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Bone marrow fat changes after gastric bypass surgery are associated with loss of bone mass

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Abstract

Bone marrow fat is a unique fat depot that may regulate bone metabolism. Marrow fat is increased in states of low bone mass, severe underweight, and diabetes. However, longitudinal effects of weight loss and improved glucose homeostasis on marrow fat are unclear, as is the relationship between marrow fat and BMD changes. We hypothesized that after Roux-en-Y gastric bypass (RYGB) surgery, marrow fat changes are associated with BMD loss. We enrolled 30 obese women, stratified by diabetes status. Before and 6 months after RYGB, we measured BMD by DXA and QCT and vertebral marrow fat content by magnetic resonance spectroscopy. At baseline, those with higher marrow fat had lower BMD. Postoperatively, total body fat declined dramatically in all participants. Effects of RYGB on marrow fat differed by diabetes status ($p=0.03$). Nondiabetic women showed no significant mean change in marrow fat (+1.8%, 95% CI −1.8% to +5.4%, $p=0.29$), although those who lost more total body fat were more likely to have marrow fat increases ($r=-0.70$, $p=0.01$). In contrast, diabetic women demonstrated a mean marrow fat change of −6.5% (95% CI −13.1% to 0%, $p=0.05$). Overall, those with greater improvements in hemoglobin A1c had decreases in marrow fat ($r=0.50$, $p=0.01$). Increases in IGF-1, a potential mediator of the marrow fat-bone relationship, were associated with marrow fat declines ($r=-0.40$, $p=0.05$). Spinal volumetric BMD decreased by 6.4% ±5.9% ($p<0.01$), and femoral neck areal BMD decreased by 4.3% ±4.1% ($p<0.01$). Marrow fat and BMD changes were negatively associated, such that those with marrow fat increases had more BMD loss at both spine ($r=-0.58$, $p<0.01$) and femoral neck ($r=-0.49$, $p=0.01$), independent of age and menopause. Our findings

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Disclosure Page

The authors have nothing to disclose.

suggest that glucose metabolism and weight loss may influence marrow fat behavior, and marrow fat may be a determinant of bone metabolism.

Keywords

SYSTEMS BIOLOGY-BONE INTERACTORS: Bone-fat interactions; NUTRITION; ANALYSIS/QUANTITATION OF BONE: Bone QCT; DXA; DISEASES AND DISORDERS OF/RELATED TO BONE: Other – Diabetes and diabetic bone fragility

Introduction

Bone marrow fat is a unique and dynamic fat depot, but its role in human physiology is still being defined. There is growing interest in bone marrow fat as a regulator of both bone and fat metabolism.[1, 2] In the marrow microenvironment, osteoblasts and adipocytes share a common mesenchymal stem cell precursor, and adipogenesis may occur at the expense of osteoblastogenesis. Indeed, greater bone marrow fat is associated with lower BMD,[3–7] more rapid BMD loss[8] and vertebral fracture, [9, 10] although this relationship may not be universal as marrow fat increases markedly during peak bone acquisition.[11] Marrow fat is also viewed by some as an endocrine organ that contributes meaningfully to the secretion of circulating hormones,[12] and this may have systemic effects on the skeleton. Manipulation of pathways linking marrow adiposity and osteoblastogenesis could constitute a future anabolic therapeutic approach for osteoporosis.

Factors that regulate marrow fat are uncertain, particularly because marrow fat appears to be subject to different regulation than visceral and subcutaneous fat. Weight loss affects marrow fat, and in young mice, caloric restriction resulted in high bone marrow fat, compared to mice on a normal diet.[13] Women with anorexia nervosa have higher bone marrow fat than controls, despite having much lower total body fat.[14] Thus, marrow fat may serve as a depot of energy stores for hematopoiesis in the setting of relative starvation.[15, 16] Further, a relative increase in or preservation of marrow fat may play a role in the decline in bone mass seen with weight loss in humans.[17–20] However, the relationship between longitudinal changes in marrow fat and bone mass during weight loss remains undefined.[21]

Another potential determinant of marrow fat is diabetes mellitus. In mouse models of both type 1 and type 2 diabetes, marrow fat content is higher than in nondiabetic controls.[22, 23] Human studies are less conclusive, although in a study of women with type 2 diabetes, higher hemoglobin A1c (HbA1c) levels were associated with greater marrow fat.[24] The physiologic significance of increased marrow fat in diabetes is not clear, but this fat depot could play a role in diabetic bone fragility. It is unknown whether improvements in glycemic control affect marrow fat in humans.

Weight loss surgery, including the Roux-en-Y gastric bypass (RYGB), results in dramatic weight loss and improvement in diabetes[25, 26] and is thus a unique opportunity to study dynamic changes in fat mass and metabolism. RYGB also has well-documented negative skeletal consequences, with substantial postoperative declines in BMD and increased fracture risk.[27–31] We performed a small pilot study,[32] and based on findings from murine

models and from women with anorexia nervosa, we hypothesized that marrow fat content would increase after RYGB. Instead, we found that change in marrow fat content was variable and appeared to differ by preoperative diabetes status as well as total fat loss.

With an expanded cohort of RYGB patients, we tested the new hypotheses that changes in glucose metabolism and fat compartments are important determinants of changes in marrow fat content, and we examined potential hormonal mediators. Moreover, now with consideration of these covariates, we expanded the scope of the study to investigate the relationship between marrow fat content and bone density changes in the setting of RYGB.

