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Effect of Discontinuation of Growth Hormone Treatment on Risk Factors for Cardiovascular Disease in Adolescents Born Small for Gestational Age

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Hyperlipidemia, diabetes mellitus type 2, and coronary heart disease have been associated with being born small for gestational age (SGA). It has been reported that GH treatment induced higher insulin levels, which has led to concern regarding the long-term effect of GH treatment in predisposed individuals such as children born SGA. In this study, we assessed the effect of discontinuation of long-term GH treatment in 47 adolescents born SGA on oral glucose tolerance tests, blood pressure (BP), and serum lipid levels for two GH dosage groups (3 vs. 6 IU/m²·d). At 6 months after discontinuation of GH treatment mean (SD) age was 16.0 (2.1) yr. Mean duration of GH treatment had been 6.9 (1.5) yr. Fasting glucose levels and 120-min area under the curve for glucose 6 months after discontinuation of GH treatment showed no difference from pretreatment levels for both GH dosage groups. After discontinuation of GH treatment, fasting insulin levels returned to

pretreatment levels (8.4 mU/liter), whereas the 120-min area under the curve for insulin decreased, compared with 6-yr levels ($P < 0.01$), regardless of GH dosage group. No significant difference was found when levels were compared with a control group. In addition, for both GH dosage groups, no significant changes in systolic and diastolic BP SD score, total cholesterol, and atherogenic index (total cholesterol/high-density lipoprotein cholesterol) were seen from 6 yr of GH until 6 months after discontinuation of GH treatment. In conclusion, in children born SGA, the GH-induced insulin insensitivity disappeared after discontinuation of GH, even after long-term GH treatment. Furthermore, the beneficial effect of GH on BP was not changed after discontinuation of GH, and most children had normal lipid levels. (*J Clin Endocrinol Metab* 88: 347–353, 2003)

SINCE THE FIRST reports of correlation between low birth weight (LBW) and high blood pressure (BP) in the 1980s (1), a large number of studies have elaborated on the consequences of LBW in relation to adult disease. Several other diseases such as hyperlipidemia, diabetes mellitus (DM) type 2, and coronary heart disease have also been associated with LBW (2, 3). Based on his findings, Barker (4) suggested that the associated adult diseases, so-called syndrome X, are programmed by undernutrition *in utero*. Impaired fetal growth, especially when timed during the mid- to late gestation, would lead to permanent changes in organ structure and physiology.

Failure to show sufficient catch-up growth in childhood is a known phenomenon in about 10–15% of children born small for gestational age (SGA) (5, 6). Several studies (7, 8) have shown accelerated growth during GH treatment. However, it has been established that GH treatment increases postprandial insulin levels, probably because of a reduction

in insulin sensitivity (9). This finding has instigated several authors to express their concern regarding long-term effects of GH treatment in predisposed individuals such as SGA children (10).

We previously reported on the effect of 6 yr of GH treatment on carbohydrate metabolism, BP, and serum lipid levels in children born SGA (11, 12). The present article focuses on the effect of discontinuation of long-term GH treatment on carbohydrate metabolism, BP, and serum lipid levels in children born SGA.

Subjects and Methods

Study group

The study group comprised 47 children born SGA who were examined 6 months after discontinuation of GH treatment. Thirty children had an oral glucose tolerance test (OGTT) 6 months after discontinuation of GH. They had participated in a multicenter, double-blind, randomized, dose-response GH trial in prepubertal short children born SGA. Four children who had discontinued GH treatment did not agree to an examination 6 months after discontinuation of GH treatment and 28 were still receiving GH treatment.

The ongoing dose-response trial evaluates the effect of two dosages of GH (3 or 6 IU GH/m² BSA/day; approximately 0.03 or 0.07 mg/kg body weight/day) on long-term growth and ultimately on final height.

Inclusion criteria for the dose-response trial were described previously (7). In short, the children were included when prepubertal with a birth length SD score and height SD score below -1.88 , without spontaneous catch-up growth and without growth failure caused by other disorders. Patients with Silver-Russell syndrome and GH deficiency

Abbreviations: 30-min ratio, Ratio of insulin to glucose at 30 min; 120-min ratio, ratio of insulin to glucose at 120 min; AUC, area under the curve for time concentration; BMI, body mass index; BP, blood pressure; CA, chronological age; CV, coefficient of variation; DM, diabetes mellitus; FH, full height; GHD, GH deficiency; HbA_{1c}, hemoglobin A_{1c}; HDL-c, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LBW, low birth weight; LDL-c, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SGA, small for gestational age; TC, total serum cholesterol.

