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High-Dose Growth Hormone Treatment of Short Children Born Small for Gestational Age

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ABSTRACT

The effect of GH administration was evaluated over 2 yr in 50 short, prepubertal, non-GH deficient children born small for gestational age, who had been randomly allocated to a group receiving no treatment or daily sc GH treatment at a dose of 0.2 or 0.3 IU/kg. At the start of the study, mean age was 5.2 yr, bone age was 4.0 yr, height SDS was −3.5, height velocity SDS was −0.8, weight SDS was −2.7, and body mass index SDS was −1.9.

Catch-up growth was observed in none of the untreated and all of the treated children. The response to GH treatment included a near doubling of growth velocity and of weight gain and a mean height increment of more than 2 SDS. GH treatment was associated with a distinct acceleration of bone maturation. The differences between the growth responses evoked by the two GH doses were minor.

The prepubertal GH-induced catch-up growth was associated with elevated serum concentrations of insulin, insulin-like growth factor-I, insulin-like growth factor binding protein-3, and osteocalcin, whereas insulin-like growth factor-II levels remained unaltered. GH treatment was well tolerated.

In conclusion, high-dose GH administration over 2 yr is emerging as a potential therapy to increase the short stature that results from insufficient catch-up growth in young children born small for gestational age. The long-term impact of this approach remains to be delineated.

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The endocrine milieu of the human fetus with growth retardation is characterized by elevated serum GH and insulin-like growth factor (IGF) binding protein-1 (IGFBP-1) concentrations and low serum levels of insulin, IGF-I, IGF-II, and IGFBP-3, a constellation reminiscent of GH resistance (1–3). Most children born small for gestational age normalize their stature during infancy through a poorly understood mechanism of catch-up growth, possibly involving augmented GH secretion (4). A minority do not show sufficient catch-up growth and maintain an exceptionally short stature at least throughout childhood (5, 6). In the latter group, the incidence of GH insufficiency may be increased and may consist of either classical GH deficiency, as diagnosed by stimulation tests, or of subtle abnormalities in the GH secretory pattern, as detected by GH profile examinations (7–10).

In the pioneering studies attempting to normalize the short stature of children with insufficient catch-up growth, GH was administered with low frequency (11, 12) or in substitution doses (9, 13, 14). The observed growth responses were heterogeneous and difficult to interpret because of the lack of parallel controls, but they were ultimately considered to be unsatisfactory, thus prompting the initial evaluation of high-dose GH schedules (15, 16). In the meantime, daily sc placebo injections were also found to have no consistent growth-promoting effect in this group of short children (16).

We present a randomized, controlled, multicenter study exploring the effect of daily and high doses of GH over 2 yr in short children born small for gestational age.

Study Design, Materials, and Methods

This 2-yr study was designed as an open-labeled, controlled, multicenter trial with three parallel groups assembled through weighted randomization. One group was not treated and two groups were treated with daily sc injections of recombinant human GH (Genotropin; Pharmacia, Stockholm, Sweden) that was administered in the evening at a dose of either 0.2 IU/kg or 0.3 IU/kg.

Inclusion criteria were 1) birth weight and/or length below −2 SD for gestational age (17), 2) height SDS for age below −2.5 (18), 3) height velocity SDS for age below +1 (18) to exclude children presenting spontaneous catch-up growth, 4) chronological age between 2 and 8 yr at study start, 5) serum GH concentration > 10 μg/L spontaneously, after exercise, glucagon, or insulin tolerance test, 6) available growth data concerning the period preceding the start of the study (preferentially 9–15 months), and 7) written informed consent.

Exclusion criteria were endocrine disorders, Turner (lymphocyte karyotype) or Down syndromes, previous or concomitant irradiation or anabolic steroid therapy, and severe chronic disease or mental retardation.

Study visits including history (baseline characteristics, adverse events, number of missed injections), auxological evaluation, bone age determination, and dose adjustment were scheduled every 6 months. Biochemical examinations were performed yearly.

