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Two Year Outcomes on Bone Density and Fracture Incidence in Patients with T2DM Randomized to Bariatric Surgery vs. Intensive Medical Therapy

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Abstract

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Drs Kashyap and Maghrabi and the Cleveland Clinic Coordinating Center for Clinical Research had full and independent access to all of the data in the study, and Dr Kashyap takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Objective—To determine the 2 yr outcomes of RYGB, sleeve gastrectomy (SG) vs. intensive medical therapy (IMT) on lean body mass, total bone mass and BMD measures from the STAMPEDE trial.

Methods—54 subjects (BMI: 36±1 kg/m^2, age: 48±4y) with T2DM (HbA_{1c}: 9.7±2%) were randomized to IMT, RYGB, or SG and underwent DXA at baseline, 1 and 2 yrs.

Results—At 2 yr, the reduction in BMI was similar after RYGB and SG, and was greater than IMT (P<0.001). Lean mass was reduced by ~10%, total bone mineral content reduced by ~8% and hip BMD reduced by ~9% in both surgical groups, and was significantly greater than IMT despite increases in vitamin D intake in all groups. The change in hip BMD correlated with weight loss (r = 0.84, P<0.0001), and changes in lean mass (r = 0.74, P<0.0001), and leptin (r = 0.53, P<0.0001). Peripheral fractures were self-reported in RYGB (4/18 patients), SG (2/19 patients) and the IMT (4/16 patients).

Conclusion—Surgically induced weight loss is associated with modest reductions in lean mass, bone mineral content and density, despite calcium and vitamin D supplementation in patients with T2DM. Awareness for bone loss is indicated for patients undergoing bariatric procedures.

Keywords

Obesity; Type 2 diabetes mellitus; Body composition; Lean mass; Bone mass; Bone density; Bariatric surgery; Gastric bypass; Sleeve gastrectomy; Leptin; Vitamin-D

Introduction

Bariatric surgery, including gastric bypass (RYGB) and sleeve gastrectomy (SG) is linked to favorable metabolic effects on obesity, insulin sensitivity, and stimulation of the entero-insulin axis leading to remission of type 2 diabetes (T2DM) as compared to intensive medical therapy (IMT) in randomized controlled trials (1–4). Although obesity is considered a protective factor for bone mineral density (BMD), the development of T2DM, which parallels obesity is paradoxically associated with poor bone quality and density (5, 6).

Some, but not all, studies have demonstrated increased fracture risk in patients with T2DM by 1.5–2 fold compared to the general population (7, 13). However, the effects of various bariatric procedures, compared to IMT, on BMD and fracture risk in patients with obesity and T2DM are not well depicted. Reduction in BMD attributed to surgically induced weight loss has been linked to nutrient deficiencies, mechanical unloading and loss of lean mass in post-bariatric subjects with severe obesity; however many additional factors specific to T2DM may impact bone health, including the effects of hyperglycemia, various adipokines, and anti-diabetic medications (5,6).

In this pre-planned exploratory substudy of the STAMPEDE trial, our aim was to evaluate the two year outcomes of RYGB, SG and IMT on lean mass, bone density changes and self-reported fracture incidence in patients with obesity and T2DM.

Methods

Study Design

The STAMPEDE trial design and substudy design has been previously reported (1,2). The first consecutive 60 subjects randomized in the main trial with 20 in a 1:1:1 ratio to each treatment group were included in the substudy. This analysis of bone and fracture incidence is exploratory in nature. At 24 months, there was 10% loss to follow up, with 17 subjects remaining in IMT, and 18 and 19 subjects remaining in the RYGB and SG groups, respectively. The medical and surgical therapies were dictated by the latest guidelines from the American Diabetes Association (ADA) and the Cleveland Clinic Endocrinology And Metabolism And Bariatric And Metabolic Institute management protocols. Calcium and vitamin-D supplementation were recommended as per clinical practice guidelines.