(GHD), however, were included in this dose-response trial. The Ethics Committees of the four participating centers in The Netherlands approved the dose-response trial. Written informed consent was obtained from the parents or custodians of each child.

Dose-response trial design

After stratification for chronological age (CA) and for spontaneous GH secretion during a 24-h GH profile, all children were randomly and blindly assigned to either one of two GH dosage groups: group A, 3 IU/m² body surface/day, or group B, 6 IU/m² body surface/day (~0.03 or 0.07 mg/kg·d, respectively) (7, 13). Biosynthetic GH (recombinant human GH Norditropin; Novo Nordisk A/S, Bagsvaerd, Denmark) was given sc once daily. To ensure the double-blind design, an equal volume of a reconstituted preparation was used. GH treatment was discontinued after either reaching final height, defined as a height velocity less than 0.5 cm over the last 6 months and/or bone age 15 yr or more for girls and 16.5 yr or more for boys, or on the decision of the patient because of satisfaction with near final height.

Physical examination

Every 3 months one physician (1991–1995, W.d.W.; 1995–1998, T.S.; 1998–2001, Y.v.P.) visited all children and measured height (14) and weight. Height was expressed as SD score for chronological age (CA) (height SD score) (15). Body mass index (BMI) was expressed as SD score for sex and CA using Dutch references (15). Every 6 months BP was measured. Systolic and diastolic BP were determined by the same Dynamap Critikon 1846SX (Southern Medical Corp.) with the children in sitting position using a cuff size corresponding to the size of their arm. BP was expressed as SD score, using age- and sex-specific reference values (16). Pubertal stage was assessed by the same investigators according to Tanner (17), using an orchidometer in boys.

Biochemical parameters

At the start, after 1 and 6 years of GH treatment, all children underwent an OGTT as previously described by Sas *et al.* (11). For the present study, we performed an OGTT 6 months after GH treatment in three of the four participating centers. To evaluate the overall responses to the oral glucose load, the following variables were described: 1) Impaired glucose tolerance (IGT) was defined according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (18): the 120-min level greater than 7.8 mmol/liter (140 mg/dl) and less than 11.1 mmol/liter (200 mg/dl); 2) the 120-min area under the curve for time concentration (AUC) during the OGTT was calculated using the trapezoidal rule; and 3) the ratio insulin to glucose at 30 min (30-min ratio) and the ratio at 120 min (120-min ratio) was calculated as an index for relative insulin resistance. Results were compared with the data of 24 normal adolescent girls aged 14.7 (0.98) yr and body mass index (BMI) 20.5 (2.0) kg/m², selected on the basis of postpubertal stage (Tanner breast stage V) as described by Potau *et al.* (19) (control group).

At start, during the dose-response trial and at 6 months after discontinuation of GH treatment, additional nonfasting blood samples were taken for determination of hemoglobin A_{1c} (HbA_{1c}) levels, total serum cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c). The atherogenic index was calculated as the ratio of TC to HDL-c. After centrifugation, all samples were frozen (–20 C) until assayed. Serum TC, LDL-c, HDL-c levels, and atherogenic index were compared with a Dutch control group of the same age (20).

Assays

The plasma glucose level was measured at the local hospital laboratories with automatic analyzers using a hexokinase-catalyzed glucose oxidase method. Plasma insulin was determined in one laboratory by RIA (Medgenix, Fleurus, Belgium). The intraassay coefficient of variation (CV) was 6–10% and the interassay CV was 6–11%. Fasting normal range was less than 20 mU/liter. Control samples were measured by a RIA, comparable with the RIA we used ($R^2 = 0.988$; $y = 0.397 + 0.925 \times x$) (19).

HbA_{1c} levels were measured in one laboratory using an automatic

HPLC analyzer (DIAMAT; Bio-Rad Laboratories, Inc., Edgemont, CA). The upper-normal assay limit is 6.6%.

