CLINICAL STUDY

Randomized GH trial with two different dosages in combination with a GnRH analogue in short small for gestational age children: effects on metabolic profile and serum GH, IGF1, and IGFBP3 levels

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Abstract

Background: GnRH analogue (GnRHa) combined with GH treatment has been proposed to increase adult height. Effect on metabolic profile and GH, IGF1, and IGFBP3 levels in short small for gestational age (SGA) children is unknown.

Objective: To assess fat mass and lean body mass SDS, percentage trunk fat, blood pressure (BP), insulin sensitivity (Si), β -cell function (disposition index, DI), lipid profile, and GH, IGF1, and IGFBP3 levels during 2 years of combined treatment.

Subjects: Forty-one pubertal short SGA children with a mean ($\pm$ S.D.) age of 12.1 ($\pm$ 1.0) years.

Design: Children received 3.75 mg of leuprolide acetate depot subcutaneously every 4 weeks, and they were randomly assigned to receive 1 mg (group A) or 2 mg (group B) of GH/m² per day.

Results: Percentage trunk fat increased in both groups, but to a lower extent in group B. Lean body mass SDS increased only in group B. Changes in BP, Si, DI, and lipids were similar in both groups. Si significantly decreased, but DI remained unchanged. Lipids remained normal. GH and IGF1 levels were significantly higher in group B.

Conclusion: Our study is the first to report that 2 years of combined treatment with a GnRHa and either 1 or 2 mg GH/m² per day does not adversely affect body composition and metabolic profile of short SGA children who come under medical attention at the onset of puberty. There was a dose-dependent effect on fat mass SDS_{height}, percentage trunk fat, lean body mass SDS_{height}, and GH and IGF1 levels in favor of treatment with GnRHa and the higher GH dose of 2 mg/m² per day.

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Introduction

GnRH analogue (GnRHa) treatment has long been used in children with central precocious puberty (CPP). Over the years, little attention has been paid to changes in metabolic profile during GnRHa treatment. Studies have focused on body composition, and were performed in children with CPP only. Some studies reported an increase in fat mass or body mass index (BMI) SDS during GnRHa treatment with a return to baseline values after discontinuation (1, 2), whereas others reported no changes (3) or even a decreased BMI SDS during GnRHa treatment (4).

In prepubertal short children born small for gestational age (SGA), GH treatment induces catch-up growth (5–7). Metabolic effects of GH treatment in

prepubertal short SGA children include the development of relative insulin resistance (IR) (8, 9) with an improvement of blood pressure (BP) and lipid profile (10). Fat mass SDS adjusted for gender and height declined significantly, whereas the increase in lean body mass SDS adjusted for gender and height reflected the normal increase as a result of the increase in height (11). In a randomized clinical trial where prepubertal short SGA children were treated with 1 or 2 mg GH/m² per day, no significant differences in BMI SDS, BP, insulin levels, and lipid profile were found between the two GH dosage groups (8, 10).

Pubertal short SGA children are frequently treated with GnRHa along with different dosages of GH to optimize adult height, despite the fact that no data are available about the GH dose effect of combined

treatment on metabolic profile and GH, insulin-like growth factor 1 (IGF1), and IGF binding protein 3 (IGFBP3) levels.

In the present randomized trial, we investigated the effect of 2 years of combined treatment with GnRHa and two different dosages of GH (1 vs 2 mg GH/m² per day) on body composition, BP, insulin sensitivity (Si), β -cell function, and lipid profile in pubertal short SGA children. Furthermore, we measured serum GH, IGF1, and IGFBP3 levels at the start of GH treatment and after 1 year of combined treatment and associated levels with the metabolic profile.

