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The Decline in Hip Bone Density Following Gastric Bypass Surgery is Associated with Extent of Weight Loss

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ABSTRACT

Context: Bariatric surgery is common and may be associated with deleterious effects on the skeleton.
Objective: Assess bone metabolism and density (BMD) following Roux-en-Y gastric bypass (RYGB).
Design: One year prospective longitudinal study.
Setting: University hospital bariatric surgery practice and metabolic bone disease unit.
Participants: 23 obese (mean BMI 47 kg/m^2) men and women, aged 20 to 64.
Intervention: None.
Main Outcome Measures: Serum PTH, 25-hydroxyvitamin D (25OHD), osteocalcin urinary N-telopeptide (NTx), and BMD.
Results: Patients lost 45 ± 2 kg one year postoperatively ($p<0.01$). PTH increased early (3 months: 43 to 50 pg/ml; $p<0.001$) and urinary calcium dropped (161 to 92 mg/24 hour; $p<0.01$), despite doubling of calcium intake (1318 to 2488 mg/d; $p<0.001$). Serum 25OHD concentrations were unchanged (23 to 26 ng/ml), although vitamin D intake increased by 260% (658 IU/d at baseline to 1698 IU/d at 12 months; $p<0.05$). Markers of bone remodeling rose ($p<0.01$ for both NTx and osteocalcin), while BMD decreased at the femoral neck (FN: 9.2%, $p<0.005$) and at the total hip (TH: 8.0%, $p<0.005$). These declines were strongly associated with the extent of weight loss (FN: $r=0.90$, $p<0.0001$; and TH: $r=0.65$, $p=0.02$). Lumbar spine and distal radius sites did not change.
Conclusions: Following RYGB there was evidence of calcium and vitamin D malabsorption. Bone turnover increased and hip bone density rapidly declined. The decline in hip BMD was strongly associated with weight loss itself. Vigilance for nutritional deficiencies and bone loss in patients both before and after bariatric surgery is crucial.

INTRODUCTION

Bariatric surgery results in significant, sustained weight loss (1), reverses many complications of obesity (2), and reduces mortality in obese individuals (3, 4). The most effective bariatric procedures combine elements that restrict the amount of food that can be consumed and reduce the intestinal surface area available for caloric absorption (5, 6). In addition to causing substantial weight loss, there is growing evidence that these procedures result in abnormalities in bone and mineral metabolism (7-11).

Several putative mechanisms may explain the changes in bone metabolism observed following bariatric surgery. Malabsorption of minerals and fat soluble vitamins, including calcium and vitamin D, has been documented (9, 10) and may result in secondary hyperparathyroidism and bone loss. Low levels of 25-hydroxyvitamin D (25OHD) and elevated parathyroid hormone (PTH) concentrations have been frequently reported (8-10). Long-standing vitamin D deficiency in obese patients (12-19), may result in metabolic and skeletal abnormalities that antedate but are only detected after surgery. Increased bone turnover and reduced bone mineral density (BMD) (7, 11) may occur as physiologic adaptations to weight loss and alterations in mechanical loading of the skeleton or as pathophysiologic responses to the surgery.

The majority of research performed in this area has been cross-sectional, and provides little evidence as to the possible mechanisms for the observed abnormalities in bone metabolism. The impact of preoperative 25OHD and PTH levels on postoperative findings has not been well explored. Furthermore, there are limited data documenting the longitudinal changes in bone density and bone turnover that occur during the postoperative period.

This prospective study was designed to evaluate changes in mineral metabolism and bone mineral density following Roux-en-Y gastric bypass (RYGB), the most commonly performed bariatric surgery procedure (6). We hypothesized that significant weight loss from RYGB would be associated with alterations in the calcium-vitamin D-PTH axis, increased bone turnover, and decreased bone mineral density (BMD).

PATIENTS AND METHODS

We prospectively evaluated 23 men and women who underwent RYGB between January 2002 and July 2005. Subjects were recruited from the outpatient Obesity Surgery Center at the New York Presbyterian Hospital at Columbia University Medical Center (CUMC). Individuals were excluded if they had conditions or were taking medications known to affect bone or mineral metabolism. All RYGB procedures were performed at CUMC and included a 20ml gastric pouch, a 150cm Roux-limb, and a 75 cm biliopancreatic limb. Patients were evaluated prior to surgery and were followed for one year postoperatively. The study was approved by the Columbia University Institutional Review Board and all subjects gave written informed consent.

