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Effects of growth hormone administration for 6 months on bone turnover and bone marrow fat in obese premenopausal women

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Abstract

Purpose—Abdominal adiposity is associated with low BMD and decreased growth hormone (GH) secretion, an important regulator of bone homeostasis. The purpose of our study was to determine the effects of a short course of GH on markers of bone turnover and bone marrow fat in premenopausal women with abdominal adiposity.

Materials and Methods—In a 6-month, randomized, double-blind, placebo-controlled trial we studied 79 abdominally obese premenopausal women (21–45y) who underwent daily sc injections of GH vs. placebo. Main outcome measures were body composition by DXA and CT, bone marrow fat by proton MR spectroscopy, P1NP, CTX, 25(OH)D, hsCRP, undercarboxylated osteocalcin (ucOC), preadipocyte factor 1 (Pref 1), apolipoprotein B (ApoB), and IGF-1.

Results—GH increased IGF-1, P1NP, 25(OH)D, ucOC, bone marrow fat and lean mass, and decreased abdominal fat, hsCRP, and ApoB compared with placebo ($p<0.05$). There was a trend toward an increase in CTX and Pref-1. Among all participants, 6-month increase in IGF-1 correlated with 6-month increase in P1NP ($p=0.0005$), suggesting that subjects with the greatest increases in IGF-1 experienced the greatest increases in bone formation. Six-month decrease in abdominal fat, hsCRP, and ApoB inversely predicted 6-month change in P1NP, and 6-month increase in lean mass and 25(OH)D positively predicted 6-month change in P1NP ($p\leq0.05$), suggesting that subjects with greatest decreases in abdominal fat, inflammation and ApoB, and the greatest increases in lean mass and 25(OH)D experienced the greatest increases in bone formation.

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Six-month increase in bone marrow fat correlated with 6-month increase in P1NP (trend), suggesting that subjects with the greatest increases in bone formation experienced the greatest increases in bone marrow fat. Forward stepwise regression analysis indicated that increase in lean mass and decrease in abdominal fat were positive predictors of P1NP. When IGF-1 was added to the model, it became the only predictor of P1NP.

Conclusion—GH replacement in abdominally obese premenopausal women for 6 months increased bone turnover and bone marrow fat. Reductions in abdominal fat, and inflammation, and increases in IGF-1, lean mass and vitamin D were associated with increased bone formation. The increase in bone marrow fat may reflect changes in energy demand from increased bone turnover.

Keywords

obesity; MR spectroscopy; bone; bone marrow fat; growth hormone; bone turnover

1. Introduction

Although obesity is traditionally viewed as protective against osteoporosis, recent studies have linked obesity to osteoporosis and increased fracture risk (1, 2). It has been suggested that visceral adipose tissue (VAT) plays a role in that it may exert detrimental effects on skeletal health (3–5), and a number of mechanisms have been potentially implicated, including dysregulation of the GH-IGF-1 axis, increased inflammation, and lower vitamin D. Visceral obesity is associated with reduced growth hormone (GH) secretion, an important regulator of bone homeostasis (6). Bone and fat cells arise from a common mesenchymal stem cell, capable of differentiating into osteoblasts or adipocytes under the control of hormones and transcription factors (7, 8). The role of GH in stem cell differentiation is complex. Replacement of GH in patients with GH deficiency due to hypopituitarism is associated with increased bone turnover (9). Expansion of the remodeling space leads to an initial decrease in bone mineral density (BMD) during the first year of GH replacement with a subsequent increase in BMD (9). GH administration has also been found to increase the size of the bone marrow preadipocyte pool in male rats (10). During puberty, a time of maximal GH secretion and peak bone acquisition, the conversion of hematopoietic to fatty marrow occurs, suggesting that bone marrow fat may be necessary for osteoblasts to produce new bone (11). No human studies on the effects of GH administration on bone turnover and bone marrow fat have been performed in obese individuals.

