

Randomized Controlled Trial to Investigate the Effects of Growth Hormone Treatment on Scoliosis in Children with Prader-Willi Syndrome

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Context: The prevalence of scoliosis in children with Prader-Willi syndrome (PWS) is 30–80%, depending on age. Although reports about effects of GH treatment on scoliosis in children with PWS are limited, scoliosis is generally considered a contraindication for GH treatment.

Objective: The aim was to study the effects of GH treatment on the onset of scoliosis and curve progression in children with PWS.

Design: We conducted a multicenter, randomized, controlled GH study in infants and prepubertal and pubertal children. Infants and prepubertal children were randomized into a GH-treated group (1.0 mg/m² · d) and a control group for 1 and 2 yr, respectively. Pubertal children were randomized to receive somatotropin 1.0 or 1.5 mg/m² · d. Yearly, x-rays of the spine were taken, and height, weight, truncal lean body mass (with dual energy x-ray absorptiometry), and IGF-I were measured.

Patients: A total of 91 children with PWS (median age, 4.7 yr; interquartile range, 2.1–7.4) participated in the study.

Main Outcome Measures: We measured the onset of scoliosis (Cobb >10°) and scoliotic curve progression.

Results: GH-treated children had similar onset of scoliosis and curve progression as randomized controls ($P = 0.27$ – 0.79 and $P = 0.18$ – 0.98 , respectively). GH treatment, IGF-I SD score (SDS), and catch-up growth had no adverse effect on the onset of scoliosis or curve progression, even after adjustment for confounders. Height SDS, truncal lean body mass, and IGF-I SDS were significantly higher in GH-treated children than in randomized controls. At baseline, a higher IGF-I SDS was associated with a lower severity of scoliosis.

Conclusions: Scoliosis should no longer be considered a contraindication for GH treatment in children with PWS. (*J Clin Endocrinol Metab* 94: 1274–1280, 2009)

Prader-Willi syndrome (PWS) is characterized by hypotonia, short stature, hyperphagia with obesity, hypogonadism, and psychological and behavioral problems (1–7). PWS results from lack of expression of the paternally derived chromosome

15q11-q13 caused by deletion, uniparental disomy, imprinting center defect, or balanced translocation (1, 8). Hypothalamic dysfunction may be responsible for many features of PWS (9–11).

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Abbreviations: BMI, Body mass index; BSA, body surface area; CI, confidence interval; iqr, interquartile range; IS, idiopathic scoliosis; LCS, long C-curve type scoliosis; OR, odds ratio(s); PWS, Prader-Willi syndrome; SDS, SD score; trunkLBM, truncal lean body mass.

Spinal deformity is a major concern for patients with PWS. Scoliosis is defined as a spinal curve with a Cobb angle of more than 10° on a standing posteroanterior radiograph. The Cobb angle is the angle between the two steepest vertebrae, *i.e.* the upper border of the upper vertebra in the curve and the lower border of the lower vertebra (12). The prevalence of scoliosis in PWS is high [30% before 10 yr of age, 80% after age 10 yr (13–15) *vs.* 2.7% in the general Dutch adolescent population (16)]. Children with PWS show two types of scoliosis (Fig. 1): long C-curve type scoliosis (LCS), often seen in children with neuromuscular disorders causing hypotonia; and scoliosis resembling idiopathic scoliosis (IS). Younger children mainly show LCS, associated with a low ratio of trunkLBM to body surface area (BSA), which is a proxy for hypotonia. Older children mainly show IS (13).

GH treatment is beneficial for children with PWS because it improves body composition (increase in lean body mass, decrease in fat percentage) and psychomotor development (17–23). In a previous report by our group, the effects of GH treatment on height and body composition of children with PWS have been described in detail (23). Accelerated growth, either spontaneous or during GH treatment, has been associated with the onset of scoliosis and scoliotic curve progression (24–29). Because scoliosis is often considered a contraindication for GH treatment in children with PWS, the need for controlled data about the effect of GH treatment on scoliosis was emphasized (30–32). We therefore performed a large randomized controlled trial. We hypothesized that GH treatment would not affect scoliosis because it also increases trunkLBM, which may counteract the adverse effects of accelerated growth on scoliosis. The primary aim of our study was to investigate the effects of GH treatment on the onset of scoliosis. The secondary aim was to study the effects of GH treatment on scoliotic curve progression. Because age and gender

are known to affect the onset of scoliosis, whereas age, gender, and severity of scoliosis affect curve progression, we adjusted for these factors in our analyses.

