CLINICAL STUDY

Treatment for 24 months with recombinant human GH has a beneficial effect on bone mineral density in young adults with childhood-onset GH deficiency

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Abstract

Objective: Discontinuation of growth hormone (GH) therapy on completion of linear growth may adversely affect bone mineral density (BMD) in young adults with childhood-onset GH-deficiency (GHD). In the present study, we analyzed the impact of GH treatment on bone in young adults with GHD. **Methods:** BMD at the lumbar spine (L2–L4), total hip, and total body was measured at baseline and after 24 months in a cohort of young adults (18–25 years; $n = 160$) with severe GHD treated with GH during childhood who were randomized to GH ($n = 109$) or no treatment ($n = 51$) in a multicenter, multinational, open-label study. GH starting doses (0.2 mg/day (males), 0.4 mg/day (females)) were increased after 1 month to 0.6 mg/day (males) and 0.9 mg/day (females) and then to 1.0 mg/day (males) and 1.4 mg/day (females) at 3 months for the remainder of the study.

Results: After 24 months, lumbar spine BMD had increased significantly more in GH-treated patients than in controls (6 vs 2%; estimated treatment difference; 3.5% (95% confidence interval, 1.52–5.51) $P < 0.001$). GH also had a significant positive effect on total hip BMD ($P = 0.015$). Total body BMD was unchanged from baseline ($P = 0.315$).

Conclusions: In young adults treated for childhood-onset GHD, there is a beneficial effect of continued GH treatment on BMD in adult life. Twenty-four months of GH treatment in these young adults was associated with an estimated 3.5% greater increase in BMD of the lumbar spine compared with controls.

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Introduction

Children with GH-deficiency (GHD) (1–3), as well as adult patients with childhood-onset or adult-onset GHD (1, 2, 4–8), exhibit reduced bone mineral density (BMD) compared with healthy controls. Specifically, in young adults (<30 years of age) with childhood-onset GHD, significant reductions in cortical thickness, cortical cross-sectional area, and overall cortical content have been reported, which in association with the smaller bone size, result in a reduced BMD compared with age- and sex-matched healthy controls (1, 2, 8, 9), placing these patients at increased risk of fracture (10). Indeed, clinical studies have shown that the prevalence of fractures is 2.7–3 times higher in adult hypopituitary patients than in age-matched controls (11, 12). Data from these studies suggest that the increased risk may be due to GHD rather than to other pituitary hormone deficiencies or their replacement (12).

A role for GH in the accretion of bone mass is supported by several lines of evidence. First, *in vitro* studies show that GH and its major effector, insulin-like growth factor-1 (IGF-1), are both mitogens for osteoblasts (13, 14). Second, increases in markers of bone remodeling occur during GH replacement therapy in adults with GHD (3, 4, 8, 15). Finally, accumulated evidence supports the finding that GH replacement in children (3, 16) and adults with GHD (8, 17, 18) improves BMD.

Normally, ~40% of skeletal mass is accrued during puberty (19), but accumulation of bone mass at various skeletal sites continues for 1–7 years after longitudinal bone growth has stopped (19, 20). However, the timing of acquisition of peak bone mass in young adults with GHD is not well researched. In a study of 16 adolescent patients (aged 15–19 years) with isolated GHD, lumbar BMD area (bone mineral content (BMC) corrected for vertebral surface area) and lumbar BMD volume (BMC

corrected for vertebral volume) were below the normal mean, and mean values of peak BMD were reduced in patients compared with controls (21). Twenty-four months after cessation of GH treatment, lumbar bone mass had declined in patients but not in controls. These results suggest that in young adults with GHD, GH replacement may be needed to support adequate bone mass accumulation in order to maintain bone mass in adult life (21–23). Furthermore, it seems likely that adolescents with severe GHD may not have achieved their peak bone mass at adult height, when GH treatment is often discontinued, and that GH may play an important role in the acquisition and maintenance of bone mass during this particular period of bone consolidation (3, 24–26). In addition to reduced BMD, some adults with childhood-onset GHD also have lower lean body mass, diminished quality of life (QoL), abnormal lipids, and impaired cardiac function compared with older adults with adult-onset GHD (27, 28). It is postulated that lack of GH during late teens and early twenties, a period when bone and muscle mass continue to accrue, and somatic development continues and contributes to the deterioration of these parameters in adults with childhood-onset GHD (29). Several studies have yielded evidence to support the efficacy of GH in preventing the adverse changes in body composition (26, 30, 31). Thus, the practice of discontinuing GH in all patients after attainment of adult height is under review and it is suggested that continuation of GH replacement in GHD individuals during the post-pubertal 'transition' phase may alleviate the metabolic complications of GH deficiency, including maturation of bone (32, 33).

