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Increases in PYY and Uncoupling of Bone Turnover Are Associated with Loss of Bone Mass After Gastric Bypass Surgery

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Abstract

Context: The gut hormones peptide YY (PYY) and ghrelin mediate in part the metabolic benefits of Roux-en-Y gastric bypass (RYGB) surgery. However, preclinical data suggest these hormones also affect the skeleton and could contribute to postoperative bone loss.

Objective: We investigated whether changes in fasting serum total PYY and ghrelin were associated with bone turnover marker levels and loss of bone mineral density (BMD) after RYGB.

Design, Setting, Participants: Prospective cohort of adults undergoing RYGB (n=44) at San Francisco academic hospitals.

Main Outcome Measures: We analyzed 6-month changes in PYY, ghrelin, bone turnover markers, and BMD by dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT). We calculated the uncoupling index (UI), reflecting the relative balance of bone resorption and formation.

Results: Postoperatively, there was a trend for an increase in PYY (+25 pg/mL, p=0.07) and a significant increase in ghrelin (+192 pg/mL, p<0.01). PYY changes negatively correlated with changes in spine BMD by QCT (r=−0.36, p=0.02) and bone formation marker P1NP (r=−0.30, p=0.05). Relationships were significant after adjustments for age, sex, and weight loss. No

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consistent relationships were found between ghrelin and skeletal outcomes. Mean 6-month UI was −3.3; UI correlated with spine BMD loss by QCT (r=0.40, p=0.01).

Conclusions: Postoperative PYY increases were associated with attenuated increases in P1NP and greater declines in spine BMD by QCT. Uncoupling of bone turnover correlated with BMD loss. These findings suggest a role for PYY in loss of bone mass after RYGB and highlight the relationship between intestinal and skeletal metabolism.

Précis

Six months after gastric bypass surgery, PYY changes negatively correlated with changes in spine BMD and P1NP. Uncoupling of bone turnover correlated with spine BMD loss.

Keywords

PYY; ghrelin; BMD; bone turnover; Roux-en-Y gastric bypass surgery

1. Introduction

Bariatric surgery is an effective strategy against morbid obesity, resulting in dramatic and sustained weight loss, resolution of obesity-related comorbidities, and a mortality benefit (1, 2). However, these otherwise beneficial procedures have negative effects on the skeleton, with dramatic increases in bone turnover, declines in bone mineral density (BMD), and increased fracture incidence (3–6). Mechanisms include mechanical unloading of the skeleton due to weight loss and nutritional deficiencies from impaired calcium and vitamin D absorption, but dynamic changes in gut hormones may also contribute to altered skeletal metabolism (7–9). Gut hormones play a crucial role in the metabolic benefits of bariatric surgery, and a growing body of literature supports the concept of a “gut-bone” axis (10, 11).

Of the gut hormones, peptide YY (PYY) and ghrelin may play a role in the skeletal effects of bariatric surgery. PYY, secreted from intestinal L-cells in response to nutrient stimulation, promotes satiety and is an important regulator of energy homeostasis (12–14). PYY directly acts on Y1 receptors on osteoblasts, and deletion of this receptor has been shown to enhance bone mass (15). $PYY^{-/-}$ mice have increased bone formation and mineral apposition rates by histomorphometry, without an effect on osteoclast surface or number, and demonstrate greater distal femoral cancellous bone volume and greater lumbar spine bone mass (16). In contrast to the negative skeletal effects of PYY, ghrelin may stimulate bone formation. Ghrelin is secreted from oxyntic glands in the gastric fundus, increases with prolonged fasting, promotes hunger, and also plays an important role in energy homeostasis (17–19). Ghrelin binds to growth hormone secretagogue receptor 1a, and therefore may promote bone formation through its effects on growth hormone and insulin-like growth factor-1 (IGF-1) secretion. Ghrelin directly stimulates osteoblast proliferation and differentiation *in vitro* and increases BMD in rats when administered intraperitoneally (20).

Efforts to understand the effects of gut hormones on skeletal metabolism after bariatric surgery have been hindered by small sample sizes and limited skeletal outcomes in prior studies. Studies have relied on bone turnover markers or areal BMD measurements by dual-energy x-ray absorptiometry (DXA) (21, 22), but DXA-based measurements of BMD may

be biased in the setting of marked weight loss due to changes in soft tissue composition surrounding bone (23, 24). Moreover, spinal BMD measurements by DXA may be influenced by degenerative changes.

