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Benefits of Long-Term GH Therapy in Prader-Willi Syndrome: A 4-Year Study

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Obesity, poor growth, and hypotonia in children with Prader-Willi syndrome (PWS) are accompanied by abnormal body composition resembling a GH-deficient state. Hypothalamic dysfunction in PWS includes decreased GH secretion, suggesting a possible therapeutic role for GH treatment. While short-term benefits of treatment with GH have been shown, whether these beneficial effects are dose dependent and persist or wane with prolonged therapy remains uncertain. Effects of 24 additional months of GH treatment at varying doses (0.3, 1.0, and 1.5 mg/m^2·d) on growth, body composition, strength and agility, pulmonary function, resting energy expenditure (REE), and fat utilization were assessed in 46 children with PWS, who had previously been treated with GH therapy (1 mg/m^2·d) for 12–24 months. Percent body fat, lean muscle mass, and bone mineral density (BMD) were measured by dual x-ray absorptiometry. Indirect calorimetry was used to determine REE and to calculate respiratory quotient. A modified Bruininks-Oseretski test of physical performance evaluated strength and agility. During months 24–48 of GH therapy, continued beneficial effects on body composition (decrease in fat mass and increase in lean body mass), growth velocity, and REE occurred with GH therapy doses of 1.0 and 1.5 mg/m^2·d ($P < 0.05$), but not with 0.3 mg/m^2·d. BMD continued to improve at all doses of GH ($P < 0.05$). Prior improvements in strength and agility that occurred during the initial 24 months were sustained but did not improve further during the additional 24 months regardless of dose. Salutary and sustained GH-induced changes in growth, body composition, BMD, and physical function in children with PWS can be achieved with daily administration of GH doses ≥1 mg/m^2. Lower doses of GH, (0.3 mg/m^2·d) effective in improving body composition in GHD adults, do not appear to be effective in children with PWS at sustaining improvement in body composition. (*J Clin Endocrinol Metab* 87: 1581–1585, 2002)

PRADER-WILLI SYNDROME (PWS), first described in 1956, is caused by either a deletion of the paternal allele in position 15q11–13 (~70% of patients) or, because the critical region of chromosome 15 is active only in the paternally inherited chromosome, maternal disomy affecting the same region or the whole of chromosome 15. (1) Affected children are characterized by obesity, hypotonia, short stature, hypogonadism, and behavioral abnormalities (2). With an incidence of 1 in every 10,000–12,000 births, PWS is the most common syndromal cause of marked obesity (3).

Many features of PWS suggest hypothalamic dysfunction, including: hyperphagia, sleep disorders, deficient GH secretion, and hypogonadism. (4–6) Recent studies have shown that GH therapy with doses of GH typically used for childhood growth (*e.g.* 1 mg/m^2·d) improves growth, body composition, physical strength and agility, as well as fat utilization. However, these measurements remain far from normal after up to 2 yr of GH therapy.

Patients and Methods

Forty-six children with genetically confirmed PWS previously treated for 12–24 months with GH therapy (1 mg/m^2·d) (7) were recruited for an additional 24 months of treatment after informed consent was obtained from parents or guardians. These children were previously part of a study (6, 7) of 54 children who received GH in a controlled randomized study for 24 months. All of these prior patients were invited to continue in this study, and 46 agreed. We know of no bias in recruitment from the original study group. The study was approved by the Human Subjects Committee of both participating institutions. In all subjects, the diagnosis of PWS was confirmed by high resolution cytogenetics, fluorescent *in situ* hybridization, and/or methylation studies. Thirty-three children had a deletion of chromosome 15q11–13, 12 children demonstrated maternal disomy, and one had an imprinting mutation. The age range of these patients was 6–17 yr with a mean of 11.9 yr. Forty-eight percent of subjects were female. During the course of this study, 5 girls developed tanner stage 2 breast development, and 5 boys had testicular development of >6cc, however, physical signs of adrenarche were present in many subjects.