The aim of this study was to investigate the efficacy of 24-months' treatment with GH on BMD in young adults with childhood-onset GHD.

Materials and methods

This was a randomized, controlled, open-label study conducted at 22 sites in 12 countries (Australia, Belgium, UK, France, Germany, Hungary, New Zealand, Norway, Poland, Spain, Sweden, and Switzerland). The study was conducted according to the guidelines of Good Clinical Practice, the Declaration of Helsinki, and with approval from the Ethical Review Boards appropriate for each of the study centers.

The primary objective of the study was to evaluate the effect of 24 months of GH treatment on BMD in young adults with childhood-onset GHD. The effect of GH treatment on markers of bone metabolism, serum IGF-1, IGF-binding protein-3 (IGFBP-3), and safety were also evaluated as secondary endpoints.

Study participants were young adults (18–25 years; body mass index, 18–30 kg/m²) diagnosed with GHD during childhood on the basis of at least one provocative test of GH secretion. All subjects had received GH during

childhood until adult height was attained. Subjects with isolated or only two (including GH) pituitary hormone deficiencies were required to undergo a further provocative GH test after their 16th birthday to confirm the diagnosis. Subjects with three or more pituitary hormone deficiencies were exempt from further testing. All GH testing was performed in accordance with the consensus guidelines that were present at the time of patient recruitment into the trial (34). Patients were excluded from the study if they had received GH treatment during the month before randomization or if they had experienced severe disease that could interfere with GH treatment or participation in the study. Other reasons for exclusion included serious cardiac, hepatic or renal disease, uncontrolled hypertension, diabetes, acromegaly, disease that could affect bone metabolism, or any malignant tumor. Female subjects were excluded if pregnant or lactating. For subjects with more than one (other than GH) known deficient hypothalamic–pituitary axis, replacement doses of thyroid, adrenal, gonadal and/or antidiuretic hormone were to have been unchanged for at least 6 months prior to attending the screening visit.

Study treatment

Patients were randomized (2:1) to 2 years of open-label treatment with either GH (Norditropin SimpleXx, Novo Nordisk A/S, Copenhagen, Denmark) or to an untreated control group. GH was initiated at a starting dose of 0.2 mg/day (males) and 0.4 mg/day (females). The dose of GH was increased to 0.6 and 0.9 mg/day in males and females respectively, at 1 month and was then raised again to 1.0 mg/day (males) and 1.4 mg/day (females) at 3 months for the remainder of the study. Higher GH doses are required in women than in men to achieve normal IGF-1 levels (30, 35). Dose reduction was allowed at the discretion of the investigator following the occurrence of GH-related side effects. GH was given as a single daily s.c. injection at bedtime using a cartridge pen (NordiPen, Novo Nordisk). Patients in the control group received no treatment during the study. The study was open and not placebo-controlled because it was deemed unethical to subject young adults to daily placebo injections for 24 months.

