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# Progressive Normalization of Growth Hormone-Binding Protein and IGF-I Levels in Treated Growth Hormone-Deficient Children*

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## ABSTRACT

The short- and long-term effects of hGH treatment on growth hormone (GH)-binding protein (GHBP) were examined in 18 prepubertal children, aged 1.5–10 y, with isolated idiopathic GH deficiency. The patients were studied before and at regular intervals during 24 mo of hGH therapy (0.6 IU/kg/wk, given daily). Pretreatment GHBP values were low: 14.6 ± 1.2% of radioactivity ($p < 0.0001$ *versus* normal prepubertal children). After the first hGH injection, GHBP levels fell significantly at 6 h (8.2 ± 1.3% of radioactivity) and then remained at basal level during the first week. Under hGH therapy, an increase in GHBP was observed, but it occurred at different times of treatment, from 1 to 12 mo, and the mean GHBP value became significantly higher than the value before treatment after 12 mo of therapy. An increase in serum IGF-I level was observed as soon as 1 wk of hGH therapy, and after 3 mo, the mean IGF-I value was normal. No correlation was found between the increase in GHBP, IGF-I levels, and the growth velocity at 12 and 24 mo of treatment. These findings support the role of GH in the regulation of GHBP/receptor in man. The time course of the GH effect appears to be progressive and variable. (***Pediatr Res* 37: 731–735, 1995**)

**Abbreviations**

**GH,** growth hormone
**GHBP,** growth hormone-binding protein
**BMI,** body mass index

Identification of the serum GHBP and demonstration that the amino acid sequence of GHBP is identical to that of the extracellular domain of the membrane GH receptor have provided new tools to study GH action in man (1, 2). In clinical research, measurement of serum GHBP is the only approach to estimate the GH receptor because there are no accessible cells in which GH receptors can be measured. In man, GHBP probably results from proteolytic cleavage of the membrane receptor as no specific mRNA for the short form of the GH receptor is detected in human tissues (3). The plasma GHBP level is believed to reflect the concentration of tissue GH receptors. In animal models, GH receptors have been shown to be modified in several pathologic situations (4). As membrane GH receptors are regulated by many factors, the level of plasma GHBP is expected to be under a multifactorial control.

Among many factors, GH has been shown to play an important role in the regulation of its receptors. However, a controversy has recently arisen concerning the effect of GH on the plasma GH binding activity. On one hand, GH is able to increase GHBP levels, as was shown in children with GH deficiency (5, 6) and also in children with idiopathic short stature (7). On the other hand, absence of GH effect on GHBP has been reported in treated GH-deficient children (8).

In this work, we have examined short-term and long-term effects of hGH treatment in prepubertal children with isolated GH deficiency. GHBP was measured longitudinally before treatment and during 24 mo after the beginning of GH therapy. Short-term effects of hGH may represent an important issue as they could be used to better predict response to hGH therapy in physiopathologic situations.

## METHODS

***Subjects and protocol.*** Eighteen prepubertal children (11 boys and 7 girls), aged 1.5–10 y (mean age: 5.6 ± 2.9 y), with isolated idiopathic GH deficiency, were studied before treatment and at regular intervals during the first 2 y of hGH therapy. GH deficiency was defined as subnormal GH responses to at least two provocative tests (peak GH < 10 μg/L), which was chosen by the French Pituitary Agency for providing hGH therapy. Recombinant hGH (Saizen, Serono Laboratories and Genotonorm, Kabi Pharmacia Laboratories) was

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given s.c. daily, at the dosage of 0.60 IU/kg/wk. All but four subjects were followed longitudinally for 2 y of treatment. Patient 14 could not be followed after 6 mo of therapy, and three patients (nos. 1, 8, and 11) were studied for 1 y only. Three patients (nos. 13, 17, and 18) entered puberty between 18 and 24 mo of the treatment; for that reason and for that time period, results for these patients were not included. Height and weight were measured before treatment and every 3 mo on hGH treatment. Height was expressed as the SD score (SDS) for chronologic age (9). Weight for height was expressed as body mass index [BMI = weight (kg)/height ($m^2$)] in SD for chronologic age (10). Growth velocities were calculated 12 mo after beginning hGH therapy by subtracting the height at baseline from the height at 12 mo. The clinical characteristics of patients are presented in Table 1.