Calciotropic hormones and markers of bone turnover were measured before surgery and 3, 6 and 12 months post-RYGB. Assessments included serum calcium, 25OHD (Nichols Advantage RIA, Nichols Institute Diagnostics, San Juan Capistrano, CA, interassay coefficient of variation [CV] 12.9%; intra-assay CV 8.4%), $1,25(OH)_2D$ (DiaSorin, Stillwater MN; interassay CV 9.7%, and intra-assay CV 4.6%). and intact PTH (Scantibodies Laboratories, Santee, CA; interassay CV 3.3%, intra-assay CV 4.8%). Biochemical markers of bone turnover included serum osteocalcin (Immunotopics International, San Clemente; interassay CV 12.5%, intra-assay CV 4.6%), and urinary N-telopeptide (Inverness Medical, Princeton, NJ, CA; interassay CV 10.3%, intra-assay CV 10.0%). BMD was assessed by dual-energy x-ray absorptiometry (DXA) at the lumbar spine (L1-L4), total hip (TH) and femoral neck (FN) in those subjects who did not exceed the weight criteria of 300 pounds (n=13). Forearm (one-third distal radius) BMD was measured in all subjects (Hologic, Model Delphi W). BMD was measured pre-operatively and 1 year postoperatively. In order to control for changes in BMD that may have occurred due to changes in body size, volumetric, three-dimensional estimation of bone density, known as bone mineral apparent density (BMaD), was

calculated at the LS and FN. BMaD (g/cm^3) was calculated as follows: BMaD = BMD/√bone area (20) .

All subjects were instructed to take calcium and vitamin D supplements according to surgical protocol. Patients between the ages of 19 and 50 were prescribed 1500 mg of calcium citrate and 600 IU of vitamin D daily; patients over the age of 50 were prescribed 1800 mg of calcium citrate and 800 IU of vitamin D daily. Standardized questionnaires were administered at each visit to assess calcium and vitamin D intake from food sources and supplements (21).

STATISTICAL ANALYSIS

Analyses were performed using SAS software (SAS Institute Inc., Cary, NC). Results are presented as mean ± SEM except where otherwise noted. Two sided p values ≤ 0.05 were considered significant. Changes in biochemistries and densitometric measures over time were analyzed with linear mixed models with a fixed effect of time of measurement and an autoregressive structure for the within-subject covariance. Pearson correlations were used to assess strength of association between changes indices of bone mineral metabolism and changes in bone density following weight loss.

RESULTS

Twenty-three subjects were followed prospectively before and after RYGB. The sample enrolled was typical of the population of patients presenting for bariatric surgery at our institution (22). Subjects were morbidly obese (mean BMI of 47 ± 1 kg/m^2), aged 20 to 64 years, and 18 (78%) were women. Of the women, 10 (59%) were premenopausal and 7 (41%) were postmenopausal. The majority of subjects were Caucasian (65%), 26% were Hispanic and 9% were African American. Baseline values and longitudinal changes in relevant parameters are depicted in Table 1. Mean daily intakes of calcium and vitamin D from food sources and supplements, 1318 ± 145 mg (range 388-2587) and 658 ± 117 IU (range 0-2054) respectively, were within the RDA for both nutrients. Despite relatively high vitamin D intake, the vast majority of subjects had serum 25OHD concentrations that were below desirable levels; 87% (N= 20) had levels below 30 ng/dl, and 43% (N= 10) had levels below 20 ng/dl. Mean PTH concentration was at the higher end of the normal range (43 ± 4 pg/ml; nl range: 10-65 pg/ml). Serum calcium, 24 hour urinary calcium, $1,25(OH)_2D$, osteocalcin and urinary NTx, were normal.

Weight loss was significant and progressive at each time point assessed after surgery. During the first year following surgery, mean weight dropped by 45 ± 2 kg ($p<0.01$). Mean BMI decreased by 16, from 47 ± 1, to 31 ± 1 kg/m^2 ($p<0.01$), by 12 months postoperatively, signifying a change in average classification from morbidly obese to just at the threshold between overweight and obese. Mean percent excess BMI loss ([BMI initial - BMI final]/[BMI initial – 25] x 100) was 72%.

