MERIT RESEARCH JOURNALS
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Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 3(5) pp. 183-190, May, 2015
Available online http://www.meritresearchjournals.org/mms/index.htm

Original Research Article

Changes in Bone Metabolism/Mineral Density Twelve Months after Laparoscopic Sleeve Gastrectomy in Morbidly Obese Pre-menopausal Women

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Abstract

Bariatric surgery for weight loss may result in nutritional deficiencies affecting bone metabolism. Laparoscopic Sleeve gastrectomy (LSG) is expected to have fewer nutritional sequelae. However, there is little information about bone metabolism after LSG. This study aimed to evaluate changes in bone metabolism and mineral density in morbidly obese women six months after LSG. Thirty two morbidly obese, premenopausal women were evaluated at baseline and 12 months after LSG for: BMD by dual-energy X-ray absorptiometry, serum collagen-type I N telopeptide (NTX-s) and N-terminal propetide of collagen type I (PINP) as markers of bone metabolism, 25 hydroxyvitamin D and intact parathyroid hormone (iPTH). Vitamin D was low in 46.8% and iPTH was high in 34.3% with elevated NTX-s and PINP. Twelve months after LSG, there was a significant increase in vitamin D, a significant decrease in iPTH and in markers of bone metabolism that correlated with weight loss. BMD was not significantly changed in spine and radius but minimally decreased in femur neck. Significant vitamin D deficiency and increase in bone turnover markers exist in morbidly obese premenopausal women. LSG was shown to improve vitamin D status and bone turnover owing to the significant weight loss with a negligible effect on BMD.

Keywords: Bone metabolism, laparoscopic sleeve gastrectomy, mineral density

INTRODUCTION

Currently, overweight and obesity represent major health hazards worldwide (James, 2008) Morbid obesity has historically been viewed as having a protective effect against the development of osteoporosis but it has an important impact on mineral and bone metabolism (Casagrande et al., 2010). Only about 5 % of patients undergoing medical treatment for severe or morbid obesity are able to achieve and maintain significant weight loss. Bariatric surgery has been shown to be the most effective method for achieving this goal (Balsiger et al., 2000) and may furthermore improve associated medical conditions (Buchwald et al., 2004; Maggard et al., 2005; Colquitt et al., 2009). However, it may also result in several health complications related to nutritional deficiencies, including bone metabolism (Wucher et al., 2008). Restrictive procedures, such as laparoscopic sleeve gastrectomy (LSG), do not involve modification of the small bowel, so that one may expect a lower rate of postoperative nutritional sequelae (Ruiz-Tovar et al., 2012). Prospective studies in subjects who have undergone LSG have shown conflicting results when they assessed bone status using bone mineral density (BMD) (Nogués et al., 2010; Pluskiewicz et al., 2012; Ruiz-Tovar et al., 2013; Carrasco et al., 2014) . Although BMD assessment using dual-emission X-ray absorptiometry (DXA) is used in the diagnosis of osteoporosis, a low BMD is not the only risk factor for fractures, but is in fact an inefficient tool by itself for identifying those at high risk

of fractures (Kanis et al., 2008). Abnormal DXA results do not always represent primary osteoporosis, they often represents secondary bone disease. When secondary bone disease is present, it should become the focus of treatment interventions (Williams, 2011).

Studies looking at osteoclast and osteoblast function after gastric bypass have shown a substantial increase in osteoclast and osteoblast function 6, 12, and 18 months after surgery (Bruno et al., 2012). Collazoa-Clavell et al. (2004) noted the development of metabolic bone disease in greater than 70% of patients have undergone a malabsorptive procedure. Another study detected increased markers of bone resorption as soon as 8 weeks after bariatric surgery (Parikh et al., 2004). However, there is little information about the evaluation of bone metabolism in patients undergoing LSG.

Considering the above observations, we conducted this study aiming to evaluate changes in bone metabolism and mineral density in morbidly obese women 12 months after LSG.