Subjects and Methods

Subjects

Between April 2002 and January 2008, 104 children were enrolled in a large randomized controlled trial investigating the effects of GH treatment in children with PWS (Table 1), after fulfilling the following inclusion criteria: genetically confirmed diagnosis of PWS by positive methylation test and age between 6 months and 16 yr. The participants were divided into three groups: infants, prepubertal children, and pubertal children. The infant group consisted of children aged 6 months to 3.5 yr. The prepubertal group consisted of girls aged 3.5 to 12 yr with Tanner breast stage less than 2 (33) and boys aged 3.5 to 14 yr with Tanner genital stage less than 2 and a testicular volume below 4 ml. The pubertal group consisted of girls aged 12 to 16 yr and boys aged 14 to 16 yr with spontaneous or induced puberty. Caloric intake and activity level of all participants were standardized. All children were naive to GH treatment at the start of the study. Children visited the Erasmus University Medical Center/Sophia Children's Hospital in Rotterdam, The Netherlands, and the study protocol was approved by the Medical Ethics Committee. Written informed consent was obtained from parents and children over 12 yr of age. Assent was obtained for children between 4 and 12 yr of age.

Design

The primary objective of our study was to investigate the effects of GH treatment on the onset of scoliosis. The secondary objective was to study the effects of GH treatment on progression of scoliosis. Infants and prepubertal children were randomized into a GH-treated group (1.0 mg/m² · d) and a control group for 1 and 2 yr, respectively. Pubertal children were randomly assigned to receive somatropin 1.0 or 1.5 mg/m² · d (Genotropin; Pfizer, New York, NY) for a follow-up period of 2 yr. During the first 4 wk of treatment, children received 0.5 mg/m² · d to prevent fluid retention. In January 2008, 38 infants (<3.5 yr) had completed the 1-yr follow-up, and 44 prepubertal and nine pubertal children had completed the 2-yr follow-up. Thus, 91 children were eligible for analysis (Table 1).

Radiographics

At the start and subsequently each year, standardized posteroanterior x-rays were taken. In young and/or hypotonic children who were not able to sit or stand, posteroanterior x-rays were taken in the supine position. All x-rays were taken in one center (Erasmus University Medical Center Rotterdam/Sophia Children's Hospital). Cobb angles were measured independently by two observers (R.F.A.d.L.v.W. and L.W.L.d.K.), as previously reported, with minimal intra- and interobserver variance (intra-class correlation coefficient = 0.998 and 0.97, respectively) (13). The orthopedic surgeon was fully blinded to the assigned treatment. If the independent measurements of Cobb angles differed between the two observers, the mean of the Cobb angles was used for analysis. Onset of scoliosis was defined as the presence of a Cobb angle of 10° or higher at 12 or 24 months of study in those without scoliosis at baseline (outcome: yes/no). Progression of scoliosis was evaluated as the change in Cobb angle over time in those with scoliosis at baseline and in those that developed scoliosis during study. Because treatment of scoliosis (bracing and surgery) prevents further curve progression, the effects of GH treatment on curve progression were only investigated in children with untreated scoliosis. For baseline characteristics of the total study population (Table 1), the Cobb angle of the scoliotic curve of children treated with a brace was set at 35° , and the Cobb angle of those surgically treated at 55° . None of the children needed to start treatment of scoliosis during the study.