Chart review was performed to obtain additional historical (i.e. medication use, smoking, fracture events) and biochemical data (i.e. 25 hydroxy vitamin D and calcium levels) at 12 and 24 month post randomization. Body composition was determined by DXA (iDXA, Lunar Prodigy, Madison, WI) scan performed by the same technician before and following randomization, and included total lean mass, bone mineral content and BMD (lumbar (L1–L4), spine and total hip). Serum leptin and adiponectin levels were obtained after a 10–12 hour fast at baseline, and 12 and 24 months. Samples were assayed by ELISA (R&D systems, Minneapolis, MN); the intra- and inter-assay coefficients of variation for both assays were 3.0% and 4.6%, respectively. To correct for inter-assay variability, all pre- and post-measurements for each individual were run on the same plate.

Statistical Analysis

This was a pre-planned substudy. Continuous variables with a normal distribution are reported as means and standard deviations (SD). Variables with a non-normal distribution are reported as medians and interquartile ranges (IQR). Categorical variables are summarized using frequencies and tested with the Chi-square statistic or Fishers exact test (two-tailed), as appropriate. One-way analysis-of-variance (ANOVA) was used to analyze continuous laboratory parameters and perform comparisons between treatment groups. Variables with a non-normal distribution were rank-transformed prior to implementing the ANOVA.

Results

Baseline characteristics have been previously reported for this cohort (1). Briefly, patients (N= 54) had a mean age of 48±4 yrs, 59.3% female (with twice as many females in the SG group vs. IMT and RYGB), 72% were Caucasian, with a mean BMI of 36±1 kg/m2 and T2DM duration of 9 years with poorly controlled glucose levels (HbA_{1c} = 9.7±2%). As expected, baseline levels of 25 hydroxy vitamin D were similarly reduced (Table 1) across the three groups with normal calcium levels (data not shown). Smoking was self-reported in 2/18 RYGB, 1/19 SG patients, and none in the IMT group. At baseline, 5/18 RYGB, 4/19 SG and 3/16 IMT patients were taking a proton pump inhibitor. Incretin mimetics were used in 13/18 RYGB, 16/19 SG and 15/16 IMT, P=0.58. Many RYGB (18/18), SG (12/19) and

IMT (10/16) patients took calcium supplementation at follow up, and all patients used vitamin-D supplementation at 12 and 24 months. Calcium citrate (600 mg twice daily) was recommended for post surgical patients while IMT used calcium carbonate (600–1200 mg/day). Eighty percent (15/19) of SG used 1000 IU Vitamin D3 and 20% used 2000 IU D3. Forty percent (7/8) of RYGB used Ergocalciferol 50,000 once weekly, 30% used Vitamin D3 2000 IU/day, and 30% used Vitamin D3 1000 IU/day. Adherence was not measured. No patients were noted to use corticosteroids, furosemide, thiazide diuretics or anticonvulsants.

At 2 years (Table 1), total body lean mass decreased significantly in the RYGB (10.1%) and SG (13.5%) groups as compared to the IMT (2.7%) group. Total body bone mineral content also decreased significantly in both the RYGB and SG (8.2% and 6.6%, respectively) groups as compared to a 0.3% reduction in the IMT group. Total hip BMD decreased by 9.5% and 9.2% in RYGB and SG groups, respectively, and this was significantly greater than IMT. Increased dose of vitamin D intake was noted in all groups compared to baseline. Although median levels for spine BMD were similar at baseline among the three groups, the absolute reduction in spine BMD was greater in SG vs. IMT (−0.29 vs. 0.01 g/cm^2, P=0.02) at 24 months with no difference noted between RYGB and IMT. As expected, leptin levels were markedly reduced, and adiponectin levels increased in both surgical groups, as compared to IMT.

Correlations (Table 2)

The change in hip BMD at 2 years in all groups combined, strongly correlated with weight loss, BMI reduction, lean mass, leptin and bone mineral content changes, and did not correlate with changes in adiponectin levels. Lean mass and bone mineral content in all groups at 2 years strongly correlated with weight loss and BMI, and to some extent with leptin reduction, but was not associated with the change in adiponectin (Table 2).