SUBJECTS AND METHODS

We performed this study of all morbidly obese premenopausal women undergoing LSG between March 2012 and December 2013. They were recruited from the obesity clinic of Specialized Medical Hospital, Mansoura University and submitted to LSG in order to have their body weight reduced. A total of thirty two women (mean age 30.37 ± 6.74 years; with body mass index (BMI) ≥40 kg/m^2 were included. After an informed consent was obtained, medical history and physical examinations were performed for each subject by an endocrinologist. Weight (kilograms) and height (meters) were measured according to standardized procedures (Lohman, 1988) and BMI (kilograms per square meter) was calculated. Four women had type 2 diabetes and they were receiving metformin only. Two women were hypertensive. None of the examined women presented with diseases which could have potentially influenced their bone metabolism such as gut malabsorption or gastric, kidney or liver diseases. None of the participants was taking medications known to affect bone or mineral metabolism (e.g. glucocorticoids, calcium supplements, vitamin D derivatives).

Bone Densitometry

Bone mineral density (BMD; grams per centimeter^2), was measured by dual-energy X-ray absorptiometry (DXA) using a Lunar DPXL densitometer (Lunar, Madison, WI; version 1.30 software) (Jebb, 1997). The machine was calibrated, according to the manufacturer's recommendations. BMD was tested for total lumbar spine (LS; L2–L4), and femoral neck (FN) , distal radius and for total body to get a Z score . Low bone density was defined as a Z score lower than –2.0 in premenopausal women (Baim et al., 2008).

Laboratory Determinations

Sampling

Eight ml venous blood sample was withdrawn from all participant after fasting 6-8 hours and distributed as follow: One ml of blood was added to tube containing K2EDTA for Complete Blood Picture, two ml into citrated tube, rapidly separated by cooling centrifuge and stored at – 20 C for iPTH assay and the rest of the sample, 5 ml was allowed to clot for 10 minutes and the serum was separated by centrifuged into two aliquots, one used for determination of liver profile, serum creatinine, fasting plasma glucose, calcium and phosphorus while the other aliquot was stored at – C until collagen-type I N telopeptide (NTX-s) and N-terminal propetide of collagen type I (PINP)

Methods of assays

1- Serum glucose, ALT, aspartate Transaminase, total bilirubin, albumin, creatinine, calcium and phosphorus were measured on a Cobas Integra 400 chemistry analyzer (Roche Diagnostics, Basel, Switzerland) using commercially available reagents.
2- CBC was measured using CELL-DYN Emerald cell counter, ABBOTT, Germany.
3- Intact PTH was measured by ELISA using Genway Biotech, San Diego, USA (Habener and Potte, 1978)
4- Collagen-type I N telopeptide (NTX-s) was measured by competitive enzyme-linked immunosorbent assay using the Osteomark NTx® serum test (Whampole Laboratories Inc., Princeton, New Jersey, USA) (Kanakis et al., 2004).
5- N-terminal propetide of collagen type I (PINP) by enzyme immunoassay using Uscn life science Inc, USA (Koivula et al., 2012).
6- 25 hydroxyvitamin D (25-OH D) was assayed by ELISA using DRG International, Inc, Germany (Armas et al., 2004).
High iPTH was defined as iPTH of more than 65 pg/mL (Ashraf et al., 2009). Low serum calcium was defined as values lower than 8.5 mg/dL (Hamoui et al., 2004). Low serum 25-OH-vitamin D was defined as values lower than 20 ng/dL (Lee et al., 2008).

Surgery

The patients were operated at the Gastrointestinal surgical Center of Mansoura University. All the

Table 1. Baseline clinical and some metabolic characteristics of the subjects studied

Characteristic	
Age (years)	30.37 ± 6.74
Weight (kg)	147.21± 23.99
BMI (kg/m2)	53.88 ± 8.28
Waist circumference (cm)	124.5 (8.75)*
Systemic arterial hypertension	2(6.25%)
Diabetes mellitus	4(12.5%)
Low serum albumin	1(3.1%)
Low serum 25-OH-vitamin D	15(46.8%)
High iPTH	11(34.3%)
Low serum Ca	3(9.3%)
Low total BMD by DEXA Z score	1(3.1%)

Results are expressed as mean ± SD or number of patients (percent of patients) *median (interquartile range)
BMI body mass index; iPTH parathyroid hormone; BMD bone mineral density

participants underwent LSG as a restrictive bariatric procedure in which a vertical gastrectomy that leaves a gastric tube along the lesser curve of the stomach was done.