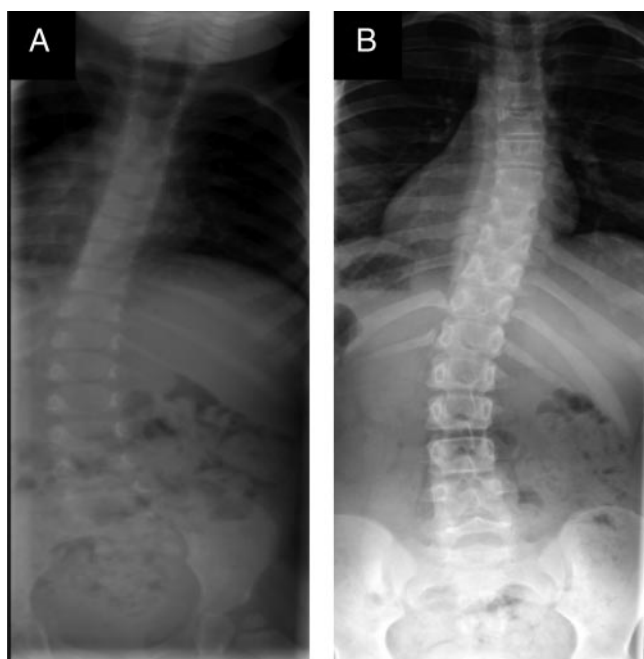


FIG. 1. Examples of LCS (A) and IS (B). Younger children mainly showed LCS, whereas pubertal children only showed IS.

TABLE 1. Baseline data

	Infants			Prepubertal			Pubertal		
	Total	GH-treated	Controls	GH-treated	Controls	GH-treated	GH-treated	GH-treated	GH-treated
No. of subjects (M/F)	91 (49/42)	19 (11/8)	19 (14/5)	23 (13/10)	21 (8/13)	6 (3/3)	6 (3/3)	3 (0/3)	3 (0/3)
Age (yr)	4.7 (2.1 to 7.4)	2.0 (1.6 to 3.1)	1.5 (1.1 to 3.0)	6.8 (5.6 to 9.7)	6.0 (4.6 to 7.5)	13.4 (11.8 to 15.9)	13.4 (11.8 to 15.9)	13.9 (12.0 to 14.8)	13.9 (12.0 to 14.8)
Height SDS	-2.2 (-3.1 to -1.3)	-2.5 (-2.8 to -0.6)	-2.0 (-3.2 to -0.9)	-1.9 (-2.8 to -0.9)	-2.6 (-3.3 to -1.9)	-3.7 (-4.0 to -2.9)	-3.7 (-4.0 to -2.9)	-2.4 (-4.8 to -1.8)	-2.4 (-4.8 to -1.8)
BMI SDS	1.1 (-0.6 to 1.9)	-0.7 (-1.1 to 1.5)	-0.8 (-1.7 to 1.7)	1.2 (0.2 to 2.6)	1.2 (1.1 to 1.7)	1.2 (-0.1 to 2.1)	1.2 (-0.1 to 2.1)	1.6 (-0.6 to 1.7)	1.6 (-0.6 to 1.7)
TrunkLBM:BSA	7.6 (7.2 to 8.1)	7.4 (6.9 to 8.0)	7.3 (7.0 to 7.7)	8.0 (7.5 to 8.4)	7.6 (7.1 to 8.1)	8.7 (8.1 to 8.9)	8.7 (8.1 to 8.9)	8.1 (7.5 to 8.4)	8.1 (7.5 to 8.4)
IGF-I SDS	-2.1 (-3.1 to -1.4)	-2.5 (-3.9 to -1.4)	-2.6 (-5.7 to -0.7)	-1.7 (-2.3 to -1.2)	-1.9 (-2.6 to -1.2)	-3.0 (-4.9 to -2.5)	-3.0 (-4.9 to -2.5)	-2.1 (-3.3 to -2.0)	-2.1 (-3.3 to -2.0)
Scoliosis (%)	33 (36)	7 (37)	4 (21)	7 (30)	9 (43)	4 (67)	4 (67)	2 (67)	2 (67)
LCS-type (%)	13 (37)	3 (43)	3 (75)	2 (25)	5 (50)	0 (0)	0 (0)	0 (0)	0 (0)
IS-type (%)	22 (63)	4 (57)	1 (25)	6 (75)	5 (50)	4 (100)	4 (100)	2 (100)	2 (100)
Treated for scoliosis (%)	12 (13)	1 (5)	1 (5)	3 (13)	2 (10)	4 (100)	4 (100)	1 (33)	1 (33)
Cobb angle (°)	19.0 (13.3 to 36.0)	15.5 (14.0 to 25.5)	18.5 (13.8 to 46.1)	14.5 (12.0 to 55.0)	16.0 (12.8 to 20.5)	36.0 (35.0 to 50.5)	36.0 (35.0 to 50.5)	21.3 (13.0 to 29.5)	21.3 (13.0 to 29.5)