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Effect of GH administration on growth was assessed by determining height, height SDS, height velocity, height velocity SDS, weight SDS, weight gain (18), body mass index (BMI) and BMI SDS (19). Catch-up growth was defined as a height velocity SDS above +1 for age during the referred interval. All bone ages were read according to the Tanner-Whitehouse II method by a single radiologist who was blinded for chronological age and treatment randomization. Height SDS for bone age, integrating height and bone age at different ages, was used as an index of final height prognosis.

Measurements of serum IGF-I, IGF-II, and IGFBP-3 concentrations were performed in samples that had been collected at the start of the study, after 2 weeks of GH administration, and after 1 and 2 yr of study, and which had been kept frozen until assay. Recombinant human IGF-I for assay purposes was obtained from Bachem (Torrance, CA) and recombinant human IGF-II was provided by Eli Lilly Research Labs. (Indianapolis, IN). IGF-I and IGF-II were iodinated by a modification of the chloramine-T method (20) to specific activities of 350–500 μCi/μg. Anti-IGF-I rabbit antiserum (UB3-189) was a gift of Drs. Louis Underwood and Judson J.Van Wyk, Division of Pediatric Endocrinology, University of North Carolina (Chapel Hill, NC) and was distributed for research use by the Hormone Distribution Program of NIDDK through the U.S. National Hormone and Pituitary Program. Following acid size-exclusion chromatography, serum IGF-I and IGF-II were measured by RIA, as previously described (21). The minimal detectable concentrations were 0.1 μg/L for IGF-I and 0.5 μg/L for IGF-II. The intra- and interassay coefficients of variation for IGF-I were 5% and 13%, respectively, and for IGF-II were 7% and 15%, respectively. Serum IGFBP-3 concentrations were measured using immunoradiometric assay kits that were generously supplied by Diagnostics Systems Labs. (Webster, Texas). Serum osteocalcin concentrations were measured by homologous RIA in a single assay run, the intraassay coefficient of variation being 6.4% at a concentration of 36 μg/L (22).

Comparisons between study groups were analyzed by Wilcoxon rank sum test for growth variables and by Student's t test for IGF, IGFBP, and osteocalcin measurements. Statistically significant differences were considered to be obtained at $P < 0.05$. Results are expressed as means ± SEM.

The study protocol was approved by the Ethics Committee of the Medical School, University of Leuven. Before study initiation, written informed consent was obtained from at least one of the parents or of the legal representatives of each child.

Results

STUDY POPULATION

Fifty-four children from eight centers were randomly allocated either to the untreated control group (n = 13) or to the group receiving GH at 0.2 IU/kg per day (n = 20) or 0.3 IU/kg per day (n = 21). Fifty-two children started the study between July 1991 and April 1992; two children allocated to the 0.3 IU/kg per day treatment group did not start.

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The 52 participating children were considered to have no specific syndrome (n = 33), Silver-Russell syndrome (n = 10), Fetal Alcohol syndrome (n = 4), Dubowitz syndrome (n = 3), 4p- syndrome (n = 1), or Lacrimo-auriculo-dento-digital syndrome (n = 1). Baseline characteristics are listed in **Table 1**. There were no significant differences between study groups for any of the baseline variables. Maternal height was 158.1 ± 6.9 cm (height SDS −0.3 ± 0.1) and paternal height was 172.5 ± 7.5 cm (height SDS −0.7 ± 0.2). Gestational age was 37.9 ± 0.4 weeks.

Table 1. Characteristics (mean ± SEM) of the cohort at the start of the study. None of the variables differed significantly among study groups.

