

The Effect of Cessation of Growth Hormone (GH) Therapy on Bone Mineral Accretion in GH-Deficient Adolescents at the Completion of Linear Growth

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In many countries, treatment of childhood-onset GH deficiency (GHD) with GH ceases when linear growth is complete. Peak bone mass occurs several years after the completion of linear growth. Given that GH has important anabolic actions on bone, discontinuation of GH therapy at the completion of linear growth may have adverse consequences for the attainment of peak bone mass in adolescent GHD patients. In this United Kingdom multicenter study, 24 adolescents (13 males, mean age 17.0 ± 1.4 yr, SD) with severe GHD were randomized to discontinue or continue GH (0.35 IU/kg·wk) at the completion of linear growth. Whole body bone mineral content (BMC) and lumbar spine bone mineral density were assessed by dual-energy x-ray absorptiometry at baseline and then at 6-month intervals for 1 yr. Markers of bone remodeling (serum bone-specific alkaline phosphatase and urinary deoxypyridinoline) were measured at the same time points. In patients who continued GH (GH+), median BMC increased by 3.8% (interquar-

tile range, 2.6, 5.9, $P < 0.001$) at 6 months; and by 6.0% (3.7–9.1, $P < 0.001$) at 12 months. In patients who discontinued GH (GH–) median BMC was unchanged at 6 and 12 months (+1.9%, -0.4 – 4.2 , $P = 0.9$; and +2.4%, 0.4 – 4.9 , $P = 0.5$, respectively, median, interquartile range). The differences in median change in BMC between the two groups at 6 and 12 months was marginally significant ($P = 0.085$ and 0.074 , respectively). Mean lumbar spine bone mineral density increased by 4.7 (95% confidence interval, 1.0, 8.2) at 12 months in patients continuing GH ($P = 0.01$), but the mean change was not statistically significant change in patients who discontinued GH [+2.7% (95% confidence interval, -0.8 , +6.2)]. These preliminary data suggest that, in adolescent patients with severe GHD, discontinuation of GH at completion of growth may limit the attainment of peak bone mass in this patient group. This may predispose to clinically significant osteopenia in later adult life. (*J Clin Endocrinol Metab* 88: 1658–1663, 2003)

IT IS COMMON CLINICAL practice to treat GH-deficient (GHD) children with recombinant human (rh) GH until linear growth is complete or there is agreement between the child's family and physician that a satisfactory height has been achieved. However, this approach requires careful reassessment in light of the demonstration that many of the adverse consequences of adult-onset GHD may be favorably influenced by treatment with rhGH (1–3). The adult GHD syndrome is characterized by altered body composition, impaired quality of life, an adverse cardiovascular risk profile, and reduced bone mass (1–3). The last of these is a potentially important factor in the decision to continue GH therapy in GHD adolescent patients because of the anabolic actions of GH on bone. Late adolescence and early adulthood is a critical time for the acquisition of bone mass and, although direct causality has yet to be established, it is hypothesized that peak bone mass (PBM) together with subsequent age-related loss are important determinants of an individual's subsequent risk of fracture later in life (4, 5). In this United Kingdom randomized, multicenter study, we compared the

effects of discontinuation or continuation of GH therapy on bone mineral accretion and serum and urine markers of bone remodeling in a group of adolescent patients with severe GHD at the completion of linear growth.

Patients and Methods

Patients

Adolescent patients with childhood-onset (CO) GHD receiving GH therapy at each of the centers were invited to participate if their height velocity was less than 2 cm/yr. Details of the underlying diagnoses and other pituitary hormone deficits of the 24 patients (mean age 17.0 ± 1.4 , SD) recruited into the study are shown in Table 1. Following discontinuation of GH therapy for 1–2 wk, persistent severe GHD was confirmed in all patients with a single dynamic test of GH reserve (Table 1). In 23 patients the diagnostic test used was an insulin tolerance test (nadir glucose concentration <2.2 mmol/liter), but one patient (no. 7) with a craniopharyngioma and multiple pituitary hormone deficiencies (see Table 1) underwent a glucagon stimulation test because of an underlying seizure disorder. All patients received appropriate replacement, where necessary, with glucocorticoid, T_4 , sex steroid, and desmopressin.

