However, the patients had been initially assessed with dual photon absorptiometry at baseline and followed with the different technique of DXA. The change in techniques would have resulted in an inappropriate and less precise comparison. After 4 yr, the investigators noted increased levels of serum PTH and osteocalcin associated with decreased levels of serum calcium and 25-hydroxyvitamin D. These results are in contrast to our patients, who were instructed to increase dietary calcium and vitamin D and who had no significant changes in serum PTH or serum vitamin D. Cundy *et al.* (9) studied patients prospectively after vertical banded gastroplasty. They showed increased BMD at baseline and decreases in hip BMD, but no change at the spine, similar to our patients.

Previous studies have reported significant abnormalities in bone mineral metabolism after different types of gastric bypass surgery (20–22). Ott *et al.* (22) examined 26 patients retrospectively 10 yr after Roux-en-Y gastric bypass surgery *vs.* seven controls. These investigators also noted decreased serum calcium, decreased serum 25-hydroxyvitamin D, and increased serum osteocalcin in the postsurgical group. Parfitt *et al.* (23) found persistent malabsorption in 52 patients 1–14 yr after jejunocolostomy. In a longitudinal study of 10 patients, serum 25-hydroxyvitamin D declined in the first year after intestinal bypass and continued to decrease for another 54 months. Investigators also found decreased serum calcium associated with loss of BMC (24). The short-term duration of our study and the supplementary calcium and vitamin D may explain the maintenance of normal levels of serum calcium and 25-hydroxyvitamin D in our patients. More recently, 16 patients were followed for 12 months after vertical banded gastroplasty and found to have a decrease in bone mass at the hip, associated with increased markers of bone resorption and formation, and no changes in serum PTH. These findings are similar to those of our patients 6 months after LRGB (25).

Other investigators have reported decreased serum leptin with LRGB and associated weight loss (26). Serum leptin was also significantly lower in our patients, who were an average of 11 months post LRGB surgery compared with our obese controls. However, there are conflicting reports on the levels of ghrelin after gastric surgery (27–30). Cummings *et al.* (28) demonstrated a 77% decrease in plasma ghrelin after gastric bypass surgery, in contrast to increased ghrelin after diet-induced weight loss. Serum ghrelin levels decreased to a lesser extent in our patients after LRGB surgery. This may reflect a lower preoperative BMI in our patients but is probably not related to time of collection, because in their study (28) no diurnal variation in ghrelin was evident in RGB patients. However, Holdstock *et al.* (29) recently reported an increase in serum ghrelin levels at 6 and 12 months after gastric bypass surgery. Therefore, ghrelin levels may differ from surgeon to surgeon or from procedure to procedure, depending upon the size of the gastric pouch or weight loss in these patients (27, 30).

There are several limitations to our study. First, although we had a total of 55 patients for comparison in the cross-sectional study, we only had 15 patients in our longitudinal study. Despite this, 3 months after surgery, we found similar significant increases in biochemical markers of bone resorption, which support the cross-sectional data. Second, we enrolled men, premenopausal women, and postmenopausal women. Sex steroid levels have been reported to change significantly in both men and women after bariatric surgery (31). We were unable to explore the relationship among sex steroid levels, changes in bone mineral, and markers of bone turnover because of the small sample size. Third, we did not have a control group who maintained weight during the study, and patients were not randomized to receive LRGB surgery. However, we felt that it would be unethical, given the documented health benefits of the surgery, to delay the procedure in eligible patients. Last, there are significant accuracy concerns with performing DXA in morbidly obese patients (17, 32). However, there was a strong correlation between BMC and bone area at the total hip and total body, suggesting that these sites are valid for repeated measures in obese subjects.

Our investigation also has several strengths. This is the

first study that examines acute changes at 3 and 9 months in patients undergoing laparoscopic gastric bypass surgery, which has recently become a standard surgical option. In addition, there was less potential for osteomalacia to occur, as in older studies, because we instructed our patients to increase dietary calcium and vitamin D after their surgery. Moreover, we used DXA, the current gold standard of bone mass assessment. Finally, we included both men and women, and the same surgeon (P.R.S.) performed the procedure on all patients.

In summary, we found that patients undergoing LRGB surgery have early increases in bone resorption associated with loss of bone mineral at the spine, hip, and total body. Supplementary calcium and vitamin D provide short-term protection against other metabolic bone diseases (*e.g.* vitamin D deficiency, hyperparathyroidism), as previously observed in older types of gastric bypass surgeries, and should be given to these patients. It would be reasonable to assess BMD, especially in postmenopausal women with other risk factors for osteoporosis. Longer studies are needed to examine whether increased bone turnover continues, whether it is more common in postmenopausal *vs.* premenopausal women or in men, and whether long-term sequelae (*i.e.* hypocalcemia, vitamin D deficiency, bone loss) develop past 12 months. It will also be important to determine which neuroendocrine or gastric factors are affected by bone loss.

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