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Carbohydrate Metabolism during Long-Term Growth Hormone (GH) Treatment and after Discontinuation of GH Treatment in Girls with Turner Syndrome Participating in a Randomized Dose-Response Study*

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ABSTRACT

To assess possible side-effects of GH treatment with supraphysiological doses on carbohydrate (CH) metabolism in girls with Turner syndrome (TS) during long term GH treatment and after discontinuation of GH treatment, the results of oral glucose tolerance tests and hemoglobin A_{1c} measurements were analyzed in 68 girls with TS participating in a randomized dose-response trial. These previously untreated girls, aged 2–11 yr, were randomly assigned to 1 of 3 GH dosage groups: group A, 4 IU/m^2·day (~0.045 mg/kg·day); group B, first year ,4 IU/m^2·day; thereafter, 6 IU/m^2·day (~0.0675 mg/kg·day); group C, first year, 4 IU/m^2·day; second year, 6 IU/m^2·day; thereafter, 8 IU/m^2·day (~0.090 mg/kg·day). After the first 4 yr, girls 12 yr of age or older started with 5 μg/kg BW·day 17β-estradiol for induction of puberty. To assess the effects of long term high dose GH treatment on CH metabolism, the 7-yr data from the oral glucose tolerance tests in 9 girls of group C were evaluated (group C1). To determine whether the changes in CH metabolism during GH treatment would persist after discontinuation of GH treatment, the data for 28 girls who had reached adult height (group A, n = 9; group B, n = 10; group C, n = 9) were evaluated at baseline, after 4 yr of GH treatment, and 6 months after discontinuation of GH.

Seven-year data for group C1 showed that glucose levels did not significantly change during GH treatment, whereas fasting insulin levels as well as glucose-induced insulin levels increased significantly. The data for the 28 girls who were treated with GH for a mean (SD) period of 85.3 (13.3) months demonstrated that the GH-induced higher insulin levels decreased to values close to or equal to pretreatment values after discontinuation of GH treatment. Changes in CH variables were not significantly related to the GH dose. Hemoglobin A_{1c} levels never showed an abnormal value. The prevalence of impaired glucose tolerance was low, and none of the girls developed diabetes mellitus.

In conclusion, long term GH treatment with dosages up to 8 IU/m^2·day in girls with TS has no adverse effects on glucose levels, but induced higher levels of insulin, indicating relative insulin resistance. The increased insulin levels during long term GH treatment decreased after discontinuation of GH treatment to values close to or equal to pretreatment values. Although the reversibility of the effects of long term GH is reassuring, the consequence of long term hyperinsulinism is still unknown. (*J Clin Endocrinol Metab* **85:** 769–775, 2000)

SHORT STATURE is one of the main features in Turner syndrome (TS) (1, 2). Although these girls are not clearly GH deficient (3), GH administration accelerates growth in a dose-dependent way (4–6). In addition, recent papers reported a considerable increase in adult height in girls with TS who started GH treatment at a relatively young age and/or who were treated with supraphysiological GH dosages (6–9).

Insulin resistance and carbohydrate (CH) intolerance have been reported in untreated girls with Turner syndrome (10–12). In addition, in adults with TS who had not received GH treatment in childhood, glucose intolerance and noninsulin- and insulin-dependent diabetes mellitus are more common than in healthy women (13, 14). As supraphysiological concentrations of GH in acromegalic patients (15) and in normal adults (16, 17) resulted in a decrease in glucose sensitivity to insulin in liver and in extrahepatic tissues, concern has been expressed regarding possible detrimental effects of long term treatment with supraphysiological GH dosages in girls with TS. In our previous report, the 4-yr results of oral glucose tolerance tests (OGTTs) were analyzed in 68 girls with TS participating in a randomized dose-response multicenter trial receiving 4, 6, or 8 IU/m^2·day. We showed that 4 yr of GH treatment did not negatively influence glucose levels, whereas insulin levels increased significantly compared to

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baseline (18). As these relatively young girls are being treated for many years until adult height is reached, the question arose as to whether the observed GH-induced insulin resistance would show a further increase during prolonged GH treatment. In addition, it is unknown whether the insulin resistance in girls with TS during long term treatment with supraphysiological GH dosages would decrease to a pretreatment level after discontinuation of GH treatment.