Overview of study population. Data represent number (percentage) or median (iqr). TrunkLBM:BSA, ratio of trunkLBM divided by body surface area (kg/m²); scoliosis (LCS/IS), total number of children with scoliosis and the number of children divided by type of scoliosis; treated for scoliosis, total number of children treated for scoliosis and the percentage of children with treated scoliosis within the total group of children. At baseline, there were no significant differences between GH-treated children and randomized controls. M, Males; F, females.

Anthropometrics

Standing height was measured with a Harpenden Stadiometer and supine length with a Harpenden Infantometer (Holtain Ltd., Crosswell, UK). Weight was assessed on an accurate scale. Height and body mass index (BMI) SD scores (SDS) were calculated, adjusted for sex and age according to Dutch references (34, 35). Height SDS, BMI SDS, and BSA were calculated with Growth Analyser 3.0 (available at www.growthanalyser.org). Growth was calculated as the increase in height SDS per year (Δ heightSDS) or the increase in centimeters per year (Δ height).

Severe scoliosis interferes with height and therefore also with Δ heightSDS. Lean body mass is known to be highly correlated with height (23, 36, 37). In our study, these two parameters also showed a strong correlation ($\rho = 0.82, P < 0.0001$; and $\rho = 0.67, P < 0.0001$ at 12 and 24 months, respectively). To analyze the effect of Δ height on the onset of scoliosis and curve progression, we therefore also used the change in trunkLBM (Δ trunkLBM) as a proxy for Δ height.

Dual energy x-ray absorptiometry

Dual energy x-ray absorptiometry (type Lunar Prodigy; GE Healthcare, Chalfont St. Giles, UK) was performed to measure the trunkLBM, defined as the total amount of lean body mass in the chest, abdomen, and pelvis. Reference values of trunkLBM in very young children were not available. To analyze the effects of GH treatment on relative muscle mass, we used a ratio of trunkLBM vs. BSA (trunkLBM:BSA ratio), as previously described (13).

Assay

Serum IGF-I levels were measured using an immunometric technique on an Advantage Automatic Chemiluminescence System (Nichols Institute Diagnostics, San Juan Capistrano, CA).

The intraassay coefficient of variation was 4%, and the interassay coefficient of variation was 6%. Because of age and sex dependency, IGF-I levels were transformed into SDS (38).

Data analysis

Data were analyzed for all children together as well as for different age categories. Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS 15.0; SPSS Inc., Chicago, IL). Data are presented as median and interquartile range (iqr). A change in Cobb angle of 5° or more was considered clinically relevant. Power calculation estimated a total number of 40 patients (comprising infants and prepubertal children) to yield a power of 0.80, in line with the international convention: assuming a clinically relevant difference between GH-treated children and controls of 0.80 in terms of Cohen’s d, an α level of 0.05 (one-tailed) and a total number of required patients of 40, the power of the study was 0.80 (39). In our primary analyses, effects of GH treatment on onset and progression of scoliosis were analyzed after adjustment for confounders, using binary logistic regression models for onset of scoliosis [see Table 3, odds ratio (OR)] and linear regression models for curve progression (see Table 4, in β). To allow comparison with other reports regarding scoliosis in PWS in which these adjustments were not performed, we additionally analyzed differences in onset of scoliosis and curve progression between GH-treated children and randomized controls with χ^2 tests and Mann-Whitney U tests.

To investigate the risk of onset of scoliosis during the study, we included all children without scoliosis at the start of the study. Goodness of fit of binary logistic regression models was assured by performing the Hosmer and Lemeshow test (correct fitting when $P > 0.05$). R² was calculated as a measure of explained variance. To investigate curve progression, we included all children with untreated scoliosis at the start of the study and those who had their onset of scoliosis during the study. Tolerance of all variables within the linear regression models was assured by calculating the variable inflation factor as a measure of multicollinearity. Nagelkerkes R² was calculated for all binary logistic and R² for all linear regression models as a measure of explained variance.

