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Changes in Bone Mineral Density, Body Composition and Adiponectin Levels in Morbid Obese Patients after Bariatric Surgery

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Abstract
Introduction Gastric bypass surgery (GBP) is increasingly used as a treatment option in morbid obesity. Little is known about the effects of this surgery on bone mineral density (BMD) and the underlying mechanisms. To evaluate changes on BMD after GBP and its relation with changes in body composition and serum adiponectin, a longitudinal study in morbid obese subjects was conducted.
Methods Forty-two women (BMI 45.0±4.3 kg/m^2; 37.7±9.6 years) were studied before surgery and 6 and 12 months after GBP. Percentage of body fat (%BF), fat-free mass (FFM), and BMD were measured by dual-energy X-ray absorptiometry and serum adiponectin levels by RIA.
Results Twelve months after, GBP weight was decreased by 34.4±6.5% and excess weight loss was 68.2±12.8%. Significant reduction ($p<0.001$) in total BMD (−3.0±2.1%), spine BMD (−7.4±6.8%) and hip BMD (−10.5±5.6%) were observed. Adiponectin concentration increased from 11.4±0.7 mg/L before surgery to 15.7±0.7 and 19.8±1.0 at the sixth and twelfth month after GBP, respectively ($p<0.001$). Thirty-seven percent of the variation in total BMD could be explained by baseline weight, initial BMD, BF reduction, and adiponectin at the twelfth month (r^2=0.373; $p<0.001$). Adiponectin at the twelfth month had a significant and positive correlation with the reduction of BMD, unrelated to baseline and variation in body composition parameters (adjusted correlation coefficient: r=0.36).
Conclusion GBP induces a significant BMD loss related with changes in body composition, although some metabolic mediators, such as adiponectin increase, may have an independent action on BMD which deserves further study.

Keywords Bone mineral density · Gastric bypass · Adiponectin · Body composition

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Introduction

Actually, overweight and obesity represents one of the major health hazards in the worldwide affecting nearly 1.1 billion subjects [1]. According to the data in the first national health survey in 2003, the prevalence of overweight, obesity, and morbid obesity in Chilean adults were 38%, 22%, and 1.3%, respectively [2]. Obesity is associated to increased mortality [3] and to a higher risk of type 2 diabetes, hyperlipidemia, sleep apnea, gallbladder disease, coronary disease, hypertension, musculoskeletal disorders, several types of cancer and psychosocial disturbances [4, 5]. Besides the greater severity of comorbidities, severe and morbid obesity (BMI between 35 and 39.9 kg/m^2 and ≥40 kg/m^2, respectively) sharply reduce life expectancy, especially in young adults [6].

In these patients, bariatric surgery is considered the most effective method to induce significant weight loss (~70% of excess weight) which is maintained in the long term. This observation is confirmed in two recent meta-analysis showing the efficacy of different types of bariatric surgery, in terms of both weight loss and comorbidities improvement [7, 8]. Therefore, Roux-en-Y gastric bypass (GBP), the most recommended technique currently used, has become the "gold-standard" technique [9–11]. Despite the beneficial results of GBP, some of the warning issues are mortality, and early and late complications. Among the most frequently observed nutritional complications are micronutrient deficiencies such as vitamin B12, folate, zinc, iron, vitamin D and calcium, due to a combination of poor food intake, maldigestion and/or malabsorption [12]. Iron deficiency anemia is the most frequent complication after GBP (≈50%), especially in premenopausal women. Emerging concern is being raised related to metabolic bone disease and osteoporosis. In subjects who have undergone bariatric surgery, previous studies have shown increased risks of metabolic bone disease, reduction in bone mineral density (BMD), bone mineral content, and fracture [13, 14].

A number of factors seems to be involved in the reduction of BMD after GBP, such as: elevated levels of serum parathyroid hormone secondary to inadequate calcium intake, intestinal Ca and vitamin D malabsorption [15], reduced biomechanical stress along the weight loss [16, 17], reduced levels of estrogens in women [16], reduction in plasma levels of leptin [18, 19] and ghrelin [20], and increased serum concentrations of adiponectin [21].

The aim of this prospective study was to assess the magnitude of the effect of changes in food intake, micronutrients supplementation, body composition, and serum levels of adiponectin on the reduction in bone mass after gastric bypass. Our hypothesis is that the main contributing factor will be the amount of calcium and vitamin D consumed by supplements.