The technique involves complete mobilization of the greater curvature together with posterior mobilization of the phreno-gastric ligament and angle of His. Then, a 38 Fr gastric calibration tube is inserted and guided over the dorsal side of the stomach down to the pylorus, then starting of the stapling technique, the first stapler is fired at a point 4-6 cm proximal to the pylorus. Other, 4-5 staplers are fired to finish the gastric sleeve.

After surgery, patients were encouraged by their surgeon and primary care physician to play sports or to do outdoor activities in all seasons, vitamin D supplements were not prescribed. Percentage weight loss was calculated according to the formula: (baseline body weight - body weight 6 months postoperative / baseline body weight) x100. Percentage excess weight loss (%EWL) was also calculated according to the formula: %EWL = (Initial weight -Final weight/ initial weight-Ideal body weight) x 100. Ideal body weight was captured from Metropolitan life tables (Deitel et al., 2007). Patients were re-evaluated by the same clinical, laboratory and radiological data 12 months postoperatively.

Statistical Analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Chapiro test was used as a test of normality of variables. Results were expressed as mean± standard deviation for normally distributed variables or median and interquartile range for non-normally distributed variables. The differences between results, obtained at baseline and at follow-up, were established, using Paired Student's t test or Wilcoxon test. P values below 0.05 were considered as statistically significant. A correlation analysis at baseline and follow-up was done by Pearson's or Spearman's test, whichever was appropriate. Individual differences between baseline and follow-up measurements, expressed as change or Δ of the measured variables, were established, and a correlation analysis was performed for them, using also Pearson's or Spearman's correlation test

RESULTS

The general clinical characteristics of the subjects studied were summarized in Table 1. The mean age was 30.37 ± 6.74. All participants were morbidly obese (BMI of 53.88±8.28 kg/m2), with median waist circumference of 124.5cm. There were two patients with diabetes mellitus (12.5%) and one with hypertension (6.25%). However, there was a high rate of low vitamin D subjects (46.8%) and high iPTH (34.3%). Three women had low Ca and only one had low total body Z score <-2 by DEXA.

Table 2 showed correlation between bone metabolism markers with some clinical data and vitamin D at baseline: vitamin D had significant negative correlation with waist circumference, body weight and BMI. Parathyroid hormone had significant positive correlation with body weight and BMI. Bone metabolism markers were significantly correlated with body weight, BMI and with vitamin D.

Baseline and 12 months postoperative data were summarized in Table 3.

The mean percentage weight loss was 25.34±5.55 % and the mean percentage excess weight loss (EWL) was 48.72±8.89% with a decrease of mean body weight from 147.21±23.99 to 109.5±17.61 ($p<0.001$). There were no

Table 2. Correlation between baseline bone metabolism markers with some clinical data and vitamin D

		Age	Waist circumference	bodyweight	BMI	Vitamin D+
Vitamin D+	*Correlation coefficient*	-0.149	-0.554**	-0.719**	-.775**	-
	p	0.417	0.001	<0.0001	<0.0001	
iPTH	*Correlation coefficient*	0.190	0.335	0.421*	0.539**	-0.421*
	p	0.298	0.061	0.016	0.001	0.016
PINP	*Correlation coefficient*	0.273	0.421*	0.406*	0.64**	-0.421**
	P	0.13	0.016	0.021	<0.0001	0.016
NTX-s	*Correlation coefficient*	0.121	0.397*	0.429*	0.665**	-0.377*
	p	0.51	0.025	0.014	<0.0001	0.037

BMI: body mass index; iPTH: parathyroid hormone; PINP: N-terminal propetide of collagen type I; NTX-s Serum collagen-type I N telopeptide
*Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)
+Correlation of vitamin D with variables was done by Spearman's test

Table 3. Baseline and 12 months after LSG values for weight, body composition, biochemical variables and bone mineral density

