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Effects of Roux-en-Y Gastric Bypass on Osteoclast Activity and Bone Density in Morbidly Obese Patients with Type 2 Diabetes

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Abstract

Introduction—Roux-en-Y gastric bypass (RYGB) is a well-established treatment for morbid obesity and type 2 diabetes. The effects of RYGB on bone metabolism and bone health are largely unknown.

Objective—Determine the changes in osteoclast function and bone density 1 year after RYGB as compared with a control group undergoing a diabetes support and education program (DSE).

Design—A prospective cohort study with patients matched for weight and age assigned to RYGB or DSE.

Setting—Large academic institution.

Patients or Other Participants—Patients with type 2 diabetes mellitus and morbid obesity (body mass index greater than 35 kg/m²).

Intervention—Subjects either received laparoscopic RYGB or DSE, which consisted of nutritional, exercise, and dietary counseling performed by a certified diabetic educator and a nutritionist three times over a year.

Main Outcome Measure—Osteoclast activity, bone mineral density.

Results—One year after, intervention subjects undergoing RYGB have a 280% increase in osteoclast activity as compared with a 7.6% increase in the DSE control group ($P < 0.001$). Furthermore, there was a statistically significant increase in sclerostin levels in subjects undergoing RYGB compared with an increase in the control group. The total bone mineral density

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later** amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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was statistically unchanged within 1 year of intervention in both groups. A statistically significant decrease in bone mineral density in the left ribs (decrease of 6.8%, $P < 0.05$) and lumbar spine (decrease of 4.0%, $P < 0.05$) was seen 1 year after RYGB.

Conclusions—There is a significant increase in osteoclast activity observed 1 year after RYGB; the long-term clinical implications of this increased bone metabolism are unknown.

Keywords

Osteoclast; Bone loss; Roux-en-Y gastric bypass; Bariatric surgery; Bone mineral density

Introduction

Obesity rates in the USA remain on the rise, increasing by almost 70% in the past decade [1, 2]. Metabolic surgery is becoming more common as well, with a 761% increase from 1998 to 2008 [3]. Metabolic surgery significantly improves glucose metabolism, decreases the risk of heart disease, and improves the quality of life [4–7]. However, an unfortunate adverse effect of metabolic surgery is post-operative bone loss. Several studies have shown that bone loss appears to persist even beyond the weight loss nadir [8–10]. In current practice, patients are routinely placed on supplemental calcium and vitamin D post-operatively to prevent bone loss. There have been multiple proposed mechanisms for bone loss following metabolic surgery including mechanical unloading secondary to substantial weight loss, vitamin D and calcium malabsorption despite adequate supplementation, and metabolic surgery-induced hormonal changes [8, 9, 11]. Historically operations like the jejunoileal bypass have resulted in significant osteoporosis and pathological fractures related to malabsorption [12, 13]. A commonly performed metabolic operation in the USA and around the world is the Roux-en-Y gastric bypass (RYGB). Patients undergoing RYGB have been shown to have a decrease in bone mineral density in the hip, femoral neck, and spine in the first 1–2 years after operation despite high doses of vitamin D and calcium supplementation [8–10, 14–16]. Studies show an increased fracture risk in these patients as well [17].

The changes in bone metabolism after RYGB are not fully characterized, and few studies include a control group comparison. The objective of this study was to determine the change in osteoclast activity 1 year after Roux-en-Y gastric bypass as compared with a control group and correlate these changes with changes in bone mineral density to determine clinical significance. We hypothesized that increased osteoclast activity would be seen 1 year after RYGB and this would correlate with a decrease in bone mineral density (BMD).

Materials and Methods

The study population consisted of subjects that participated in a prospective cohort study evaluating the effects of RYGB versus diabetes support and education program (DSE) on insulin sensitivity and insulin secretion in patients with morbid obesity with type 2 diabetes. All the subjects enrolled in the trial had been diagnosed with type 2 diabetes and morbid obesity (body mass index (BMI) > 35). The subjects were selected to undergo either RYGB or DSE depending on subject selection and/or insurance approval for RYGB. There were initially 67 patients with obesity enrolled with T2DM. Thirty-two participants were recruited

for RYGB surgery but 2 were withdrawn after they ended up not undergoing surgery. Another 35 were enrolled in the DSE program but 4 were withdrawn after 2 subjects failed to show for baseline testing and 2 had fasting blood glucose > 300 mg/dL on the morning of testing. Patients were matched on age, gender, and body weight. Participants in the RYGB group had significantly greater BMI and waist circumference than those in the DSE group. The metabolic profiles were similar between the two groups as well as the diabetes therapy. The matching process was verified every 10 enrollments in the RYGB group. This study demonstrated that patients that underwent RYGB surgery had marked improvement in body composition, glucose homeostasis, and glucostatic parameters at 1 year. In comparison, patients who were enrolled in the DSE program had a decrease in glucose homeostasis and glucostatic parameters despite no change in body composition [4]. Using the previously obtained serum samples and DEXA results from this index study, we were able to perform this retrospective analysis on changes in bone metabolism in subjects undergoing RYGB compared with a DSE control group. The study protocol was approved by the institutional review board, and all subjects gave informed consent to participate in this study.

