Risk Factors for Diabetes Mellitus Type 2 and Metabolic Syndrome Are Comparable for Previously Growth Hormone-Treated Young Adults Born Small for Gestational Age (SGA) and Untreated Short SGA Controls

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Context: Low birth weight might increase risk of diabetes mellitus type 2 and metabolic syndrome (MS). GH has insulin-antagonistic properties. Therefore, long-term follow-up of GH-treated children born small for gestational age (SGA) is important.

Objective and Patients: The objective of the study was to evaluate insulin sensitivity (Si) and disposition index (DI), all components of the MS and IGF-I and IGF binding protein (IGFBP)-3 levels in 37 previously GH-treated young SGA adults in comparison with 25 untreated short SGA controls.

Results: GH-treated subjects were 22.3 (1.7) yr old. Mean duration of GH treatment had been 7.3 (1.3) yr. Mean period after discontinuation was 6.5 (1.4) yr. Si and DI were comparable for GH-treated and untreated SGA subjects. Fasting glucose and insulin levels increased during GH treatment but recovered after discontinuation. Body mass

index, waist circumference, high-density lipoprotein cholesterol levels, and triglycerides were equivalent. Systolic and diastolic blood pressure and cholesterol were significantly lower in GH-treated subjects. Thirty-two percent of untreated controls *vs.* none of the GH-treated subjects had an increased blood pressure. GH-induced rises in IGF-I and IGFBP-3 levels had completely recovered after GH stop.

Conclusion: At 6.5 yr after discontinuation of long-term GH treatment, Si, DI, fasting levels of glucose and insulin, body mass index, waist circumference, and IGF-I and IGFBP-3 levels were equivalent for GH-treated and untreated young SGA adults. Systolic and diastolic blood pressure and serum cholesterol were even lower in GH-treated subjects. These data are reassuring because they suggest that long-term GH treatment does not increase the risk for diabetes mellitus type 2 and MS in young adults. (*J Clin Endocrinol Metab* **92: 160–165, 2007**)

I N EPIDEMIOLOGICAL STUDIES, an inverse association has been reported between birth weight and the risk of diabetes mellitus type 2 (DM-II) and metabolic syndrome in adulthood (1–3). Approximately 10% of children born small for gestational age (SGA) fail catch-up growth and remain short with a height below −2 SD scores (SDS) (4, 5). GH treatment has recently been approved for short SGA children, and currently they comprise a large group of GH-treated children, accounting for 30% of new cases (Dutch Growth Foundation, Rotterdam, The Netherlands).

Because GH has been associated with increased insulin levels and insulin resistance (6–9), concern has been expressed regarding the late consequences of GH treatment on

risk factors for DM-II and associated comorbidities, especially in possibly predisposed subjects, such as SGA children. Because GH use in this population will sharply increase in the coming years, long-term follow-up is important.

It was previously shown that short SGA children had reduced insulin sensitivity before receiving GH, which further declined during GH therapy (10–12). Most studies reported a recovery of insulin sensitivity and insulin levels to pretreatment levels within 3–6 months after withdrawal of GH treatment (13, 14). It was also reported that SGA children had a higher systolic blood pressure and more often hypercholesterolemia (15, 16). GH treatment resulted in a significant reduction in systolic blood pressure as well as a reduction in cholesterol levels, which remained so until 6 months after discontinuation of GH therapy (15).

However, there are no long-term follow-up data on risk factors for DM-II and metabolic syndrome after discontinuation of GH treatment in subjects born SGA. In the present study, we evaluated fasting insulin and glucose levels, blood pressure, body mass index (BMI), fasting serum lipids, and serum levels of IGF-I and IGF binding protein (IGFBP)-3 in young adults born SGA from start of GH treatment until 6.5 yr after discontinuation of GH. At 6.5 yr after discontinuation, all these outcome variables were compared with those of un-

treated short SGA controls and a frequently sampled iv glucose tolerance test (FSIGT) with tolbutamide was performed.

