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Original article

Bone mass loss after sleeve gastrectomy: A prospective comparative study with gastric bypass

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A B S T R A C T

Introduction: Bariatric surgery is the most effective option for the treatment of patients with a high risk of complications due to their obesity. However, it brings about a series of changes in calcium and vitamin D metabolism and an increase in resorption which lead to a loss of bone mass.

Aim: The objective of this study is to compare sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) as regards loss of bone mass using bone densitometry and bone remodelling markers.

Patients and methods: Fifteen women with morbid obesity were included, 8 by SG and 7 by RYGB, with a mean age of 47.8±9 and mean body mass index 43.3±3.4. Bone mass measurements were made on the lumbar spine, femur and distal radius, and the bone remodelling markers N-telopeptide (NTx) and bone alkaline phosphatase (BALP), as well as vitamin D levels before and 12 months after surgery.

Results: A significant bone mass loss was observed was observed with SG and RYGB, in the lumbar spine and hip, whilst no differences were observed in the radial. The percentage bone mass loss was less in the column and femur after SG than with RYGB, although it did not reach statistical significance, 4.6%±4.4 (mean±SD) and 6.3%±5.4 (mean±SD), respectively. At 12 months the Ntx increased for both types of surgery, and the BAP was only increased for SG.

Conclusion: SG causes less, although not significant, bone mass loss compared to RYGB.

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Pérdida de masa ósea tras gastrectomía tubular: estudio prospectivo comparativo con el *bypass* gástrico

Palabras clave:
Cirugía bariátrica
Densitometría ósea
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Marcadores de remodelado óseo

R E S U M E N

Introducción: La cirugía bariátrica es la opción más eficaz para el tratamiento de los pacientes con alto riesgo de complicaciones por su obesidad. Sin embargo, provoca una serie de alteraciones metabólicas sobre el calcio y la vitamina D y un aumento de la resorción que conllevan una pérdida de masa ósea.

Objetivo: El objetivo del estudio es la comparación de la gastrectomía tubular (GT) con el bypass gástrico en Y de Roux (BGYR) respecto a la pérdida de masa ósea medida mediante densitometría y marcadores de remodelado óseo.

Pacientes y métodos: Se incluyeron 15 mujeres con obesidad mórbida, 8 en la GT y 7 en el BGYR, de edad media 47,8 ± 9 con un índice de masa corporal 43,3 ± 3,4. Se realizaron mediciones de la masa ósea a nivel de columna, fémur y tercio distal del radio y marcadores de remodelado óseo N-telopéptido (NTx), y fosfatasa alcalina específica ósea (FAO), así como niveles de vitamina D antes y a los 12 meses de la intervención.

Resultados: Se observó una pérdida significativa de masa ósea con la GT y el BGYR, en columna lumbar y cadera mientras que en el radio no se observaron diferencias significativas. El porcentaje de pérdida de masa ósea fue menor en columna y fémur tras la GT que con el BGYR, aunque sin llegar a la significación estadística, 4,6% ± 4,4 (media ± DE) y 6,3% ± 5,4 (media ± DE) respectivamente. A los 12 meses el NTx aumentó para ambos tipos de intervención y las FAO aumentaron sólo para la GT.

Conclusión: La GT provoca una pérdida menor de masa ósea, aunque no significativa, respecto el BGYR.

Introduction

Bariatric surgery is probably the most effective option for treating patients at high risk of complications due to obesity. The criteria for its indication are well established, as are the effects of surgery in the medium and long term. Among the metabolic disorders produced by bariatric surgery are those that affect the metabolism of calcium and vitamin D, leading to an increase in bone resorption and loss of bone mass.[1,2] The mechanism by which this effect on bone metabolism is produced is complex and goes beyond simple caloric restriction after surgery and involves numerous hormones and molecules such as oestrogens, leptin, adiponectin, amylin, insulin and others.[3]

Currently, the surgical technique of gastric bypass Roux-en-Y (GBRY) is performed in more than 80% of the bariatric surgery interventions, according to the American Society for Metabolic and Bariatric Surgery (ASMBS). However, the nutrient malabsorption disorders that it causes have led to the search for alternatives. One of the surgical options that has been suggested as an alternative for minimising the effects on bone metabolism is tubular gastrectomy (TG), commonly known as "sleeve gastrectomy", a restrictive bariatric technique in which most of the stomach is removed, including the *fundus* and body, from the antrum to the angle of His. The advantages of this technique include shorter surgery time, less surgical risk and a reduced risk of vitamin deficiencies, anaemia, and possible osteoporosis by not performing an intestinal bypass. There is currently little data on the effects of TG and the comparison with GBRY on bone metabolism, bone mineral density (BMD) and fracture risk.