Our group conducted a prospective cohort study of gastric bypass surgery and skeletal health, the largest to date to use advanced skeletal imaging modalities including qualitative computed tomography (QCT) in addition to DXA. In this ancillary study, we measured changes in PYY and ghrelin and examined relationships between those changes and changes in bone turnover markers and BMD by DXA and QCT. Given that multiple factors influence postoperative bone resorption and formation, we calculated the uncoupling index; this relative measure reflects the balance between bone resorption and formation markers, and its novel application in the bariatric surgery context may elucidate underlying mechanisms. We hypothesized that changes in PYY and ghrelin are associated with bone turnover marker levels and BMD loss after gastric bypass surgery.

2. Material and Methods

2.1 Study population

This was an ancillary investigation to a larger study that examined calcium metabolism and skeletal changes after gastric bypass surgery (3, 7). We recruited adults aged 25 to 70 years from two academic bariatric surgery centers (the University of California, San Francisco, and the San Francisco Veterans Affairs Medical Center). Participants were eligible if they were scheduled for an upcoming gastric bypass procedure. We excluded women who were perimenopausal (defined as last menses >3 months but <5 years ago), in order to minimize skeletal changes unrelated to gastric bypass surgery. Premenopausal women on stable hormonal contraception, postmenopausal women on stable menopausal hormone therapy, and men on stable testosterone were eligible. We excluded those who used medications known to impact bone metabolism, including bisphosphonates or teriparatide (in the last year or for >12 months ever), oral glucocorticoids, and thiazolidinediones. Other exclusion criteria included prior bariatric surgery, weight >159 kg (the DXA scanner weight limit), estimated glomerular filtration rate <30 mL/min/1.73m^2, and disorders of calcium or bone metabolism (e.g., primary hyperparathyroidism or Paget's disease).

Of the 48 participants who contributed pre- and postoperative data to the study, this ancillary study includes the 44 with available preoperative and 6-month postoperative serum samples.

2.2 Study protocol

Participants attended study visits preoperatively and at 6 months postoperatively. We provided each participant with 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 the postoperative period. Low 25-hydroxyvitamin D levels were repleted after enrollment with a target level >30 ng/mL, and vitamin D supplements were postoperatively titrated to maintain that target level.

The Roux-en-Y gastric bypass procedure was performed in a standardized laparoscopic fashion at both academic bariatric surgery centers. This included a 30-mL gastric pouch, a gastrojejunal anastomosis created with a 25-mm circular stapler, an antecolic and antegastric Roux limb 100 to 150 cm in length, and an end-to-side jejunostomy.

Our institutional review board approved the study protocol, and all participants provided written informed consent. The study was registered at www.clinicaltrials.gov ().

2.3 Biochemical assays

Serum samples were collected preoperatively and at 6 months postoperatively after an overnight fast. Serum chemistries were measured and 25-hydroxyvitamin D levels were determined by liquid chromatography tandem mass spectrometry (LC-MS/MS), and intact parathyroid hormone (PTH) was measured by automated chemiluminescent immunoassay (ADVIA Centaur, Siemens Healthineers, Erlangen, Germany). 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). Serum bone turnover markers C-terminal telopeptide of type I collagen (CTX), procollagen type 1 N propeptide (P1NP), bone-specific alkaline phosphatase (BSAP), and osteocalcin (OC) were measured by automated immunoassay (iSYS, Immunodiagnostic Systems, Scottsdale, AZ, USA), with inter- and intra-assay CVs 6.2% and 3.2%, 4.6% and 2.9%, 7.3% and 1.6%, and 6.1% and 2.5%, respectively. Total PYY and total ghrelin were measured by ELISA (EMD Millipore, St. Charles, MO, USA) from participants with complete sets of baseline and 6-month serum samples (n=44). PYY had inter- and intra-assay CVs of 7.4% and 2.3%, respectively, with a lowest level of detection at 6.5 pg/mL. Ghrelin had inter- and intra-assay CVs of 6.6% and 1.3%, respectively, with a lowest level of detection at 50 pg/mL.