	Total (n = 52)	NoGH (n = 13)	0.2 IU/kg per day GH (n = 20)	0.3 IU/kg per day GH (n = 19)
Birthweight (g)	1972.0 ± 76.0	1996.0 ± 136.0	2082.0 ± 139.0	1842.0 ± 115.0
Birthlength (cm)	42.3 ± 0.6	42.1 ± 1.1	42.3 ± 1.1	42.5 ± 0.9
Chronological age (yr)	5.2 ± 0.3	4.9 ± 0.5	5.4 ± 0.5	5.1 ± 0.4
Bone age (yr)	4.0 ± 0.3	3.7 ± 0.5	4.5 ± 0.5	3.7 ± 0.5
Height SDS	−3.5 ± 0.1	−3.4 ± 0.3	−3.5 ± 0.2	−3.7 ± 0.2
Height velocity (cm/yr)	6.8 ± 0.3	6.7 ± 0.7	6.6 ± 0.4	7.0 ± 0.5
Height velocity SDS	−0.8 ± 0.1	−0.6 ± 0.3	−0.9 ± 0.2	−0.7 ± 0.3
Weight (kg)	12.6 ± 0.5	12.0 ± 0.8	13.2 ± 0.9	12.3 ± 0.7
Weight SDS	−2.7 ± 0.1	−2.8 ± 0.2	−2.5 ± 0.2	−2.9 ± 0.2
BMI	13.8 ± 0.2	13.5 ± 0.4	14.0 ± 0.4	13.8 ± 0.4
BMI SDS	−1.9 ± 0.2	−2.0 ± 0.4	−1.8 ± 0.4	−1.8 ± 0.3
Serum IGF-I (μg/L)	108.0 ± 9.0	108.0 ± 21.0	107.0 ± 15.0	108.0 ± 14.0
Serum IGF-II (μg/L)	664.0 ± 39.0	699.0 ± 103.0	557.0 ± 44.0	748.0 ± 60.0
Serum IGFBP-3 (mg/L)	3.34 ± 0.21	3.35 ± 0.38	3.34 ± 0.33	3.36 ± 0.38
Serum osteocalcin (μg/L)	68.0 ± 2.0	63.0 ± 3.0	69.0 ± 3.0	69.0 ± 2.0

Two children dropped out of the study for psychosocial reasons, one control after the start visit and one child of the 0.2 IU/kg per day treatment group after 19 months. Thus, a total of 50 children completed the 2-yr study, 12 controls and 19 children in each of the treatment groups.

None of the participating children entered puberty during the course of the study.

GH DOSE

The number of missed injections was requested at each visit. Over 2 yr, less than 10 injections were said to be missed in 36/38 treated children; in two children, respectively, 3% and 8% of the injections were reportedly omitted.

After 6, 12, and 18 months, GH doses were adjusted for weight gain. Assuming a linear weight gain over each episode of 6 months, the mean individual GH dose over 2 yr was 0.192 IU/kg per day (range 0.184–0.199) in the 0.2 IU/kg per day group and 0.284 IU/kg per day (range 0.275–0.289) in the 0.3 IU/kg per day group.

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HEIGHT

Catch-up growth (0–2 yr) was observed in none of the untreated children and in all of the treated children (**Fig. 1**). Children with and without specified syndromes appeared to present similar growth responses.

The height velocity (0–2 yr) of the untreated children (5.7 ± 0.3 cm/yr) was lower ($P < 0.001$) than that of the treated children. The height velocity (0–2 yr) in the 0.2 IU/kg per day group (10.2 ± 0.2 cm/yr) was lower ($P < 0.05$) than in the 0.3 IU/kg per day group (11.0 ± 0.4 cm/yr). The height velocity during the first year was higher than during the second year of treatment, both in the 0.2 IU/kg per day group (11.5 ± 0.4 cm/yr *vs.* 8.8 ± 0.2 cm/yr) and in the 0.3 IU/kg per day group (12.0 ± 0.4 cm/yr *vs.* 10.0 ± 0.3 cm/yr).

The height velocity SDS (0–2 yr) of the untreated children (−0.9 ± 0.3) was lower ($P < 0.001$) than that of the treated children. The height velocity SDS over 2 yr was 4.3 ± 0.3 in the 0.2 IU/kg per day group and 5.2 ± 0.4 in the 0.3 IU/kg per day group, being similar in the two groups during the first year (5.3 ± 0.3 *vs.* 5.8 ± 0.4), but lower during the second year ($P < 0.01$) in the 0.2 IU/kg per day group (3.0 ± 0.3) as compared with the 0.3 IU/kg per day group (4.3 ± 0.4).

The gain in height SDS (0–2 yr) in the untreated children (0.2 ± 0.1) was limited ($P < 0.001$) compared with the gain in the treated children, being 2.1 ± 0.1 in the 0.2 IU/kg per day group and 2.5 ± 0.1 in the 0.3 IU/kg per day group. After 2 yr, all untreated children still had a height SDS below −2.2, whereas this was no longer the case for 35/38 treated children.