	Baseline (No 32)	12th months (No 32)	*P* value	Normal range
BMI	53.88± 8.28	40.21±6.5	<0.0001	
Body weight	147.21±23.99	109.5±17.61	<0.0001	
Δ body weight		37.71±11.88		
% weight loss		25.34±5.55		
% EWL		48.72±8.89		
hemoglobin(g/dL)	12.28±1.19	12.18±1.29	0.49	
Serum albumin	4.35±0.34	4.23±0.21	0.144	3.5-5.5
Fasting glucose	110.71±27.74	99.81±8.67	0.02	70-110
Serum Ca	9.88±0.8	9.94±0.74	0.198	8.5–10.5
Serum ph	3.99±0.41	4.06±0.36	0.027	3-4.5
iPTH (pg/mL)	49.9±17.03	42.5±12.94	<0.0001	10-55
25-OH-vitamin D (pg/dL)*	24.5(22.63)	43.5(24.25)	<0.0001	30-75
PINP(ng/mL)	71.8±19.04	69.01±18.56	0.001	19-83
NTX-s (nM BCE)	21.41±6.33	15.58±6.37	<0.0001	6.2-19
Spine BMD (g/cm2)	1.119±0.27	1.122±0.271	0.4	
FN BMD (g/cm2)	1.019±0.168	1.015±0.167	0.04	
Radius BMD (g/cm2)	0.599±0.111	0.597±0.11	0.09	

Results are expressed as mean ± SD * median (interquartile range)
BMI: body mass index; EWL: excess weight loss; iPTH: parathyroid hormone; BMD: bone mineral density; PINP: N-terminal propetide of collagen type I; NTX-s Serum collagen-type I N telopeptide, nM BCE: nM bone collagen equivalents

significant changes in mean hemoglobin, albumin or Ca. Fasting blood glucose decreased from 110.71±27.74 to 99.81±8.67 (p=0.02). Vitamin D showed a significant increase and PTH presented a significant decrease, when comparing pre- and postoperative values (p<0.001). Serum collagen-type I N telopeptide (NTX-s) as a marker of bone resorption and serum N-terminal propeptide of type 1 procollagen (PINP) as a marker of bone formation decreased significantly 12 months postoperative (p<0.001 and p=0.001 respectively. There