The aim of this randomised prospective pilot study is to compare the impact of these two surgical techniques on mineral metabolism and bone mass in patients undergoing bariatric surgery.

Patients and methods

Study design

Randomised, prospective, pilot study

Scope

Hospital del Mar, Barcelona

Patients

Inclusion criteria

Morbidly obese women between 18-55 years of age. Body mass index (BMI) greater than 40 or a BMI greater than 35 with additional co-morbidity: Type 2 DM, sleep apnoea, obesity-hypoventilation disorder, severe arthropathy in weight-bearing joints, cardiovascular disease and dyslipidemia.

Exclusion criteria included the following: obesity secondary to endocrine diseases and psychiatric disorders or other diseases that formally contraindicate surgery.

The study was approved by the Ethics Committee of the Hospital del Mar/Municipal Institute for Medical Research. All patients signed an informed consent after being fully

informed of the risks and benefits of each type of surgical intervention (SI).

Surgical technique

All procedures were performed using laparoscopy and by the same surgical team. In the TG, a longitudinal tubulisation of the stomach was performed from 5 cm proximal to the pylorus to the angle of His using a 36 French gauge orogastric tube placed along the lesser curvature of the stomach. The GBRY technique consists of performing a 15-30 cc gastric reservoir in the subcardial area with a 150 cm antecolic antegastric Roux-en-Y alimentary loop, a 25 mm circular-stapled gastrojejunostomy and an exclusion of the first 50 cm of jejunum. All patients received dietary instructions and a daily multivitamin containing 600 UI/ml cholecalciferol.

Bone mass measurement

Bone mass measurements were made using densitometry using dual-photon absorptiometry (DEXA) with dual-beam X-ray power supply, employing a HOLOGIC QDR 4500SL densitometer with APEX® software version 12.7.3 (Hologic, Walthman, Massachusetts, USA). BMD was measured at the lumbar spine L2-L4 (LS), femoral neck (FN), total hip (TH) and distal end of the radius, at the third proximal (1/3 PR) and at the ultradistal site (UD). The measurements were made within the three months prior to and twelve months after SI. We followed the criteria of the World Health Organization (WHO) for categorising patients as: normal for T-scores above -1 standard deviation (SD), osteopaenia for T-scores between –1.0 and –2.5 SD and osteoporosis for T-scores below –2.5 SD.[4]

For assessing prevalent vertebral fractures, a conventional x-ray was performed on the dorsal and lumbar spine and the presence of a fracture was considered when there was a greater than 20% decrease in any of the anterior, middle or posterior heights with respect to the adjacent vertebra, following Genant's semiquantitative criteria.[5]

Biochemistry and bone turnover markers

Analytical determinations were performed of total serum calcium (Ca), phosphorus (P), 25 hydroxy-vitamin D (25-OH Vit D) and intact parathyroid hormone (PTH) within three months prior to and 12 months after SI. Ca and P were measured by colorimetry using a Roche MODULAR® ANALYTICS D/P autoanalyser (Interseries coefficient of variation <4.6% and <5%, respectively), 25-OH Vit D by means of chemiluminescent immunoassay (CLIA) with a DiaSorin LIAISON® autoanalyser (interseries coefficient of variation <16%) and PTH by means of solid-phase chemiluminescent immunoassay with a Siemens IMMULITE® 2000 autoanalyser (interseries coefficient of variation <8%).

The MBRs were determined: N-telopeptide (NTx) and bone formation in bone alkaline phosphatase blood (BAP). NTx was measured in fresh urine in the morning using amplified chemiluminescence immunoassay in the VITROS ECi® autoanalyser of Ortho-Clinical-Diagnostics (interseries coefficient of variation <12%) and BAP by means of chemiluminescence immunoassay with the Beckman Coulter Access® autoanalyser (interseries coefficient of variation <6%).

Statistical analysis

We used the Student's t-test and analysis of variance (ANOVA) for the continuous variables. We performed a multiple regression analysis for age, preoperative weight, weight loss at 12 months and type of SI variables to analyse their influence on the changes in the dependent variable BMD.

The study was considered a pilot, starting with the hypothesis that we would observe a difference in bone loss between the two techniques of at least 5%. Therefore, in order to later calculate sample size for a subsequent prospective study, we decided that a group of 12 patients who had undergone the two surgical techniques (six for GBRY and six for TG) would be sufficient. The sequence of treatment allocation was generated in the randomisation module of the True Epistat statistical software. Statistical analysis was carried out using SPSS 13.0 for Windows. All results are presented with mean±SD.