Subjects and Methods

Subjects

Previously GH-treated SGA subjects. The study group comprised 37 subjects born SGA who had previously been participating in a multicenter, double-blind, randomized, dose-response GH trial that originally involved 79 children (17, 18). The dose-response GH trial started in 1991 and evaluated the effects of two doses of GH, 1 and 2 mg GH/ m²·day, on long-term growth and adult height. Inclusion criteria for the GH trial have previously been described (17). In short, the children were included when prepubertal, with a birth length and height SDS below −1.88, without signs of any catch-up growth in height and without growth failure caused by other disorders. All children were randomly and blindly assigned to either group A or B: group A received 1 mg GH per square meter per day, and group B received 2 mg GH per square meter per day. Biosynthetic GH was administered sc once daily and GH treatment was stopped after reaching adult height.

The present follow-up study was performed in 2005. Inclusion criteria were a period of at least 4 yr after discontinuation of GH treatment and being treated with GH for more than 4 yr. Forty-two of the original 79 participants were not included for the following reasons: for 20 subjects, the period after discontinuation of GH treatment was less than 4 yr, four children dropped out during the original GH trial due to either lack of motivation (n = 2), precocious puberty (n = 1), or GH insensitivity (n = 1), two subjects were lost to follow-up, two emigrated, one subject died due to a road accident, five persons did not respond to the invitation letter, and eight subjects did not want to participate due to either lack of interest (n = 4) or fear of venous punctures (n = 4). Initial characteristics of the eligible 37 GH-treated SGA subjects were comparable with those of the 42 subjects who were excluded, except for age at inclusion (8.5 *vs.* 6.3 yr, respectively; $P < 0.001$) and duration of GH treatment (7.4 *vs.* 9.4 yr, respectively; $P < 0.001$).

Untreated short SGA controls. All outcome variables at 6.5 yr after GH stop were compared with those of 25 short young adults born SGA who had never received GH treatment. These subjects were part of a large cohort of young adults participating in a follow-up study evaluating risk factors for DM-II and cardiovascular disease. They were selected on their birth length and current height, which were both below −1.88 SDS.

The GH trial and the follow-study were approved by the medical ethics committees of the participating centers. Written informed consent was obtained from all participants or their parents.

Study design

The previously GH-treated SGA subjects were monitored longitudinally. At start, after 6 yr of GH treatment and 6 months and 6.5 yr after discontinuation of GH, height and weight were measured and BMI was calculated. Height and BMI were expressed in SDS adjusting for sex and age according to Dutch reference data (19, 20). Systolic and diastolic blood pressure (BP) were measured by a Dinamap Critikon (Southern Medical Corp., Baton Rouge, LA) and expressed in SDS, using sex- and height-matched reference values (20, 21). At the same time points, fasting blood samples were taken for determination of glucose, insulin, fasting glucose to insulin ratio, hemoglobin A1c (HbA1c), serum cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TGs), and IGF-I and IGFBP-3 levels. Serum IGF-I and IGFBP-3 levels were converted into SDS to adjust for sex and age, using reference values for healthy children with normal stature determined in the same laboratory (22). After centrifugation all samples were frozen (−80 C) until assayed.

At 6.5 yr after discontinuation of GH, we also performed a FSIGT with tolbutamide (23). Glucose and insulin levels were measured in all samples and used for calculation of insulin sensitivity (Si), glucose effectiveness (Sg), acute insulin response (AIR) and disposition index (DI) using Bergman's MINMOD MILLENNIUM software (24). Si quantifies the capacity of insulin to promote 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 equals AIR ∗ Si and indicates the degree of glucose homeostasis. In addition, family history of DM-II was recorded and waist circumference was measured at the level of the umbilicus using a nonextendable measuring tape.

