Bone mineral content and bone metabolism during physiological GH treatment in GH-deficient adults – an 18-month randomised, placebo-controlled, double blinded trial

Simone Bjerregård Sneppen, Hans Christian Hoeck, Gina Kollerup, Ole Helmer Sørensen, Peter Laurberg and Ulla Feldt-Rasmussen

Department of Endocrinology, National University Hospital, Copenhagen, and 1 Aalborg Hospital and 2 The Osteoporosis Research Centre, Copenhagen, Denmark

(Correspondence should be addressed to Ulla Feldt-Rasmussen, Department of Endocrinology PE 2131, National University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; Email: ufeldt@rh.dk)

Abstract

Objective: To evaluate the effect of physiological adult growth hormone (GH) replacement on bones.

Design: Thirty-six prospective severely growth hormone-deficient (GHD) adults (22 females and 14 males) were randomised to either 18 months of GH (0.03 mU/kg/day) or placebo treatment.

Methods: Bone mineral density and content (BMD, BMC) and body composition were evaluated by dual energy X-ray absorptiometry at baseline and after 6, 12 and 18 months. Serum concentrations of insulin-like growth factor-I (IGF-I), IGF binding protein 3, osteocalcin, carboxyterminal propeptide of type I collagen, carboxyterminal crosslink telopeptide of type I collagen, amino-terminal propeptide of type III procollagen and urine pyridinolin and deoxypyridinolin were determined.

Results: IGF-I levels increased from 63.2 μg/l (±10.1) to 193.6 (±25.8) μg/l (mean (±S.E.)) (P, 0.001 compared with placebo). Markers of bone turnover increased significantly from 142% to 227% of baseline values (all P, 0.001 compared with placebo). Body composition changes were an increase of lean body mass and a decrease of fat mass resulting in a reduction of percentage body fat of −1.8 (±3.8) in the GH-treated group vs an increase of 1.0 (±2.9) in the placebo-treated group (P, 0.002).

Conclusions: No significant difference in BMD or BMC between the GH and placebo groups was found after 18 months. At several sites the variances of changes from baseline were significantly greater in the GH than in the placebo group, indicating an impact of the treatment. From baseline to 6 months an insignificant reduction of total BMD was seen while an increase of BMD was found from 6 to 18 months in the GH group compared with the placebo group.

This placebo-controlled trial confirmed the longer term open studies on the effect on bones in patients with GHD, with an initial overrepresentation of bone resorption followed by an increase in BMD which at 18 months had reached baseline level.

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Introduction

The most obvious effect of growth hormone (GH) on bone is that of longitudinal somatic growth. In adulthood, clinical and experimental studies have demonstrated an effect of GH and insulin-like growth factor-I (IGF-I) on bone remodelling. Growth hormone stimulates proliferation of osteoblast-like cells from trabecular bone explants (1) or osteoblast-like cell lines (2) whereas in mature osteoblasts GH stimulates markers of differentiation.

Several clinical studies have consistently reported a lower bone mineral content (BMC) and bone mineral density (BMD) in severe GH-deficient (GHD) patients, compared with normal healthy controls (2–5). In addition, an increased fracture rate has been observed in hypopituitary patients (6–8). The reduced BMD and BMC in GHD patients has been ascribed to GHD per se. In theory, GH substitution therapy should improve bone mineralisation and reduce fracture risk in these patients. An increase of BMD and BMC following GH treatment has been reported in several (9–16) but not all (17) open trials. However, except for one study (18, 19), the verification of such findings in randomised, placebo-controlled, double blinded trials with appropriate treatment doses of GH has not been possible. GH treatment for 6 months seems to induce a relative loss of BMD/BMC. Trials of 9 and 12 months
duration also showed a reduction of BMD in the GH-treated group (20, 21). The aim of the present investigation was to evaluate the effect of 18 months of GH substitution therapy on BMD/BMC and biochemical markers of bone turnover in GHD patients in a randomised, double blinded, placebo-controlled trial using physiological doses of GH.