Materials and Methods

Study population

We recruited women ≥25 years of age from two academic bariatric surgery centers (University of California, San Francisco and the San Francisco Veterans Affairs Medical Center). Women were eligible if they were scheduled for a future RYGB procedure. Enrollment was stratified by preoperative diabetes status, defined by having HbA1c ≥6.5% or a prior physician's diagnosis of diabetes plus use of an antidiabetic medication. It was determined that a sample size of 26 would provide approximately 80% power to detect a difference in marrow fat change between women with and without diabetes. We excluded women who were perimenopausal (defined as last menses >3 months but <5 years ago) in order to minimize sex hormone and BMD changes unrelated to the surgical weight loss. We included premenopausal women on stable hormonal contraception and postmenopausal women on stable hormone therapy. We also excluded women who used medications known to impact bone metabolism or marrow fat, including bisphosphonates or teriparatide (in the last year or for >12 months ever), oral glucocorticoids (>5 mg prednisone equivalent daily for >10 days in the last 3 months), and thiazolidinediones. Other exclusion criteria included prior bariatric surgery, estimated glomerular filtration rate <30 mL/min, and weight >350 lbs, due to magnetic resonance (MR) scanner capacity.

The first 11 participants were recruited from a study of the effects of RYGB on calcium metabolism and the skeleton,[33] and marrow fat data from those 11 pilot participants were included in a prior report.[32] We subsequently enrolled and followed the remainder of the participants after the parent and pilot studies were completed.

We provided each participant with a chewable calcium citrate supplementation at an individualized dose to achieve a total daily calcium intake of approximately 1200 mg, with reevaluation of dietary calcium intake and adjustment of the supplement dose during study participation. Low 25OHD levels were repleted following enrollment with a target level ≥30 ng/mL, and vitamin D supplements were titrated to maintain that target level.

The institutional review board approved the study protocol. All participants provided written informed consent.

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) Imaging Protocols

Preoperatively and 6 months postoperatively, MR data were acquired using a GE MR750 wide bore scanner (GE Healthcare, Milwaukee, WI, USA) with embedded posterior phased array coils (GEM suite, GE Healthcare). The imaging protocol included a standard clinical sagittal T2-weighted Fast Spin Echo (FSE) sequence: repetition (TR)/echo time (TE) = 5000/87 ms, echo train length = 32, field of view = 22 cm, slice thickness = 6 mm. This was used for visualization of lumbar vertebrae and for prescription of the spectral acquisition box. Single voxel MRS was acquired in the L3 and L4 vertebrae using the Stimulated Echo Acquisition Mode (STEAM) sequence with the following parameters: TR/TE = 3000/20 ms, 64 averages without water suppression, data points = 4096, voxel size = 15 × 15 × 20 mm^3 = 4.5 cm^3. The spectral box positioning was in the middle of the vertebral body, and the box size was kept constant for all subjects. Outer volume saturation bands were used to eliminate potential contamination of outside signals.

^{1}H-MRS Data Analysis

The spectral data were analyzed using jMRUI software.[34] Line broadening (approximately 5 Hz) was applied to the free induction decay (FID) data, followed by spectral reconstruction, zero-order and first-order phase correction by maximizing the amplitudes of the real part of the spectrum, baseline correction and frequency shift correction. The water and fat peaks were fitted using AMARES, a time-domain MRS quantification algorithm implanted in the jMRUI software. Lorentzian line-shape models were chosen. Spectral peaks were assigned based on previously published studies:[35] water peak at 4.7 ppm and fat peak at 1.3 ppm (the bulk CH_2 methylene protons). Bone does not contribute to the signal with this technique. The area under each peak was calculated, and marrow fat content was determined as fat / (fat + water) × 100%. Study team members responsible for MRS analysis were blinded to patient characteristics, including diabetes status.

Longitudinal reproducibility of the ^{1}H-MRS technique was previously evaluated in 6 healthy, normal weight adult women.[32] These women were scanned twice, with the two scans 6 months apart. Mean 6-month coefficient of variation (CV) for L3-L4 marrow fat content was 3.8% (range 0.2% to 5.6%).

Body Composition and Bone Mineral Density

Preoperatively and 6 months postoperatively, BMI was calculated as weight/height^2 (kg/m^2). Whole body fat (grams), lean mass (grams) and areal BMD (aBMD, g/cm^2) were measured by DXA (Hologic Discovery W and Horizon A densitometers, Bedford, MA, USA). Each participant had her preoperative and postoperative imaging on the same machine. Modified half-body scans were utilized if a participant's body dimensions exceeded the scanning area width.[36] Vertebral volumetric BMD (vBMD, g/cm^3) at the L3 and L4 vertebrae was measured by QCT (GE VCT64 scanner; General Electric, Milwaukee, WI, USA). Findings on QCT were evaluated according to methods described previously (Mindways Software, Austin, TX, USA).[37, 38] We measured visceral adipose tissue area (cm^2) using a single axial slice at the mid-L4 vertebrae by CT. Fascial borders of the internal abdominal wall were traced manually using a previously described approach.[39]

Laboratory Measures

Serum samples were collected preoperatively and 6 months postoperatively after an overnight fast. Serum chemistries, a lipid panel, and HbA1c were measured, 25OHD levels were determined by liquid chromatography tandem mass spectrometry (LC-MS/MS), and remaining sera were stored at −70°C until batch analysis was done for other analytes in a central laboratory (Maine Medical Center Research Institute, Scarborough, ME, USA). IGF-1 was measured by an automated immunoassay (iSYS; Immunodiagnostic Systems, Scottsdale, AZ, USA), with interassay and intraassay CVs of 5.1% and 2.2%, respectively. The adipokine leptin was measured by ELISA (R&D Systems, Minneapolis, MN, USA), with interassay and intraassay CVs of 4.3% and 3.2%, respectively. Total estradiol was measured by ELISA (Alpco Diagnostics, Salem, NH, USA), with interassay and intraassay CVs of 8.7% and 7.8%, respectively.