The results of GH treatment on growth were described previously by our group (19). In the present study we investigated the effects of GH treatment on CH metabolism in a subgroup receiving GH in a dose up to 8 IU/m^2·day during 7 yr of GH treatment. In addition, in girls who had been treated with 4, 6, or 8 IU GH/m^2·day and had reached adult height, changes in CH metabolism were evaluated during GH treatment as well as after discontinuation of GH treatment.

Subjects and Methods

Study group and treatment regimens

Sixty-eight previously untreated girls with TS were enrolled in a multicenter GH dose-response study in The Netherlands. The diagnosis was confirmed by lymphocyte chromosomal analysis. Inclusion criteria were chronological age between 2–11 yr, height below the 50th percentile for healthy Dutch girls (20), and a normal thyroid function. Exclusion criteria were associated endocrine and/or metabolic disorders, growth failure caused by other disorders or emotional deprivation, hydrocephalus, previous use of drugs that could interfere with GH treatment, and spontaneous puberty (21). Written informed consent was obtained from the girls and their parents or custodians. The study protocol was approved by the ethics committee of each participating center.

After stratification for chronological age and height SD score for chronological age girls were randomly assigned to group A (n = 23) receiving 4 IU/m^2 body surface·day (equivalent to 0.045 mg/kg·day), group B (n = 23) receiving 4 IU/m^2·day in the first year followed by 6 IU/m^2·day (~0.0675 mg/kg·day), or group C (n = 22) receiving 4 IU/m^2·day in the first year, 6 IU/m^2·day in the second year, and thereafter 8 IU/m^2·day (~0.090 mg/kg·day).

Biosynthetic human GH (Norditropin, Novo Nordisk A/S, Bagsvaerd, Denmark) was given sc once daily at bedtime using a pen injection system. Every 3 months the total GH dose was adjusted to the calculated body surface. According to the study protocol, treatment was stopped when subjects had grown less than 1 cm over 6 months. However, when girls were satisfied with the height achieved, they elected to stop GH treatment before study criteria for the termination of treatment had been reached. In the first 4 yr of GH treatment, no estrogens for pubertal induction were given to the girls. After 4 yr of GH treatment, estrogen therapy was immediately started in the girls who were older than 12.0 yr of age. The younger girls started estrogen therapy at a yearly visit after reaching the age of 12 yr. In the first 2 yr of estrogen therapy, the girls received 5 μg 17β-estradiol/kg BW·day (orally), in the third year they received 7.5 μg/kg·day and thereafter 10 μg/kg·day. After discontinuation of GH treatment, the dose of estrogens was further increased depending on the clinical signs of breast development.

Study protocol

Before the start of treatment (baseline) and every 3 months after the start of GH treatment, all children were seen at their local hospital for a physical examination, including measurements of standing height (H) and weight (W). Height was expressed as SD score, using references for healthy Dutch girls (20), as well as references for Dutch-Swedish-Danish references for girls with TS (2). Body mass index [BMI; weight (kilograms)/height (meters)^2] was expressed as the SD score for sex and chronological age (20).

Glycosylated hemoglobin (HbA_{1c}) was determined yearly. The girls of all 3 GH dosage groups who had reached adult height had undergone an OGTT at baseline, after 4 yr of GH treatment, and 6 months after discontinuation of GH treatment. Additional OGTTs were performed in a random sample of 10 girls from group C (group C1) at 6, 18, 30, 60, and 84 months after the start of GH treatment. A single team performed all OGTTs after 3 days of unrestricted diet supplemented with 100 g carbohydrate (Fantomalt) and after overnight fasting. Glucose (1.75 g glucose/kg BW; maximum, 50 g) was administered orally within 5 min. Blood samples were collected at 0, 30, 60, 90, 120, 150, and 180 min, and plasma glucose and insulin levels were measured.

