Bone density and turnover in young adult patients with growth hormone deficiency after 2-year growth hormone replacement according with gender

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ABSTRACT. GH deficiency (GHD) in adults is accompanied by reduced bone mass that may revert only after 2 yr of GH replacement. However, it is unclear whether the gender may modify bone responsiveness to GH replacement in adults. In this study we have evaluated whether bone mineral density (BMD) and turnover improve after GH replacement according to patients' gender. BMD at lumbar spine (LS) and femoral neck (FN), serum osteocalcin (OC), and urinary cross-linked N-telopeptides of type I collagen (Ntx) were assessed in 64 hypopituitaric patients (35 men, 30-50 yr) before and 2 yr after the beginning of GH replacement. Values of IGF-I and BMD at LS and at FN were expressed as Z-scores. At study entry, IGF-I and BMD resulted similar among men and women with GHD. During GH replacement, IGF-I levels increased in both men and women without any difference in the percentage of IGF-I increase between the genders (p=0.47). In women receiving estrogen replacement, however, the percentage of IGF-I increase (p<0.05), and the Z IGF-I score (p<0.001) were significant lower than estrogen untreated women, although IGF-I levels were similar in the 2 groups (p=0.53). The GH dose adjusted for body weight required to restore normal age- and sex- matched IGF-I levels was lower in men than in women (p<0.001), and was higher in women receiving than in those not receiving estrogen replacement (p<0.05). In contrast, hypogonadal men treated with testosterone and eugonadal men received a similar GH dose (p=0.97). Also OC, Ntx levels, lumbar and femoral BMD improved (p<0.001) in all patients. Nevertheless, a greater increase in lumbar BMD increase was observed in men than in women (8.0±2.1 *vs* 2.6±0.4%; p<0.05). No significant difference was revealed in bone parameters in women treated or untreated with estrogen replacement and in men treated or not with testosterone replacement for concomitant hypogonadism. At the multiple correlation analysis, gender was a stronger predictor for the required GH dose than the age (p<0.001 and p=0.02, respectively). In conclusion, a 2-yr GH replacement normalizes IGF-I levels, increases bone mass and improves bone turnover both in men and in women with GHD without any difference between the 2 groups, provided that the dose of GH was modulated on the basis of IGF-I levels. Women receiving oral estrogens should receive a GH dose approximately doubled, as compared to men and women not receiving oral estrogens, to achieve similar effects on bone density and turnover. In particular, GH replacement dose, to be successful on bone mass and turnover, depends on gender in hypopituitary patients aged below 50 yr.

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INTRODUCTION

GH plays a critical role in bone growth during childhood and in bone remodeling during adulthood (1, 2). Reduced bone mineral density (BMD) is, thus, frequently associated with GH deficiency (GHD) in adults (2-4). This is clinically relevant, since both bone density and content are correlated with the fracture risk (5) and patients with GHD have a greater prevalence of fractures than the general

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population (6, 7). However, Mazziotti et al. found that in patients with GHD, about one-half of the fractures occurred in the presence of a normal BMD. This may suggest that the quality rather than the quantity of the bone may be more impaired in presence of GHD. This study also demonstrated that the fracture prevalence in GHD patients, as well as the fracture number, was significantly higher in untreated *vs* treated patients with GH replacement (8).

Decreased BMD was observed both in patients with isolated GHD and in those with multiple pituitary hormone deficiencies (MPHD), suggesting that GHD *per se*, probably *via* a reduced IGF-I production, plays a key role in determining bone loss in these patients (7-10). We had also observed that bone mass was impaired more severely in the patients with more severe GHD while the patients with partial GHD or with hypopituitarism and normal GH secretion had a normal bone mass and turnover (11).

There is an evident sexual dimorphism of the somatotroph axis in animals and in humans (12). After GH replacement in adult GHD patients, improvements of body composition, lipid metabolism, and bone mass are more evident in men than in women both with adulthood- and childhood- onset GHD (13-15). The pattern of change in lean body mass and fat mass was divergent in males and females requiring a higher dose in the latter than in the former (15). A negative influence of the estrogen milieu on the GH responsiveness is likely, also supported by the evidence that healthy elderly women receiving estrogens had a reduced effect of GH treatment on body composition, bone turnover, and metabolic parameters compared to those not receiving estrogens (16). However, the previous studies on the different GH responsiveness on the bone according with gender included patients with a wide range of age, from young to elderly. Since aging and menopause affect bone mass and turnover, and in childhood bone turnover is faster than in adulthood, we have re-evaluated bone mass and turnover in a large selected series of adult patients with GHD, in the context of hypopituitarism, and with age ranging 30-50 yr, before and after 2 yr of GH replacement to analyze the impact of GHD and its replacement on the bone according gender in adult age.