Materials and methods

Protocol and study design

The patients were prospectively recruited from two centres (Copenhagen and Aalborg) and participated in an 18-month randomised, placebo-controlled, double blinded study of GH treatment. Each sex was randomised separately. The patients underwent dual energy X-ray absorptiometry (DEXA scanning), measurement of markers of bone turnover and safety parameters, as well as clinical examination before treatment and at 6, 12 and 18 months of treatment. Furthermore, the patients were seen for clinical evaluation at 3, 9 and 15 months. IGF-I and IGFBP-3 were first analysed when the treatment code was broken at the end of the study.

Treatment regimen

The patients injected themselves daily subcutaneously at bedtime with an injection pen system (Kabi pen). GH treatment doses (Genotropin, Pharmacia & Upjohn, Stockholm, Sweden) were 0.02 IU/kg/day for 4 weeks, followed by 0.03 IU/kg/day for the remaining period.

Patients

Forty patients, 18 males with a mean age of 43 years (range 23–57) and 22 females with a mean age of 41 years (range 21–60) were included in the study after informed consent. All patients (of which 2 had childhood onset GHD) had GHD of a minimum of two years duration, with a maximally stimulated peak GH response following insulin tolerance test below 3.0 μg/l. All patients had been on stable substitution therapy for other insufficient hormone axes for a minimum of 6 months prior to entering the study. Thirty-six patients completed the full 18 months of the study. 17 randomised to GH (11 females, 6 males) and 19 randomised to placebo treatment (11 females, 8 males). The characteristics of GH vs placebo in the 36 patients at baseline were: (median and range) age (years) 44 (21–59) vs 44 (23–60), weight (kg) 75 (45–110) vs 75 (52–113), height (cm) 168 (147–191) vs 166 (150–189), and body mass index (BMI) 25.9 (17.2–34.7) vs 26.3 (22.4–39.6). The characteristics of the patients are given in Table 1.

Biochemical markers of bone turnover, IGF-I and IGFBP-3

At baseline and after 6, 12 and 18 months treatment serum (S) and urine (U) samples for the measurement of markers of bone turnover, IGF-I and IGFBP-3 were obtained in the morning, after an overnight fast, and stored at −20°C until completion of the study. All samples from one patient were analysed in the same assay.

S-osteocalcin was measured by an ELISA kit from DAKO, Copenhagen, Denmark. Intra-assay coefficients of variation were 4.6% at 5.0 μg/l and 3.3% at 23.6 μg/l. Interassay coefficients of variation were 7.8% at 3.4 μg/l and 4.7% at 13.4 μg/l. The sensitivity of the assay was 0.2 μg/l and the detection limit was 1.0 μg/l. The reference range determined from 230 healthy adults was 2.6–10.4 μg/l (in-house validation by the Osteoporosis Research Centre, Copenhagen).

Serum concentration of the carboxyterminal propeptide of type I procollagen (S-PICP) was measured by a radioimmunoassay (RIA) kit from Orion Diagnostica, Turku, Finland. The intra- and interassay coefficients of variation were <3.1 and <6.6% respectively. The reference ranges were 50–170 μg/l for women and 38–202 μg/l for men (22).

Serum concentration of the carboxyterminal cross-linked telopeptide of type I collagen (S-ICTP) was measured by an RIA kit from Orion Diagnostica. The intra-assay coefficient of variation was <6.2% at 3.8 μg/l and interassay coefficient of variation was
<7.9% at 3.3 μg/l. The reference range was 1.8–5.0 μg/l (23).

Urinary hydroxypyridinolin (U-Pyr) and deoxypyridinolin (U-DPyr) were measured by HPLC as described by Kollerup et al. (24). Intra- and interassay coefficients of variation were 5 – 7% and 12 – 14% respectively. In 89 healthy normal adult subjects (62 women and 27 men) the mean value ± S.D. for Pyr/mmol creatinine was 38.8 ± 10.8 nmol/mmol creatinine (range 16.0–61.7) and for DPyr it was 13.0 ± 4.6 nmol/mmol creatinine (range 4.5–32.3).