Obesity is also associated with chronic inflammation and proinflammatory cytokines and lipoproteins, which have been shown to promote osteoclast differentiation and bone resorption (12, 13). Furthermore, vitamin D, a regulator of bone metabolism, is inversely associated with obesity and fat mass, and vitamin D deficiency is emerging as a risk factor for the metabolic syndrome. We have shown that administration of GH in obese premenopausal women reduces abdominal fat, lipoproteins and inflammatory markers (14). However, the effects of GH on markers of bone turnover and stem cell differentiation and bone marrow fat in obesity are not known.

Utilizing this previously described cohort (14), we examined the effects of GH administration for 6 months on markers of bone turnover and stem cell differentiation and

bone marrow fat in premenopausal women with abdominal obesity. We hypothesized that GH administration for 6 months would increase bone formation and increase bone marrow fat, and that increased bone formation is associated with or mediated by an improvement in body composition (decrease in abdominal fat and increase in muscle mass), an increase in circulating 25(OH)D, and a reduction in inflammatory cytokines and lipoproteins.

2. Material and Methods

The study was approved by the institutional review board of Partners HealthCare Inc. and was Health Insurance Portability and Accountability Act compliant. Written informed consent was obtained from all subjects prior to performance of any study procedures.

2.1. Subjects

Our study population has been described previously (14). Subjects were recruited from the community through advertisements. Inclusion criteria were: women from 18–45 years, eumenorrhea, BMI ≥ 25 kg/m^2, waist circumference >88 cm (15), IGF-1 level within the lowest 2 quartiles for age (only 1 subject was excluded based on this criterion), stable weight (defined as weight loss or weight gain ≤ 5 pounds in the preceding 3 months). Exclusion criteria included smoking, pregnancy or breastfeeding, hypothalamic or pituitary disorders, diabetes mellitus or other chronic illnesses, estrogen or glucocorticoid use, use of statins, anti-hypertensives, or regular use of aspirin. Eighty subjects met criteria and were enrolled in the study; one subject was discontinued due to a positive pregnancy test at the baseline visit before any procedures were performed or study medication was dispensed. Seventy-nine subjects completed the baseline visit and 50 subjects completed the 6-month visit. Nineteen subjects withdrew for personal reasons, eight for medical causes, one for oral contraceptive initiation, and one due to IV access issues. Baseline clinical characteristics, body composition, and marrow fat have been previously reported on a subset of these subjects (3, 4, 16–21), and 6-month body composition and cardiovascular risk markers have been reported (14). No 6-month marrow fat, bone turnover markers, and vitamin D have been reported.

2.2. Study design

The study protocol, hormone doses employed, and assays has been described previously (14). Briefly, the study was a 6-month, double-blind, randomized, placebo-controlled trial performed at the Massachusetts General Hospital General Clinical Research Center. The following tests were performed at baseline and 6-month: serum IGF-1, bone formation marker procollagen type 1 amino-terminal propeptide (P1NP), bone turnover marker undercarboxylated osteocalcin (ucOC) and bone resorption marker carboxy-terminal collagen crosslinks (CTX), 25-hydroxyvitamin D [25(OH)D], preadipocyte factor 1 (Pref-1), a marker of stem cell differentiation, high sensitivity CRP (hsCRP), and apolipoprotein B (ApoB). Samples were drawn after an overnight fast. Computed tomography (CT) at the level of the 4th lumbar vertebra for abdominal fat, and dual-energy x-ray absorptiometry (DXA) for total fat and lean mass, and proton magnetic resonance spectroscopy (1H-MRS) of the 4th lumbar vertebral body for quantification of bone marrow fat content were performed at baseline and 6-month.

After baseline evaluation, subjects were randomized to receive daily subcutaneous recombinant human GH (Genentech, Inc., South San Francisco, CA) or placebo, which was identical in appearance to the GH, for 6 months. Starting GH dose was 4 micrograms per kilogram per day. Subjects were asked to inject the study medication before bed. GH doses were adjusted based on IGF-1 levels by a physician not involved in the study, using an algorithm based on pre-treatment IGF-1 level and an IGF-1 level target in the upper normal age-appropriate range. Participants in the placebo group were sham dose adjusted to maintain study-subject and investigator blinding. Compliance with GH administration was tested by analysis for the presence of 22-kDa hGH, which becomes predominant after administration of rhGH (14).