The TC level was measured using an automated enzymatic method (21) with the CHOD-PAP high performance reagent kit (Boehringer, Mannheim, Germany). TC analysis was subject to the quality assessment program of the World Health Organization Regional Lipid Reference Center (Prague, Czech Republic). HDL-c and LDL-c were measured by the same method after precipitation. For HDL-c, the phosphotungstate method of Burstein was modified (22). LDL-c precipitation was performed with polyvinyl sulfate (Boehringer). The overall CV for TC, HDL-c, and LDL-c was 2.9%, 3.7%, and 5.8%, respectively. Lipid levels for the control group were measured by the same assays in the same laboratory (20). Except for plasma glucose, all determinations were performed in the same laboratories.

Statistical analyses

To maintain the double-blind design until all participants reached final height, an independent statistician (P.M.) performed the statistical analyses and summarized the results per treatment group in such a way that it was impossible for the investigator to identify individual patients. Accordingly, data are expressed as mean (SD) values unless otherwise specified. For the 30-min ratio, the 120-min ratio, and the atherogenic index, the geometric mean (95% range: the back-transformed ± 2 SD range of the log transformed variable) was used because of the positively skewed distributions involved. Differences in continuous variables were tested by paired Student's *t* tests. Differences between zero and SD score values at various time points during the study were tested by one-sample Student's *t* tests. Differences between groups were tested using a two-sample Student's *t* test unless otherwise specified. Correlations were estimated after adjustment for GH dosage. A *P* value less than 0.05 was considered significant. All calculations were performed using SPSS version 9.0 (SPSS, Inc., Chicago, IL).

Results

Table 1 shows the clinical data of the 47 children. Both GH dosage groups had similar initial characteristics. Three children had Silver-Russell syndrome. Seventeen children had GHD at start. Mean (SD) age at 6 months after discontinuation of GH treatment was 16.0 (2.1) yr. No significant differences were found in clinical data and serum glucose or insulin levels between the 30 children who underwent an OGTT at 6 months after discontinuation of GH treatment and the 17 children who did not.

Fasting glucose levels at 6 yr of GH treatment had increased significantly, compared with pretreatment ($P < 0.05$) but returned to pretreatment level for both GH dosage groups at 6 months after discontinuation of GH treatment (Fig. 1). The AUC for glucose showed no change either at 6 yr of GH treatment or 6 months after discontinuation of GH treatment. Fasting glucose levels and the AUC for glucose were not significantly different between the GH dosage

TABLE 1. Clinical data (n = 47)

	Group A (3 IU/m ² ·d)	Group B (6 IU/m ² ·d)
Male/female	16/7	11/13
Gestational age (wk)	37.7 (3.1)	36.3 (4.1)
Birth length SD score	–3.4 (1.4)	–3.8 (1.7)
Birth weight SD score	–2.3 (1.2)	–2.8 (0.9)
CA (yr) at start	8.6 (1.5)	8.3 (1.9)
Height SD score at start	–2.9 (0.8)	–2.8 (0.6)
BMI SD score at start	–0.9 (1.5)	–1.0 (1.0)
GH duration	7.2 (1.2)	6.6 (1.7)

Data expressed as mean (SD).