BONE AGE

During the 2 yr of study, the annual bone age increment in the untreated children (0.84 ± 0.07 yr) was less ($P < 0.001$) than in the treated children, the increments being similar in the 0.2 IU/kg per day group (1.35 ± 0.16 yr) and in the 0.3 IU/kg per day group (1.33 ± 0.24 yr).

Gain in height SDS for bone age (0–2 yr) was virtually absent in the untreated children (0.0 ± 0.3) and lower ($P < 0.05$) than in the treated children, who had similar increases in height SDS for bone age with 0.2 IU/kg per day (1.0 ± 0.2) and with 0.3 IU/kg per day group (1.2 ± 0.4).

Fig. 1. Individual heights of short boys (*left panels*) and girls (*right panels*) born small for gestational age are plotted at the start of the study (○) and after 2 yr (●) together with the annualized height velocities observed over 2 yr (▲). Children received either no GH treatment (*upper panels*) or GH treatment at a dose of 0.2 IU/kg per day *(middle panels)* or 0.3 IU/kg per day (*lower panels*). Reference curves for height and height velocity represent the mean ± 2 SD for chronological age (yr) (18).

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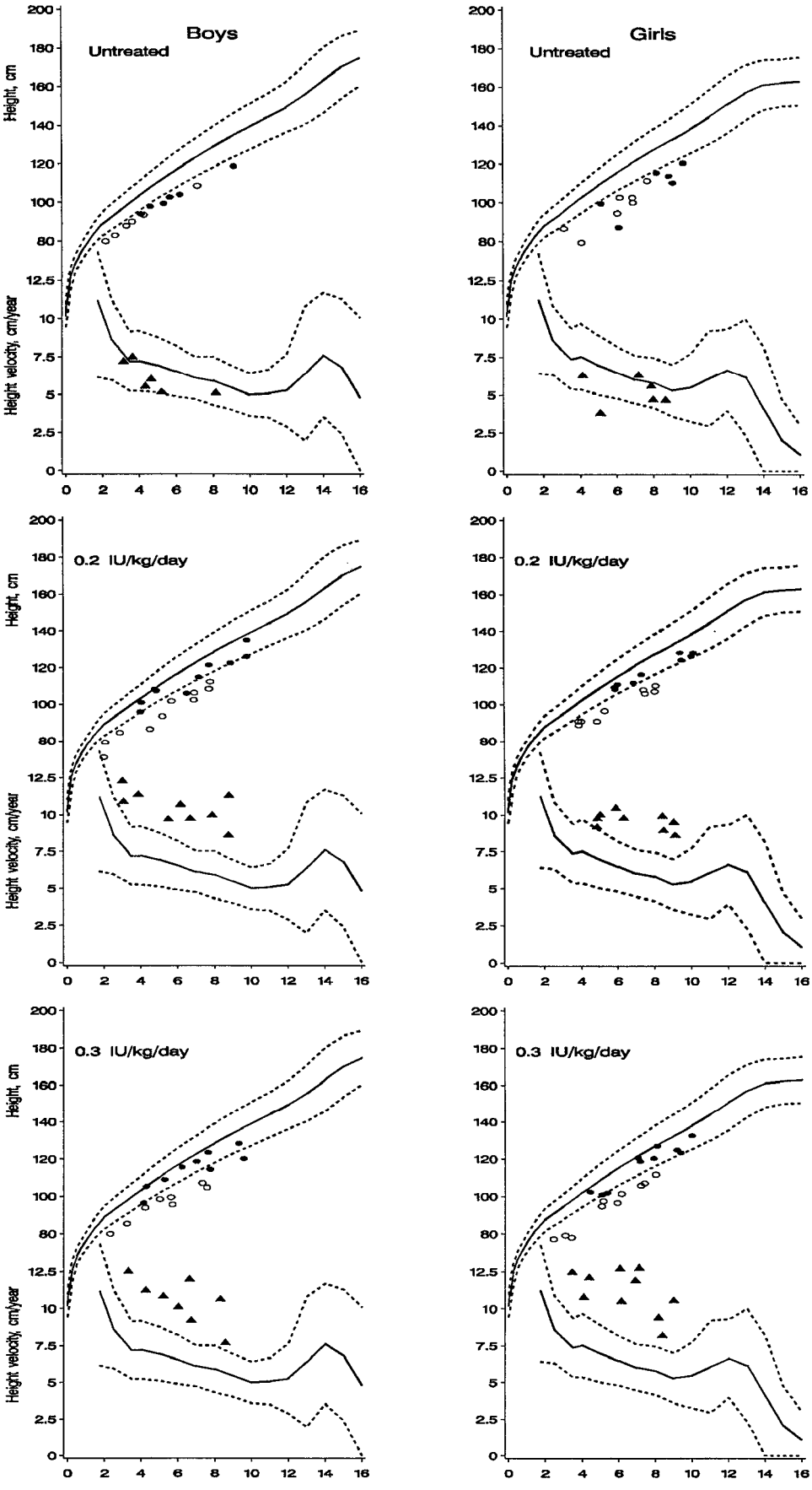

