

# Bone Loss Is Correlated to the Severity of Growth Hormone Deficiency in Adult Patients with Hypopituitarism\*

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## ABSTRACT

Reduced bone mineral density (BMD) has been reported in patients with isolated GH deficiency (GHD) or with multiple pituitary hormone deficiencies (MPHD). To investigate whether the severity of GHD was correlated with the degree of bone mass and turnover impairment, we evaluated BMD at the lumbar spine and femoral neck; circulating insulin-like growth factor I (IGF-I), IGF-binding protein-3 (IGFBP-3), and osteocalcin levels, and urinary cross-linked N-telopeptides of type I collagen (Ntx) levels in 101 adult hypopituitary patients and 35 sex- and age-matched healthy subjects.

On the basis of the GH response to arginine plus GHRH (ARG+GHRH), patients were subdivided into 4 groups: group 1 included 41 patients with a GH peak below  $3 \mu\text{g/L}$  ( $0.9 \pm 0.08 \mu\text{g/L}$ ), defined as very severe GHD; group 2 included 25 patients with a GH peak between  $3.1\text{--}9 \mu\text{g/L}$  ( $4.7 \pm 0.4 \mu\text{g/L}$ ), defined as severe GHD; group 3 included 18 patients with a GH peak between  $9.1\text{--}16.5 \mu\text{g/L}$  ( $11.0 \pm 0.3 \mu\text{g/L}$ ), defined as partial GHD; and group 4 included 17 patients with a GH peak above  $16.5 \mu\text{g/L}$  ( $28.3 \pm 4.3 \mu\text{g/L}$ ), defined as non-GHD. In all 35 controls (group 5), the GH response after ARG+GHRH was above  $16.5 \mu\text{g/L}$  ( $40.7 \pm 2.2 \mu\text{g/L}$ ). In patients in group 1, circulating IGF-I ( $P < 0.001$ ), IGFBP-3 ( $P < 0.05$ ), osteocalcin ( $P < 0.001$ ), and urinary Ntx levels ( $P < 0.001$ ) were lower than those in group 3–5, which were not different from each other; the  $t$  score at the lumbar spine ( $-1.99 \pm 0.2$ ) and that at the femoral neck ( $-1.86 \pm 0.3$ ) were lower than those in groups 3 ( $-0.5 \pm 0.7$ ,  $P < 0.01$  and  $-0.3 \pm 0.7$ ,  $P < 0.01$ , respectively), 4 ( $-0.5 \pm 0.2$ ,  $P < 0.01$  and  $-0.3 \pm 0.7$ ,  $P < 0.01$ , respectively), and 5 ( $-0.5 \pm 0.2$ ,  $P < 0.001$  and  $0.0 \pm 0.02$ ,  $P < 0.001$ , respectively). In patients in group 2, circulating IGF-I and IGFBP-3 levels were not different from those in group 1, whereas the  $t$  scores at the lumbar spine ( $-1.22 \pm 0.3$ ) and femoral neck

( $-0.9 \pm 0.3$ ) were significantly higher and lower, respectively, than those in groups 1 and 5 ( $P < 0.05$ ) but not those in groups 3 and 4, and serum osteocalcin and urinary Ntx levels were significant higher than those in group 1 and lower than those in groups 3–5 ( $P < 0.001$ ).

To evaluate the effect of isolated GHD vs. MPHD, patients were subdivided according to the number of their hormonal deficits, such as panhypopituitarism with (10 patients) or without (31 patients) diabetes insipidus, GHD with 1 or more additional pituitary deficit(s) (36 patients), isolated GHD (7 patients), 1–2 pituitary hormone deficit(s) without GHD (10 patients), and normal anterior pituitary function (7 patients). The  $t$  score at the lumbar spine and femoral neck and the biochemical parameters of bone turnover were not significantly different among the different subgroups with similar GH secretions.

