

# Recombinant Growth Hormone (GH) Therapy in GH-Deficient Adults: A Long-Term Controlled Study on Daily Versus Thrice Weekly Injections

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## ABSTRACT

Currently, replacement recombinant GH (rGH) therapy in GH-deficient (GHD) adults is performed in daily injections. This modality of treatment is not complied with by the totality of GHD patients, who are supposed to receive life-long replacement. The aim of our study was to compare daily vs. thrice weekly (TIW) rGH injection effects on lipid profile, body composition, bone metabolism, and bone density in 34 GHD patients (13 women and 21 men; median age, 39 yr; range, 30–55 yr) randomly assigned to different therapeutic regimens. Group A included 18 patients receiving daily rGH injections, and group B included 16 patients receiving TIW injections of rGH. The starting dose of rGH was 10  $\mu\text{g}/\text{kg}\cdot\text{day}$  in both groups. Subsequently, the dose was adjusted to maintain serum insulin-like growth factor I (IGF-I) concentrations in the normal age-adjusted range. IGF-I levels were assessed before and after 1, 3, 6, and 12 months of rGH treatment, and lipid profile, body composition, bone metabolism, and bone density were evaluated before and after 6 and 12 months of treatment. Thirty-four healthy subjects served as controls.

In the basal condition, lipid profile, body composition, bone metabolism, and bone density were significantly different in patients compared to controls. Conversely, patients included in groups A and B had similar serum IGF-I levels, lipid profile, body composition, bone metabolism, and bone density. After 3 months of rGH treatment, IGF-I levels were normalized in 15 of 18 patients (83.3%) in group A and in 7 of 16 patients (43.7%) in group B ( $\chi^2 = 4.21$ ;  $P = 0.04$ ). At this time point, serum IGF-I levels in patients in group A ( $202 \pm 57.5$

$\mu\text{g}/\text{L}$ ) were significantly higher than those in patients in group B ( $155 \pm 45.1 \mu\text{g}/\text{L}$ ;  $P = 0.001$ ). After 6 months of therapy, serum IGF-I levels were normalized in all patients and were similar in both groups ( $223 \pm 35.2$  vs.  $212 \pm 41.4 \mu\text{g}/\text{L}$ , A vs. B, respectively). IGF-I levels remained normal until the 12-month follow-up.

After 6 months of rGH replacement, total cholesterol, low density lipoprotein cholesterol, triglycerides, bioelectrical impedance, and body fat mass were significantly reduced, whereas high density lipoprotein cholesterol levels and lean body mass were significantly increased in both groups of patients, without any difference between them. No further change in lipid profile and body composition was observed after 12 months of treatment. Serum bone GLA protein and procollagen III levels were significantly increased after 6 months, and a downward trend was observed after 12 months of rGH replacement. However, a slight, but significant, increase in bone mineral density was observed in both groups only after 12 months ( $P = 0.0001$ ). All patients in group B had good compliance to the TIW treatment, whereas 5 patients in group A had poor compliance to the treatment ( $\chi^2 = 3.2$ ;  $P = 0.07$ ).

In conclusion, our randomized, prospective, and controlled study confirmed that rGH therapy with TIW injection regimen is effective in normalizing IGF-I levels and improving lipid profile, body composition, bone metabolism, and bone density. It also demonstrated that this efficacy is comparable to that observed in patients treated with daily rhGH therapy, with few side-effects and good compliance. (*J Clin Endocrinol Metab* 85: 3720–3725, 2000)

**T**HE EFFICACY of GH replacement in GH deficiency (GHD) was demonstrated in 1958 in children (1) and at the beginning of 1990s was also reported in adults (2–6). The standard treatment regimen, using extracting GH, involved a three times weekly (TIW) dosing schedule, because it was shown to be efficacious and convenient (7). After the introduction of recombinant human GH (rGH) in clinical practice, the higher efficacy of daily than TIW administration was suggested as a more physiological replacement than a reduced frequency of hormone administration (8).

Although the use of rGH in the treatment of GH-deficient (GHD) adults is well established, the final efficacy of GH therapy is still unknown, and the issue of which is the op-

timal dosing schedules remains unclear (9). In adult life, the goal of GH treatment is to restore and/or ameliorate the abnormalities in energy metabolism, body composition, muscle mass and strength, cardiovascular structure and function, and bone metabolism and density without causing side-effects and with good compliance to the treatment (10). Currently, to this aim rGH replacement in GHD adults is performed by daily injections, such as in children, even if using lower doses (9). In a previous study we demonstrated that rGH replacement given TIW could normalize body composition and cardiac abnormalities (11). Short-term GH administration TIW was also shown to be effective in both GHD (12, 13) and other conditions (14).

