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DETERMINING CHANGES IN BONE METABOLISM AFTER BARIATRIC SURGERY IN POSTMENOPAUSAL WOMEN

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Abstract

BACKGROUND: Accelerated bone loss is a known complication after bariatric surgery. Bone mineral density has been shown to decrease significantly after Laparoscopic Roux-en-Y gastric bypass (RYGB). Laparoscopic sleeve gastrectomy (SG) effects on bone density are largely unknown. This should be considered for those with increased preoperative risk for bone loss, such as postmenopausal females.

METHODS: This prospective clinical trial included postmenopausal patients, with BMI ≥ 35k/m^2, being evaluated for either RYGB or SG. Patients with history of osteoporosis, estrogen hormone replacement therapy, active smoking, glucocorticoid use, or weight > 295 pounds were excluded. Patients underwent DEXA scans preoperatively and one year postoperatively with measurement of total body bone mineral density (BMD) and bone mineral content (BMC) as well as regional site specific BMD and BMC.

RESULTS: A total of 28 patients were enrolled. 16 (57.1%) patients underwent RYGB and 12 (42.9%) patients underwent SG. Median preoperative BMI was 44.2k/m^2 (IQR 39.9, 46.6). Median change in BMI at 12 months was −11.3k/m^2 (IQR −12.8, -7.9). A significant reduction in total body BMC was seen when comparing preoperative measurements to postoperative measurements (2358.32 vs 2280.68 grams; p=0.002). Regional site BMC and BMD significantly decreased in the ribs and spine postoperatively (p=<0.02) representing the greatest loss in the axial

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DISCLOSURES
Dr. A. Daniel Guerron is an advisor for Levita and Phenomix, speaker for Gore and Medtronic, and proctor for Biom'up. Dr. Dana Portenier is and advisor for Medtronic, consultant for Medtronic and Intuitive, and speaker for Teleflex, Gore, Medtronic and Levita. Dr. Jin Yoo is a consultant for Gore, Medtronic and Novadaq, and a speaker for Teleflex, Stryker, Gore, Medtronic and Novadaq. Dr. Chan Park is a consultant for Gore and Teleflex. Dr. Andrew R Luhrs, Dr. Gerardo Davalos, Mr. Reginald Lerebours, Dr. Lawrence Tabone, Dr. Philip Omotosho, and Dr. Alfonso Torquati have no conflicts of interest or financial ties to disclose.

skeleton. Comparing those who underwent RYGB to SG there was no significant difference between the two groups when evaluating changes in total or regional site BMD.

CONCLUSION: Postmenopausal women were found to have decreased BMD and BMC after RYGB and SG, suggesting that high-risk women may benefit from postoperative DEXA screening. Further study is needed to determine the clinical significance of these findings. It is unknown if these changes in BMD are due to modifiable factors (Vitamin D level, activity level, hormone status, etc.), and whether BMD and BMC is recovered beyond one year.

Keywords

Bariatric; Weight Loss; Postmenopausal; Bone Metabolism; DEXA

INTRODUCTION

Metabolic surgery significantly improves glucose metabolism, decreases the risk of heart disease, and improves the quality of life [1–3]. An adverse effect of metabolic surgery is a decrease in bone mineral density (BMD). While obesity is protective against osteoporosis in postmenopausal women [4], the weight loss seen after bariatric surgery is known to lead to accelerated bone loss [5–8]. The loss of BMD after metabolic surgery has been attributed to a decreased vitamin D and calcium absorption. Historically operations like the jejunoileal bypass have resulted in significant osteoporosis and pathological fractures from this malabsorption [9]. Today patients are routinely placed on supplemental calcium and vitamin D after surgery to prevent bone loss. Despite aggressive calcium and vitamin D supplementation, patients undergoing RYGB have been shown to have a decrease in bone mineral density in the hip and femoral neck as early as one year after operation despite high dose vitamin D and calcium supplementation [10].