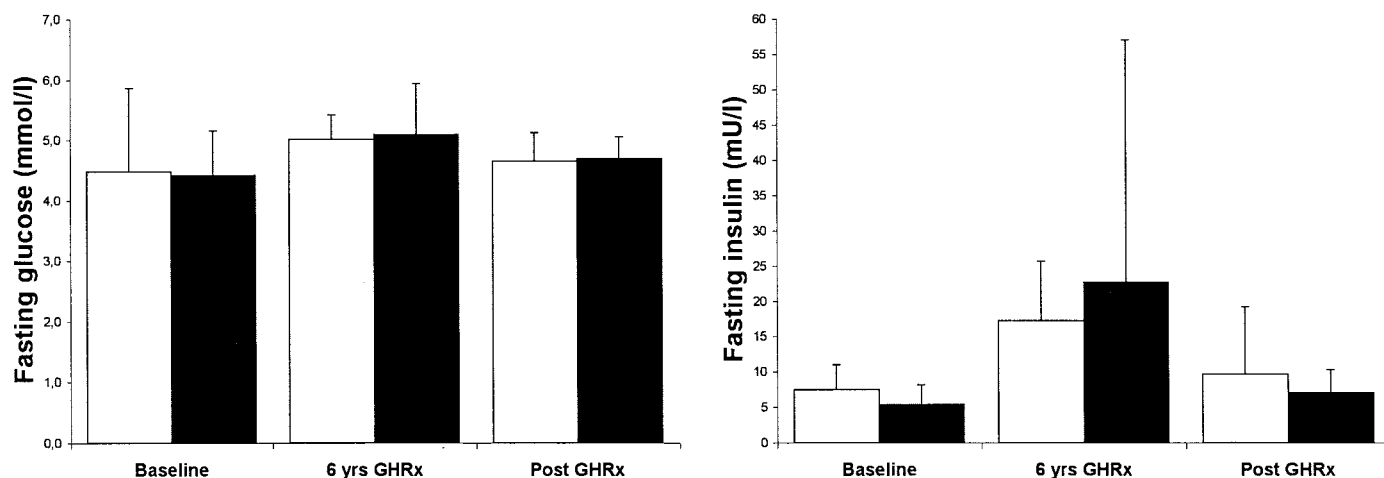


FIG. 1. Mean (+SD) fasting glucose levels (*left*) and fasting insulin levels (*right*) before treatment, at 6 yr of GH treatment, and at 6 months after discontinuation of treatment for group A (□) and B (■), respectively.

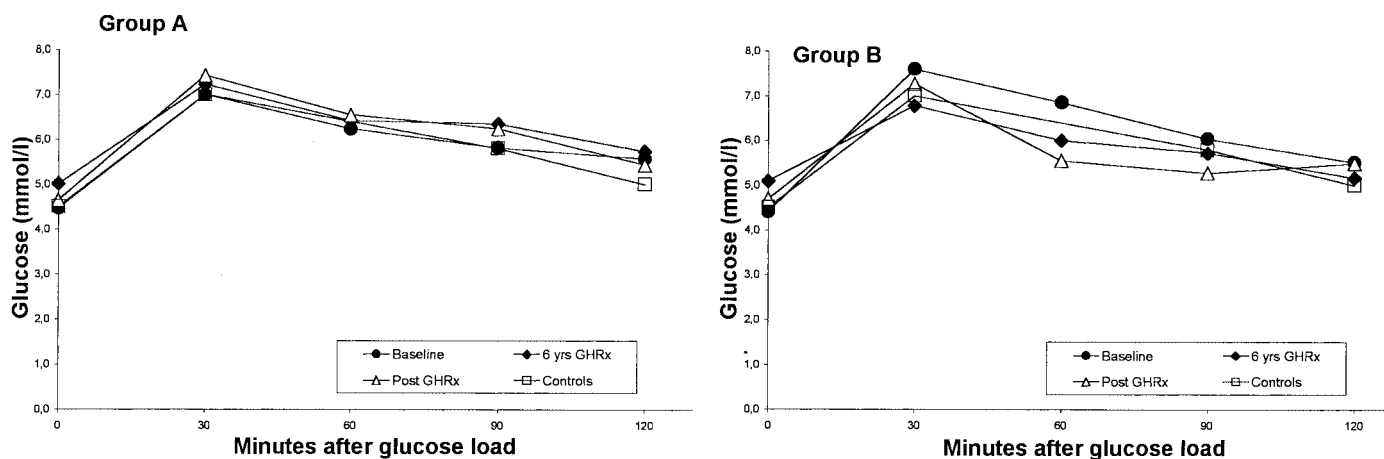


FIG. 2. Mean glucose levels during OGTT for group A (*left*) and group B (*right*) before treatment (●), at 6 yr of GH treatment (◆), at 6 months after discontinuation of treatment (△), and for the control group (□).

groups. Similarly, no significant differences were found between the GH-treated group and the control group (Fig. 2).

Fasting insulin levels had increased at 6 yr of GH treatment, compared with at pretreatment ($P < 0.001$) but returned to pretreatment levels 6 months after discontinuation of GH treatment (Fig. 1). Also, the AUC for insulin showed a significant increase from 3349 (1643) min·mU/liter before treatment to 6157 (2368) min·mU/liter at 6 yr of GH treatment ($P < 0.001$). At 6 months after discontinuation of GH treatment, the AUC for insulin, 4645 (3641) min·mU/liter, had significantly decreased, compared with the 6-yr level ($P < 0.01$) but remained higher than before treatment ($P < 0.05$). Compared with the control group, however, the AUC for insulin at 6 months after discontinuation of GH treatment showed no significant difference. No significant differences between GH dosage groups were found for change in fasting insulin levels and AUC for insulin (Fig. 3).

