Growth Parameters and Predictors of Growth in Short Children With and Without Growth Hormone (GH) Deficiency Treated With Human GH: a Randomized Controlled Study

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Summary
Seventy-seven prepubertal short children with heights below the third centile for age and gender were divided into three groups according to their peak GH response to clonidine and insulin provocation. Group (I) included 30 children with peak GH response <7 µg/l, group (II) included 19 children, with GH peak response between 7 and 10 µg/l, and group (III) included 24 children with GH peak >10 µg/l. Each group was divided into two subgroups, a and b. Subgroups (I)b, (II)a and (III)b were treated daily for 1 year with subcutaneous recombinant human growth hormone (GH) 15 U/m²/week, and group (I)a was treated with GH (30 U/m²/week). Before initiation of treatment, the chronological age, the height standard deviation score (HtSDS), and the bone age delay did not differ among the study subgroups. The height growth velocity (GV) and insulin-like growth factor-I concentrations were significantly higher in group (II), with normal GH response to provocation, compared to those for group (I) with GH deficiency. All the children had normal thyroid function and normal glucose tolerance. CT examination of the hypothalamo-pituitary area revealed a picture of empty sella (either partial or complete) in 35 per cent of the children in group (I) and 21 per cent of children in group (II). After 1 year of GH therapy, the HtSDS, GV, and IGF-I concentrations increased significantly in the four subgroups treated with GH compared to their pretreatment values and to their controls. All the children in group (I) were responders (increment in GV of 2 cm²/year above the pretreatment GV), of the nine subjects treated in group (II)a, one child was a non-responder and of the 12 children in group (III)a three children were non-responders. GV was non-significantly higher in group (I)a (30 U/m²/week) v. group (II)b (15 U/m²/week). GV of children in groups (I)b, with abnormal GH response to provocation, was significantly higher than GV of children in group (II)a. Bone age advanced by less than 1 year in the treated groups (0.84 ± 0.14 years) v. the untreated groups (0.73 ± 0.3 years). None of the children had impaired glucose tolerance or abnormal thyroid function after 1 year of GH therapy. In all the treated children, GV after 1 year of GH treatment was correlated significantly with the pretreatment GV (r = -0.63, P < 0.01), peak GH response to provocation (r = -0.59, P < 0.01), IGF-I concentration (r = -0.54, P < 0.01), and positively with the GH dose (r = 0.589, P < 0.01). In group (III) children, with normal GH reserve, GV correlated significantly with the pretreatment GV (r = -0.48, P < 0.01) and negatively with the GH peak response to provocation (r = -0.25, P < 0.05).

In conclusion, GH therapy improved GV of children growing along or parallel to the 3rd centile, irrespective of their GH response to provocation, without untoward effect on skeletal maturation, thyroid function or glucose tolerance.

Introduction
The classic definition of growth hormone (GH) deficiency depends on failure to respond to two stimulation tests and growth rate less than some arbitrary limit for age in the absence of other explanations for short stature and growth failure. The definition of an adequate response to GH has varied with the author, but is usually a serum level of 5, 7, or 10 µg/l. Short children with normal GH response to provocation respond to GH therapy with accelerated growth rate. This accelerated growth rate might be due to higher circulating levels of GH during therapy; however, some of these children...
might have neurosecretory dysfunction of GH or bioinactive GH.10

The limitations of defining normality by pharmacological GH testing have been shown by Spiliotis et al.9 and Bercu et al.11 Lin et al.12 and Rose et al.13 reported that 24-hours endogenous GH studies did not offer any diagnostic advantage over stimulation tests because the mean GH values in patients with GH deficiency overlapped significantly with those of normal children. Therefore, the results of both the secretagogue testing and secretory profiles have not proved useful in predicting who will respond to exogenous GH therapy and evaluation of growth rate in response to a therapeutic trial of GH might be necessary in many cases.

We report the effect of treatment with GH for 1 year on the growth of 51 short prepubertal children, 30 children with GH deficiency (GH peak <7 µg/l), nine children randomly selected from 19 children with partial GH deficiency (GH peak >7 <10 µg/l), and 12 children randomly selected from 24 children with normal GH response (GH peak >10 µg/l) and compare them with those for the untreated children.