Materials and Methods

Subjects

Forty-two adult women (age 37.7±9.6 years; age range 19–55 years), with BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with comorbidities such as type-2 diabetes, hypertension, dyslipidemia, sleep apnea, osteoarthritis, among other conditions, who underwent RYGBP in the Department of Surgery of the University of Chile Clinical Hospital were prospectively studied. The mean BMI was 45.0±4.3 kg/m^2: five patients had a BMI lower than 40 (range 39.3–39.8 kg/m^2), 31 patients had a BMI between 40 and 49.9, and six patients presented a BMI ≥50 kg/m^2 (range 50.1–59.2). All patients who agreed to enter the study signed an authorized consent form. The study was approved by the Ethics Committee for Human Investigation of the University Clinical Hospital. The surgical technique consisted of a 95% distal gastrectomy, with resection of the bypassed stomach, leaving a small gastric pouch of 15–20 ml. [22]. Then, an end-to-side gastrojejunostomy with circular stapler No. 25 was performed. The length of the Roux-loop was 125–150 cm. All patients underwent complete preoperative evaluation.

Before and 6 and 12 months after surgery, the following evaluations were carried out in all patients: anthropometry, food survey, resting energy expenditure (REE), body composition analysis, bone mineral density measurement, and serum adiponectin concentration. In all patients, calcium (640–1,000 mg) and vitamin D (400–800 U) were prescribed as an oral supplementation for the entire period of observation.

Anthropometric, Food Intake, and Supplements Evaluations

Weight was measured to the nearest 0.1 kg on a digital scale (Seca®, Vogel & Halke GMBH & Co, Germany), and height (m) was measured to the nearest 0.1 cm with a scale-mounted stadiometer. BMI (kg/m^2) was calculated. Waist (WC) and hip (HC) circumferences (cm) were registered according to the procedures recommended by the Anthropometric Standardization Reference Manual [23]. At baseline, and at the sixth and twelfth month of the postoperative period, patients were interviewed by a dietitian and were enquired to fill a 3-day record of food intake. The recorded data were analyzed using a computer program (Food Processor II®, ESHA Research, Salem, OR, USA) to calculate energy, protein, and calcium intake. A strict record of all types of vitamin and mineral supplements were kept throughout the study.

Body Composition

Fat-free mass (FFM, kg), Body fat (BF, kg), bone mineral density (BMD, g/cm^2), and bone mineral content (g) were measured by dual-energy X-ray absorptiometry (DXA) using a Lunar DPX-L densitometer (Lunar, Madison, WI; version 1.30 software) [24, 25]. BMD and BMC were examined in total body, lumbar spine, and total hip. BF was analyzed in the total body, trunk, and in the ROI (Region of Interest). ROI is a rectangular area defined by horizontal lines placed inferiorly on the top of the iliac crests and superiorly at three pixels above the previous line [26].

Adiponectin Analysis

In serum obtained from morning-fasted blood samples, adiponectin was analyzed by radioimmunoassay using a kit from Linco Research Inc. (St. Charles, MO, USA).

Table 1 Baseline demographics, anthropometrics, body composition and energy metabolism characteristics of patients before bariatric surgery (n=42)

	Mean±SD	Range
Age (years)	37.7±9.6	19–55
Body weight (kg)	113.9±14.6	88.4–145.5
Excess of weight (kg)	58.0±12.0	40.4–83.4
BMI (kg/m^2)	45.0±4.3	39.3–59.2
Waist (cm)	119.4±10.2	99–141
Hip (cm)	134.5±11.8	107–162
Body fat (%)	47.8±5.1	34.5–57.1
Trunk body fat (%)	45.4±4,8	33.6–56.9
ROI body fat (%)	49.2±4.3	41.1–58.6
Total BMD (g/cm^2)	1.23±0.05	1.14–1.34
Total *T*-score (SD)	1.21±0.74	−0.30–2.73
Spine BMD (g/cm^2)	1.49±0.11	1.25–1.69
Spine *T*-score (SD)	2.44±0.77	0.80–3.80
Pelvis BMD (g/cm^2)	1.28±0.09	1.08–1.44
Pelvis *T*-score (SD)	1.58±0.98	−0.40–3.30

BMI Body mass index, *ROI* region of interest located in abdominal area 1 cm above iliac crest, *BMD* bone mineral density evaluated by dual X-ray absorptiometry, *T-score* difference between measure and mean value of young adult women in standard deviations