MATERIALS AND METHODS

Subjects

Sixty-four hypopituitary patients (35 men, 29 women, age 30-50 yr) with a diagnosis of GHD (see below) entered this study after their informed consent had been obtained. The patients were consecutively selected from hypopituitaric patients with GHD admitted at our Department from 1996-2000. Sixty-four sex-, age- and BMI-matched healthy subjects (35 men, 29 women, age 30-50 yr) served as control. 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 128 subjects drank more than 4 cups of coffee per day or more than 2 drinks containing alcohol. Forty-eight patients and 45 controls were non-smokers, while the remaining were mild smokers (less than 10 cigarettes per day). None had active peptic ulcer disease or abnormal renal and/or hepatic function. We excluded active peptic ulcer disease on the basis of absence of signs and/or symptoms due to ulcer disease. To assess liver and kidney function we performed azotemia, creatinemia, indirect creatinine clearance measurement, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase, total, direct, and indirect bilirubin, alkaline phosphatase (ALP). All patients had been previously operated on *via* trans-sphenoidal and/or trans-cranic route for non-functioning pituitary adenoma, meningioma or craniopharyngioma and 11 (17.2%) of them had also been irradiated. All patients have a diagnosis of adult onset GHD. According to our previous studies (17, 18), the estimated duration of GHD was calculated from the time of diagnosis of the pituitary tumor and was 8.4±0.8 yr in women (median 8 yr) and 9.5±0.8 yr in men (median 9 yr). Since acromegaly, Cushing's disease, and hyperprolactinemia notably influence bone density and turnover *per se* (19-21), patients with these lesions were excluded from this study. Patients aged below 30 yr were also excluded to rule out a suboptimal growth bone as were patients above 50 yr to rule out any interference of age-related bone loss. For these reasons we excluded 40 GHD patients. A variable degree of pituitary insufficiency was found in the 64 patients, as shown in Table 1. Hormone replacement therapy with L-thyroxin (50-100 μg po daily), cortisone acetate (25-37.5 mg po), and intranasal desmopressin (5-20 μg/day) was given where appropriate. Eighteen men with hypogonadism were treated with testosterone-enanthate (250 mg im monthly), 17 women were on oral estroprogestinic replacement, while the remaining 12 women received no estrogen supplementation. Adequacy of hormone replacement therapy was periodically assessed by serum free thyroid hormones, testosterone, urinary free cortisol, serum and urinary Na^+ and K^+ and blood pressure measurements; all parameters were in normal range in all patients at study entry.

Study protocol

At study entry, serum calcium, phosphorus, azotemia, creatinemia, AST, ALT, γ-glutamyl transferase, total, direct, and indirect bilirubin, ALP, 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 assessment of BMD measured at lumbar spine and femoral neck levels were performed in all subjects. Plasma IGF-I concentrations were assayed in the patients group before and after 1, 2, 3, 6, 12, and 24 months of GH replacement, while in the control group IGF-I was assessed before and after 12 and 24 months. Assessment of bone mass and biochemical parameters were repeated after 12 and 24 months of GH replacement. All subjects were tested with arginine

Table 1- *Clinical characteristics of the 64 patients and controls.*

	Patients	Controls	*p*
No.	64	64	-
Females/Males	29/35	29/35	-
Age range (yr)	30-50	30-50	-
Mean age (yr)	36.5±1.13	35.8±1.2	ns
BMI (kg/m^2)	26.1±1.4	25.8±1.3	ns
Disease duration (yr)	9.3±0.6	/	-
Pituitary deficiencies (%)	93.7	0	-
FSH, LH	56.3	0	-
TSH	70.3	0	-
ACTH	54.6	0	-
GH peak after ARG+GHRH (μg/l)	3.5±0.4	42.5±2.2	0.000
IGF-I (μg/l)	120.0±7.45	268.8±12.4	0.000
Serum osteocalcin levels (μg/l)	2.3±0.1	8.4±0.6	0.000
Urinary Ntx (nmol BCE/mmol Cr)	29.1±1.4	95.9±2.4	0.000
L1-L4 T score	–2.1±0.2	–0.5±0.2	0.000
L1-L4 Z score	–1.7±0.2	–0.4±0.3	0.000
Femoral neck T score	–1.6±0.1	–0.3±0.3	0.000
Femoral neck Z score	–0.7±0.2	–0.2±0.1	0.027

BMI: body mass index; ARG: arginine; Ntx: cross-linked N-telopeptides of type I collagen; BCE: bone collagen equivalent; Cr: creatinine.