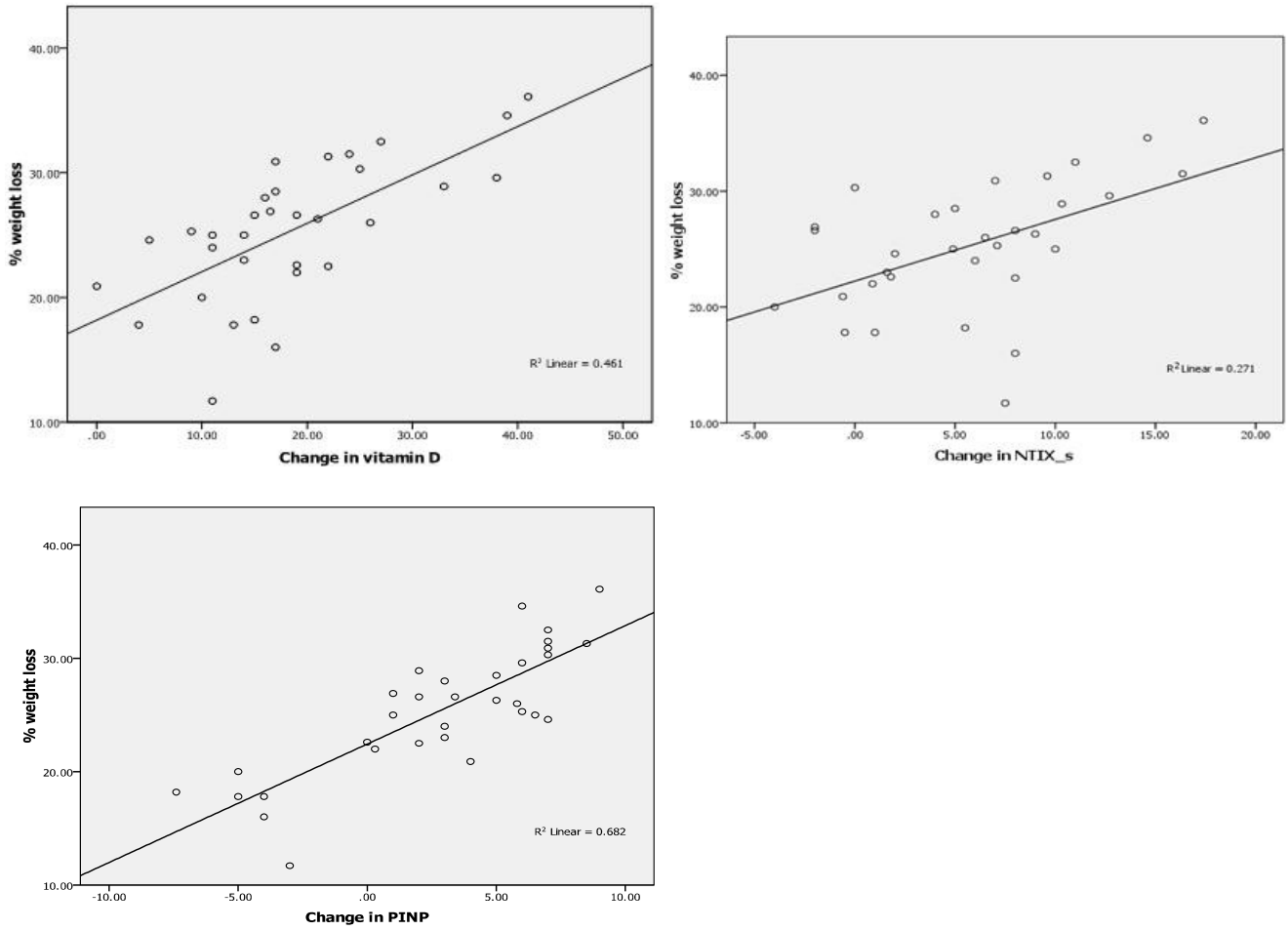
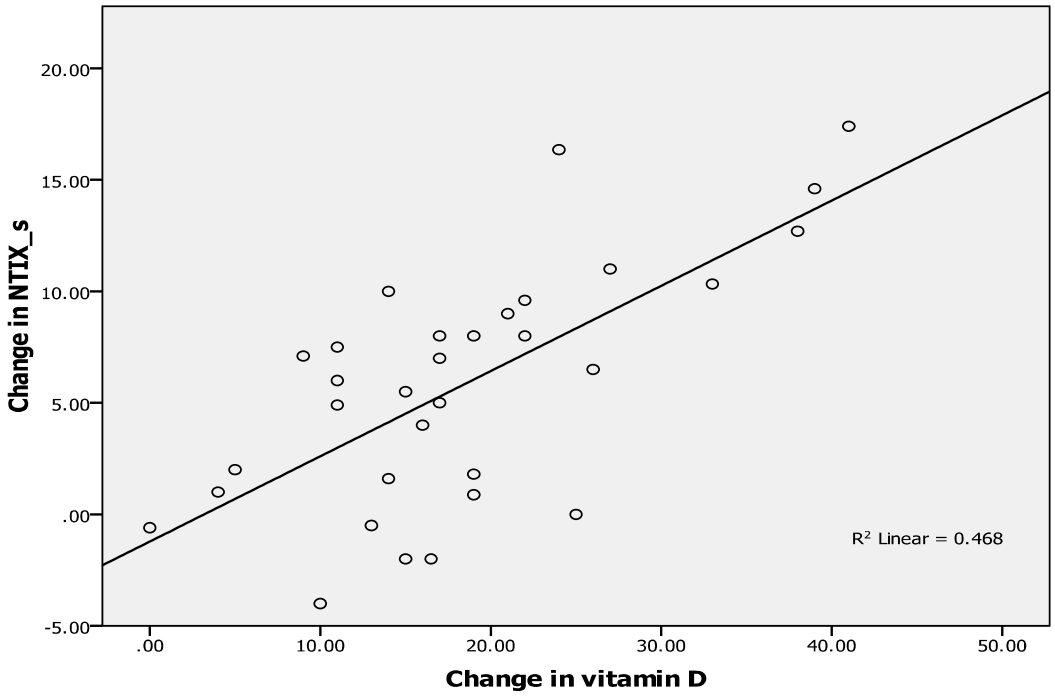


Figure 1. Correlation between % weight loss and changes in vitamin D, NTX-s and PINP



