Effects of 42 months of GH treatment on bone mineral density and bone turnover in GH-deficient adults

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Abstract

Objective: To study the effects of GH treatment for up to 42 months on bone mineral density (BMD) and bone turnover.

Design and methods: BMD with dual energy X-ray absorptiometry, serum type I procollagen carboxy-terminal propeptide (PICP), serum type I collagen carboxy-terminal telopeptide (ICTP) and serum IGF-I were assessed in 71 adults with GH deficiency. There were 44 men and 27 women, aged 20 to 59 (median 43) years. Thirty-two patients completed 36 months and 20 patients 42 months of treatment.

Results: The BMD increased for up to 30–36 months and plateaued thereafter. In the whole study group, the maximum increase of BMD was 5.0% in the lumbar spine (P < 0.001), 5.9% (P < 0.01) in the femoral neck, 4.9% (NS, P > 0.05) in the Ward’s triangle and 8.2% (P < 0.001) in the trochanter area. The serum concentrations of PICP (202.6 ± 11.5 vs 116.3 ± 5.4 mg/l; mean - S.E.M.) and ICTP (10.5 ± 0.6 vs 4.4 ± 0.3 μg/l) doubled (P < 0.001) during the first 6 months of GH treatment but returned to baseline by the end of the study (130.0 ± 10.4 and 5.6 ± 0.7 mg/l respectively), despite constantly elevated serum IGF-I levels (39.6 ± 4.1 nmol/l at 42 months vs 11.9 ± 0.9 nmol/l at baseline; P < 0.001). The responses to GH treatment of serum IGF-I, PICP, ICTP (P < 0.001 for all; ANOVA) and of the BMD in the lumbar spine (P < 0.05), in the femoral neck and the trochanter (P < 0.001 for both) were more marked in men than in women. At the end of the study the BMD had increased at the four measurement sites by 5.7–10.6% (P < 0.01–0.001) in patients with at least osteopenia at baseline and by 0.1–5.3% (NS P < 0.05) in those with normal bone status (P < 0.001 for differences between groups; ANOVA). Among patients who completed 36–42 months of treatment, the number of those with at least osteopenia was reduced to more than a half. The response of BMD to GH treatment was more marked in young than in old patients at three measurement sites (P < 0.05–<0.001; ANOVA). In the multiple regression analysis the gender and the pretreatment bone mass appeared to be independent predictors of three measurement sites, whereas the age independently determined only the vertebral BMD.

Conclusions: GH treatment in GH-deficient adults increased BMD for up to 30–36 months, with a plateau thereafter. Concurrently with the plateau in BMD the bone turnover rate normalized. From the skeletal point of view GH-deficient patients exhibiting osteopenia or osteoporosis should be considered as candidates for GH supplementation of at least 3–4 years.

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Introduction

Bone mineral density (BMD) is reduced in adults with growth hormone (GH) deficiency (1), especially in those with childhood-onset disease (2), but also in subjects who developed the deficiency in adulthood (3–5). As a consequence of low BMD, GH-deficient adults have a doubled fracture rate compared with healthy controls (6).

GH replacement therapy in GH-deficient adults accelerates whole body bone remodeling, demonstrated not only by biochemical markers of bone resorption and bone formation (7–19) but also by histomorphometry (20). After an initial decline (12–14, 21, 22) BMD has increased in studies in which treatment with GH has continued for 12 months or more (14–16, 18, 19, 21, 23, 24). The response of BMD to GH replacement therapy has been more marked in patients with childhood-onset rather than adult-onset GH deficiency (14, 22, 23), in male rather than female patients (18), and in those subjects with a low pretreatment bone mass (18, 24).
In studies published to date the effect of GH treatment on BMD of the lumbar spine and the forearm has been followed for 4 years (25) and on that of the upper femur at longest only for 2 years (18). Thus, more long-term data are needed to show whether the increase in BMD continues or plateaus over time. In the present trial we followed the effects of GH replacement therapy on bone mass and markers of bone turnover for up to 42 months in a cohort of 71 adults with GH deficiency, the great majority of them having an adult-onset form of the disease.