Materials and methods

Subjects

The study group consisted of 45 short SGA children (29 girls) who were at the beginning of puberty. They were included in a randomized trial investigating two dosages of GH in combination with GnRHa treatment (3.75 mg of s.c. leuprolide acetate depot given every 4 weeks). Children who met the following inclusion criteria were included in the study: i) birth length and/or birth weight SDS below -2 for gestational age (12), ii) chronological age of 8 years or older at the start of the study, iii) current height SDS below -2.5 or a predicted adult height SDS below -2.5 (calculated as height at the start of puberty plus 20 cm for girls and plus 30 cm for boys, according to Dutch references (13)), and iv) early pubertal stage, defined as Tanner breast stage 2 or 3 in girls and a testicular volume of 4–8 ml in boys (14), and a GnRH agonist test result indicating central puberty (peak LH 10 IU/l or more) (15). Exclusion criteria were i) a complicated neonatal period, with signs of severe asphyxia (defined as Apgar score <3 after 5 min), ii) long-term complications of respiratory ventilation such as bronchopulmonary dysplasia, iii) endocrine or metabolic disorders, chromosomal defects, growth failure caused by other disorders (such as emotional deprivation, severe chronic illness, and

chondrodysplasia) or syndromes (except for Silver–Russell syndrome, no children with Silver–Russell syndrome were included in this study), and iv) previous or present medication that could interfere with growth or GH treatment. The study was approved by the medical ethics committee of the participating centers, and written informed consent was obtained from parents or custodians and children aged 12 years or older.

Four children (two in each GH dosage group) were excluded during the 2-year observation period. Two girls did not meet the response criteria retrospectively. Treatment was stopped in one girl and one boy because of non-compliance.

Study design

After 3 months of GnRHa treatment, children were randomized into two GH dosage groups after stratification for gender, pubertal stage (Tanner stage 2 or 3), and parental height SDS (one parent with height SDS below -2 or both parents with height SDS within the normal range; Fig. 1). Children were assigned to group A receiving 1 mg GH/m² per day (~ 0.033 mg/kg per day) or to group B receiving 2 mg GH/m² per day (~ 0.067 mg/kg per day), Genotropin (Somatropin). GH was administered subcutaneously once daily at bedtime. The GH dose was adjusted to the calculated body surface area thrice monthly.

Complete overnight GH profiles were determined in 33 children as described previously (16), one at the start of GH treatment and one after ~ 1 year of combined treatment following a s.c. GH injection at 2000 h. Height was measured using a Harpenden stadiometer, and was expressed as SDS for calendar age and sex (13). Systolic and diastolic BPs were measured with an automated device. The mean of three measurements was used for analysis. Since height is an important determinant of BP, BP was expressed as SDS to adjust for height and gender (17). Fat mass and lean body mass were measured by dual-energy X-ray absorptiometry scans on one machine (DXA; Lunar Prodigy, GE Healthcare, Chalfont, St Giles, UK). Fat mass and

Figure 1 Schematic representation of the study design.

lean body mass were expressed as SDS to adjust for gender and height ($\text{SDS}_{\text{height}}$) (18). Percentage trunk fat was calculated as $(\text{trunk fat}/\text{total trunk mass}) \times 100$.

Glucose homeostasis

At the start of GnRHa treatment and after 1 year of combined treatment, a modified frequently sampled i.v. glucose tolerance test (FSIGT) with tolbutamide was performed as described previously (19). Si, glucose effectiveness (Sg), acute insulin response (AIR), and disposition index (DI) were calculated using Bergman's MINMOD Millennium software (20). Si quantifies the capacity of insulin to stimulate glucose disposal, and Sg reflects the capacity of glucose to mediate its own disposal. The AIR, an estimate of insulin secretory capacity, was measured as the area under the curve from 0 to 10 min corrected for baseline insulin levels. DI is calculated as $\text{AIR} \times \text{Si}$, and is an estimate of β -cell function.