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WEIGHT AND BMI

Weight gain (0–2 yr) averaged 3.6 ± 0.4 kg in untreated children and was twice as high ($P < 0.001$) in treated children, 6.9 ± 0.6 in the 0.2 IU/kg per day group and 7.8 ± 0.5 kg in the 0.3 IU/kg per day group.

The gain in weight SDS (0–2 yr) in the untreated children (0.4 ± 0.1) was lower ($P < 0.001$) than in the 0.2 IU/kg per day group (1.3 ± 0.1), which in turn was lower ($P = 0.01$) than in the 0.3 IU/kg per day group (1.8 ± 0.1).

BMI and BMI SDS remained similar in the three groups after 1 and 2 yr. BMI of the study population was 13.8 ± 0.2 at start and 14.4 ± 0.3 after 2 yr, whereas BMI SDS was, respectively, −1.9 ± 0.2 and −1.3 ± 0.2.

HEMATOLOGY, BIOCHEMISTRY, THYROID AXIS, AND INSULIN

Mean hemoglobin, hematocrit, erythrocyte, leukocyte, and thrombocyte counts, hemoglobin A_{1c} and glucose in peripheral blood, serum total T_4, free T_4, thyrotropin, creatinine, and urea, as well as urinary glucose, protein, and microscopic examination remained within normal limits and similar in untreated and treated children after 1 and 2 yr.

Fasting serum insulin concentrations were twice as high ($P = 0.01$) in treated children compared with untreated children both after 1 yr (20.3 ± 2.2 mU/L *vs.* 10.6 ± 2.4 mU/L) and 2 yr (18.9 ± 3.0 mU/L *vs.* 9.4 ± 1.3 mU/L) with no difference between the two treatment groups. After 2 yr, all hemoglobin A_{1c} values were within normal range.

IGF-I, IGF-II, IGFBP-3, AND OSTEOCALCIN

At the start of the study, serum IGF-I concentrations of the participating children (**Table 1** and **Fig. 2**) were similar to those of short children without GH deficiency and without prenatal growth retardation (21). After 2 weeks of GH treatment, serum IGF-I levels had approximately doubled ($P < 0.001$), being 198 ± 23 μg/L in the 0.2 IU/kg per day group and 256 ± 31 μg/L in the 0.3 IU/kg per day group. After 1 yr, IGF-I concentrations in the untreated children (145 ± 23 μg/L) were lower ($P < 0.01$) than in the 0.2 IU/kg per day group (274 ± 30 μg/L), which were in turn lower ($P < 0.05$) than in the 0.3 IU/kg per day group (392 ± 43 μg/L). After 2 yr, serum IGF-I levels in the 0.3 IU/kg per day group increased further to 655 ± 69 μg/L, being 2-fold higher ($P < 0.0001$) than in the 0.2 IU/kg per day group (332 ± 29 μg/L), which in turn were 2-fold higher ($P < 0.01$) than in the untreated children (168 ± 46 μg/L).