To evaluate the overall responses to the oral glucose load, apart from the glucose and insulin levels at the various time points, 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 (22): 2-h level more than 7.8 mmol/L (140 mg/dL) and less than 11.1 mmol/L (200 mg/dL); 3) 3-h area under the curve for time-concentration corrected for fasting levels during the OGTT (AUCab), calculated using the trapezoidal rule; and 3) the ratio of insulin/glucose at 30 min and the ratio at 120 min, calculated as an index for relative insulin resistance.

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 was 6–10% and the interassay coefficient of variation was 6–11% (fasting normal range, <20 mU/L). HbA_{1c} levels were measured in one laboratory using an automatic high pressure liquid chromatography analyzer (DIAMAT, Bio-Rad Laboratories, Inc., Edgemont, CA). The upper normal assay limit is less than 6.6%.

Statistical analyses

Results are expressed as the mean (SD) unless indicated otherwise. Differences in variables between time points were tested using paired Student's *t* tests. Differences in the change in values between the GH dosage groups were first tested by a linear trend test to assess a possible dose-dependent effect. In case of a significant result, this was followed by comparisons between two groups with Student's *t* tests. Correlations between variables were assessed with Pearson's correlation coefficient. $P < 0.05$ was considered significant.

Results

Four girls (group A, n = 1; group B, n = 2; group C, n = 1) dropped out of the study long before reaching adult height because of noncompliance. In all 4 cases no problems with the CH tolerance were involved in the decision to discontinue the treatment. Data for these 4 girls were not used for the analysis of long term GH treatment. Table 1 lists the baseline clinical data of the remaining 9 girls of group C1 who have been followed for 7 yr as well as those of the 28 girls who have reached adult height. None of these 28 girls belonged to the subgroup C1. Although it is obvious that the 9 girls of

TABLE 1. Mean (SD) baseline data for each treatment group

	Group C1	Group A	Group B	Group C
No. of girls	9	9	10	9
Baseline age (yr)	4.4 (1.7)	8.0 (1.0)	8.6 (1.6)	8.5 (1.3)
Baseline $HSDS_{CA}$ (RvW)	−2.3 (1.1)	−2.9 (1.2)	−2.8 (0.7)	−2.8 (0.8)
Baseline $HSDS_{CA}$ (DSD)	0.4 (1.1)	0.0 (1.5)	0.2 (0.8)	0.1 (1.0)
Karyotype: 45,X	8	6	9	7
Karyotype: other	1	3	1	2

Karyotype (45,X; other) is expressed in numbers of patients. $HSDS_{CA}$, Height SD score for chronological age; RvW, Roede van Wieringen references for healthy Dutch girls; DSD, Dutch-Swedish-Danish references for girls with Turner syndrome.

group C1 were younger than the other 28 girls because of sampling variability, there were no relevant differences in baseline variables between the groups.

OGTTs during 7 yr of GH treatment in group C1

At baseline, none of the girls had an abnormal glucose response during the OGTT. After 6 and 18 months of treatment, in one girl IGT was found (glucose levels after 120 min, 8.4 and 9.8 mmol/L, respectively). Thereafter, she had normal OGTTs. None of the girls developed diabetes mellitus. Figure 1 shows the mean glucose and insulin levels during the OGTTs, respectively, at baseline and after 4 and 7 yr of GH treatment. Table 2 lists the CH variables at the three time points during the study period. Fasting glucose levels and the AUCab for glucose did not significantly change during treatment. Fasting insulin levels increased significantly during the first 4 yr of GH treatment compared to baseline levels ($P = 0.031$) and had increased further after 7 yr of GH treatment, resulting in levels significantly higher than those after 4 yr of GH treatment ($P = 0.014$). The AUCab for insulin had increased significantly in the first 4 yr of GH treatment ($P < 0.001$) without a further increase thereafter. The insulin/glucose ratio at 30 and 120 min, respectively, increased significantly during the first 4 yr of GH treatment ($P = 0.003$ and $P = 0.001$, respectively) without significant changes thereafter.

One of the girls started estrogen therapy after 6 yr of GH treatment, and another girl had some spontaneous breast development (Tanner breast stage II) after 57 months of GH treatment. Excluding these two girls from the analysis, similar patterns in the development in CH variables during GH treatment were found in this prepubertal group as in the total group of nine girls (data not shown).