Hormone assays

Fasting insulin levels during FSIGTs were measured in one laboratory (IRMA; Medgenix, Biosource Europe, Nivelles, Belgium). The intra-assay coefficient of variance (CV) was 1.9%, and the inter-assay CV was 6.3%. Fasting insulin levels at 3 months after the end of GnRHa treatment were measured using a chemiluminescent assay on an Immulite 2000 analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). Both methods were highly correlated ($r^2=0.98$) using the following formula: $Y (\text{Immulite}) = 0.6922X (\text{IRMA}) - 0.1761$. A conversion factor of 6.89 was used to transform data from mU/l (IRMA) to pmol/l (Immulite). Homeostasis model assessment (HOMA)-IR index was calculated using a computer model (21). Total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein-cholesterol, non-esterified fatty acids (FFAs), and triglycerides (TGs) were determined as described previously (22). Apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), and lipoprotein (a) (lp(a)) were determined by rate nephelometry on the IMMAGE Immunochemistry system according to the manufacturer's instructions (Beckman Coulter, Mijdrecht, The Netherlands). Between-run CV values were 4.2, 2.8, and 6.9% for the lipoproteins at the levels of 0.94, 0.53, and 0.35 g/l respectively. GH, IGF1, and IGFBP3 levels were measured as described previously (16).

Statistical analysis

Results for body composition, BP, Si, β -cell function, and lipid profile are presented as mean ($\pm$ s.d.). Percentage trunk fat, AIR, DI, insulin levels, HOMA-IR, and TG and lp(a) levels were log-transformed before analysis in order to have a Gaussian distribution. SDS were

compared with population means (zero SDS) using one-sample *t*-tests. To correct for multiple testing and some missing data, the changes over time and differences between groups A and B were analyzed using repeated-measurement analysis with a categorical effect for time and an interaction term for time and GH dose (SAS 9.1 (SAS Institute Inc., Cary, NC, USA)).

GH profiles were analyzed using the Pulsar program (23, 24). Mean and maximum GH levels were derived from this program. Analyses were performed using the statistical package SPSS (version 11.0; SPSS Inc., Chicago, IL, USA) for Windows, and the results for GH profiles and IGF1 and IGFBP3 levels are expressed as median (interquartile range). The Mann-Whitney test was used for differences between groups. The Wilcoxon signed rank test was used to determine differences between points in time within groups. To test for linear relationships, partial correlations were determined for groups A and B together, with adjustment for GH dosage. A *P* value <0.05 was considered significant.

Results

Clinical characteristics

Table 1 lists the clinical data. At the start of GH treatment, all children had clinical suppression of puberty and prepubertal overnight LH and FSH profile patterns as we reported previously (25, 26). No significant differences were found between groups A and B or between boys and girls.

Metabolic profile during combined treatment

All analyses were adjusted for gender and Tanner stage at the start of GnRHa treatment, since body composition, Si, and several lipid parameters were significantly different between boys and girls or between children with Tanner stages 2 and 3.

Table 1 Clinical characteristics of short small for gestational age (SGA) children. Data are expressed as mean ($\pm$ s.d.).

	Group A (1 mg GH/m ² per day)	Group B (2 mg GH/m ² per day)
Number (female)	22 (13)	19 (13)
Gestational age (weeks)	38.3 (± 2.4)	37.3 (± 3.5)
Birth weight SDS	-2.0 (± 1.1)	-1.9 (± 0.83)
Birth length SDS	-2.7 (± 1.1)	-2.4 (± 0.72)
Age (years)	12.1 (± 1.0)	12.1 (± 0.95)
Bone age (years)	11.4 (± 1.1)	11.1 (± 0.9)
Height SDS	-2.7 (± 0.68)	-2.8 (± 0.70)
Target height SDS	-0.65 (± 0.77)	-0.46 (± 0.75)
Tanner stage 2	18	15
Tanner stage 3	4	4

Body composition

At the start of GnRHa treatment, mean fat mass $\text{SDS}_{\text{height}}$ was significantly lower than the population mean in both groups ($P < 0.0001$; Fig. 2). After 1 year of combined treatment, fat mass $\text{SDS}_{\text{height}}$ had decreased significantly in group B only ($P < 0.0001$). At 3 months after the stop of GnRHa treatment, fat mass $\text{SDS}_{\text{height}}$ had significantly increased in both groups ($P = 0.0001$). In group A, fat mass $\text{SDS}_{\text{height}}$ was significantly higher compared with baseline ($P < 0.0001$), and was similar to the population mean. In group B, fat mass $\text{SDS}_{\text{height}}$ returned to values comparable to those at baseline, remaining significantly lower than the population mean ($P = 0.03$).