2.3. Endocrine testing

25(OH)D, P1NP, and CTX were measured by IDS-iSYS Multi-Discipline Automated Analyzer based on chemiluminescence technology (Immunodiagnostic Systems, Inc., Fountain Hills, AZ). Minimum detection limits are: 25(OH)D 3.6 ng/ml, P1NP <1.0 ng/ml, and CTX 0.023ng/ml. Pref-1 was measured with the Quantikine human Pref-1 immunoassay (ELISA) (R&D Systems, Minneapolis, MN) with a mean minimum detectable level of 0.012 ng/ml. ucOC was measured by solid phase enzyme immunoassay (Takara/Clontech) with a detection range of 0.125–8 ng/ml. Coefficient of variation (cv) are <5% for all assays. The assays used for IGF-1, hsCRP and ApoB have been described previously (14).

2.4. 1H-MR spectroscopy of bone marrow

1H-MRS of the 4th lumbar vertebral body was performed in 36 subjects at baseline and 23 subjects at 6-month to determine bone marrow lipid content using a 3.0T MR imaging system (Siemens Trio, Siemens Medical Systems, Erlangen, Germany) as previously described (22). Subjects who underwent 1H-MRS did not differ in baseline characteristics and response to GH compared to subjects who did not undergo 1H-MRS and were equally distributed between the GH and placebo groups. Fitting of all 1H-MRS data was performed using LCModel (version 6.3-0K, Stephen Provencher, Oakville, Canada). Metabolite quantification was performed using eddy current correction and water scaling. A customized fitting algorithm for bone marrow analysis provided estimates for all lipid signals combined (0.9, 1.3, and 2.3 ppm). LCModel bone marrow lipid estimates were automatically scaled to unsuppressed water peak (4.7 ppm) and expressed as lipid to water ratio [%]. CV for bone marrow fat quantification is 3% at our institution.

2.5. Dual-energy X-ray-absorptiometry

Total body fat and lean mass were assessed in all subjects on a Hologic QDR 4500 scanner (Hologic Inc., Waltham, MA) (precision error of 1.7% for fat mass and of 2.4% for fat-free mass).

2.6. Computed Tomography (CT)

Each subject underwent single-slice CT of the abdomen at the level of L4 as previously described (21). Abdominal subcutaneous adipose tissue (SAT), visceral adipose tissue

(VAT), and total adipose tissue (TAT) were determined (CV <1% for fat area quantification).

2.7. Statistical analysis

JMP Statistical Database Software (version 5.0.1; SAS Institute, Cary, NC) was used for statistical analyses. The measures were secondary endpoints. The primary outcome variable was the bone formation marker P1NP.

Baseline means and mean 6-month changes (6-month value minus baseline value) were compared with ANOVA. Univariate regression models were constructed with the GH and placebo groups combined to determine hormonal and body composition predictors of bone markers and BM fat and non-parametric Spearman rank correlation coefficients are reported. Multivariate standard least squares regression modeling was performed to control for age and treatment group (GH vs placebo). Forward stepwise regression modeling was also performed to determine the strongest predictors of bone formation marker P1NP levels. $P \leq 0.05$ was used to denote significance and $p \leq 0.1$ was used to denote a trend. Data are presented as mean ± SEM.

3. Results

Baseline subject characteristics are shown in Table 1. Thirty-nine subjects were randomized to receive GH and 40 subjects to receive placebo. Of the 50 subjects who completed the 6-month visit, 28 were on GH and 22 on placebo. Both groups were of comparable age, BMI, body composition, IGF-1 levels and bone marker levels. The mean GH dose for the GH treatment group at 6 months was 1.7±0.1 mg/day. These doses resulted in a mean IGF-1 level increase from 137.9±81 ng/ml at baseline to 212.3±12.2 ng/ml at 6-months and a mean IGF-1 standard deviation score (SDS) increase from −1.7±0.1 ng/ml at baseline to −0.1±0.3 at 6 months ($p<0.0001$ compared to placebo). As previously reported, compliance analysis revealed full compliance in 46%, intermittent rhGH use in 43%, and non-compliance in 11% of subjects in the GH group (14). There was no significant difference in reported side effects between the GH and placebo groups. There was one serious unrelated adverse event: development of cancer in a study subject who was receiving placebo. One subject was discontinued from the study at 3 months secondary to a 2-hour glucose greater than 200 mg/ml, a pre-specified drop criterion. Four subjects had 2-hour glucose levels greater than 200 mg/ml at six months, one of whom was receiving placebo. No other serious related or unrelated adverse events occurred during this study (14).