All patients attended the clinic at the screening visit (1–5 weeks before randomization), the randomization visit, and at months 1, 3, 6, 12, 18, and 24. BMD of the lumbar spine (L1–L4), total body and total hip was assessed by dual energy X-ray absorptiometry (DEXA) at time of starting GH treatment and at months 6, 12, 18, and 24. Hologic densitometers (Hologic QDR 4500, Hologic Inc., Waltham, MA, USA) were used according to the protocol. Baseline and follow-up scans were performed on the same instrument for each patient. To control for possible differences between scanners at the different sites standardization procedures were carried out using a phantom (Hologic Spine Phantom) for

calibration at all participating sites. DEXA data were transferred electronically for all readings to be performed centrally. Longitudinal stability of the scanners during the study was assessed from the DEXA spine phantom data which was reviewed monthly at the central site (Synarc Inc., Ballerup, Denmark) and corrective action was applied if necessary. Serum levels of alkaline phosphatase were determined using standard assay techniques. Serum levels of IGF-1 and IGFBP-3 were determined at a central laboratory with a solid-phase, enzyme-labeled chemiluminescent immuno-metric assay (Immulite 2000 IGF-1 and IGFBP-3; DPC) using an Immulite 2000 analyzer (Siemens Medical Services, Camberley, Surrey, UK). These assays each have an interassay variation of 6.8% in assay midrange. Intra-assay coefficient of variation was in accordance with the manufacturer's kit guidance. Age-specific reference ranges were used (median (central 95% range); IGF-1, age 18 years, 308 (163–584) ng/ml; ages 21–25, 203 (116–358) ng/ml; IGFBP-3, age 18 years, 4.9 (3.1–7.9) µg/ml; ages 21–25 years, 5.1 (3.4–7.8) µg/ml). Bone scans and biochemical samples were analyzed centrally at MDS Pharma Services Central Lab GmbH, Hamburg, Germany. Data from all efficacy and safety laboratory tests was sent electronically from MDS Pharma to the Contract Research Organization (Jellinggaard ApS, Eriksvej 2, DK-2600 Glostrup, Denmark) who performed the data management for the trial.

Safety was assessed by recording all patient- and investigator-reported treatment-emergent adverse events (AEs) during the study.

Statistical analysis

With a 5% significance level and 80% power, it was estimated that 144 evaluable subjects were required to detect a minimum clinically significant change of 3% in BMD of the lumbar spine after 24 months. Assuming a dropout rate of 20%, 180 subjects were planned to be enrolled in the study.

The primary efficacy endpoint, change in lumbar spine BMD during 24 months, was compared between study groups using an ANCOVA model with baseline BMD as covariate. Actual BMD measurements at baseline and at months 6, 12, 18, and 24 were evaluated in a repeated measure ANCOVA with treatment, visit, interaction between treatment and visit, country, age, and baseline BMD as covariates. The model contained a random subject effect. Secondary endpoints were analyzed in the same way as the primary endpoint. A 5% significance level was used and all tests were two sided. For IGF-1 and IGFBP-3, SDS were calculated relative to laboratory reference values. Analyses were conducted on the intent-to-treat population which comprised all randomized subjects who received at least one dose of GH or who participated as an untreated control.

Figure 1 Study design.

Results

After informed consent, 160 patients (GH, $n=109$; control, $n=51$) were randomized and all were included in the statistical analyses (Fig. 1).

Baseline demographic characteristics of patients, by study group, are summarized in Table 1. No significant differences in baseline demographic characteristics were observed between groups. The number of patients in both treatment groups that had pituitary hormone deficiencies in addition to GHD and were receiving hormone replacement therapies is shown in Table 1.

Table 1 Baseline demographic characteristics of patients.

	GH ($n=109$)	Control ($n=51$)
Male:female (%)	60:40	67:33
Age (years)	21.1 (2.3)	21.4 (2.1)
Height (cm)	165.7 (11)	167.5 (8.8)
Weight (kg)	63.5 (15)	65.4 (13)
BMI (kg/m ²)	22.9 (3.5)	23.2 (3.4)
Pituitary hormone deficiencies		
Panhypopituitarism	3	3
Partial hypopituitarism	1	–
Hypogonadotrophic hypogonadism	1	–
Partial gonadotropin deficiency	1	–
Partial cortisol deficiency	1	–
Hormone replacement therapy		
Hydrocortisone	3 (+1 emergency use only)	3
Thyroxine	3	3
DDAVP (desmopressin)	2	1
Oestradiol	1	–
Progestogen	1	–
Oral contraceptive pill (as hormone replacement)	4	1
Testosterone	1	2

BMI, body mass index; GH, growth hormone. Note that patients may have more than one pituitary hormone deficiency and might receive more than one hormone replacement therapy.