Historically the laparoscopic roux-en-y gastric bypass (RYGB) was the most commonly performed bariatric surgery; however, in 2013 the laparoscopic sleeve gastrectomy (SG) surpassed the RYGB as the most commonly performed procedure and in 2017 the SG represented 59.4% of all cases performed while RYGB represented only 17.8% [11]. The changes in bone metabolism after SG are largely unknown. While it seems that SG has a similar effect on BMD [12–14] this effect has not been well described despite the growing popularity of SG. These consequences will be of increasing importance as bariatric patients age and should be considered for those with increased preoperative risk for bone loss, such as postmenopausal females.

The primary objective of this study is to determine the extent to which altered bone metabolism, in post-menopausal females one year after SG and RYGB, affects total body and regional site specific bone mineral density as detected on dual-energy X-ray absorptiometry (DEXA) scan.

MATERIALS AND METHODS

This was a single center prospective cohort study. The study was performed at the Duke University Center for Metabolic and Weight Loss Surgery in Durham, North Carolina. The

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study was supported through the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Foundation Award, granted in 2013. Institutional Review Board approval was obtained prior to enrolling patients. Patients were recruited during the new patient evaluation and seminar and written informed consent was obtained at that time. The decision regarding surgical technique, RYGB or SG, was based on patient's and surgeon's judgment. Patients were enrolled from June of 2013 through April of 2017.

All patients were screened for vitamin and micronutrient deficiencies as a part of the initial preoperative visit. If deficiencies were identified these were aggressively repleted in the preoperative period and levels rechecked prior to surgery. All patients were required to consult with a dietician prior to surgery and were counseled to begin healthy eating practices; such as, eliminating carbonated beverages, calorie logs, and avoiding high carbohydrate and high fat foods. Two weeks prior to surgery, patients were instructed to follow a liver shrinking diet. Primary guidelines for this diet are: 700–800 calories per day, less than three carbohydrate servings per day, no added sugar, avoid high fat foods, drink greater than 64 ounces hydrating fluids per day, and focusing on protein rich foods. Finally, the day before surgery, patients were instructed to follow a clear liquid diet which includes a Glycemic Drink. Postoperatively, all patients were placed on commercially available bariatric vitamin and micronutrient supplementation. Serum vitamin and micronutrient levels were routinely assessed after surgery and any deficiencies repleted. Management practices did not differ between patients undergoing SG or RYGB.

DEXA

Patients underwent Dual-energy X-ray absorptiometry (DEXA) scans after daily calibrations with a standardized control using a total-body narrow fan-beam scanner (Discovery A™, Hologic Marlborough, MA) preoperatively and 12 months postoperatively. Preoperative DEXA scans were performed in the majority of patients within two weeks of surgery with a mean imaging to surgery interval of 8.25 days. Height and weight were measured at these time points. All studies were performed using the same device and were performed by a certified technician. Scan analysis was performed using GE Encore using Hologic software version 13.3. This software allows for adjustment of regions of interest including the sagittal line, which controls the left-right body distribution of tissue. Measurements obtained included total body bone mineral density (g/cm^2), total bone mineral content (g), and site specific bone mineral density (g/cm^2), bone mineral content (g), fat mass (g), and lean mass (g) at the following sites: skull, cervical, thoracic, and lumbar spine, distal radius, femoral neck, and total hip. The total body bone mineral density was used to calculate a t-score and z-score for each patient. T-Score reports the patient's bone density as it differs from the bone density of a healthy 30-year old adult with a lower T-Score equating to lower bone density. A T-Score greater than or equal to −1.0 is considered normal, between −1.0 and −2.5 diagnostic of osteopenia, and below −2.5 diagnostic of osteoporosis. The Z-Score reports the patient's bone density as compared to what is considered normal in a person of equal body size and age. Of note, this score can be misleading in older adults and results are only relied upon in children, teens, premenopausal women, and younger men. A Z-Score of greater than −2.0 is considered normal.

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Inclusion Criteria

Patients were enrolled if they were postmenopausal (defined as a history of no menstrual bleeding for greater than one year), had a BMI ≥ 35kg/m^2, a stable weight for previous three months, and were otherwise being scheduled for RYGB or SG.