Statistical Analysis

The design of the study considered obtaining results at different periods after GBP in the same subjects. Repeated measures of ANOVA model were used to evaluate the effects of this surgery on variables such as body composition, BMD, and adiponectin concentration. The Bonferroni test was applied for multiple comparisons. To evaluate the association among variables, Spearman's correlation coefficient analyses were performed [27]. Regression analysis models were performed to evaluate the association between the reduction in BMD, as the dependent variable, and changes in body composition, nutritional intake, vitamin and mineral supplementation, and twelfth-month adiponectin levels, as independent variables. To adjust for the potential effects of baseline body composition parameters and for changes in body weight and total and regional body fat, partial correlation coefficients between reduction in BMD and twelfth-month adiponectin levels were computed. SPSS 10.0® statistical software was used for all the analysis (SPSS Inc, Chicago IL, USA). Statistical significance was considered at p<0.05.

Results

Anthropometrics, body composition and bone mineral density characteristics of the forty-two patients before GBP are showed in Table 1. Al baseline, no patient presented a BMD at a risk level of osteoporosis (*T*-score ≤−1 standard deviation) in the analyzed regions.

Changes in body composition, BMD, and serum adiponectin levels at the sixth and twelfth-month post surgery are shown in Table 2. Twelve months after GBP weight loss ranged between 21.8% and 49.6% of initial weight, BF between 23.0% and 79.0%, and FFM between 5.9 y 29.4%. Excess weight loss 12 months after GBP was 68.2±12.8% (range, 36.8–95.8). All changes in body composition were statistically significant (p<0.001) among the three points of evaluation (baseline, sixth, and twelfth

Table 2 Changes in weight, body composition, and adiponectin

Variable	Baseline	Sixth month	Twelfth month	Change (%)[a]
Weight (kg)	113.9±14.6*	82.1±11.1*	74.5±9.9*	−34.4±6.5
BMI (kg/m^2)	45.0±4.3*	32.5±3.9*	29.5±3.9*	−34.4±6.5
Body fat (kg)	54.9±11.6*	33.9±9.5*	26.3±8.5*	−52.1±12.4
Fat-free mass (kg)	58.9±5.8*	48.2±3.8*	48.2±3.6**	−18.0±5.1
Waist (cm)	119.4±10.2*	95.6±8.8*	89.8±8.4*	−24.7±5.1
Hip (cm)	134.5±11.8*	113.2±10.1*	106.9±9.5*	−20.3±5.4
Trunk body fat (kg)	24.2±6.0*	17.2±6.6*	12.8±4.4*	−46.2±16.5
ROI body fat (kg)	1.57±0.41*	0.88±0.27*	0.68±0.25*	−55.8±13.9
Total BMD (g/cm^2)	1.23±0.53*	1.21±0.64*	1.19±0.63*	−3.0±2.1
Spine BMD (g/cm^2)	1.49±0.11*	1.42±0.14*	1.38±0.14*,***	−7.4±6.8
Pelvis BMD (g/cm^2)	1.28±0.09*	1.19±0.09*	1.14±0.09*	−10.5±5.6
Adiponectin	11.4±4.3*	15.7±4.8*	19.8±6.6*	+97.0±99.9

BMI Body mass index, *ROI* region of interest, *BMD* bone mineral density evaluated by dual X-ray absorptiometry
[a] Percent variation between baseline and final value.
*p<0.001, significant difference between all measures
**p<0.001 significant difference with basal measures
***p<0.05, significant difference with previous measure

month), except FFM which showed no change between month 6 and 12 post GBP.

After GBP, significant reductions in total BMD, spine BMD and pelvis BMD were observed ($p<0.001$; Fig. 1). The change in BMD at the twelfth month showed a significant difference among total BMD (−3,0±2,1%), spine BMD (−7,4±6,8%) and pelvis BMD (−10,5±5,6%; $p<0.001$). Considering total and spine BMD no patient fell to a level considered as osteopenia (T-score ≤−1 and >2.5 standard deviations) or osteoporosis (T-score ≤−2.5 standard deviations). Osteopenia however, was present in 4 patients according to pelvis BMD measured 12 months after GBP (T-score range, −1 to −1.7 standard deviations). Total BMD decrease was positively correlated ($p<0.05$) with baseline weight ($r=0.36$), initial FFM ($r=0.33$), percentage of weight loss ($r=0.33$), adiponectin change ($r=0.34$), and absolute adiponectin at the twelfth-month post GBP ($r=0.35$). After multiple regression analysis, 37% of the reduction of BMD could be explained by the following variables: baseline weight, baseline BMD, BF reduction and adiponectin at the twelfth-month post GBP ($r^2=0.373$; $p<0.001$). After adjusting for covariates (baseline weight, initial BF, initial BMD, weight loss, total, and regional BF loss), adiponectin concentrations at the twelfth month had a positive correlation with BMD decrease (adjusted correlation coefficient: $r=0.35$; $p<0.05$).