2.4 Body composition and skeletal imaging

Preoperatively and 6 months postoperatively, body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Whole-body fat and lean mass (g), and areal BMD (g/cm^2) were measured preoperatively and 6 months postoperatively by DXA (Hologic Discovery W densitometer; Hologic, Bedford, MA, USA). Modified half-body scans were employed if a participant's body dimensions exceeded the width of the scanning area (26). Spinal volumetric BMD (g/cm^3) at the L_3 and L_4 vertebrae was assessed by QCT (General Electrics VCT64 scanner; General Electric, Milwaukee, WI, USA), using previously described methods and software (Mindways Software, Austin, TX, USA) (27, 28).

2.5 Statistical analysis

We assessed baseline characteristics for normality and determined means ± standard deviations (SD) or medians (interquartile ranges, IQR) as appropriate. We calculated an uncoupling index to assess the relative balance of bone resorption and formation, based on a formula proposed by Eastell et al. (29) and others (30, 31). The mean and SD of the baseline values for each bone turnover marker were first determined. Then *Z*-scores were calculated for each subject at each time point, using the formula: (Subject value – $\text{Mean}_{\text{baseline}}$)/ $\text{SD}_{\text{baseline}}$. The uncoupling index was calculated as the difference between the average of the *Z*-scores for the bone formation markers from the *Z*-score of the bone resorption marker:

($Z_{P1NP} + Z_{BSAP} + Z_{OC}$)/3 – Z_{CTX}. Other groups have calculated the uncoupling index using reference data for bone turnover markers rather than baseline values (29, 32), therefore this method was utilized as well. We also calculated the uncoupling index using only P1NP and CTX, the bone formation and resorption markers that are more commonly available. With both methods, a negative uncoupling index would indicate an imbalance favoring resorption, whereas a positive uncoupling index would indicate an imbalance favoring formation.

Paired *t* tests or Wilcoxon signed-rank tests were used to determine whether study outcomes changed between preoperative and 6-month postoperative time points. All reported values had a normal distribution, therefore we used Pearson's rank coefficient of correlation to characterize the unadjusted relationship between changes in gut hormones and the uncoupling index with skeletal changes. As this is a small exploratory study, no formal adjustments for multiple comparisons were made. Instead, we avoided over-interpretation of isolated findings of nominal statistical significance by examining the magnitude, direction, and consistency of estimated effects, and by interpreting findings in the light of relevant biology. We used linear models to estimate associations between 6-month changes in PYY, ghrelin, and the uncoupling index with skeletal outcomes. We considered age, race, sex, diabetes status, weight loss, and use of hormone therapy (oral contraceptive, menopausal hormone therapy, or testosterone therapy) as potential covariates. Given our modest sample size, we performed stepwise regression with backward selection in order to determine key influential variables. Using a significance level threshold of p=0.20 for removal from the model, we found sex and weight loss to be key variables. Given the important effects of age on gut hormones and skeletal outcomes, we included age in our model for face validity. Residuals were used to check the assumptions of normality and linearity and to check for influential points. Data were analyzed using Stata 14 software (StataCorp, College Station, TX, USA).

3. Results

3.1 Baseline characteristics

Participants were 45 ± 12 (mean ± SD) years old (Table 1). Thirty-four (77%) of the participants were women, and 57% of the participants were white. Mean preoperative weight was 122 ± 19 kg, and mean BMI was 44 ± 7 kg/m^2. All participants had areal BMD *Z*-scores by DXA within the expected range for age.

Mean fasting PYY and ghrelin levels were 155 ± 95 pg/mL and 444 ± 245 pg/mL, respectively. One participant had a baseline ghrelin measurement that could not be detected and was thus excluded from analyses of ghrelin level.

3.2 Changes in body composition and gut hormones after gastric bypass surgery

All participants lost weight in the 6 months after gastric bypass surgery, with a mean (standard error of the mean, SEM) weight loss of 31 kg (1 kg) ($p<0.01$, Table 2). Total body fat mass decreased by 40 % (1 %) and total body lean mass decreased by 13 % (1 %) ($p<0.01$ for both).

There was a trend towards an increase in PYY level, 25 pg/mL (13 pg/mL) (p=0.07), and ghrelin level significantly increased after surgery, 192 pg/mL (36 pg/mL) (p<0.01). Changes in PYY and ghrelin did not correlate with age or differ by sex, race, or hormone use (data not shown). Ghrelin changes negatively correlated with total body fat change, but otherwise there were no correlations between gut hormones and body composition or metabolic parameters (Table 3).