Study protocol

Following confirmation of persistent GHD, all patients recommenced GH therapy for a period of 3 months, at the dose previously prescribed by their pediatric endocrinologist. At the end of this time, patients were randomized either to discontinue GH (GH–) or continue GH (GH+) (Genotropin, Pharmacia Corp., Uppsala, Sweden) at a fixed weight-

Abbreviations: BAP, Bone-specific alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval; CO, childhood onset; DpD, deoxypyridinoline; GHD, GH deficiency; LS, lumbar spine; PBM, peak bone mass; rh, recombinant human.

TABLE 1. Diagnoses and pituitary hormone deficiencies

Patient no.	Age	Sex	BMI (kg/m ²)	Peak GH on retesting (mU/liter)	Etiology	Treated pituitary hormone deficiencies	Cont/discont GH
1	20	M	20.5	<0.5	Idiopathic MPHD	ACTH, TSH, FSH/LH	Disc
2	19	F	23.1	<0.5	Germinoma	ACTH, TSH, FSH/LH, ADH	Cont
3	18	M	30.3	<0.5	Septo-optic dysplasia	ACTH, TSH, FSH/LH	Disc
4	16	F	25.8	4.7	ALL	ACTH, TSH, FSH/LH, ADH	Cont
5	17	F	22.4	<0.5	Idiopathic MPHD	FSH/LH	Disc
6	16	M	23.3	7.9	Congenital		Disc
7	16	F	18.5	4.8	Nasopharyngeal rhabdomyosarcoma		Cont
8	18	F	32.8	<0.5	Idiopathic MPHD	ACTH, TSH, FSH/LH	Disc
9	16	F	35.5	<0.5	Idiopathic MPHD	ACTH, TSH, FSH/LH	Disc
10	14	F	44.0	<0.5	Craniopharyngioma	ACTH, TSH, FSH/LH, ADH	Disc
11	18	M	30.1	<1.0	Idiopathic MPHD	ACTH, TSH, FSH/LH	Cont
12	16	F	22.4	1.3	Isolated		Disc
13	17	M	18.4	<1.0	Isolated		Disc
14	16	M	17.4	12.1	Idiopathic MPHD	ACTH	Disc
15	15	F	32.5	1.6	Isolated		Cont
16	16	M	34.5	7.7	Medulloblastoma		Cont
17	17	M	18.0	8.3	Temporal lobe glioma		Cont
18	18	F	31.1	0.8	Craniopharyngioma	ACTH, TSH, FSH/LH, ADH	Disc
19	16	M	27.3	5.3	ALL		Cont
20	16	M	24.9	6.2	Ependymoma		Disc
21	18	M	33.6	0.5	Craniopharyngioma		Cont
22	19	M	35.5	1.1	Astrocytoma	ACTH, TSH	Cont
23	18	M	24	<0.5	Idiopathic MPHD	ACTH, TSH, FSH/LH	Cont
24	17	F	23.4	8.4	Isolated		Cont

Cont, Continued; Disc, discontinued.

based dose of 0.35 IU/kg·wk for 1 yr. Mean doses of additional hormone replacement therapies were identical between the two groups with no alteration in dose during the course of the study. There was no difference between the two groups either in mean time since the onset of puberty (spontaneous or induced) or the dose/duration of GH therapy before inclusion in the study. The protocol was approved by the Ethics Committee of each center and all patients gave informed, written consent.

Measurements

Total bone mineral content (BMC) and lumbar spine (LS) bone mineral density (BMD) were measured by dual-energy x-ray absorptiometry, using either a QDR-1000 (Hologic, Inc., Waltham, MA) or DPX (Lunar Corp., Madison, WI) densitometer. Baseline and follow-up scans were performed on the same instrument for each patient, and each instrument underwent daily standard calibration using the appropriate manufacturer's phantom. Serum bone-specific alkaline phosphatase (BAP) and urinary deoxypyridinoline (DpD) were measured by ELISA (Quidel Corp., San Diego, CA). The manufacturer's reported inter- and intraassay coefficients of variation for BAP ranged between 5.0% and 7.6% and 3.9% and 5.8% respectively. The equivalent ranges for DpD are 3.1–4.8% and 4.3–8.4%. Serum IGF-I was measured by standard RIA after formic acid-acetone extraction, with inter- and intraassay coefficients of variation of 10.4% and 2.7%, respectively.