A significant correlation was found between the GH peak after ARG+GHRH and IGF-I, osteocalcin, urinary Ntx levels, and the  $t$  score at the lumbar spine, but not that at the femoral neck level. A significant correlation was also found between plasma IGF-I levels and the  $t$  score at the lumbar spine and femoral neck, serum osteocalcin, and urinary Ntx. Multiple correlation analysis revealed that the  $t$  score at the lumbar spine, but not that at the femoral neck, was more strongly predicted by plasma IGF-I levels ( $t = 3.376$ ;  $P < 0.005$ ) than by the GH peak after ARG+GHRH ( $t = -0.968$ ;  $P = 0.338$ ).

In conclusion, a significant reduction of BMD associated with abnormalities of bone turnover parameters was found only in patients with very severe or severe GHD, whereas normal BMD values were found in non-GHD hypopituitary patients. These abnormalities were consistently present in all patients with GHD regardless of the presence of additional hormone deficits, suggesting that GHD plays a central role in the development of osteopenia in hypopituitary patients. (*J Clin Endocrinol Metab* 84: 1919–1924, 1999)

GH PLAYS an important role in the regulation of bone growth in childhood and of bone remodeling in adulthood (1, 2). GH deficiency (GHD) in adult subjects is accompanied by a decrease in bone mass (3) and an increased incidence of bone fractures (4, 5). A reduction in bone mineral

density (BMD) has been reported in patients with isolated GHD as well as in patients with multiple pituitary hormone deficiencies (MPHD) (6–8), suggesting that GHD *per se* plays a significant role in the development of osteopenia. Associated other pituitary hormone deficits and/or replacement therapies can also be important factors in the pathogenesis of bone loss. Whether the severity of GHD, evaluated by the GH response to a pharmacological stimulus, is associated with the severity of bone status impairment has never been investigated in adult GHD patients.

In a previous study (9), we have shown that the degree of the GH response to an arginine plus GHRH (ARG+GHRH) test was correlated with the severity of the lipid profile ab-

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normality, but not with changes in body composition. In addition, the peak GH response to ARG+GHRH was correlated with insulin-like growth factor I (IGF-I) concentrations (9).

To look for a possible correlation between the extent of the GH response to ARG+GHRH and the severity of bone mass and turnover impairment, we measured the BMD at the levels of lumbar spine and femoral neck together with biochemical parameters of bone turnover in a large series of adult hypopituitary patients. The effects of isolated GHD and MPHGD were also evaluated in patients subdivided according to their hormonal deficits.

## Subjects and Methods

### Subjects

One hundred and one hypopituitary patients (46 males and 55 females; age, 16–73 yr) and 35 healthy subjects (15 males and 20 females; age, 18–70 yr) entered this study after their informed consents had been obtained. None of the subjects of this study had taken any drug or medication known to affect skeletal or mineral metabolism. In addition, none of the 136 subjects had habitual ingestion of coffee greater than 4 cups/day or more than 2 alcohol containing beverages/day. Seventy-six patients and 19 controls were nonsmokers, and the remaining subjects were mild smokers (<15 cigarettes/day). Furthermore, none of the patients had active peptic ulcer disease or abnormal renal and/or hepatic function. All patients had been previously operated on via the transphenoidal and/or transcranial route for nonfunctioning pituitary adenoma, meningioma, or craniopharyngioma, and 17 of them had also been irradiated. A variable degree of pituitary insufficiency was found in the 101 patients, as shown in Table 1. Hormone replacement therapy with L-T<sub>4</sub> (50–100 µg daily, orally), cortisone acetate (25–37.5 mg/day), and intranasal desmopressin (5–20 µg/day) was given where appropriate. Males with hypogonadism were treated with testosterone enanthate (250 mg monthly, im), whereas premenopausal females were given estrogen-progestin replacement. The adequacy of hormone replacement therapy was periodically assessed by means of serum free thyroid hormones, testosterone, urinary free cortisol, and serum and urinary Na<sup>+</sup> and K<sup>+</sup> measurements. At study entry, these hormonal parameters were in the normal range for age in all patients. None of the patients had ever received GH treatment.