3.3 Changes in calciotropic hormones, bone turnover markers and BMD after gastric bypass surgery

Despite small postoperative decreases in 25-hydroxyvitamin D levels, with active supplementation the 6-month mean level was 38 ± 12 ng/mL (Table 2). Serum PTH increased by 7 pg/mL (3 pg/mL), p=0.03. All bone turnover markers significantly increased after surgery (Table 2). At the hip, areal BMD by DXA decreased after surgery, with declines of 5.1 % (0.7 %) at the femoral neck and 4.7 % (0.7 %) at the total hip (p<0.01 for all). There was no significant change in spine areal BMD measured by DXA, 0 % (0.8 %), p=0.96. However, spine volumetric BMD by QCT decreased by 6.8 % (0.8 %), p<0.01.

In unadjusted analyses, 6-month changes in PYY were associated with changes in P1NP, OC, and spine volumetric BMD by QCT (Table 3). Six-month changes in ghrelin were associated with changes in spine BMD by DXA. After adjustment for age, sex, and weight loss, the relationships that remained statistically significant were between PYY and P1NP, and PYY and spine volumetric BMD. One standard deviation increase in PYY was associated with a 7.9 ng/mL decrease in P1NP (p=0.04); because the majority of participants had increases in bone turnover and P1NP level, this indicates that greater increases in PYY were associated with attenuated increases in P1NP. One standard deviation increase in PYY was associated with a 0.003 g/cm^3 (1.6%, p=0.03) decrease in spine volumetric BMD, indicating that greater increases in PYY were associated with greater declines in spine volumetric BMD (Figure 1).

3.4 Uncoupling index and the relationship between bone turnover markers with BMD changes

Postoperatively, the uncoupling index was −3.3 ± 2.0, representing a greater than 3-fold relative increase in bone resorption markers compared to bone formation markers. The 6-month uncoupling index did not correlate with changes in PYY or ghrelin (Table 3). However, the 6-month uncoupling index did correlate with change in spine volumetric BMD (r=0.40, p=0.01), such that a greater imbalance favoring bone resorption was associated with greater spine BMD loss (Figure 2). In a model adjusted for age, sex and weight loss, a standard deviation change in the uncoupling index favoring bone resorption was associated with a 0.003 g/cm^3 (1.9%, p=0.01) decrease in spine volumetric BMD. There were no relationships identified between the 6-month uncoupling index and changes in hip BMD by DXA. The uncoupling index was also calculated using manufacturer reference data for bone turnover markers and with only P1NP and CTX, and similar results were obtained.

4. Discussion

We analyzed the relationships between gut hormones and skeletal outcomes in a prospective cohort study of adults undergoing gastric bypass surgery, seeking to explore potential contributors to declines in bone mass observed after surgical weight loss. We found that greater increases in PYY were associated with greater 6-month declines in spine volumetric BMD. As described previously, biochemical markers of bone resorption and bone formation rose dramatically after surgery. However, we demonstrated here that increases in PYY correlated with attenuated increases in the bone formation marker P1NP. The uncoupling of bone turnover, as measured by the uncoupling index, was also associated with changes in BMD, such that those with a greater postoperative uncoupling favoring resorption had worse declines in BMD by QCT.

Independent of weight loss, changes in PYY negatively correlated with BMD changes after gastric bypass surgery. This relationship was detected with QCT assessments of volumetric BMD and not by DXA assessments of areal BMD. After gastric bypass surgery, volumetric BMD changes at the spine are generally more substantial than areal BMD changes (33, 34), and QCT-based assessments may be a more accurate measure in the setting of dramatic weight loss (35). We suspect we were able to detect a relationship between changes in PYY and spine volumetric BMD because the spine has more trabecular bone, which is considered more metabolically active. It is likely that the other multifactorial causes of skeletal loss after gastric bypass surgery, including mechanical unloading, have differential effects on cortical bone and are responsible for BMD loss at the hip. The correlation between PYY and BMD was modest and speaks to the multiple factors influencing BMD loss after bariatric surgery (5, 36). For example, our group has previously reported that BMD loss differs by sex and menopause status, although not explained by changes in estradiol level, and that greater BMD loss is associated with greater weight loss and greater increases in PTH (3). To our knowledge, our study is the first to report that longitudinal changes in PYY are associated with changes in BMD. These prospective findings add evidence to the potential causal role of PYY in skeletal metabolism and support the concept of a “gut-bone” axis. Our results are consistent with cross-sectional studies that reported a negative correlation between PYY and BMD in adolescent girls with anorexia nervosa and in premenopausal exercising women (37–39), although not in a population-based study in Newfoundland (40). Perhaps the relationship between PYY and BMD is only appreciable in states of altered energy metabolism and elevations in PYY.