Statistical analyses

Total body BMC and LS BMD were expressed as a percentage from baseline on account of the different densitometers used at each of the centers. The Shapiro-Wilk *W* test was used to establish whether data were normally distributed. Within each group, *t* tests with unequal variance were used to assess changes in BMC and BMD. Differences in the percentage change in BMC and BMD between the two groups were examined using the Mann-Whitney *U* test. For markers of bone remodeling, regression analyses of values at 6 and 12 months were performed, using baseline BAP or DpD as a covariant and GH+ or GH– as a binary variable. Statistical analyses were performed using Stata Statistical Software 7.0 (Stata Corp., College Station, TX).

Results

Baseline characteristics

There were no systematic differences between the two groups in gender, body mass index, serum IGF-I (Fig. 1), duration of GH therapy, GH dose in childhood, or mean time since the onset of puberty (either spontaneous or induced by exogenous sex steroid) to inclusion in the study.

Serum IGF-I

In those who continued GH, there was no statistically significant change in serum IGF-I throughout the study (Fig. 1). However, in those discontinuing GH, serum IGF-I declined between baseline and 6 months ($P < 0.001$), with no statistically significant change thereafter (Fig. 1).

Total body BMC

Changes in total body BMC (median, interquartile range) are given in Table 2 and shown graphically in Fig. 2. There was no statistically significant change in BMC in the GH– group at either 6 ($P = 0.63$) or 12 months ($P = 0.85$). In contrast, BMC increased significantly in the GH+ group at both 6 and 12 months ($P < 0.001$ for both 0–6 and 0–12 months).

The difference in median percentage change between the GH+ and GH– groups was marginally significant at both 6 and 12 months ($P = 0.085$ and 0.074 , respectively). Excluding the outlier in the GH– group, whose total BMC declined by approximately 25% over the course of the study (Fig. 2), continuation of GH was associated with a mean increase in BMC, over and above that observed in the GH– group, of 1.7% [95% confidence interval (CI) -0.5 , $+4.0$, $P = 0.14$] at

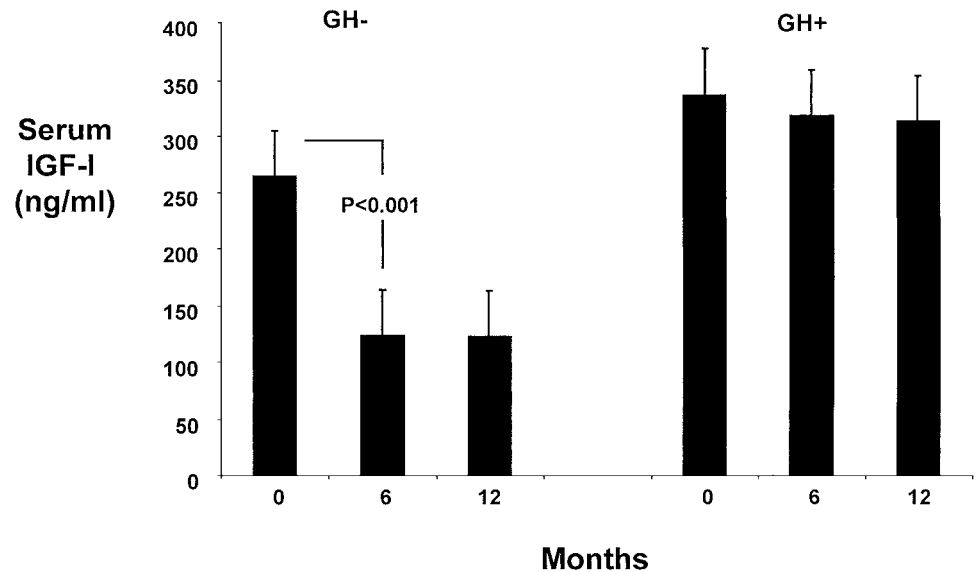


FIG. 1. Serum IGF-I (mean \pm SEM) vs. time in patients who continue (GH+) or discontinue (GH-) rhGH therapy.