### Study protocol

At study entry, serum calcium, phosphorus, and creatinine and circulating alkaline phosphatase, intact PTH, and osteocalcin (OC) were assayed twice in a single sample. Urinary cross-linked N-telopeptides of type I collagen (Ntx), calcium, phosphorus, and creatinine were assayed in the 24-h urinary collection the day before the study. Assay of IGF-I and IGF-binding protein-3 (IGFBP-3) levels and assessment of BMD measured at the lumbar spine and femoral neck levels were performed

in all patients. All subjects were tested with ARG+GHRH. ARG (arginine hydrochloride, Damar, Naples, Italy) was administered at a dose of 0.5 g/kg up to a maximal dose of 30 g slowly infused from 0–30 min; GHRH (1–29, Geref, Serono, Rome, Italy) was given at a dose of 1 µg/kg as an iv bolus at time zero. Blood samples were taken every 15 min from –15 to 90 min. According to recent studies (9–12), showing that adult patients with a GH peak after an insulin tolerance test of less than 3 µg/L had a GH response to ARG+GHRH below 9 µg/L, whereas normal subjects had a GH response after ARG+GHRH always greater than 16.5 µg/L, we classified the GH response after ARG+GHRH in our 101 subjects as follows: very severe GHD (GH peak, <3 µg/L), severe GHD (GH peak, 3.1–9 µg/L), partial GHD (GH peak, 9.1–16.5 µg/L), and normal (GH peak, >16.5 µg/L).

### Assessment of BMD

In all patients and controls, BMD was assessed by dual x-ray absorptiometry. Measurement of the integral bone density in the lumbar spine (L1–L4) and femoral neck was performed using a Hologic QDR 1000 analyzer (Hologic, Inc., Waltham, MA). Data were expressed as the *t* score and as grams per cm<sup>2</sup>. Patients were considered osteopenic when the *t* score was between –1 and –2.5 and were considered osteoporotic when the *t* score was lower than –2.5.

### Assays

All hormone measurements were performed using the same reagents in two laboratories at the Department of Molecular and Clinical Endocrinology and Oncology, University Federico II of Naples, and the Department of Endocrinology, University of Turin. Assay performances were similar in the two laboratories. Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits. The sensitivity of the assay was 0.2 µg/L. The intra- and interassay coefficients of variation (CVs) were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by IRMA after ethanol extraction. The normal ranges in 20- to 30-yr-old, 31- to 40-yr-old, 41- to 50-yr-old, and over 50-yr-old men were 108–458, 92–483, 100–316, and 78–213 µg/L, respectively, whereas in women these values were 118–523, 112–506, 96–288, and 78–268 µg/L, respectively. The sensitivity of the assay was 0.8 µg/L. The intraassay CVs were 3.4%, 3.0%, and 1.5% for low, medium, and high points of the standard curve, respectively. The interassay CVs were 8.2%, 1.5%, and 3.7% for low, medium, and high points of the standard curve. Plasma IGFBP-3 was measured by RIA after ethanol extraction. The normal ranges in 20- to 30-yr-old, 31- to 40-yr-old, 41- to 50-yr-old, and over 50-yr-old subjects were 2.1–7.6, 1.7–7.3, 2.1–4.3, and 2–4 mg/L, respectively. The sensitivity of the assay was 0.5 µg/L. The intraassay CVs were 3.9%, 3.2%, and 1.8% for low, medium, and high points of the standard curve, respectively. The interassay CVs were 0.6%, 0.5%, and 1.6% for low, medium, and high points of the standard curve. PTH was assayed by the IRMA method; the normal range was 9–55 pg/mL. Serum OC levels were measured by RIA; the normal range was 3.0–13.0 µg/L. Urinary Ntx levels were measured by enzyme-linked immunosorbent assay; the normal ranges were 23–110 and 13–96 nmol

**TABLE 1.** Clinical characteristics of the 101 patients grouped on the basis of the GH response after ARG plus GHRH and of the 35 controls