Serum adiponectin concentrations increased by 48% at sixth month and by 97% at the twelfth-month post GBP ($p<0,001$). The increase in adiponectin at the twelfth month was negatively correlated with baseline adiponectin levels ($r=-0.61$; $p<0.001$) and positively correlated with the percentage of initial weight loss ($r=0.41$; $p<0.01$), percentage of initial body fat loss ($r=0.48$; $p<0.005$), percentage of initial trunk fat mass loss ($r=0.42$; $p<0.01$), and percentage of initial ROI fat mass loss ($r=0.47$; $p<0.005$).

In relation to nutrient intakes, a significant reduction was observed in energy intake at 6 months after GBP (14.6±5.9 vs. 10.9±3.8 kcal/kg/day; $p<0.001$), although energy intake at the twelfth month showed no difference with baseline intake (14.3±2.8 kcal/kg/day). Protein intake (g/kg/day) showed no significant difference at sixth and twelfth-month post GBP (0.56±0.22 years 0.69±0.17 g/kg/day, respectively) compared to baseline values (0.61±0.19 g/kg/day).

Dietary calcium intake was no different between initial estimation (486±222 mg/day; 95% Confidence Interval (CI): 158–832 mg/day) and the records obtained at sixth (393±230 mg/day; 95% CI: 116–838 mg/day) and twelfth-month post GBP (468±289 mg/day; 95% CI: 102–1069 mg/day). Calcium intake from supplements was lower in the first 6 months post surgery (393±230 mg/day; 95% CI: 319–815 mg/day) compared to the sixth to twelfth-month period (468±289 mg/day; 95% CI: 349–973 mg/day; $p<0,001$). Vitamin D intake from supplements was also lower at the first period (322±191 U/day; 95% CI: 143–652 U/day) compared to the second period (412±236 U/day; 95% CI: 185–762 U/day). No correlation was observed between dietary calcium intake or supplemental Ca plus vitamin D and the changes of total BMD, spine BMD and pelvis BMD.

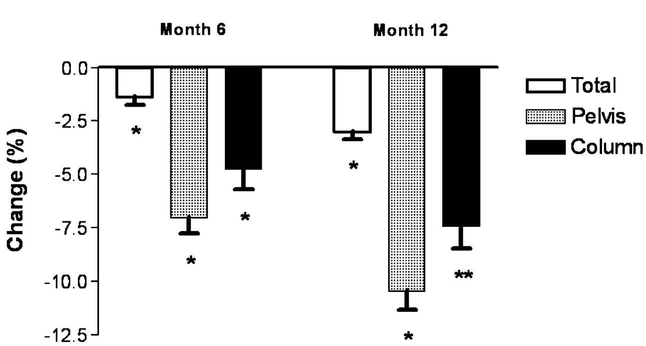

Fig. 1 Bone mineral density after gastric bypass: changes with respect to baseline. *Significant change from previous value with $p<0.001$, **significant change from previous value with $p<0.05$

Discussion

Beneficial effects of bariatric surgery in morbid obese patients are widely recognized, especially those related to correction of comorbidities [7, 10]. Some potential side-effects however, such as decreased bone mineral density (BMD), are only partially understood. The most dramatic effects of bariatric surgery on bone mineral density have been noted mainly, but not exclusively, in malabsorptive surgery [28]. Roux-en-Y gastric bypass (GBP), although having a malabsorption component, is predominantly a restrictive technique. The extent and clinical implications of potential adverse effects of GBP on bone metabolism are matter of debate [13, 29–31].

In the present study, we observed a 3% decrease of total BMD after 1 year of GBP, with column and pelvis (7.4% and 10.5%, respectively) being their main contributors, which is in agreement with previous reports [13, 29, 30].

The site-dependent differential changes of BMD observed suggest that the effect of reduced body weight accompanied with less mechanic load is highly relevant in determining BMD. Nevertheless, a similar effect could also be induced by secondary hyperparathyroidism [32–34]. This condition is more frequent in individuals older than the subjects studied here. We did not determine parathyroid-related parameters in our subjects; therefore, we cannot disregard the presence of such effect.