After having received GH at 1 mg/m^2·d for up to 24 months, subjects were randomized to one of three dosing regimens: 0.3 mg/m^2·d (0.063 mg/kg·wk), 1 mg/m^2·d (0.2 mg/kg·wk), or 1.5 mg/m^2·d (0.3 mg/kg·wk) of GH (Nutropin, Genentech, Inc., South San Francisco, CA) for 24 additional months (Fig. 1). Height was measured on a Harpenden stadiometer at 6-month intervals. Anthropometric measurements (head, face, body proportions, hands, and feet) using calipers or tape measures and compared with normative data available for age and gender, as well as bone age were determined annually according to the method of Greulich and Pyle, and spine films screening for scoliosis were obtained at baseline and, if indicated, at 6-month intervals. Total and regional percent body fat, lean body mass, and bone mineral density (BMD) were measured by dual-energy x-ray absorptiometry (Lunar Corp., Madison, WI). Resting energy expenditure (REE) and respiratory quotient (RQ) were determined by indirect calorimetry (Medgraphics, Minneapolis, MN) in a subset of subjects (n = 26) after a fast of at least 12 h. To account for differences in body habitus of children with PWS, normative data for energy expenditure were derived from Fleisch (in kilocalories per square meter per hour based on body surface area) rather than from formulas based on age and gender alone.

Stimulated GH levels had been measured after administration of oral clonidine (0.15 mg/m^2) before GH therapy. Fasting levels of IGF-I, osteocalcin, type 1 procollagen, cholesterol (total, HDL, and LDL), free fatty acids, free thyroxine by equilibrium dialysis, and thyroid stimulating hormone levels, as well as fasting and 2-h post-

Abbreviations: BMD, Bone mineral density; LBM, lean body mass; PWS, Prader-Willi syndrome; REE, resting energy expenditure; RQ, respiratory quotient.

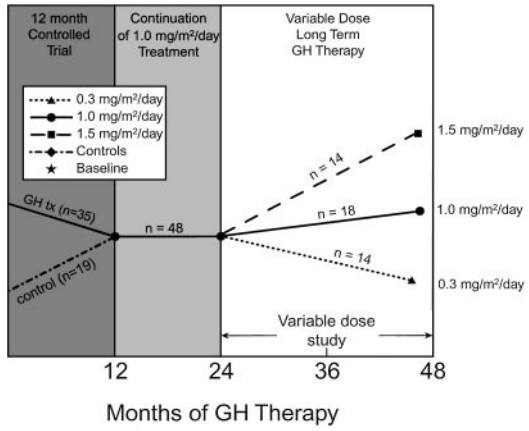

FIG. 1. Protocol for 4-yr study showing number of patients during each phase of the study. This current study representing 24–48 months of therapy is labeled "variable dose of long-term GH treatment."

glucose challenge (1.75 g/kg) glucose and insulin levels were measured at 0, 12, 24, 36, and 48 months (Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA).

Physical strength and agility was tested by a physiotherapist, blinded to treatment status using a modified Bruininks-Oseretsky test (8), in which children were timed as they ran to a block, picked up the block, and returned, assessed lower extremity strength during a dynamic task (standing broad jump), trunk strength (sit-ups), and upper extremity strength (number of repetitions of elbow flexion with dumbbell weights).

It was recommended that the subjects' caloric intake prescribed by their primary care provider be maintained throughout the study, and 3-d diet histories were recorded and analyzed using Computrition software. Parents also completed a sleep questionnaire soliciting symptoms of sleep apnea, the Children Behavior Checklist, and a 7-d exercise record every 6 months. Data were analyzed using a *t* test for paired samples or two related samples. Statistical software used was SAS version 6.12 (SAS Institute, Cary, NC).

Results

Patient characteristics and study results are summarized in Tables 1 and 2, Figs. 1–4, and presented as mean ± SD.

Growth and GH axis

Stimulated peak GH levels before GH therapy were <10 μg/liter in all 46 subjects (mean = 1.9 ± 2.1 μg/liter). At the time of dosage randomization, after 12–24 months of GH treatment at 1 mg/m²·d, children demonstrated a mean height SDS for age of −0.5 ± 1.4 (Table 1) with a mean growth velocity of 7.6 ± 2.5 cm/year (growth velocity SDS = 2.9 ± 2.3). The mean IGF-I level was 408 ± 121 kU/liter.