GH peak after ARG + GHRH:	Patients				Controls, GH >16.5 µg/L
	GH < 3 µg/L	GH 3.1–9 µg/L	GH 9.1–16.5 µg/L	GH >16.5 µg/L	
Mean (±SEM) µg/L	0.9 ± 0.08	4.7 ± 0.4	11.0 ± 0.3	28.3 ± 4.3	40.7 ± 2.2
No. of patients	41	25	18	17	35
Females/males	16/25	15/10	12/6	12/5	20/15
Age range (yr)	18–70	16–65	21–53	21–56	18–70
Mean (±SEM) age	44.4 ± 1.8	37.1 ± 2.8	36.7 ± 2.6	36.3 ± 3.2	47.1 ± 2.7
Disease duration (yr)	11.1 ± 0.8	9.4 ± 1.3	7.1 ± 1.9	2.8 ± 0.4	
Pituitary deficiencies (no. of patients)	38	22	7	7	0
Pituitary deficiencies (%)	92.7	88	39	41	0
FSH, LH	78	72	17	17	0
TSH	73	60	11	0	0
ACTH	73	68	0	12	0
Diabetes insipidus	24	0	11	12	0

bone collagen equivalent (BCE)/mmol in males and females, respectively. Urinary and serum calcium, phosphorus, creatinine, and alkaline phosphatase were assayed using standard methods in our laboratory.

### Statistical analysis

ANOVA followed by Newman-Keuls test was used for the inter-group comparison to calculate the *t* scores for the lumbar spine and femoral neck among groups. Regression analysis was performed to correlate bone parameters to GH peak after ARG+GHRH and IGF-I levels. Multiple regression analysis was performed, taking the GH peak after ARG+GHRH as the dependent variable *vs.* age, disease duration, *t* score at the lumbar spine and femoral neck, serum OC, and urinary Ntx as independent variables by calculating the coefficient for the variables related to GH peak after ARG+GHRH at the linear correlation. Data are reported as the mean  $\pm$  SEM. The limit of significance was set at 5%.

### Results

On the basis of the GH response to ARG+GHRH, 41 patients had very severe GHD (GH peak,  $0.9 \pm 0.08 \mu\text{g/L}$ ; group 1), 25 patients had severe GHD (GH peak,  $4.7 \pm 0.4 \mu\text{g/L}$ ; group 2), 18 patients had partial GHD (GH peak,  $11.0 \pm 0.3 \mu\text{g/L}$ ; group 3), and 17 patients had normal GH responses (GH peak,  $28.3 \pm 4.3 \mu\text{g/L}$ ; group 4). In the 35 controls (group 5), the GH response after ARG+GHRH was  $40.7 \pm 2.2 \mu\text{g/L}$ .

Plasma IGF-I concentrations in patients in groups 1 ( $76.5 \pm 7.6 \mu\text{g/L}$ ) and 2 ( $80.3 \pm 7.5 \mu\text{g/L}$ ) were similar and lower ( $P < 0.001$ ) than those in groups 3–5, which were not different from each other ( $170.9 \pm 40.6$ ,  $186.5 \pm 20.1$ , and  $188.8 \pm 11.1 \mu\text{g/L}$ , respectively). IGF-I concentrations were below the normal range for age in 28 patients in group 1 (68.3%), 15 in group 2 (60%), and 2 in group 3 (11.1%) and were normal in all subjects in groups 4 and 5. Similarly, IGFBP-3 concentrations in groups 1 ( $2.1 \pm 0.3 \text{ mg/L}$ ) and 2 ( $2.2 \pm 0.3 \text{ mg/L}$ ) were similar and lower than those in groups 3 ( $3.5 \pm 0.7 \text{ mg/L}$ ;  $P < 0.05$ ), 4 ( $3.6 \pm 0.8 \text{ mg/L}$ ), and 5 ( $3.8 \pm 0.2 \text{ mg/L}$ ;  $P < 0.05$ ). Plasma IGFBP-3 concentrations were below the normal range for age in 24 patients in group 1 (58.3%), 10 in group 2 (40%), and 1 in group 3 (5.5%) and were normal in all subjects in groups 4 and 5.

PTH, urinary and serum calcium, phosphorus, and creatinine, and alkaline phosphatase were similar in the five groups of patients (data not shown).