The negative relationship between PYY and bone turnover markers was consistent with the BMD findings. As described previously, postoperative increases in biochemical markers of both resorption and bone formation were striking. We found that those with greater increases in PYY had mitigated increases in P1NP. Since bone turnover is coupled and in this case driven by bone resorption, dampening of the P1NP response could contribute to uncoupling of the processes, and ultimately to BMD loss. Similarly, an inducible over-expression model of PYY demonstrated uncoupling at the histomorphometric level with decreased bone formation and increased osteoclast surface and number in both female and male mice (16). To our knowledge, only one other study has evaluated the relationship between changes in PYY and bone turnover markers after bariatric surgery. In 11 diabetic participants who

underwent gastric bypass surgery, Yu et al. reported a positive correlation between 1-year changes in fasting PYY with changes in both CTX and P1NP (21). It is unclear why the direction of the correlation (positive versus negative) would contrast with our results, but it may be due to differences in the patient characteristics, sample size, or study duration. Our results advance the field by providing observations from a relatively large sample size with data 6-months after surgery, a particularly active period of metabolic and skeletal change.

To further examine the relative effects of bone resorption and formation after gastric bypass surgery, we calculated an uncoupling index and evaluated its relationship with changes in BMD. The uncoupling index has been used by others in clinical research settings, and has been shown to predict rates of bone loss after menopause (41) and BMD response to PTH therapy in postmenopausal women with osteoporosis (30, 31). Based on formulas proposed by Eastell et al. and Lane et al. (29, 30), we found a greater than 3-fold relative increase in bone resorption markers compared to bone formation markers. For comparison, an uncoupling index favored resorption by merely 0.8-fold in postmenopausal women with osteoporosis and 1.4-fold in female atheletes participating in non-weight bearing activities (29, 42). To our knowledge, we are the first to quantify the imbalance of bone turnover in this unique patient population, and this 3-fold relative increase in our cohort speaks to the dramatic changes in skeletal metabolism that occur after gastric bypass surgery. While the uncoupling index did not correlate with changes in PYY, it did correlate with changes in spine volumetric BMD by QCT. Our novel application of the uncoupling index to the bariatric surgery context demonstrates that it may be a helpful tool for quantifying uncoupling of bone turnover and understanding mechanisms of bone loss after bariatric surgery, where the driving force is increased bone resorption but suppression of bone formation may also play a role.

We also examined the relationship between changes in ghrelin and skeletal outcomes after gastric bypass. Although ghrelin has an important role in hunger and hunger decreases after bariatric surgery (43), we found that ghrelin levels actually increased. Our results are consistent with heterogeneous reports in the literature of ghrelin after gastric bypass surgery, with reports of increases, decreases, and no change in ghrelin levels (22, 44, 45). Ghrelin plays a complex role in energy metabolism, and the heterogeneity in results may reflect differences in study design, sample collection or ghrelin assay. We found changes in ghrelin negatively correlated to changes in spine areal BMD, although this relationship may have been confounded by weight loss, since ghrelin is associated with fat mass and weight loss is associated with bone loss. Indeed, the relationship ghrelin and BMD did not persist after adjustments for age, sex, and weight loss. Furthermore, other studies, including the inChianti study, have reported a positive association between ghrelin and BMD (46, 47). In contrast to the ghrelin findings, PYY levels increased as hypothesized and correlated with skeletal changes after surgery in unadjusted and adjusted analyses. Since PYY acts on the Y1 receptors on osteoblasts and ghrelin binds to the growth hormone secretagogue receptor 1a, the effects of PYY are thought to be distinct from ghrelin.