Results

Patients

After the selection process was complete, 15 patients were included in the study, 8 in TG and 7 in GBRY. The mean age was 47.8±9.0 with a BMI of 43.3±3.4. Table 1 shows the patient characteristics according to the bariatric surgery technique used. Patients included in the GBRY had a preoperative weight significantly higher than those included in the TG, although their BMI was not significantly different. Also, weight loss at 12 months was higher in the GBRY group (Table 1).

None of the patients had complications during or after surgery.

Bone mass

Table 2 shows the BMD results prior to the SI. There were no significant differences between the two groups in any of the locations measured. Following the WHO classification criteria prior to the SI, all patients met the densitometry criteria for normality except for two patients in the TG group who had osteopaenia in LS and one in LS and FN.

The paired results between the baseline BMD measurement before and at 12 months of the SI, considering both groups as a whole, showed significant losses in the LS, FN, TH and UD locations, while at the 1/3 PR level there were no significant differences (Table 3).

When each of the SI types were considered separately, significant bone loss was also observed with TG and GBRY at

Table 1 – Patient characteristics for each of the two bariatric surgery techniques

	TG (n=8) Mean±SD	GBRY (n=7) Mean±SD	P
Age, years	49.63±9.6	45.86±8.6	NS
Height, cm	158.3±0.05	165.0±0.09	NS
Preoperative weight, kg	108.9±6.3	116.7±5.5	.025
Preoperative BMI	43.5±3.2	43.1±3.9	NS
Weight at 12 months, kg	76.5±8.2	71.4±8.2	NS
BMI at 12 months	30.5±2.6	26.2±2.7	.01
Weight difference, kg	–32.4±8.7	–45.3±9.1	.015
BMI difference	–13.0±3.6	–16.8±4.1	NS

BMI indicates body mass index; GBRY, gastric bypass Roux-en-Y; NS, non-significative; SD, standard deviation; TG, tubular gastrectomy.

Table 2 – BMD prior to SI according to each type of SI*

	Mean±SD	P
BMD LS		
TG	1.013±0.13	
GBRY	1.100±0.10	NS
BMD FN		
TG	0.883±0.09	
GBRY	0.869±0.04	NS
BMD TH		
TG	1.009±0.07	
GBRY	1.054±0.07	NS
BMD 1/3 Radius		
TG	0.661±0.06	
GBRY	0.695±0.07	NS
BMD Ultra		
TG	0.415±0.03	
GBRY	0.433±0.02	NS

BMD indicates bone mineral density; FN, femoral neck; GBRY, gastric bypass Roux-en-Y; LS, lumbar spine L2-L4; NS, non-significative; SD, standard deviation; SI, surgical intervention; TG, tubular gastrectomy; TH, total hip; Third proximal of radius (1/3 PR); UD, ultradistal of radius.
*Values expressed in g/cm^2.

the LS, FN and TH levels while at the radius level there were no significant differences (Table 3).

In terms of percentage bone loss, in general, a lower bone loss was observed for TG when compared to GBRY but without reaching statistical significance in any of the locations. In the LS, the percentage of loss was 4.6%±4.4 and 6.3%±5.4 in the TG and GBRY, respectively. In the hip, the percentage of loss was 8.3%±5.2 and 10.8%±3.8 and in the TH it was 7.1%±3.7 and 11.1%±6.3 in the TG and the GBRY, respectively. In the radius, the percentage of bone loss in the 1/3 PR was 0.2%±9.3 and 0.1%±7.5 and at the UD level was 3.2%±6.3 and 5.9±8.2 in the TG and GBRY, respectively.

In the multivariate analysis, the variables of age, preoperative weight, percentage of weight at 12 months and the type of SI showed no significant relationship with BMD loss in any of the locations analysed.

In the dorsal and lumbar spine x-rays, no vertebral fractures were found in any of the patients before the SI or 12 months afterwards.

Biochemistry and bone turnover markers

Table 4 shows the results for Ca, P, 25-OH Vit D and PTH prior to and 12 months after SI. There were no significant differences between the two groups in any of the parameters analysed before the SI. The Ca, P and PTH values were within normal ranges at 12 months after the SI and there were no significant differences with respect to the values prior to the SI. The 25-OH Vit D values increased significantly at 12 months only after TG. When the paired results were compared to the baseline MBR values prior to and 12 months after the SI, considering both groups together, there was a significant increase in the level of the resorption marker NTx whereas there were no significant changes for BAP (Table 5). When we compared the MRO prior to and at 12 months for each of the two types of SI, there was a significant increase for NTx in both types of SI and a significant decrease in BAP for only TG (Table 5).