3.1. Effects of GH administration on bone

6-month changes in the GH and placebo groups are summarized in Table 2. Six months of GH increased the bone formation marker P1NP and bone turnover marker ucOC compared to placebo ($p=0.0007$ and $p=0.01$, respectively) (Figure 1), and there was a trend toward an increase in the bone resorption marker CTX in the GH group at 6 months compared to placebo ($p=0.08$). GH also increased 25(OH)D at 6 months compared to placebo ($p=0.0002$), and there was a trend toward an increase in Pref-1 levels ($p=0.07$). At baseline (pre-treatment), 32 subjects were vitamin D deficient [25(OH)D < 20 ng/ml] and 25 subjects

were vitamin D insufficient [25(OH)D < 30 ng/ml]. Within the GH group, a 6-month increase in vitamin D levels from insufficient to normal was seen in 3 subjects, from deficient to insufficient in 4 subjects, and from deficient to normal in 1 subject. Within the placebo group, 1 subject increased her vitamin D level from deficient to insufficient, while 3 subjects decreased their vitamin D levels from insufficient to deficient and 2 subjects decreased their vitamin D levels from normal to insufficient.

Six months of GH therapy increased L4 bone marrow fat compared to placebo (p=0.003) (Figure 2).

3.2. Effects of GH administration on body composition, inflammatory markers and apo B

As previously reported, GH decreased abdominal TAT and SAT by CT at 6 months compared to placebo (delta 6-month TAT GH vs placebo: −28±9.7 vs 1.5±11.0 cm^2, p=0.04, delta 6-month SAT: −19.9±7.4 vs 5.2±8.6 cm^2p=0.02), while there was no significant change in VAT between the two groups (p=0.6) (14). There was a significant increase in lean mass in the GH group at 6 months compared to placebo (delta 6-month lean mass: 1.9± 0.5 vs 0.1±0.4 kg, p=0.04) (14). GH decreased hsCRP (delta 6-month hsCRP: −1.1±0.3 vs 0.07±0.3, p=0.002) and ApoB (delta 6-month Apo B: −9.1±3.4 vs 3.9±4.2 p=0.04) at 6-month compared to placebo (14).

3.3. Predictors of bone formation marker P1NP and bone marrow fat

Within the entire group, six-month change in P1NP correlated with 6-month change in CTX (r=0.35, p=0.03) and 6-month change in ucOC (r=0.42, p=0.008), likely reflecting the coupling of bone formation and resorption. Six-month change in IGF-1 correlated with 6-month change in P1NP (r=0.55, p=0.0005) (Figure 3a), suggesting that, in general, subjects with the greatest increases in IGF-1 levels experienced the greatest increases in bone formation. The association remained significant after controlling for age (p=0.01). Six-month change in abdominal fat was inversely associated with 6-month change in P1NP (r= −0.40, p=0.05) (Figure 3b), independent of age and treatment group (GH vs placebo) (p=0.02), suggesting that subjects with the greatest reductions of abdominal fat experienced, in general, the greatest increases in bone formation. Six-month increase in P1NP correlated with 6-month increase in lean mass (r=0.46, p=0.003), independent of age and treatment group (GH vs placebo) (p=0.04), suggesting that subjects with the greatest increases in lean mass experienced, in general, the greatest increases in bone formation marker levels. Six-month change in P1NP levels correlated with 6-month change in 25(OH)D (r= 0.48, p=0.003) (Figure 3c), suggesting that subjects with the greatest increase in circulating 25(OH)D had, in general, the greatest increase in bone formation marker levels. However, after controlling for age and treatment group, the association became a trend (p=0.08). Six-month change in hsCRP inversely correlated with 6-month change in P1NP (r= −0.41, p=0.04) (Figure 3d), independent of age (p=0.04), suggesting that subjects with the greatest decreases in inflammation experienced, in general, the greatest increases in bone formation. The association lost significance after controlling for treatment group (p=0.7). Six-month change in ApoB correlated inversely with 6-month change in P1NP (r= −0.31, p= 0.05), suggesting that subjects with the greatest decreases in lipoproteins experienced, in general,

the greatest increases in bone formation marker levels. However, the association lost significance after controlling for age and treatment group (p=0.2)