TABLE 2. Changes in total body BMC

	Median	Interquartile range
GH-		
6 months	+1.9	-1.2, +4.5
12 months	+2.4	+0.1, +5.3
GH+		
6 months	+3.8	+2.8, +6.1
12 months	+6.1	+2.8, +9.3

Percentage change in BMC (median and interquartile range) in patients who discontinue (GH-) or continue (GH+) GH.

6 months; and 2.9% (95% CI 0.1, +5.7% points, $P = 0.043$) at 12 months.

LS BMD

At baseline, all except one subject had an LS T-score of -1 or less (median, -1.99 ; range, -3.43 – 1.04). Changes in LS BMD (median, interquartile range) are given in Table 2 and shown graphically in Fig. 2. There was no significant difference between the two groups in the percentage change in LS BMD at either 6 or 12 months (Mann-Whitney U test, $P = 0.84$ and 0.45 , respectively). However, LS BMD appeared to increase on average in both groups during the study period; this was significant for the GH+ group at 12 months but not for the GH- group ($P = 0.012$ and 0.15 , respectively). Mean percentage changes at 12 months were 104.6% (95% CI 101.0–108.2) and 102.6% (95% CI 99.1–106.2) for GH+ and GH-, respectively (Table 3 and Fig. 3).

Markers of bone remodeling

The mean \pm SD for BAP and DpD are given in Table 4. There was a statistically significant difference between the two groups at 6 months ($P = 0.019$) but not at 12 months ($P = 0.56$; Fig. 4). These data are supported by a regression analysis using the baseline measure as a covariate in which the effect of continuation of GH between was associated with a mean serum BAP 21 IU/liter higher than in patients who discontinue GH (95% CI 2.2–40.5, $P = 0.031$). The residuals from these regressions did not differ significantly from nor-

mal. There was no significant effect on DpD at either 6 or 12 months in either group (data not shown).

Discussion

The development of osteoporosis, with its attendant risk of fragility fracture, is in part related to the PBM achieved in early adulthood. Adolescence is a crucial time for the acquisition of bone mass (4–6); during pubertal maturation, areal BMC and BMD at the LS and femur increase by 4- to 6-fold over 3 yr (11–14 in girls and 13–16 in boys) (5), such that approximately 37% of skeletal mass is accrued between pubertal stages 2 and 5 (5). Bone mineral accretion continues after this time, although the precise timing of the attainment of PBM, defined as the highest level of bone mass achieved as a result of normal growth (5), is not certain and varies between skeletal sites. Areal BMD at the femur peaks around the age of 20 yr, whereas maximum total skeletal mass occurs 6–10 yr later (5), well after the cessation of GH therapy in GHD patients treated to facilitate linear growth. These observations, together with the effects of rhGH on body composition and well-being in adult hypopituitarism (1–3), demand a critical reevaluation of the traditional timing of cessation of GH therapy in GHD young adults.

Epidemiological and twin studies suggest that up to 80% of the variability in PBM is accounted for by heritable factors, but environmental influences (including physical activity, nutrition, and endocrine function) may modify the ability of an individual to attain his or her genetic potential for bone mass (7). The increase in gonadal steroid secretion around the time of puberty is the most important hormonal regulator of bone accretion, but in recent years GH has received increasing attention as a potentially important factor for several reasons. First, GH and its major effector, IGF-I, are both mitogens for osteoblasts *in vitro* (8–10). Second, GH therapy for adults with GHD is associated with a stimulation of bone remodeling and sustained increases in BMD (11, 12). Last, patients with CO GHD (both isolated GHD and associated with multiple pituitary hormone deficiencies) are relatively osteopenic, compared with age-matched healthy controls