Figure 2 Change in dual energy X-ray absorptiometry-derived bone mineral density during the 24-month treatment period in GH-treated and untreated subjects. Data are shown as repeated mean estimates (estimated mean) with 95% confidence intervals.

The numbers of patients who completed the study period were 92 GH-treated and 40 control subjects. The reasons for discontinuation were mainly patient decision; only five patients withdrew due to AEs (GH group, Cushing's syndrome (recurrence), edema and papillary thyroid cancer; control group, increased weight (two patients), skin striae on the upper parts of both legs). Mean (S.D.) GH dose at the 24-month visit was 17.9 (6.3) µg/kg per day.

GH dose

The median (min–max) GH dose at the 24-month visit was 1.0 (0.6–1.4) mg/day. Five patients required a reduction in GH dose. Dose reduction was in the range of 20–36% in each case and was done at either the 12- or 18-month visit.

Efficacy

The change in lumbar spine BMD from baseline during the 24-month study period is shown in Fig. 2. GH treatment was associated with a significantly greater increase in BMD from baseline to end of treatment compared with controls (6.0 vs 2.0%, estimated treatment difference 3.5%; 95% confidence interval (CI) 1.5–5.5, $P < 0.001$). As expected, a net loss in bone mass was observed during the initial 6 months of GH treatment, after which there was a net increase in bone mass (Fig. 2).

Table 2 summarizes changes from baseline in BMD of total hip (femoral neck, trochanter, and Ward's triangle) and total body. Compared with controls, the GH treatment effect was statistically significant for total hip BMD (treatment effect (GH-control), 95% CI 2.43% (95% CI 0.48, 4.43), $P = 0.015$), but not for total body BMD (0.51% (–0.49, 1.53), $P = 0.315$). As observed for the lumbar spine, BMD of the total hip and total body

decreased during the first 6–12 months of GH treatment after which a net increase was reported.

Markers of bone remodeling

Mean ($\pm$ S.D.) baseline values for alkaline phosphatase were similar between treatment groups (GH, 73.4 ± 27.4 ; controls, 79.4 ± 36.4). During the first 6 months of GH treatment, there was an initial increase in alkaline phosphatase, which was followed by a decline over the next 18 months (Fig. 3). At 24 months, there was a statistically significant difference in mean alkaline phosphatase levels between GH-treated patients and controls (estimated treatment difference, 12 IU/l; 95% CI 2.65–21.35; $P = 0.012$).

Mean serum IGF-1 levels were not different between treatment groups at baseline (Table 3). In GH-treated patients, mean serum IGF-1 levels increased from baseline during the initial 6 months of treatment then remained approximately constant for the remainder of the treatment period. At 24 months, serum IGF-1 levels were significantly higher than in controls ($P < 0.0001$; Table 3). Expressed as SDS, GH treatment was associated with a normalization of the IGF-1 SDS from -2.25 (1.38) at baseline to 1.39 (3.85) at 24 months. In controls, the IGF-1 SDS remained below normal levels throughout the study (Table 3). Elevated IGF-1 values (> 2 SDS) were recorded in 16 patients in the GH treatment group (none in untreated controls) during the study accounting for 5% (33/612) of all IGF-1 observations.

Mean IGFBP-3 levels also increased with GH treatment and were significantly higher in GH-treated patients than in controls at 24 months ($P < 0.0001$; Table 3). Similarly, the IGFBP-3 SDS at 24 months had increased from below to within the normal range in GH-treated subjects, but not in controls (Table 3).

Table 2 Changes from baseline in bone mineral density (BMD) of the total hip and total body after 24 months of GH treatment and in untreated control subjects and analysis of covariance (ANCOVA) of the two groups using treatment and baseline level as covariate.

