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Effects of Roux-en-Y gastric bypass and sleeve gastrectomy on bone mineral density and marrow adipose tissue

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ABSTRACT

Bariatric surgery is associated with bone loss but skeletal consequences may differ between Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), the two most commonly performed bariatric procedures. Furthermore, severe weight loss is associated with high marrow adipose tissue (MAT); however, MAT is also increased in visceral adiposity. The purpose of our study was to determine the effects of RYGB and SG on BMD and MAT. We hypothesized that both bariatric procedures would lead to a decrease in BMD and MAT. We studied 21 adults with morbid obesity (mean BMI 44.1 ± 5.1 kg/m^2) prior to and 12 months after RYGB ($n = 11$) and SG ($n = 10$). All subjects underwent DXA and QCT of the lumbar spine and hip to assess aBMD and vBMD. Visceral (VAT) and subcutaneous (SAT) adipose tissue was quantified at L1–L2. MAT of the lumbar spine and femur was assessed by 1H-MR spectroscopy. Calcitropic hormones and bone turnover markers were determined. At 12 months after surgery, mean weight and abdominal fat loss was similar between the RYGB and SG groups. Mean serum calcium, 25(OH)-vitamin D, and PTH levels were unchanged after surgery and within the normal range in both groups. Bone turnover markers P1NP and CTX increased within both groups and P1NP increased to a greater extent in the RYGB group ($p = 0.03$). There were significant declines from baseline in spine aBMD and vBMD within the RYGB and SG groups, although the changes were not significantly different between groups ($p = 0.3$). Total hip and femoral neck aBMD by DXA decreased to a greater extent in the RYGB than the SG group ($p < 0.04$) although the change in femoral vBMD by QCT was not significantly different between groups ($p > 0.2$). MAT content of the lumbar spine and femoral diaphysis did not change from baseline in the RYGB group but increased after SG ($p = 0.03$). Within the SG group, 12-month change in weight and VAT were positively associated with 12-month change in MAT ($p < 0.04$), suggesting that subjects with less weight and VAT loss had higher MAT. In conclusion, RYGB and SG are associated with declines in lumbar spine BMD, however, the changes are not significantly different between the groups. RYGB may be associated with greater decline of aBMD at the total hip and femoral neck compared to SG. MAT content increased after SG and this was associated with lower weight and VAT loss.

1. Introduction

Bariatric procedures are increasingly used in patients with morbid obesity to reduce weight and to treat comorbidities. Roux-en-Y gastric bypass (RYGB) is the most commonly performed bariatric procedure followed by sleeve gastrectomy (SG) [1]. Although RYGB and SG are highly effective for reduction of weight and metabolic comorbidities, their effects on the skeleton appear harmful. Studies have shown detrimental effects of bariatric surgery on bone and mineral metabolism [2–4] and an increase in fracture risk [5,6].

Skeletal consequences may differ between RYGB and SG. SG involves resection of the gastric fundus, which secretes ghrelin, known to be stimulatory to osteoblasts, whereas bypassing of the small bowel in RYGB leads to malabsorption and other hormonal disturbances that may cause direct and deleterious effects on bone [7,8]. Patients typically lose more weight at one year following RYGB compared to patients who undergo SG [9] and data from animal studies suggest that bone loss after RYGB is greater than after SG [10]. Only a few studies have compared the effects of RYGB vs SG on bone in humans [11–16], and these have reported conflicting results, with some suggesting that RYGB leads to greater bone loss than SG, whereas others find similar rates of bone loss after both procedures. Of note, all studies used dual-energy X-ray absorptiometry (DXA) to determine bone mineral density (BMD). DXA assesses areal bone mineral density (aBMD), which is susceptible to artifactual changes following extreme weight loss [17], whereas

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quantitative computed tomography (QCT) measures volumetric bone mineral density (vBMD), which is less susceptible to changes in body size [18]. No studies have assessed the effects of RYGB and SG on vBMD by QCT.

Furthermore, bone strength is determined not only by BMD but also its micro-environment, and it is hypothesized that marrow adipose tissue (MAT) negatively affects bone strength [19]. Severe weight loss is associated with high MAT [20] which may contribute to impaired skeletal health after bariatric surgery. On the other hand, visceral adiposity is associated with high MAT [21] and loss of visceral adipose tissue following bariatric surgery might lead to a decrease in MAT. Furthermore, alterations in MAT may contribute to artifact in the assessment of BMD by both DXA and QCT modalities [22,23]. The non-invasive quantification of MAT using proton magnetic resonance spectroscopy (1H-MRS) has improved the feasibility of quantifying MAT content and allows longitudinal assessments in vivo. A recent pilot study of 11 women with morbid obesity undergoing RYGB showed a decrease in MAT in diabetic patients ($n = 6$) while there was no change in non-diabetic patients ($n = 5$) six months after surgery [24]. However, no studies have compared the effects of RYGB vs SG on MAT. The purpose of our study was to determine the effects of RYGB and SG on aBMD, vBMD, and MAT. We hypothesized that both bariatric procedures would lead to a decrease in BMD and a decrease in MAT content 12 months after surgery.

2. Materials and methods

Our study was IRB approved and Health Insurance Portability and Accountability Act compliant. Written informed consent was obtained from all subjects prior to performance of any study procedures.