Statistical analysis

Means and medians were calculated for baseline characteristics. Differences in baseline characteristics between diabetic and nondiabetic participants were assessed using χ^2, Mann-Whitney, and Student's t-tests. For all participants and for each diabetes stratum, we used Wilcoxon signed-rank tests or paired t-tests as appropriate to determine whether study outcomes changed between preoperative and 6-month postoperative time points. Similarly, we used Mann-Whitney and t-tests to assess between-group differences in these changes. We used Spearman's rank and Pearson's correlation tests to characterize the unadjusted relationship between changes in marrow fat and changes in other study parameters. We used linear models to estimate adjusted associations between 6-month changes in marrow fat and BMD, adjusting for biologically plausible covariates including age and menopausal status. Data were analyzed using Stata 14 software (StataCorp, College Station, TX, USA).

Results

Baseline participant characteristics and correlations

Participants were 48 ± 12 (mean ± SD) years old (Table 1). All of the diabetic women had type 2 diabetes, and these 14 women had a mean preoperative weight of 109.3 ± 16.3 kg with mean BMI of 41.6 ± 5.3 kg/m^2. They were less obese than the 16 women without diabetes, who had a mean preoperative weight of 124.7 ± 14.9 kg and BMI 45.5 ± 5.4 ($p=0.01–0.05$ for between-group difference). Mean HbA1c level for those with diabetes was 7.6 ± 1.2%, while it was 5.7 ± 0.5% for those without diabetes ($p<0.01$). Of the women with diabetes, 79% were prescribed antidiabetic medication, including 29% who were on insulin. Baseline BMD at the spine, femoral neck, and total hip did not differ by diabetes status.

Mean preoperative marrow fat content in all participants was 49.6%, and there were no significant differences between diabetic and nondiabetic participants. At baseline, marrow fat content was positively associated with age, such that older participants had higher marrow fat content ($r=0.42$, $p=0.02$) (Table 2). There was a negative correlation between marrow fat and BMI, such that more obese participants had lower marrow fat content ($r=-0.37$, $p=0.04$).

At baseline, vertebral marrow fat content was inversely associated with BMD. Those with higher marrow fat content had lower vertebral vBMD (r=−0.72, p<0.01), and this was similar for women with and without diabetes. Those with higher marrow fat content had lower femoral neck aBMD (r=−0.65, p<0.01). Correlations with aBMD were r=−0.40, p=0.03 at the total hip, and r=−0.27, p=0.14 at the lumbar spine.

Changes in body composition and metabolic measures after RYGB

Of the initial 30 women who underwent baseline measurements, 25 women returned 6 months after RYGB. Two women moved away, 2 women had sleeve gastrectomy rather than RYGB, and 1 woman was unable to return due to limited time. After RYGB, all participants had dramatic weight loss, including total body fat loss (Table 3, Supplemental Tables 1 and 2). Participants lost a mean 27.3 ± 6.8 kg in weight and 19.3 ± 4.8 kg of total body fat (or 35.2 ± 9.7% of total body fat) over the 6 months. There were no significant differences in weight loss, although there was a trend for those with diabetes to lose a larger percentage of total body fat compared to those without diabetes. HbA1c decreased, more so in the participants with diabetes (−1.9 ± 1.1%, p<0.01 vs. baseline) compared to those without diabetes (−0.4 ± 0.4%, p<0.01). Of the 13 participants with preoperative diabetes, 10 participants (77%) had discontinued antidiabetic medication and had HbA1c <6.5% at the postoperative visit. There was a trend towards a difference in insulin-like growth factor 1 (IGF-1) change between those with and without diabetes. Those with diabetes had a 33 ng/mL increase (95% CI +2 to +64 ng/mL, p=0.04), while IGF-1 levels were stable in nondiabetics (+1 ng/mL, 95% CI −16 to +19 ng/mL, p=0.86; p=0.07 for difference between groups). There was no significant change in 25OHD or estradiol level (data not shown).

Changes in marrow fat after RYGB

Despite dramatic weight loss after RYGB, marrow fat content did not change significantly overall (−2.5%, 95% CI −6.5 to +1.4%, p=0.20). However, there was a significant difference in marrow fat change between participants with and without diabetes (8.3% difference, p=0.03) (Figure 1A). In nondiabetic women, marrow fat content was stable (+1.8%, 95% CI −1.8 to +5.4%, p=0.29), while in diabetic women, there was a significant decline (−6.5%, 95% CI −13.1% to 0%, p=0.05). Marrow fat content change was more variable in those with diabetes vs. those without diabetes, but in a sensitivity analysis excluding 2 diabetic women who were at the extremes of marrow fat change (11.5% gain and 27.8% loss), results were unchanged (8.0% difference, p=0.01).

Marrow fat change correlated with other metabolic changes after RYGB. In the cohort overall, greater declines in HbA1c were associated with declines in marrow fat (r=0.50, p=0.01) (Figure 1B). Increases in IGF-1 levels were associated with declines in marrow fat (r=−0.40, p=0.05) (Supplemental Figure 1). There was a trend towards a relationship between changes in visceral and marrow fat (r=0.38, p=0.06). We did not detect a significant association between age, lean mass, estradiol, leptin or lipid changes and changes in bone marrow fat.