The aim of this randomized, prospective, and controlled trial was to compare the effects of daily vs. TIW rGH injections on lipid profile, body composition, bone metabolism, and bone density in GHD adult patients treated for 12 months.

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## Subjects and Methods

### Patients

Thirty-four patients (13 women and 21 men; median age, 39 yr; range, 30–55 yr) with a diagnosis of GHD in adulthood (see below) and low insulin-like growth factor I (IGF-I) levels for age were enrolled in this study. All patients gave informed written consent to the study, which was approved by local ethical committees of the II University of Naples and the Federico II University of Naples. The criteria of inclusion were 1) normal growth and development; 2) peak GH serum below 9 mU/L (1  $\mu\text{g/L}$  = 3 mU/L) after insulin tolerance test (in 16 patients) or below 27 mU/L after arginine plus GHRH test (in 18 patients); and 3) serum IGF-I levels below the normal range for age in at least 3 different measurements performed during the last 3 months before entering the study. None of the patients had received GH treatment in the year preceding inclusion in the study. All patients except 4 with idiopathic GHD had been previously operated on via the transsphenoidal and/or transcranial routes for PRL-secreting adenomas (6 patients), nonfunctioning pituitary adenoma (13 patients), craniopharyngioma (8 patients), or Sheehan's syndrome (3 patients). Five patients had panhypopituitarism and diabetes insipidus, 10 patients had panhypopituitarism, 4 patients had FSH/LH and TSH deficiency, 2 had FSH/LH and ACTH insufficiency, 9 patients had FSH-LH deficiency, and 4 patients had GHD alone. Hormone replacement therapy with L-T<sub>4</sub> (50–100  $\mu\text{g}$ , orally, daily), cortisone acetate (25–37.5 mg/day), and intranasal desmopressin (5–20  $\mu\text{g}$ /day) was given where appropriate. Hypogonadism was treated in men with testosterone enanthate (250 mg, im, monthly) and in women with standard estrogenic association. The adequacy of hormone

replacement therapy was periodically assessed by serum free thyroid hormones, testosterone, urinary free cortisol, and serum and urinary Na<sup>+</sup> and K<sup>+</sup> measurements. These hormonal parameters were in the normal range for age in all patients for at least 6 months before enrollment. Thirty-four healthy subjects in the group of students, physicians, and parents who volunteered for this study were used as controls.

### Study protocol

The GHD diagnosis was performed by insulin tolerance test or arginine plus GHRH test as previously reported (15–18). All patients were submitted to magnetic resonance imaging of the sellar region, which showed no evidence of intrasellar or parasellar tumor. Patients were randomly assigned to different therapeutic regimens with rGH; group A included 18 patients receiving daily rGH injections, and group B included 16 patients receiving TIW injections of rGH. The computed randomization stratified patients to assure balance between the groups with respect to sex and age. The starting dose of rGH was 10  $\mu\text{g/kg}\cdot\text{day}$  in both groups so as to treat all patients with an identical weekly dose. Subsequently, the dose was adjusted on the basis of serum IGF-I concentrations up to the middle of the normal range for sex and age. The final rGH dose was  $6.1 \pm 1.8 \mu\text{g/kg}\cdot\text{day}$ , without a significant difference between the two groups (group A,  $6.1 \pm 1.6$ ; group B,  $6.2 \pm 1.9 \mu\text{g/kg}\cdot\text{day}$ ). At enrollment, lipid profile, body composition, bone metabolism, and bone density at two sites in the nondominant radius were evaluated in all patients. Fasting blood samples were drawn at 0900 h (the day after GH injection) for IGF-I, bone GLA protein (BGP), procollagen III (PIIINP), total cholesterol and triglycerides, high density

**TABLE 1.** Clinical and biochemical features of controls and GH-deficient patients before and after 12 months of GH therapy