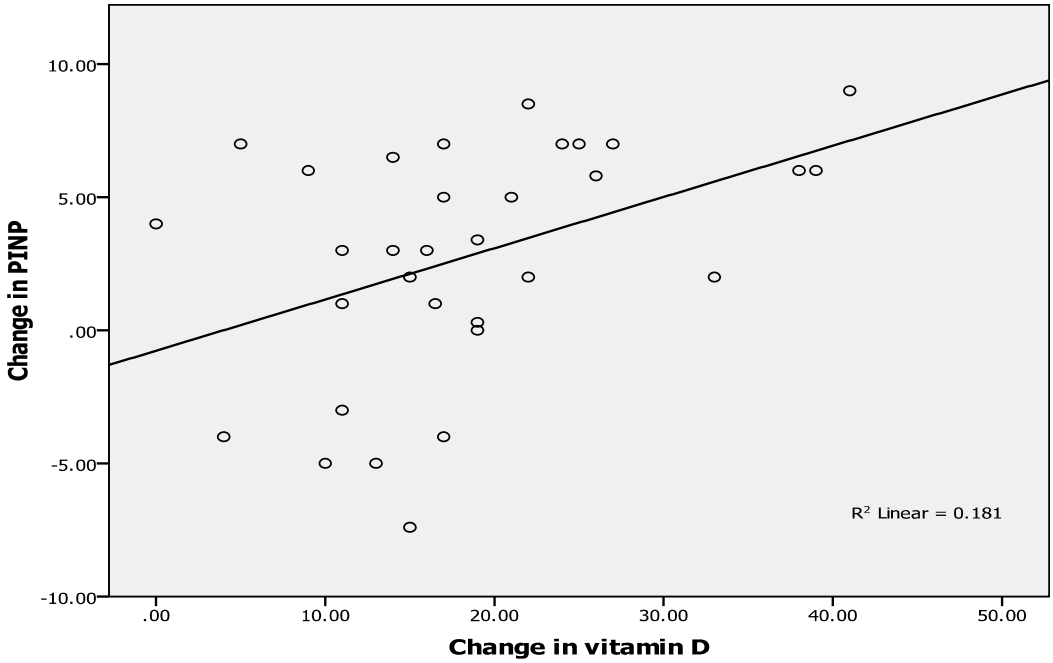


Figure 2. Correlation between changes in vitamin D and changes in NITX_s and PINP

was a reduction in BMD at the femoral neck (p=0.04).There was no significant change in BMD at the spine or the radius (p=0.4 and 0.09) respectively.

Figure 1 showed correlations between changes in vitamin D (a), NTX-s(b), and PINP (c) with percentage weight loss 12 months postoperatively. R^2 was 0.461, 0.271 and 0.682 respectively. Figure 2 showed that changes in NTX-s (a) and PINP(b) correlated with changes in vitamin D.

DISCUSSION

This study, evaluating 32 morbidly obese women candidates for LSG, demonstrated that successful results of body size reduction were possible. The mean EWL of 48% was noted in our group, which is in the average in comparison to the results of 40 % (Weiner et al., 2007) and 55% (Bohdjalian et al., 2010) presented by previous studies.

At baseline in 46.8% vitamin D deficiency was found and elevated PTH in 34.3 % with a significant negative correlation between vitamin D levels and baseline BMI. Other authors reported low 25-hydroxyvitamin D in 25.4 %(Ernst et al., 2009), 57.4% (Gemmelet al., 2009) and 68.1% (Flancbaum et al., 2006) of their patients. The difference between the values could be explained by factors that interfere with vitamin D metabolism such as the differences in age, race, sex, and body fat percentage (Lee et al., 2008). Insufficient exposure to sunlight may also be regarded as a factor contributing to Vitamin D deficiency. Despite sunlight availability throughout the year in our country, inadequate sunlight exposure in morbid obese could be considered secondary to little or complete absence of physical activity and psychological liability that make these patients prefer living indoors (Gehrer et al., 2010). However, low serum vitamin D concentration in morbidly obese individuals with the associated systemic inflammation does not necessarily indicate that the body stores are depleted (Aasheim et al., 2008). Sequestration of vitamin D in fat, and a physiologic adaptation to the need for more bone mass to support increased weight may explain vitamin D deficiency in morbidly obese individuals (Lee et al., 2008; V et al., 2008). The results of this study indicate that levels of vitamin D tend to increase and PTH to decrease significantly. After 12 months we had only 2 patients with vitamin D deficiency (6.2%) and three with elevated PTH (9.3%). Ruiz-Tovar et al, (2013) demonstrated similar results and after longer term observation (one and two years). Changes in vitamin D level in our study were found to have significant correlation with percentage weight loss. Therefore, the significant increase in vitamin D could be attributed to the significant weight loss that released the sequestrated vitamin D from adipose tissue.