In women without diabetes, although marrow fat change was stable on average, individuals who had more total body fat loss tended to have increases in marrow fat content (r=−0.70,

p=0.01) (Figure 2). This relationship was also observed for weight loss and marrow fat change. We did not observe a significant association between total body fat or weight change and marrow fat change in the entire cohort or the women with diabetes (Supplemental Table 3).

Changes in BMD after RYGB and Correlations with Marrow Fat Change

BMD decreased 6 months after RYGB, with overall aBMD changes of −4.3 ± 4.1% at the femoral neck and −4.1 ± 2.8% at the total hip, and a spinal vBMD change of −6.4 ± 5.9% ($p<0.01$ for all). Mean change in aBMD at the lumbar spine was −0.7 ± 3.5% (p=0.31). Those without diabetes had greater femoral neck aBMD decline after RYGB compared to those with diabetes, with similar trends in the spine vBMD and aBMD changes (Table 3).

Not only was marrow fat content associated with BMD at baseline, as stated above, but also longitudinal changes in marrow fat content and BMD were inversely related (Figure 3, Supplemental Table 3), such that those with increases in marrow fat content had more BMD loss in both spine vBMD ($r=-0.58$, $p<0.01$) and femoral neck aBMD ($r=-0.49$, p=0.01). After adjustment for age and menopausal status, for each SD increase in vertebral marrow fat content change, vertebral vBMD declined by an additional 2.9% (p=0.02) and femoral neck aBMD by an additional 2.5% ($p<0.01$). There was not evidence of a correlation between changes in marrow fat and total hip aBMD ($r=-0.07$, p=0.75) or lumbar spine aBMD ($r=-0.30$, p=0.14).

Discussion

In our longitudinal study of 30 obese women stratified by preoperative diabetes status, we examined vertebral marrow fat content and BMD changes over the 6 months after RYGB. We demonstrated a novel finding in humans: that marrow fat changes correlated with BMD decline, such that those with increases in marrow fat content had greater decreases in BMD. Further, changes in glucose metabolism and fat compartments appear to be associated with marrow fat change.

Cross-sectional studies have demonstrated an inverse relationship between marrow fat content and BMD,[3–7] and in our study, baseline marrow fat content negatively correlated with spinal vBMD and femoral neck and total hip aBMD. Six months after RYGB, mean spinal vBMD declined by 6.4% and femoral neck aBMD by 4.3%, on par with the declines reported in other studies of RYGB.[40, 41] We showed, longitudinally, that changes in marrow fat were negatively correlated with changes in BMD at both the spine and femoral neck, relationships that were not explained by age or menopausal status. Although marrow adipocyte characteristics differ in the spine compared to the femur,[42] and our study involved vertebral marrow fat evaluation only, others have demonstrated moderate correlations between the two sites.[43] While animal studies of caloric restriction demonstrate inconsistent results regarding marrow fat (with some studies showing that bone loss occurs in the setting of stable or declining marrow fat),[44, 45] our findings are consistent with those of Griffith *et al.*, whose study of elderly postmenopausal women showed that baseline femoral neck marrow fat content was a predictor of BMD change by serial DXA. After four years, those with higher marrow fat at baseline had greater femoral neck BMD

loss (4.7% vs. 1.6%, p=0.06).[8] Our study design went one step further, though, by assessing marrow fat *change* and documenting an association with BMD loss.

A novel finding of our study is that improvement in glycemic control is associated with longitudinal marrow fat change in humans. There was a significant difference in marrow fat response to RYGB between women with and without diabetes. Among the entire cohort (women with and without diabetes), those with greater HbA1c improvements had greater marrow fat declines. These findings complement the literature that suggests that diabetes is a state of increased marrow fat.[46] Insulin resistance is associated with higher circulating free fatty acids and triglyceride storage in ectopic sites such as the liver and muscle. In a mouse model of insulin resistance, marrow fat expansion occurred concurrently with insulin resistance.[47] Animal models of both type 1 and type 2 diabetes have demonstrated increased marrow fat and bone mass loss compared to controls.[48, 22, 23] In humans, marrow fat differences with diabetes are less clear,[49, 43, 50, 32] although in one recent study of morbidly obese adults, participants with type 2 diabetes had higher amounts of marrow fat than nondiabetics.[51] Similarly, Baum *et al.* found in their study of 26 postmenopausal women (13 with type 2 diabetes and 13 age- and BMI-matched controls) that those with higher HbA1c levels had higher vertebral marrow fat content ($r=0.83$, $p<0.01$).[24] In our study, we did not identify a higher mean marrow fat content among diabetic vs. nondiabetic women, but our longitudinal findings support the influence of glucose metabolism on marrow fat. We did observe greater BMD declines in those without diabetes, compared to those with diabetes, which would support the implication that marrow fat decreases could attenuate bone loss. However, because other bariatric studies have not reported differences in bone loss by diabetes status, we are cautious about the interpretation of this result and acknowledge that skeletal effects of diabetes and bariatric surgery are complex.