Subjects and methods

Patients

Seventy-one adults (44 men, 27 women) with known pituitary deficiency of adult onset ($n = 59$) or childhood onset (age at diagnosis 16 years or less, $n = 12$) and a median age of 43 years (range 20–59 years) participated in the trial conducted at four Finnish University Hospitals (Table 1). The median age at diagnosis of GH deficiency was 41 years (range 6–59 years). At the start of treatment 11 of 12 patients with childhood-onset GH deficiency were aged 30 years or less. The diagnosis of GH deficiency was based upon a maximum peak GH response (assayed by polyclonal competitive RIAs) of less than 10 mU/l (5 mg/l) to stimulation by glucagon (70% of the patients) or clonidine (27%), or insulin-induced hypoglycemia (3%). Patients with childhood-onset disease were retested at the beginning of the study. The median known duration of GH deficiency before the trial was 1.8 (range 0–39) years. When needed, patients received adequate and stable replacement therapy with glucocorticoids, thyroxine, gonadal steroids and desmopressin. Ninety-four percent of the patients used at least one of these replacement therapies (Table 1), which were kept constant during the entire study period. Before the trial they had used replacement therapies for 1–27 (median 8) years.

Study protocol

Patients were entered in a 6 month randomized double-blind trial of either GH or placebo. Subsequently, they were enrolled into an open trial for 12 months, after which the patients were offered an opportunity to continue GH treatment; 46 decided to do so. During the first 4 weeks of treatment the daily GH (Genotropin, Pharmacia & Upjohn Oy, Vantaa, Finland) dose was 0.018 IU (6 mg)/kg body weight (BW) as an s.c. injection at bedtime, and the target dose thereafter was 0.036 IU (12 mg)/kg BW daily (2.5 IU/day for a subject of 70 kg BW). The dose was reduced in the event of side-effects. At the start of the study and every subsequent 6 months, physical and laboratory examinations were performed, including measurements of BMD. The body mass index (BMI) was calculated as BW in kilograms divided by height in meters squared. For those patients who were randomized to placebo in the double-blind

| Table 1 Clinical characteristics of 71 adult patients with GH deficiency. |
|--------------------------|----------|----------|
|                          | All      | Men      | Women    |
| Number                   | 71       | 44       | 27       |
| Age (years) at start     | 43 (20–59) | 42 (20–59) | 44 (22–58) |
| Number of patients with childhood-onset disease | 12       | 9        | 3        |
| Age (years) at diagnosis | 41 (6–59)  | 39 (6–59)  | 43 (11–58) |
| Known duration (years) of GH deficiency | 1.8 (0–39)  | 3.3 (0–39)  | 1.1 (0–16) |
| Cause of pituitary deficiency | Pituitary adenoma | 33       | 21       | 12       |
|                          | Craniopharyngioma | 18       | 13       | 5        |
|                          | Idiopathic   | 8        | 4        | 4        |
|                          | Other        | 12       | 6        | 6        |
| Hormonal replacement therapy | Corticosteroids | 59       | 37       | 22       |
|                          | Levothyroxine | 61       | 38       | 23       |
|                          | Sex steroids  | 59       | 41       | 18       |
|                          | Desmopressin | 23       | 14       | 9        |
|                          | Some other drug | 49       | 28       | 21       |
| Isolated GH deficiency   | 3          | 2        | 1        |
phase of the study, data collected at the end of the placebo phase were taken as the basal values.

Informed written consent was obtained from all patients. The study was approved by the local ethical committees of Oulu, Tampere and Turku University Hospitals and that of Third Department of Medicine, Helsinki University Central Hospital.