Metabolic syndrome components

At 6.5 yr after discontinuation of GH treatment, the various components of the metabolic syndrome were assessed in both the previously GH-treated and untreated SGA subjects. According to criteria formulated by Adult Treatment Panel III (ATP III), metabolic syndrome is diagnosed if three or more of the following symptoms are present: central obesity [waist circumference ≥ 102 (males) or 88 cm (females)], raised TG levels (TG ≥ 1.7 mmol/liter), reduced HDL-c levels [HDL-c < 1.0 (males) or 1.3 (females) mmol/liter], high blood pressure (systolic ≥ 130 and/or diastolic BP ≥ 85 mm Hg), and increased fasting glucose levels (glucose ≥ 6.1 mmol/liter) (25).

Assays

Glucose levels were determined on a VITROS analyzer 750 (Orthoclinical Diagnostics, Johnson & Johnson, Beers, Belgium). Serum insulin levels were measured by an immunoradiometric assay (Medgenix, Biosource Europe, Nivelles, Belgium). The intraassay coefficient of variation was 2–4.7% (19–405 pmol/liter) and the interassay coefficient of variation was 4.2–11.3% (32–375 pmol/liter). HbA1c levels were measured using an automatic HPLC analyzer (DIAMAT; Bio-Rad Laboratories, Inc., Edgemont, CA). The upper-normal assay limit was 6.6%. Serum levels of cholesterol, LDL-c, HDL-c, and TGs were measured using an enzymatic colorimetric test on the Hitachi 917 analyzer (Roche Diagnostics, Mannheim, Germany). Serum IGF-I and IGFBP-3 levels were determined in one laboratory by a specific RIA as previously described (26, 27).

Statistics

Analyses were carried out using the computer statistical package SPSS for Windows (version 11.1; Chicago, IL). Statistical analyses in the GH-treated SGA subjects were performed for group A and B separately and the groups together. Because outcome variables were not different between the GH dosage groups, data are shown for both groups together, unless indicated otherwise. Results are expressed as mean (SD), except for Si, AIR, Sg, and DI, which were log transformed before analysis and expressed as median (interquartile range). Changes over time were analyzed with repeated measures of variance (mixed models ANOVA). First, an F test was performed to test whether time had a significant effect. To correct for multiple testing, $P < 0.005$ ($\alpha = 0.05/10$) was considered statistical significant. Then only when $P < 0.005$, repeated measures of variance (mixed models ANOVA) was used to test differences between baseline and the different time points.

Differences between GH-treated SGA subjects and untreated short SGA controls were evaluated using independent-samples *t* test and Fisher's exact test for proportions. For linear relationships between continuous variables, Pearson's correlation coefficients were used. Before the study, a power calculation with a significance levels (α) of 0.05 and a chosen power of 80% estimated that there should be at least 17 subjects in each group to identify a difference of 20% in insulin sensitivity. A difference of 20% in insulin sensitivity was considered clinically relevant.

Results

Clinical characteristics and family history of DM-II

Clinical characteristics of the previously GH-treated SGA subjects (n = 37) and untreated SGA controls (n = 25) are shown in Table 1. Within the GH-treated SGA group, only gestational age was different between groups A (n = 19) and B (n = 18) [37.8 (3.2) *vs.* 35.2 (4.3) wk, respectively; P = 0.042]. Compared with untreated SGA controls, gestational age, birth length, and birth weight SDS were lower in GH-treated SGA subjects, whereas current height SDS was significantly

TABLE 1. Clinical characteristics of previously GH-treated SGA subjects and untreated SGA controls

	GH-treated SGA group (n = 37)	Untreated short SGA controls (n = 25)
Male/female	22/15	11/14
Gestational age	36.6 (3.9)[a]	39.6 (1.3)
Birth length SDS	−3.6 (1.5)[b]	−2.9 (0.7)
Birth weight SDS	−2.6 (1.0)[a]	−1.8 (0.8)
Height SDS at start GH treatment	−2.9 (0.7)	
Height SDS at present study	−1.4 (1.0)[a]	−2.6 (0.6)
Age at start GH treatment (yr)	8.5 (1.7)	
Age at stop GH treatment (yr)	15.8 (1.4)	
Age at follow-up study (yr)	22.3 (1.7)[b]	21.0 (1.7)
GH duration	7.3 (1.3)	
Period after GH stop	6.5 (1.4)	