The 30-min and 120-min ratios had increased significantly at 6 yr of GH treatment, compared with pretreatment levels ($P < 0.001$, $P < 0.05$, respectively). At 6 months after discontinuation of GH treatment, the 30-min ratio returned to

pretreatment values for group A. For group B, however, the 30-min ratio remained increased, compared with pretreatment values ($P < 0.001$). The 120-min ratio, at 6 months after discontinuation of GH treatment, was comparable with pretreatment values, showing no differences between GH dosage groups.

After 6 yr of GH treatment, we found IGT in 1 of 27 children (4%), and at 6 months after discontinuation of GH treatment, IGT was present in 3 of 29 children (10%). One of the children with IGT at 6 yr of GH treatment also had IGT at 6 months after discontinuation of GH treatment. The other children had IGT only once during GH treatment or after discontinuation of GH treatment. None of the children developed DM type 1 or 2.

The HbA_{1c} values after 6 yr of GH treatment had significantly decreased from 5.1 (0.3) before treatment to 4.8 (0.4) at 6 yr of GH treatment ($P < 0.001$), whereas no change was found 6 months after discontinuation of GH treatment [4.7 (0.3)]. Throughout the years, all individual HbA_{1c} levels remained within normal range.

BMI sd score after 6 yr of GH treatment had increased

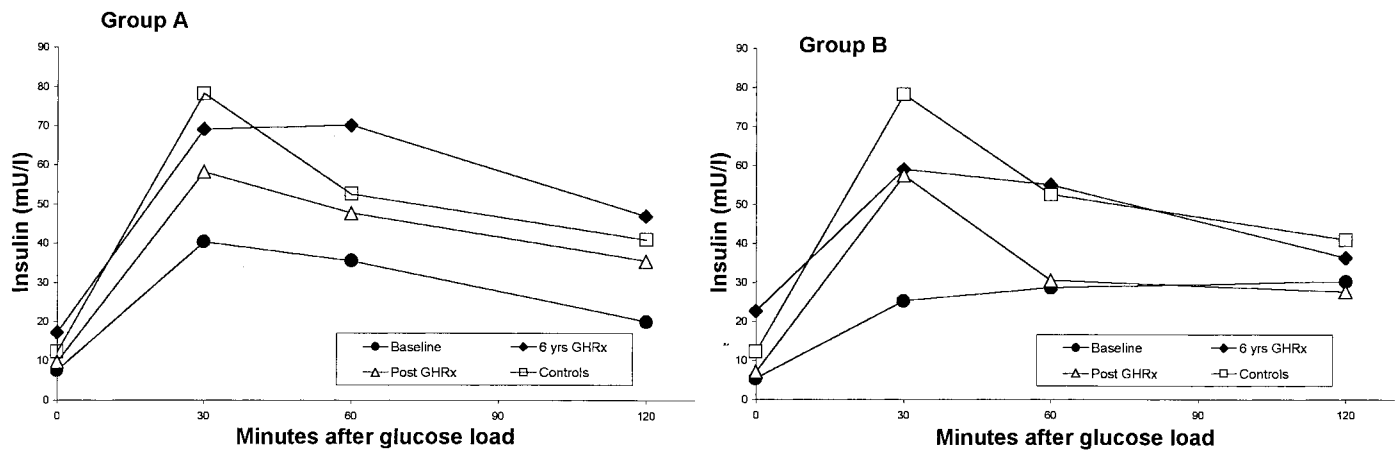


FIG. 3. Mean insulin levels during OGTT for group A (left) and group B (right) before treatment (●), at 6 yr of GH treatment (◆), at 6 months after discontinuation of treatment (△), and for the control group (□).