OGTTs at baseline, after 4 yr of treatment, and after discontinuation of GH in 28 girls of groups A, B, and C

Figure 2 shows the mean glucose levels during the OGTTs at baseline, after 4 yr of GH treatment, and 6 months after discontinuation of GH treatment in groups A (n = 9), B (n = 10), and C (n = 9), respectively. These 28 girls have reached adult height after a mean (SD) duration of GH treatment of 85.3 (13.3) months. Before the start of treatment, in 2 girls of group C IGT was found (glucose levels after 120 min, 7.9 and 8.0 mmol/L, respectively). Both girls had no IGT during GH treatment, but after discontinuation of treatment, IGT was found again in 1 of these girls (glucose level after 120 min, 8.0 mmol/L). After 4 yr of GH treatment, another girl of group B had IGT (glucose level after 120 min, 8.4 mmol/L); however, after discontinuation of GH treatment the OGTT results for this girl were normal. None of the girls developed diabetes mellitus.

Table 3 shows that fasting glucose levels had significantly increased after 4 yr of GH treatment ($P = 0.003$) and had significantly decreased after discontinuation of GH treatment to baseline levels ($P = 0.002$). The AUCab for glucose was significantly decreased compared to baseline ($P = 0.013$) after 4 yr of GH treatment, without a further significant change after discontinuation of GH treatment. No significant differences in the change in fasting glucose levels or AUCab for glucose between the GH dosage groups were found.

Figure 3 demonstrated the mean insulin levels during the OGTTs for groups A, B, and C, respectively. The fasting insulin levels were increased after 4 yr of GH treatment ($P < 0.001$) and decreased after discontinuation of GH treatment ($P = 0.002$; Table 3). However, fasting insulin levels after discontinuation of GH treatment were still significantly higher than baseline levels ($P < 0.001$). Although there seems to be a trend toward higher fasting insulin levels with higher GH dosages after 4 yr of GH treatment, this was not statistically significant. The AUCab for insulin was significantly increased after 4 yr of treatment ($P = 0.003$) and significantly decreased after discontinuation of GH treatment ($P = 0.001$) to pretreatment levels. No significant differences in the change in AUCab for insulin between the GH dosage groups were found.

The ratio of insulin to glucose at 30 min significantly increased during GH treatment ($P < 0.001$) and was followed by a significant decrease after discontinuation of GH treatment ($P = 0.009$; Table 3). However, the ratio at 30 min after discontinuation of GH treatment were still significantly higher than baseline levels ($P = 0.010$). The ratio at 120 min was significantly increased after 4 yr of GH treatment compared to baseline ($P < 0.001$) and was followed by a significant decrease after discontinuation of GH treatment to base-