Among women without baseline diabetes, we can assess effects of RYGB with less concurrent change in glycemic control. Despite a 32% loss of total body fat, there was on average no significant change in marrow fat. This adds to the evidence that marrow fat functions as a unique fat depot and does not necessarily decline even with dramatic reductions in total fat mass. We had hypothesized that dramatic weight loss might actually increase marrow fat content, based on rodent and human models of starvation. Caloric restriction in young mice is associated with higher levels of marrow fat, and women with anorexia nervosa have striking elevations of marrow fat compared to controls.[13, 14] While the group of women without diabetes did not demonstrate change in marrow fat on average, *individual* changes in marrow fat ranged from +11% to −9%. This variability is partly accounted for by differences in loss of total body fat. Those who lost more total body fat were more likely to have increases in marrow fat ($r=-0.70$, $p=0.01$). It is possible that those with the greatest losses of total body fat had related metabolic changes more similar to a state of starvation. Ultimately, the physiologic underpinnings of weight loss in an obese person are likely to be distinct from those of weight loss in a normal or underweight person (as in anorexia). This distinction is suggested by the results of a recent study in mice, in which mice fed a high-fat diet then switched to a normal diet experienced weight loss and a decrease in marrow fat at the tibia and femur.[52]

We observed a distinct trend for the relationship between marrow fat and visceral fat. At baseline, those with more visceral fat had higher marrow fat content, and those who lost more visceral fat tended to have a decrease in marrow fat. There may be common metabolic factors that regulate both marrow and visceral fat, just as marrow fat has been associated with intrahepatic and intramyocellular lipids.[53] The positive relationship between the visceral and marrow fat depots has been observed in cross-sectional studies[24, 54, 55] and a longitudinal study of bariatric surgery,[56] although it was not found in a longitudinal study of dietary weight loss.[57] Thus, the relationship between changes in marrow fat and other fat depots does not appear uniform and may depend on the relative contribution of visceral fat loss.

Regulators of the marrow fat-bone relationship are not understood, although the growth hormone and IGF-1 axis may be implicated due to its role in lipolysis and bone formation. We identified an inverse relationship between IGF-1 and marrow fat changes, such that women who had increases in serum IGF-1 levels tended to have declines in marrow fat. Interestingly, women with diabetes had an increase in IGF-1 after RYGB, which may be due to dramatic improvements in glycemic control.[58] IGF-1 changes did not correlate with BMD change in our study (data not shown), but IGF-1's anabolic effects on bone are undisputed, and a positive relationship between IGF-1 level and BMD has been observed in other human studies.[59, 60] Rats subjected to hypophysectomy had increased marrow fat and reduced bone growth and mineralizing perimeter, which were reversed with GH replacement.[61] In a cross-sectional study of obese premenopausal women, those with higher levels of IGF-1 had lower vertebral marrow fat content, independent of age and BMI.[55] IGF-1 may thus be a mechanistic link between marrow fat and BMD.

While changes in marrow fat content may play a role in loss of bone mass, RYGB-induced bone loss is presumably multifactorial. In our data, even those with decreases in marrow fat content still lost BMD, signaling that other mechanisms are at play. These mechanisms may include mechanical unloading of the skeleton and changes in levels of sex hormones, adipokines, and gut-secreted hormones. We see, however, that those with decreases in marrow fat have mitigated declines in bone mass compared to those with marrow fat increases, indicating that marrow fat change could contribute to the skeletal effects of RYGB.

Two other studies have examined vertebral marrow fat in subgroups of participants who have had RYGB. In 11 people undergoing RYGB, Bredella *et al.* found no significant change in vertebral marrow fat content after 12 months, and no relationship between marrow fat and BMD changes.[56] These RYGB participants, 2 of whom had diabetes, were compared to 10 individuals who underwent sleeve gastrectomy, in whom marrow fat content increased. Similarly, Ivaska *et al.* found no significant 6-month change in vertebral marrow fat content in 7 RYGB patients or 14 sleeve gastrectomy patients.[62] In contrast, we were able to detect a relationship between change in marrow fat content and BMD loss and to further explore the relationship between glycemic change and marrow fat, due to our somewhat larger sample size and study design including stratified enrollment by diabetes status. Larger studies with the consideration of diabetes status are needed to confirm our findings.

A limitation of this study is the modest duration of follow-up. Changes in marrow fat content over 6 months may be different than long-term changes in marrow fat after weight loss stabilization, although the majority of weight loss is achieved during the first 6 months after RYGB. We did not manage each diabetic participant's antidiabetic medication regimen; prior to surgery, the majority of diabetic participants were treated with an oral antidiabetic medication or insulin, and there was variable discontinuation of these medications 6 months after RYGB. In addition, given the stratification by diabetes status, the subgroups were relatively small, and correlations observed for the combined cohort were not always statistically significant for the subgroups. For example, the relationship between marrow fat change and spinal vBMD loss was definite among those with diabetes but not statistically significant among those without diabetes, therefore we cannot be certain this association is valid in the nondiabetic population. Finally, we did not measure femoral marrow fat, so although vertebral and femoral marrow fat are modestly correlated,[43] future studies are needed to determine if changes in femoral marrow fat directly correlate with BMD loss. A strength of our study is the use of advanced skeletal imaging. There are concerns about DXA artifact in the setting of marked weight loss due to changes in soft tissue composition,[63, 64] and we used QCT to measure volumetric BMD at the L3 and L4 vertebrae. Obesity and weight loss can also influence QCT assessments, but QCT avoids the traditional biases of DXA.[65] Marrow fat may also influence BMD measurements, although the estimated size of such an effect is much smaller than the effects we report.[66]

In conclusion, our study demonstrated that longitudinal changes in marrow fat content correlated with BMD declines 6 months after RYGB. Glucose metabolism was an important determinant of marrow fat change, and improvements in glycemic control were associated with decreases in marrow fat content. In those without diabetes, marrow fat content was maintained on average after RYGB, but the extent of total fat loss correlated with variability in marrow fat change such that those with greater total fat loss tended to have increases in marrow fat. Regulators of the marrow fat-bone relationship are uncertain, but our data suggest that IGF-1 may play a role. Further research is needed to understand mechanisms for the marrow fat-bone interaction and possible regulation by glucose metabolism. Ultimately, understanding the role of marrow fat in bone metabolism could lead to the development of strategies targeted to the prevention and treatment of osteoporosis, skeletal complications of bariatric surgery, and diabetic bone fragility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Authors' roles: Study design: ALS, AVS, and DMS. Study conduct: TYK, XL, LS, SJR, JTC, AMP, and ALS. Data collection: TYK, ALS. Data analysis: TYK, XL, KX, DP and ALS. Data interpretation: TYK, AVS, XL, DMB, DMS and ALS. Drafting manuscript: TYK. Revising manuscript content: All authors. Approving final version of manuscript: All authors. TYK and ALS take responsibility for the integrity of the data analysis.