One limitation of our study is that we were only able to measure the total levels of PYY and ghrelin. While the active forms of these hormones ($PYY_{3–36}$ and acyl ghrelin) are important for energy homeostasis (19, 48), their roles in skeletal metabolism are less clear, and there is

evidence that the inactive forms (included in the total we measured) may play a role. For example, $PYY_{1–36}$ has affinity for the Y1 receptor on osteoblasts, and des-acyl ghrelin has been shown to modulate osteoblast proliferation (49, 50). We were also unable to evaluate the prandial profiles of these gut hormones, although others did not find a relationship between postprandial changes in PYY and CTX in the 10 days and 1 year after gastric bypass surgery (21). Finally, our study is limited by the absence of a nonsurgical control group and by its short duration.

In conclusion, greater increases in PYY were associated with greater declines in spine volumetric BMD by QCT after gastric bypass surgery. Bone turnover marker levels rose dramatically, but increases in PYY were associated with mitigated increases in the bone formation marker P1NP. There was a 3-fold relative increase in bone resorption over formation, and uncoupling of bone turnover correlated with spine BMD loss. Our results offer unique insights into the gut-bone axis. Understanding mechanisms of BMD loss after bariatric surgery may lead to targeted prevention and treatment of potential skeletal complications of this otherwise beneficial procedure.

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Abbreviations:

BMD	bone mineral density
BMI	body mass index
CTX	C-terminal telopeptide of type I collagen
DXA	dual energy x-ray absorptiometry
PTH	parathyroid hormone
PYY	peptide YY
P1NP	procollagen type 1 N propeptide
QCT	quantitative computed tomography
RYGB	Roux-en-Y gastric bypass
UI	uncoupling index

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Highlights

- Gut hormone and bone changes were assessed 6 months after gastric bypass surgery
- Peptide YY changes negatively correlated with BMD and bone formation marker changes
- Uncoupling of bone turnover correlated with spine BMD loss

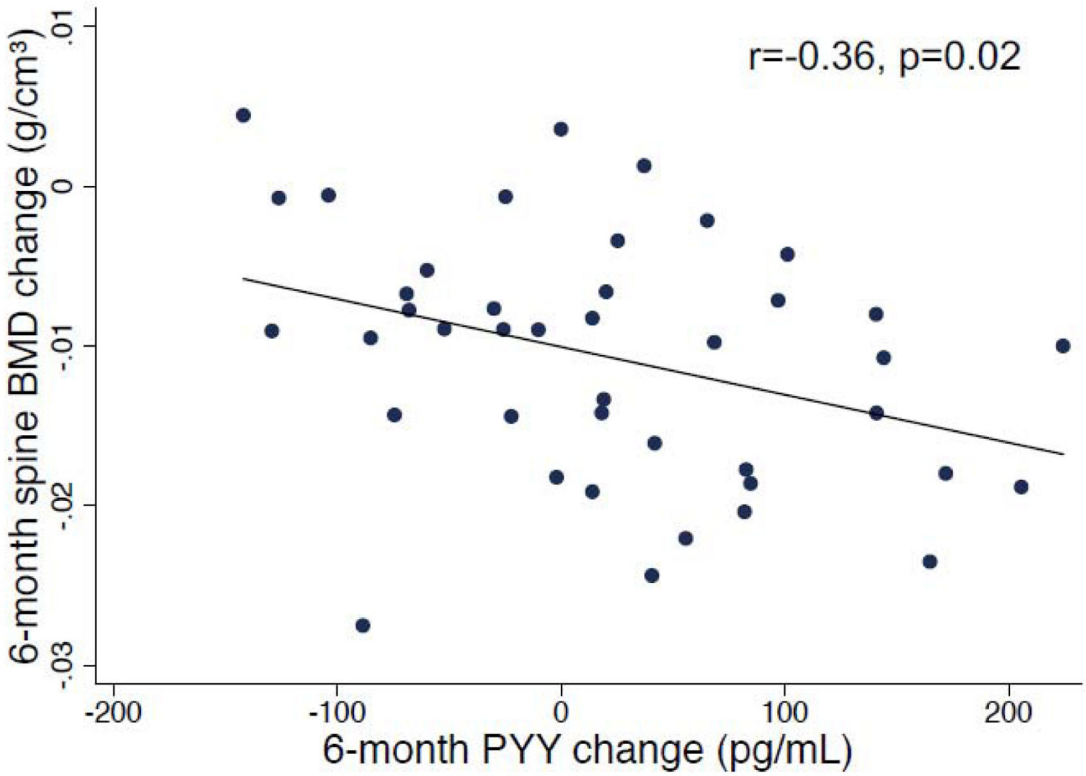

Figure 1.
Six-month change in fasting PYY is negatively correlated with changes in spine volumetric BMD by QCT.