In group 1, the *t* scores at the lumbar spine ( $-1.99 \pm 0.2$ ) and femoral neck ( $-1.86 \pm 0.3$ ) were lower than those in groups 3 ( $-0.5 \pm 0.7$ ,  $P < 0.01$  and  $-0.3 \pm 0.7$ ,  $P < 0.01$ , respectively), 4 ( $-0.5 \pm 0.2$ ,  $P < 0.01$  and  $-0.3 \pm 0.7$ ,  $P < 0.01$ , respectively), and 5 ( $-0.5 \pm 0.2$ ,  $P < 0.001$  and  $0.0 \pm 0.02$ ,  $P < 0.001$ , respectively; Fig. 1). Serum OC levels were lower in patients in group 1 ( $1.7 \pm 0.1 \mu\text{g/L}$ ) than in those in groups 3–5 ( $5.6 \pm 0.4$ ,  $6.1 \pm 0.3$ , and  $7.4 \pm 1.1 \mu\text{g/L}$ , respectively;  $P < 0.001$ ; Fig. 2). Similarly, urinary Ntx were lower in patients in group 1 ( $20.1 \pm 1.0 \text{ nmol BCE/mmol creatinine}$ ) than in those in groups 3–5 ( $50.7 \pm 1.1$ ,  $91.9 \pm 3.2$ , and  $96.1 \pm 1.0 \text{ nmol BCE/mmol creatinine}$ , respectively;  $P < 0.001$ ; Fig. 2). Patients in group 2 had *t* scores at the lumbar spine ( $-1.22 \pm 0.3$ ) and femoral neck ( $-0.9 \pm 0.3$ ) significantly higher and lower, respectively, than those in groups 1 and 5 ( $P < 0.05$ , respectively; Fig. 1), but not those in groups 3 and 4. Conversely, in group 2, serum OC and urinary Ntx levels were significantly higher than those in group 1 and were lower

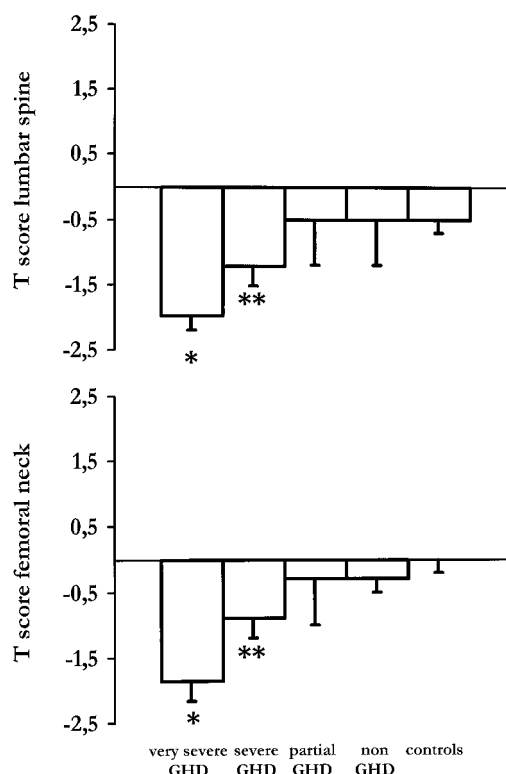


FIG. 1. Lumbar spine BMD (top panel) and femoral neck BMD (bottom panel) evaluated as *t* scores in the five groups of subjects divided on the basis of the GH response to ARG+GHRH test: very severe GHD, GH peak below  $3 \mu\text{g/L}$ ; severe GHD, GH peak between  $3.1$ – $9 \mu\text{g/L}$ ; partial GHD, GH peak between  $9.1$ – $16.5 \mu\text{g/L}$ ; non-GHD, GH peak above  $16.5 \mu\text{g/L}$ ; and controls, GH peak above  $16.5 \mu\text{g/L}$ . \*,  $P < 0.001$ , group 1 *vs.* groups 3–5. \*\*,  $P < 0.05$ , group 2 *vs.* groups 1 and 5.

than those in groups 3–5 ( $2.6 \pm 0.1 \mu\text{g/L}$  and  $30.5 \pm 0.8 \text{ nmol BCE/mmol creatinine}$ , respectively;  $P < 0.001$ ; Fig. 2).

