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

Marije van Dijk, Ellen M. N. Bannink, Yvonne K. van Pareren, Paul G. H. Mulder, and Anita C. S. Hokken-Koelega

Department of Pediatrics (M.v.D., E.M.N.B., Y.K.v.P., A.C.S.H.-K.), Division of Endocrinology, Sophia Children’s Hospital, and Department of Epidemiology and Biostatistics (P.G.H.M.), Erasmus Medical Center, 3000 CB Rotterdam, The Netherlands

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)
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 ± 6.3 yr, respectively; P < 0.001) and duration of GH treatment (7.4 ± 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 using an enzymatic colorimetric test on the Hitachi 917 analyzer (Roche Diagnostics, Mannheim, Germany). Serum IGFBP-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 < 0.05 (α = 0.05/10) was considered statistically significant. Then only when P < 0.05, 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 level (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 from 0 to 10 min corrected for baseline insulin levels. DI equals AIR * Sg 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 85 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 (Ortho-clinical Diagnostics, Johnson & Johnson, Beers, Belgium). Serum insulin levels were measured by an immunoradiometric assay (Medgenix, Bio-source 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,不存在端点；Carpenter, 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 IGFBP-I and IGFBP-3 levels were determined in a laboratory by a specific RIA as previously described (26, 27).
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 \((P < 0.001)\).

### 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 \((P < 0.001)\).

### 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 \((P < 0.001)\).

### 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 \((P < 0.001)\).

### 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 \((P < 0.001)\).

### 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...
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, fasting 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. In addition, the GH-induced rise in glucose and insulin levels, BMI, waist circumference, and IGF-I levels were comparable for previously GH-treated and untreated SGA subjects.

---

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

| Symptom                  | 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)                   | 4.7 (0.5)                    | 4.9 (0.5)                    | 5.0 (0.4)                    |
| Insulin (μU/liter)       | 6.2 (3.5)            | 16.0 (8.0)                  | 8.8 (7.4)                    | 9.3 (3.9)                    | 10.7 (5.4)                   |
| Fasting Glucose          | 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)                   | 4.7 (0.4)                    | 5.2 (0.3)                    | 5.4 (0.3)                    |
| Systolic BP (mm Hg)      | 106.7 (11.1)         | 111.4 (12.7)                | 115.3 (12.6)                 | 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)                   | 75.7 (6.3)                   |
| Systolic BP SDS          | 1.1 (0.9)            | 0.3 (1.2)                   | 0.3 (1.2)                    | 0.0 (1.7)                    | 1.3 (0.9)                    |
| Diastolic BP SDS         | 0.0 (0.1)            | -0.5 (0.6)                  | 0.3 (0.8)                    | 0.1 (0.6)                    | 1.0 (0.5)                    |
| BMI (kg/m²)              | 14.7 (1.8)           | 19.1 (2.8)                  | 20.6 (2.8)                   | 22.4 (2.2)                   | 22.6 (3.3)                   |
| BMI SDS                  | -0.9 (1.3)           | 0.1 (1.0)                   | 0.2 (1.0)                    | -0.1 (0.7)                   | 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)                   | 4.1 (0.6)                    | 4.3 (0.8)                    | 4.8 (1.1)                    |
| LDL-c (mmol/liter)       | 2.8 (0.8)            | 2.2 (0.6)                   | 2.5 (0.6)                    | 2.6 (0.7)                    | 2.8 (0.7)                    |
| HDL-c (mmol/liter)       | 1.4 (0.3)            | 1.1 (0.2)                   | 1.1 (0.2)                    | 1.3 (0.3)                    | 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)           | 1.9 (0.7)                   | -0.4 (0.7)                   | -0.6 (1.0)                   | -0.6 (1.0)                   |
| IGFBP-3 SDS              | -0.9 (0.9)           | 1.2 (1.0)                   | -1.6 (0.6)                   | -1.2 (0.7)                   |                      |

Data expressed as mean (SD). 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 < 0.001.

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.

---

**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%)         | 10/23 (43.5%)               |
| High BP                    | None                 | 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.
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
We thank Mrs. J. Dunk, J. van Nieuwakasteel, and J. C. Bruinings, research nurses, for their technical assistance and help with data collection. We greatly acknowledge the physicians who participated in the original GH trial: E. C. A. M. Houdijk, M.D., Ph.D., VU University Medical Centre, Amsterdam, The Netherlands; M. Jansen, M.D., Ph.D., Wilhelmina Children's Hospital, Utrecht, The Netherlands; and H. M. Reeser, M.D., Ph.D., Juliana Children's Hospital, The Hague, The Netherlands.