Subjects seemed to follow postoperative dietary instructions, as dietary calcium intake nearly doubled during the first three months (from 1318 to 2488 mg per day; $p<0.01$), and remained significantly elevated at 6 ($p<0.01$) and 12 months ($p<0.01$) postoperatively. Similarly, vitamin D intake increased significantly from baseline to 6 months (658 ± 117 IU/d to 1195 ± 188 IU/d; $p<0.05$) and was increased by 2.5 fold at 12 months (658 ± 117 IU/d 1698 ±354 IU/d; $p <0.05$). Despite this, serum 25OHD levels did not increase at any time-point (See Figure 1), and the majority of subjects continued to have sub-optimal vitamin D levels at 12 months (91% were < 30 ng/ml, and 35% were <20 ng/ml).

Although dietary calcium intake increased over the first three postoperative months, 24-hour urinary calcium paradoxically decreased from 112 mg to 77mg/g creatinine ($p<0.01$). A simultaneous increase in PTH was observed, from 43 pg/ml at baseline to 50 pg/ml at 3 months ($p<0.01$; Figure 2). Mean urinary calcium rose after 3 months but tended to be lower than at baseline ($p<0.06$) until a year after surgery, while PTH values returned to baseline by 6 months. Serum $1,25(OH)_2D$ did not significantly change post-operatively.

One year after bariatric surgery, there was evidence of significant declines in hip bone density (Figure 3) BMD decreased by 9.2% at the femoral neck ($p<0.005$) and by 8.0% at the total hip ($p<0.005$). Bone loss of a magnitude greater than the site specific least significant

change was nearly ubiquitous at the hip (12 of 13 at the TH, and 10 of 13 at the FN). Declining BMD was strongly associated with the extent of weight loss (FN: r=0.90, p<0.0001; and TH: r=0.65, p=0.02; Figure 4). Bone loss at the femoral neck was also associated with higher PTH levels (r=0.55, p=0.06).

BMD did not change significantly at either the lumbar spine (LS) or the distal one-third radius (DR) sites. In a subset of 7 patients BMD fell at the spine. These patients also lost bone at the hip sites, included both pre- and postmenopausal women and had no other distinguishing features. Radius BMD declined in only 2 of 23 patients. Conversely, BMD rose above the least significant change in only 3 at the LS, 3 at DR, one at the FN, and in none of the patients at the total hip. Bone mineral apparent density (BMaD) was calculated in order to control for changes in BMD that may have occurred due to changes in body size. BMaD at the FN declined by 5.6% (p<0.01) and BMaD at the LS did not significantly change, reflecting similar patterns to those we observed with areal BMD measurements.

Biochemical markers of bone turnover (urinary NTx and serum osteocalcin) began to increase as early as 3 months and continued to rise progressively throughout the first postoperative year (Table 1). There was robust evidence of bone resorption early after surgery, with a rise in Urinary NTx levels by 57% at 3 months (p<0.01), 86% at 6 months (p<0.01), and 106% at 12 months (p<0.01). A less dramatic, but significant increase was seen in the bone formation marker, osteocalcin, which gradually rose to 39% above baseline at 12 months (p<0.01).

DISCUSSION

Because Roux-en-Y gastric bypass bypasses the duodenum, the primary site of calcium absorption (23) these procedures have been postulated to result in calcium malabsorption, as well as secondary hyperparathyroidism, and vitamin D deficiency. Although these findings have been reported in cross-sectional studies of patients following surgery, the extent to which these abnormalities might have existed prior to bariatric surgery, and their evolution following intervention has been unclear. This prospective study of morbidly obese individuals found evidence of malabsorption and elevated bone turnover beginning early in the postoperative period. By one year following surgery, there was evidence of rapid bone loss at both the femoral neck and total hip, the magnitude of which was associated with the extent of weight loss.

Calcium malabsorption (8, 24) and hypocalcemia (25) have been reported following RYGB. In this report, there was evidence of impaired calcium absorption at the earliest postoperative measurement (3 months). Our data confirm a prior report (7) of reduced urinary calcium excretion in patients with declining bone density following gastric bypass. We extend previously available data with the finding of a concomitant rise in PTH levels. Furthermore, this study documents the parathyroid response despite a doubling of calcium intake. Malabsorption of vitamin D is also shown, as patients had no increase in 25OHD concentrations in the face of a 2.6-fold increase in vitamin D intake.