After 1 year of combined treatment, percentage trunk fat had increased significantly in group A only ($P = 0.002$). At 3 months after the stop of GnRHa treatment, percentage trunk fat had significantly increased in both groups, but to a lower extent in group B. Percentage trunk fat was significantly higher compared with baseline in both groups ($P < 0.001$).

At the start of GnRHa treatment, lean body mass $\text{SDS}_{\text{height}}$ was significantly lower than the population mean in both groups ($P < 0.0001$; Fig. 2). At 3 months

after the end of GnRHa treatment, lean body mass $\text{SDS}_{\text{height}}$ had significantly increased in group B only ($P = 0.007$). In both groups, lean body mass $\text{SDS}_{\text{height}}$ remained significantly lower compared with the population mean.

During the study period, there was a significant GH dose effect on fat mass $\text{SDS}_{\text{height}}$ ($P = 0.01$) and percentage trunk fat ($P = 0.03$). The GH dose effect on lean body mass $\text{SDS}_{\text{height}}$ showed a trend towards significance ($P = 0.07$).

Blood pressure

At the start of GnRHa treatment, mean systolic BP was significantly higher than the population mean ($P < 0.0001$; Table 2). A mean systolic BP SDS above the normal range ($> +2$ SDS) was found in 27% of the study subjects.

Systolic BP SDS did not significantly change during the study period, and was similar in groups A and B. Diastolic BP SDS had significantly increased after 1 year of combined treatment and remained higher at 3 months after the stop of GnRHa treatment, albeit still within the normal range. All values were comparable between groups A and B.

Insulin sensitivity and β -cell function

Si had significantly decreased and AIR had significantly increased after 1 year of combined treatment. Sg and DI remained comparable to baseline (Table 2). After 1 year of combined treatment, fasting insulin levels and HOMA-IR had significantly increased as well.

At 3 months after the end of GnRHa treatment, insulin levels and HOMA-IR remained similar to the levels after 1 year of combined treatment. All values were comparable between groups A and B.

Lipid profile

Mean serum lipid levels remained within the normal range during the study period, and were similar in groups A and B. At the start of GnRHa treatment, lp(a) levels were above the normal range (> 0.3 g/l) in 27% of the children. During the study period, percentages were 34 and 24% after 1 year of combined treatment and at 3 months after the stop of GnRHa treatment respectively.

Overnight GH profiles during combined treatment

At the start of GH treatment (3 months after the start of GnRHa treatment), mean and maximum GH levels were comparable for groups A and B and for boys and girls.

After 1 year of combined treatment, mean and maximum GH levels significantly increased in both

Figure 2 Changes in body composition and percentage trunk and limb fat during the study period. Data are expressed as mean ($\pm$ s.e.m.). Diamonds represent values during treatment with GnRHa and 1 mg GH/m² per day. Squares represent values during treatment with GnRHa and 2 mg GH/m² per day. Mean percentage trunk fat = (trunk fat/total trunk mass) $\times$ 100. * $P < 0.01$, # $P < 0.05$.

Table 2 Blood pressure, insulin sensitivity, and lipids at the start of GnRHa treatment, after 1 year of combined treatment and 3 months after the end of GnRHa treatment in short small for gestational age (SGA) children. Data are expressed as model estimate (95% CI), after adjustment for gender and Tanner stage at baseline.