Exclusion Criteria

Patients were excluded if they had a documented history of osteoporosis or were currently receiving medical treatment for osteoporosis with bisphosphonates, teriparatide, raloxifene, or denosumab. Further exclusion criteria were weight of more than 295 pounds (weight limit of dual-energy X-ray absorptiometry machine as recommended by the manufacturer), use of estrogen hormone replacement therapy within the last year, active smoking, current glucocorticoid use or history of glucocorticoid use for greater than one year.

Statistics

Summary data regarding demographic information were compiled. Categorical variables are summarized with frequency counts and percentages; continuous variables are summarized with means with standard deviations, or medians with interquartile ranges (IQR). Univariable analyses describing differences between RYGB and SG procedure groups were compared using Wilcoxon Rank-Sum tests for continuous variables and Fisher's Exact test for categorical variables.

Preoperative and postoperative fat mass, lean mass, bone mineral content (BMC), BMD, T-Score, and Z-Scores were compared using paired t-tests for normally distributed variables, and Wilcoxon sign rank tests for variables that were not normally distributed or had outliers. To account for multiple testing, a Bonferroni correction was applied to these paired tests. Analyses were conducted using R version 3.4.3 (Vienna, Austria).

RESULTS

A total of 28 patients were enrolled. 16 (57.1%) women underwent RYGB and 12 (42.9%) underwent SG. The median age was 57.5 years (Interquartile range [IQR]: 53.0, 62.0). This was not significantly different between those undergoing RYGB and SG. The median preoperative weight was 247 pounds (IQR: 226.0, 275.0) with a median BMI of 44.2 kg/m^2 (IQR: 39.9, 46.6). Preoperative weight and BMI were similar between those undergoing RYGB and SG. 19 (67.9%) women were white with the remaining patients identifying as black [Table 1].

Postoperatively the 28 women weighed a median of 187.5 pounds (IQR: 166.5, 209) lost a median of 66.5 pounds (IQR: −75.3, -46.0). No detectable change in height was measured in any of the patients in our sample. The median BMI following surgery was 32.4 kg/m^2 (IQR: 30.1, 35.2) achieving a median change in BMI of −11.3 kg/m^2 (IQR: −12.8, -7.9). Those who underwent RYGB had significantly greater weight loss as compared to SG (median 72.8 pounds (IQR: 51.0, 83.5) vs 49.0 pounds (IQR: 43.5, 68.0), p = 0.02) and had a greater change in BMI (median −12.6 kg/m^2 [IQR: −14.4, −8.3] vs −9.1 kg/m^2 [IQR: −11.4, −7.5],

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p = 0.03) [Table 2]. As compared to RYGB, those who underwent SG had a similar changes in total and region BMD.

Analyzing all patients, there was a significant decrease in postoperative fat mass in all extremities and the trunk. Similarly, there was a significant decrease in lean mass at all regional sites postoperatively [Table 3]. There was a significant difference in preoperative and postoperative total body BMC (2358.32 grams [SD 268.33] vs 2280.68 grams [SD 271.15]; p=0.002). Additionally, postoperative regional site BMC significantly decreased postoperatively in the spine, and right rib (p<0.001; p=0.01). Postoperative regional BMD was significantly reduced in the spine and right rib (p<0.001; p=0.02). A trend toward a decrease in postoperative T-Score was noted however this failed to reach significance (p=0.06) [Table 4].

DISCUSSION

The benefits of bariatric surgery are well described. Beyond substantial excess weight loss, bariatric surgery leads to resolution or reduction of comorbidities including: diabetes, hyperlipidemia, hypertension and obstructive sleep apnea. Resolution of these comorbidities increases both longevity and quality of life [15–17]. Adams et al. illustrated significantly reduced long-term mortality, decreasing adjusted all-cause mortality by 40%. Similarly rates of death from coronary artery disease were decreased by 56%, by 92% for diabetes, and 60% for cancer [18]. However, bariatric surgery has been shown to have a significant deleterious effect on the skeletal system with the existing literature noting the most profound effects after malabsorptive procedures [19].