To evaluate the effect of isolated GHD *vs.* MPHD, patients were subdivided according to the number of hormonal deficits, such as panhypopituitarism with (10 patients) or without (31 patients) diabetes insipidus, GHD with 1 or more additional pituitary deficit(s) (36 patients), isolated GHD (7 patients), 1–2 pituitary hormone deficit(s) without GHD (10 patients), and normal anterior pituitary function (7 patients). The *t* score at the lumbar spine and femoral neck and the biochemical parameters of bone turnover were not significantly different among the different subgroups with similar GH responses to ARG+GHRH (Table 2).

A significant correlation was found between the GH peak after ARG+GHRH and IGF-I ( $r = 0.674$ ;  $P = 0.000$ ), OC ( $r = 0.738$ ;  $P = 0.000$ ), urinary Ntx levels ( $r = 0.852$ ;  $P = 0.000$ ), and *t* score at the lumbar spine ( $r = 0.256$ ;  $P = 0.035$ ), but not that at the femoral neck ( $r = 0.185$ ;  $P = 0.175$ ). A significant correlation was also found between plasma IGF-I levels and the *t* score at the lumbar spine ( $r = 0.405$ ;  $P = 0.002$ ) and femoral neck ( $r = 0.363$ ;  $P = 0.014$ ), serum OC ( $r = 0.509$ ;  $P = 0.000$ ), and urinary Ntx levels ( $r = 0.471$ ;  $P < 0.001$ ; Table 3). Multiple correlation analysis revealed that the *t* score at the lumbar spine, but not at the femoral neck, was more strongly predicted by plasma IGF-I levels ( $t = 3.376$ ;  $P < 0.005$ ) than by the GH peak after ARG+GHRH ( $t = -0.968$ ;  $P = 0.338$ ).

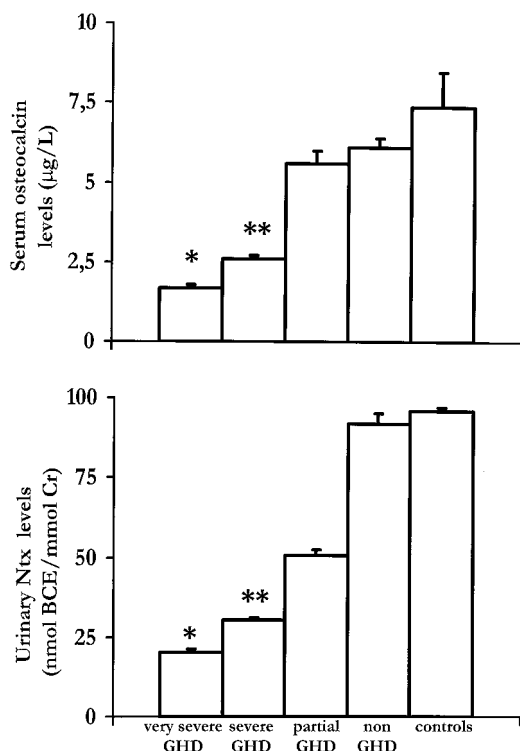


FIG. 2. Serum OC (top panel) and urinary Ntx (bottom panel) levels in the five groups of patients divided on the basis of the GH response to ARG+GHRH test: very severe GHD, GH peak below 3 µg/L; severe GHD, GH peak between 3.1–9 µg/L; partial GHD, GH peak between 9.1–16.5 µg/L; non-GHD, GH peak above 16.5 µg/L; and controls, GH peak above 16.5 µg/L. \*,  $P < 0.001$ , group 1 vs. groups 3–5. \*\*,  $P < 0.001$ , group 2 vs. groups 1 and 3–5.