	Start of GnRHa treatment (n=41)	One year of combined treatment (n=41)	Three months after the stop of GnRHa treatment (n=41)
Systolic BP SDS	1.59 (1.24–1.94)*	1.26 (0.87–1.65)*	1.39 (1.04–1.74)*
Diastolic BP SDS	0.22 (0.00–0.45)	0.52 (0.27–0.78) [†]	0.57 (0.36–0.79) [‡]
Si × 10 ⁻⁴ /min (μU/ml)	7.38 (6.00–8.76)	4.61 (3.71–5.50) [†]	ND
Sg × 10 ⁻² /min	3.47 (2.98–3.96)	3.42 (2.94–3.89)	ND
AIR (mU/l)	421 (326–543)	790 (643–971) [†]	ND
DI (AIR × Si)	2569 (2012–3279)	3105 (2514–3838)	ND
Insulin (pmol/l)	48.1 (41.7–55.5)	75.0 (63.8–88.1) [†]	79.2 (66.7–94.0) [‡]
HOMA-IR	0.91 (0.79–1.06)	1.39 (1.19–1.63) [†]	1.43 (1.20–1.70) [‡]
TC (mmol/l) (3.0–5.5)	4.16 (3.99–4.33)	4.20 (4.00–4.40)	4.33 (4.13–4.53) [‡]
LDL-c (mmol/l) (1.3–3.4)	2.28 (2.11–2.46)	2.44 (2.25–2.64) [†]	2.36 (2.19–2.52)
HDL-c (mmol/l) (0.9–1.9)	1.41 (1.31–1.52)	1.63 (1.51–1.76) [†]	1.55 (1.44–1.66) ^{‡,§}
TG (mmol/l) (0.4–1.6)	0.76 (0.66–0.86)	0.79 (0.67–0.94)	0.92 (0.75–1.13) [‡]
FFA (mmol/l) (0.2–1.0)	0.52 (0.45–0.59)	0.69 (0.59–0.79) [†]	0.51 (0.42–0.60) [§]
Apo-A1 (g/l) (0.9–1.6)	1.39 (1.32–1.46)	1.56 (1.47–1.65) [†]	1.45 (1.38–1.53) [§]
Apo-B (g/l) (0.5–1.3)	0.71 (0.66–0.75)	0.73 (0.68–0.77)	0.72 (0.67–0.77)
Lp(a) (g/l) (≤0.3)	0.09 (0.06–0.13)	0.14 (0.09–0.21) [†]	0.14 (0.09–0.22) [‡]

AIR, DI, insulin levels, HOMA-IR, and triglyceride and Lp(a) levels were log-transformed prior to analysis. The values between brackets represent reference ranges for healthy children; ND, not determined. * $P < 0.0001$ compared with the population mean (0 SDS); [†] $P < 0.03$: 1 year of combined treatment, compared with the start of GnRHa treatment; [‡] $P < 0.03$: 3 months after the stop of GnRHa treatment, compared with the start of GnRHa treatment; [§] $P < 0.02$: 3 months after the stop of GnRHa treatment, compared with 1 year of combined treatment.

groups, and levels were significantly higher in group B (Table 3). Following the s.c. GH injection at 2000 h, GH levels remained significantly higher above 40 and 20 mU/l in group B compared with group A ($P < 0.0001$; Fig. 3). No correlations were found between GH profile characteristics and age, bone age, gender, pubertal stage, and peak LH level during a GnRH agonist test and fat mass SDS.

IGF1 and IGFBP3 levels during combined treatment

At the start of GH treatment (3 months after the start of GnRHa treatment), IGF1 and IGFBP3 levels were significantly lower than the respective population means ($P < 0.0001$; Table 3). IGF1 levels were comparable for groups A and B and for boys and girls. IGFBP3 levels were significantly lower in group A, but were comparable for boys and girls. IGF1 levels correlated with IGFBP3 levels ($r = 0.62$, $P < 0.0001$) and mean GH levels ($r = 0.36$, $P = 0.04$). IGFBP3 levels correlated with mean GH levels ($r = 0.39$, $P = 0.03$).

After 1 year of combined treatment, IGF1 levels increased to levels significantly higher than the population mean ($P < 0.0001$) in both groups. IGF1 levels were significantly higher in group B. In group B, 88.9% of the children had IGF1 levels in the highest quintile (> 0.84 SDS) and 27.8% had IGF1 levels above 2 SDS compared with 43.8% ($P = 0.005$) and 6.3% (NS) of children in group A respectively. IGF1 levels were comparable for boys and girls.