TABLE 3. Odds ratios for the risk of onset of scoliosis

	Infants at 12 months (n = 27)						Prepubertal children (n = 28)											
	Model 1		Model 2		Model 3		12 months				24 months							
	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P
Age	0.68	0.54	0.49	0.32	0.50	0.37	0.62	0.06	0.63	0.06	0.63	0.06	1.00	1.00	0.99	0.95	0.97	0.86
Gender	4.16	0.18	12.53	0.06	12.80	0.08	0.38	0.31	0.28	0.21	0.28	0.20	0.56	0.49	0.34	0.26	0.28	0.22
GH	3.33	0.26			0.89	0.96	0.42	0.36			1.46	0.80	0.28	0.13			2.81	0.59
ΔtrunkLBM			2.06	0.45	2.25	0.69			0.46	0.17	0.38	0.29			0.47	0.06	0.30	0.19
R ²		0.19		0.29		0.29		0.29		0.33		0.34		0.12		0.19		0.20

Binary logistic regression models depicting the effects of parameters on the risk of onset of scoliosis, expressed as OR. Gender: 0 = male, 1 = female. GH treatment: 0 = no GH treatment, 1 = GH treatment. ΔtrunkLBM, increase in truncal muscle mass in kilograms; R², explained variance by the model.

year ($P < 0.0001$). Thus, catch-up growth was the most prominent during the first year of GH treatment. Compared with controls, BMI SDS tended to be lower in GH-treated children at 12 months of study ($P = 0.05$), but was not significantly different at 24 months of study ($P = 0.19$). GH treatment significantly decreased the hypotonia of the truncal muscles, shown by an increase in ΔtrunkLBM and ΔtrunkLBM:BSA ratio. There was a significant correlation between IGF-I SDS and trunkLBM:BSA ratio ($r = 0.51$ with $P < 0.0001$; and $r = 0.41$ with $P < 0.0001$, at 12 and 24 months of study, respectively). During our study, there were no adverse effects of GH treatment.

Effects of GH treatment on scoliosis

Infants (0 to 3.5 yr)

During 12 months of study, there was no significant difference between GH-treated infants and randomized controls with regard to onset of scoliosis, curve progression ($P = 0.71$ and $P = 0.48$; Table 2), and start of treatment for scoliosis ($P = 1.00$).

Table 3 shows the OR for the risk of onset of scoliosis. Corrected for age and gender, GH treatment had no significant effect on the risk of onset of scoliosis, with an OR [95% confidence interval (CI)] of 3.33 (0.41–27.2) ($P = 0.26$, model 1). Also, ΔtrunkLBM as a proxy for Δheight did not affect the risk of onset of scoliosis, with an OR (95% CI) of 2.1 (0.3–13.7) ($P = 0.45$, model 2). In our final model (model 3), both GH treatment and ΔtrunkLBM did not increase the risk of onset of scoliosis in infants with PWS.

Table 4 shows the effect (β) of different variables on the progression of scoliosis. Corrected for age and gender, IGF-I SDS had no significant effect on the progression of scoliosis during 12 months of study, with a β (95% CI) of 1.20 (–1.0 to 3.4) ($P = 0.24$, model 1). Also, ΔtrunkLBM as a proxy for Δheight did not affect the progression of scoliosis during 12 months of study [β (95% CI), 7.19 (–19.1 to 33.5), $P = 0.51$; model 2]. In our final model (model 3), IGF-I SDS, ΔtrunkLBM, and the severity of scoliosis at start of study had no significant effect on the progression of scoliosis in infants with PWS.

Results were similar when ΔheightSDS was included in our models instead of ΔtrunkLBM.

Prepubertal children (3.5 to 12/14 yr)

During 12 and 24 months of study, there was no significant difference between GH-treated prepubertal children and randomized controls with regard to onset of scoliosis, curve progression (12 months, $P = 0.52$ and $P = 0.60$; 24 months, $P = 0.14$ and $P = 0.27$; Table 2), and start of treatment for scoliosis (both $P = 1.00$).