At the start of the study, serum IGFBP-3 levels were normal (**Table 1** and **Fig. 2**) (23). IGFBP-3 concentrations rose markedly ($P < 0.005$) after 2 weeks of GH treatment, from 3.34 ± 0.33 mg/L to 4.62 ± 0.23 mg/L in the 0.2 IU/kg per day group and from 3.36 ± 0.38 mg/L to 5.13 ± 0.37 mg/L in the 0.3 IU/kg per day group. After 1 and 2 yr, serum IGFBP-3 levels in the untreated children (3.88 ± 0.48

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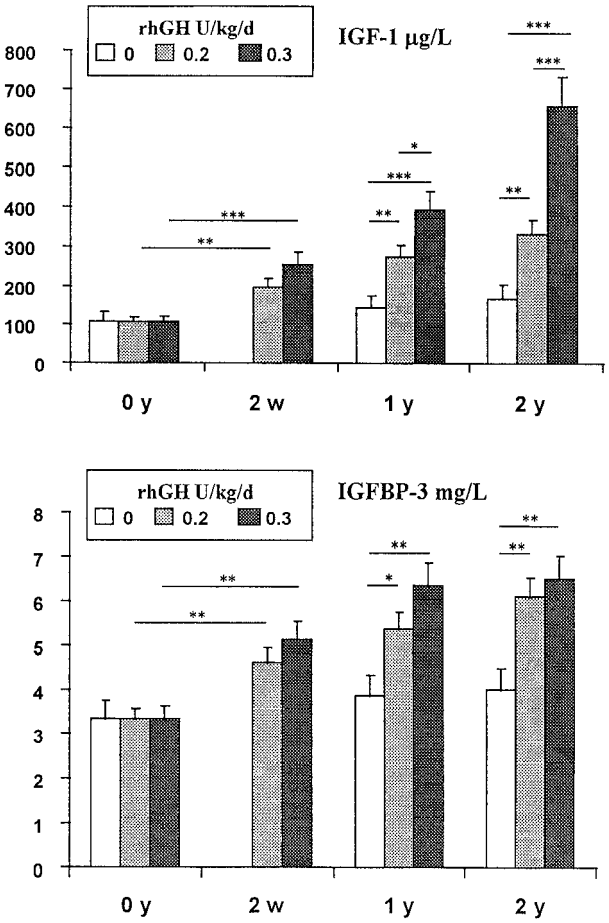
mg/L, respectively, 4.00 ± 0.58 mg/L) were lower ($P < 0.01$) than in the 0.2 IU/kg per day group (5.37 ± 0.42 mg/L, respectively, 6.10 ± 0.35 mg/L) and lower than in the 0.3 IU/kg per day group (6.35 ± 0.49 mg/L, respectively, 6.50 ± 0.52 mg/ L). In contrast to serum IGF-I, the IGFBP-3 concentrations of the two treatment groups were not significantly different after 1 or 2 yr.

Fig. 2. Serum IGF-I and IGFBP-3 concentrations (mean ± SEM) at the start of the study, after 2 weeks, 1 yr, and 2 yr in untreated children and in children receiving GH at a daily sc dose of 0.2 or 0.3 IU/kg. Results at the start of the study and after 2 weeks are compared within treatment groups. Results obtained after 1 yr and 2 yr are compared among untreated and treated groups. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.



At the start of the study, serum IGF-II concentrations of the study population (**Table 1**) were comparable with those of age-matched, normally growing children (21). In contrast to circulating IGF-I and IGFBP-3, the serum concentrations of IGF-II do not appear to be altered by high-dose GH administration over 1 and 2 yr, respectively, as no significant differences were detected between the IGF-II levels of untreated children (756 ± 108 pig/L, respectively, 881 ± 125 µg/L) and those in the 0.2 HJ/kg per day group (745 ± 72 µg/L, respectively, 834 ± 53 µg/L) or in the 0.3 IU/kg per day group (944 ± 101 µg/L, respectively, 966 ± 56 µg/L).

At the start of the study, circulating osteocalcin concentrations were normal (**Table 1**) (22). Osteocalcin levels were unaltered after 2 weeks of GH treatment. After 1 and 2 yr, osteocalcin

concentrations in untreated children (59.9 ±1.9 µg/L, respectively, 72.5 ± 7.3 µg/L) were lower ($P < 0.05$) than in the 0.2 IU/kg per day group (89.4 ± 5.9 µg/L, respectively, 100.0 ± 8.6 µg/L) and in the 0.3 IU/kg per day group (93.6 ± 9.9 gg/, respectively, 102.7 ± 9.8 µg/L), there being no difference between the two treatment groups.