	Controls (n = 34)	GHD patients (n = 34)		P <sup>a</sup>	P <sup>b</sup>
		Baseline	12 months		
Age (yr)	41 ± 10	39 ± 10		NS	
Sex (F/M)	12/22	13/21		NS	
IGF-I ( $\mu\text{g/L}$ )	228.3 ± 42.0	71.5 ± 26.0	226.2 ± 44.0	0.0001	0.0001
Triglycerides (mg/dL)	106.0 ± 18.0	173.2 ± 38.0	125.0 ± 35.0	0.0001	0.0001
Total cholesterol (mg/dL)	168.0 ± 22.0	223.0 ± 40.0	175.0 ± 25.0	0.0001	0.0001
LDL cholesterol (mg/dL)	101.0 ± 8.0	117.0 ± 16.0	97.6 ± 13.0	0.002	0.0001
HDL cholesterol (mg/dL)	51.6 ± 6.0	35.8 ± 6.0	49.3 ± 5.5	0.0001	0.0001
BI (ohms)	565.6 ± 77.0	737.1 ± 111.0	611.8 ± 98.0	0.0001	0.0001
FBM (%)	23.0 ± 3.1	30.6 ± 4.0	25.4 ± 2.2	0.0001	0.0001
LBM (%)	77.0 ± 3.1	69.4 ± 4.0	74.6 ± 2.2	0.0001	0.0001
BGP ( $\mu\text{g/L}$ )	6.0 ± 2.5	2.7 ± 1.5	5.2 ± 2.6	0.0001	0.0001
PIIINP (KU/L)	1.0 ± 0.5	0.7 ± 0.2	0.8 ± 0.3	0.015	0.005
Proximal density (mg/cm <sup>2</sup> )	674.0 ± 40.0	589.0 ± 36.0	643.4 ± 29.0	0.0001	0.0001
Distal density (mg/cm <sup>2</sup> )	505.0 ± 45.0	390.0 ± 39.0	474.0 ± 39.0	0.0001	0.0001

<sup>a</sup> Baseline GHD values *vs.* controls.

<sup>b</sup> Twelve months *vs.* baseline.

**TABLE 2.** Clinical and biochemical features in two groups of GH-deficient patients at study entry and after 12 months of GH therapy

	Baseline			12th month		
	Group A (n = 18)	Group B (n = 16)	P	Group A (n = 18)	Group B (n = 16)	P
Age (yr)	43 ± 15	39 ± 13	0.52			
Sex (F/M)	7/11	6/10	0.71			
IGF-I ( $\mu\text{g/L}$ )	70.6 ± 28.0	60.6 ± 26.0	0.32	218.6 ± 42.0 <sup>a</sup>	233.5 ± 45.0 <sup>a</sup>	0.16
Triglycerides (mg/dL)	174.3 ± 14.5	182.0 ± 45.0	0.60	124.4 ± 48.0 <sup>a</sup>	130.5 ± 34.0 <sup>a</sup>	0.75
Total cholesterol (mg/dL)	215.2 ± 40.0	209.6 ± 47.0	0.73	165.5 ± 25.0 <sup>a</sup>	180.0 ± 25.0 <sup>b</sup>	0.23
LDL cholesterol (mg/dL)	116.8 ± 15.0	115.0 ± 17.0	0.81	98.1 ± 10.0 <sup>b</sup>	97.3 ± 16.0 <sup>b</sup>	0.45
HDL cholesterol (mg/dL)	36.7 ± 7.1	38.9 ± 8.2	0.50	50.3 ± 8.0 <sup>a</sup>	49.1 ± 4.0 <sup>a</sup>	0.53
BI (ohms)	742.0 ± 125.0	718.0 ± 82.0	0.59	624.8 ± 75.0 <sup>a</sup>	592.8 ± 71.0 <sup>a</sup>	0.20
FBM (%)	31.6 ± 2.9	29.6 ± 4.7	0.62	24.4 ± 3.0 <sup>a</sup>	25.6 ± 2.0 <sup>b</sup>	0.16
LBM (%)	68.4 ± 2.9	70.4 ± 4.7	0.62	75.6 ± 3.0 <sup>a</sup>	74.4 ± 2.0 <sup>b</sup>	0.16
BGP ( $\mu\text{g/L}$ )	2.4 ± 1.1	3.0 ± 2.0	0.30	4.3 ± 2.6 <sup>b</sup>	6.3 ± 2.7 <sup>a</sup>	0.14
PIIINP (KU/L)	0.7 ± 0.2	0.6 ± 0.1	0.84	0.9 ± 0.1 <sup>b</sup>	0.8 ± 0.2 <sup>b</sup>	0.43
Proximal density (mg/cm <sup>2</sup> )	589.0 ± 32.0	586.0 ± 41.0	0.85	639.0 ± 36.0 <sup>a</sup>	648.0 ± 26.0 <sup>a</sup>	0.42
Distal density (mg/cm <sup>2</sup> )	379.0 ± 38.0	398.0 ± 23.0	0.15	473.2 ± 38.0 <sup>a</sup>	465.5 ± 43.0 <sup>a</sup>	0.68

<sup>a</sup> P < 0.01, 12th month *vs.* baseline for both group A and group B.