Data expressed as mean (SD).
[a] GH-treated SGA subjects *vs.* untreated SGA controls: $P < 0.001$.
[b] GH-treated SGA subjects *vs.* untreated SGA controls: $P < 0.05$.

higher ($P < 0.001$). At 6.5 yr after GH stop, GH-treated SGA subjects were 1.3 yr older. Mean duration of GH treatment had been 7.3 (1.3) yr and period after discontinuation of GH was 6.5 (1.4) yr.

Of the GH-treated SGA subjects, 10 of 25 (40.0%) had a positive family history for DM-II, compared with 10 of 23 (43.5%) of the untreated SGA controls.

Insulin sensitivity and glucose homeostasis

FSIGT results are listed in Table 2. At 6.5 yr after GH stop, Si, Sg, AIR, and DI were not significantly different between the previously GH-treated and untreated SGA subjects. Interestingly, DI tended to be higher in GH-treated SGA subjects, although not significantly ($P = 0.077$).

Table 3 shows fasting levels of glucose, insulin and HbA1c, and fasting glucose to insulin ratio. Fasting glucose and insulin levels increased significantly during GH treatment ($P = 0.002$ and $P < 0.001$) but were not significantly different from baseline anymore at 6 months after discontinuation. At 6.5 yr after discontinuation, glucose and insulin levels were higher than at baseline ($P = 0.003$ and $P < 0.001$, respectively) but comparable with untreated SGA controls. Fasting glucose to insulin ratio did not change significantly over time and was comparable for GH-treated and untreated SGA subjects at 6.5 yr after discontinuation. HbA1c decreased during GH treatment ($P < 0.001$) but returned to baseline values at 6.5 yr after discontinuation of GH. At that time, HbA1c was lower in GH-treated than untreated SGA subjects ($P = 0.007$). None of the GH-treated or untreated SGA subjects had elevated fasting glucose levels according to ATP III criteria (25).

TABLE 2. FSIGT results in previously GH-treated SGA subjects and untreated SGA controls

	GH-treated SGA group	Untreated short SGA controls
Si $* 10^{-4}/\text{min}^{-1}$ (μU/ml)	5.8 (4.6–8.6)	5.7 (3.3–8.5)
Sg $* 10^{-2}$ (m/d)min^{-1}	1.85 (1.63–2.18)	1.95 (1.76–2.25)
AIR (mU/liter)	466 (305–800)	446 (259–720)
DI (AIR $*$ Si)	3516 (1846–4638)	2289 (1529–3534)

Data expressed as median (interquartile range).

BP

Systolic and diastolic BP are shown in Table 3. In the GH-treated SGA subjects, baseline systolic BP SDS was significantly higher than zero ($P < 0.001$), whereas diastolic BP SDS was similar to zero. During GH treatment, both systolic and diastolic BP SDS decreased significantly ($P < 0.001$ and $P = 0.004$, respectively). At 6.5 yr after discontinuation of GH treatment, systolic BP SDS was significantly lower than at baseline ($P < 0.001$), whereas diastolic BP SDS was equivalent to baseline values. Both were not different from zero SDS. The previously GH-treated SGA subjects had a significantly lower systolic and diastolic BP than untreated SGA controls ($P < 0.001$). According to ATP III criteria, none of the GH-treated SGA subjects had an increased systolic or diastolic BP, compared with eight of 25 (32.0%) of the untreated SGA controls ($P < 0.001$) (25).