Multivariate analyses models were formulated using age, gender, smoking status, height, BMI, and use of PPIs and TZDs to identify predictors of change in hip BMD. When weight loss (change in BMI) was excluded from the model, both age (P=0.004) and reduction in leptin (P<0.001) were significant with other variables controlled. However, when weight loss (BMI) was included in the model, the effect of leptin and age was no longer significant since both variables are likely co-linear. Thus, after controlling for age, gender, smoking, height, PPI and TZD, the change in BMI was the single most important determinant of BMD loss in the hip.

Peripheral fractures were self-reported in RYGB (4/18 patients), SG (2/19 patients) and the IMT (4/16 patients) groups. Remarkably, 7 were spontaneous tarsal or metatarsal fractures with no history of trauma, the remaining (2 ankle and 1 arm fractures) were related to trauma in the IMT group.

Discussion

Despite the increased recognition that bariatric surgery has important metabolic benefits for patients with morbid obesity, data from this randomized control trial in patients with type 2 diabetes indicates that surgically induced weight loss is associated with modest reductions in

lean mass, total bone mineral content and density of the hip, and spine. Despite the lack of change in bone mineral content and density in the IMT group, fracture rates were similar in this group as compared to RYGB.

Intestinal bypass surgery is associated with malabsorption of a number of macro and micronutrients resulting in deficiencies which are compounded by noncompliance to oral supplementation that has been noted in up to ~60% of patients (8,11). Our finding on loss of lean mass following bariatric surgeries is consistent with previous studies in which DEXA was used to assess body composition. These studies found that most patients lose both lean mass and bone mass especially within the first year following surgery, despite self-reported participation in conventional exercise programs (9,11,10). Our data extends these finding to 2 years of follow-up post-bariatric surgery and reflect a time when weight loss has stabilized.

Although several prospective observational studies have reported a decline in hip BMD up to 10 years after bariatric surgery, randomized controlled data on long term BMD responses to bariatric surgery are limited (11). Our prospective randomized controlled study exhibited greater reduction in hip BMD following both RYGB and SG than that in the IMT group. This seems to be a general finding after bariatric surgery, particularly RYGB (11,15).

The clinical implications of the potential adverse effects of bariatric surgery on bone metabolism are a matter of debate (5,18). Decreased calcium and vitamin-D intake and absorption, secondary hyperparathyroidism and reduced mechanical load on the skeleton are the main contributory factors underlying reduced bone after bariatric surgery (5,11,14,18); however, in patients with SG the reasons for vitamin-D and calcium deficiencies are not well understood (8,16). Supplementation with these nutrients is recommended, although, there is no current agreement on the optimal amount to be provided after bariatric surgery (5). It is also significant to note that vitamin-D deficiency is estimated to be present in ~60% of patients with severe obesity prior to surgery, and this is attributed to adipose tissue sequestration/storage of 25 hydroxy vitamin D (8,11). Thus, these patients may be at greater risk for developing postoperative deficiencies which are difficult to replete with very high doses of vitamin-D supplementation (8,11,17).

Although our patients maintained normal calcium levels during the trial, we observed a reduction in their hip BMD. Alterations in bone metabolism after bariatric surgery pose a long-term risk of fragility fractures (8,12,18). Remarkably, six of our bariatric, both RYGB and SG, and one IMT patients self-reported tarsal/metatarsal non-traumatic fractures by the end of the 2nd year post randomization. Unfortunately, there is no current consensus on how to assess and prevent fractures in this at risk population (12). Multiple factors may affect the bone density status in our study population including medications (ie. PPIs, TZDs, and incretins), smoking status, and change in metabolic factors such as leptin and adiponectin levels. Roughly 24% of our surgical patients, both RYGB and SG, and 18% of IMT patients were using PPIs long term. GERD treated with PPIs is not uncommon in patients post-bariatric, but the development of osteopenia, osteoporosis, and fractures post-bariatric surgery has been reported after ingestion of PPIs, especially at higher doses, which could present after 1 year of PPI therapy (14). A number of patients were using a TZD during the