<sup>b</sup> P < 0.05 12th month *vs.* baseline for both group A and group B.

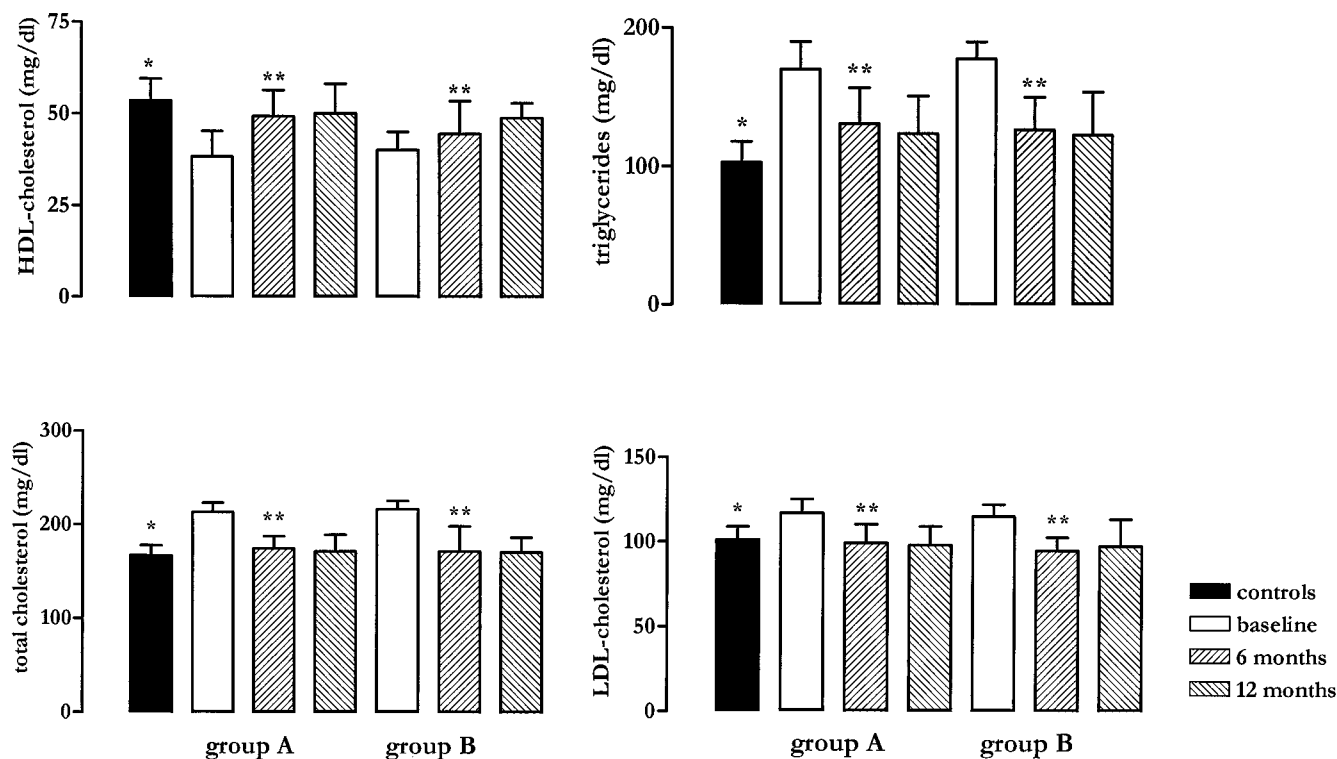


FIG. 1. Total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol before and after 6 and 12 months of rGH therapy in two groups of GHD patients. \*,  $P < 0.05$  vs. baseline values of both groups. \*\*,  $P < 0.05$  vs. baseline values of the same group.

lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol assays. IGF-I levels were assessed after 1, 3, 6, and 12 months of treatment. The patients were visited at each time point of the follow-up and were asked about the appearance of side-effects such as arthralgia, myalgia, headache, soft tissue swelling, and paresthesiae, and these symptoms were graded as mild, moderate, or severe. Lipid profile, body composition, bone mass, and bone turnover were reevaluated after 6 and 12 months of therapy.