Growth rates varied significantly according to GH dosage [0.3 mg/m²·d group mean 4.4 ± 2.2 cm/yr, 1.0 mg/m²·d group mean 4.4 ± 2.3 cm/yr, and 1.5 mg/m²·d mean 5.9 ± 3.1 cm/year ($P < 0.05$ for high dose)]. Growth rates between 24–36 and 36–48 months were as follows: in the high-dose group 6.1 cm/yr and 5.8 cm/yr, for the standard dose group 5.2 cm/yr and 4.4 cm/yr, and for the low dose group 4.2 cm/yr and 4.4 cm/yr. Bone age progressed a mean of 2.0 ± 0.3 yr in all groups over the 2-yr period. Mean IGF-I varied significantly between each group [0.3 mg/m²·d mean 368 ± 56 kU/liter, 1.0 mg/m²·d mean 555 ± 51 kU/liter, and 1.5 mg/m²·d mean 636 ± 56 kU/liter, corresponding to −0.2 SDS, 0.7 SDS, and 1.1 SDS for each dose ($P < 0.05$ between groups)].

TABLE 1. Patient characteristics and growth data (n = 46)

Gender (% female)	48%
Age (mean)	12.0 yr
Peak GH (μg/liter)	1.9 ± 2.1
Height SD score	−0.5 ± 1.4
% body fat	40.3 ± 10
LBM (kg)	28.7 ± 6.7
Mean weight (kg)	45.1 ± 12.1
Weight SD score	0.7 ± 1.6
Bone age	11.4 ± 2.1
Scoliosis (°)	14.7 ± 11

Body composition

Mean percent body fat before any GH therapy was 46.3 ± 8.4%, and before randomization for variable GH dose was 40.3 ± 10.0% (following 12–24 months of prior GH therapy). Further GH-induced changes in body fat varied significantly with GH dose. After 24 months, mean % body fat was 49 ± 5.0% in subjects treated with 0.3 mg/m²·d GH, 43.1 ± 8.6% in subjects treated with 1.0 mg/m²·d, and 39.1 ± 10.2% in subjects treated with 1.5 mg/m²·d ($P < 0.001$ between all groups; Fig. 2). Changes in lean body mass (LBM) were also dose dependent. Before variable dose GH therapy, all patients demonstrated a mean LBM of 28.9 ±6.7kg. LBM was unchanged in the 0.3 mg/m²·d group (mean 30.1 ± 7.2 kg), but increased significantly in both the 1.0 mg/m²·d group (mean 35.1 ± 7.1 kg) and 1.5 mg/m2·d group (mean 34.9 ± 6.9 kg; $P < 0.001$ compared with baseline and to 0.3 mg/m²·d group; Fig. 3).

BMD

BMD increased with prolonged GH therapy regardless of dosage administered. Before various GH dose therapy, all patients demonstrated a mean total body BMD of 0.94 ± 0.09 g/cm². Mean BMD increased following 24 months of either 0.3 mg/m²·d or 1.0 mg/m²·d to 1.03 ± 0.09 g/cm², and treatment with 1.5 mg/m²·d to 1.02 ± 0.11 g/cm² ($P < 0.01$ from the start of variable dosage study period, but P = NS when comparing response to different dosages). Osteocalcin levels did not demonstrate a dose effect, measuring 9.5 ± 4.3 nmol/liter, 11.2 ± 5.9 nmol/liter, and 11.7 ± 5.7 nmol/liter (68 ± 28, 73 ± 39, and 76 ± 35 ng/ml, between low, standard, and high dose, respectively (P = NS). Procollagen levels also did not demonstrate a dose effect, measuring 288 ± 79, 317 ± 150 and 403 ± 205 μg/liter between low, standard, and high dose, respectively (P = NS).