The 18 patients were investigated for biologic parameters before and 6, 12, and 24 mo after the onset of hGH treatment. The short-term response to the hGH treatment was evaluated in 10 of them, and blood samples were collected before and at 6, 12, 24, and 48 h, 8 d, and 1 and 3 mo after the beginning of treatment. For technical reasons, some blood samples could not be obtained for all measurements. After the first 48 h of treatment, sampling was performed between 14 and 20 h after the last hormone injection.

Informed consent was obtained from the parents.

***Procedures.*** Blood samples were collected during the study period, and sera were stored at −20°C until assayed. Periodic samples were measured in the same assay.

GHPB was measured by HPLC-gel filtration, as previously described (11). Briefly, 100 μL of serum were incubated with 100 μL of potassium phosphate, 0.1 M, pH 7.0, containing $^{125}$I-hGH ($1 \times 10^5$ cpm). After 20 h at 4°C, the incubation was injected onto HPLC Protein Pak 300 sw column (Waters, Milford, MA). Elution was performed isocratically using degassed buffer pumped at a rate of 0.5 mL/min. Radioactivity was recorded on line using a Berthold LB 504 γ detector connected to a computer. To evaluate nonspecific binding, 2 μg of hGH were added to the incubation. The binding of $^{125}$I-hGH is expressed as the percentage of total radioactivity (radioactivity in the individual peak divided by total radioactivity in the peaks). The interassay coefficient of variation was 8% (11). In some serum samples, the GH concentration was elevated, and the binding of $^{125}$I-hGH to GHBP had to be corrected for occupancy of the receptor by GH. Such a correction was done for samples containing GH at a concentration >6 μg/L, as previously reported (5); this was the case for all blood samples collected 6 h after the first GH injection and for one sample collected at 12 h.

**Table 1.** *Growth parameters of the group of 18 children with isolated GH deficiency before and after 12 and 24 mo of GH treatment*

| | Height (SDS) | Growth velocity (cm/y) | Growth velocity (SDS) | BMI (SDS) |
|---|---|---|---|---|
| Baseline | −3.3 ± 1.3 | 4 ± 1.4 | −2.6 ± 1.3 | −0.3 ± 1.1 |
| 12 mo | −2.3 ± 1.1* | 9.5 ± 1.9* | 3.3 ± 1.8* | −0.8 ± 0.9*** |
| 24 mo | −1.8 ± 1.1** | 7.0 ± 1.4*** | 1.1 ± 0.9** | −0.9 ± 0.9 |

Results are expressed as mean ± SD. SDS = SD score.

* $p = 0.0002$ *vs* baseline; ** $p = 0.003$ *vs* baseline; *** $p = 0.01$ *vs* baseline.

None of the patients of the study group developed detectable GH antibodies as observed on the elution profiles from HPLC-gel filtration of $^{125}$I-hGH incubated with serum. The GH concentration was measured by immunoradiometric assay using polyclonal antibodies (Pharmacia, Saint-Quentin en Yvelines, France). IGF-I was measured by RIA, after acid gel filtration (12). IGF-I antibody was kindly donated by Dr. P. Chatelain, Lyon, France.

***Statistics.*** Results are expressed as mean ± SEM. Statistical differences between groups were assessed using variance analysis. If overall significant differences were present, specific differences between two time periods were sought by the Wilcoxon signed rank test (with a Bonferroni correction for simultaneity). The Mann-Whitney *U* test was used to compare data in two different groups. Correlation between variables was evaluated by linear regression analysis.

## RESULTS

In 18 children with isolated GH deficiency, basal GHBP values were lower (14.6 ± 1.2% of radioactivity, $p < 0.001$) than in normal prepubertal children (mean value in a group of 15 prepubertal normal children: 24.8 ± 1.7%) (11). As shown in Table 2, values ranged from 7.0 to 25.4% of radioactivity. In this group of prepubertal children, no relationship was found between GHBP levels and chronologic or bone age. However, a positive correlation was found between GHBP levels and BMI before treatment, as shown in Fig. 1 ($r = 0.63$, $p = 0.005$).

GHBP and GH levels for 48 h after the first hGH injection are presented in Fig. 2. In the group of 10 children studied for the short-term hGH response, the GH peak at 6 h was associated with a significant decrease in GHBP ($p < 0.005$). Both GH and GHBP returned to baseline 24 h after the first hGH injection (Fig. 2 and Table 3). Under hGH treatment, an increase in GHBP was observed in all patients but two (patients 10 and 14); however, in one patient GHBP could not be assayed after 6 mo of treatment and in the other one, GHBP was normal before hGH therapy. Increase in GHBP occurred slowly and at different times of GH therapy: in the group of 10 patients evaluated for the short-term hGH response (Table 3), it was observed after 1 mo for two patients, at 3 mo for one patient, at 6 mo for one patient, and thereafter (12 or even 24 mo) for the others. As shown in Fig. 3 and Table 2, when results for all patients were analyzed, the mean GHBP value became significantly higher than the value before treatment after 12 mo of therapy ($p = 0.006$). The difference between 12 and 24 mo was not significant.