**BMD measurement**

BMD at the lumbar spine and at three femoral sites (femoral neck, trochanter area, Ward’s triangle) was measured by dual energy X-ray absorptiometry. A Hologic DEXA-1000 (Hologic Inc., Waltham, MA, USA) densitometer was used in Helsinki and Turku, and Lunar DEXA (Lunar Radiation Inc., Madison, WI, USA) equipment in Oulu and Tampere. The coefficients of variation (CV) for precision of the BMD measurements for the densitometers used varied from 0.9 to 1.7% in the lumbar spine and from 1.1 to 2.5% in the femoral neck. To present BMD results, percent changes from baseline were calculated. Standardized T score analyses, which compare individual bone density determinations with those of a young normal population of the same gender, were used for definition of osteoporosis and osteopenia. According to the criteria defined by the WHO, T scores more than 2.5 S.D. below the mean of normal bone status were tested vs women. There was no difference in the trochanter (P > 0.05) (Fig. 1A–D). Significant increases in BMD were noticed at the trochanter area after 12 months, and at the lumbar spine, the femoral neck and the Ward’s triangle after 18 months of GH treatment. The BMD in the lumbar spine increased by 2.4% (P < 0.001) after 24 months, by 5.0% (P < 0.001) after 36 months and by 4.8% (P < 0.001) after 42 months of GH treatment (Fig. 1A). At the femoral neck the respective increases were 3.4 (P < 0.001), 5.9 (P < 0.001) and 5.7% (P < 0.01) (Fig. 1B). At the Ward’s triangle the BMD increased by 4.0% (P < 0.05) after 24 months, by 4.6% (NS) after 36 months and by 4.9% (NS) after 42 months of GH treatment (Fig. 1C). As analyzed separately, the increases in BMD for the 20 patients who completed the 42 months of treatment were similar to those presented above for the whole study population (Fig. 1A–D).

**Biochemical assays**

Blood samples were drawn in the morning after an overnight fast. The serum concentration of insulin-like growth factor-I (IGF-I) was determined by RIA after acid–alcohol extraction (Nichols Institute, San Juan Capistrano, CA, USA) with intra- and interassay CV ranging from 3 to 9%.

The serum concentrations of carboxy-terminal propeptide of type I procollagen (PICP) and the carboxy-terminal cross-linked telopeptide of type I collagen (ICTP) were determined by RIA kits from Orion Diagnostica, Oulunsalo, Finland. The intra-assay and interassay CV for these assays ranged from 3 to 9%.

**Statistics**

A paired t-test was used in testing the changes from baseline with the null hypothesis stating no change was to be expected. If the null hypothesis turned out to be wrong, the size of differences and relations between variables were modeled using stepwise multiple regression analysis. Differences in response to GH between women vs men, young vs old patients, and patients with osteopenia vs normal bone status were tested by ANOVA. Furthermore, stepwise linear regression analysis was used to determine independent predictors of the response in BMD to treatment. Those given for the program included gender, duration of treatment, pretreatment bone mass, age, age squared and 100/age. The contribution of each variable to the explained variance was calculated using standardized correlation coefficients (β coefficients).

**Results**

Fifty-eight patients completed the 18-month trial (12–18 months on GH). During the first 18 months six patients were withdrawn from the study due to adverse effects (myalgia in three, edema in two, elevated blood glucose in one), one patient appeared to have mild diabetes even at entry (a protocol violation), four patients did not want to continue the study, and one patient was otherwise lost from the follow-up. One patient presented with meningioma. His pituitary tumor had been treated with surgery and radiation treatment 20 years before the trial; no computed tomography or magnetic resonance imaging study was performed at entry. From 18 months onwards all drop-outs were consent withdrawals. Thirty-two patients completed 36 months and 20 patients 42 months of treatment; a difference in these numbers is due to the placebo phase at the beginning of the study. The mean BMI remained unchanged throughout the study (28.3 ± 0.6 kg/m²) at entry, 29.8 ± 1.1 kg/m² at 36 months, 29.6 ± 1.2 kg/m² at 42 months; mean ± S.E.M., NS).

**BMD**

At baseline the BMD was lower in patients with childhood-onset disease than in those with adult-onset GH deficiency in the trochanter (P < 0.05) but not in other measurement sites. During the first 6 months of GH treatment the BMD seemed to decline at all the four measurement sites, significantly so only at the femoral neck (−0.9%, P < 0.05) (Fig. 1A–D). Significant increases in BMD were noticed at the trochanter area after 12 months, and at the lumbar spine, the femoral neck and the Ward’s triangle after 18 months of GH treatment. The BMD in the lumbar spine increased by 3.4% (P < 0.001) after 24 months, by 5.0% (P < 0.001) after 36 months and by 4.8% (P < 0.001) after 42 months of GH treatment (Fig. 1A). At the femoral neck the respective increases were 3.4 (P < 0.001), 5.9 (P < 0.001) and 5.7% (P < 0.01) (Fig. 1B). At the Ward’s triangle the BMD increased by 4.0% (P < 0.05) after 24 months, by 4.6% (NS) after 36 months and by 4.9% (NS) after 42 months of GH treatment (Fig. 1C). As analyzed separately, the increases in BMD for the 20 patients who completed the 42 months of treatment were similar to those presented above for the whole study population (Fig. 1A–D).
Biochemical measurements