ADVERSE EVENTS

Four adverse events were classified as serious, although conceivably not related to GH administration. One treated child received antibiotics iv for possible osteomyelitis of the distal tibia. Three children were hospitalized in relation to viral diseases: one untreated child with Silver-Russell syndrome for care of varicella skin lesions, one treated child with Silver-Russell syndrome for herpes stomatitis, and one treated child with 4p- syndrome for varicella, complicated by a febrile convulsion. GH administration was not interrupted in the three treated children.

In one child with Dubowitz syndrome, initiation of GH treatment (0.2 IU/kg per day) was followed within weeks by an aggravation of cutaneous eczema, which improved without treatment interruption.

During the first year, a possible increase in size or number of pigmented nevi was reported but not quantified in three treated children (one on 0.2 IU/kg per day and two on 0.3 IU/kg per day); GH treatment was continued; no (further) nevi increases were seen.

Discussion

Daily administration of high-dose GH for 2 yr was found to induce a pronounced catch-up growth in short, prepubertal children born small for gestational age.

A distinct feature of the present study is the randomly assigned, fully parallel, untreated control group. This cohort had short stature with limited weight gain and no significant catch-up growth, but also slow bone age progression, thus maintaining final height prognosis, as judged by the unaltered height SDS for bone age after 2 yr. These control data consolidate the notion that the studied children, if left untreated, are indeed bound to remain exceptionally short, at least throughout childhood (5, 6).

The documented magnitude of the GH-induced catch-up growth is unprecedented in short children born small for gestational age. In comparison with untreated children, growth velocity approximately doubled, as did weight gain, the latter presumably being caused by increments of bone and muscle rather than of adipose tissue (24). The responsiveness to high-dose GH treatment does not appear to be based on preexistent GH deficiency and/or GH resistance because stimulated GH release was normal before study inclusion; serum IGF-I, IGF-II, IGFBP-3, and osteocalcin concentrations were normal at study start; and the latter markers remained normal in the control group throughout the study (21–23). The differences between results obtained with daily GH doses of 0.2 and 0.3 IU/kg were relatively modest (though statistically significant for

several variables), suggesting that near-maximal GH effects are exerted in this dose range. Factors that may have contributed to the observed growth responses in this study, as compared with previous reports, include high frequency and dosage of GH administration, ongoing dose adjustments for weight gain, apparently excellent treatment compliance, and characteristics of the studied population, such as young chronological age, delayed bone age, extremely short stature, low-normal growth velocity and inclusion of some syndromes, and of prematurely born children. Because most treated children had a nearly normalized stature after 2 yr of high-dose GH treatment, interruption of GH administration for 2 yr was done as the next phase of this study.

The catch-up growth induced by GH is associated with a definite acceleration of bone maturation, which was identical for both dose regimens and in line with previous experience (15, 16). However, after 2 yr, both GH doses had led to an increase of height SDS for bone age. It remains to be verified whether this effect will be retained without continuing GH treatment.

GH-induced, prepubertal catch-up growth in this population was accompanied by a rise in circulating insulin, osteocalcin, IGF-I (3- to 6-fold), IGFBP-3 (nearly 2-fold), and IGF-I/IGFBP-3 ratio, in the presence of unaltered concentrations of IGF-II. This constellation is both qualitatively and quantitatively reminiscent of the normal pubertal growth acceleration (21–23). Although high-dose GH treatment may have induced some degree of insulin resistance, no significant alterations in fasting blood glucose or hemoglobin A_{1c} were identified after 2 yr. Serum IGF-I concentrations were differentially increased by the two high GH doses, in contrast to insulin, osteocalcin, and IGFBP-3, which were similarly augmented in this dose range. Interestingly, the most elevated IGF-I values were measured after 2 yr, when the growth response was already waning.

In conclusion, high-dose GH administration over 2 yr is emerging as a potential therapy to increase the short stature that results from insufficient catch-up growth in young children born small for gestational age. However, the long-term impact of this approach remains to be delineated.

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