Low 25OHD levels have been well described in obese cohorts (12-19), and are no longer assumed to be a simply a sequelae of bariatric surgery. The majority of our subjects did indeed have vitamin D insufficiency prior to surgery. No further decline in levels of 25OHD was noted postoperatively. This lack of change, seen despite more than doubling of vitamin D intake to mean levels well above the Recommended Daily Allowance, implies malabsorption, and confirms previous findings. (7-11, 26, 27) The data suggest that patients who have insufficient vitamin D stores preoperatively may at greater risk for developing postoperative deficiencies, and consuming amounts well above the RDA may not be adequate to meet their postoperative needs. Further, it has been hypothesized that vitamin D is sequestered in the adipose tissue of obese subjects (15), and may be released into the circulation over time with weight loss. While we are unable to comment on this in our cohort, if vitamin D release from adipose tissue did occur during the postoperative period, the absence of an increase in circulating 25OHD levels would suggest the presence of even more severe malabsorption. Many (8, 9, 25-28), but not all

(7, 11, 29) studies, have documented hyperparathyroidism following bariatric surgery. Differences in PTH levels observed by these authors may have related to disparities in preoperative vitamin D status, different repletion protocols for calcium and vitamin D, or varying length of follow-up. Differences in surgical techniques could also explain the presence or absence of secondary hyperparathyroidism, as longer roux limbs have been associated with lower vitamin D levels and subsequently higher PTH concentrations (30). We observed a transient rise in PTH at 3 months. The frequent longitudinal follow-up we performed may have allowed us to capture patterns in PTH missed by other studies.

To date, there have been limited data on the skeletal sequelae of alterations in mineral metabolism following bariatric surgery. Several reports on bone markers do not include preoperative data (8, 27). In one longitudinally followed cohort, NTx increased by 319% 9 months after RYGB but levels of bone formation markers did not significantly change (7). Our data suggest a high bone turnover state following bypass surgery, with significant, progressive increases in markers of both formation and resorption persisting throughout the first year, (NTx: 106% and osteocalcin: 39%).

While several cross-sectional studies have reported a decline in hip bone density 3 (27) and 10 (31) years following bariatric surgery, prospective data on bone density response to bariatric surgery are limited. The two small prospective studies done to date reported declines in both lumbar spine and total hip BMD. The results of this report confirm the decline at the total hip, and extend the findings to include a significant loss at the femoral neck.

While decreased BMD at the hip after RYGB seems to be a uniform finding, changes reported at the lumbar spine have been more variable. Our study did not find any decline in spine BMD, as did Coates et al (7). Their extremely modest decline (3%) may have been within machine error, or missed in this small cohort. Alternatively, it is possible that while the effect of weight loss on BMD predominated at the hip sites (discussed below), the more cancellous lumbar spine may have benefited from a contribution of the anabolic effect of the increased PTH. In our study, as well as in the other reports in which postoperative PTH levels increased, lumbar spine BMD did not decline (27, 31).

The decrement in bone density was strongly associated with extent of weight loss, a finding not reported in previous cohorts following bariatric surgery. The preferential loss of bone at the hip, a weight-bearing site, suggests that this could be a response to unloading of the skeleton. This change in mechanical stress as a cause for remodeling, leads to elevations in bone turnover and subsequent reductions in BMD. The strong association between extent of weight loss and amount of bone loss provides further support for this hypothesis. Bone loss has been shown to occur in individuals who lose even small amounts of weight from caloric restriction, both in observational studies (32) and interventional trials using energy-restrictive diets (33, 34). In one such intervention trial, women in the highest quartile for weight loss had a decrease in hip BMD almost three times greater than those in the other quartiles (33). As in our cohort, no changes in LS BMD were observed with weight loss. It should also be noted that the decline in BMD at the femoral neck tended to be associated with increases in PTH levels, suggesting that the reasons for the decline we observed may be multi-factorial. In addition to the mechanical unloading of weight loss, a component of parathyroid hormone mediated bone loss, as seen in other hyperparathyroid states, may have contributed at this site as well.

This study has several limitations. As with other prospective studies in this field, the sample size, and particularly the number of subjects in whom axial BMD measurements could be obtained, is limited. Anomalies in DXA measurement have also been reported with weight loss, related to changes in adipose tissue density and distribution (35, 36). These artifactual changes appear to be significant at the spine and hip sites, but not the radius (37). While the results of these studies are not uniform, it is possible that some of the observed changes could be accounted for by the measurement tool itself. However, data suggest that Hologic machines, which were utilized in

this study, may artifactually elevate BMD with weight loss (36). Thus, it is possible that the measurement artifact related to weight loss blunted even more significant declines at the total hip and femoral neck, and could possibly hide declines at the lumbar spine as well. Furthermore, in order to minimize the potential effects of artifactual changes in areal BMD measurements which are found with significant weight loss, we confirmed our findings with a calculation of bone mineral apparent density (BMAD) at the sites of interest.