#### Body composition analysis

Body composition was investigated by whole body bioelectrical impedance (BI) analysis using a portable impedance analyzer. The results are expressed in ohms. Body fat percentage (FBM) was determined after calculating lean body mass (LBM) and fat mass from measured impedance and reactance using the RJL Systems computer program (Bia-101, Florence, Italy), as previously reported (11, 17).

#### Bone density measurement

Bone mineral density (BMD), expressed as milligrams per  $\text{cm}^2$ , was measured by planar scanning with a forearm dual photon absorptiometer. The evaluation was performed at two sites in the nondominant radius: one third of the total length (proximal site) and 2–4 mm (ultra-distal site) from the ulnar plate of the forearm (proximal to the base of the styloid process of the ulna). These sites were standardized for evaluation of compact and trabecular bones, respectively (19).

#### Biochemical assays

Serum IGF-I was measured by immunoradiometric assay (Diagnostic Systems Laboratories, Inc., Webster, TX). The sensitivity of the assay was  $0.80 \mu\text{g/L}$ . The intraassay coefficients of variation were 3.4%, 3.0%, and 1.5% for low, medium, and high points of the standard curve, respectively. The interassay coefficients of variation were 8.2%, 1.5%, and 3.7% in our laboratory for low, medium, and high points of the standard curve, respectively. In our laboratory the normal ranges in 20- to 30-, 31- to 40-, 41- to 50-, and over 50-yr-old men were 108–458, 92–483, 100–316,

and 78–213  $\mu\text{g/L}$ , respectively, whereas in women they were 118–523, 112–506, 96–288, and 78–268  $\mu\text{g/L}$ , respectively. BGP and PIIINP were measured by RIA commercial kits (Henning, Berlin, Germany; and Farnos, Turku, Finland, respectively). The sensitivity of the assay and the coefficients of intra- and interassay variabilities in our laboratory were 1.8  $\mu\text{g/L}$ , 4.6%, and 5.9% for BGP and 0.08  $\text{kU/L}$ , 2.5%, and 3.2% for PIIINP, respectively. Measurements of total cholesterol, triglycerides, and HDL and LDL cholesterol were made with commercial kits.

#### Statistical analysis

Statistical analysis was performed using SPSS, Inc., software (SPSS, Inc. Evanston, IL). Comparison between groups A and B for both baseline and on-treatment characteristics were made with the two-tailed  $\chi^2$  test and Student's  $t$  test for paired and unpaired data. ANOVA for repeated measures followed by Bonferroni's test were used for evaluating differences between baseline and 6- and 12-month GH treatment periods.  $P < 0.05$  was considered statistically significant. Results are expressed as the mean  $\pm$  SD of values unless otherwise stated.

## Results

At study entry, lipid profile, body composition, bone metabolism, and bone density were significantly different in patients compared to controls (Table 1). GH treatment induced a progressive increase in IGF-I levels up to the sixth month in GHD patients; thereafter IGF-I levels remained stable throughout the 12-month study period. After 12 months of GH treatment, normalization of total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels together with improvement of body composition parameters and increase in BMD were observed (Table 1).

In both groups of patients no difference was found in IGF-I levels, lipid profile, body composition, bone metabolism, or bone density (Table 2). After 3 months of rGH treatment,