Serum IGF-I concentration was increased from $11.9 \pm 0.9$ to $39.8 \pm 2.5$ nmol/l after 6 months of treatment ($P < 0.001$), with no change thereafter. During the first 6 months of GH treatment serum PICP concentration doubled from $112.6 \pm 5.4$ to $202.6 \pm 11.5$ mg/l ($P < 0.001$), with a steady decline back to baseline ($130 \pm 47$ mg/l; there was no statistical difference from baseline) during the following 36 months. Serum ICTP concentration behaved similarly. During the first 6 months of treatment it increased from $4.4 \pm 0.3$ to $10.5 \pm 0.6$ mg/l ($P < 0.001$) and decreased thereafter to $5.6 \pm 0.7$ mg/l at the end of the study (no statistical difference from baseline). As analyzed separately, the changes in serum IGF-I, PICP and ICTP for those 20 patients who completed 42 months of treatment were similar to those presented above for the whole study population (data not shown).

Comparisons between men and women

As shown in Fig. 2A–D the BMD increased significantly more in male than in female patients at the lumbar spine ($P < 0.05$, ANOVA), the femoral neck ($P < 0.001$) and at the trochanter ($P < 0.001$), but not at the Ward’s triangle. Among the 32 patients who completed 36 months of treatment, 40% of the men had at least osteopenia in the lumbar spine and 60% at the femoral neck at the start of GH treatment; the respective percentages for female patients were 25% in the lumbar spine and 33% at the femoral neck. After 3 years of GH treatment the prevalence of osteopenia was halved among male patients and had reduced to 17 and 25% among female patients in the lumbar spine and in the femoral neck respectively. Of the 20 patients who completed 42 months of treatment, 7 men and 6 women had at least osteopenia in the lumbar spine and 8 men and 5 women at the femoral neck before treatment. After treatment the number of these patients had reduced to three men and three women at the lumbar spine and to two men and three women at the femoral neck.

The responses of serum IGF-I, PICP and ICTP to GH treatment were all more marked in male than
female patients ($P < 0.001$, ANOVA) (Fig. 3A–C). At baseline only serum PICP was higher in men than in women ($122.2 \pm 7.5$ vs $94.8 \pm 4.9 \mu g/l$, $P < 0.01$).

Comparisons between patients with low vs high bone mass at baseline

To study the effect of pretreatment bone mass on BMD in response to GH therapy the patients were divided into low and high bone mass groups on the basis of the presence of osteopenia at the femoral neck at the start of the trial. Consequently, the low bone mass group comprised 31 and the high bone mass group 33 patients at baseline. As shown in Fig. 4A–D, at all the four measurement sites patients with low bone mass demonstrated more marked increases in BMD than patients with high bone mass. After 2 years of treatment the increases in BMD at the four measurement sites ranged from 5.6 to 9.3% in the low bone mass group ($P < 0.01–0.001$) and from 1.6 to 3.3% in the high bone mass group (NS). After 3 years the respective changes were 6.3 to 13.0% ($P < 0.01–0.001$) and 2.3 (NS) to 6.2% ($P < 0.05$). At the end of the study the BMD had increased by 5.7 to 10.6% ($P < 0.01–0.001$) in the low bone mass group and by 0.1 to 5.3% (NS) in the high bone mass group. The statistical significancies for differences between the groups remained the same even when analyzed in terms of absolute changes (data not shown).

Effect of age

To study the effect of age on the response in BMD to GH treatment the patients were divided into young and old groups on the basis of the median age. As shown in Fig. 5A–D the increases in BMD were more marked in young than in old patients in the lumbar spine ($P < 0.05$, ANOVA), the femoral neck ($P < 0.05$) and in the trochanter ($P < 0.001$). Eleven of twelve patients with childhood-onset disease belonged to the younger group of patients. The increases in BMD were more marked in patients with childhood-onset than adult-onset GH deficiency in the femoral neck ($P < 0.05$) and in the Ward’s triangle ($P < 0.05$).

Multiple regression analysis

To determine the independent predictors of the response in BMD to GH treatment stepwise linear regression analysis was performed. As presented in Table 2 the gender and the pretreatment bone mass appeared to be independent predictors at three measurements sites, whereas the age independently determined only the BMD at the lumbar spine. The models calculated explained, however, only from 7 to
31% of the variation in the response of BMD to GH treatment.