Decrease in bone mineral density after bariatric surgery has been measured on dual-energy x-ray absorptiometry (DEXA) scan. Fleischer et al. documented a decrease in bone mineral density as measured on DEXA scan of 9.2% in the femoral neck and 8.0% in the total hip one year after Roux-en-Y gastric bypass [10]. Vilarrasa et al. documented a change in bone mineral density of 10.2% at the femoral neck and 3.2% in the lumbar spine one year after Roux-en-Y gastric bypass surgery [7]. While this effect has been well described after RYGB, recent data suggests that SG may have a similar effect on bone metabolism and skeletal health [5, 16, 19–21]. Despite these data, the effect SG has on BMD and skeletal health still remains controversial and unfortunately most studies have small numbers and the quality of the data remains poor.

In this study, we noted significant weight loss in postmenopausal women after RYGB and SG. Greater weight loss was seen in those who underwent RYGB. At one year postoperatively, these women had significant decreases in both lean and fat mass on DEXA imaging. Similar changes in body composition after bariatric surgery have previously been described [22]. Additionally, this study demonstrates significant effects on BMC and BMD, in postmenopausal women after both RYGB and SG. One year after RYGB or SG, we noted a significant decrease in total, spine, and right rib BMC, as well as, spine and right rib BMD.

There are few comparative studies evaluating bone loss after SG and RYGB, and those that exist have garnered varied results. Bredella et al observed similar degrees accelerated bone

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loss at the lumbar spine one year after both SG and RYGB, while Nogues et al reported greater bone loss in the spine after RYGB compared to SG, and Hsin et al showed no change in lumbar spine BMD following RYGB and SG [13, 14, 23]. In this study we observed a decline in total and regional BMC/BMD with no detectable difference in BMD changes for those who underwent SG as compared to RYGB. These results may suggest that there is similar bone loss in malabsorptive operations and restrictive operations despite superior weight loss after RYGB.

The mechanisms affecting bone metabolism after bariatric surgery are certainly multifactorial and are likely different depending on the operation performed. Site specific changes in BMC/BMD suggest that mechanical load is relevant in the maintenance of bone integrity. In this study we found the most significant regional change in BMC/BMD to be at the spine. These findings are consistent with other studies which have shown significant bone loss in the axial skeleton after bariatric operations [24–26]. These results may be due to changes in mechanical load. This idea is supported by the fact that obesity has been shown to be protective against osteoporosis, an effect which is magnified in postmenopausal women [27]. As weight is lost, whether by surgical or non-surgical means, mechanical load on the axial skeleton is reduced which is known to lead to bone loss [4, 28].

However, the exact mechanism of bone loss after weight loss surgery remains unclear and more study is needed. There are a number of significant hormonal and metabolic changes that result from weight loss surgery; which may differ depending on the bariatric operation used. In this study, more weight was lost after RYGB but this did not translate to greater bone loss. This may be in part due to different mechanisms of bone loss for patients undergoing SG and RYGB. This is supported by the finding that changes in body composition and weight have a greater correlation with bone loss in patients undergoing SG as compared to RYGB; suggesting that mechanical forces may play a greater role in bone loss after SG while malabsorption and hormonal changes may have a more significant effect on bone metabolism after RYGB [13, 20].

Limitations

There are several limitations to this study. First of all, the follow up period was relatively short and the sample size was small. This study did not measure serum markers of bone metabolism and this will be an area of future study. This study has small numbers and may not be sufficiently powered to detect a difference in BMD loss between SG and RYGB. As expect, we observed decreases in both lean and fat mass after SG and RYGB. Some studies have suggested that BMC/BMD estimates on DEXA scan may be artificially increased with increased tissue depth, as seen in the obese patient. The observed changes in body composition may have confounded our results. However these effects are limited in more recent systems and DEXA scan is still considered accurate for measuring BMC/BMD in the obese patient [29]. Additionally, while patients were monitored for vitamin deficiencies and hormonal imbalances; we did not collect data as to whether patients were taking vitamin or micronutrient supplementation prior to surgery or whether deficiencies were noted postoperatively. These factors may have had a significant effect on bone metabolism; however, these were not included in our analysis. This is an intended area of future study.