IGFBP3 levels increased significantly and similarly in both groups. Compared with the population mean,

IGFBP3 levels remained only significantly lower in group A ($P = 0.01$). Levels were comparable for boys and girls.

During combined treatment, IGF1 levels only correlated with IGFBP3 levels ($r = 0.50$, $P = 0.003$).

Discussion

Our study is the first to report metabolic effects in pubertal short SGA children during combined treatment with a GnRHa and 1 or 2 mg GH/m² per day. Children treated with GnRHa and the higher GH dose of 2 mg/m² per day developed less fat mass SDS_{height}, less percentage trunk fat, and more lean body mass SDS_{height}. BP, Si, and lipid profile were similar in both GH dosage groups. As expected, Si significantly decreased, but the DI did not change in either group. Lipids remained within normal reference ranges. GH and IGF1 levels were significantly higher in children treated with GnRHa and 2 mg GH/m² per day.

At the start of GnRHa treatment, fat mass SDS_{height} was significantly lower than the population mean in both groups, consistent with findings in prepubertal short SGA children (11). In children treated with GnRHa and 2 mg GH/m² per day, fat mass SDS_{height} remained significantly lower than the population mean. Percentage trunk fat increased in both GH dosage groups, but to lower values in children treated with GnRHa and 2 mg GH/m² per day. Several studies reported an increase in fat mass or BMI SDS during GnRHa treatment in children with CPP (1, 2). This might be explained by lower GH levels during GnRHa treatment, as reported in children with GH deficiency

	Group A (1 mg GH/m ² per day) (n=16)		Group B (2 mg GH/m ² per day) (n=18)	
	Start of GH treatment	One year of combined treatment	Start of GH treatment	One year of combined treatment
Mean GH (mU/l)	8.5 (4.7–11.3)	25.2 (19.7–31.4)	9.6 (6.5–11.5)	53.4 (45.5–63.3)
Max GH (mU/l)	39.3 (26.4–49.4)	60.0 (44.3–83.6)	49.0 (35.9–61.9)	109 (96.8–145)
GH > 40 mU/l (h)		2.8 (0.67–3.9)		7.2 (6.3–8.8)
GH > 20 mU/l (h)		7.8 (5.4–8.3)		10.8 (8.8–11.3)
GF1 SDS	−0.93 (−2.2 to −0.11)	0.81 (0.55–1.1)	−0.58 (−1.5 to 0.38)	1.5 (1.2–2.5)
ΔIGF1 SDS		1.7 (1.1–2.3)		1.9 (1.1–3.0)
GFBP3 SDS	−1.5 (−2.0 to −0.83)	−0.55 (−0.74 to −0.14)	−0.83 (−1.4 to −0.46)	0.26 (−0.04–0.77)
ΔIGFBP3 SDS		1.0 (0.32–1.4)		1.1 (0.89–1.6)
			<i>P</i> = 0.001	<i>P</i> < 0.0001
			<i>P</i> = 0.001	<i>P</i> = 0.001
			<i>P</i> < 0.0001	<i>P</i> < 0.0001
			<i>P</i> = 0.001	NS
			<i>P</i> < 0.001	<i>P</i> < 0.001
				NS

²Group B versus group A: after 1 year of combined treatment with GnRH and GH. During combined treatment, compared with the start of Gn treatment.

At the start of GnRHa treatment, Si was lower and insulin secretion was higher in our pubertal short SGA children compared with the reported values in pre-pubertal short SGA children (22). This was expected, since healthy pubertal children have a physiologic IR with a compensatory increase in insulin secretion (34). During 1 year of combined treatment, Si significantly decreased and AIR significantly increased. The DI remained similar to baseline, reflecting that β -cells were able to compensate for the reduction in Si by increasing their insulin secretion. Si and AIR were comparable between both GH dosage groups. Since IGF1 levels were significantly higher during treatment with GnRHa and 2 mg GH/m² per day, albeit within the normal range, this might be explained by the fact that the insulin-like effects of IGF1 counterbalance the insulin-antagonistic effects of GH (35).