As expected, plasma IGF-I concentrations were low before treatment (42 ± 5.8 μg/L, $p = 0.0001$ *versus* normal children). Increase in IGF-I occurred sooner than increase in GHBP (Fig. 3): it was significant after 8 d of hGH therapy ($p < 0.02$). At 3 mo of treatment, the mean serum IGF-I level was normal and reached a plateau thereafter. There was no significant difference between IGF-I levels at 3, 6, 12, and 24 mo. No correla-

**Table 2.** *GHBP values in 18 children with isolated GH deficiency, before and during the first 2 y of hGH therapy*

| Patients | Age (y) | Bone age (y) | Baseline | Treatment period (mo) | | |
|---|---|---|---|---|---|---|
| | | | | 6 | 12 | 24 |
| 1 | 1.5 | 1.0 | 10.5 | 20.0 | 23.6 | |
| 2 | 1.8 | 0.8 | 10.6 | 27.5 | 24.0 | 26.9 |
| 3 | 2.6 | 1.5 | 8.3 | | 21.5 | 18.8 |
| 4 | 2.5 | 1.5 | 22.0 | | 18.8 | 33.5 |
| 5 | 3.7 | 2 | 14.9 | | 24.7 | 24.1 |
| 6 | 3.8 | 3 | 19.4 | | 26.4 | 31.0 |
| 7 | 3.9 | 2 | 7.3 | 11.0 | 24.9 | 27.9 |
| 8 | 4.3 | 2 | 18.8 | 22.2 | 23.2 | |
| 9 | 4.4 | 1.5 | 17.2 | | 18.5 | 20.3 |
| 10 | 4.9 | 3 | 25.4 | 23.9 | | 25.4 |
| 11 | 6.5 | 2.5 | 14.4 | 25.6 | 22.4 | |
| 12 | 7.3 | 5 | 16.9 | | | 27.5 |
| 13 | 7.8 | 4.5 | 7.0 | 7.9 | 15.0 | |
| 14 | 8.0 | 4.0 | 16.6 | 14.5 | | |
| 15 | 8.3 | 5.5 | 12.7 | 10.9 | | 23.4 |
| 16 | 9.5 | 7.3 | 16.5 | 20.6 | | 41.4 |
| 17 | 9.8 | 7.5 | 14.7 | 12.5 | 21.9 | |
| 18 | 10.3 | 6.0 | 10.1 | 15.5 | 23.6 | |
| Mean ± SEM | 5.6 ± 0.7 | 3.4 ± 0.5 | 14.6 ± 1.2 | 17.7 ± 1.9 | 22.2 ± 0.9 | 27.3 ± 1.9 |

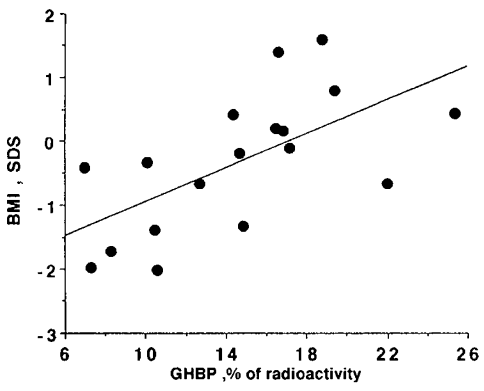


**Figure 1.** Relationship between BMI and serum GHBP levels in 18 GH-deficient children. $r = 0.63$; $p = 0.005$.

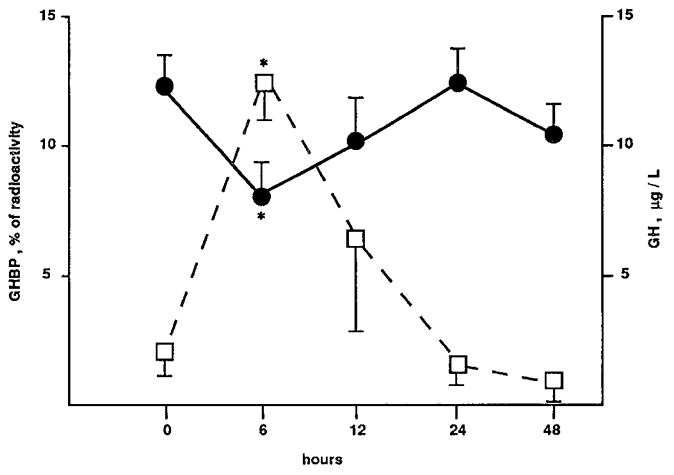


**Figure 2.** Serum GHBP (●) and GH (□) levels during the first 48 h of treatment. Each value represents the mean ± SEM of results obtained in the patients. * $p < 0.005$ *vs* value at time 0.

tion was found between either GHBP and IGF-I levels or their increment under hGH therapy.