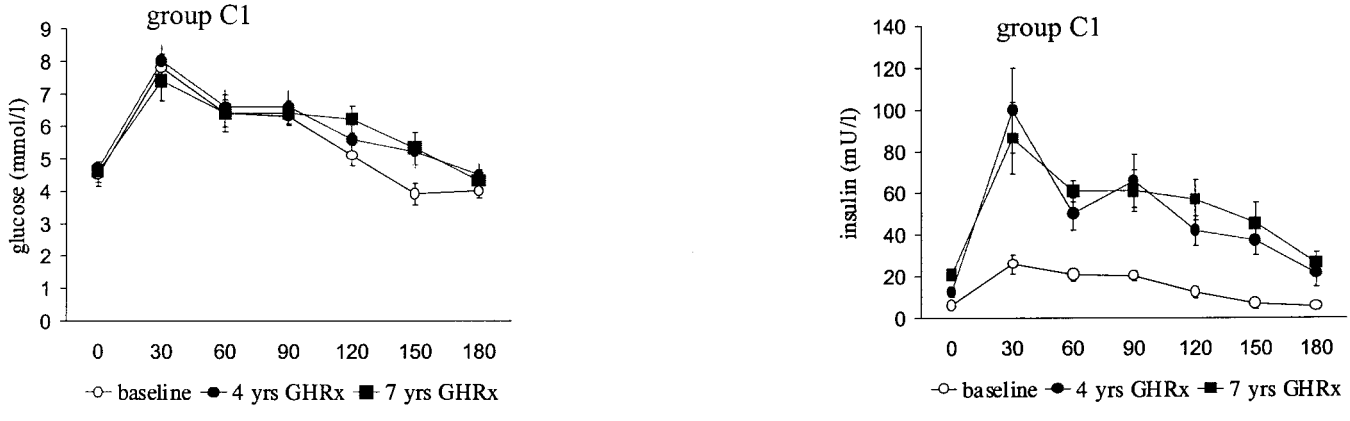

FIG. 1. Mean (SE) glucose levels (*left panel*) and insulin levels (*right panel*) during the OGTTs, at baseline, after 4 yr of GH treatment, and after 7 yr of GH treatment for group C1.

TABLE 2. Carbohydrate variables of the nine girls of subgroup C1 during 7 yr of GH treatment (0, 4, and 7 yr)

	Baseline	4 yr	7 yr
Fasting glucose (mmol/L)	4.5 (1.0)	4.7 (0.3)	4.6 (0.9)
AUCab glucose (mmol/L·min)	207 (185)	266 (161)	253 (107)
Fasting insulin (mU/L)	6.2 (5.6)	12.3 (6.1)[a]	20.7 (7.5)[b,c]
AUCab insulin (×1000 mU/L·min)	1.6 (1.1)	7.1 (2.8)[d]	6.4 (2.4)[d]
Ratio insulin/glucose, 30 min (mU/mmol)	3.2 (1.5)	12.5 (7.8)[b]	11.7 (6.0)[b]
Ratio insulin/glucose, 120 min (mU/mmol)	2.3 (1.3)	7.2 (2.8)[b]	8.8 (3.7)[b]

Values are the mean (SD). AUCab, three-hour area under the curve above fasting levels.
[a] $P < 0.05$ *vs.* baseline.
[b] $P < 0.01$ *vs.* baseline.
[c] $P < 0.05$ *vs.* 4 yr of GH treatment.
[d] $P < 0.001$ *vs.* baseline.

line levels ($P = 0.001$). None of the changes in the ratios was significantly different between the GH dosage groups.

As obesity is associated with insulin resistance, we analyzed the development of the SD scores of BMI in the 9 girls of group C1 during 7 yr of GH treatment and in the 28 girls of groups A, B, and C during and after discontinuation of GH treatment (Table 4). In the 9 girls of group C1, the baseline BMI SD score was not significantly different from zero. After 4 yr of GH treatment, the BMI SD score had increased significantly ($P = 0.003$) to values higher than zero ($P = 0.036$), without obvious changes thereafter. However, the increment in insulin levels during GH treatment were not correlated with the increment in BMI SD score. In the 28 girls, the baseline BMI SD score was significantly higher than zero ($P = 0.002$) and increased significantly during GH treatment ($P = 0.043$). After discontinuation of GH treatment, the BMI SD score was significantly higher than that after 4 yr of GH treatment ($P = 0.002$). Thus, the BMI SD score showed a different pattern than the insulin levels during GH treatment and after discontinuation of GH treatment.

HbA_{1c}

All individual HbA_{1c} levels in the total group of 65 girls were within the normal range. HbA_{1c} levels showed an overall significant decrease during 7 yr of GH treatment compared to baseline levels [mean (SD), from 4.8 (0.5) to 4.6 (0.5); $P < 0.001$], without differences between GH dosage groups. In the girls who had discontinued GH treatment, the mean (SD) HbA_{1c} level in the last year of GH treatment [4.8 (0.4)] was not significantly different from baseline [5.0 (0.4)]. Compared to values in the last year of GH treatment, the HbA_{1c} levels had decreased significantly after discontinuation of GH treatment [from 4.8 (0.4) to 4.4 (0.4); $P < 0.001$].