Discussion

At present, the insulin tolerance test is the diagnostic test of choice for GH deficiency (27); most normal subjects show a peak GH concentration of more than 5 mg/l (28). This test was used only in the minority of the present patients, and in a third of the patients GH deficiency was ascertained with the clonidine test, which is less useful in adults than in children (28). However, we know that among patients with hypothalamic–pituitary disease and one or more additional pituitary deficits, GH deficiency is present in 80–100% of the patients (29). Ninety-four percent of the present patients needed at least one replacement therapy for other pituitary deficits. This, together with clearly lowered responses in glucacon or clonidine stimulation tests, confirms GH deficiency of our patients. In several subjects GH deficiency was established for the first time just before the study. The median duration of need for other replacement therapies was, however, 8 years in our patients, showing that most likely they also had GH deficiency of a long duration. More than a half of the patients dropped out before the completion of 3 years of treatment. Most subjects interrupted the trial, since they did not subjectively feel benefit from GH injections; only the minority stopped treatment due to adverse effects.

Consistent with previous findings (12–14, 21, 22) BMD tended to decline during the first 6 months of GH treatment. Thereafter BMD increased and exceeded the baseline level statistically significantly at the trochanter area at 12 months and at the three other measurement sites at 18 months. In the study of Johansson et al. (18), the BMD increased by 3.8% in the lumbar spine, by 4.1% in the femoral neck, by 5.6% in the trochanter and by 4.9% in the Ward’s triangle after 2 years of GH treatment. The respective increases of 3.4, 3.4, 5.4 and 4.0% in the present investigation agree well with these previous data. After 2 years, bone mass in our study increased for up to 30–36 months but plateaued thereafter. A similar plateau in vertebral BMD was not observed in the study of Kann et al. (25) but direct comparisons are made difficult by the fact that instead of percent changes from baseline the results in that study were expressed as percentages of age- and sex-related normal values (25).

As previously observed (7–19), the markers of bone turnover increased in response to GH. To reflect bone formation we measured serum PICP. Serum osteocalcin and total and bone-specific alkaline phosphatase have been used for the same purpose with similar results (7–19). As a sign of increased bone resorption, serum ICTP rose in our patients in response to GH treatment. In previous GH studies, increased bone resorption has been demonstrated using either the same marker (17, 18), the urinary excretion of pyridinoline and deoxypyridinoline (8, 19), hydroxyproline (10, 14) or type I collagen amino-terminal telopeptide (24). Taking all these bone marker findings into account, it seems quite obvious that GH treatment accelerates bone turnover, both bone formation and bone resorption. Recently, the same conclusion was reached in a histomorphometric study in GH-deficient adults (20).

An interesting new finding in our study was the normalization of the serum concentrations of PICP and ICTP after 42 months of GH treatment. The reliability of this finding was supported by the fact that the normalization took place at the same time as the increase in BMD started to level off. A similar normalization of serum ICTP and PICP was not observed in the study of Kann et al. (25) but the maximum increases of the markers were much less in that study than in the present one. On the other
Figure 4 BMD (mean ± S.E.M.) in response to GH treatment of up to 42 months at the lumbar spine (A), the femoral neck (B), the Ward’s triangle (C) and the trochanter area (D) in patients with at least osteopenia at the femoral neck at baseline and in those with normal bone status.

Figure 5 BMD (mean ± S.E.M.) in response to GH treatment of up to 42 months at the lumbar spine (A), the femoral neck (B), the Ward’s triangle (C) and the trochanter area (D) in patients with age below and above median at baseline.
hand, in one study, after 24 months of therapy, serum levels of osteocalcin decreased to pretreatment values while urinary hydroxyproline and serum alkaline phosphatase remained elevated (10). In another study, after an initial rise, serum PICP and osteocalcin were almost back to baseline level after 30 months of GH treatment (14). Importantly, as in our study the normalization of bone turnover occurred in the face of constantly elevated serum IGF-I levels (14). The mechanism of the dissociation between bone turnover rate and elevated serum IGF-I levels remains totally obscure.