	GH (n=109)	Control (n=51)	GH versus control (P value)
Lumbar spine BMD (g/cm²)			
Baseline	0.91 (0.13)	0.93 (0.11)	
24 months	0.96 (0.14)	0.94 (0.11)	
Change from baseline	0.05 (0.05)	0.02 (0.04)	$P = 0.0006$
Total hip BMD (g/cm²)			
Baseline	0.88 (0.14)	0.90 (0.12)	
24 months	0.90 (0.14)	0.89 (0.12)	
Change from baseline	0.02 (0.05)	0 (0.04)	$P = 0.015$
Total body BMD (g/cm²)			
Baseline	0.98 (0.11)	0.99 (0.10)	
24 months	1.00 (0.12)	1.00 (0.09)	
Change from baseline	0.02 (0.03)	0.02 (0.02)	$P = 0.315$

Figure 3 Change in serum alkaline phosphatase levels during the 24-month treatment period in GH-treated and untreated subjects. Data are shown as repeated mean estimates (estimated mean) with 95% confidence intervals.

Safety

A total of 254 AEs were reported by 84 (53%) patients. GH treatment was well tolerated and a similar proportion of patients on active treatment and controls experienced AEs (55 vs 47%). The most common AEs were infections and head louse infestations which occurred in 29% of patients in the GH group and 35% of untreated controls. AEs that were considered possibly or probably related to GH were reported by 13.8% of patients, the most common of which was edema (reported in 5.5% of patients). Serious AEs were reported by 6.4% of patients in the GH group and 5.9% in the untreated group. Two of these events in the GH group were considered by the investigator as possibly related to trial drug (hypertensive hydrocephalus after 6 months of GH treatment and

recurrence of Cushing's syndrome in a patient with panhypopituitarism following neurosurgery for a hypophysis adenoma 4 years prior to entering the trial). The patient with hypertensive hydrocephalus temporarily discontinued treatment but reported no permanent cerebral damage.

Discussion

In this study, 24 months of treatment with GH in young adults with childhood-onset GHD was associated with a significant (6%; $P < 0.001$) increase in BMD of the lumbar spine, as assessed by DEXA. This was accompanied by a significant (2.4%; $P = 0.015$) increase in BMD of the total hip. No increase in total body BMD was detected in our study. Several recent studies have assessed the effects of GH replacement on BMD at completion of linear growth in children (36–39). Consistent with our findings, in a smaller study involving 24 adolescents with severe GHD, 12 months' GH therapy was associated with a 4.7% increase in mean lumbar spine BMD from baseline compared with a 2.7% change in those who discontinued treatment, while the median whole body BMC increased by 6% in GH-treated patients and remained unchanged in untreated patients (36). In another study in 149 post-pubertal GH-deficient patients (mean age 19 years) who had terminated GH at adult height, significant increases in total BMC were observed in patients treated for 24 months with GH at a daily dose of 0.0125 mg/kg ($9.5 \pm 8.4\%$) or 0.025 mg/kg ($8.1 \pm 7.6\%$) compared with untreated controls ($5.6 \pm 8.4\%$; ANCOVA, $P = 0.008$ with no significant GH dose effect) (38). In that study, BMC increased predominantly at the lumbar spine

Table 3 Changes from baseline in insulin-like growth factor-1, insulin-like growth factor binding protein-3, insulin-like growth factor-1 SDS, and insulin-like growth factor binding protein-3 SDS after 24 months of GH treatment and in untreated control subjects and analysis of covariance (ANCOVA) of the two groups using treatment and baseline level as covariate.

	GH (n=109)	Control (n=51)	GH versus control (P value)
IGF-1 (mg/l)			
Baseline	132.9 (128.1)	165.2 (163.5)	
24 months	361.6 (259.5)	115.5 (113.2)	
Change from baseline	244.0 (231.9)	−21.9 (52.3)	$P < 0.0001$
IGFBP-3 (mg/l)			
Baseline	3.8 (2.0)	3.9 (2.0)	
24 months	5.5 (2.1)	3.3 (1.8)	
Change from baseline	1.7 (2.1)	−0.1 (0.9)	$P < 0.0001$
IGF-1 SDS			
Baseline	−2.7 (−3.8 to 4.5)	−2.4 (−3.7 to 3.7)	
24 months	0.4 (−3.6 to 12.06)	−2.5 (−3.6 to 3.8)	
Change from baseline	3.4 (−1.9 to 13.4)	0.1 (−1.9 to 1.4)	$P < 0.0001$
IGFBP-3 SDS			
Baseline	−0.9 (−4.5 to 5.3)	−1.1 (−3.7 to 2.2)	
24 months	0.8 (−4.0 to 5.8)	−1.6 (−3.8 to 3.3)	
Change from baseline	1.5 (−8.5 to 6.9)	−0.1 (−1.5 to 3.1)	$P < 0.001$