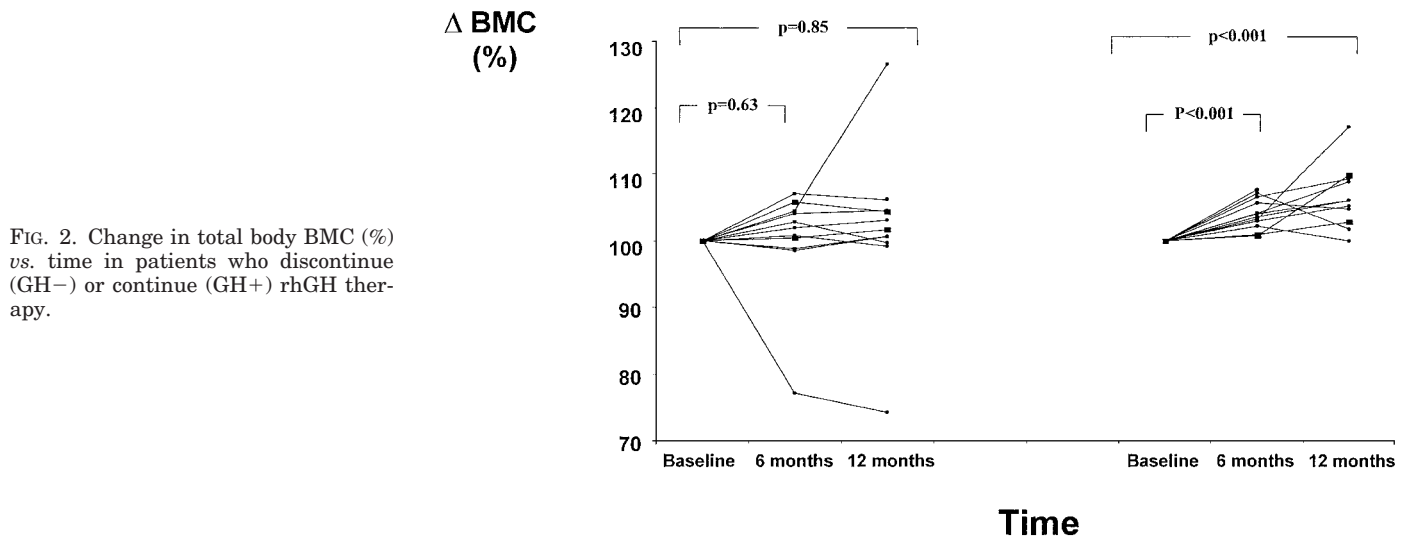


FIG. 2. Change in total body BMC (%) vs. time in patients who discontinue (GH-) or continue (GH+) rhGH therapy.

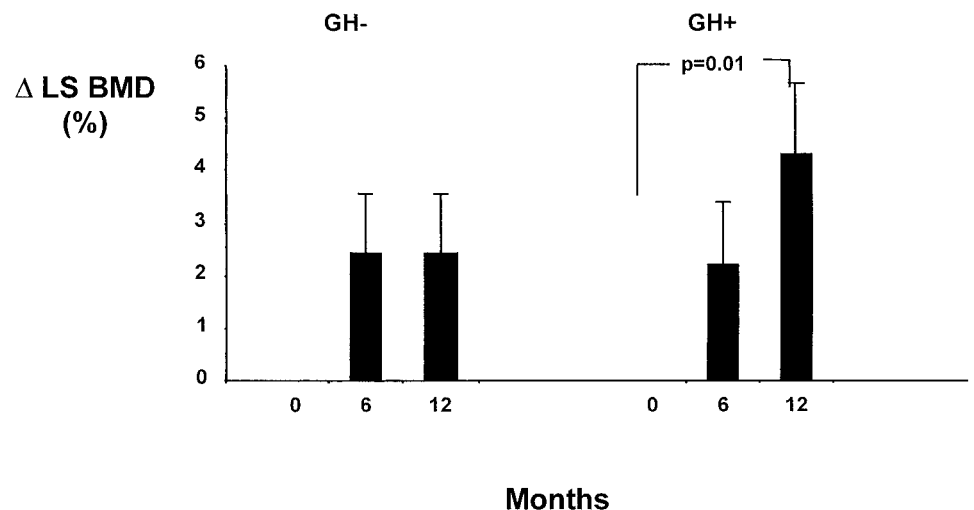


FIG. 3. Change in LS BMD (%) vs. time in patients who continue (GH+) or discontinue (GH-) rhGH therapy (mean \pm SEM).