Discussion

To our knowledge, this is the first report describing CH metabolism during long term GH treatment as well as after discontinuation of GH treatment in girls with TS, treated with dosages up to 8 IU/m^2·day. Previous studies reported increased insulin levels with or without changes in glucose levels after relatively short periods of GH treatment (23, 24). To optimize the GH treatment in girls with TS in the present study, treatment was started at a younger age, and some of the girls received a higher GH dosage than that used in other studies. In a previous report we demonstrated that in most of these girls, GH treatment resulted in a normalization of height during childhood as well as a normalization of adult height. Although the growth response was higher in the groups receiving higher GH dosages, the difference in growth response was quite small in proportion to the difference in GH dose (19). The present study showed that 7 yr of treatment with a high GH dose in these girls did not negatively influence glucose levels, but induced higher levels of insulin. Although fasting insulin levels showed a sustained increase during GH treatment, the glucose-induced increase in insulin showed no further increase after 4 yr of treatment. The increase in insulin levels during GH treatment without marked changes in glucose levels indicated relative insulin resistance.

As our study did not include untreated girls with TS, other factors causing insulin resistance cannot be entirely ruled out. One may speculate that the increment in insulin levels was due to estrogens. However, similar patterns in insulin levels were seen in girls who remained prepubertal during the entire study period. As increased body mass is related to insulin resistance, the increase in insulin resistance during the study period could be explained by the increase in body mass. However, no relationships were found between the increase in insulin levels during GH treatment and the increment in BMI SD score. Therefore, we can conclude that GH treatment is the main cause of the observed relative insulin resistance.

In addition, our study demonstrated that the increased insulin levels during long term GH treatment with 4, 6, or 8 IU/m^2·day in 28 girls with TS decreased after discontinuation of GH treatment to values close or equal to pretreatment values. These results are in line with reported preliminary short term data (25, 26). In a previous study by our group, GH treatment with 6 IU/m^2·day in 18 relatively older girls with TS showed that the increased insulin levels during the entire GH treatment period had decreased significantly at 6 months after discontinuation of GH treatment (25). Saenger *et al.* found similar results in nine girls with TS (26).

Although fasting insulin levels decreased after discontinuation of GH treatment, these levels were still significantly higher than pretreatment levels. One can speculate that this is due to a partial irreversibility of the GH-induced insulin resistance. However, compared to the insulin levels during OGTTs in healthy girls reported previously by Potau *et al.* (27), the insulin levels after discontinuation of GH treatment in the girls in our study are quite comparable. Therefore, it is more likely that these higher fasting insulin levels after