BMI, fasting serum samples, and DEXA scans were obtained from subjects at the time of enrollment and 12 months post-treatment. The fasting serum samples were stored in a freezer at - 80 °C. All samples were analyzed at the completion of the study, except for the analysis of sclerostin. Osteoclast activity was measured using Serum CrossLaps® (Immuno Diagnostic Systems, Fountain Hills Arizona) enzyme-linked immunosorbent assay (ELISA). The ELISA kit measures C-terminal telopeptides (CTX) of type I collagen in human serum which is a marker of osteoclast activity. CTX concentrations correlate with bone loss and are used clinically to monitor for progression of osteoporosis and effectiveness of bone-conserving therapies [18]. Sclerostin was measured using a BioMedica® ELISA kit. Sclerostin is secreted by osteoclasts and is a bone formation antagonist [19]. BMD was measured with whole-body DEXA scans obtained with a total-body narrow fan-beam scanner (Hologic Discovery A, Bedford, MA) using Encore software version 13.3 (General Electric, Fairfield, CT). The Hologic Discovery A scanner has a weight limit of 300 pounds.

Subjects undergoing RYGB had the procedure performed in a standard laparoscopic fashion with the creations of an approximately 30-mL gastric pouch, a 100-cm Roux-limb, and a 50-cm biliopancreatic limb. The gastrojejunostomy and enteroenterostomy were fashioned with a linear stapler technique. The procedure was performed by a team of experienced bariatric surgeons at an accredited high-volume program. All subjects undergoing RYGB were placed on 800 IU of vitamin D and 1200 mg of calcium carbonate daily to prevent bone loss from nutritional malabsorption. There was 100% compliance with vitamin D and calcium supplementation as these subjects were closely monitored in the study. Subjects enrolled in the DSE met with a certified diabetic educator and a nutritionist three times during the yearlong study. These sessions focused on encouraging weight loss through diabetic education, exercise, and nutrition.

The mean of all continuous variables was reported along with the standard deviation (SD). Serum CTX concentrations between subjects undergoing RYGB versus the control DSE group were compared using a nonpaired sample *t* test. Sclerostin concentrations were analyzed in pre-menopausal and post-menopausal groups for both the RYGB group and the

control DSE group. Changes in concentration at pre-intervention and 12 months post-intervention were compared using a paired sample *t* test. The BMD of each group was compared at pre-intervention and 12 months post-intervention using a paired sample *t* test. Nominal variables between the two groups including gender and race were compared using a Chi-squared test. A *P* value of less than 0.05 was considered statistically significant.

Results

Sixty-one subjects were enrolled in the trial with 30 subjects undergoing RYGB and 31 subjects undergoing DSE. The subjects in the two groups were well matched for age (49.6 ± 1.4 years versus 47.4 ± 1.5 years, $P = 0.292$) and gender (66.7% female versus 67.7% female, $P = 0.929$). There was a higher percentage of Caucasians in the RYGB group and lower percentage of African Americans compared with the DSE group, but not statistically significant (Caucasian 76.6% versus 45%, African American 20% versus 45%, Hispanic 3% versus 6%, Asian 0% versus 3%, $P = 0.08$). The DSE group had a lower initial BMI compared with the RYGB group (40.1 ± 0.9 kg/m² versus 43.4 ± 0.8 kg/m², $P < 0.05$). And the RYGB group had a significant decrease in BMI 12 months after intervention compared with the control group (-12.2 ± 0.8 kg/m² versus 0.3 ± 0.4 kg/m², $P < 0.001$).

All serum samples from the RYGB group ($n = 30$) were analyzed on the CTX ELISA, while one subject in the control group did not have enough serum drawn for analysis and was excluded ($n = 30$). Initial serum CTX concentration for the two groups were equivalent (RYGB 0.340 ± 0.145 ng/mL versus control 0.356 ± 0.158 ng/mL, $P = 0.685$). At 12 months, there was a significant increase in serum CTX concentration in the RYGB group (0.950 ± 0.370 ng/mL) compared with the control group (0.383 ± 0.180 ng/mL). The changes in serum CTX levels in the RYGB were significantly higher than those in the control group (0.610 ± 0.319 ng/mL versus 0.027 ± 0.141 ng/mL, $P < 0.001$), depicted in Fig. 1.