Serum concentration of the amino-terminal propeptide of type III procollagen (S-PIIINP) was measured by an RIA from Orion Diagnostica. Intra- and interassay coefficients of variation were 2.4% and 5.3% respectively. The reference interval for adults was 1.7–4.2 μg/l (25).

S-IGF-I was determined by competitive RIA using polyclonal rabbit anti-IGF-I antiserum. The method was developed and validated in-house by Pharmacia. At a concentration of 202 μg/l the intra- and interassay coefficients of variation were 3.1 and 10.0% respectively.

S-IGFBP-3 was determined by ELISA (Diagnostic System Laboratories Inc., Webster Texas, USA). Interassay coefficient of variation was determined to 5.5%.

### Statistical methods

Sample size was based on an S.D. of 5% to give the opportunity to detect a true difference of 4.5% change in BMD in L2-L4 with a power of 80% and an alpha level of 5%. All values are given as the mean (± S.D.) unless stated otherwise. Changes within treatment groups were tested by two-sided t-test for dependent variables and differences between groups by t-test for independent variables. Treatment effects were evaluated as differences between changes from
Table 2. IGF-I and IGFBP-3 during 18 months of GH (n = 17) treatment in a randomised, placebo (n = 19) controlled, double blinded study of 18 months duration. Values are given as means (±S.D.).

<table>
<thead>
<tr>
<th></th>
<th>IGF-I (μg/l)</th>
<th></th>
<th>IGF-I (μg/l)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>12 months</td>
<td>18 months</td>
</tr>
<tr>
<td>GH</td>
<td>63.2 (±41.8)</td>
<td>185.0 (±104.5)</td>
<td>193.6 (±106.2)</td>
<td>168.6 (±96.7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>73.6 (±37.6)</td>
<td>73.6 (±36.5)</td>
<td>78.2 (±41.3)</td>
<td>76.3 (±38.5)</td>
</tr>
<tr>
<td>P-value</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P-values for difference of changes from baseline between the GH+ and placebo-treated groups. NS, not significant.

baseline (Δ) for patients treated with GH and placebo (P) (ΔGH versus ΔP) and by a test of differences in variance between treatment groups. Z-score calculations based on age- and sex-matched reference ranges were performed for DEXA measurements and IGF-I.

**Ethics**

The study was approved by the regional Ethical Committees and the Danish National Board of Health (ref no. 5312-163-1993). All patients gave their written informed consent.

**Results**

**IGF-I and IGFBP-3**

IGF-I and IGFBP-3 in serum increased significantly during GH treatment as shown in Table 2. A differential response to GH treatment between male and female patients was found, with male patients obtaining IGF-I levels in the upper normal range (mean 1.6 Z-score) while the IGF-I for female patients remained in the lower normal range (mean −1.4 Z-score). Three contributing factors were identified. (i) At baseline female patients had a significantly lower IGF-I Z-score than males −4.5 (±2.2) vs −2.6 (±2.0) (P = 0.01). (ii) The increase in IGF-I Z-score following GH was higher in male than in female patients (4.7 to 5.1 vs 2.8 to 3.3 Z-scores) although the difference only reached significance at 18 months (P = 0.02). (iii) One female was IGF-I non-responsive and thus suspected of non-compliance. If this patient was omitted from the analysis the IGF-I Z-score for females reached a mean of −0.8.

**Bone mineral density/bone mineral content at baseline**

No significant differences were found at baseline between the Z-scores of the GHD patients and normal healthy controls, either for total body BMC or for BMD at any of the measured sites. Whole body BMC (mean (±s.d.)) was −0.26 (1.50). Regional measurements of BMD were: L2, 0.08 (1.4); L3, 0.03 (1.6); L4, 0.13 (1.7); femoral neck, 0.09 (1.3); femoral trochanter, −0.15 (1.2). Included in the data were thirteen patients who in addition to GHD had a condition predisposing for low bone mineral content. One male had been unsubstituted with testosterone for approximately 25 years until 2 years prior to the study. The Z-score values of the BMD/BMC parameters for this patient were between −3.4 and −4.3. Seven patients (one male) were treated successfully for Cushing’s disease (6 randomised to placebo, one to GH) more than 6 years prior to entering the study, and 5 patients had been treated for prolactinoma (2 placebo, 3 GH). Their Z-scores at baseline did not differ significantly from those of the other patients.