Furthermore, because of ethical considerations, our study did not include a randomized control group. Finally there are no data on the clinical sequelae of the decline in hip bone density we observed.

In summary, following bariatric surgery we found evidence of calcium and vitamin D malabsorption and secondary hyperparathyroidism early in the postoperative period despite marked increases in calcium (100%) and vitamin D (260%) intake. In association with substantial weight loss following bariatric surgery, bone turnover increased and hip bone density rapidly declined. The decline in hip BMD was strongly associated with the weight loss itself. The small sample size of this study argues for larger, long-term studies to answer the critical question of how these losses relate to bone quality and fracture risk. For the present, a high degree of vigilance for nutrition al deficiencies and bone loss in patients both before and after bariatric surgery is crucial.

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Table 1. Baseline values and longitudinal changes in obese subjects after RYGB

	Baseline	3 months	6 months	12 months
Weight (kg)	130.7 ± 5.4	108.4 ± 4.3**	100.4 ± 4.3**	85.9 ± 4.3**
BMI (kg/m^2)	47.0 ± 1.3	38.6 ± 1.2**	35.5 ± 1.1**	30.8 ± 1.0**
Total Calcium Intake (mg/day)	1318 ± 145	2488 ± 178**	2596 ±134**	2349 ± 150**
Total Vitamin D Intake (IU/day)	658 ± 117	971 ± 100	1195 ± 188*	1698 ± 354*
Serum Calcium (8.4-9.8 mg/dl)	9.6 ± 0.06	9.6 ± 0.04	9.5 ± 0.05	9.5 ± 0.06
Serum Albumin (4.1-5.3 g/dl)	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	4.2 ± 0.1
Serum PTH (14-66 pg/ml)	43 ± 4	50 ± 5**	42 ± 5	43 ± 3
Serum 25OH Vitamin D (20-100 ng/ml)	23.3 ± 1.6	25.6 ± 1.8	25.6 ± 1.4	25.8 ± 1.8
$1,25(OH)_2D$ (25-66 pg/ml)	33 ± 4	35 ± 4	35 ±4	32 ± 4
24-hour Urinary Calcium (50-300 mg/d)	161 ± 22	92 ± 15**	112 ± 12**	135 ± 18
24-hour urinary Calcium. Creatinine (mg/g)	112 ± 13	77 ± 13**	81 ±15	106 ± 14
Urinary NTx (3-65 BCE/mmol Cr)	35 ± 2	55 ± 4**	65 ± 4**	72 ± 6**
Serum Osteocalcin (2.5-11.7 ng/ml)	4.4 ± 0.3	5.2 ± 0.2**	5.6 ± 0.3**	6.1 ± 0.3**

Results are means ± SEM
*$p < 0.05$ compared to baseline
**$p< 0.01$ compared to baseline

FIGURE LEGENDS

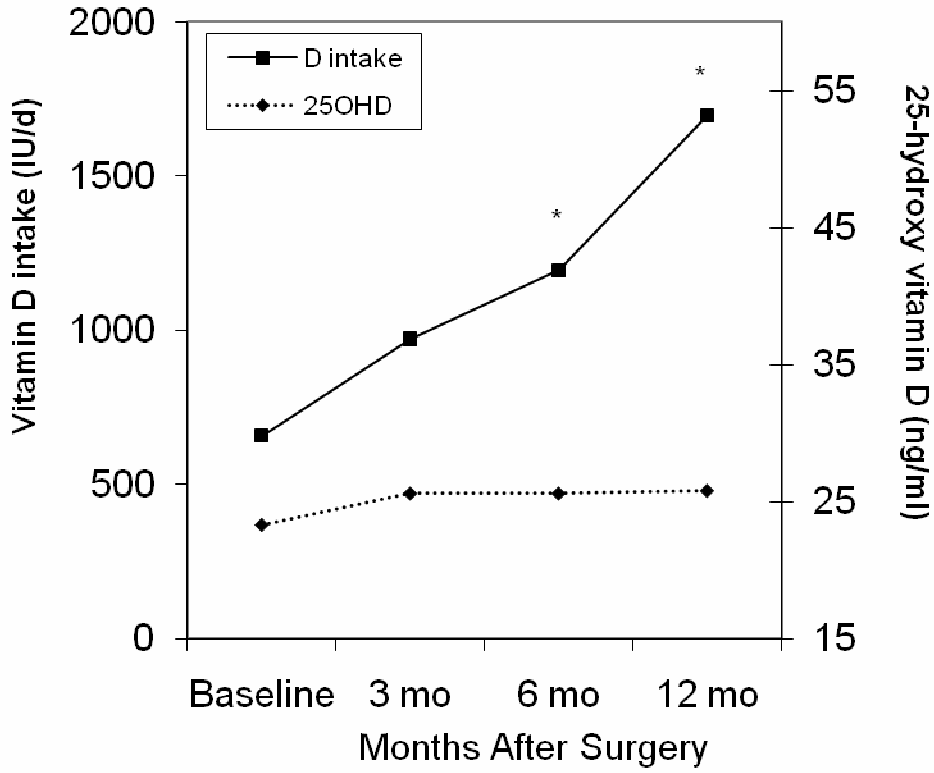
Figure 1. Serum 25-hydroxy vitamin D levels unchanged despite marked increase in vitamin D intake following Roux-en-Y gastric bypass. * Denotes change from preoperative baseline at $P<0.05$