trial. TZDs have been shown to reduce bone formation, BMD, and increase risk of fractures by directing osteoblast precursors toward the adipocytein bone, rather than the osteoblast lineage (7). Smoking is identified as a risk factor for decreased BMD and fractures in the general population but the exact mechanism is not well understood; studies of similar effect in patients undergoing bariatric surgery are limited (19). Only 3 out of 37 patients in the bariatric groups, but none of the IMT patients in our study continued to smoke throughout the trial. Leptin and adiponectin produced by adipocytes may regulate bone metabolism and be involved in osteoporosis pathophysiology (1,20). The net effect of leptin on bone formation is thought to be favourably induced by directly affecting its surrounding osteoblast activity, resulting in skeletal preservation. In contrast, adiponectin appears to exert a negative effect on bone mass (5,12, 20). Thus the drop in leptin levels seen following surgery may be linked to increased bone turnover. In addition, poor glycemic control (HbA_{1c} ≥8% or on insulin therapy) in diabetic patients is associated with an increased risk of fracture, especially in those with longer duration of diabetes (21,22). Several theories try to explain this association; some attribute the increased risk of fracture in diabetic subjects to physiological changes resulting from chronic hyperglycemia which could degrade bone quality through inhibition of osteocalcin, increased reactive oxygen species, bone accumulation of advanced glycation end products, or inhibition of insulin-like growth factor 1 (21,23). Others suggest that increased risk of falling due to micro- or macro-vascular complications of diabetes could contribute to increased risk of fracture (21, 24).

Our fracture data are supported by one other large retrospective, population-based fracture study in the UK that determined fracture incidence for 2.2 years following bariatric surgery vs. a BMI matched non-surgical cohort, and showed no increase in relative fracture risk related to surgery. In contrast, increased fracture risk was noted 3–10 years following surgery particularly in those with greater reductions in BMI (25). Further controlled studies are warranted to determine post-bariatric fracture rates.

Our study is not without limitations. Almost all differences between the RYGB and SG groups were not significant, likely because the study was not adequately powered to detect modest differences between those groups. While the changes in BMD observed suggest that the reduction of lean and bone mass leads to decreased mechanical load is highly relevant in determining BMD, we cannot neglect the fact that a similar effect could also be induced by secondary hyperparathyroidism and/or diabetes itself. We did not determine the parathyroid related parameters during this trial. Similarly, calcium metabolism determinations of bone formation and degradation including the possible effects of PPIs and TZDs were not carried out. Fractures were self-reported during adverse event reporting, but documentation from X-rays or physician reports was not used for verification particularly of site. Also, menopause status was not obtained in women. Lastly, there is growing evidence that DEXA may have limited utility in accurately assessing bone outcomes following surgical weight loss due to changing fat-lean tissue ratios in the region of interest, fan-beaming hardening and other factors (26).

Conclusion

Surgically induced weight loss is associated with modest reductions in lean mass, bone mass and BMD, despite calcium and vitamin-D supplementation in patients with uncontrolled T2DM and obesity. In addition, vigilance for on-going nutritional deficiencies and bone loss in patients before and after bariatric surgery is critical. Efforts to reduce or discontinue PPIs should be assessed frequently. Future studies are warranted to thoroughly investigate the long-term effects of bariatric surgery on BMD and calcium metabolism to better understand bone loss and its clinical implications on patients undergoing bariatric procedures.

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What is already known about this subject?

Bariatric surgery has favorable metabolic effects on conditions of obesity, insulin sensitivity and T2DM.

T2DM has been associated with worsening bone health and increased fracture risk.

What does this study add?

Increased awareness of surgically induced weight loss effects on bone density and fracture risk despite calcium and vitamin D supplementation in patients with T2DM