In agreement with the observation of Johansson et al. (18) the increases in serum PICP and ICTP as well as in BMD in response to GH treatment were more marked in men than in women. It is also noteworthy that before treatment osteopenia and osteoporosis were more frequent among male than female patients. Thus, estrogens somehow lessen the effects on the skeleton of both GH deficiency and GH replacement therapy. There are several reasons to postulate that bigger doses of GH are needed in women than in men to accomplish similar bone gain in response to GH treatment. The mean daily serum concentrations of GH are higher in healthy women than in healthy men (30). In one study the response of serum IGF-I to one s.c. injection of GH (0.1 mg/kg) was less in healthy women than men, and in postmenopausal females the response was further lessened by oral estrogen replacement therapy (31). Finally, as shown also in the present study, when GH doses are determined on a weight basis for GH-deficient adults, the serum IGF-I levels remain lower in women than in men (18, 32).

Clinically, it is important that in accordance with two previous studies (18, 33) the effect of GH treatment was most prominent in patients with osteopenia or osteoporosis. In the low bone mass group (at least osteopenia), the BMD increased by 6.3% in the lumbar spine, by 11.4% in the femoral neck, by 13.0% in the Ward’s triangle and by 11.6% in the trochanter area after 3 years of GH treatment. Moreover, in more than a half of the patients the criteria of osteopenia disappeared or there was an improvement of the bone state from osteoporosis to osteopenia.

Also the age appeared to determine the response in BMD to GH treatment, with a greater increase in young than in old subjects. Nevertheless, the multiple regression analysis showed that the age seemed to be of less significance than the gender or the pretreatment bone mass, independently determining only the vertebral BMD. In contrast to our finding, no significant correlations were found between the patient’s age and the response to treatment in terms of changes in BMD in the study of Johansson et al. (18). A part of the younger patient group in the present study were those with childhood-onset GH deficiency who have a greater potential to respond with an increase in bone mass to GH treatment than subjects with adult-onset GH deficiency (14, 22, 23). In them the beneficial effect of GH treatment may still be due to an increase in peak bone mass.

The present study indicates that from the skeletal point of view GH-deficient patients exhibiting osteopenia or osteoporosis should be considered candidates for GH supplementation. However, longer-lasting studies are needed to establish whether the positive effects on BMD are persistent and are really associated with a reduction in fracture risk. Furthermore, our findings of the normalization of bone turnover and the plateau in increase of bone mass warrant longer.

### Table 2 Dependency of the response (percent change from baseline) in BMD on the duration (months) of GH treatment, gender (1 for men, 0 for women), pretreatment bone mass (PBM; 0 for osteopenia, 1 for normal BMD), and age (years) on the basis of multiple regression analysis.

<table>
<thead>
<tr>
<th>Region</th>
<th>Regression Equation</th>
<th>Total Correlation</th>
<th>Duration</th>
<th>Gender</th>
<th>PBM</th>
<th>R²</th>
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<td>Lumbar spine</td>
<td>−3.19 + (1.07 × Gender) + (0.188 × Duration) + (64.4/Age)</td>
<td>r = 0.47, r² = 0.22</td>
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<tr>
<td></td>
<td>β coefficients: 0.094* for gender, 0.450*** for duration, 0.095* for 100/age</td>
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<td>Femoral neck</td>
<td>−0.86 + (1.43 × Gender) + (0.189 × Duration) − (2.11 × PBM)</td>
<td>r = 0.47, r² = 0.22</td>
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<tr>
<td></td>
<td>β coefficients: 0.113* for gender, 0.406*** for duration, 0.175*** for PBM</td>
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<tr>
<td>Ward’s triangle</td>
<td>0.94 + (0.131 × Duration) − (3.01 × PBM)</td>
<td>r = 0.26, r² = 0.07</td>
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<tr>
<td></td>
<td>β coefficients: 0.187*** for duration, 0.166** for PBM</td>
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<td>Trochanter</td>
<td>−1.28 + (2.25 × Gender) + (0.207 × Duration) − (1.59 × PBM)</td>
<td>r = 0.56, r² = 0.31</td>
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<td>β coefficients: 0.195*** for gender, 0.491*** for duration, 0.145** for PBM</td>
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*P < 0.05, **P < 0.01, ***P < 0.001.
comparative studies, in which after 3–4 years of GH treatment patients are randomized either to continue on treatment or to stop using it.

Acknowledgements

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