Discussion

The relationship between weight, BMI and risk of low bone mass and osteoporotic fracture is well known. Ravn et al,[6] in a prospective study of postmenopausal women, showed the relationship between low BMI and bone mass and how losing weight is significantly correlated with the loss of bone mass. Furthermore, a recent meta-analysis of the main epidemiological studies showed that a high BMI correlates with a lower risk of fractures and as such with a protective capacity.[7] A low BMI, on the other hand, is related to a greater risk of osteoporotic fractures, for example, with a BMI of 35, the risk of osteoporotic fractures decreases by 26% while a BMI of 20 increases the risk by 27%.

The changes that bariatric surgery causes in bone metabolism are also known.[8-11] It is believed that during the

Table 3 – BMD before and at 12 months after the SI, jointly and for each type of SI*

	Both mean±SD	P	TG (n=8) mean±SD	P	GBRY (n=7) mean±SD	P
BMD L2-L4						
Baseline	1.054±0.12		1.013±0.13		1.100±0.10	
12 months	0.995±0.10	.001	0.967±0.125	.033	1.026±0.07	.022
BMD FN						
Baseline	0.876±0.07		0.883±0.09		0.869±0.04	
12 months	0.792±0.06	.0001	0.808±0.08	.003	0.774±0.04	.0001
BMD TH						
Baseline	1.030±0.07		1.009±0.07		1.054±0.07	
12 months	0.933±0.06	.0001	0.936±0.07	.001	0.929±0.05	.005
BMD 1/3 Radius						
Baseline	0.677±0.07		0.661±0.06		0.695±0.07	
12 months	0.673±0.06	NS	0.656±0.05	NS	0.693±0.06	NS
BMD Ultra						
Baseline	0.423±0.03		0.415±0.03		0.433±0.02	
12 months	0.404±0.04	.03	0.401±0.04	NS	0.407±0.04	NS

BMD indicates bone mineral density; FN, femoral neck; GBRY, gastric bypass Roux-en-Y; LS, lumbar spine L2-L4; SD, standard deviation; SI, surgical intervention; TG, tubular gastrectomy; TH, total hip; Third proximal of radius (1/3 PR); UD, ultradistal of radius.
*Values expressed in g/cm^2.

Table 4 – Biochemistry and hormones prior to and 12 months after SI

	Before	12 months
Ca (mg/dl)		
Sleeve	9.3±0.3	9.4±0.2
By-pass	9.4±0.4	9.4±0.3
P (mg/dl)		
Sleeve	3.4±0.5	3.9±0.2
By-pass	3.3±0.6	3.7±0.5
25-OH VitD (ng/ml)		
Sleeve	24.3±16.0	37.4±19.5*
By-pass	20.1±12.5	24.4±17.8
PTH (pg/ml)		
Sleeve	50.1±25.3	43.8±12.8
By-pass	46.0±26.1	37.0±14.7

25-OHVitDindicates25hydroxy-VitaminD;Ca,calcium;P,phosphorus; PTH, intact parathyroid hormone; SI, surgical intervention. *P=.03.

first year a patient can lose up to 4.5% of the BMD measured in LS and up to 9.27% in TH.[12] These data have led to the search for alternatives to the more invasive bariatric surgery such as by-pass surgery and efforts to reduce this loss of bone mass related to the reduction in BMI.

The results of this study show a significant loss of BMD in LS, FN and TH with both SI techniques evaluated (GBRY and TG) with a higher percentage of loss in the hip than in the spine, results similar to those observed by other authors.[12]

This difference in the percentage loss of BMD in the hip may be explained by the fact that the hip has a greater cortical bone component than trabecular. However, this hypothesis would not be confirmed by the changes in BMD at the distal end of the radius, especially in 1/3 PR, which is a particularly cortical region.

When comparing the two techniques, the results show a lower percentage loss of bone mass with TG than with GBRY at the lumbar spine level and at the hip, although this difference was not statistically significant. The multivariate analysis has also shown that neither the type of SI or the weight loss achieved at 12 months influences the loss of BMD. As for the length of the Roux-en-Y loop, Gleysteen JJ conducted a study that compared various loops of different lengths: 41-61 cm, 130-160 cm and 115-250 cm. No differences were found in resulting weight loss, either in the short or long term, between obese patients undergoing intervention with longer loops. Loops shorter than 61 cm, however, did result in weight loss.[13]

The advantages of TG over GBRY are a shorter surgery time, lower surgical risk by avoiding anastomosis, preservation of the pylorus thus avoiding dumping, unaltered gastrointestinal motility and the absence of an intestinal bypass, which avoids the risk of vitamin deficiencies, lack of calcium absorption and an excessive loss of BMD.