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This study had a recruitment period that was significantly more lengthy than expected. This was primarily due to strict exclusion criteria (the weight limitations of the Discovery A™) and a number of changes in key personnel during the enrollment process which led to significant delay.

Conclusion

In conclusion, in this small pilot study, postmenopausal women one year after RYGB and SG, were found to have decreased total BMC and regional BMC/BMD at the spine. No difference was detected between those undergoing SG as compared to RYGB. Postmenopausal women who are at risk for osteopenia and osteoporosis may benefit from postoperative DEXA screening, particularly if other risk factors for osteopenia or osteoporosis are identified, such as Vitamin D or Calcium deficiencies, prior fragility fractures, or family history. Further study is required to determine the mechanism of action, whether the magnitude of the effect is similar between operations, whether this effect is due to the modifiable factors (Vitamin D level, activity level, hormone status, etc.), and whether BMD and BMC is recovered beyond one year.

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Table 1:

Preoperative Demographics

	RYGB (N=16)	SG (N=12)	Total (N=28)	P-Value
Height (inches)	64.0 (62.5, 65.5)	62.8 (62.0, 64.3)	63.8 (62.0, 65.0)	0.51[1]
Weight (pounds)	261.5 (235.0, 276.8)	231.5 (220.8, 264.5)	247.0 (226.0, 275.0)	0.09[1]
BMI (kg/m2)	45.0 (42.8, 47.3)	40.5 (38.5, 45.5)	44.2 (39.9, 46.6)	0.13[1]
Age (years)	58 (53, 62)	57.5 (54, 62)	57.5 (53, 62)	0.91[1]
Race				0.69[2]
Black	6 (37.5%)	3 (25.0%)	9 (32.1%)	
White	10 (62.5%)	9 (75.0%)	19 (67.9%)	

Data presented as median with interquartile range or number with percentile as appropriate.

[1] – Wilcoxon Rank Sum Test ;

[2] – Fisher's Exact Test

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Table 2:

Postoperative Demographics

	RYGB (N=16)	SG (N=12)	Total (N=28)	P-Value
Weight (pounds)	187.5 (171.5, 209.5)	187.5 (164.5, 205.0)	187.5 (166.5, 209.0)	0.53
Change in Weight (pounds)	−72.8 (−83.5, -51.0)	−49.0 (−68.0, -43.5)	−66.5 (−75.3, -46.0)	0.02
Height (inches)	64.0 (62.5, 65.5)	62.8 (62.0, 64.3)	63.5 (62.0,65.0)	0.46
Change in Height (inches)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.0
BMI (kg/m2)	32.4 (31.0, 35.0)	32.4 (29.1, 36.3)	32.4 (30.1, 35.2)	0.80
Change in BMI (kg/m2)	−12.6 (−14.4, -8.3)	−9.1 (−11.4, -7.5)	−11.3 (−12.8, -7.9)	0.03

Data presented as median with interquartile range. P value calculated using Wilcoxon Rank Sum Test.

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Table 3:

Preoperative versus Postoperative Regional Fat and Lean Mass Comparisons

	Preoperative Mean/Median (IQR/SD)	Postoperative Mean/Median (IQR/SD)	Adjusted p-value
Regional Fat Mass in grams			
Left Arm	3294.3 (2706.4 – 4037.1)	2100.8 (1739.7 – 2622.8)	<0.001 [1]
Right Arm	3018.1 (2742.9 – 3716.1)	2306.4 (1928.4 – 2700.6)	0.002 [1]
Trunk	27246.7 (24160.2 – 30762.3)	17123.8 (12752.3 – 20614.1)	<0.001 [1]
Left Leg	9036 (7847.8 – 10416.9)	6170.1 (5534.8 – 7602.1)	<0.001 [1]
Right Leg	9285 (8095.3 – 10830.4)	6351.6 (5453.9 – 7553.9)	<0.001 [1]
Head	1047.8 (937.6 – 1221.4)	962.8 (902.2 – 1131.6)	0.09 [1]
Regional Lean Mass in grams			
Left Arm	2867.1 (2510.8 – 3081.6)	2345.1 (2122.7 – 2694.2)	<0.001 [1]
Right Arm	2967 (485.1)	2612.7 (433.9)	0.009 [2]
Trunk	28206 (25106.6 – 30990)	24539.7 (22328.5 – 26500.3)	<0.001 [1]
Left Leg	9883.9 (9130.5 – 10886)	8199.2 (7633.5 – 9330.5)	<0.001 [1]
Right Leg	10464.1 (9275.3 – 11293.4)	8567 (7572 – 9578.4)	0.005 [1]
Head	3162.3 (3000.2 – 3409.7)	2943.6 (2786.9 – 3154.5)	<0.001 [1]