### Discussion

GHD in adults is associated with increased fat mass, reduced lean mass, osteopenia, impaired fibrinolysis, altered cardiac structure and function, unfavorable glucose and lipid metabolism, reduced exercise capacity, and reduced quality of life (3, 13, 14). Reduced BMD has been widely reported in hypopituitary patients (3–8), although the roles of individual pituitary hormone deficiency and/or of replacement therapy in the development of bone loss have not been firmly elucidated. The pathogenesis of the reduced bone mineral content and density in patients with childhood-onset GHD is probably the lack of attainment of bone mass during adolescence (1, 2), whereas in patients with adult-onset GHD it is less clear. Patients with isolated GHD as well as those with congenital GH insensitivity were osteopenic compared to controls (15). The decrease in BMD was similar between patients with isolated GHD and those with MPPHD, suggesting that GHD *per se* was a causal factor in the development of osteopenia (6–8). Prolonged treatment with GH resulted in increased BMD (13, 15–24). Furthermore, patients with the lowest BMD before treatment demonstrated the greatest BMD increase, with the result being that 40–50% of previously osteopenic patients had normal BMD after 2 yr of therapy (20, 23). In addition, low BMD and poor quality of life have been reported in adults with long lasting panhypopituitarism receiving adequate replacement therapy with

$T_4$ , cortisone acetate, and sex steroids, but not receiving GH (4).

In this cross-sectional study we have shown that only patients with very severe or severe GHD have a significant reduction of BMD, associated with abnormalities of bone turnover parameters. These abnormalities were found in all patients with GHD regardless of the presence of additional hormone deficits. Normal BMD values were found in non-GHD hypopituitary patients, thus indicating that GH plays a central role in the development of osteopenia in patients with hypopituitarism. This hypothesis is substantiated by the observation that the GH response to ARG+GHRH was directly correlated with the degree of bone loss. In fact, patients with partial GHD (group 3) had normal BMD values, and their serum IGF-I concentrations were not different from those in non-GHD hypopituitary patients and control subjects. As the effect of GHD on bone is principally mediated by IGF-I (1, 2), the normal BMD values of this group may be explained by their normal IGF-I concentrations. However, we have previously shown that adults with GHD have subtle abnormalities of lipid metabolism (9). It is tempting to speculate that a slightly reduced GH secretion may have direct effects on lipid metabolism but is still capable of maintaining normal IGF-I production, thus explaining the different clinical findings between partial and severe GHD.

Bone metabolism is influenced by virtually all pituitary hormones, either directly or via their target organ products. Although overt hyperthyroidism has clearly negative effects on bone mass, the skeletal effects of  $T_4$  administration are more controversial (25). Mild chronic overreplacement with thyroid hormones is also associated with accelerated bone loss (26, 27). Recently, Hanna *et al.* (27) reported that replacement doses of  $T_4$  had no adverse effects on the spine, femoral neck, or total hip in patients with central hypothyroidism (27). The effect of replacement therapy with glucocorticoids on bone mass in patients with hypocortisolism is limited. Patients with Addison's disease may have an increased incidence of osteoporosis as a consequence of mild subclinical glucocorticoid overreplacement during a period of many years (28). On the other hand, glucocorticoid replacement therapy has no adverse effects on BMD in patients with 21-hydroxylase deficiency (29), but a 30% reduction in daily hydrocortisone dose leads to a 19% rise in OC levels, indicating increased bone formation (30). Hypogonadism causes osteoporosis in men and women (31), and replacement therapy with sex hormones increases bone turnover and bone mass (32, 33). A recent study reported significant bone impairment in patients with central diabetes insipidus, which was not prevented or reversed by standard dose replacement with intranasal desmopressin (34).

Interestingly, all non-GHD patients had normal BMD, leading us to hypothesize that they were receiving appropriate replacement treatments.