(ARG)+GHRH test according to Ghigo et al. (22). ARG (arginine hydrochloride) was administered at the dose of 0.5 g/kg, up to a maximal dose of 30 g slowly infused from time 0 to 30 min while GHRH (23-24) was given at the dose of 1 μg/kg as iv bolus at time 0. Blood samples were taken every 15 min from –15 up to 90 min. According with previous findings in normal lean population (25-28), the GH response after ARG+GHRH was classified as follows: very severe GHD when GH peak was ≤3 μg/l, severe GHD when GH peak was 3.1-9 μg/l, partial GHD when GH peak was 9.1-16.5 μg/l, and non-GHD or normal response in healthy subjects when GH peak was ≥16.5 μg/l. All the 64 patients included in this study had a GH peak after GHRH+ARG <9 μg/l. Thus we included both patients with very severe and severe GHD. Before and after 12 and 24 months of GH replacement all patients had undergone magnetic resonance imaging of the sellar region that showed no evidence of tumor recurrence.

Treatment protocol

All patients received a starting GH dose of 4 μg/kg/day. Subsequently, the dose was adjusted on the basis of serum IGF-I concentrations up to the 50th percentile of the normal age range.

Assessment of bone mineral density

In all patients and controls, BMD was assessed by dual x-ray absorptiometry. Measurement of the integral bone density at lumbar spine (L1-L4) and femoral neck was performed by Hologic QDR 1000 analyzer (Hologic Inc., Waltham, MA, USA). All measurements were performed by the same investigator, blind in respect to patients or control study and to follow-up. Data were expressed as T and Z score and in g/cm^2. Osteopenia was diagnosed when T score was between –1 and –2.5 while osteoporosis when T score was lower than –2.5. Coefficient of precision in our institution is 1% for lumbar spine and 1.5% for femoral neck.

Assays

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 inter-assay coefficients of variation (CV) were 4.5 and 7.9%, respectively. Plasma IGF-I was measured by radioimmunoassay (RIA) after ethanol extraction. The normal range in 20-30, 31-40, and 41-50 yr old men is 118-513, 112-493, and 100-316 μg/l, respectively, whereas in women it is 110-450, 100-400, and 96-288 μg/l, respectively. The sensitivity of the assay is 0.8 μg/l. The intra-assay CV were 3.4, 3.0, and 1.5% for the low, medium and high points of the standard curve, respectively. The inter-assay CV were 8.2, 1.5, and 3.7% for the low, medium, and high points of the standard curve. PTH was assayed by IRMA method; the normal range is 9-55 ng/l. Serum OC levels were measured by RIA method; the normal range was in adults 3.0-13.0 μg/l. Urinary Ntx levels were measured by enzyme-linked immunosorbent assay method; the normal range in adult men and women is 23-110 and 13-96 nmol bone collagen equivalent (BCE)/mmol, respectively. Urinary and serum calcium, phosphorus and creatinine, and alkaline phosphatase were assayed using standard methods in our laboratory.

Statistical analysis

The statistical analysis was carried out using SPSS Inc. (Cary, NC) package by analysis of variance followed by the Newman-Keuls test for the inter-group comparisons and the paired t test for the intra-group comparisons. The correlation analysis was performed by the regression analysis. Data are reported as mean±SEM. The significance was set at 5%.

RESULTS

Baseline study

On the basis of the GH response to ARG+GHRH, 64 patients were classified as severe GHD (GH peak ranging 0.1-8.9 µg/l, mean GH peak: 3.5±0.4 µg/l). In the 64 controls, the GH response after ARG+GHRH was 42.5±2.2 µg/l (Table 1). Plasma IGF-I levels were significantly lower in GHD patients than in controls (Table 1) ($p<0.0001$), and they were below the normal range for age in 32 (50%) patients. In addition, in the entire GHD population the Z score of IGF-I was –2.21±0.08 without any difference between men (–2.24±0.14) and women (–2.17±0.18; $p=0.7$). Patients and controls had similar age and BMI (Table 1), PTH, urinary and serum calcium, phosphorus and creatinine, and alkaline phosphatase (data not shown).