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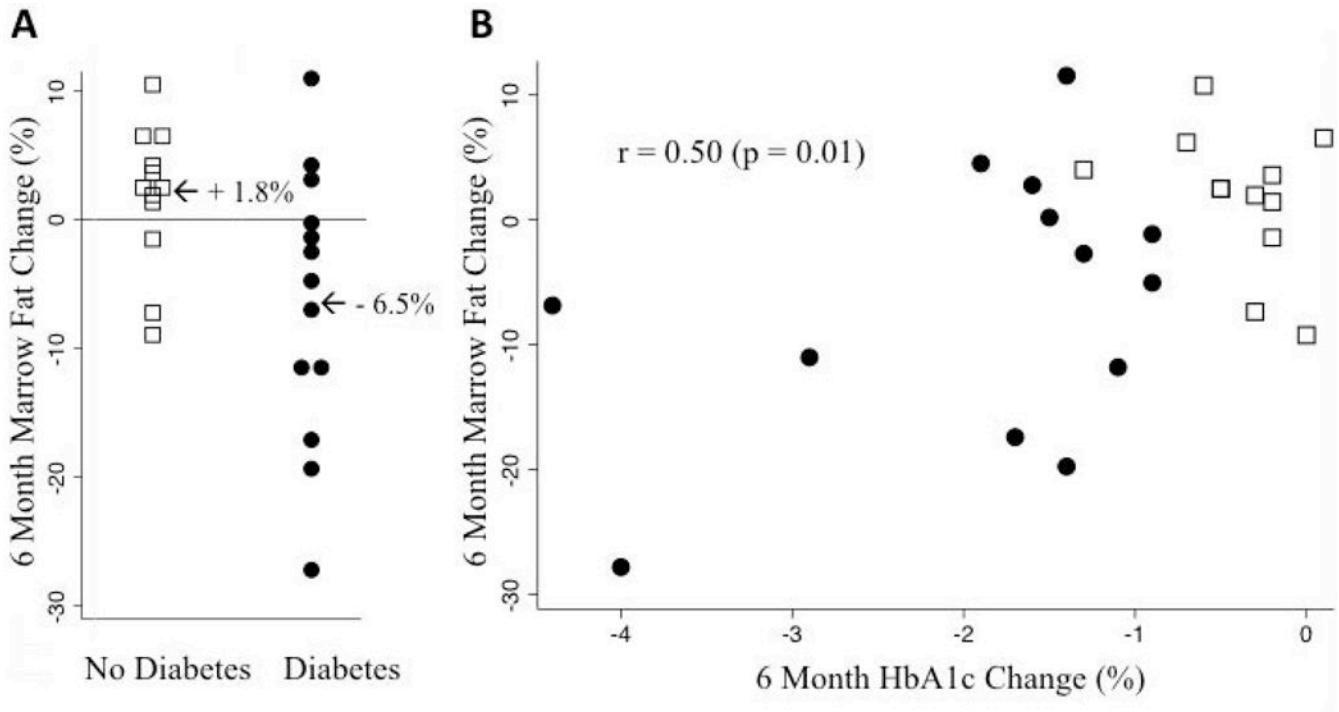

Figure 1.

Six-month changes in vertebral marrow fat content, stratified by preoperative diabetes status (A), and correlated with changes in hemoglobin A1c (B). Dark circles represent participants with preoperative diabetes, and white squares represent participants without preoperative diabetes.