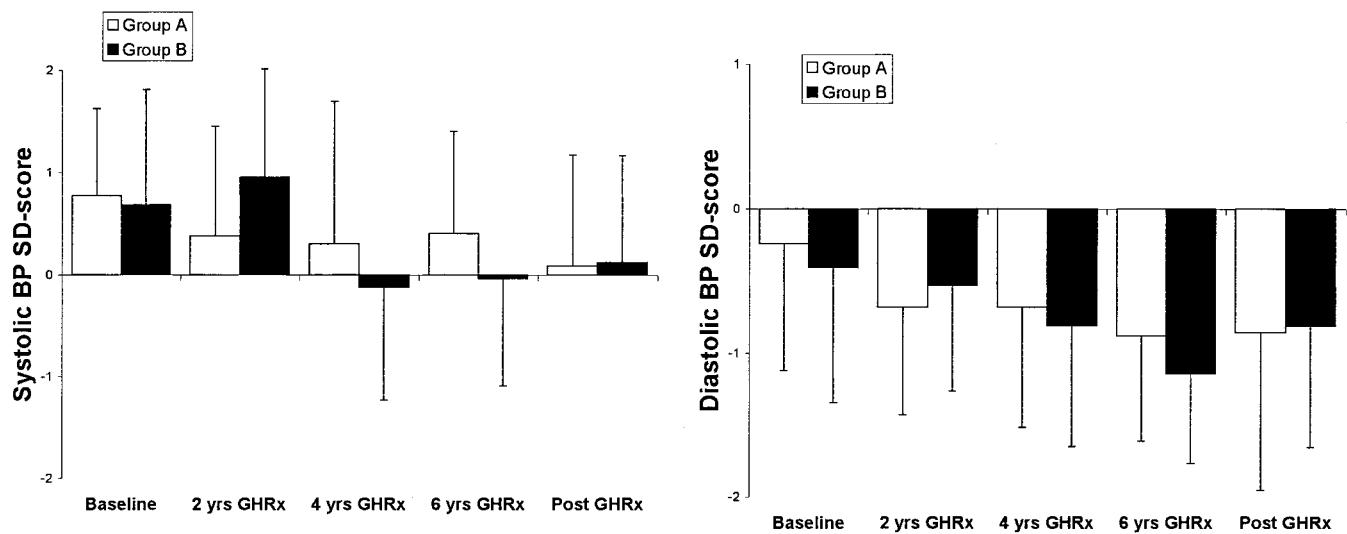


FIG. 4. Mean (SD) systolic BP SD score (left) and diastolic BP SD score (right) using age-matched reference values before GH treatment, at 6 yr of GH treatment, and at 6 months after discontinuation of treatment for group A (□) and group B (■).

significantly, compared with the pretreatment BMI SD score of -1.0 (1.2) ($P < 0.001$). As a result, the mean BMI SD score of -0.2 (1.1) at 6 yr was not significantly different from zero. At 6 months after discontinuation of GH treatment, mean BMI SD score was -0.1 (1.3), showing no significant difference, compared with 6-yr values. The change in BMI SD score was not significantly different between GH dosage groups.

Systolic and diastolic BP decreased significantly during 6 yr of GH treatment ($P < 0.05$, $P < 0.001$, respectively) to values not significantly different from zero for systolic BP and significantly lower than zero for diastolic BP ($P < 0.001$) (Fig. 4). After discontinuation of GH treatment, no change in systolic and diastolic BP was seen. The changes in BP were not significantly different between GH dosage groups.

Serum TC, LDL-c, and HDL-c levels significantly decreased after 6 yr of GH treatment, compared with the start ($P < 0.001$ for all) (Table 2). After discontinuation of GH treatment, TC levels showed no change, compared with 6-yr levels for both sexes, whereas LDL-c and HDL-c levels increased significantly for girls only ($P < 0.01$, $P = 0.01$, re-

spectively). Discontinuation of GH treatment did not result in a change in atherogenic index, compared with 6-yr values. Compared with the control group, serum TC, LDL-c but also HDL-c levels were significantly lower in the GH-treated group at 6 months after discontinuation of GH treatment, after correction for age and gender ($P < 0.001$, $P < 0.01$, $P < 0.01$, respectively). The atherogenic index, however, was not significantly different at 6 months after GH treatment, compared with the control group (Table 2). The changes in serum lipid levels were not significantly different between the GH dosage groups.