In conclusion, a significant reduction of BMD associated with abnormalities of bone turnover parameters was found only in patients with very severe or severe GHD, whereas normal BMD values were found in non-GHD hypopituitary patients. These abnormalities were consistently present in all patients with GHD regardless of the presence of additional hormone deficits, suggesting that GHD, probably via re-

**TABLE 2.** Bone mass and turnover study in the 101 patients subdivided in accordance with the GH peak after the ARG plus GHRH test and the presence of additional hormone deficiencies

	No. of patients	Serum osteocalcin levels ( $\mu\text{g/L}$ )	Urinary Ntx (nmol BCE/mmol creatinine)	L1-L4 BMD ( $\text{g/cm}^2$ )	L1-L4 <i>t</i> score	Femoral neck BMD ( $\text{g/cm}^2$ )	Femoral neck <i>t</i> score
Patients with GH <3 ( $\mu\text{g/L}$ )							
Panhypopituitarism + diabetes insipidus	10	2.0 $\pm$ 0.4	18.4 $\pm$ 2.9	0.88 $\pm$ 0.05	-1.8 $\pm$ 0.4	0.72 $\pm$ 0.08	-2.1 $\pm$ 0.7
Panhypopituitarism	17	1.7 $\pm$ 0.1	19.5 $\pm$ 1.3	0.85 $\pm$ 0.03	-2.0 $\pm$ 0.2	0.74 $\pm$ 0.04	-1.9 $\pm$ 0.3
GHD + 1-2 additional deficit(s)	14	1.9 $\pm$ 0.5	22.4 $\pm$ 1.1	0.86 $\pm$ 0.04	-1.9 $\pm$ 0.3	0.77 $\pm$ 0.06	-1.5 $\pm$ 0.4
Patients with GH 3.1-9 ( $\mu\text{g/L}$ )							
Panhypopituitarism	14	2.7 $\pm$ 0.1	30.3 $\pm$ 1.2	0.88 $\pm$ 0.03	-1.7 $\pm$ 0.3	0.78 $\pm$ 0.06	-1.3 $\pm$ 0.5
GHD + 1-2 additional deficit(s)	11	2.6 $\pm$ 0.2	30.6 $\pm$ 1.3	0.96 $\pm$ 0.05	-1.0 $\pm$ 0.5	0.81 $\pm$ 0.05	-1.0 $\pm$ 0.5
Patients with GH 9.1-16.5 ( $\mu\text{g/L}$ )							
GHD + 1-2 additional deficit(s)	11	6.0 $\pm$ 0.5	52.0 $\pm$ 2.0	1.1 $\pm$ 0.1	-0.3 $\pm$ 0.8	0.91 $\pm$ 0.1	-0.04 $\pm$ 0.9
Isolated GHD	7	5.2 $\pm$ 0.3	49.0 $\pm$ 2.8	0.89 $\pm$ 0.11	-1.2 $\pm$ 0.9	0.81 $\pm$ 0.01	-1.21 $\pm$ 0.3
Patients with GH >16.5 ( $\mu\text{g/L}$ )							
1-2 pituitary hormone deficit(s)	10	6.15 $\pm$ 0.4	91.5 $\pm$ 5.3	0.99 $\pm$ 0.01	-0.3 $\pm$ 0.8	0.92 $\pm$ 0.1	-0.2 $\pm$ 0.1
Normal anterior pituitary function	7	6.0 $\pm$ 0.42	92.5 $\pm$ 6.14	0.97 $\pm$ 0.01	-1.0 $\pm$ 0.8	0.89 $\pm$ 0.08	-0.4 $\pm$ 0.2

**TABLE 3.** The linear correlation study

			r	P
GH peak	<i>vs.</i>	Femoral neck <i>t</i> score	0.185	0.175
		L1-L4 <i>t</i> score	0.256	0.035
		Urinary Ntx	0.852	0.000
		Serum OC	0.738	0.000
		Plasma IGF-I	0.674	0.000
IGF-I	<i>vs.</i>	Femoral neck <i>t</i> score	0.363	0.014
		L1-L4 <i>t</i> score	0.405	0.002
		Urinary Ntx	0.471	0.000
		Serum OC	0.509	0.000
Femoral neck <i>t</i> score	<i>vs.</i>	Serum OC	0.166	0.220
		Urinary Ntx	0.212	0.117
L1-L4 <i>t</i> score	<i>vs.</i>	Serum OC	0.328	0.006
		Urinary Ntx	0.209	0.083

duced IGF-I production, plays a central role in the development of osteopenia in hypopituitary patients.

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