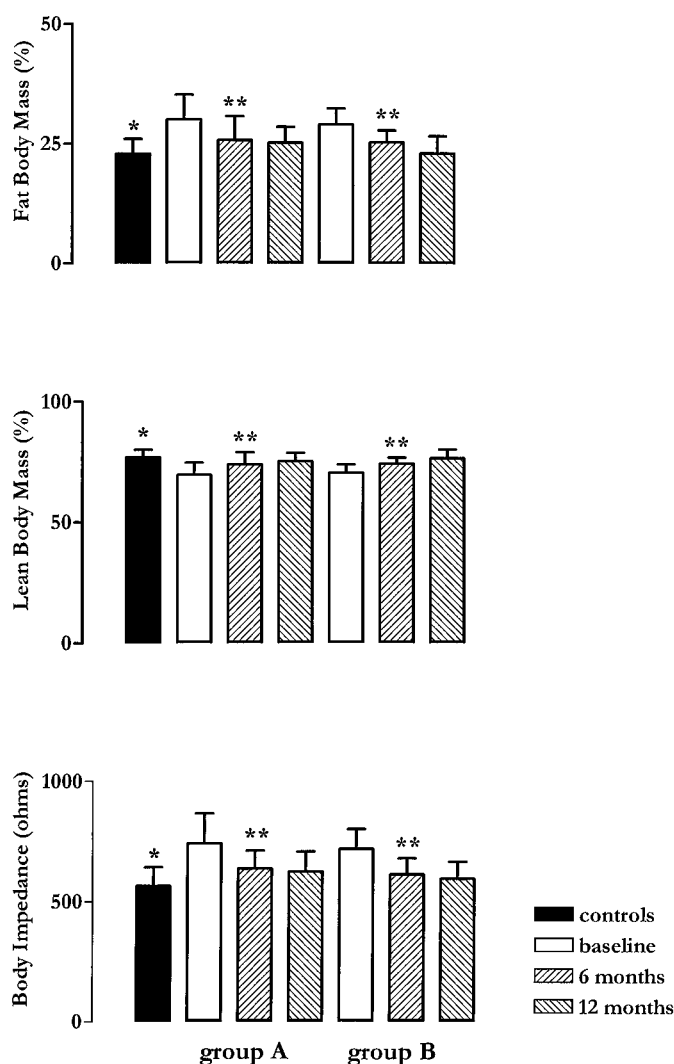


FIG. 2. BI, FBM, and LBM before and after 6 and 12 months of rGH therapy in two groups of GHD patients. \*,  $P < 0.05$  vs. baseline values of both groups. \*\*,  $P < 0.05$  vs. baseline values of the same group.

IGF-I levels were normalized in 15 of 18 patients (83.3%) in group A and in 7/16 patients (43.7%) in group B ( $\chi^2 = 4.21$ ;  $P = 0.04$ ). At this time point, serum IGF-I levels in patients in group A were significantly higher than those in patients in group B ( $202 \pm 57.5$  vs.  $155 \pm 45.1$   $\mu\text{g/L}$ ;  $P = 0.001$ ). Moreover, IGF-I levels were slightly higher than baseline after 1 month of treatment in both groups. After 6 months of therapy, serum IGF-I levels were normalized in all patients and were similar in both groups ( $223 \pm 35.2$  vs.  $212 \pm 41.4$   $\mu\text{g/L}$ , group A vs. group B). IGF-I levels remained normalized until the 12-month follow-up.

Total cholesterol, LDL cholesterol, and triglyceride levels were significantly reduced, and HDL cholesterol levels were significantly increased after 6 months of rGH treatment in both groups of patients (Fig. 1). Similarly, after 6 months, significant decreases in BI and FBM ( $P = 0.0001$ ) and a significant increase in LBM ( $P = 0.0001$ ) were observed in both groups (Fig. 2) without any significant change in bone density (Fig. 3). No further change in lipid profile, BI, FBM, or LBM was observed after 12 months (Figs. 1 and 2). After 6

months, serum BGP and PIIINP levels were significantly increased ( $P = 0.0001$ ; Fig. 3), whereas a downward trend of bone metabolism parameters was found after 12 months (Fig. 3). A slight, but significant, increase in BMD was observed in both groups after 12 months ( $P = 0.0001$ ).

#### Tolerability

Mild arthralgia was reported during the first week of treatment by five patients receiving the daily rGH treatment regimen. Pain at the joint sites, particularly of the hands, knees, and feet, was reported during the morning and spontaneously disappeared with treatment continuation. No side-effects were reported by patients receiving the TIW rGH treatment during the 12 months of follow-up. No patient in either treatment regimen schedule withdrew from treatment because of side-effects. All patients in group B had good compliance to the treatment, whereas five patients in group A had poor compliance to rGH treatment ( $\chi^2 = 3.2$ ;  $P = 0.07$ ). The rGH dose was identical in groups A and B for the first 3 months of treatment, whereas it was progressively reduced on the basis of the appearance of side-effects and/or normalization of IGF-I levels until they reached  $6.1 \pm 1.6$  and  $6.2 \pm 1.9$   $\mu\text{g/kg}\cdot\text{day}$  in groups A and B, respectively.

#### Discussion

The most important finding of the present study is the evidence that the TIW regimen of rGH replacement was as effective as the daily regimen in improving and/or normalizing IGF-I levels, lipid profile, body composition, and bone mass and turnover in adult GHD patients.