BMD at lumbar spine and at femoral neck was significantly lower in patients than in controls but it was similar in GHD women and men (Table 2). T and Z BMD scores at lumbar spine and at femoral neck, serum OC levels and urinary Ntx (Table 1) were significantly lower in patients than in controls but they were similar in GHD women and men (Table 2). GH peak after ARG+GHRH was significantly correlated with IGF-I (r=0.307, $p=0.01$), OC (r=0.335, $p=0.01$) and urinary Ntx levels (r=0.694, $p<0.001$); age was correlated with IGF-I levels (r=–0.394, $p<0.01$), Z BMD score at lumbar spine (r=0.250, $p<0.05$) and at femoral neck (r=0.513, $p<0.001$).

Two years after GH replacement

All patients achieved IGF-I levels in the 50th percentile of normal range. GH treatment induced a progressive increase of IGF-I levels until the 6th month, afterwards IGF-I levels remained stable throughout the study period. IGF-I levels increased similarly in men and women (239.9±6.2 *vs* 226.3±6.9 µg/l, $p=0.47$) without any difference in the percentage of IGF-I increase (174.1±31.2 *vs* 301.7±97.1%, $p=0.18$). Similarly, Z IGF-I score increased similarly in men (from –2.17±0.08 to 0.07±0.13) and women (from –2.24±0.14 to –0.18±0.2). In women receiving estrogen replacement, however, the percentage of IGF-I increase (139.8±44.8 *vs* 530.9±213.8%, $p<0.05$), and the Z IGF-I score (0.6±0.2 *vs* –0.8±0.2, $p<0.001$) were significant lower than estrogen untreated women, although IGF-I levels were similar in the two groups (231.5±9.3 *vs* 222.6±9.8 µg/l, $p=0.53$). The GH dose adjusted for body weight required to restore normal age- and sex- matched IGF-I levels was lower in men than in women (0.54±0.034 *vs* 0.67±0.034 mg/daily, $p<0.001$), and was higher in women receiving than in those not receiving estrogen replacement (0.67±0.034 *vs* 0.47±0.07 mg/daily, $p<0.05$). The maximal dose used in this study was 0.84 mg/day in men and 1 mg/day in women. In contrast, hypogonadal men treated with testosterone and eugonadal men received a similar GH dose (0.49±0.07 *vs* 0.49±0.03 mg/daily, $p=0.97$).

Table 2 - *Bone mass and turnover study in the men and women with GH deficiency (GHD) and in the controls at study entry.*

	GHD men	GHD women	Controls men	Controls women
No.	35	29	35	29
IGF-I levels (µg/l)	102.4±5.4	111.1±13.9	271.4±19.9	266.3±15.5
Serum osteocalcin levels (µg/l)	2.2±0.1	2.4±0.1	8.2±2.2	8.7±2.1
Urinary Ntx (nmol BCE/mmol Cr)	27.5±1.7	30.9±2.2	96.0±12.7	94.7±10.1
L1-L4 BMD (g/cm^2)	0.859±0.003	0.807±0.002	1.030±0.005	1.002±0.006
L1-L4 T score	–2.1±0.2	–2.1±0.2	–0.5±0.2	–0.4±0.2
L1-L4 Z score	–1.8±0.3	–1.5±0.2	–0.4±0.1	–0.3±0.1
Femoral neck BMD (g/cm^2)	0.790±0.002	0.739±0.02	0.945±0.01	0.857±0.004
Femoral neck T score	–1.7±0.2	–1.5±0.2	–0.3±0.6	–0.3±0.1
Femoral neck Z score	–0.8±0.2	–0.6±0.2	–0.2±0.1	–0.1±0.1

BMD: bone mineral density; BCE: bone collagen equivalent; Ntx: cross-linked N-telopeptides of type I collagen; Cr: creatinine.