Table 3 shows the OR for the risk of onset of scoliosis. Corrected for age and gender, GH treatment had no significant effect on the risk of onset of scoliosis after 12 and 24 months of study with an OR (95% CI) of 0.42 (0.07–2.7) at 12 months and 0.3 (0.05–1.5) at 24 months of study ($P = 0.36$ and $P = 0.16$, respectively; model 1). Also, ΔtrunkLBM as a proxy for Δheight did not affect the risk of onset of scoliosis after 12 and 24 months

TABLE 4. Multiple linear regression models (β) for influences on curve progression

	Infants, 0–12 months (n = 15)						Prepubertal children (n = 26)											
	Model 1		Model 2		Model 3		0–12 months				12–24 months							
	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Age	3.05	0.34	4.75	0.40	4.73	0.44	–1.32	0.07	–0.87	0.24	–0.50	0.44	1.19	0.14	0.87	0.29	1.00	0.25
Gender	11.85	0.06	12.81	0.09	8.27	0.46	–2.94	0.40	–4.71	0.20	–3.29	0.30	3.32	0.35	4.98	0.19	5.18	0.18
IGF-I SDS	1.20	0.24	0.38	0.81	0.41	0.81	–0.24	0.69	0.59	0.47	0.45	0.52	1.36	0.09	0.03	0.98	–0.26	0.85
ΔtrunkLBM			7.19	0.51	7.84	0.52			–3.95	0.16	–4.13	0.09			2.91	0.22	3.30	0.18
Cobb at start					–0.47	0.59					–0.71	0.03					–0.24	0.52
R ²		0.47		0.52		0.56		0.28		0.37		0.57		0.25		0.31		0.33

Multiple linear regression models depicting the effects of parameters on curve progression, defined as the Cobb angle of the main scoliotic curve, expressed in β . Gender: 0 = male, 1 = female. ΔtrunkLBM, increase in truncal muscle mass in kilograms; Cobb at start, Cobb angle of the scoliotic curve at start of study; R², explained variance by the model. Significant P values are shown in bold.

of study, with an OR (95% CI) of 0.46 (0.1–1.4) at 12 months and 0.47 (0.2–1.0) at 24 months of study ($P = 0.17$ and $P = 0.06$, respectively; model 2). In our final model (model 3), both GH treatment and Δ trunkLBM did not increase the risk of onset of scoliosis in prepubertal children with PWS after 12 and 24 months of study.

Table 4 shows the effect (β) of different variables on the progression of scoliosis. Corrected for age and gender, IGF-I SDS had no significant effect on the progression of scoliosis during the first and second year of the study, with a β (95% CI) of -0.24 (-1.5 to 1.0) during the first year and 1.3 (-0.3 to 2.9) during the second year of study ($P = 0.69$ and $P = 0.10$, respectively; model 1). Also, Δ trunkLBM as a proxy for Δ height did not significantly affect the progression of scoliosis, with a β (95% CI) of -3.95 (-9.6 to 1.8) during the first year and 3.7 (-3.9 to 11.3) during the second year of study ($P = 0.16$ and $P = 0.32$, respectively; model 2). In our final model with the highest explained variance (model 3, $R^2 = 0.57$), a more severe scoliosis at the start of the study and a higher Δ trunkLBM during the first year were associated with a tendency for regression of scoliosis [β (95% CI) of Δ trunkLBM, -4.1 (-9.1 to 0.8) with $P = 0.09$; β (95% CI) of severity at start, -0.71 (-1.30 to -0.11) with $P = 0.03$]. During the second year of GH treatment, IGF-I SDS, Δ trunkLBM, and Cobb angle at start of study had no significant effect on curve progression in prepubertal children with PWS.

Results were similar when Δ heightSDS was included in our models instead of Δ trunkLBM.