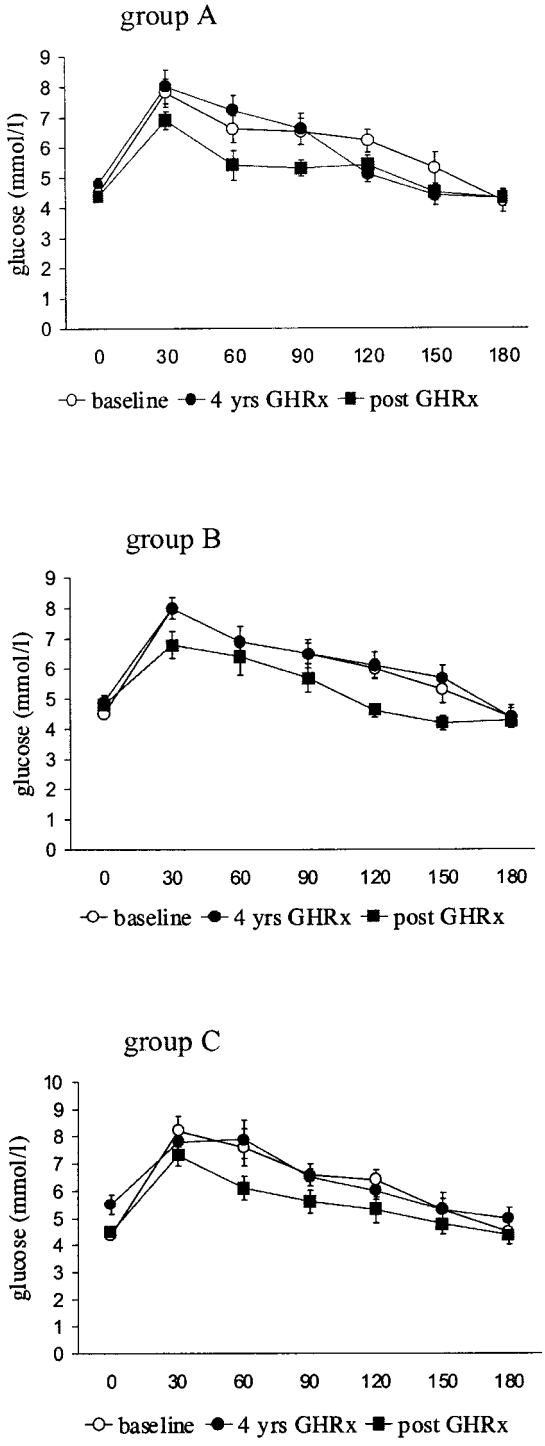

FIG. 2. Mean (SE) glucose levels during the OGTTs, at baseline, after 4 yr of GH treatment, and after discontinuation of GH treatment (post GHRx), for groups A, B, and C, respectively.

discontinuation of GH treatment compared to pretreatment levels may be explained by the normal increase in insulin levels during childhood. Moreover, estrogen treatment and obesity are associated with insulin resistance. In the present study at the start of GH treatment and after 4 yr of GH treatment, none of the girls received estrogens, whereas after discontinuation of GH treatment, all girls were receiving

TABLE 3. Carbohydrate variables of group A, B, and C before (baseline) and after 4 yr of GH treatment (GHRx) and after discontinuation of GH treatment

	Baseline				After 4 yr of GHRx				6 months after discontinuation of GHRx			
	Group A	Group B	Group C	Groups A + B + C	Group A	Group B	Group C	Groups A + B + C	Group A	Group B	Group C	Groups A + B + C
Fasting glucose (mmol/L)	4.5 (0.6)	4.5 (0.4)	4.4 (0.4)	4.5 (0.5)	4.8 (0.6)	4.9 (0.7)	5.5 (1.0)	5.1 (0.8)[a]	4.4 (0.4)	4.8 (0.4)	4.5 (0.7)	4.6 (0.5)[b]
AUCab glucose (mmol/L·min)	300 (103)	306 (190)	356 (165)	320 (154)	218 (141)	257 (185)	166 (167)	215 (165)[c]	169 (111)	103 (112)	192 (154)	153 (128)[d]
Fasting insulin (mU/L)	5.2 (2.5)	6.3 (2.3)	5.7 (1.7)	5.8 (2.2)	15.3 (5.5)	19.9 (10.2)	25.2 (17.6)	20.1 (12.3)[d]	13.7 (4.6)	9.8 (3.8)	13.9 (5.7)	12.4 (5.0)[b,d]
AUCab insulin (×1000 mU/L·min)	4.2 (2.0)	3.9 (2.5)	4.1 (1.2)	4.1 (1.9)	5.6 (2.6)	9.0 (4.8)	5.1 (1.8)	6.7 (3.8)[a]	3.8 (1.7)	3.2 (2.0)	4.6 (3.2)	3.9 (2.3)[b]
Ratio insulin/glucose, 30 min (mU/mmol)	6.0 (3.1)	5.3 (2.5)	5.0 (1.4)	5.4 (2.4)	9.5 (2.5)	16.7 (11.6)	9.3 (2.4)	12.0 (7.8)[d]	9.1 (4.1)	8.9 (7.9)	7.3 (4.5)	8.5 (5.7)[b,c]
Ratio insulin/glucose, 120 min (mU/mmol)	4.6 (2.4)	4.8 (3.0)	5.1 (1.5)	4.8 (2.3)	7.6 (2.8)	9.1 (3.7)	8.4 (3.6)	8.4 (3.3)[d]	6.0 (1.9)	3.4 (1.5)	6.9 (3.9)	5.4 (3.0)[b]

Values are the mean (SD). AUCab, 3-h area under the curve above fasting levels.
[a] $P < 0.01$ *vs.* baseline.
[b] $P < 0.01$ *vs.* 4 yr of GH treatment.
[c] $P < 0.05$ *vs.* baseline.
[d] $P < 0.001$ *vs.* baseline.