BMD significantly increased both at lumbar spine and at femoral neck both in men and in women, without difference between the two groups (Fig. 1). The Z BMD score significantly increased both at lumbar spine (from –1.7±0.2 to –1.3±0.1; $p<0.001$) and at femoral neck (from –0.7±0.2 to –0.4±0.1; $p<0.001$) in the entire population. Men and women achieved similar T and Z scores both at lumbar spine and femoral neck (Fig. 1). The percentage of BMD increase at lumbar spine (8.0±2.1 *vs* 2.6±0.4%; $p<0.05$), but not at femoral neck (5.6±1.1 *vs* 4.7±0.9%; $p=0.54$), was significant higher in men than in women with GHD. Serum OC and urinary Ntx levels normalized in all patients and were similar in men and women (Fig. 1). No difference was found in bone mass and bone parameters between women receiving or not receiving estrogen replacement, men receiving or not testosterone (Fig. 2, 3). Multiple regression analysis revealed that the GH dose was more strongly predicted by gender (t=–3.97, $p<0.001$) than by the age (t=–2.37, $p=0.02$).

DISCUSSION

In the present study, we observed that GH replacement increases bone mass and turnover similarly in men and women with GHD and independently from age and menopausal state, but the GH dose employ-

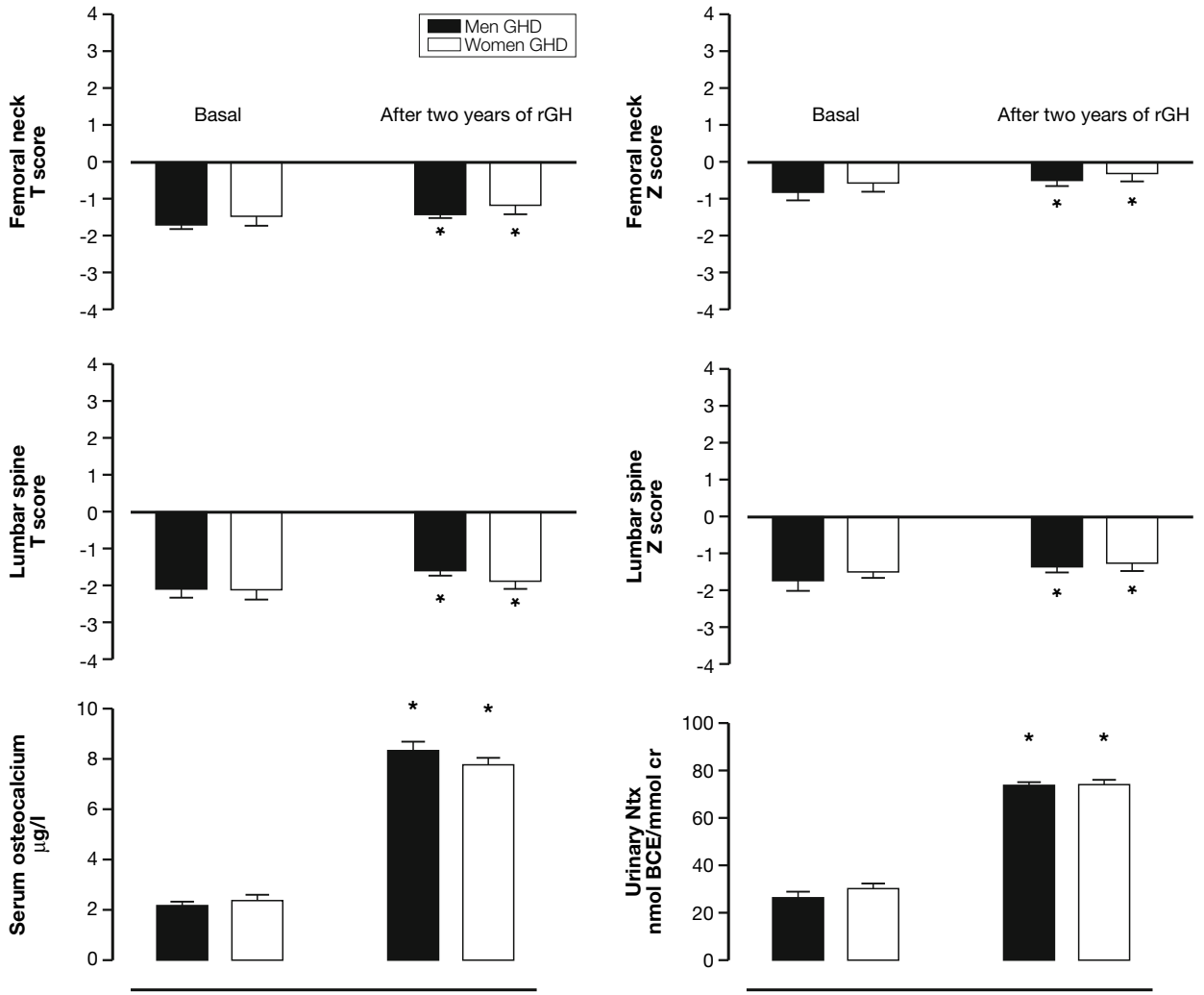

Fig. 1 - *Bone mineral density at femoral neck (top) and at lumbar spine (middle), evaluated as T score (left panel) and Z score (right panel), and serum osteocalcin (bottom, left) and urinary cross-linked N-telopeptides of type I collagen (Ntx) (bottom, right) in men (closed bars) and women (open bars) with GH deficiency before and after 2 yr of GH replacement. *: p<0.001 post-treatment values vs basal values. rGH: recombinant GH.*

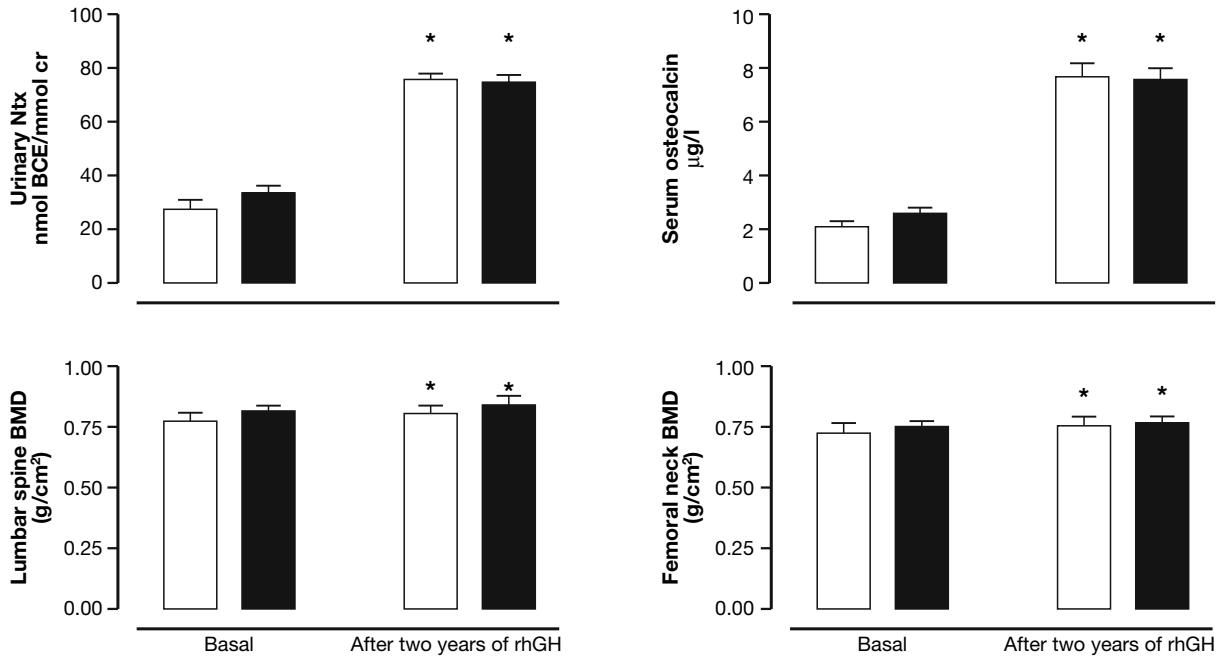

Fig. 2 - *Urinary cross-linked N-telopeptides of type I collagen (Ntx)(top, left), serum osteocalcin (top, right), bone mineral density BMD (g/cm²) at lumbar spine (bottom, left) and at femoral neck (bottom, right) in estrogen-untreated women (open bars) and in women receiving estrogen replacement (closed bars) with GH deficiency before and after 2 yr of GH replacement. *: p<0.001 post-treatment values vs basal values. BCE: bone collagen equivalent. rhGH: recombinant human GH.*