2.1. Subjects

Subjects with morbid obesity were recruited from the MGH Weight Center. Inclusion criteria were age ≥18 years and plan to undergo RYGB or SG. Exclusion criteria were history of medical disorders known to affect bone metabolism, use of bone-active medication, pregnancy, weight >182 kg (due to limitations of the MRI scanner) and contraindications to MRI, such as the presence of a pacemaker or metallic implant. Subjects who were scheduled for bariatric surgery and met inclusion criteria were invited to participate in the study and were scheduled for the baseline visit. There were no drop-outs before or during the baseline visit.

Study visits were performed at baseline (prior to bariatric surgery) and 12 months after surgery. Each subject underwent a history and physical examination, fasting blood tests, DXA, QCT, and 1H-MRS at baseline and 12 months. Type 2 diabetic status was assessed by self-report and/or use of diabetic medications.

2.2. Calcitropic hormones and bone turnover markers

The following blood tests were obtained after an overnight fast: calcium, and 25-hydroxyvitamin D, parathyroid hormone (PTH) (intra- and interassay coefficient of variations (CV) ≤ 3%), procollagen type 1 N-terminal propeptide (PINP) (intra- and interassay CVs ≤ 6%) and serum type 1 cross-linked C-telopeptide (CTX) (intra- and interassay CVs ≤ 3%) as previously described [25].

2.3. Bone mineral density assessment

2.3.1. Dual-energy X-ray absorptiometry (DXA)

Areal bone mineral density (aBMD, g/cm^2) of the lumbar spine (L1–L4), total hip and femoral neck was assessed using DXA (QDR Discovery, Hologic, Inc., Bedford, MA). We have previously established that the same-day in vivo scanning precision at our center is 0.007, 0.008, and 0.012 g/cm^2 for PA spine, total hip, and femoral neck, respectively [26]. If necessary, manual retraction of pannus overlying the proximal femur was performed during hip measurements.

2.3.2. Quantitative computed tomography (QCT)

Volumetric bone mineral density (vBMD) of the lumbar spine (L1–L2) and proximal femur was assessed using a 16-multidetector-row CT scanner (LightSpeed Pro, GE Healthcare, Waukesha, WI, USA). Subjects were placed supine in the CT scanner on a calibration phantom (Mindways Software, Inc., Austin, TX, USA), and helical scanning of L1–L2 and from the proximal articular surface of the femoral head to 1 cm below the lesser trochanter, was performed using the following parameters: 120 kV, 100 mA (L1–L2), 120 kV, 200 mA (proximal femur), slice thickness of 2.5 mm, FOV of 500 mm and table height of 144 mm (2-year CV ≤ 2%) [27].

Analysis of vBMD of L1–L2, total hip, and femoral neck was performed with QCTPro software (Mindways Software, Inc., Austin, TX) as previously described [25].

2.4. Marrow adipose tissue assessment

Subjects underwent proton MR spectroscopy (1H-MRS) of the 1st and 2nd lumbar vertebrae (L1–L2) and the left proximal femoral metaphysis and mid-diaphysis. All studies were performed on a 3.0-T MR imaging system (Siemens Trio; Siemens Medical Systems, Erlangen, Germany) after an overnight fast. Single-voxel 1H-MR spectroscopy data were acquired by using a point-resolved spatially localized spectroscopy pulse sequence without water suppression (TR/TE 3000/30, eight acquisitions, 1024 data points, and receiver bandwidth of 1000 Hz). For each voxel placement, automated optimization of gradient shimming was performed [28].

Fitting of all 1H-MRS data was performed using LCModel (version 6.3-0K, Stephen Provencher, Oakville, Canada). Metabolite quantification was performed using eddy current correction and water scaling. A customized fitting algorithm for bone marrow analysis provided estimates for all lipid signals combined (0.9, 1.3, 1.6, 2.3, and 5.3 ppm). LCModel bone marrow lipid estimates were automatically scaled to unsuppressed water peak (4.7 ppm) and expressed as lipid to water ratio. Average MAT content of L1–L2 was assessed (6-month CV 12%) [29].

2.5. Abdominal fat assessment

Visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) compartments were quantified at the level of L1–L2 using the CT performed for BMD assessment. Fat attenuation coefficients were set at −50 to −250 Hounsfield unit as described by Borkan et al. [30]. and VAT and SAT cross sectional areas (CSA) (cm^2) were assessed based on offline analysis of tracings obtained utilizing commercial software (VITRAK; Merge/eFilm, Milwaukee, WI) (CV 2.5%).

All QCT and 1H-MRS acquisitions and analyses were performed blinded to the surgical procedure under the supervision of a musculoskeletal radiologist with 11 years of experience (M.A.B.).

2.6. Statistical analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Baseline characteristics were assessed by independent *t*-tests or Fisher's exact tests. Twelve-month changes between the RYGB and SG groups were compared by ANOVA and 12-month changes within the groups were assessed using paired *t*-tests. We also performed exploratory analyses to determine whether gender or diabetic status modulated the outcomes. Nonparametric Spearman rank correlation coefficients are reported. P-value < 0.05 was used to denote significance. Data are presented as mean ± SD.