Energy expenditure

Changes in REE following prolonged GH therapy varied according to GH dosage. Before any GH therapy mean REE was 22.5 ± 4.2 kcal m²/h, before randomization to variable dose GH mean REE was 29.0 ± 6.2 kcal m²/h. After 48 months, mean REE was 30.3 ± 5.1 kcal/m²·h in those treated with 0.3 mg/m²·d ($P = 0.058$), 32.9 ± 6.7 kcal/m²·h in those treated with 1.0 mg/m²·d ($P = 0.051$), and 35.3 ± 5.9 kcal/m²·h in those receiving 1.5 mg/m²·d ($P < 0.01$). Before dosage

TABLE 2. Metabolic effects of long-term GH therapy in PWS

	1.5 mg/m²·d	1.0 mg/m²·d	0.3 mg/m²·d
Δ Cholesterol	−0.6 ± 0.3 mmol/liter[a]	−0.5 ± 0.2 mmol/liter[a]	−0.15 ± 0.2 mmol/liter
Δ LDL	−0.6 ± 0.2 mmol/liter[a]	−0.75 ± 0.2 mmol/liter[a]	−0.2 ± 0.3 mmol/liter
Δ HDL	0.2 ± 0.1 mmol/liter[a]	0.26 ± 0.1 mmol/liter[a]	0.1 ± 0.1 mmol/liter
Δ REE	742 ± 81 kcal·d[a]	519 ± 95 kcal·d[a]	551 ± 101 kcal·d
Δ Fasting insulin	49 ± 29 pmol/liter	39 ± 21 pmol/liter	14 ± 14 pmol/liter
Δ 2-h glucose	0.16 ± 0.3 mmol/liter	0.3 ± 0.3 mmol/liter	0.5 ± 0.4 mmol/liter
Δ RQ	−0.03 ± 0.02	−0.03 ± 0.05	−0.02 ± 0.03

[a] $P < 0.05$ compared with baseline; all others, P = NS.

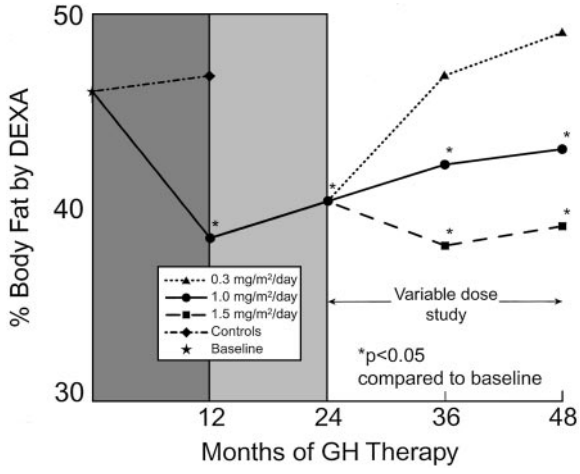

FIG. 2. Change in percent body fat by DEXA during long term GH therapy. *Solid circles* represent mean body fat of children on 1 mg/m²·d (during months 24–48), *solid triangles* represent mean body fat of PWS children treated with 0.3 mg/m²·d, and *solid squares* represents mean % body fat of PWS children treated with 1.5 mg/m²·d.

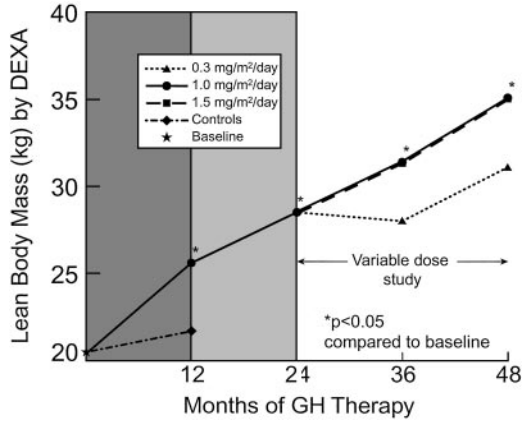

FIG. 3. Change in lean body mass determined by DEXA during long-term GH therapy. *Solid circles* represent mean body fat of children on 1 mg/m²·d (during months 24–48), *solid triangles* represent mean body fat of PWS children treated with 0.3 mg/m²·d, and *solid squares* represents mean % body fat of PWS children treated with 1.5 mg/m²·d.

randomization, RQ determination was 0.79 ± 0.06 at baseline, 0.81 ± 0.05 with low dose, 0.79 ± 0.04 with standard, and 0.79 ± 0.06 with high dose, indicating continued utilization of fat for energy for standard and high dose of GH (Fig. 4).