Figure 2. Changes dietary calcium intake, parathyroid hormone (PTH) levels, and 24-hour urinary calcium excretion over the first postoperative year following Roux-en-Y gastric bypass. * Denotes change from preoperative baseline at $P<0.05$

Figure 3. Change in bone mineral density one year after Roux-en-Y gastric bypass. Presented as % change (and standard error of the mean) in BMD from preoperative baseline at each measurement site *$P < 0.005$ compared to baseline

Figure 4. Relationship between decline in BMD at the hip (femoral neck and total hip) and extent of weight loss at one year following Roux-en-Y gastric bypass. Association measured by Pearson correlation coefficient r.

Figure 1


2000
1500
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Vitamin D intake (IU/d)
D intake
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55
45
35
25
15
25-hydroxy vitamin D (ng/ml)
Baseline
3 mo
6 mo
12 mo
Months After Surgery

Figure 2

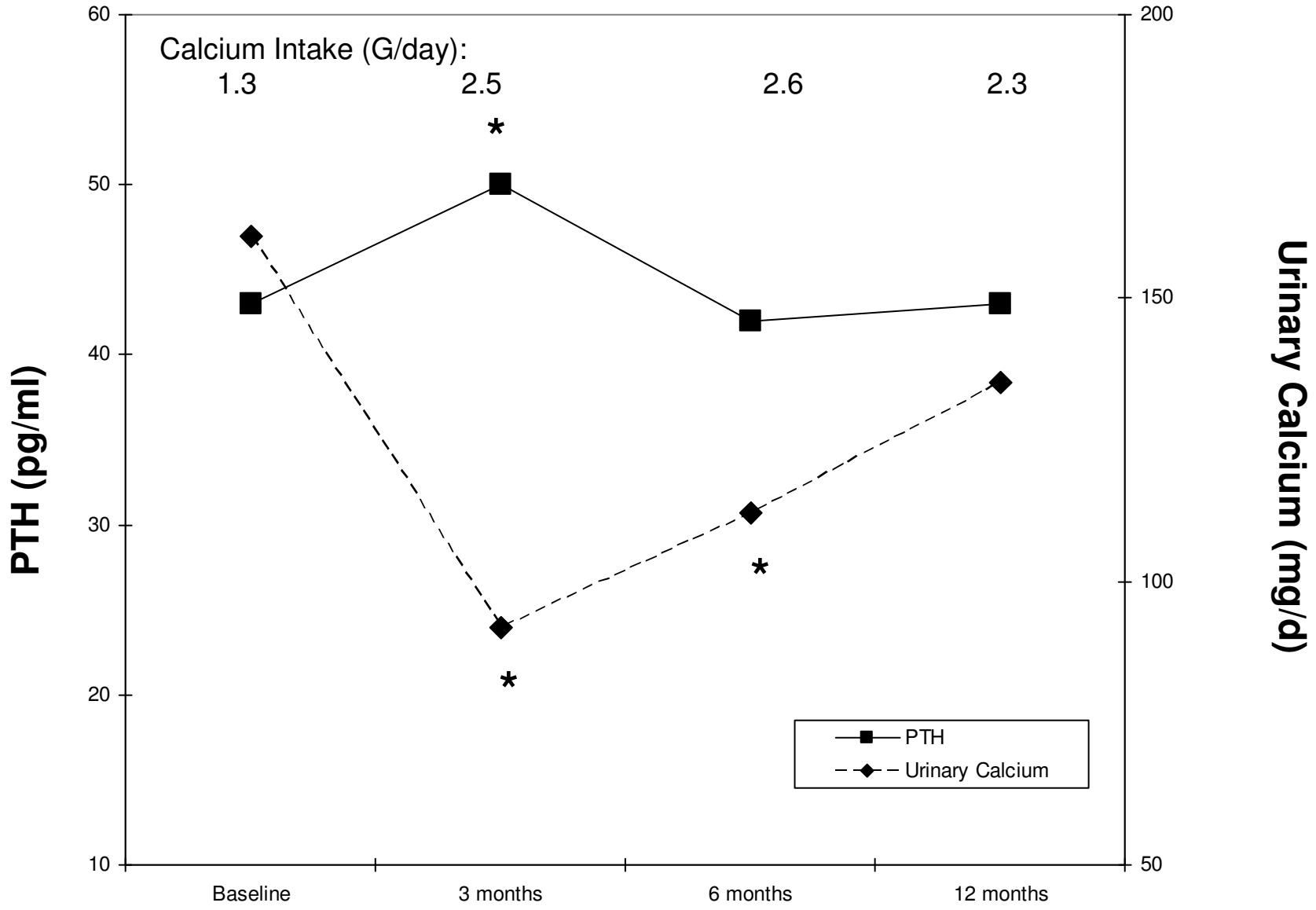

Calcium Intake (G/day):
1.3
2.5
2.6
2.3
*
*
*
60
50
40
30
20
10
200
150
100
50
PTH (pg/ml)
Urinary Calcium (mg/d)
PTH
Urinary Calcium
Baseline
3 months
6 months
12 months