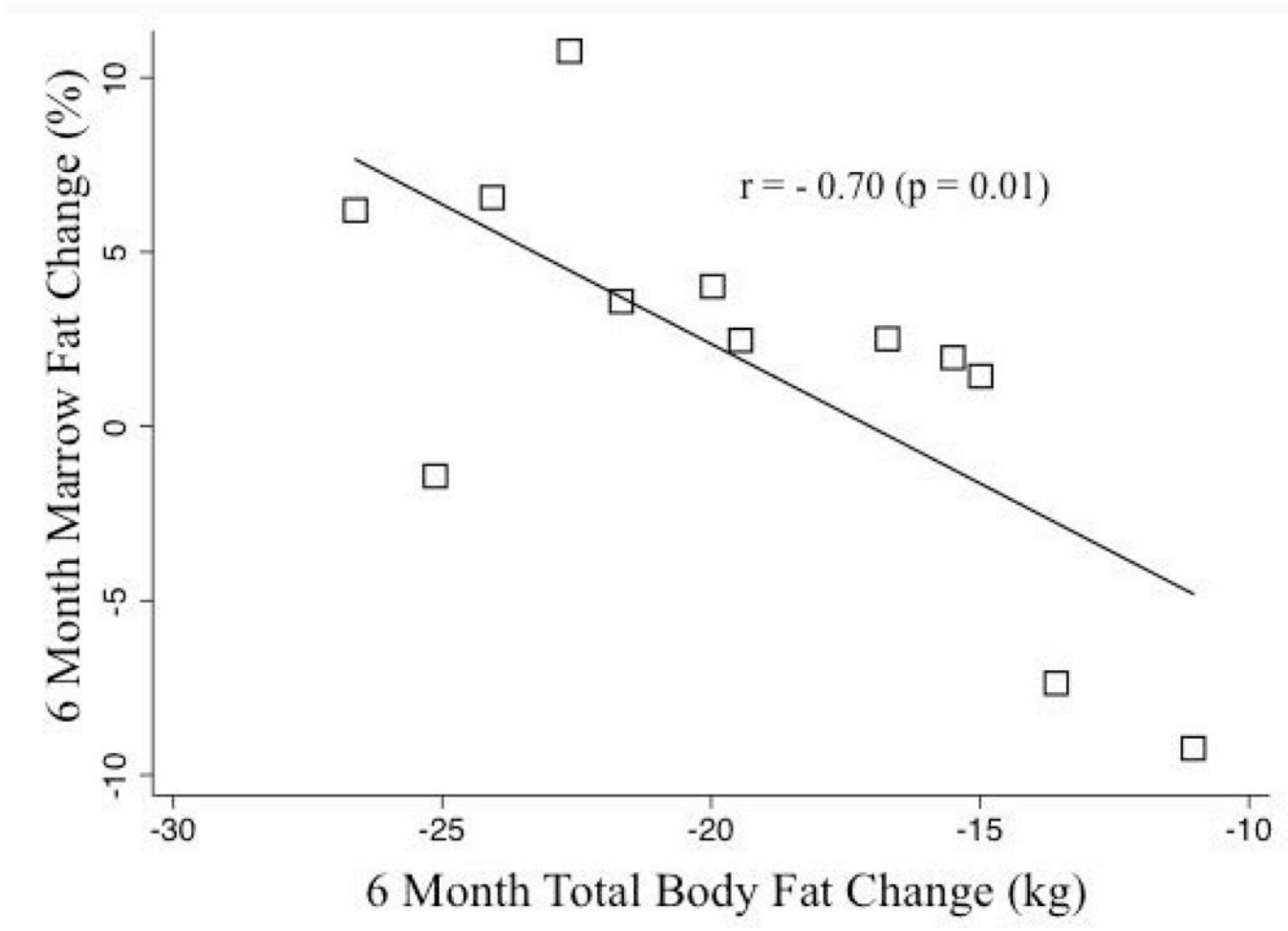

Figure 2.
Correlation between 6-month changes in total body fat and vertebral marrow fat content in participants without preoperative diabetes.

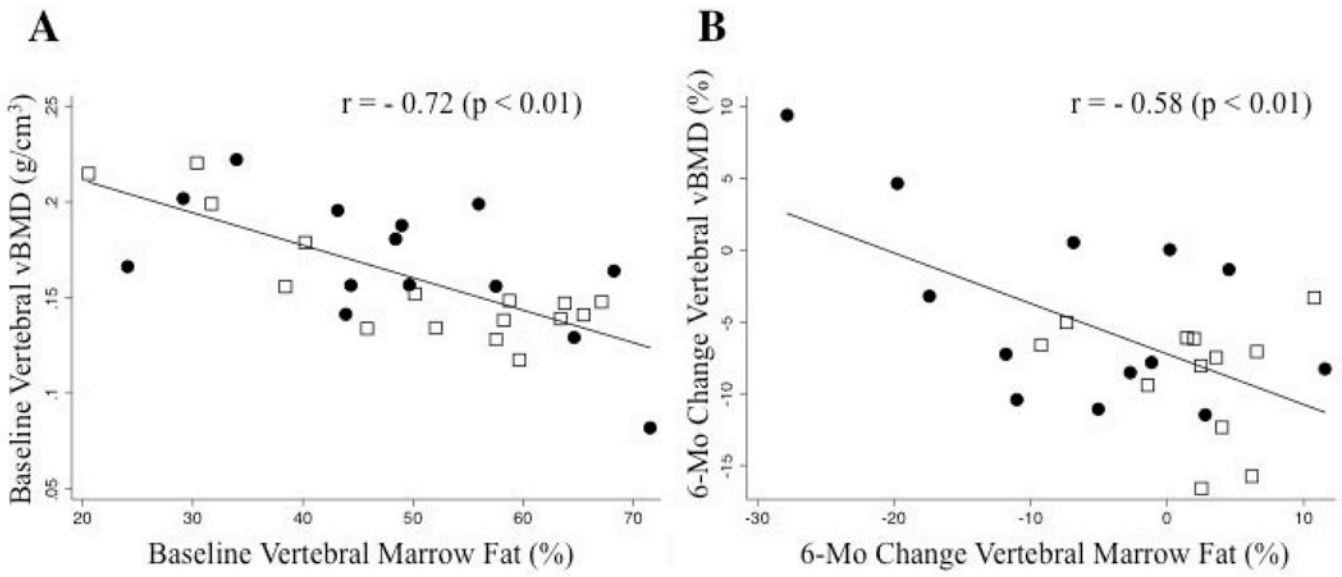

Figure 3.

Correlation between vertebral marrow fat content and vertebral volumetric bone mineral density at baseline (A) and with 6-month changes (B). Dark circles represent participants with preoperative diabetes, and white squares represent participants without preoperative diabetes.