Muscle strength and agility

In contrast to significant improvements observed during the initial 24 months of GH therapy (7), strength, and agility, neither improved nor regressed during an additional 24 months of GH therapy at any dose.

Carbohydrate and lipid metabolism

At the start of this study (following 12–24 months of prior GH therapy), 9% of subjects had 2-h glucose levels between 130–144 mg/dl. Two-hour glucose tolerance testing and insulin levels at 48 months were not significantly different at any GH dose compared with 24 month data. Levels of total cholesterol, LDL-C, and HDL-C are shown in Table 2. A trend ($P = 0.06$) in GH dose-dependent effects on total cholesterol levels was observed: 0.3 mg/m²·d group mean 5.22 ± 1.3 mmol/liter (202 ± 53 mg/dl), 1.0 mg/m²·d group mean 4.37 ± 0.9 mmol/liter (169 ± 35 mg/dl), and 1.5 mg/m²d group mean 4.03± 1.2 mmol/liter (156 ± 47 mg/dl).

Nutrition

To avoid possible confounders, no dietary restrictions were imposed as part of this study. Families, however, did complete a 3-d sample diet record at each study visit. The data from 24–48 months of GH therapy was examined to determine the relative impact of diet *vs.* GH dose. Dietary intake was standardized by calculating the average calorie per centimeter. The average caloric intake did not differ significantly among the three groups. Both ANOVA and linear regression models indicated a significant ($P = 0.06$) effect for dose.

Scoliosis

Seventy percent of subjects had mild to moderate (5–20 degrees) thoracolumbar scoliosis on spine films before any GH therapy. There was no significant difference in scoliosis progression between the treated and control groups during the first year, no significant progression in spine curve measurements during the subsequent 3 yr of GH therapy, and no difference in scoliosis progression noted in different GH dosage groups.

Other effects

Two subjects had headaches felt to be consistent with pseudotumor cerebri within 3 wk of institution of GH treatment with resolution after temporary cessation and gradual reinstitution of therapy. Three patients were treated with thyroid replacement for mild central hypothyroidism. In all 3 patients, slightly low free T_4 was noted with a nonelevated TSH. All patients had thyroid testing at the time of GH stimulation, and all patients were euthyroid before the start

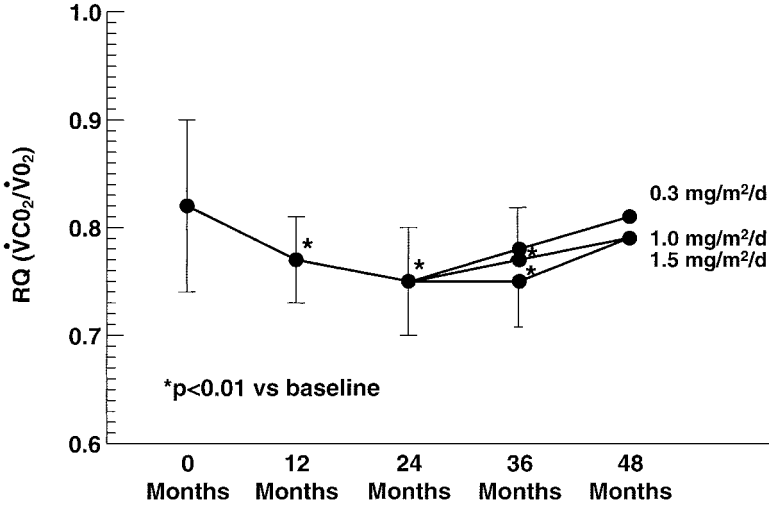

FIG. 4. Change in RQ (VCO_2/VO_2) during long-term GH therapy treatment. During months 24–48 the mean response to various dose GH is shown.

of this study (on thyroid replacement, with blood level confirmation).