Patients and Methods
The subjects were selected from children referred to our Pediatric Endocrinology clinic, University of Alexandria Children's Hospital, Alexandria, Egypt. Height was determined on a stadiometer by a trained independent observer and was taken as the average of three measurements. The subjects were at least three times the 3rd percentile in height for chronological age. A pretreatment height growth velocity (GV) was determined from a minimum of three height measurements obtained at 3-month intervals during a 12-month period of observation. Height standard deviation scores were calculated according to the formula: HtSDS = (X1 - X2)/SD, where X2 and SD are age-matched population mean height and SD, respectively, and X1 is the subject height. Normal population data were according to Tanner et al.14

Informed consents were obtained for the study (approved by Alexandria University Ethical Committee). A venous blood sample was obtained for estimation of plasma urea and electrolytes and serum calcium, liver function tests, and complete blood count. None of the children had hemoglobinopathy, hepatic or renal impairment. After an overnight fast, all children underwent two provocative tests for GH release, on two different days. A venous blood sample was obtained at 8-hours for determination of insulin-like growth factor-I (IGF-I), GH, T4, and TSH concentrations, and an oral dose of clonidine 0.15 mg/m² was given and blood collected at 30-min intervals for 2 hours. On the next day and after an overnight fast insulin tolerance test (0.15 units insulin/kg body weight) was performed and blood samples obtained at 0, 15, 30, 45, 60, 90, and 120 min.

The serum was separated from the individual sample and frozen at −20°C till analysed for GH. GH and IGF-I concentrations were determined by the immunoradiometric assay employing reagents purchased from Nichols Institute (San Juan Capistrano, CA). Intra- and interassay coefficient of variation were 2.6 and 6.8 for GH values, and 4.7 and 8.8 for IGF-I values, respectively. Skeletal age was examined at yearly interval according to the atlas of Greulich and Pyle.15 No child had a reduced weight relative to height, other systemic disease, history of head trauma or cranial irradiation, malnutrition, psychosocial dwarfism or hypothyroidism. CT examination of the hypothalamic pituitary area was performed in all the children who did not mount normal GH peak (>10 µg/l).

According to the peak GH response to provocation, three groups of short children were identified and recruited for the study: group (I) included 34 children with peak GH response to provocation >7 µg/l, group (II) included 19 children with peak GH response to provocation between 7 and 10 µg/l, and group (III) included 24 children with normal peak GH response (>10 µg/l). Each group was further subdivided at random into two subgroups, a and b.

After determination of height velocity a standard oral glucose tolerance test (dextrose 1.75 g/kg, max 50 g) was performed16,17 and plasma glucose measured by glucose oxidase method. Subjects were treated with GH as follows: group (I)a (n = 20) received 30 U/m²/week as daily subcutaneous dose at 20-h and groups (I)b (n = 14), (II)a (n = 9), and (III)a (n = 12) received 15 U/m²/week as daily subcutaneous dose at 20-h. Groups (II)b (n = 10) and (III)b (n = 12) did not receive any GH or anabolic steroids. The subjects were seen at 3-month intervals for determination of height and adjustment of dosage based on surface area. The height GV was calculated from the height at the beginning and end of the year of therapy. The actual time interval of measurement was between 0.96 and 1.04 years. Four children in group (I)b had to be excluded from the study because of lack of compliance. Circulating IGF-I, FT4, and TSH concentrations were remeasured and oral glucose tolerance test was performed for all the children after 1 year of being in the study.

Data are presented as the mean ± SD. ANOVA test was used to compare analyte concentrations in the different groups when the data were normally distributed and Wilcoxon test was used when the data were not normally distributed. Paired Student t-test was used to analyse changes in each group before and after 1 year. Simple linear regression was used to test correlation between variables.

Results
Table 1 shows the anthropometric and hormonal data of all children. The subjects were prepubertal;
bone age was < 10 years at initiation of therapy. Use of this bone age excluded any effect of the adolescent growth spurt as a factor in the response to GH therapy. The chronological age and the bone age delay did not differ significantly among the three study groups. The height velocity of patients in group III was significantly higher than those in group I. HtSD did not differ among the three groups. Group III had significantly higher IGF-I concentrations compared to group I.

Table 2 presents growth and hormonal data of the different subgroups before and after 1 year of follow-up. The chronological age and the degree of bone age delay did not differ among the six subgroups either before or after 1 year of follow-up. The peak GH response to provocation and IGF-I concentration were significantly lower in group I v. group III. After 1 year of GH therapy, the HtSD, GV, and IGF-I concentration increased significantly in the four subgroups treated with GH compared to their pretreatment values. A positive response was considered when GV was 2 cm or more per year above the pretreatment GV. Subjects with positive response were termed responders and the others were termed nonresponders. All children treated in group I (n=30) were responders. Of nine subjects in group (II)a, one child was non-responder (GV increment = 1.6 cm/year), and of the 12 subjects in group (III)a, three children did not have an increase in growth rate above the limit during the year (GV increments 1.1, 1.4, and 1.8 cm/year). GV was non-significantly higher in group (I)a (9.9 ± 2.25 cm/year) (GH dose = 30 U/m²/week) v. group (I)b (8.1 ± 1.5 cm/year) (GH dose 15 U/m²/week). GV, HtSDS, and IGF-I concentration increased significantly in the treated groups (II)a and (III)a compared with 0.73 (0.32) years in the control groups [(II)b and (III)b].