(13, 14). Although the greater bone mass seen in patients treated with rhGH, as opposed to cadaveric GH, suggests that suboptimal supplies of GH may be partly responsible for this observed disadvantage (15), there remains concern that discontinuation of GH at the completion of linear growth may limit the attainment of PBM in adolescent GHD patients.

Against this background, this United Kingdom randomized, multicenter study provides preliminary evidence that, in adolescent patients with CO GHD who remain severely GHD at the completion of linear growth, cessation of GH therapy is associated with a lack of increment of total body BMC over 1 yr. In contrast, continuation of GH therapy is associated with a rise in whole body BMC of approximately 6% over the same period: an amount that approximates to previous longitudinal studies in healthy adolescents (4, 5). The statistical analysis of these data are complicated by the fact that a single patient in the GH- group (patient 19 with a craniopharyngioma) lost more than 20% of BMC at 6 months, with a further 3% loss between 6 and 12 months. Although little is known about the consequences of discontinuation of GH replacement in adolescent patients with structural hypothalamo-pituitary disease, in the presence of

adequate gonadal steroid replacement, such a finding is unexpected and might potentially falsely exaggerate the skeletal benefits of continuation of GH. The patient's data have therefore been excluded from a subsidiary comparison, between the two groups, of the change in BMC over the course of the study (see above). This analysis suggests that the two groups appear to be divergent in their behavior and that patients in the GH- group may be compromised in their ability to achieve their PBM. Continuation of GH is associated with an increment in BMC of approximately 3% over and above that seen in patients who discontinue GH, an amount that would represent 2 yr of bone loss later in life in a typical postmenopausal woman (16). The discrepancy between the groups is less marked with respect to LS BMD than whole body BMC, implying that GH is facilitating bone accretion at both cortical and trabecular sites.

The mechanism underlying the apparent disadvantage of those patients who discontinue GH has not been clearly identified in this study, although a reduction in bone formation is an obvious possible candidate. BAP is a tetrameric glycoprotein released by osteoblasts during bone mineralization (17) and is a well-characterized biochemical marker

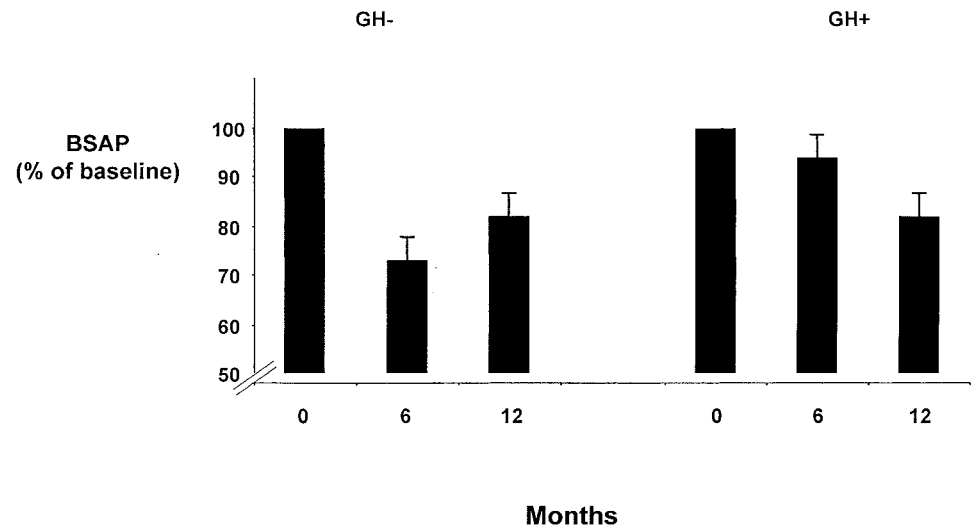


FIG. 4. BAP (U/liter) *vs.* time in patients who continue (GH+) or discontinue (GH-) rhGH therapy (mean \pm SEM).