Table 1

Baseline characteristics prior to surgery

	All subjects (n=30)	Diabetic subjects (n=14)	Nondiabetic subjects (n=16)	P-value
Age, year	48.2 ± 11.7	48.2 ± 12.0	48.1 ± 11.9	0.98
Postmenopausal, n	11 (37%)	4 (29%)	7 (44%)	0.39
Race, n				
White	13 (43%)	6 (43%)	7 (44%)	0.57
Black	10 (33%)	4 (29%)	6 (38%)	
Hispanic	6 (20%)	4 (29%)	2 (13%)	
Asian	1 (3%)	0 (0%)	1 (6%)	
Weight, kg	117.5 ± 17.1	109.3 ± 16.3	124.7 ± 14.9	0.01
BMI, kg/m^2	43.7 ± 5.7	41.6 ± 5.3	45.5 ± 5.4	0.05
Total body fat, kg	56.9 ± 10.6	51.3 ± 10.1	61.8 ± 8.6	< 0.01
Total body lean mass, kg	56.6 ± 8.0	54.3 ± 8.1	58.5 ± 7.6	0.15
Visceral fat, cm^2	177.9 ± 79.3	197.3 ± 96.9	161.0 ± 58.0	0.22
HbA1c, %	6.6 ± 1.3	7.6 ± 1.2	5.7 ± 0.5	< 0.01
25OHD, ng/mL	41.3 ± 12.2	44.9 ± 13.3	38.1 ± 10.7	0.13
IGF-1, ng/mL	89.8 ± 36.9	88.8 ± 41.3	90.7 ± 33.9	0.89
Total cholesterol, mg/dL	155 (137 – 199)	146 (126 – 163)	188 (144 – 212)	0.08
Triglyceride, mg/dL	94 (79 – 125)	92 (80 – 124)	96 (76 – 131)	0.92
Leptin, ng/mL	53 (35 – 66)	45 (27 – 53)	64 (51 – 68)	0.05
aBMD (DXA), g/cm^2				
Femoral neck	0.908 ± 0.144	0.917 ± 0.169	0.900 ± 0.124	0.75
Total hip	1.073 ± 0.151	1.115 ± 0.192	1.035 ± 0.095	0.18
Lumbar spine	1.134 ± 0.137	1.177 ± 0.151	1.096 ± 0.114	0.11
vBMD (QCT), g/cm^3				
Lumbar spine	0.161 ± 0.033	0.167 ± 0.036	0.156 ± 0.031	0.37
Spine marrow fat (MRS), %	49.6 ± 13.9	48.8 ± 14.0	50.2 ± 14.2	0.79

Values are means ± SD, counts (percentages) or median (interquartile range)

P-values are for between group differences

Areal BMD (aBMD); volumetric BMD (vBMD); magnetic resonance spectroscopy (MRS)

Table 2

Body composition and skeletal correlates of vertebral marrow fat content at baseline

	Baseline vertebral marrow fat content (%) (n = 30)
Age	r=0.42, p=0.02
Body mass index	r=−0.37, p=0.04
Total body fat mass	r=−0.30, p=0.10
Total body lean mass	r=−0.36, p=0.05
Visceral fat	r=0.33, p=0.07
Femoral neck aBMD	r =−0.65, p<0.01
Total hip aBMD	r =−0.40, p=0.03
Lumbar spine aBMD	r =−0.27, p=0.14
Lumbar spine vBMD	r =−0.72, p<0.01

Values are Pearson's coefficients of correlation and corresponding p-values

Areal bone mineral density (aBMD); volumetric bone mineral density (vBMD)

Table 3

Six-month changes after Roux-en-Y gastric bypass

	All subjects (n = 25)	Diabetic subjects (n = 13)	Nondiabetic subjects (n = 12)	Between-group p-value
Weight, kg	−27.3 ± 6.8 *	−27.3 ± 7.2 *	−27.4 ± 6.6 *	0.96
Total body fat, kg	−19.3 ± 4.8 *	−19.3 ± 4.9 *	−19.3 ± 4.9 *	1.00
Total body fat, %	−35.2 ± 9.7 *	−38.4 ± 10.5 *	−31.7 ± 7.7 *	0.08
Total body lean mass, kg	−7.2 ± 3.1 *	−7.3 ± 2.9 *	−7.0 ± 3.4 *	0.82
Visceral fat, %	−44 ± 17 *	−49 ± 18 *	−39 ± 16 *	0.15
HbA1c, abs %	−1.2 ± 1.1 *	−1.9 ± 1.1 *	−0.4 ± 0.4 *	<0.01
IGF-1, ng/mL	+18 ± 44	+33 ± 51 *	+1 ± 28	0.07
Total cholesterol, mg/dL	−1 (−20 – +13)	+5 (−20 – +36)	−5 (−15 – +3)	0.40
Triglyceride, mg/dL	−8 (−32 – +1) *	−13 (−37 – +1)	−6 (−31 – +3)	0.55
Leptin, ng/mL	−29 (−36 – −19) *	−28 (−35 – −17) *	−32 (−41 – −26) *	0.30
aBMD (DXA), %				
Femoral neck	−4.3 ± 4.1 *	−2.5 ± 4.3	−6.2 ± 2.9 *	0.02
Total hip	−4.1 ± 2.8 *	−4.0 ± 3.0 *	−4.2 ± 2.7 *	0.82
Lumbar spine	−0.7 ± 3.5	+0.4 ± 2.8	−2.0 ± 4.0	0.09
vBMD (QCT), %				
Lumbar spine	−6.4 ± 5.9 *	−4.2 ± 6.5 *	−8.7 ± 4.2 *	0.05
Marrow fat (MRS), abs %				
Lumbar spine	−2.5 ± 10	−6.5 ± 11	+1.8 ± 5.6	0.03

Values are means ± SD or median (interquartile range)

Areal BMD (aBMD), volumetric BMD (vBMD), magnetic resonance spectroscopy (MRS)

* $p < 0.05$ compared to baseline