Data presented as median with interquartile range or mean with standard deviation as appropriate.

[1] – Wilcoxon Sign Rank Test;

[2] – Paired T-Test

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Table 4:

Preoperative versus Postoperative BMC/BMD comparisons

	Preoperative Mean/Median (SD/IQR)	Postoperative Mean/Median (SD/IQR)	Adjusted p-value
Bone Mineral Content (BMC) in grams			
Total BMC	2358.32 (268.33)	2280.68 (271.15)	0.002 [1]
Head BMC	530.70 (461.44, 597.83)	509.13 (459.70, 593.16)	1.00 [2]
Left Arm BMC	148.14 (139.98, 166.80)	146.61 (130.32, 158.66)	1.00 [2]
Right Arm BMC	153.25 (22.95)	159.89 (19.84)	1.00 [1]
Left Rib BMC	95.14 (29.04)	83.86 (18.19)	0.22 [1]
Right Rib BMC	104.14 (28.13)	88.57 (21.02)	0.01 [1]
Total Spine BMC	142.23 (27.51)	124.91 (22.13)	<0.001 [1]
Lumbar Spine BMC	54.88 (48.32, 66.76)	56.41 (45.48, 67.45)	1.00 [2]
Pelvis BMC	249.34 (212.55, 267.57)	219.64 (186.68 – 251.07)	0.06 [2]
Left Leg BMC	434.34 (412.46, 456.27)	417.24 (401.06, 459.94)	1.00 [2]
Right Leg BMC	425.06 (402.63, 458.79)	425.89 (386.16, 457.81)	1.00 [2]
Bone Mineral Density (BMD) in grams/cm^2			
Total BMD *	1.13 (1.11, 1.19)	1.11 (1.08, 1.18)	0.09 [2]
Head BMD *	2.60 (2.33, 2.94)	2.43 (2.24, 2.76)	0.56 [2]
Left Arm BMD *	0.71 (0.67, 0.75)	0.71 (0.68, 0.74)	1.00 [2]
Right Arm BMD	0.73 (0.05)	0.73 (0.04)	1.00 [1]
Left Rib BMD	0.69 (0.11)	0.64 (0.10)	1.00 [1]
Right Rib BMD	0.69 (0.12)	0.64 (0.10)	0.02 [1]
Total Spine BMD	0.91 (0.12)	0.83 (0.10)	<0.001 [1]
Lumbar Spine BMD	1.12 (0.99, 1.28)	1.07 (1.00, 1.19)	1.00 [2]
Pelvis BMD *	1.26 (1.21, 1.38)	1.21 (1.15, 1.29)	0.50 [2]
Left Leg BMD *	1.17 (1.13, 1.23)	1.15 (1.11, 1.20)	1.00 [2]
Right Leg BMD *	1.15 (1.12, 1.21)	1.15 (1.11, 1.21)	1.00 [2]
T-score *	0.20 (−0.43, 0.80)	0.00 (−0.75, 0.70)	0.06 [2]
Z-score *	0.55 (0.20, 1.30)	0.35 (−0.10, 1.05)	1.00 [2]

Data presented as median with interquartile range or mean with standard deviation as appropriate.

[1] – Paired T-Test ;

[2] – Wilcoxon Sign Rank Test;

* - contains ties of zeros, resulting in approximate p-values