As expected, the growth velocity increased under hGH therapy, with a significant improvement in height. The mean BMI value was decreased after the first year of hGH treatment (Table 1). Neither the growth velocity before and under treatment nor the increase in the growth velocity during the studied period were correlated with GHBP or IGF-I levels before therapy. No correlation was observed between the increase in GHBP, IGF-I levels, and the growth velocity at 12 and 24 mo of hGH therapy.

## DISCUSSION

This study *1*) confirms that GH-deficient children have a low plasma GH binding activity and *2*) demonstrates that GH treatment normalizes GHBP levels progressively and that the increase in GHBP follows rather than precedes the increase in IGF-I plasma levels.

The low GHBP value found in this group of 18 children with isolated GH deficiency is comparable to the value that was reported previously by us (5) and by Tauber *et al.* (13). Normal GHBP values were also found in GH-deficient children (6, 8). However, in the report by Hochberg *et al.* (6), the etiology of the GH deficiency has not been specified, and in the work of Martha *et al.* (8), one third of the patients presented associated deficiencies of several pituitary hormones. To have a group as homogeneous as possible, prepubertal children with isolated idiopathic GH deficiency were selected to be included in our study.

After the first hormone injection, elevated GH concentration at 6 h was accompanied by a decrease in GH binding activity. This result must be interpreted with caution as high GH concentrations interfere with GHBP determination because of receptor occupancy; even though correction was done for the high GH concentration, the GHBP levels at 6 h post-injection could have been somewhat underestimated. However, a decrease in the number of total GH binding sites has been demonstrated in liver membranes of hypophysectomized rats which had received a single injection of GH (14); this acute

**Table 3.** *GHBP values in 10 children with isolated GH deficiency, studied for the short-term hGH response*

| Patients | Age (y) | Baseline h 0 | Treatment period h 6 | h 12 | h 24 | h 48 | d 8 | mo 1 | mo 3 |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 1.8 | 10.6 | 10.4 | 7.3 | 9.8 | 8.0 | | | 12.0 |
| 3 | 2.6 | 8.3 | 1.5 | 4.4 | 8.8 | 7.5 | | 6.8 | 8.5 |
| 7 | 3.9 | 7.3 | 5.4 | 7.1 | | 10.4 | 8.6 | 6.0 | 10.1 |
| 12 | 7.3 | 16.9 | 8.9 | 12.9 | 18.6 | 15.8 | 13.7 | 16.3 | 13.5 |
| 13 | 7.8 | 7.0 | 4.3 | | 7.3 | 6.9 | 5.1 | 6.1 | 12.5 |
| 14 | 8.0 | 16.6 | 14.6 | 20.10 | 14.9 | 14.4 | | 9.6 | 16.1 |
| 15 | 8.3 | 12.7 | 8.2 | 10.8 | 12.8 | 10.9 | 7.8 | 8.2 | 7.5 |
| 16 | 9.5 | 16.5 | 8.6 | 11.5 | 12.8 | 14.1 | | 24.7 | 13.3 |
| 17 | 9.8 | 14.7 | 11.6 | 11.6 | 16.2 | | 11.3 | 9.7 | 8.8 |
| 18 | 10.3 | 10.1 | | 5.3 | 8.0 | 9.5 | 11.0 | 16.5 | 12.5 |
| Mean ± SEM | 6.9 ± 0.9 | 12.1 ± 1.3 | 8.2 ± 1.3 | 10.1 ± 1.6 | 12.1 ± 1.3 | 10.8 ± 1.1 | 9.6 ± 1.2 | 11.5 ± 2.1 | 11.5 ± 0.9 |

GHBP values are expressed as the percentage of total radioactivity.