A significant correlation was found between AUC for glucose and AUC for insulin at 6 months after discontinuation of GH treatment ($r = 0.67$, $P < 0.0001$). BMI SD score correlated significantly with fasting insulin levels, systolic BP SD score, and the atherogenic index at 6 months after discontinuation of GH treatment ($r = 0.58$ ($P < 0.01$), $r = 0.32$ ($P < 0.05$), and $r = 0.42$, $P < 0.05$, respectively), but no correlation was found between BMI SD score and diastolic BP SD score or 120-min glucose level at 6 months after discontinuation of

TABLE 2. Serum lipid levels

	Group A	Group B	Control group
TC (mmol/liter)			
Pre-GH	4.9 (0.7)	4.6 (0.8)	
6 yr GH	4.1 (0.5)	3.8 (0.6)	
Post-GH	4.1 (0.5)	4.0 (0.7)	4.6 (0.8)
LDL-c (mmol/liter)			
Pre-GH	2.9 (0.5)	2.7 (0.9)	
6 yr GH	2.4 (0.5)	2.0 (0.7)	
Post-GH	2.5 (0.5)	2.3 (0.7)	2.8 (0.7)
HDL-c (mmol/liter)			
Pre-GH	1.5 (0.3)	1.4 (0.2)	
6 yr GH	1.1 (0.2)	1.0 (0.2)	
Post-GH	1.1 (0.2)	1.1 (0.4)	1.3 (0.3)
Atherogenic index ^a (TC/HDL-c)	3.0 (2.0–4.5)	3.0 (1.3–6.7)	3.7 (2.3–6.1)

Data expressed as mean (SD).

^a Geometric mean (95% range).

GH treatment. The atherogenic index at 6 months after discontinuation of GH treatment was also significantly correlated to diastolic BP SD score ($r = 0.43$, $P < 0.05$) but did not significantly correlate with systolic BP SD score, fasting insulin, or 120-min glucose levels.

Regarding the change in fasting glucose, fasting insulin, 30-min ratio, 120-min ratio, or AUC for insulin from start until 6 months after discontinuation of GH treatment, no correlation was found with the change in BMI-SD score.

Discussion

We present the results describing the effect of discontinuation of long-term GH treatment on carbohydrate metabolism, BMI, BP, and serum lipid levels in children born SGA. Our results showed that discontinuation of long-term GH treatment in adolescents born SGA normalized both fasting insulin and stimulated insulin levels after a significant increase during GH treatment. Furthermore, we found that discontinuation of GH did not alter the positive influence of GH on BMI and BP and had no effect on the atherogenic index (TC/HDL-c).

Previously, we have shown that stimulated glucose levels remained unchanged and fasting glucose levels rose slightly during 6 yr of GH treatment. In addition, both fasting and stimulated insulin levels increased significantly (11). It has been reported that GH treatment increases serum insulin levels in conditions such as GHD, Turner syndrome, and renal diseases (23, 24). This has been attributed to a GH-induced reduction of insulin sensitivity. Also, it has been reported that postprandial glucose levels increase in individuals with a reduced insulin sensitivity (25).

Our present results show that after discontinuation of GH treatment, fasting glucose and fasting insulin levels returned to pretreatment levels. This indicates that the rise in glucose and insulin levels were indeed a result of GH treatment. In other patient groups, such as girls with Turner syndrome and adolescents with and without GHD, similar results were found after discontinuation of GH treatment (24, 26, 27). Although fasting insulin levels at 6 months after discontinuation of GH treatment decreased to pretreatment levels, stimulated insulin levels did not. The reason posttreatment-stimulated insulin levels did not completely return to pre-

treatment levels might have various reasons. First, patients were prepubertal at start and postpubertal after discontinuation of GH treatment. Euglycemic clamp tests or frequently sampling iv glucose tolerance tests have shown that insulin sensitivity in healthy children decreases during puberty. Also, in these studies, postpubertal insulin sensitivity did not return to prepubertal values (19, 28, 29). The higher insulin levels were attributed to a reduced insulin sensitivity in normal puberty and postpuberty (28). Thus, the reduced insulin sensitivity, compared with baseline in our patients, might be explained by their postpubertal stage. This is supported by the fact that posttreatment-stimulated insulin levels were comparable with those of healthy adolescent peers. Second, the BMI SD score increased during GH treatment. Because a higher BMI is associated with higher insulin levels, this might also explain the higher posttreatment-stimulated insulin levels, compared with pretreatment levels (30, 31). In accordance, we found that adolescents with high fasting and stimulated insulin levels after discontinuation of GH treatment had a significantly higher BMI SD score. Third, posttreatment-stimulated insulin levels might be influenced by the fact that these adolescents were born SGA. Significantly higher insulin levels have been found after an oral glucose load in young adults born SGA, compared with normal controls (32, 33).