Data are mean (s.d.) for IGF-I and IGFBP-3 and median (range) for IGF-I SDS and IGFBP-3 SDS. GH, growth hormone; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; SDS, SD score.

rather than at the femoral neck or head. Data from a meta-analysis of the relationship between BMD and fracture risk suggest that a 1 s.d. reduction in lumbar spine BMD is associated with an increase in relative risk for fracture at any site of 1.5% (95% CI 1.4–1.7) (40). Hence, it has been suggested that GH treatment in post-pubertal young adults with childhood-onset GHD should be continued in the transition phase after linear growth is complete and until peak bone mass is achieved, with the aim of preventing osteopenia and the early incidence of osteoporosis and reducing the attendant risk of fracture due to bone fragility if peak bone mass is not achieved in early adulthood (19, 20).

The increase in BMD at the lumbar spine and total hip but not in total body BMD in our study, suggesting a decrease in BMD in some regions, is not unexpected given the different types of bone throughout the body. Histomorphometric studies (41) in normal subjects suggest structural differences at the cellular level between the axial and appendicular skeleton. The response of bone to GH may therefore be dependent on the type of bone, either cortical or trabecular, predominating at the site being assessed (37, 42). Longer follow-up may be required to assess the impact of continued GH therapy on whole body BMD. Nevertheless, the finding in our study that bone mass accretion with continued GH replacement beyond the achievement of adult height is particularly marked at the lumbar spine (38) is of considerable clinical impact given the vulnerability of this site to osteoporotic fractures in later life (43). Further studies may be warranted on the impact of GH therapy on osteoporosis and fracture incidence in this population.

Consistent with the results of this study, in a 10-year follow-up study in 23 childhood-onset GH-deficient men (mean age 29 years at treatment start), GH replacement was associated with a significant increase in BMD of the lumbar spine compared with baseline; a reduction in BMD was observed in control subjects (44). In the control subjects, BMD of the hip also decreased significantly compared with baseline whereas in GH-treated subjects, BMD in the hip was not significantly different from baseline values. It is known that peak bone mass is achieved during early adult life (at around the age of 30 years) and thereafter there is a slow decline in BMD with age. In the study reported by Arwert *et al.* (44), a natural decrease in BMD was apparent during 10 years of follow-up in controls but not in GH-treated patients.

In vitro studies have demonstrated that GH stimulates the proliferation of osteoblasts (45). GH also increases biomarkers of bone turnover in normal subjects (46) as well as adults (47) and children (21) with GHD. In the present study, DEXA measurements showed a net loss of BMD at the lumbar spine, total hip, and total body during the initial 6 months of treatment, followed by a steady increase in BMD at these sites. In the first months after GH therapy is begun, bone mineral resorption