Figure 3

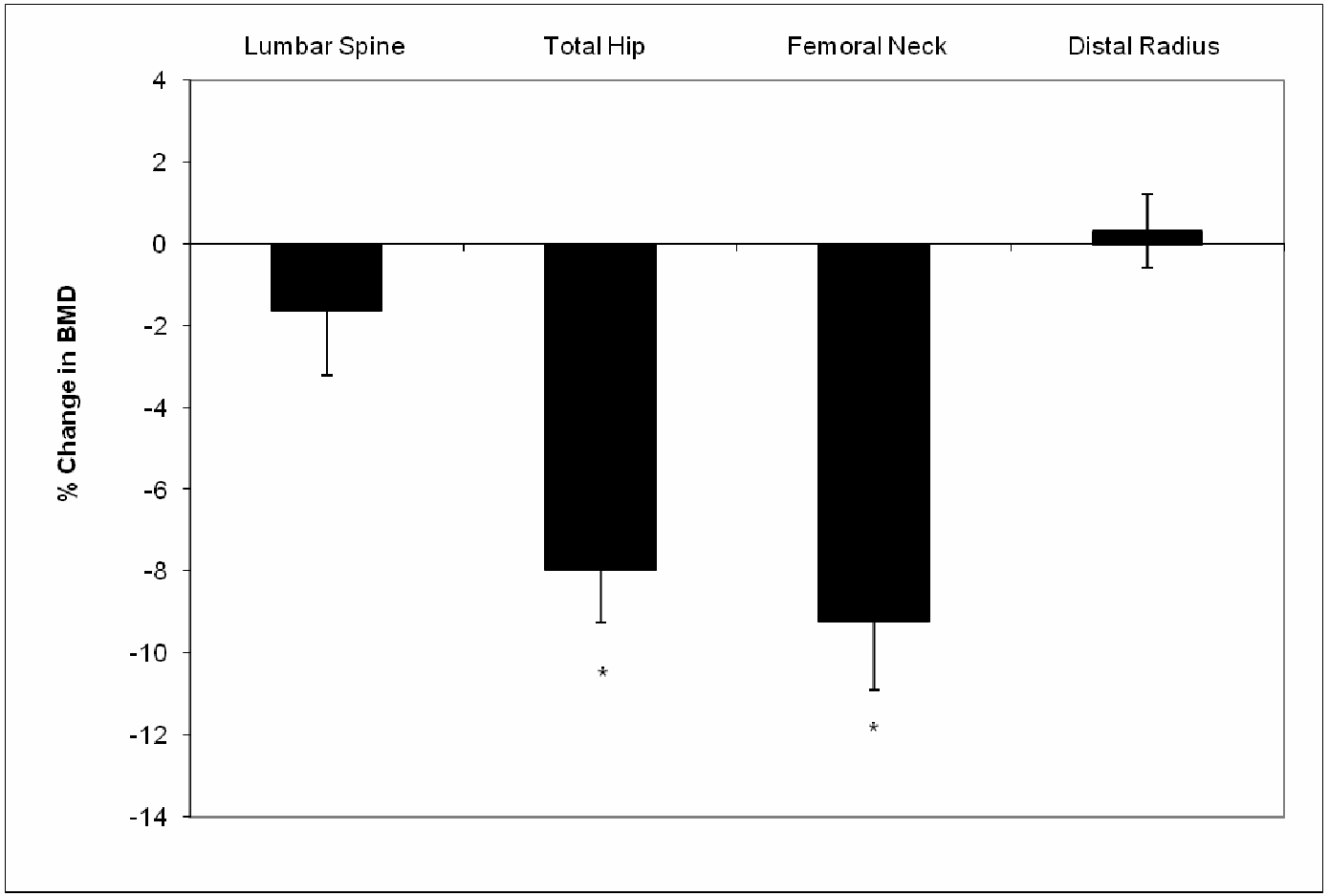
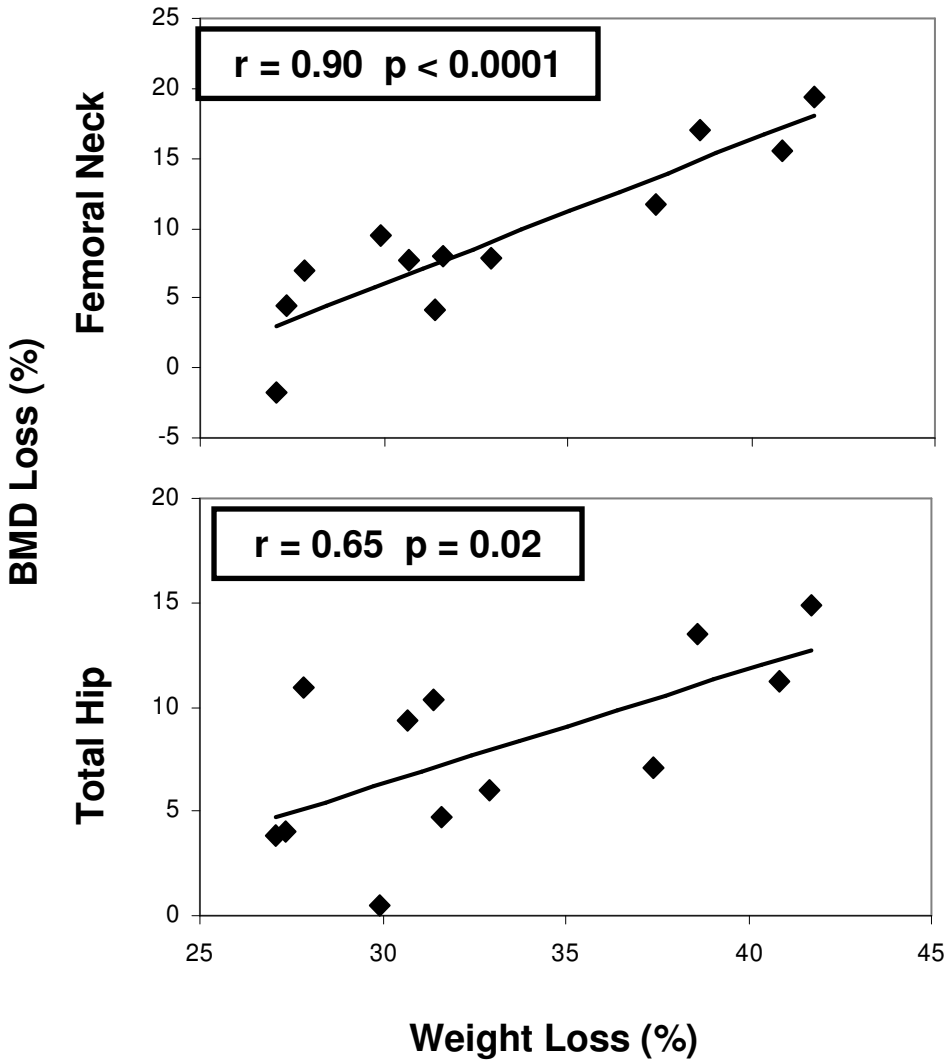

Lumbar Spine
Total Hip
Femoral Neck
Distal Radius
% Change in BMD
4
2
0
-2
-4
-6
-8
-10
-12
-14
*
*

Figure 4


r = 0.90 p < 0.0001
Femoral Neck
r = 0.65 p = 0.02
Total Hip
BMD Loss (%)
Weight Loss (%)
25
20
15
10
5
0
-5
30
35
40
45