TABLE 3. Percentage change in LS BMD (mean, 95% CI) in patients who discontinue (GH-) or continue (GH+) GH

	Mean	95% CI
GH-		
6 months	+1.7	-1.2, +4.5
12 months	+2.6	-0.8, +6.2
GH+		
6 months	+2.3	-0.7, +5.9
12 months	+4.7	+1.0, +8.2

of bone formation (17, 18). In GHD adults, serum and urine markers of bone turnover are typically below the adult reference ranges (19). Levels increase with GH therapy as bone remodeling is stimulated (19, 20), and this is accompanied by long-term increases in BMD at both cortical and trabecular sites (12). Pediatric reference ranges for BAP and DpD (a cross-link of mature type I collagen and a sensitive marker of bone resorption) are poorly defined. Although the fall in BAP between 0 and 6 months in the GH- group might suggest that a reduction in osteoblastic activity underlies the observed failure of accretion of bone mass in patients who discontinue GH, this and the later reduction in BAP in the GH+ group again could also be compatible with the decline in markers of bone turnover seen at the end of normal puberty. A much larger study, with examination of the relationship between baseline markers of bone turnover and subsequent bone mineral accretion, would be required to clarify this point.

To our knowledge, this is the first report of a randomized study of the consequences of discontinuation *vs.* continuation of GH on bone mineral accretion in GHD adolescents at final height. It is interesting to compare our results with those of a recent observational study of bone mass accretion after the completion of linear growth in patients treated with GH in childhood (21). No differences were observed in accumulation of bone mass over 2 yr after discontinuation of GH therapy between subjects who remained severely GHD *vs.* those who were GH sufficient. It should be noted, however, that the GH dosing regimens used in this study were associated with serum IGF-I levels markedly higher than control subjects. Furthermore, the mean age of the patients was

TABLE 4. Serum BAP (IU/liter, median and interquartile range) in patients who discontinue (GH-) or continue (GH+) GH

	Median	Interquartile range
GH-		
Baseline	74.5	55.6–96.0
6 months	44.5	37.8–66.3
12 months	44	33.7–70.3
GH+		
Baseline	81.5	66.5–90.8
6 months	71	60–84.5
12 months	51	43.5–65.9

approximately 19 yr, compared with 17 in our study, again suggesting that the window in which GH contributes to bone mineral accretion after linear growth is complete may be relatively narrow.

In this study, a fixed, weight-based dose of 0.35 IU/kg·wk was selected as being approximately midway between typical pediatric and adult maintenance GH doses. Although somewhat empirical, this choice of GH dose produced physiological mean serum IGF-I concentrations in the GH-treated group (Fig. 1), and in no patient was a serum IGF-I concentration outside the age-adjusted reference range recorded at any stage of the study. Optimum GH dosing regimens for adolescent GHD patients are less well defined than for adult hypopituitary patients (22). Hence, if these preliminary findings on bone mineral accretion in adolescent GHD patients are confirmed in other studies, it will be important to establish GH treatment protocols that maximize clinical benefit but, with the help of robust age-related reference ranges for GH dependent serum markers, minimize the risk of excess GH exposure.

In conclusion, this United Kingdom multicenter, randomized study provides important preliminary evidence that cessation of GH therapy at final height may compromise the potential for patients with ongoing severe GHD to attain PBM. Further studies, with a cross-over design, will be required to determine whether this apparent disadvantage is recoverable if GH is recommenced at a later date and what the optimum dosing schedules should be in this important patient group. The study has underlined the emerging role

for GH on somatic development after the completion of linear growth and demands a reexamination of the traditional timing of cessation of GH therapy in GHD adolescent patients treated with GH in childhood.

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