Table 1

Clinical Changes at 12 and 24 Months: Body composition and BMD

	IMT (N=17)	RYGB (N=18)	SG (N=19)	P-Value[1]	P-Value[2]	P-Value[3]
Body weight - kg						
Baseline	109.4(91, 122.6)	107.6(92.8, 112.5)	98.5(87.9, 107.4)	0.556	0.129	0.303
% Change at 12 months	−0.6(−5.4, 3.6)	−26.3(−30.9, −18.9)	−24.7(−29.7, −21.2)	<0.001	<0.001	0.725
% Change at 24 months	−0.3(−3.6, 1.2)	−25.3(−32, −18.3)	−23.4(−27.1, −17.1)	<0.001	<0.001	0.346
Lean Mass - kg						
Baseline	62.9(49.6, 71.3)	62.9(53, 70.4)	50.6(45.3, 52.2)	0.838	0.029	0.042
% Change at 12 months	−0.7(−3.4, 0.9)	−9.3(−13.3, −5)	−10.5(−13.4, −9.7)	<0.001	<0.001	0.149
% Change at 24 months	−2.7(−5.3, −0.4)	−10.1(−14, −8.5)	−13.5(−16, −10.1)	<0.001	<0.001	0.42
Bone Mass - kg						
Baseline	3.3(3.1, 3.8)	3.2(2.8, 3.6)	2.7(2.6, 2.9)	0.272	0.005	0.067
% Change at 12 months	−0.4(−1.5, 0.8)	−5.3(−7.8, −3.2)	−4.4(−5.8, −2.3)	<0.001	<0.001	0.213
% Change at 24 months	0.3(−1, 1.6)	−8.2(−9.8, −6.2)	−6.6(−8.1, −3.9)	<0.001	<0.001	0.13
Total Hip BMD - g/cm2						
Baseline	1.2(1.1, 1.3)	1.1(1.0, 1.3)	1.1(1.1, 1.2)	0.43	0.021	0.56
% Change at 12 months	0.36(−1.0, 0.8)	−6.6(−9.3, −3.8)	−7.6(−8.5, −5.7)	<0.001	<0.001	0.51
% Change at 24 months	−0.3(−1.8, 0.9)	−9.5(−13.2, −6.7)	−9.2(−12, −5.4)	<0.001	<0.001	0.38
Lumbar Spine BMD - g/cm^2						
Baseline	1.3(1.2, 1.5)	1.3(1.1, 1.5)	1.2(1.1, 1.3)	0.41	0.08	0.95
% Change at 12 months	1.7(−1.2, 3.9)	−0.1(−2.1, 3.4)	−0.7(−3.1, 1.9)	0.29	0.1	0.44
% Change at 24 months	0.8(−0.7, 2.2)	0.4(−1.9, 2.2)	−2.3(−4.8, 1.6)	0.37	0.02	0.19
Vitamin D levels - ng/ml						
Baseline	19.5(16, 24.5)	21.1(18.9, 26.3)	26.3(17.2, 37.8)	0.47	0.11	0.17
% Change at 12 months	24.0(−12.6, 55.9)	50.2(12.9, 180)	8.0(−25, 33.4)	0.18	0.36	0.03
% Change at 24 months	34(0.1, 75.1)	174.3(47.9, 193.4)	37.9(−23.9, 126.1)	0.07	1.0	0.1

P-Value[1], Intensive medical therapy vs. gastric bypass; P-Value[2], Intensive medical therapy vs. sleeve gastrectomy; P-Value[3], Gastric bypass vs. sleeve gastrectomy.

Abbreviations: IMT, Intensive Medical Therapy; RYGB, Roux-en-Y Gastric Bypass; SG, Sleeve Gastrectomy; BMI, Body Mass Index.

Unless otherwise specified, data are expressed as median and interquartile range. % changes are from baseline.

Table 2

Correlation between BMD, body composition parameters and leptin at 24 Months in all groups

Parameter	Lean mass	Bone mass	Weight loss	BMI	Leptin	Adiponectin
Hip BMD						
P-Value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.07
r	0.74	0.77	0.84	0.84	0.53	0.62
Lean mass						
P-Value		< 0.0001	< 0.0001	< 0.0001	0.0006	0.01
r	1	0.58	0.84	0.83	0.45	0.93
Bone mass						
P-Value	< 0.0001		< 0.0001	< 0.0001	0.0002	0.18
r	0.58	1	0.71	0.71	0.49	0.19

N=54 patients; r = Pearson correlation coefficient. Abbreviations: BMI, Body Mass Index.