**Biochemical markers of bone turnover**

Both markers of bone resorption and bone formation showed a significant increase following GH treatment (Fig. 1). The maximal value for all bone metabolism markers except osteocalcin was found at the 6-month visit. Thereafter, the values of the parameters showed a tendency to decline.

**Bone mineral density/bone mineral content during therapy**

No significant treatment effect was observed when comparing changes from baseline between the GH- and placebo-treated groups after 18 months. Results of BMD measurements are summarised in Table 3. The variances of changes from baseline were greater in the GH- than in the placebo-treated group, reaching significance for BMD of total body (P = 0.03), lumbar spine (P = 0.001), femoral neck (P = 0.01) and femoral trochanter (P = 0.04) (Table 3 and Fig. 2).

To identify a possible GH responsive sub-group, post-hoc data stratification was performed. Patients were stratified by gender and by total body BMD below or above the median value. Within the GH-treated group, a greater increase in total body BMD was found in the low BMD group (P = 0.02 for percentage changes from baseline and P = 0.03 for actual BMD (g/cm²). No differential response to GH treatment was found between males and females, nor between patients with and without previous hormone overproduction.
Figure 1 Markers of bone turnover during 18 months of GH (●) treatment in a randomised, placebo-controlled (▲), double blinded study. Values are given as means (±S.E.). The P values for differences of change from baseline between GH- and placebo-treated patients are *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. Creat, creatinine.

Table 3 Bone mineral density (BMD) in patients treated with GH (n = 17) or placebo (n = 19) during 18 months randomised treatment. Values are changes from baseline (= 100%) after 6, 12 and 18 months of treatment (means (±S.D.)).

<table>
<thead>
<tr>
<th>Location</th>
<th>6 months^a</th>
<th>12 months^a</th>
<th>18 months^a</th>
<th>Difference of variance GH18 vs P18^b</th>
<th>Post nadir effect^c ΔGH06-18 – ΔP06-18 (mean increase %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body</td>
<td>98.52 (±0.87)</td>
<td>100.09 (±0.79)</td>
<td>102.27 (±1.05)</td>
<td>P = 0.03</td>
<td>0.85</td>
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<tr>
<td>GH</td>
<td>97.53 (±0.77)</td>
<td>100.25 (±1.08)</td>
<td>100.38 (±0.58)</td>
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</tr>
<tr>
<td>Lumbar spine L2-L4</td>
<td>99.36 (±1.06)</td>
<td>100.69 (±1.30)</td>
<td>101.21 (±1.77)</td>
<td>P = 0.001</td>
<td>1.38</td>
</tr>
<tr>
<td>GH</td>
<td>100.02 (±0.88)</td>
<td>100.09 (±0.89)</td>
<td>100.48 (±0.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>98.98 (±0.79)</td>
<td>98.90 (±0.90)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Femoral neck</td>
<td>99.32 (±1.34)</td>
<td>100.77 (±1.81)</td>
<td>101.13 (±1.82)</td>
<td>P = 0.01</td>
<td>3.18</td>
</tr>
<tr>
<td>GH</td>
<td>100.14 (±1.18)</td>
<td>98.98 (±0.79)</td>
<td>98.90 (±0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>99.58 (±1.12)</td>
<td>99.32 (±0.93)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Femoral trocanter</td>
<td>99.13 (±1.03)</td>
<td>99.58 (±1.12)</td>
<td>102.34 (±1.59)</td>
<td>P = 0.04</td>
<td>3.04</td>
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<tr>
<td>GH</td>
<td>100.00 (±0.72)</td>
<td>99.22 (±0.93)</td>
<td>100.68 (±0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>99.58 (±1.12)</td>
<td>99.32 (±0.93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal forearm</td>
<td>98.48 (±1.23)</td>
<td>100.53 (±1.42)</td>
<td>103.12 (±3.20)</td>
<td>P = 0.59</td>
<td>9.53</td>
</tr>
<tr>
<td>GH</td>
<td>103.61 (±2.37)</td>
<td>103.25 (±2.33)</td>
<td>98.72 (±3.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>99.87 (±0.34)</td>
<td>99.62 (±0.50)</td>
<td>99.92 (±0.52)</td>
<td>P = 0.33</td>
<td>0.26</td>
</tr>
<tr>
<td>Proximal forearm</td>
<td>99.78 (±0.39)</td>
<td>100.00 (±0.25)</td>
<td>99.62 (±0.49)</td>
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</table>