Six-month change in bone marrow fat correlated with 6-month change in P1NP (trend) (r=0.45, p=0.08), suggesting that subjects with the greatest increases in bone formation experienced, in general, the greatest increases in bone marrow fat. Six-month change in bone marrow fat correlated with 6-month change in IGF-1 (trend) (r=0.42, p=0.07), suggesting that subjects with the greatest increases in IGF-1 experienced, in general, the greatest increases in bone marrow fat formation. There was a trend toward a positive correlation between 6-month change in Pref-1 with 6-month change in bone marrow fat (r= 0.41, p=0.07), consistent with known effects of Pref-1 as a regulator of stem cell differentiation into the adipocyte lineage.

When 6-month change in P1NP levels was entered as a dependent variable and 6-month change in total abdominal fat, lean mass, 25(OH)D, and hsCRP as independent variables in a forward stepwise regression model, 6-month change in lean mass and abdominal fat were the only predictors of 6-month change in P1NP (p=0.004 for both measures) and explained 19% and 17% of P1NP variability, respectively. When 6-month change in IGF-1 was added as independent variable into the model, 6-month change in IGF-1 was the only predictor of 6-month change in P1NP (p<0.0001) and explained 52% of P1NP variability.

4. Discussion

Our study showed that a short course (6 months) of GH administration to abdominally obese premenopausal women increases bone formation markers and bone marrow fat. Direct effects of GH and IGF-1 likely play a role, and in addition, the increase in bone formation with GH administration may be in part mediated by an improvement in body composition with a reduction in abdominal fat and an increase in lean mass, an increase in circulating 25(OH)D, and a decrease in inflammatory cytokines and lipoproteins.

Although obesity has been thought to be protective against the development of osteoporosis, strong evidence now links accumulation of fat, particularly in the abdominal depot, with bone loss (1, 2). Potential mechanisms for obesity-induced bone loss include deleterious effects of inflammatory cytokines and lipoproteins on bone and low levels of circulating 25(OH)D. Inflammatory cytokines, such as hsCRP, which are elevated in abdominal obesity, promote osteoclast differentiation and bone resorption (12). In a large prospective study of older men and women, elevated inflammatory markers were a strong predictor of fracture risk (23). Moreover, lipids and lipoproteins, which are elevated in abdominal obesity, have been shown to inhibit osteoblast differentiation and to enhance osteoclast differentiation and survival (12, 24). Statin therapy to lower hyperlipidemia is associated with increased BMD and decreased fracture risk (25, 26) and bisphosphonates lower serum LDL cholesterol and apoB (27), supporting a connection between bone and lipid metabolism. In addition, vitamin D levels are reduced in patients with abdominal adiposity (28), in part due to sequestration of vitamin D, a fat soluble molecule, in adipose tissue.

Obesity is also a state of relative GH and IGF-1 deficiency, critical regulators of bone homeostasis, and abdominal adipose tissue is a strong negative determinant of GH secretion

(29). Adult-onset GH deficiency is also complicated by reduced BMD and increased fracture risk, and GH replacement in these patients leads to an increase in markers of bone turnover (9, 30). Bone remodeling, with a prominent augmentation in bone formation, increases within a few months of GH therapy, before an increase in BMD is apparent. The expansion of the remodeling space may lead to an initial decrease in BMD; a subsequent increase in BMD ensues in 12 to 18 months (9, 30). GH also directly stimulates the carboxylation of osteocalcin, a marker of bone turnover (31). Consistent with these data, our study showed that GH administration for 6 months to obese women increased markers of bone turnover. Recent studies have shown that the bone turnover marker ucOC also functions as a regulator of bone and glucose homeostasis (32–34). In fact, genetically modified mice with increased ucOC activity were protected from diet-induced obesity and type 2 diabetes (34). Our study is the first to show that GH administration increases ucOC in obese individuals.