However, the results of this study show that BMD loss also occurs although with a lower loss percentage. Additionally, the findings of the MRO show an increase in resorption and a decrease in bone formation with both SI, although BAP does not become significant in GBRY, probably due to the problem of sample size.

The results of similar studies without gastric bypass show increases in the MRO of resorption and also a decrease in

Table 5 – MRO prior to and 12 months after SI, jointly and separately for each SI type

	Both SI (Mean±SD)	P	TG (n=8) (Mean±SD)	P	GBRY (n=7) (Mean±SD)	P
BAP (mcg/l)						
Baseline	15.4±3.2		17.2±2.2		13.2±3.2	
12 months	13.8±3.9	NS	14.4±1.6	.025	13.1±6.1	NS
NTx (nmol/mmolCreat)						
Baseline	45.8±18.8		40.8±16.6		50.0±20.9	
12 months	102.1±36.5	.0001	98.0±38.5	.013	105.6±37.9	.004

BAP indicates bone alkaline phosphatase; GBRY, gastric bypass Roux-en-Y; NTx, N-telopeptide; SD, standard deviation; SI, surgical intervention; TG, tubular gastrectomy.

leptin measured in the blood when using the technique of vertical banded gastroplasty.[9] This finding may partly explain the results of our study in which a similar BMD loss occurred for both surgical techniques and is therefore more related to weight loss than to absorption disorders and changes in the nutritional and hormonal parameters of calcium metabolism.[11,14] Along these lines, we note the close relationship suggested by some authors between fat and bone,[15] with a clear increase in osteoclastic activity even in healthy postmenopausal women who lose weight.[16]

From the hormonal standpoint, there is well-established relationship between glucose, calcitonin and parathyroid hormone,[17] all of which are mediated by changes produced from glucose, proteins and fat through insulin and other substances such as amylin.[18] In our study, levels of 25 OH Vit D increased significantly with TG and remained unchanged with GBRY, confirming the results of other studies in which this SI technique was related to a need for supplementation with high doses of vitamin D to prevent secondary hyperparathyroidism that promotes bone resorption and loss of bone mass.[19-21] Valdera et al[19] performed a retrospective study that reviewed the long-term impact, between 1-5 years, on bone metabolism with GBRY. They found a clear correlation between levels of C-telopeptide, a marker of bone resorption similar to NTx, and PTH levels. These data reflect the persistence of increased bone resorption with secondary hyperparathyroidism continued for a long period after bariatric surgery, thus reaffirming the need for vitamin D supplementation or at least determining the levels of 25 OH Vit D on a continuous basis even several years after GBRY surgery.

Adipocyte cells are relevant in this entire process mainly because their regulation depends largely on leptin, which has the ability to encode both cells involved in the process.[22]

The mechanisms by which bone mass loss is produced following bariatric surgery are diverse and do not depend solely on the possible poor absorption of calcium and vitamin D. Weight loss causes a decrease in leptin levels[23] resulting in decreased production of osteoprotegerin (OPG) and increased resorptive activity of osteoclasts due to OPG not producing a blocking effect on RANKL.

Leptin, in addition to its ability to regulate the osteoblast differentiation system,[24] has leptin receptors on the osteoblasts and also intervenes in the osteoclast regulation system OPG-RANK-RANKL. Bruno et al[25] have recently shown a decrease in leptin levels correlated with BMD loss and changes in the patients' MRO with GBRY at 18 months of SI.

One of the limitations of this pilot study is the sample size. The results of this study need to be confirmed through a similarly designed study but with a greater sample size in order to include the preventive treatment for bone mass loss in patients undergoing TG in medical protocols as a recommendation. Leptin levels in the blood also need to be analysed in order to confirm the hypothesis of its correlation with BMD loss.

In conclusion, this study shows that there is a lower, although not significant, bone mass loss with TG than with GBRY, which gives rise to the recommendation for a preliminary evaluation and monitoring of BMD and parameters related with bone metabolism regardless of the surgical technique employed. In addition, it is recommended to evaluate the introduction of anti-resorptive agents separate from the necessary nutrients such as vitamin D.

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Conflicts of interest

The authors affirm that they have no conflicts of interest.

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