Since the first report of Raben in 1958 (1), pituitary GH has been used in the therapy of children with GHD (7). Before the wide availability of rGH in 1985, the standard GH treatment regimen involved a TIW dosing schedule. Subsequently, several studies reported that the administration of rGH in daily injections was more effective on linear growth than that of TIW dosing (20, 21). However, contrasting results have been reported by others (22). More recently, it was speculated that the advantage of daily administration is limited to the first period of therapy (23). Nevertheless, it should be considered that the physiological spontaneous pulsatile GH secretion can not be reproduced by either TIW or daily sc injections. In experimental models the regimen of two to four injections per day was demonstrated to be better than one injection in promoting longitudinal bone growth, whereas more frequent administration did not add any further positive effect (24–26). However, the role played by physiological GH pulsatility on growth and metabolism in humans is still debated, and it is unknown whether a closer imitation of the normal endogenous GH secretory pattern would improve the clinical response to rGH therapy in GHD children (27).

In adults with GHD the question of rGH replacement is further complicated by the lack of a clear-cut clinical marker such as linear growth in children, so that the dose applied and the parameters that should be measured varied largely in different reports (9, 10, 28). However, a general agreement exists in modifying the GH dose to recover IGF-I secretion to the age-adjusted normal range (9). Currently, IGF-I is probably the best biochemical marker of the response to long-