ed was significantly lower in men than in women.
Reduced BMD has been widely reported in hypopituitary patients (3, 4, 6-11), although the role of individual pituitary hormone deficiency and/or of replacement therapy in the development of bone loss has not been firmly elucidated. The decrease in bone mass is similar in patients with isolated GHD or MPHD, and this reduction has been shown both in childhood and adulthood onset GHD patients (9, 10). In a recent study we demonstrated that only patients with very severe or severe GHD have a significant reduction in BMD, whereas non-GHD hypopituitary patients have normal BMD values (11). Bone mass and turnover abnormalities were consistently present in all patients with GHD, regardless of additional hormone deficits, suggesting that GHD *per se* is a causal factor in the development of osteopenia (11).
The peak bone mass is considered to be achieved within the 3rd decade of life and the failure in achieving the peak bone mass might be a determinant in the future development of osteopenia (2). Since the majority of patients with GHD acquire the deficit after the age of 30 and they have a decrease of bone mass, GH clearly emerges as a crucial factor for the maintenance of the adult bone mass. In this context, patients with GHD generally have a delayed timing of peak bone mass (PBM) compared to normal individuals suggesting that GH treatment should be continued until the attainment of PBM, independently of the final height achieved (25).
Treatment with GH increases BMD (26-30); in addition, GH treatment improves bone turnover, as inferred by the evaluation of the markers of bone formation and resorption (27, 31, 32). Furthermore, patients with the lowest BMD before treatment demonstrated the greatest BMD increase, with the result that 40-50% of osteopenic patients achieved a normal BMD after 2 yr of therapy (28, 29). Some skeletal sites were demonstrated to respond to GH replacement better than others: in fact, the beneficial effects of GH on the bone are more evident at the lumbar spine than at the trochanter level (2, 33). However, long-term fracture prediction using BMD remains controversial, as does the additional contribution from assessing bone turnover or clinical risk factors (34). It should be considered that the reduction of 1 SD in BMD from the age-specific mean population value confers a 2- to 3-fold increase in fracture risk (34, 35). Recently, Mazziotti et al. found that in patients with GHD about one-half of the fractures occurred in the presence of a normal BMD and the prevalence of fractures was significantly higher in untreated *vs* treated GHD patients, although no significant difference was found in T-

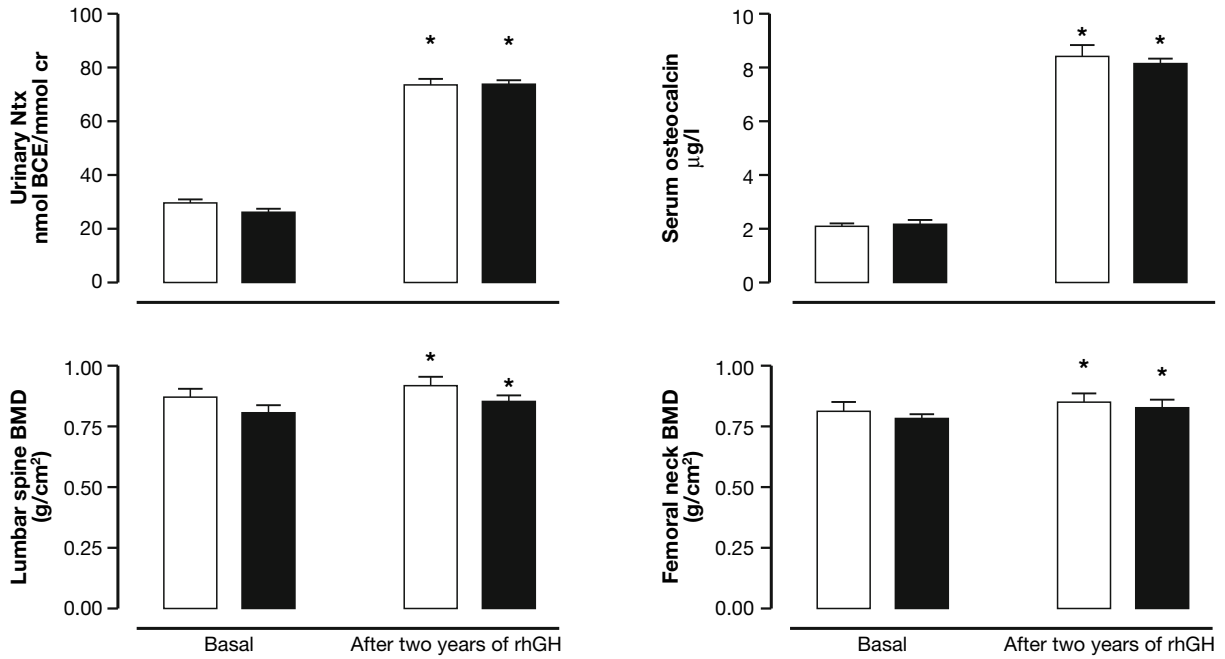

Fig. 3 - *Urinary cross-linked N-telopeptides of type I collagen (Ntx)(top, left), serum osteocalcin (top, right), bone mineral density (BMD)(g/cm²) at lumbar spine (bottom, left) and at femoral neck (bottom, right) in androgen-untreated men (open bars) and in men receiving androgen replacement (closed bars) with GH deficiency before and after 2 yr of GH replacement. *:* p*<0.001 post-treatment values* vs *basal values. rhGH: recombinant human GH.*