Discussion

Diminished GH secretion is a frequent finding in children with PWS (5, 6, 9–11). That this reduction in GH represents true GH deficiency rather than suppression by obesity is supported by several observations (12, 13). In contrast to normal or accelerated growth typically seen in healthy non-PWS obese children, children with PWS usually show diminished growth by 5–8 yr of age. IGF-I levels in children with PWS are in the low or low-normal range, unlike patients with overnutrition who demonstrate high-normal IGF-I levels (14, 15). Perhaps most significantly, body composition of PWS children strongly resembles that seen in states of severe GH deficiency (reduced LBM, increased fat mass), in contrast to nutritionally obese subjects (increased LBM and fat mass) (16). These findings, combined with accompanying hypothalamic disturbances characteristic of the syndrome, strongly support the presence of GHD as a feature of PWS, and suggest that some manifestations of the PWS phenotype could be improved by exogenous GH therapy (12). Results of 1-yr (controlled trial) 2 yr, or longer of GH therapy in PWS patients have been previously published by our group and others (6, 7, 17–21). Specifically, 12–24 months of GH therapy in these children decreases fat mass, increases lean body mass, increases linear growth, and in one study, increased fat utilization (6). Documented changes in physical function (strength and agility testing) in PWS children treated with GH (6), which translated to acquisition of new gross motor skills, appeared to be important "real-life" benefits for these children. While these findings suggested that GH therapy may potentially lessen some disabilities associated with PWS, determining the long-term value of this intervention required demonstration of sustained benefits during more prolonged therapy.

During months 24–48 of GH therapy, further changes in body composition (lack of increase in fat mass and increase in lean body mass), growth velocity, and REE occurred with administration of either 1 mg/m^2·d or 1.5 mg/m^2·d of GH, but not with 0.3 mg/m^2·d. Prior improvements in BMD, and strength and agility that occurred during an initial 24 months, were sustained during these additional 24 months (48 months total) regardless of dose. The rate of change in body composition slowed but did not regress during more prolonged GH therapy at doses ≥1.0 mg/m2·d. It is important to note that changes in BMD and body composition occur with normal growth and advancing age. Nevertheless, changes in these PWS children exceed those reported over a 24-month period in healthy non-PWS late-childhood subjects based on reference data for BMD and fat-free mass (22, 23). In contrast, 24 months of GH therapy at a lower dose (sufficient to alter body composition in adult GHD patients) resulted in regression toward body fat percentages observed before GH therapy.

Response of children with PWS to GH is greatest during the first 12 months with regard to growth rate, decreases in body fat, increases in REE, improvements in physical function, and laboratory alterations in carbohydrate and lipid metabolism. Thus, a diminution in response to GH during prolonged GH therapy, observed in virtually all growth studies of GH therapy, applies to other GH metabolic effects in children with PWS. Further, in spite of these encouraging results, these data indicate that GH therapy given at doses up to 1.5 mg/m^2·d is not capable of normalizing body composition in PWS. This could reflect the influence of non-GH factors regulating body composition affected by the genetic mutation causing PWS and/or the relatively late institution of GH therapy following a critical period of abnormal adipose and muscle development in infancy. Studies underway of earlier institution of GH therapy will address these possibilities.

Conclusion

Children with PWS demonstrate profoundly abnormal body composition, with a similar phenotype as is seen in classic GHD. Administration of GH to GHD children not only restores linear growth but also promotes growth of LBM, decreases fat mass by increasing fat oxidation and total body energy expenditure, increases BMD following an initial period of increased bone resorption, and improves cardiovascular risk factors. This report provides evidence that sal-

utary GH-induced changes in growth, body composition, and physical function in children with PWS can be sustained for an extended duration (up to 48 months). These changes, however, require GH doses of $\geq 1.0\ mg/m^2 \cdot d$; *i.e.* lower doses of GH, effective in improving body composition in GHD adults, do not appear to be effective in children with PWS. Conversely, BMD increased during additional 24 months of therapy regardless of GH dose. While these longer-term results of GH treatment in PWS children are encouraging, a cautious interpretation is still appropriate. Body composition and physical function, while improved, remained significantly abnormal after 4 yr of GH therapy. The fact that percent body fat in PWS children exceeds that observed in patients with severe GHD also makes it likely that factors other than deficiency of GH contribute to the accumulation of this extraordinary fat mass. Nevertheless, this study showed a significant improvement of body composition and physical function in children with PWS receiving long-term GH therapy of sufficient dose. While GH therapy is currently approved for *growth failure* secondary to PWS, these other benefits alone may justify a trial of GH therapy.

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