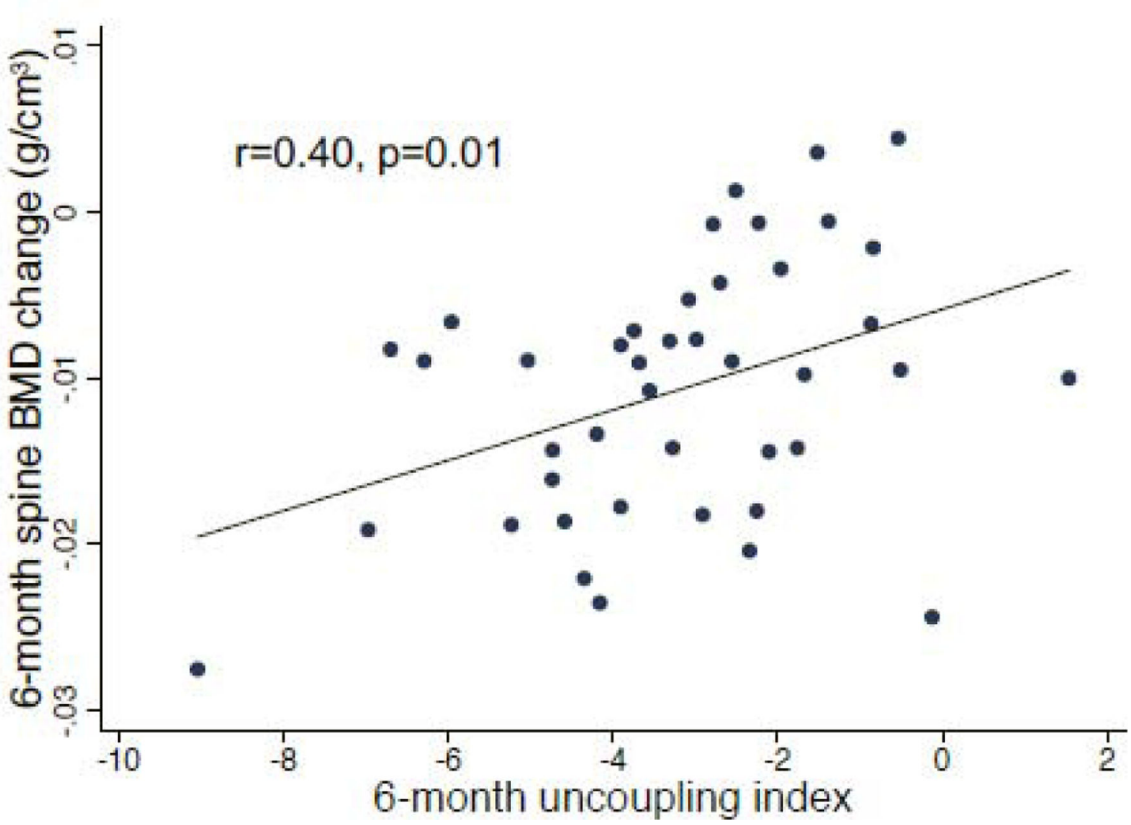

Figure 2.
The uncoupling index at 6 months is correlated with change in spine volumetric BMD by QCT.

Table 1.

Baseline characteristics of study participants.