score (8). This may suggest that the quality rather than the quantity of the bone may be more impaired in presence of GHD. In our study we found that BMD at lumbar spine and at femoral neck was significantly lower in GHD patients than in controls, but it was similar in GHD women and men. After 2 yr of GH replacement, BMD significantly increased both at lumbar spine and at femoral neck both in men and in women, provided that the dose of GH was modulated on the basis of IGF-I levels.

A gender difference in response to GH has also been observed (13-15). In fact, it has been reported that male GHD patients are more responsive to GH replacement than women in improving body composition, lipid metabolism (13-15). In fact, some studies demonstrated that GHD males have a higher increase in biochemical markers of bone turnover, whereas GHD females have a higher increase in total bone mineral content and BMD (28, 36). In a recent study, it has been observed that the improvement of bone mass was greater in men, despite receiving significantly lower doses of GH, than in women, reinforcing the hypothesis of a gender difference in the sensitivity to GH (14). At further support it has been reported that male GHD patients have a greater benefit from long-term GH replacement than females, in which BMD has been reported stable rather than increased (37). In men, a synergy between GH and androgens at the peripheral level seems to exist, while an antagonistic action between estrogens and GH seems to occur in women. In addition, in healthy individuals estrogens seem to have a central effect at the hypothalamus-pituitary level, acting to increase GH secretion (38). However, in women, the increased GH secretion induced by estrogens is not accompanied with an increase of IGF-I levels (34). This finding could be also due to a relatively lower peripheral sensitivity to GH in women with a compensatory increase in GH secretion (12). On the other hand, it has been demonstrated that, in healthy adults, the IGF-I response to GH was reduced with age in males, and with oral estrogen therapy in postmenopausal women. In particular, the increase of IGF-I in young women in follicular phase was intermediate between older women receiving oral estrogen and those not receiving, indicating a predominant effect of estrogen over age in women with regard to responsiveness to GH (39).

However, previous studies reporting the gender difference of GH replacement on bone are unsatisfactory as there are wide age differences in cohorts of patients studied. In fact, it is well known that suboptimal bone growth in childhood and adolescence

is as important as bone loss to the development of osteoporosis. Furthermore, both men and women experience an age-related decline in BMD starting in midlife. In the present study, to overall these confounding factors we analyzed a selected population of GHD patients aged 30-50 yr.

In this line, in the current study, the GH dose necessary to gain and maintain normal IGF-I levels was higher in female than in male GHD patients confirming previous data and further underlying the necessity for individualized dose (13, 40, 41), but the percentage of IGF-I was similar in men and in women. In contrast, the percentage of IGF-I increase was lower in women receiving than in those not receiving estrogen replacement. This observation confirms the influence of the estrogen milieu on the IGF-I response to GH replacement, and supports an inhibitory role for oral contraceptives in reducing all three components of the IGF-I ternary complex (42) and in modulating the susceptibility to GH therapy (42, 43). However, bone mass and turnover increased both in men and in women without any difference between the 2 groups. The only difference between men and women observed in the current study was a significantly higher percentage of BMD increase at lumbar spine in men. It should be, however, pointed out that lumbar spine was shown to respond better to GH replacement than other bone sites (2, 33). Whether a longer-term GH treatment could induce a better effect also on femoral neck or other bone sites in men, cannot be ruled out.

In conclusion, a 2 yr GH replacement normalizes IGF-I levels, increases bone mass and improves bone turnover both in men and in women with GHD without any difference between the two groups, provided that the dose of GH was modulated on the basis of IGF-I levels. Women receiving oral estrogens should receive a GH dose approximately doubled, as compared to men and women not receiving oral estrogens, to achieve similar effects on bone density and turnover. In particular, GH replacement dose, to be successful on bone mass and turnover, depends on gender in hypopituitary patients aged below 50 yr.

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