Pubertal children (12/14 to 16 yr)

A GH dose of $1.5 \text{ mg/m}^2 \cdot \text{d}$ in pubertal children ($n = 3$) resulted in a higher height velocity and IGF-I SDS compared with those treated with $1.0 \text{ mg/m}^2 \cdot \text{d}$ ($n = 6$; $P = 0.046$ and $P = 0.08$, respectively; data not shown). Three of nine pubertal children had no scoliosis at the start of the study and had no onset of scoliosis during the study. Six pubertal children had scoliosis at the start of the study, but there was no difference in the number of children treated for scoliosis or in curve progression between those treated with a dose of 1.0 and $1.5 \text{ mg/m}^2 \cdot \text{d}$ (data not shown).

Discussion

Our randomized controlled trial shows that there was no significant difference between GH-treated children and randomized controls with regard to onset of scoliosis, curve progression, and start of treatment of scoliosis. In both the infant and prepubertal groups, GH treatment, Δ heightSDS, Δ trunkLBM (used as a proxy for Δ height), and IGF-I SDS were not associated with an increased risk of onset of scoliosis or curve progression, both before and after correction for confounders. Thus, GH treatment not only improves height SDS and trunkLBM of children with PWS (17–23), but it also has no adverse effects on the onset of scoliosis and curve progression.

Some authors have described an association between increased GH levels and a higher rate of curve progression in children without PWS (27–29). In contrast to these reports, our data

show that a higher baseline IGF-I SDS was associated with a lower severity of scoliosis, suggesting a protective effect of higher IGF-I SDS in children with PWS. Because IGF-I SDS was also positively associated with the trunkLBM:BSA ratio, the protective effect may be due to a higher trunkLBM. In our randomized controlled trial, GH-treated children had a significantly higher IGF-I SDS and Δ trunkLBM, but IGF-I SDS was not associated with the progression of scoliosis. The Δ trunkLBM, however, was associated with a tendency for regression of scoliosis, but only during the first year of the study.

The prepubertal group provides the most accurate information about the effects of GH treatment on scoliosis because all x-rays were taken in standing position and children were followed in a 2-yr randomized controlled trial. GH treatment and catch-up growth had no adverse effect on the onset of scoliosis or curve progression. Notably, our results show that those with a more severe scoliosis at the start of the study and a higher catch-up growth had a tendency for regression of scoliosis during the first year of the study. This effect was not seen during the second year. Our study is the first randomized controlled trial investigating the effects of GH treatment on scoliosis in a large group of children with PWS. Our data indicate that even severe scoliosis should not be considered a contraindication for GH treatment in children with PWS. The findings are in line with a retrospective study demonstrating that GH treatment did not affect scoliosis in these children (14).

Although our main aim was to investigate the onset and progression of scoliosis in a randomized controlled GH trial in infants and prepubertal children, we did not want to withhold GH treatment from a small group of pubertal children with PWS. In this group of pubertal children, we found that a higher dose of GH ($1.5 \text{ mg/m}^2 \cdot \text{d}$) increased height velocity and IGF-I SDS and was not associated with an accelerated onset of scoliosis or curve progression.

Infants had a controlled period of 1 yr and prepubertal children of 2 yr. This period is not very long for follow-up. However, in orthopedic practice visits are scheduled every 4 to 6 months to monitor progression. Therefore, changes occurring during GH treatment can easily be noted during 1 or 2 yr of follow-up. Moreover, if GH treatment would have adverse effects on scoliosis by stimulating growth, one would especially notice this during the period with the highest gain in height SDS, *i.e.* catch-up growth during the first year of GH treatment. In our opinion, 1 or 2 yr of follow-up is sufficient to identify the effects of GH-induced catch-up growth on the onset or progression of scoliosis. Our final models in infants and prepubertal children explained 20–57% of variances (R^2). In the future, when more data on the pathogenesis of scoliosis become available, perhaps our models might be improved.

In conclusion, our randomized controlled GH trial in a large group of children with PWS shows that GH treatment had no adverse effects on the onset of scoliosis and curve progression. A higher baseline IGF-I SDS was associated with a lower severity of scoliosis. Thus, scoliosis should not be considered a contraindication for GH treatment in children with Prader-Willi syndrome. Because of the high prevalence of scoliosis and the potential associated morbidities in patients with PWS, it is recommended

to perform frequent physical examinations and yearly radiographic examination, independently from GH treatment.

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