^a No significant differences were found for changes from baseline, nor for differences between treatment groups at any time-points.
^b Significant difference of variance between changes from baseline at 18 months in the GH-versus the placebo (P)-treated groups indicate an impact of GH treatment on BMD.
^c From 6–18 months the mean increase of BMD (%) was numerically greater in the GH- than in the placebo (P)-treated patients at all locations, and statistically significantly greater at 3 of 6 locations.
The increased bone turnover, as evidenced by the increase in biochemical markers of bone resorption and formation (Fig. 1), was corroborated by a characteristic pattern of BMD and BMC over time. A decrease in BMD from baseline to 6 months in the GH-treated group as compared with placebo treatment did not reach significance, whereas an increase in BMD from 6 to 18 months was significant for total body, femoral neck, femoral trochanter and distal forearm, when comparing GH with placebo treatment (Table 3 and Fig. 2).

**Body composition**

GH in comparison with placebo treatment caused an increase in total lean body mass, and a decrease in total fat mass; thus an increase in total body lean/fat ratio and a reduction of percentage body fat occurred. Total body mass remained unchanged (Fig. 3).

**Discussion**

GH substitution therapy for 18 months had no statistically significant effect on mean BMD or BMC compared with placebo treatment. Of note, however, after 18 months the variations from baseline in the GH-treated group were significantly greater for BMD of total body, lumbar spine, femoral neck and trochanter. Such heterogeneity may be indicative of treatment impact or subgroup effect in this prospectively included group of mixed patients with severe GHD.

The highly significant increase of all biochemical markers of bone turnover would, in keeping with the paradigm of bone remodeling as a diphasic process, cause an initial overweight of bone resorption before new bone formation could take place. The decline of bone mass from baseline to 6 months was not significantly larger in the GH than in the placebo group. From 6 to 18 months there was a significantly greater increase in BMD in the femoral neck, the femoral trochanter and the distal forearm in the GH as compared with the placebo group, while the changes at the remaining sites were not significant. It is tempting to speculate that a net gain of bone mass might be seen after an even longer duration of treatment, which has now been demonstrated in an open trial (26). Post hoc data stratification suggested that patients with low BMD might be more responsive to treatment than...
those with higher BMD, which is in keeping with previous results (15).

Thus, our findings are in keeping with the only three previously published randomised placebo-controlled trials of more than 6 months duration. In a 12-months double blinded study of 29 patients, Hansen et al. (20) found a significant decrease of whole body BMD and radius BMD, while the changes at the remaining locations were not significant. In a 9 + 9 months double blinded cross-over study with a 3-months washout period interposed, a significant decrease in total body BMD was found in both trial arms after the GH treatment period (21). Partially converse results were reached in a study of 40 entirely male adult onset GHD patients. The study was single blinded, dose titrated with cross-over design of 18+18 months duration with no interposed washout period. After the initial 18-month period, a significant slope equivalent to an increase in BMD was reported for spine and hip measurements, but not for forearm and total body. When GH was compared with placebo, BMD only increased significantly at 2 of the 7 sites studied (18). During a further 18 months of observation after cross-over of GH and placebo treatment, BMD continuously increased in the group withdrawn from GH treatment, as did BMD in the patients newly started on GH at the spine and hip sites, but not BMD of forearm and total body. Thus no statistically significant differences were reported between GH and placebo for any of the 7 sites investigated (19).