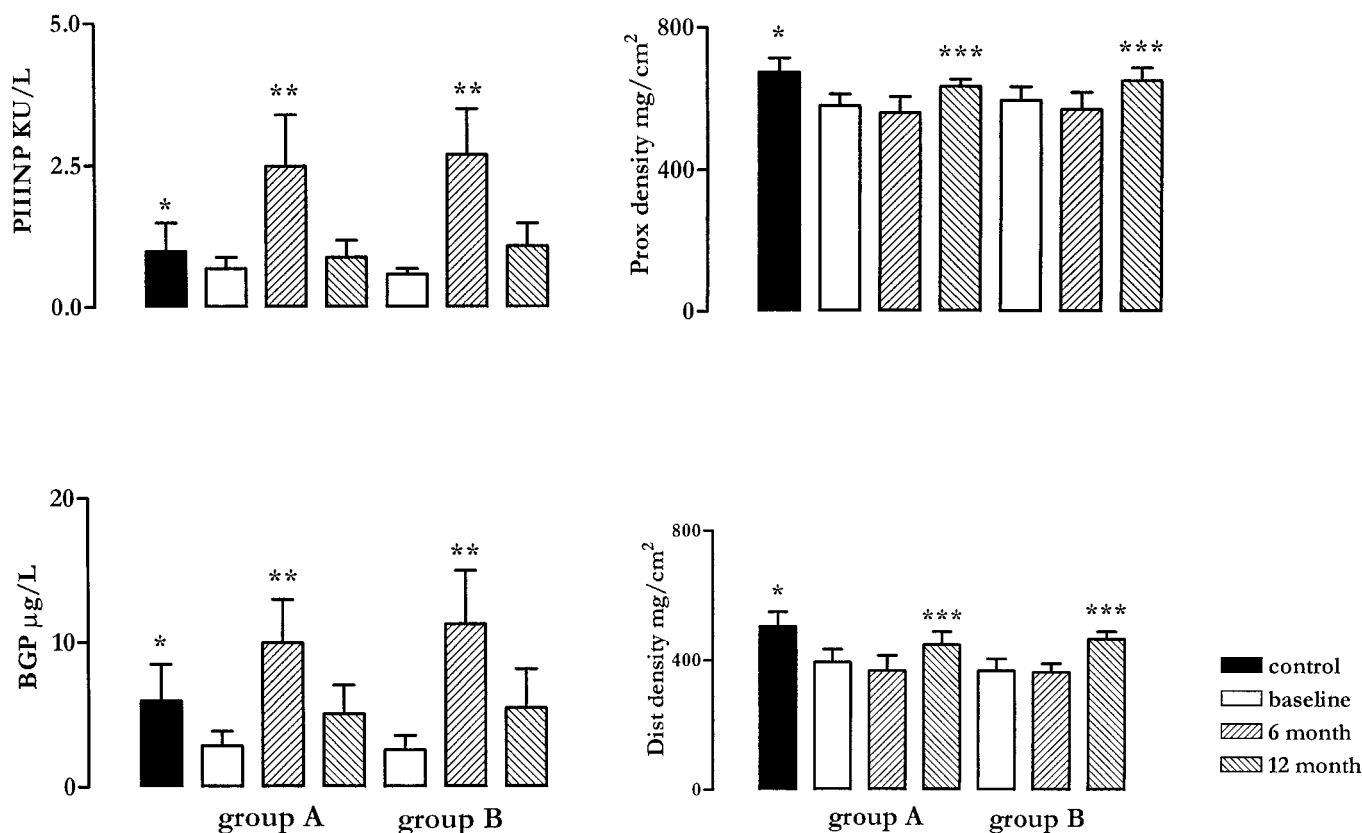


FIG. 3. Bone metabolism (serum BGP and PIIINP) and density at proximal (Prox) and distal (Dist) sites of the radius before and after 6 and 12 months of rGH therapy in two groups of GHD patients. \*,  $P < 0.05$  vs. baseline values of both GHD groups. \*\*,  $P < 0.05$  vs. baseline and 12 month values of the same group. \*\*\*,  $P < 0.05$  vs. baseline values of the same group.

term rGH therapy (29) even if serum IGF-I levels were reported not to be correlated with the modifications of body composition and intermediate metabolism induced by short-term rGH replacement (30, 31). On the other hand, IGF-I levels, although reflecting the spontaneous GH secretion (32), are not constantly low in adult patients with GHD. In fact, normal IGF-I levels were reported in 73.3% of patients with partial GHD, in 40.6% of patients with severe GHD, and in 29.2% of patients with very severe GHD (17). However, as IGF-I levels were the first end point of the current study, all 34 patients included had IGF-I levels constantly below the normal age-adjusted range. In this light, the current series of patients can be considered as rather homogeneous for IGF-I secretion. In fact, IGF-I levels do not fluctuate during the day, and different regimens of rGH replacement were reported to cause no significant difference in the increase in serum IGF-I levels (24, 33). As a further support to these observations, no difference in the increase in serum IGF-I levels was observed in our GHD patients treated with either daily injections or TIW injections after 6 months of treatment. In contrast, during the first 3 months of GH replacement, normal IGF-I levels were achieved in 83.3% of patients treated with daily injections and in only 43.8% of those receiving TIW injections. The possibility that IGF-I decreased the day after the GH injection, thus causing a delay in IGF-I normalization in patients treated with the TIW schedule, cannot be ruled out. However, all patients normalized their IGF-I levels after 6 months

of GH replacement. In keeping with IGF-I normalization after 6 months of therapy normalization of the lipid profile, an increase in LBM and a decrease in FBM were found in patients treated daily and in those treated TIW to a similar extent and in line with previous observations using different frequency of rGH injections (34–36). On the other hand, rGH administration on alternate days was recently reported to induce a sustained increase in the rate of protein synthesis and lipolysis in GHD adults (31). At partial variation with lipid profile and body composition parameters, no change in BMD was observed in our patients after 6 months, although notable increases in osteoblastic activity, as shown by BGP levels, and in collagen synthesis, as shown by PIIINP levels, were observed. This finding was consistently observed during both treatment regimens. After 12 months of treatment, a downward trend of metabolic bone indexes was observed in both groups of patients, in line with other reports (37, 38). At the end of the treatment, daily and TIW GH injections did not produce further significant amelioration of body composition parameters compared to those at the sixth month of follow-up. In contrast, BMD was slightly, but significantly, increased, confirming previous data (19, 37, 38). The increase in BMD after 12 months of rGH treatment, despite a downward trend of bone turnover and soft tissue indexes, is not surprising, as a synchronized activation of basic remodeling units can be observed at the beginning of rGH therapy, followed by a loss of synchronization until a new steady state

is achieved (37). However, it is relevant to note that bone mass and turnover were modified to a similar extent in both patients receiving daily rGH injections and those receiving TIW injections.

In conclusion, our randomized, prospective, and controlled study confirmed that rGH therapy with the TIW injection regimen is effective in improving lipid profile, body composition, bone metabolism, and bone density. It also demonstrated that the efficacy of TIW treatment is comparable with that of a daily regimen. No side-effects and good compliance were observed in all patients treated with the TIW schedule. As the beneficial effects of rGH treatment are considered to last unless treatment is withdrawn (19), and therefore, the therapy should theoretically be performed lifelong, we suggest that TIW GH replacement can be applied in long-term treatment of GHD adults.

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