BMI and waist circumference

BMI SDS and waist circumference are shown in Table 3. In the GH-treated SGA subjects, baseline BMI SDS was significantly lower than zero ($P < 0.001$). During GH treatment, BMI SDS increased significantly ($P < 0.001$) to values similar to zero. At 6.5 yr after discontinuation of GH, BMI SDS of the previously GH-treated SGA subjects was not different from the untreated SGA controls. Waist circumference was similar for GH-treated and untreated SGA subjects and also after adjustment for sex and height. None of the GH-treated SGA subjects had an increased waist circumference, compared with one of 25 (4.0%) of the untreated SGA controls according to ATP III criteria (25).

Serum lipid levels

Fasting serum lipid levels are listed in Table 3. During GH treatment, serum cholesterol, LDL-c, and HDL-c levels decreased significantly ($P < 0.001$). At 6.5 yr after stop, cholesterol and LDL-c levels were still lower than baseline values ($P = 0.016$), whereas HDL-c levels were equivalent. TG levels did not change during GH treatment. At 6.5 yr after GH stop, serum cholesterol levels were significantly lower in GH-treated SGA subjects than untreated SGA controls, whereas HDL-c and TG levels were comparable. According to ATP III criteria, six of 37 (16.2%) of the GH-treated SGA subjects had high TG levels and six of 37 (16.2%) had low HDL-c levels, compared with four of 24 (16.7%) and 10 of 23 (43.5%) ($P = 0.034$) of the untreated SGA controls, respectively (25).

Metabolic syndrome

Table 4 shows the different components of the metabolic syndrome. According to ATP III criteria, none of the GH-treated SGA subjects had metabolic syndrome, compared with two of 25 (8.0%) of the untreated short SGA controls (25).

Serum IGF-I and IGFBP-3 levels

Table 3 shows serum IGF-I and IGFBP-3 levels. In GH-treated SGA subjects, baseline IGF-I and IGFBP-3 SDS were significantly lower than zero. During GH treatment, IGF-I and IGFBP-3 SDS increased significantly ($P < 0.001$), resulting in values higher than zero ($P < 0.001$). At 6.5 yr after

TABLE 3. BP, BMI, serum lipids, and IGF-I and IGFBP-3 levels in previously GH-treated SGA subjects and untreated SGA controls

	GH-treated SGA group				Untreated short SGA controls
	Baseline	6 yr of GH	6 months after GH	6.5 yr after GH	
Glucose (mmol/liter)	4.2 (1.0)	5.0 (0.6)[a]	4.7 (0.5)	4.9 (0.5)[a,b]	5.0 (0.4)
Insulin (mU/liter)	6.2 (3.5)	16.0 (8.0)[c]	8.8 (7.4)	9.3 (3.9)[c]	10.7 (5.4)
Fasting G/I	1.1 (1.4)	0.4 (0.2)	0.7 (0.4)	0.6 (0.2)	0.6 (0.3)
HbA1c (%)	5.0 (0.3)	4.8 (0.4)[c]	4.7 (0.4)[c]	5.2 (0.3)[d,e]	5.4 (0.3)
Systolic BP (mm Hg)	106.7 (11.1)	111.4 (12.7)[f]	115.3 (12.6)[c]	111.9 (8.9)	121.5 (11.6)
Diastolic BP (mm Hg)	57.9 (9.5)	55.7 (7.2)	59.4 (9.2)	63.8 (6.3)[a,b,g]	75.7 (6.3)
Systolic BP SDS	1.1 (0.9)[h]	0.3 (1.2)[c]	0.3 (1.2)[c]	0.0 (1.7)[c,g]	1.3 (0.9)
Diastolic BP SDS	0.0 (1.1)	−0.5 (0.6)[a,j]	0.3 (0.8)	0.1 (0.6)[b,i,g]	1.0 (0.5)[h]
BMI (kg/m²)	14.7 (1.8)	19.1 (2.8)[c]	20.6 (2.8)[c]	22.4 (2.2)[c,d]	22.6 (3.3)
BMI SDS	−0.9 (1.3)[c]	0.1 (1.0)[c]	0.2 (1.0)[c]	−0.1 (0.7)[c]	0.2 (1.2)
Waist circumference (cm)				74.9 (6.7)	74.9 (9.2)
Cholesterol (mmol/liter)	4.6 (0.8)	3.6 (0.6)[c]	4.1 (0.6)[c]	4.3 (0.8)[f,b,e]	4.8 (1.1)
LDL-c (mmol/liter)	2.8 (0.8)	2.2 (0.6)[c]	2.5 (0.6)[c]	2.6 (0.7)[c]	
HDL-c (mmol/liter)	1.4 (0.3)	1.1 (0.2)[c]	1.1 (0.2)[c]	1.3 (0.3)[d]	1.2 (0.3)
TGs (mmol/liter)	1.0 (0.6)	1.4 (0.8)	1.2 (0.6)	1.4 (1.3)	1.0 (0.6)
IGF-I SDS	−0.9 (1.1)[h]	1.9 (0.7)[c,h]		−0.4 (0.7)[f,j]	−0.6 (1.0)[j]
IGFBP-3 SDS	−0.9 (0.9)[h]	1.2 (1.0)[c,h]		−1.6 (0.6)[c,e,h]	−1.2 (0.7)[h]