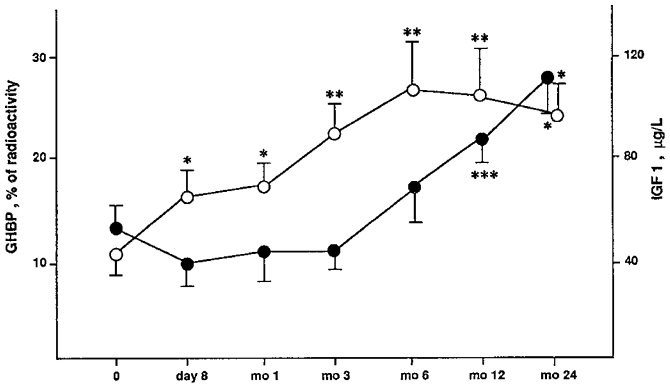


**Figure 3.** Evolution of the mean levels of GHBP (●) and IGF-I (○) during the first 24 mo of GH therapy. Normal values for the age group are: GHBP = 24.8 ± 1.7% of radioactivity, IGF-I = 100 ± 5 µg/L. * $p < 0.02$, ** $p < 0.005$ *** $p < 0.0001$ *vs* value at time 0.

down-regulation of the liver membrane GH receptors contrasted with the up-regulation of GH receptors that was demonstrated during prolonged GH administration in rats (15).

Later, during the first week of treatment, no changes in the GHBP levels were observed for any of the patients. The length of time necessary for GH to induce GHBP was different from one patient to the other. It took 1–12 mo to observe this effect, which is certainly longer than the time necessary for the hormone to up-regulate the liver membrane GH receptors in rats (15). An age-related increase in GHBP has been shown in several reports (11, 16, 17). However, in this group of GH-deficient children, the effect of hGH therapy on GHBP is greater than the age effect observed in normal children (11) and in untreated children with idiopathic short stature, over a time period of 18 mo (7). No relationship was found between the effect of hGH on GHBP levels and the other responses to the treatment, such as the increase in serum IGF-I levels and in growth velocity.

In the study by Hochberg *et al.* (6), a progressive increase of GHBP during hGH therapy was also found in children with idiopathic GH deficiency, and the increase was observed sooner than in our group of children inasmuch as it was significant after 3 mo of treatment. But, in the recent report by Martha *et al.* (8), prepubertal GH-deficient children had normal basal GHBP levels and no consistent effect of the treatment on GHBP was observed. Absence of GH effect on the GHBP levels could be explained by a lower dose of hGH which was given three times a week *versus* daily injections in our protocol. Moreover, the time of blood collection in relationship to the hormone injection, which might be critical to detect a GH effect on the GHBP level, was not specified (8). Another important recent study emphasizes the importance of the mode of hGH administration: in GH-deficient children, the GH effect on GHBP is more pronounced and more consistent with continuous infusion than with daily injections (13). Examples of up-regulation of GHBP by GH have been observed in children with growth disorders (5–7, 13). In children with isolated GH deficiency, a GH effect can be observed when the GHBP levels before treatment is low (5, 6, 13) as is also found in the present study. The reason for a normal basal GHBP value in the study by Martha *et al.* (8) *versus* a low value in other studies including this one (5, 13), has to be clarified.

An inverse relationship has been shown between the high affinity serum GHBP and 24 h release of GH in boys aged 7–18 y, under normal physiologic conditions (18). No discussion of the possible effect of other hormones, such as testosterone, was mentioned in this work, whereas GH and testosterone have been shown to have opposite effects on the regulation of GHBP (5). The mechanism by which GH affects the level of GHBP will not be clear before more is known about the generation of the binding protein.

A positive correlation between serum GHBP pretreatment levels and BMI was found in this study as in others (19–22), suggesting that nutritional factors affect BMI and GHBP in parallel. As expected, IGF-I levels increased significantly during the first 3 mo of hGH treatment, and they remained constant thereafter. IGF-I increment was not correlated to the growth velocity during the first 2 y of treatment. These results are in accordance with previous reports (23, 24) which did not show correlation between linear growth velocity and IGF-I levels after chronic hGH administration to GH-deficient children. Neither the increase nor the absolute activity of IGF-I and GHBP were correlated, with large variations in individual responses.

Similar to membrane GH receptors, the serum GHBP level is controlled by multiple factors, among which GH plays an important role. The time course of the GH effect is progressive

and variable. Thus, under the conditions of this study, it seems impossible to use the short-term effects of GH on the GHBP as a test to assess a hormonal or an auxologic response. A better knowledge of the biosynthesis and of the exact roles of the GHBP is needed to interpret the variations of the GH binding activity measured in human plasma.

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