The effect of GH administration on stem cell differentiation and bone marrow fat has not been studied in humans, and our study is the first to examine the effects of GH administration on bone marrow fat content in obese women. Animal studies have shown that GH deficient rats have an increased number and size of bone marrow adipocytes which return to normal following GH administration (7). A study in hypophysectomized rats has shown increased bone lipid levels, despite reduced adipocyte precursors, compared to controls, and administration of GH enhanced the adipocyte and osteoblast precursor pool size, supporting the hypothesis that GH increases adipocyte and osteoblast precursors in bone marrow (35). We found increased bone marrow fat content of the lumbar spine following 6 months of GH administration compared to placebo, and the increase in marrow fat content was positively associated with an increase in bone formation, suggesting that the bone marrow adipocytes may serve as an energy source for the increased bone turnover. Furthermore, the increase in marrow may serve to fill the incompletely mineralized remodeling space. We also found an increase in Pref-1, an important regulator of stem cell differentiation, following GH administration compared to placebo, and the increase in Pref-1 was associated with an increase in bone marrow fat. Our results are consistent with a prior study in GH deficient subjects in which GH administration for 3 months increased serum Pref-1 levels compared to placebo (36). This is in contrast to a study in mice, in which GH administration using hydrodynamic-based gene transfer procedure reduced serum Pref-1 levels (37). The reason for the discrepant results is unclear and may reflect a differential response to GH in humans and mice. We hypothesize that longer-term GH administration for 18-month would decrease bone marrow fat and Pref-1 after more complete mineralization of the remodeling space.

In addition to the anabolic effects on bone, GH is also an important regulator of lipolysis. GH increases adipocyte lipolysis and lipid turnover, and states of GH deficiency due to pituitary disease are associated with increased abdominal fat (38). GH is also an important mediator of inflammation. GH has cytokine-like effects and its administration results in decreased hsCRP levels in patients with GH deficiency due to pituitary disorders or obesity (14, 39). GH administration also decreases cholesterol and apoB (14, 39). GH and IGF-1 also act on the renal tubules to increase production of active 1,25 dihydroxyvitamin D (40). Our data show that GH administration for 6 months to obese premenopausal women decreases abdominal fat, hsCRP and apoB, and increases circulating 25(OH)D, and that

these changes are associated with an increase in bone formation. The increase in circulating 25(OH)D may be due to GH-induced loss of abdominal fat and subsequent release of sequestered fat soluble 25(OH)D from adipose tissue into the blood stream.

GH also increases lean mass (9, 14), an important positive predictor of bone formation. In our study, the increase in lean mass was positively associated with the increase in bone formation.

Our study had several limitations. First is the relatively high drop-out rate. However, our dropout rate was similar compared to other obesity studies (41, 42) and was similar in the GH and placebo groups. Second, bone marrow fat was only assessed in a subset of subjects. We were able to detect a significant difference between the groups in bone marrow fat content, which suggests that we had adequate power for this endpoint. Third, we did not have BMD measurements available to assess the effects of GH on BMD.

In conclusion, our study showed that short-term GH administration to abdominally obese premenopausal women increases markers of bone formation and bone marrow fat. The increase in bone formation is associated with a decrease in abdominal fat, inflammation and lipoproteins and an increase in IGF-1 levels, 25(OH)D and lean mass. Whether the increases in bone formation reflects direct effects of GH and/or IGF-1 levels or is in part mediated by changes in body composition, increases in circulating 25(OH)D levels and decreases in systemic inflammation and Apo B is unknown and warrants further study. The effects of a longer course of GH therapy in obese individuals, such as has been shown to increase BMD in hypopituitary populations, are unknown and warrant further investigation.

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Highlights

- 6-month GH administration to obese premenopausal women increases bone formation and bone marrow fat.
- Increased bone formation is associated with decreased abdominal fat, inflammation and lipoproteins.
- Increased bone formation is associated with increased lean mass and vitamin D.