Data expressed as mean (SD). G/I, Glucose to insulin ratio.
[a] Compared with baseline values: $P < 0.005$.
[b] Compared with 6 months after GH: $P < 0.05$.
[c] Compared with baseline values: $P < 0.001$.
[d] Compared with 6 months after GH: $P < 0.001$.
[e] GH-treated SGA subjects *vs.* untreated short SGA controls: $P < 0.05$.
[f] Compared with baseline values: $P < 0.05$.
[g] GH-treated SGA subjects *vs.* untreated short SGA controls: $P < 0.001$.
[h] Compared with zero: $P < 0.001$.
[i] GH-treated SGA subjects *vs.* untreated short SGA controls: $P < 0.005$.
[j] Compared with zero: $P < 0.005$.

discontinuation of GH, IGF-I and IGFBP-3 SDS had decreased and were significantly lower than zero again ($P = 0.003$ and $P < 0.001$, respectively). IGF-I SDS was comparable for GH-treated and untreated SGA subjects, whereas IGFBP-3 SDS was slightly lower in the GH-treated group ($P = 0.046$). None of the SGA subjects had IGF-I levels greater than 2 SDS.

Correlations

Si did not correlate with blood pressure, waist circumference, serum lipids, or IGF-I and IGFBP-3 SDS in the GH-treated SGA subjects, whereas in untreated short SGA controls, Si was inversely related to cholesterol levels (r = −0.45, $P = 0.031$) and IGF-I (r = −0.53, $P = 0.008$) and IGFBP-3 SDS (r = −0.51, $P = 0.011$). DI did not correlate with any of the outcome variables.

Discussion

Our longitudinal follow-up study shows that at 6.5 yr after discontinuation of long-term GH treatment, Si, AIR, DI, fast-

TABLE 4. Metabolic syndrome components in previously GH-treated SGA subjects and untreated SGA controls, according to ATP III criteria (25)

Symptoms	GH-treated SGA group	Untreated short SGA controls
Central obesity	None	1/25 (4.0%)
High TGs	6/37 (16.2%)	4/24 (16.7%)
Low HDL-c levels	6/37 (16.2%)[a]	10/23 (43.5%)
High BP	None[b]	8/25 (32.0%)
High fasting glucose	None	None
More than three symptoms	None	2/25 (8.0%)

[a] Compared with untreated short SGA controls: $P = 0.034$.
[b] Compared with untreated short SGA controls: $P < 0.001$.

ing glucose and insulin levels, BMI, waist circumference, and IGF-I levels were comparable for previously GH-treated and untreated SGA subjects. Systolic and diastolic BP and serum cholesterol were significantly lower in previously GH-treated SGA subjects.

Small size at birth has been associated with a higher risk of DM-II and metabolic syndrome in adulthood (1–3). In the present study, risk factors for DM-II and metabolic syndrome were longitudinally measured in previously GH-treated SGA subjects and compared with untreated short SGA controls.