Figure 3 Mean GH levels for each time point during the overnight GH profile after 1 year of combined treatment with GnRHa and GH. Open squares represent group A and solid squares represent group B.

At the start of GnRHa treatment, mean serum lipid levels were within the normal range, although lp(a) levels were above the normal range (>0.3 g/l) in 27% of the pubertal short SGA children. High lp(a) levels have been associated with an increased risk of developing cardiovascular disease in several studies (36, 37). Although some lipids showed a significant temporary increase (LDL-c, FFA, and Apo-A1 levels), and others increased more steadily over time (TC and TG levels), the actual increase and subsequent decrease in levels were very small, and lipids were similar in both groups. The clinical significance of these small changes in lipid levels is therefore considered negligible.

During combined treatment, mean and maximum GH levels were lower in our study group compared with levels in prepubertal SGA children treated with GH only (38). Moreover, maximum GH levels in children treated with GnRHa and 2 mg GH/m^2 per day were similar to maximum GH levels in prepubertal children treated with 1 mg GH/m^2 per day. In the latter study, GH levels were determined with the same assay in the same laboratory. We previously reported that GH levels significantly decreased during 3 months of GnRHa treatment (16), similar to reports in patients with precocious puberty treated with GnRHa (39–41). This is probably partly due to diminution of sex steroids (42). Thus, the lower GH levels in our study group might well be a result of simultaneous treatment with GH and a GnRHa. Nonetheless, following a s.c. GH injection at 2000 h, GH levels in short SGA children treated with GnRHa and 2 mg GH/m^2 per day remained above 20 mU/l for almost 11 h, demonstrating that these children have elevated GH levels for a great part of the day. GH and IGF1 levels increased significantly in both GH dosage groups, but to significantly higher levels in the 2 mg GH/m^2 per day group. Dose-dependent rises have been described in prepubertal short children born SGA, GH-deficient adolescents, and girls with Turner syndrome (38, 43, 44). The percentage of children with IGF1 SDS above 2 SDS was not significantly different

between the groups. However, 27.8% of the children treated with 2 mg GH/m^2 per day had IGF1 levels above 2 SDS. Concern has been expressed about the association of high IGF1 levels during several years and long-term cancer risk (45). Although pubertal short SGA children will be treated for a relatively short period of time, it is important to monitor IGF1 levels during the treatment.

Our study has some limitations. Since GH treatment in short SGA children was approved by the FDA in 2001 and by the EMEA in 2003, our medical ethics committee did not allow us to treat pubertal short SGA children solely with a GnRHa or to include a control group without any treatment. We did not include a study group of pubertal short SGA children treated with GH only, because this is investigated in another GH trial. In the future, it would be interesting to compare adult height results between these two studies. Since many clinicians started treating short SGA children with GnRHa and GH, despite the fact that there are no safety data, it is important to report safety data on metabolic profile in relation to GH and IGF1 levels before adult height data will be available. Adult height data will have to be awaited before a definitive conclusion can be drawn whether combined treatment with GnRHa and either 1 or 2 mg GH/m^2 per day will result in an optimal adult height without adversely affecting metabolic outcome.

In conclusion, our study is the first to report that 2 years of combined treatment with a GnRHa and either 1 or 2 mg GH/m^2 per day does not adversely affect body composition and metabolic profile of short SGA children who come under medical attention at the onset of puberty. There was a dose-dependent effect on fat mass $\text{SDS}_{\text{height}}$, percentage trunk fat, lean body mass $\text{SDS}_{\text{height}}$, and GH and IGF1 levels in favor of treatment with GnRHa and the higher GH dose of 2 mg/m^2 per day. BP, Si, and lipid profile were similar between the two GH dosage groups.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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