Sclerostin concentration was obtained at a later date, and therefore, patients were excluded due to an unavailability of serum sample ($n = 47$). In the group undergoing RYGB ($n = 21$), the mean sclerostin concentration was decreased post 12 months of intervention in the pre-menopausal group (46.6 ± 6.4 to 38.5 ± 5.2 pmol/L), while it was increased in the post-menopausal group (32 ± 10.5 to 40.9 ± 7.9 pmol/L) (see Fig. 2). In the DSE control group ($n = 20$), the mean sclerostin concentration was unchanged post 12 months of intervention in the pre-menopausal group (36.7 ± 3.4 to 36.3 ± 4.6 pmol/L) and decreased in the post-menopausal group; however, results were non-significant (34.1 ± 2.8 to 31.9 ± 3.4 pmol/L), depicted in Fig. 3 ($P = 0.09$).

The initial total BMD between the two groups was similar (1.188 g/cm² versus 1.211 g/cm², $P = 0.460$). The total body surface area was decreased at 12 months post-RYGB but not statistically significant (2099 cm² versus 2048 cm², $P = 0.089$). The total bone mineral content was decreased at 12 months in the RYGB group but not statistically significant (2506 g versus 2440 g, $P = 0.072$). Both groups had little change in the total BMD at 12 months post-intervention (RYGB -0.2% change at 1 year, DSE -0.2% change at 1 year). At 12 months, the RYGB group had a significant decrease in BMD at the left ribs (0.702

g/cm² versus 0.653 g/cm², $P < 0.05$) and the lumbar spine (1.149 g/cm² versus 1.104 g/cm², $P < 0.05$). There was also a non-significant decrease in BMD in the right arm (0.777 g/cm² versus 0.758 g/cm², $P = 0.088$) and the thoracic spine (0.934 versus 0.904, $P = 0.099$) in the RYGB group. In the control group, there was no significant change in BMD at the 1-year follow-up DEXA (see Table 1).

Discussion

This study is the first to quantitate the increase in osteoclast activity and changes in BMD after RYGB using a non-surgical control group for comparison. We observed a 280% increase in osteoclast activity observed at 12 months post-RYGB compared with the control group that had only a 7.6% increase in osteoclast activity. This study demonstrates that there is a clear increase in bone resorption at 12 months post-RYGB. When we evaluated changes in BMD as measured by DEXA scan, we did not see a significant change that would correlate with our laboratory results. This is contrary to previous studies that have shown a statistically significant decrease in BMD at 1 year after RYGB, specifically in the hip and spine [8–10, 14–16]. We observed a decrease in BMD in some site-specific areas that were not seen in the control group, although overall this was not what was expected given the significant increase in osteoclast activity found in these patients. A study by Shanbhogue et al. examined 25 subjects post-RYGB at 12 months and 24 months and saw an increase in CTX1 and P1NP as well as a decrease in hip and spine BMD despite the attainment of weight, fat, and lean body mass [20]. Yu et al. studied 30 adults undergoing RYGB and 20 non-surgical controls and found that spine and total hip BMD declined progressively throughout the 24 months while it remained constant in the control group, despite stable serum calcium and vitamin D levels [10]. Our study looked at CTX1 and BMD but also utilized a non-surgical control group to highlight the difference in osteoclast activity that occurs specifically with metabolic surgery. There are only a handful of other studies that have had a non-surgical comparator group for controls [21–23].

Furthermore, we did not see a difference in sclerostin activity between the RYGB group and the control group. However, when the changes in sclerostin activity were analyzed between pre- and post-menopausal groups in patients undergoing RYGB versus a control group, post-menopausal women undergoing RYGB had an increase in sclerostin activity compared with the pre-menopausal group. Our results emphasize that post-menopausal women undergoing RYGB surgery are at particularly high risk of increased sclerostin activity and therefore a presumed subsequent increased rate of bone loss. The increase in sclerostin following metabolic surgery has been demonstrated by multiple other studies [15, 24]. Our study analyzed this increase in sclerostin activity in this specific high-risk population.