This study showed that twelve months after LSG, DEXA scan levels were not significantly changed at lumbar spine nor at the radius from the baseline levels, with a decrease of borderline significance at the femoral neck (p=0.04). Previous studies assessed bone status after LSG based on DEXA showed conflicting results. Carrasco et al. (2014) showed that loss of BMD was significant only for total body, while others reported a relatively modest decrease especially at the femoral neck (Pluskiewicz et al., 2012), Nogues et al. (2010) described a more pronounced decrease in BMD in femur than in

spine revealing that femur is a more sensible location for BMD changes. Only Ruiz-Tovar et al. (2013) reported progressive increase in BMD values for spine only but they did not examine the femur. These conflicting results could be related to different preoperative BMI, or to different postoperative weight loss, which would be consistent with the hypothesis that bone loss is an adaptation to the reduced load on the skeleton. It is to be noted that in our patients, despite the slight reduction in BMD observed at the femoral neck, its magnitude cannot be considered severe as there was no incidence of low BMD 6 months after surgery. We had one case of BMD Z score<2 SD who was already in this Z score range before surgery.

Abnormal DXA in a bariatric surgery patient, it often represents secondary bone disease due to nutritional deficiencies (Williams, 2011). Primarily restrictive procedures such as sleeve gastrectomy are associated with fewer incidences of nutritional complications as compared to more complex procedures such as gastric bypass and malabsorptive procedures (Gehre et al., 2010; Basfi-Fer et al., 2012). Therefore, to adequately evaluate bone metabolism after surgery, it is crucial to measure specific bone serum markers as well as DEXA. Markers of bone reabsorption are interesting to study in situations which could progress with bone loss, such as the postoperative period of morbidly obese patients (Eastell et al., 2000). Bone reabsorption markers, such as deoxypyridinoline and the cross-linked N-telopeptides and C telopeptides of type I bone collagen, have been introduced in order to be more specific markers for metabolic breakdown of bone collagen. Serum-based markers of bone turnover tend to show less variability when compared to urine-based markers (Eastell et al., 2000). At baseline our patients had increase in markers of bone turnover, characterized by increases in bone formation and resorption and there was a positive correlation between these elevated levels and BMI suggesting that patients with morbid obesity could experience higher bone turnover. In addition, the trend toward a significant negative correlation between these markers and vitamin D may represents an increased need for more calcium absorption. Casagrand et al.(2010) reported a significant increase in bone turnover markers in morbid obesity but there are very few studies that have evaluated bone turnover in morbidly obese individuals after barietric surgery especially after LSG. The results of this study demonstrated a significant decrease in NTX-s ($p>0.0001$) and a less decrease in the bone formation marker P1NP ($p=0.001$). These changes were found to have significant correlation with vitamin D increase and weight loss. So we can speculate that, with weight loss, the vitamin D sequestrated in the adipose tissue is freed and enters bloodstream and thus its serum level increases. Subsequently, vitamin D increases the intestinal absorption of calcium, decrease resorption of bone as a source of calcium. Although the improvement of vitamin D state and PTH could not be reflected clearly on BMD, we could demonstrate improvement in bone metabolism in the form of decrease in bone turnover as early as 12 months after LSG.

This study then provides evidence which suggests that LSG would be favored for morbidly obese patients with an existing diagnosis of osteoporosis or patients at high risk for osteoporosis, such as postmenopausal females and pediatric patients when bone anabolism is favored.

One of the limitations of this study is its application on women only, the reason for this was that only few males during the study period were encouraged to do surgical intervention to reduce their body weight so we could not get a comparable male group. In conclusion, significant vitamin D deficiency and increase in bone turnover markers exist in our morbidly obese pre-menopausal women. After 12 months, LSG was shown to improve vitamin D status and bone turnover owing to the significant weight loss with negligible effect on BMD.

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