During the 6 yr of GH treatment, we found no differences between the two GH dosage groups regarding fasting or postprandial glucose and insulin levels. After discontinuation of GH treatment, however, we observed that in the higher GH-dosage group (group B), the decrease in the 30-min ratio for insulin/glucose was significantly less profound than in the lower GH-dosage group (group A). Because the 30-min ratio for insulin/glucose is an indicator for insulin resistance, this finding might suggest that long-term treatment with a higher GH dose of 6 IU/m²·d (~ 0.07 mg/kg·d) increases the degree of insulin resistance in children born SGA even after discontinuation of GH treatment. Compared with the control group, however, the mean 30-min ratio of group B still falls into the normal range.

Because insulin resistance, either on its own or in combination with β -cell dysfunction, causes IGT, we evaluated the number of children in our group with IGT. We found that after 6 yr of GH treatment, 1 of 27 children (4%) had IGT, and at 6 months after discontinuation of GH treatment, IGT was present in 3 of 29 children (10%). This result might be explained by the fact that puberty induces higher 120-min glucose levels (28, 29). The predisposition for insulin resistance and IGT in this group of adolescents born SGA, however, might also be responsible. Several studies found evidence for insulin resistance in untreated short children born SGA (34, 35). Also, being born with a LBW is associated with IGT and DM type 2 (3, 36). On the other hand, mean glucose levels at 6 months after discontinuation of GH decreased to pretreatment levels, individual HbA_{1c} levels never exceeded the normal range, and none of the children developed DM type 1 or 2.

Systolic and diastolic BP did not change after discontinuation of GH treatment. Another study evaluating the effect of discontinuation of GH in adolescents with GHD showed similar results (37). It has been reported that children and

young adults born with a LBW had a significantly higher systolic BP (38–41). In some studies this relationship was also found when LBW was corrected for gestational age (41), but in others it was not (32, 42). We reported, previously, that before start of GH treatment, children born SGA had a significantly higher systolic BP than reference values, which decreased to normal during GH treatment (11). Our present study shows that after discontinuation of GH treatment, systolic BP was not different to age- and sex-matched reference values, whereas diastolic BP was even significantly lower than reference values. These results contrast with data of untreated subjects born SGA and might reflect a positive influence of GH on blood pressure in this patient group.

During GH treatment serum TC, LDL-c, and HDL-c levels decreased. Discontinuation of GH treatment resulted in a slight increase in both LDL-c and HDL-c levels and no change in total cholesterol levels. Previous reports have shown that discontinuation of GH treatment in adolescents with GHD resulted in either no effect on serum lipids (43) or an increase in TC and LDL-c levels, without change in HDL-c levels (37, 44). The increase in both LDL-c and HDL-c in our children might also be an age effect (45, 46). We found that the atherogenic index after discontinuation of GH treatment was comparable with a control group of similar age. The lack of difference in serum lipid levels between the two GH dosage groups suggests that the changes in lipid levels were not related to GH treatment.

After discontinuation of GH treatment, we found a positive correlation among the atherogenic index, BMI *SD* score, systolic and diastolic BP *SD* score, and fasting insulin level. This might suggest that in some adolescents born SGA, a clustering of risk factors for cardiovascular disease, as described by Barker (4), is already present. A recent epidemiological study, however, reported that an increased risk for hypertension was mostly present in overweight young SGA adults (47). Therefore, a possible strategy to prevent an increased risk for cardiovascular disease in subjects born SGA might be to prevent overweight.

In conclusion, in children born SGA, the GH-induced insulin insensitivity disappeared after discontinuation of GH, even after long-term GH treatment. Furthermore, the beneficial effect of GH on BP was not changed by discontinuation of GH. Although most children had normal serum lipid levels, we did find a clustering of risk factors for cardiovascular disease, which may point to their predisposition. Whether long-term GH treatment will contribute to longevity, however, remains to be investigated.

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