	Participants (n=44)
Age, years	45 ± 12
Women, n (%)	34 (77%)
Postmenopausal	9 (26%)
Race, n (%)	
White	25 (57%)
Black	8 (18%)
Hispanic	5 (11%)
Asian	3 (7%)
Native American or Alaskan	1 (2%)
Diabetes, n (%)	18 (41%)
Weight, kg	122 ± 19
Body mass index, kg/m^2	44 ± 7
Total body fat, kg	56 ± 12
Total body lean mass, kg	62 ± 12
Hemoglobin A_{1c}, %	6.3 ± 1.3
25-hydroxyvitamin D, ng/mL	42 ± 11
PTH, pg/mL	46 ± 25
PYY, pg/mL	155 ± 95
Ghrelin, pg/mL	444 ± 245
CTX, ng/mL	0.262 ± 0.127
P1NP, ng/mL	36 ± 14
BSAP, mcg/L	14 ± 5
OC, ng/mL	11 ± 4
Uncoupling index	0.0 ± 0.7
Areal BMD (DXA), g/cm^2	
Femoral neck	0.951 ± 0.126
Total hip	1.125 ± 0.136
Spine	1.167 ± 0.139
Areal BMD (DXA), *Z*-score	
Femoral neck	+1.1 ± 0.9
Total hip	+1.5 ± 1.0
Spine	+1.3 ± 1.4
Volumetric BMD (QCT), g/cm^3	
Spine (L3-L4)	0.161 ± 0.038

Values are means ± SD unless otherwise stated

Table 2.

Changes in body composition, metabolic parameters and skeletal outcomes 6 months after Roux-en-Y gastric bypass (RYGB) surgery.

	Preoperation	6-months postoperation	*P*-value
Weight, kg	122 ± 19	91 ± 14	<0.01
Total body lean mass, kg	62 ± 12	54 ± 10	<0.01
Total body fat mass, kg	56 ± 12	34 ± 9	<0.01
Total body fat, %	46 ± 6	37 ± 7	<0.01
Hemoglobin A_{1c}, %	6.3 ± 1.3	5.4 ± 0.8	<0.01
25-hydroxyvitamin D, ng/mL	42 ± 11	38 ± 12	0.05
PTH, pg/mL	46 ± 25	53 ± 20	0.03
PYY, pg/mL	155 ± 95	180 ± 85	0.07
Ghrelin, pg/mL	444 ± 245	636 ± 248	<0.01
CTX, ng/mL	0.262 ± 0.127	0.993 ± 0.371	<0.01
P1NP, ng/mL	36 ± 14	75 ± 28	<0.01
BSAP, mcg/L	14 ± 5	17 ± 7	<0.01
OC, ng/mL	11 ± 4	27 ± 11	<0.01
Areal BMD (DXA) (g/cm^2)			
Femoral neck BMD	0.951 ± 0.126	0.900 ± 0.108	<0.01
Total hip BMD	1.125 ± 0.136	1.072 ± 0.135	<0.01
Spine BMD	1.167 ± 0.139	1.166 ± 0.140	0.96
Volumetric BMD (QCT) (g/cm^3)			
Spine BMD	0.161 ± 0.038	0.150 ± 0.037	<0.01

Values are means ± SD or median (interquartile range)

Table 3.

Unadjusted correlations between 6-month changes in gut hormones with changes in body composition, metabolic and skeletal parameters after gastric bypass surgery.

	PYY, pg/mL	Ghrelin, pg/mL
Body composition and metabolic parameters		
Weight, kg	r=0.08, p=0.60	r=−0.19, p=0.23
Total body fat, kg	r=0.12, p=0.44	**r=−0.31, p=0.04**
Total body lean mass, kg	r=0.03, p=0.85	r=0.08, p=0.60
Hemoglobin A_{1c}, %	r=−0.08, p=0.61	r=0, p=0.98
Skeletal parameters		
6-month UI	r=0.06, p=0.72	r=−0.21, p=0.18
CTX, ng/mL	r=−0.25, p=0.10	r=0.04, p=0.82
P1NP, ng/mL	**r=−0.30, p=0.047**	r=−0.11, p=0.48
BSAP, mcg/L	r=−0.19, p=0.21	r=−0.16, p=0.30
OC, ng/mL	**r=−0.32, p=0.04**	r=−0.03, p=0.85
Femoral neck areal BMD, g/cm^2	r=−0.01, p=0.93	r=−0.20, p=0.19
Total hip areal BMD, g/cm^2	r=0.23, p=0.13	r=0.28, p=0.07
Spine areal BMD, g/cm^2	r=−0.06, p=0.71	**r=−0.34, p=0.03**
Spine volumetric BMD, g/cm^3	**r=−0.36, p=0.02**	r=−0.04, p=0.82