Several long term but uncontrolled studies have claimed effects on bone mass. The studies which have frequently been designed as open observational follow-up to short term randomised trials, uniformly tend to show an initial significant decline of BMD or BMC at several sites during GH therapy followed by an increase in BMD from 6 months onwards (9–16). However, total body BMD was shown to remain significantly reduced after 12 months of GH treatment (17). In a Finnish multicentre study (15) subanalysis revealed that significant treatment effects were found only in patients who were osteopenic at baseline and, further, that treatment response was significantly more pronounced in male than in female patients. Similarly among 44 patients, the 13 patients with baseline Z-scores below $-2$ S.D. had a more pronounced increase than the remaining patients after 2 years of treatment (9).

In the present study, GHD patients did not, contrary to several previous reports, have reduced BMD or BMC when compared with age-related normal ranges. One previous study similarly found elderly patients with adult onset GHD not to be osteopenic (27) The present baseline cohort had been recruited to the study from long term follow-up at a tertiary referral centre, where case records documented relevant testing and clinical evaluation for signs and symptoms of hypopituitarism. Also relevant prescription of substitution therapy was documented. The importance of the influence from other axes than GH was clearly illustrated by the only outlier whose baseline BMD/BMC values were around $-4$ S.D. This patient had by choice abstained from testosterone substitution for 25 years.

Substitution therapy for other insufficient pituitary axes had to be stable for 6 months prior to the start of GH treatment. Institution of sex steroid substitution
several years prior to GH treatment may have a potential effect on BMD/BMC during the GH study period. As the present study was placebo controlled, any confounder would be expected to influence equally the results in both groups. Yet, by chance 6 of 7 patients with previously treated Cushing’s disease received placebo, but without apparent influence on the outcome of the study. The possibility of confounders is especially concerning when open studies claim a treatment effect at time points when placebo-controlled studies unequivocally do not. It should, however, be noted that the statistical power of the present study was too weak to detect significant changes less than 4.5%.

DEXA measurements do not distinguish between measuring cortical or trabecular bone. Histomorphometry on transiliac bone biopsies before and after 12 months of GH versus placebo treatment (28) indicated that the bone balance of trabecular bone was unaltered. Similarly, in GH treatment studies of aged rats in which there were no changes in cancellous bone of vertebral bodies, there was an increase in cortical bone volume and compressive mechanical strength of the vertebral body (29). GH furthermore increased the area of bone, which is not necessarily accounted for in the DEXA measurement.

The major concern of bone mineral status in GHD patients is the correlation between low BMD/BMC and risk of fracture. A retrospective epidemiological study (6), a cross-sectional radiological study of vertebral heights in GHD patients (7), and data from a pharmacovigilance study (8) have substantiated the concern by documenting an increased fracture rate in hypopituitary patients. A significant correlation has been found between GH status expressed as peak GH at stimulation test and IGF-I and bone mineral status of lumbar spine and femoral neck (5). It is, however, difficult to conclude from such studies that GH therapy of adult onset GHD protects against osteoporosis and fractures. A number of factors may cause bias: (i) some patients may have had onset of disease before attainment of peak bone mass; (ii) long term partial hypopituitarism may have been present prior to diagnosis; (iii) lack of compliance with substitution therapy may have been present, as well as (iv) intercurring conditions or medications affecting bone metabolism, and (v) GH increased the area of bone which is not necessarily accounted for in the DEXA measurements. Finally, (vi) fracture risk may be increased due to neurological or visual deficits, with overtly or discretely impaired balance, co-ordination and motor activity, with an increased tendency to fall.

In summary, this placebo-controlled trial confirmed longer-term open studies (15, 21, 26, 30) on the effect of GH replacement on bones in patients with adult onset GHD. Available evidence indicates an initial overrepresentation of bone resorption and probably increased bone area, followed by an increased BMD, thus perhaps explaining the decreased fracture risk.

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