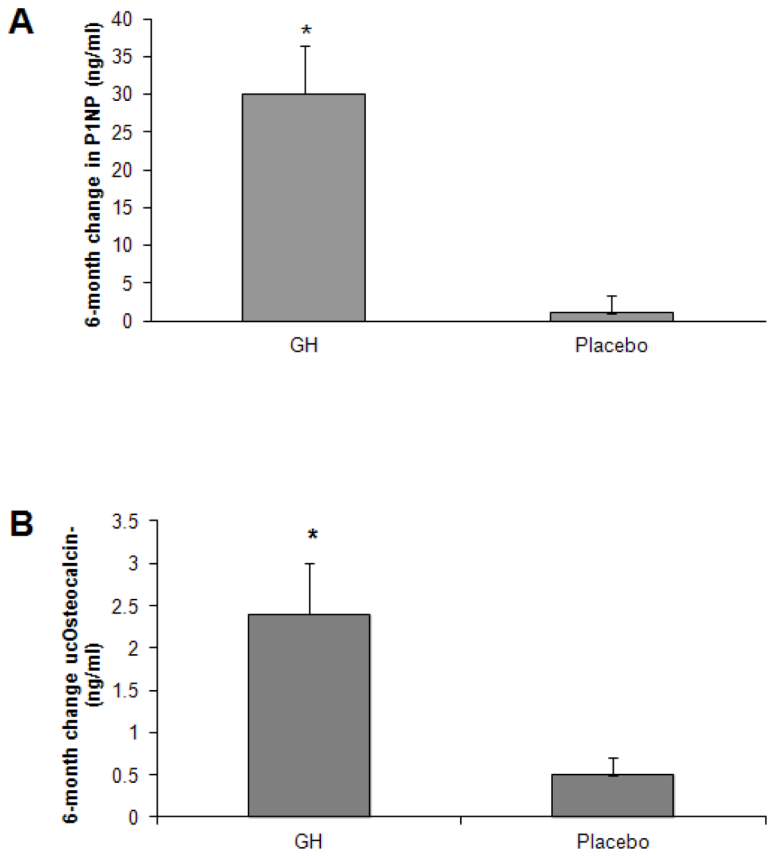

Figure 1.

Mean (±SEM) change in P1NP (A) and undercarboxylated (uc) osteocalcin (B), over 6 months of GH administration versus placebo. *, $p < 0.05$ vs. placebo

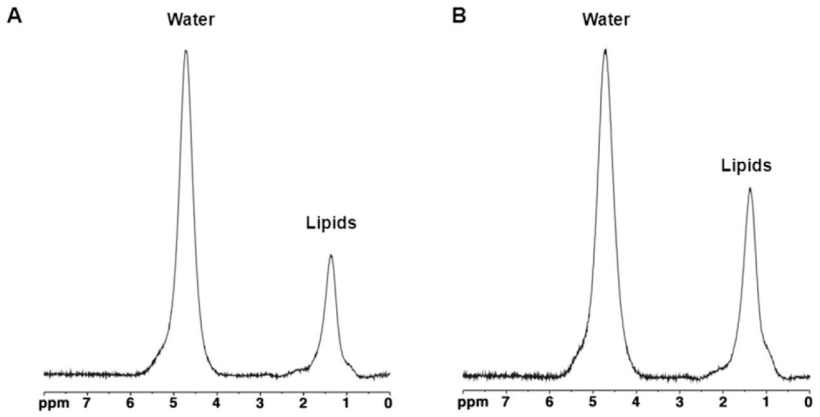

Figure 2.

1H-MR spectroscopy of bone marrow in a 40 year-old obese woman (BMI 34.9 kg/m^2) before (A) and after (B) 6 months of GH administration. There is increased bone marrow lipid content following GH administration (0.44 vs 0.63 lipid-water ratio). For purposes of visual comparison, the amplitude of unsuppressed water was scaled identically.