Received May 17, 2006. Accepted October 16, 2006.

Address all correspondence and requests for reprints to: Marije van Dijk, Erasmus Medical Center, Sophia Children's Hospital, Department of Pediatrics, Division of Endocrinology, PO Box 2060, 3000 CB Rotterdam, The Netherlands. E-mail: m.vandijk1@erasmusmc.nl.

This work was supported by Novo Nordisk A/S, Bagsvaerd, Denmark, and Novo Nordisk Farma BV, Alphen a/d Rijn, The Netherlands. Disclosure Statement: The authors have nothing to disclose.

References
1. Barker DJ, Bull AR, Osmond C, Simmonds SJ 1990 Fetal and placental size and risk of hypertension in adult life. BMJ 301:259–262
2. Barker DJ, inlet DJ, Fall CH, Osmond C, Phillips J, Clark PM 1993 Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidemia (syndrome X): relation to reduced fetal growth. Diabetologia 36:62–67
3. Phillips DJ, Barker DJ, Hales CN, Hirst S, Osmond C 1994 Thinness at birth and cardiovascular disease in later life. Diabetologia 37:690–694
4. Karlberg J, Albertsson-Wikland K 1995 Growth in full-term small-for-gestational-age infants: from birth to final height. Pediatr Res 38:743–739
5. Hokken-Koelega AC, De Ridder MA, Remmen RJ, De Muinck Keizer-Schrama SM, Drop SL 1995 Children born small for gestational age: do they catch up? Pediatr Res 38:267–271
6. Bratusch-Marrain PR, Smith D, DeFronezo RA 1992 The effect of growth hormone on glucose metabolism and insulin secretion in man. J Clin Endocrinol Metab 55:975–982
7. Moller N, Butler PC, Antsiferov MA, Alberti KG 1989 Effects of growth hormone on insulin sensitivity and forearm metabolism in normal man. Diabetologia 32:105–110
8. Heytstra RA, Bouwland WD, Caprio S, Silver D, Sherwin RS, Tamborlane WV 1997 Decreased insulin sensitivity and compensatory hyperinsulinemia after hormone treatment in children with short stature. J Clin Endocrinol Metab 82:3324–3328
9. Cutfield WS, Wilton P, Benmarker H, Albertsson-Wikland K, Chatelain P, Ranke MB, Price DA 2000 Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. Lancet 355:610–613
10. Hofman PL, Cutfield WS, Robinson EM, Bergman RN, Menon RK, Sperling MA, et al. 1997 Insulin resistance in short children with intrauterine growth retardation. J Clin Endocrinol Metab 82:402–406
11. Arends NJ, Boonstra VH, Duivenvoorden HJ, Hofman PL, Cutfield WS, Hokken-Koelega AC 2005 Reduced insulin sensitivity and the presence of cardiovascular risk factors in short prepubertal children born small for gestational age (SGA). Clin Endocrinol (Oxf) 62:44–50
12. Sas T, Mulder P, Aarnout HC, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A 2001 Carbohydrate metabolism during long-term growth hormone treatment in children with short stature born small for gestational age. Clin Endocrinol (Oxf) 54:243–251
13. van Pareren Y, Mulder P, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A 2000 Effect of discontinuation of growth hormone treatment on risk factors for cardiovascular disease in adolescents born small for gestational age. J Clin Endocrinol Metab 88:347–353
14. de Zegher F, Ong K, van Helvoort M, Mohn A, Woods K, Dunger D 2002 High-dose growth hormone (GH) treatment in non-GH-deficient children born small for gestational age: does it induce growth responses related to pretreatment GH secretion and associated with a reversible decrease in insulin sensitivity. J Clin Endocrinol Metab 87:148–151
15. Sas T, Mulder P, Hokken-Koelega A 2000 Body composition, blood pressure, and lipid metabolism before and during long-term growth hormone (GH) treatment in children with short stature born small for gestational age either with or without GH deficiency. J Clin Endocrinol Metab 85:3786–3792
16. Tenhola S, Martikainen A, Rahiala E, Hergard E, Halonen P, Voutilainen R 2000 Serum lipid concentrations and growth characteristics in 12-year-old children born small for gestational age. BMJ 320:623–628
17. Sas T, de Waal W, Mulder P, Houdijik M, Jansen M, Reeser M, Hokken-Koelega A 1999 Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, double-blind, dose-response trial. J Clin Endocrinol Metab 84:3064–3070
18. Van Pareren Y, Mulder P, Houdijik M, Jansen M, Reeser M, Hokken-Koelega A 2003 Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial. J Clin Endocrinol Metab 88:3384–3390
19. Roede MJ 1990 The secular trend in The Netherlands. The third national-wide growth study. Arztl Jugendkd 81:330–336

Downloaded from https://academic.oup.com/jcem/article-abstract/92/1/160/2598304 by guest on 16 March 2020
20. Viet AL, van den Hof S, Elvers LH, Ocke MC, Vossenaar M, Seidell JC, Otten F, van Veldhuizen H 1993 Blood pressure nomograms for children and adolescents, by height, sex, and age, in the United States. J Pediatr 123:871–898.