Unlike the femur neck and pelvis having predominantly cortical bone, the column has a higher proportion of trabecular bone. The latter is metabolically more active and, in consequence, it may be more sensitive to humoral factors [21].

Although the literature mentions decreased calcium and vitamin D intake/absorption, secondary hyperparathyroidism and reduced mechanic load on the skeleton as the main factors involved in reduced BMD after GBP, recent evidence suggests that a number of hormonal factors may also participate in this process [28]. The knowledge about the extent of involvement and the mechanisms underlying such effects is limited. Leptin concentration is markedly affected by drastic weight modifications as those observed after GBP. Its association with BMD is rather weak however [19], possibly because this hormone has a dual role. On one hand, it shows an indirect pro-osteoclastic activity by activating the sympathic system and stimulating of β2 adrenergic receptors. On the other hand, it inhibits osteoclastic differentiaton by participating in the cocaine–amphetamine-regulated transcript pathway (CART) [28]. Adiponectin has a clear anti-osteogenic activity, demonstrated by in vitro studies, probably through its role as ligand of necrosis factor kappa β (NFKβ) receptor [35, 36]. Berner et al. [36] have demonstrated that adiponectin and its receptors (AdipoR1 and AdipoR2) are expressed in human osteoblasts, and also that the supplementation of culture medium with recombinant adiponectin enhances the proliferation of osteoblasts. Adiponectin also is negatively associated with BMD in humans, independently of their body fat mass [21]. In our study, as expected, adiponectin was dramatically increased after GBP. Up to our knowledge, this is the first study reporting a significant association between serum adiponectin and reduction of BMD in non-menopausal women after 1 year of GBP. Since both variables were also associated to initial body fat mass, weight change and fat mass change after 1 year of GBP, correlation analyses were conducted adjusting these variables. Such correction did not affect the described association.

In terms of the effects of dietary changes as determinants of the modifications of BMD in this type of patients, it has been suggested that low intakes of calcium and vitamin D associated to low consumption of dairy products after GBP may be responsible for the increase of PTH and stimulation of bone resorption, especially at the cortical bone. As a result, supplementation with these nutrients seems to be widely justified. Nevertheless, there is no agreement on the optimal amount to be provided after GBP. In the study by Goode et al., secondary hyperparathyroidism post BPG could not be corrected with the administration of 1,200 mg of calcium and 8 µg of vitamin D, although the period of observation was only up to 6 months [29]. In our study, the prescribed daily calcium and vitamin D supplements ranged between 640 and 1,000 mg for calcium and between 400 and 800 IU for vitamin D. Those amounts of supplementation are in agreement with the recommendations of Johnson et al. [30]. As expected, the actual amount consumed varied according the compliance of the individuals. In our study, this reached 83% of the planned amount on average. Finally, the reduction of BMD was not correlated to dietary calcium intakes or to the consumption of calcium plus vitamin D from supplements.

The lack of association between BMD change and calcium and vitamin D total intakes may be explained by the anatomical alterations produced by the GBP. This modification would reduce calcium absorption, which takes place mainly at the duodenum and proximal jejunum. It would also favor fat and fat-soluble vitamins malabsorption as consequence of impaired combination with bile salts.

Since all variables significantly associated to BMD change (initial weight, weight loss, fat mass loss, final adiponectin) only explain 37% of the variance, it is possible that calcium and vitamin-D-impaired absorption is actually playing a major role. In our study, calcium absorption determinations were not carried out. Among the clinical implications of the results, it could be speculated that calcium and vitamin D supplementation, unless they are provided in very high amounts, will have a modest effect preventing BMD decrease.

BMD decrease seems to be highly associated to weight loss in both surgical and non-surgical interventions [16, 37]. This, along with the concomitant adiponectin increase, would condition a loss of protective effect of obesity against osteoporosis [30, 38]. According to Johnson et al. [30, 39], BMD decrease is made evident mainly during the first year, which is also the period when the major weight changes are observed. Beyond that point, both body weight and BMD tend to remain stable.

In conclusion, in our group of non-menopausal women studied after 1 year of gastric bypass, BMD was significantly reduced, mainly at the pelvis. BMD decrease was more important in the patients with greater values of initial body weight, initial BMD, fat mass loss and final serum adiponectin. Adiponectin involvement in the process of bone modeling may explain, at least partially, the decrease of BMD observed after GBP. In order to achieve a better understanding of these observations and their implications, further studies including a wide range of calcium and vitamin D supplements and calcium absorption measurements are needed.

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