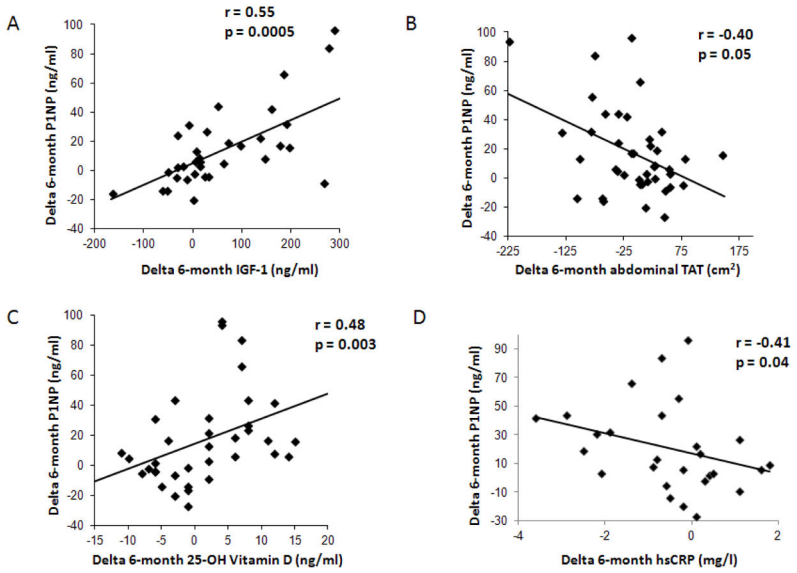

Figure 3.

Regression analysis of 6-month change in P1NP on 6-month change in IGF-1 (A), abdominal total adipose tissue (TAT) (B), 25-OH Vitamin D (C), and hsCRP (D).

Table 1

Baseline characteristics

	GH group	Placebo group	*p*
Age (years)	35.7±1.1	36.1±1.1	0.8
BMI (kg/m^2)	34.8±0.8	34.9±0.9	0.9
P1NP (ng/ml)	45.7±3.2	44.3±2.6	0.7
CTX (ng/ml)	0.33±0.04	0.25±0.03	0.06
uc Osteocalcin (ng/ml)	2.6±0.4	2.3±0.4	0.6
25OHD (ng/ml)	24.2±2.9	24.3±1.6	1.0
Pref-1 (ng/ml)	0.22±0.01	0.27±0.04	0.2
Bone marrow fat l/w ratio (%)	0.57±0.09	0.59±0.05	0.9

Data presented as mean±SEM. BMI: body mass index, P1NP: procollagen type 1 amino-terminal propeptide, CTX: carboxy-terminal collagen crosslinks, uc: undercarboxylated, Pref-1: preadipocyte factor 1

Table 2

Bone parameters in premenopausal obese women who completed both baseline and 6-month visits treated with GH or placebo for 6 months

Variable	Treatment	Baseline	6 months	Delta 6 months	*p*-baseline	*p*-between groups
P1NP (ng/ml)	GH	44.3±4.1	74.4±7.2	30.0±6.5	0.7	**0.0007**
	Placebo	41.9±4.3	41.2±4.2	−0.8±2.8		
CTX (ng/ml)	GH	0.32±0.05	0.46±0.06	0.15±0.06	0.07	0.08
	Placebo	0.21±0.03	0.23±0.02	0.02±0.03		
uc Osteocalcin (ng/ml)	GH	2.6±0.4	5.0±0.6	2.4±0.6	0.6	**0.01**
	Placebo	2.3±0.4	2.8±0.5	0.5±0.2		
25OHD (ng/ml)	GH	20.2±2.1	24.9±2.4	4.7±1.4	0.5	**0.0002**
	Placebo	22.4±2.3	18.2±2.2	−4.2±1.6		
Pref-1 (ng/ml)	GH	0.22±0.01	0.25±0.03	0.02±0.02	0.2	0.07
	Placebo	0.27±0.04	0.25±0.01	−0.02±0.02		
Bone marrow fat l/w ratio (%)	GH	0.53±0.08	0.57±0.08	0.04±0.03	0.3	**0.003**
	Placebo	0.62±0.07	0.53±0.06	−0.9±0.03		

Data presented as mean±SEM. P1NP: procollagen type 1 amino-terminal propeptide, CTX: carboxy-terminal collagen crosslinks, uc: undercarboxylated, Pref-1: preadipocyte factor 1