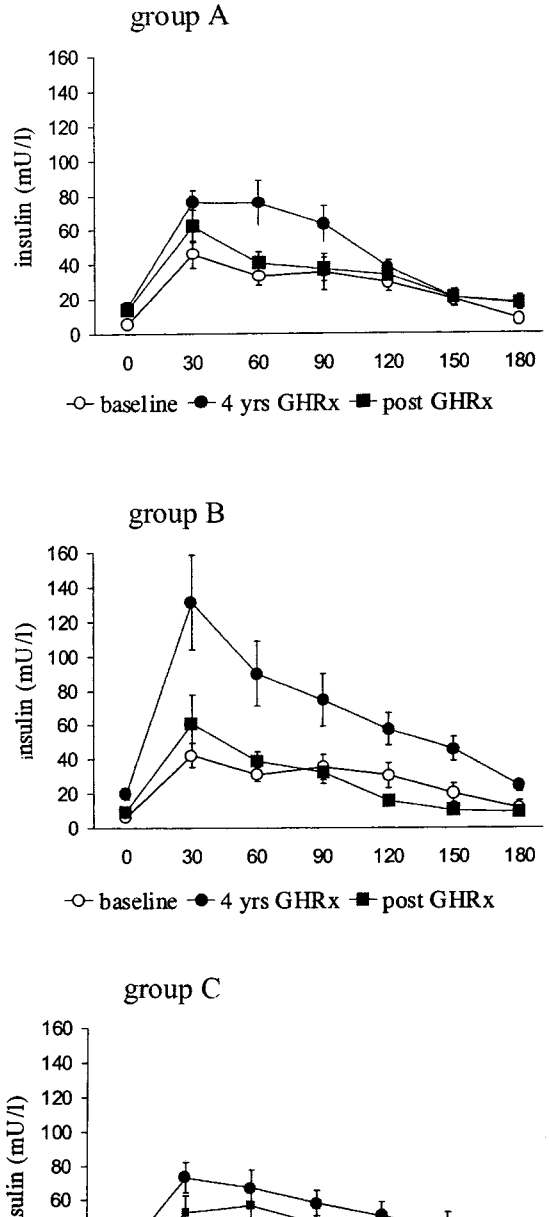

FIG. 3. Mean (SE) insulin levels during the OGTTs, at baseline, after 4 yr of GH treatment, and after discontinuation of GH treatment (post GHRx), for groups A, B, and C, respectively.

estrogen treatment. Furthermore, the BMI SD score after discontinuation of GH treatment was considerably higher than that before the start of treatment. Therefore, rather than the GH treatment itself, estrogen treatment and the increased body mass may explain the higher fasting insulin levels after discontinuation of GH treatment compared to pretreatment levels.

Although it is reassuring that the effects of long term GH treatment on CH metabolism are reversible, the consequences of hyperinsulinism during most of the childhood period on the risk of CH intolerance in adulthood is unknown. Therefore, long term follow-up of these women is required. In addition, more sophisticated methods, such as glucose clamp or the more recent developed minimal model method, could lead to improved insights into the CH metabolism in these girls during and after long term GH treatment.

TABLE 4. Mean (SD) BMI SD score of the 28 girls during and after discontinuation of GH treatment as well as of the nine girls of group C1 during 7 yr of GH treatment (0, 4, and 7 yr)

BMI SD score	Group C1	Group A	Group B	Group C
Baseline	−0.5 (0.8)	0.6 (1.2)	0.8 (1.0)	0.6 (1.0)
4 yr	0.5 (0.6)	1.0 (1.0)	1.0 (1.0)	0.8 (0.8)
7 yr	0.6 (0.7)			
6 months after stop GHRx		1.4 (1.0)	1.3 (0.8)	1.3 (0.9)

BMI, Body mass index; GHRx, GH treatment.

In conclusion, long term GH treatment with dosages up to 8 IU/m^2·day in girls with TS has no adverse effect on glucose metabolism, but induced higher levels of insulin, indicating relative insulin resistance. The increased insulin levels during long term GH treatment decreased after discontinuation of GH treatment to values close to or equal to pretreatment values. Although the reversibility of the effects of long term GH treatment is reassuring, the long term consequences of hyperinsulinism during childhood are still unknown.

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