predominates over mineral disposition as more bone remodeling units are activated and the remodeling space is expanded, resulting in a net loss in BMD (48). This is subsequently reversed, leading to a progressive increment in BMD (6, 7). The observations of an initial net loss in BMD in the present study are consistent with findings from other studies. In 64 young adults who were treated with GH during childhood but had since discontinued GH treatment for at least 12 months, a dose-related decline in lumbar spine BMD was observed between baseline and month 6 after starting GH treatment, at a dose of 0.0125 or 0.025 mg/kg per day, that was followed by a dose-related increase to 24 months (31). At 24 months, the mean ($\pm$ s.d.) increase in BMD from baseline was 3.3 (3.9) and 5.2 (4.7)% in the 0.0125 and 0.025 mg/kg per day GH groups as compared with 1.3 (2.8)% in placebo-treated patients. Furthermore, in a comparison of the effects of long-term (36 months) and short-term (6–12 months) GH replacement therapy on BMD in patients with adult-onset GHD, long-term GH therapy was associated with beneficial effects on BMD, particularly at the lumbar spine and trochanter (49). By contrast, the short course of GH therapy led to a decline in lumbar spine and Ward's area BMD while on treatment. Together, these observations suggest that beneficial effects of GH treatment on BMD may require at least a 9–10-month treatment period. Likewise, other studies have demonstrated no improvement in BMD with GH treatment although there has been an increase in terms of osteoid, mineralizing, and eroded surfaces without any change in adjusted apposition rate, mineral apposition rate, and bone formation rate consistent with a delay or lengthened remodeling period with a possible delay in mineralization (50–52). Furthermore, *in vitro* data indicate that while long-term GH appears to promote mineralization, short-term treatment does not promote proliferation of osteoblast precursors or induce expression of late osteogenic markers (53).

In our study, the bone turnover marker, alkaline phosphatase, was demonstrated to reflect the effectiveness of GH therapy. Alkaline phosphatase levels increased during GH treatment, peaking 6 months after initiation of treatment, consistent with an initial increase in bone resorption with GH therapy, and thereafter alkaline phosphatase declined towards pre-treatment levels. Similar findings have been reported by other authors (37, 54). In GH-deficient children, Greig *et al.* (54) showed increased levels of alkaline phosphatase and osteocalcin during the first months of GH therapy that persisted for 24 months. In adult-onset GHD, alkaline phosphatase levels increased within 3 months of GH therapy then decreased at 12 months of therapy (55). A significant correlation between changes in serum levels of alkaline phosphatase and improvement in lumbar spine BMD has been demonstrated (56). It is noteworthy that Crippa *et al.* demonstrated an age-dependent influence of GH on

alkaline phosphatase and alkaline phosphatase mRNA expression in cultured human osteoblastic cells, with the greatest effect observed in adolescents (13–16 year olds) followed by young adults (18–35 years) while the expression of evaluated genes was not affected by GH in cultures from adults (57).

The effect of GH on bone is mediated, at least in part, by IGF-1, and bone mass is known to be linked to circulating levels of IGF-1 (58). The present study shows that GH treatment was associated with a significant (twofold) increase in IGF-1 levels from baseline, resulting in a normalization of IGF-1 levels within the treatment period. A similar response to GH therapy has been reported in other GH treatment studies in young GHD adults with childhood onset disease (28, 31). As glucocorticoid replacement therapy was stable and adequate in patients included in this study, it is unlikely that substitution of corticotrophic deficiency affected the observed GH response.

Moreover, in addition to the observed beneficial effects on BMD of continued GH treatment in patients with childhood-onset GHD patients after adult height has been achieved, continued lifelong therapy is also suggested to alleviate at least some of the aspects of the reduced physical and psychological health associated with GHD in adult life (59, 60). Severe quality of life (QoL) impairment is evident in a significant proportion of adults with GHD, and the beneficial effects of physiological GH replacement on QoL in affected individuals are well documented (61).

In conclusion, the results of this study support that continuation of GH therapy in the transition phase after completion of longitudinal growth may be necessary to allow patients with ongoing severe GHD to normalize peak bone mass. While the efficacy of GH in the prevention of fractures in GH deficient patients is not unequivocally documented, a protective action of GH on trabecular bone, in particular, may be evident. Further evaluation is warranted to establish the clinical benefit of this effect.

Declaration of interest

G S Conway has received honoraria from Pfizer for lecture fees; MS-C, K R, A K have nothing to declare; P Chanson has been an investigator in clinical trials sponsored by the pharmaceutical industry (Pfizer, Eli Lilly, Novo Nordisk, Serono), has received funds for organizing education, and is a member of the International Advisory Board of HypoCSS (Hypopituitary Control and Complication Study), which is sponsored by Eli Lilly; M Tauber has received honoraria for lecture fees; M Zacharin has nothing to declare.

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