There was no change in the FT4 or TSH concentrations before or after therapy in all the study groups. None of the children had impaired glucose tolerance after 1 year of GH treatment (Table 3).

CT examination of the hypothalamic-pituitary area in children with abnormal GH response to provocation revealed a picture of empty sella (partial or complete) in 12 out of the 34 children (35 per cent) in group (I) and in four out of the 19 children (21 per cent) in group (II). GV of children with empty sella (n=9) treated with GH for one year (8.5 ± 1.4 cm/year) was similar to GV of children without empty sella in groups (I) and (II)a (n=30) (8.7 ± 1.2 cm/year).

GV after 1 year of GH therapy in all the study children was correlated significantly with GV before starting therapy (r = -0.63, P<0.01), GH peak response to provocation (r = -0.589, P<0.01), IGF-I concentration before therapy (r = -0.539, P<0.01) and positively with the GH dose (r = 0.585, P<0.01). No significant correlation was found between GV after therapy and the degree of bone age delay (r = 0.09). IGF-I concentration before therapy was correlated significantly with the peak GH response to provocation (r = 0.782, P<0.01).

In children with normal GH response (group III), GV after treatment correlated significantly with the pretreatment GV (r = -0.482, P<0.01) and negatively with the GH peak response to provocation (r = -0.25, P<0.05). Pretreatment IGF-I concentration was not correlated significantly with GV on treatment (r = -0.07).

Discussion
With unlimited supplies of recombinant GH, pediatricians have to select those short children who will benefit from GH therapy. In this controlled randomized study we demonstrated a significant improvement of height growth velocity after GH therapy in two groups of patients with abnormal,
but different, GH response to provocation tests, as well as in a group of short children with normal GH response to provocation (constitutional short stature). The GV increments in GH deficient children were higher in the group treated with the higher dose of GH ([30 U/m²/week, group (I)a] v. those treated with the lower dose (15 U/m²/week). After 1 year of GH therapy, no significant difference in GV was detected among groups (II)b, (II)a, and (III)a, who were receiving the same dose of GH (15 U/m²/week), despite their different GH response to provocation. These results denote the importance of GH dose as a predictor of growth rate in short children irrespective of their GH reserve. Of the 12 children with constitutional short stature [group (III)a] nine were responders (75 per cent). In concert with our findings, Raiti et al., reported that of 48 short children who had normal GH responses to provocative tests, 45 responded to 6 months of GH therapy with improved GV. Kaplan and Grumbach, treated 34 short children with GH and reported a response in 80 per cent.

In our study the best predictors for the 1-year growth outcome of short children (n = 51) (with normal and abnormal GH response to provocation) treated with GH was the GH dose and their GV before treatment, together yielding a regression correlation coefficient of 0.74. In addition, their GH peak response to provocation and IGF-I concentrations were correlated significantly and inversely with their GV on treatment. In the short normal group (III), the best predictor for the 1-year growth outcome was their pretreatment GV and dose of GH yielding a regression coefficient of 0.78. These findings are in agreement with those reported by Hindmarsh et al. and Zadik et al.

Serum IGF-I concentrations have been regarded by some as having predictive value in assessing response to GH treatment. In our study, there was a good correlation (r = 0.64, P < 0.01) between pretreatment IGF-I levels and GV on GH treatment in children with GH deficiency [groups (I)a, (I)b, and (II)a]. However, our data indicated a poor relation between IGF-I levels and GV in children with normal GH response to provocation. This can be explained by the predominantly paracrine origin of IGF-I, so that serum concentrations need not necessarily reflect important changes in tissue concentrations.

Administration of human GH has been associated with some alterations in thyroid function, reduced thyroxine and triiodothyronine concentrations, and blunted thyroid stimulating hormone response to thyrotropin-releasing hormone. None of the children in our study developed low free thyroxine or high TSH while on GH treatment.

The increased GH secretion in acromegalic patients has been associated with hyperinsulinaemia and carbohydrate intolerance, which was reversible after removal of the hypophyseal adenoma.
adults, intravenous infusion of GH induced insulin resistance with impaired suppression of hepatic glucose production and decreased insulin-dependent glucose disposal.\textsuperscript{26,27} None of our children developed glucose intolerance as measured by oral glucose loading after one year of GH therapy. In agreement, Aman et al.\textsuperscript{8} have demonstrated that 3 years of GH treatment (0.1 U/kg/day) in prepubertal children without GH deficiency did not produce any negative effect on fasting plasma glucose concentrations or glucose disposal rates, despite a moderate hyperinsulinaemia during the first year of treatment.

This study has shown that giving GH to children growing along or parallel to the 3rd height centile leads to a significant increase in growth velocity without an untoward effect on skeletal maturation, glucose tolerance, or thyroid function.

### References


17. World Health Organization Expert Committee on...