At 6.5 yr after discontinuation of GH, Si, AIR, and DI were equivalent in GH-treated SGA subjects and untreated SGA controls. In addition, the GH-induced rise in glucose and insulin levels recovered after GH was stopped. At 6.5 yr after discontinuation, none of the GH-treated subjects either had increased fasting glucose levels or developed DM-II. GH has well-known insulin-antagonistic effects, and its use has been associated with a reduction in Si and hyperinsulinemia (13, 14, 23, 28). We show that these changes are reversible after discontinuation of GH treatment and remain so until at least 6.5 yr after discontinuation. Because insulin sensitivity and insulin secretory capacity are both strong predictors of the subsequent development of DM-II (29), our data are reassuring and suggest that long-term GH treatment of short SGA children does not have permanent effects on glucose homeostasis or increase the risk on DM-II.

Young GH-treated SGA adults had a normal systolic and diastolic BP SDS at 6.5 yr after discontinuation of GH treatment. In contrast, both systolic and diastolic BP SDS were significantly higher than zero in untreated SGA controls. Low birth weight has been associated with hypertension in

later life, and several studies have reported an increased systolic BP in SGA adolescents (30, 31). Before start of treatment, we also found an elevated systolic BP in our SGA subjects, which decreased during GH treatment (15). Taken these data together, GH treatment might have long-lasting beneficial effects on blood pressure in short SGA subjects.

Before start of GH treatment, our short SGA children had a low BMI, which normalized during GH treatment (15). Both BMI SDS and waist circumference were comparable for GH-treated and untreated SGA subjects. It has been demonstrated that the GH-induced increase in BMI is due to a rise in muscle mass rather than fat mass (32, 33). Given the fact that waist circumference is positively related to height (34) and that the GH-treated SGA subjects were taller than the untreated SGA controls, it might be that the latter have relatively more fat mass. Further studies comparing body composition and fat distribution in GH-treated and untreated SGA subjects are necessary to confirm this.

In the present study, serum cholesterol was lower in GH-treated SGA subjects than the untreated SGA controls, whereas HDL-c and TGs were equivalent for both groups. During GH treatment, serum levels of cholesterol, LDL-c, and HDL-c fell during the first year and remained stable thereafter (15). After discontinuation, cholesterol and LDL-c levels were lower than baseline values. Tenhola *et al.* (16) previously reported a higher incidence of hypercholesterolemia among SGA children, and it has also recently been shown that young SGA adults had significantly higher TG and lower HDL-c levels, compared with controls appropriate for gestational age (35). Hence, our data imply that GH treatment might have positive effects on lipid metabolism, which still persists after discontinuation of GH.

IGF-I and IGFBP-3 levels were significantly lower than zero SDS at baseline. During GH treatment, both increased significantly, resulting in values higher than zero. Previous studies have shown that GH treatment of short SGA subjects induces dose-dependent rises in GH, IGF-I, and IGFBP-3 levels (17, 36, 37). Concern has been expressed that persistently high GH and IGF-I levels could increase cancer risk in later life (38). Reassuringly, at 6.5 yr after discontinuation, serum IGF-I and IGFBP-3 levels had decreased and were comparable with those of untreated short SGA controls, indicating that the GH-induced rise in IGF-I and IGFBP-3 levels is completely reversible after discontinuation of GH.

In conclusion, our follow-up study shows that at 6.5 yr after discontinuation of long-term GH treatment, Si, DI, fasting levels of glucose and insulin, BMI, waist circumference, and IGF-I and IGFBP-3 levels were comparable for GH-treated and untreated young SGA adults. In addition, it turned out that systolic and diastolic BP and serum cholesterol were even lower in GH-treated subjects. These data are reassuring because they suggest that long-term GH-treatment does not increase the risk for DM-II and metabolic syndrome in young adults.

Acknowledgments

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