21. Rosner B, Prineas RJ, Loggie JM, Daniels SR 1993 Blood pressure levels in prepubertal children with chronic renal insufficiency and severe growth retardation. J Clin Endocrinol Metab 71:688–695.

22. Cutfield WS, Jackson WE, Jefferies C, Robinson EM, Breier BH, Richards GE, Hofman PL 2003 Reduced insulin sensitivity during growth hormone therapy for short children born small for gestational age. J Pediatr 142:113–116.

23. Pacini G, Bergman RN 1986 MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Programs Biomed 29:23:113–122.

24. 2001 Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 285:2486–2497.

25. 1986 MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Programs Biomed 23: 113–122.

26. Hokken-Koelega AC, Hackeng WH, Stijnen T, Wit JM, de Muinck Keizer-Schrama SM, Drop SL 1990 Twenty-four-hour plasma growth hormone (GH) profiles, urinary GH excretion, and plasma insulin-like growth factor-I and II levels in prepubertal children with chronic renal insufficiency and severe growth retardation. J Clin Endocrinol Metab 71:688–695.

27. Blum WF, Ranke MB, Kietzmann K, Gauggel E, Zeisel HJ, Bierich JR 1996 Changes in serum insulin-like growth factor I (IGF-I) and IGF-binding protein-3 levels during growth hormone treatment in prepubertal short children born small for gestational age. J Clin Endocrinol Metab 81:3902–3908.

28. Bogaasewski M, Jansson C, Rosberg S, Albertsson-Wikland K 1996 Changes in serum insulin-like growth factor I (IGF-I) and IGF-binding protein-3 levels during growth hormone treatment in prepubertal short children born small for gestational age. J Clin Endocrinol Metab 81:3902–3908.

29. Lyssenko V, Almgren P, Anevski D, Perfekti R, Lahti K, Nissen M, Isomaa B, Forsen B, Homstrom N, Saloranta C, Taskinen MR, Groop L, Tuomil T 2005 Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. Diabetes 54:166–174.

30. Pharaoh PO, Stevenson CJ, West CR 1998 Association of blood pressure in adolescence with birthweight. Arch Dis Child Fetal Neonatal Ed 79:F114–F118.

31. Leon DA, Johansson M, Rasmussen F 2000 Gestational age and growth rate of fetal mass are inversely associated with systolic blood pressure in young adults: an epidemiologic study of 165,136 Swedish men aged 18 years. Am J Epidemiol 152:597–604.

32. Leger J, Garel C, Fjellestad-Paulsen A, Hassan M, Czernichow P 1998 Human growth hormone treatment of short-stature children born small for gestational age: effect on muscle and adipose tissue mass during a 3-year treatment period and after 1 year’s withdrawal. J Clin Endocrinol Metab 83:3512–3516.

33. Arends NJ 2003 Short SGA children: etiological aspects, metabolic consequences and effects of GH treatment pediatric endocrinology. Rotterdam, The Netherlands: Erasmus University; 93–110.

34. Fredriks AM, van Baaren S, Fekkes M, Verloove-Vanhorick SP, Wit JM 2005 Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? Eur J Pediatr 164:216–222.

35. Jaquet D, Dehghmoun S, Chevenne D, Collin D, Czernichow P, Levy-Marchal C 2005 Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth. Diabetologia 48:849–855.

36. Boguszewski M, Jansson C, Rosberg S, Albertsson-Wikland K 1996 Changes in serum insulin-like growth factor I (IGF-I) and IGF-binding protein-3 levels during growth hormone treatment in prepubertal short children born small for gestational age. J Clin Endocrinol Metab 81:3902–3908.

37. van Dijk M, Mulder P, Houdijk M, Mulder J, Noordam K, Odink RJ, Rongen-Westeraeken C, Voorhoeve P, Waeltens J, Stokvis-Brantsma J, Hokken-Koelega A 2006 High serum levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I) during high-dose GH treatment in short children born small for gestational age. J Clin Endocrinol Metab 91:1390–1396.

38. Renehan AG, Zwahlen M, Minder C, O’Dwyer ST, Shalet SM, Egger M 2004 Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 363:1346–1353.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.