There are multiple important clinical implications for this study. Roux-en-Y gastric bypass is a procedure with numerous positive effects besides rapid weight loss. Patients often experience improvements in other comorbidities including insulin resistance, type 2 diabetes, HTN, dyslipidemia, and obstructive sleep apnea [4–7]. However, bone loss as a negative consequence should be considered in patients undergoing metabolic surgery. Often preventative measures are taken prior to surgery to prevent bone loss. However, it is seen that the bone loss occurs even with adequate vitamin D and calcium supplementation.

Further preventative measures should be investigated such as structured physical activity programs and nutritional monitoring. A study by Muschitz et al. showed that pre-operative and post-operative vitamin D and calcium supplementation along with a physical activity program reduced the negative impact of metabolic surgery on bone health [25, 26]. It should be recognized that bone loss occurs even after the weight loss nadir, and therefore, bone health should be monitored long term to decrease fracture risk. This should especially be considered in post-menopausal women, a population at high risk for bone loss as seen in our study results. The role of menopausal status in bone loss in patients undergoing metabolic surgery deserves further exploration.

This study demonstrated changes in both osteoclast and sclerostin activity in patients undergoing metabolic surgery when compared with a non-surgical group. There was also a negative impact on site-specific BMD; however, the clinical significance of these changes is uncertain. Long-term studies are necessary in order to evaluate the impact on fracture risk. Furthermore, our non-surgical control group did demonstrate any significant change in BMI, possibly contributing to decreased osteoclastic activity when compared with the surgical group. A study that compares 2 groups with similar weight loss (both surgical and non-surgical) could be a future direction for this study that could help to delineate whether changes in osteoclastic activity are secondary to weight loss versus metabolic changes. Another limitation of this study is the small sample size. Future studies could include a larger sample size and a multi-center trial investigating the role of metabolic surgery on BMD and osteoclastic activity.

In summary, our study emphasized the negative impact of metabolic surgery on osteoclast and sclerostin activity as well as BMD using a non-surgical control group. Clinicians should consider bone health when evaluating patients for bariatric surgery, specifically in high-risk populations such as post-menopausal woman as defined in this study. Further investigation into the role that menopausal status plays in bone loss following metabolic surgery is essential. Additional research is also fundamental in order to create guidelines for addressing bone health in the perioperative period.

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Fig. 1. Osteoclastic activity 12 months after Roux-en-Y gastric bypass. Serum concentration (ng/mL) of C-terminal telopeptides of type I collagen (CTX) given as mean $\pm$ standard deviation. *Significant difference at 12 months in CTX concentration in subjects who underwent RYGB versus the control group ($P < 0.05$, 2-tailed t test)

Fig. 2. Circulating sclerostin in the gastric bypass group. Serum concentration (pmol/L) of sclerostin given as mean $\pm$ standard deviation

Fig. 3. Circulating sclerostin in the control group. Serum concentration (pmol/L) of sclerostin given as mean $\pm$ standard deviation

Table 1

Changes in bone mineral density 12 months after Roux-en-Y gastric bypass

	RYGB ^a (n = 24)			Control (n = 27)		
	BMD ^b at baseline	% change ^c	BMD ^b at 12 months	BMD ^a at baseline	% change ^c	BMD ^b at 12 months
Left arm	0.758 ± 0.093	- 1.7	0.745	0.776 ± 0.098	1.5	0.788
Right arm	0.776 ± 0.088	- 2.3	0.758	0.798 ± 0.081	2.0	0.814
Left ribs	0.702 ± 0.073	- 6.8 *	0.654	0.706 ± 0.080	0.5	0.710
Right ribs	0.683 ± 0.095	- 4.5	0.652	0.682 ± 0.076	- 2.0	0.668
Thoracic spine	0.934 ± 0.122	- 3.2	0.904	0.953 ± 0.109	- 2.3	0.931
Lumbar spine	1.149 ± 0.165	- 4.0 *	1.103	1.157 ± 0.143	- 1.1	1.144
Pelvis	1.313 ± 0.182	- 2.2	1.284	1.332 ± 0.155	1.1	1.347
Left thigh	1.273 ± 0.185	0.1	1.274	1.222 ± 0.094	- 0.7	1.213
Right thigh	1.246 ± 0.173	0.2	1.249	1.207 ± 0.085	0.5	1.213
Head	2.588 ± 0.396	0.0	2.588	2.702 ± 0.416	- 0.9	2.678
Total body	1.188 ± 0.111	- 0.2	1.186	1.206 ± 0.107	- 0.2	1.204

^aRoux-en-Y gastric bypass (RYGB)^bBone mineral density (BMD) measured in mean grams per cm² ± SD^cPercentage change in bone mineral density at 12-month follow-up compared with baseline* $P < 0.05$ (paired *t* test)