Glucose Turnover and Insulin Clearance After Growth Hormone Treatment in Girls With Turner's Syndrome

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The study was performed to elucidate, by means of a euglycemic-hyperinsulinemic clamp, whether insulin sensitivity, lipid levels, posthepatic insulin delivery, and insulin clearance are impaired in girls with Turner's syndrome in the absence of previous treatment (T0) and after 6 (T6) and 12 (T12) months of growth hormone (GH) therapy (GHT). The study was performed in six girls with Turner's syndrome and eight healthy girls. We found that previously untreated girls with Turner's syndrome had a normal insulin activity on glucose metabolism. GHT progressively and significantly decreased hepatic insulin sensitivity. In fact, residual hepatic glucose release (HGR), which was 19.6 ± 4.7 mg/m^2 · min at T0, doubled at T6 (39.3 ± 5.1 mg/m^2 · min) and showed a threefold increase at T12 (68.7 ± 10.8 mg/m^2 · min, $P < .05$ *v* T0). On the contrary, GHT did not show an appreciable influence on peripheral insulin sensitivity. Insulin clearance was higher in girls with Turner's syndrome than in control girls at T0 (30.0 ± 2.8 *v* 20.2 ± 1.1 mL · kg^{-1} · min^{-1}). It decreased to normal values at T6 (18.2 ± 2.0 mL · kg^{-1} · min^{-1}, $P < .05$ *v* T0) and remained at normal levels at T12 (23.8 ± 2.9 mL · kg^{-1} · min^{-1}). The posthepatic insulin delivery rate significantly increased at T6 and T12, suggesting increased insulin secretion. In conclusion, we found that insulin-stimulated glucose turnover was normal in girls with Turner's syndrome before therapy. One year of GHT was successful in stimulating the growth rate, but significantly decreased the insulin suppressibility on HGR with only slight changes in peripheral insulin sensitivity. In addition, an increase in the insulin posthepatic delivery rate and a normalization of insulin clearance were present, probably to counteract hepatic insulin resistance.

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TURNER'S SYNDROME is characterized by metabolic and endocrine defects. Insulin resistance has been described as an early metabolic defect of Turner's syndrome, primarily involving the pathway of intracellular glucose metabolism.[1,2] Moreover, metabolic abnormalities such as carbohydrate intolerance and non–insulin-dependent diabetes mellitus have been recorded with a higher incidence in girls affected by Turner's syndrome than in normal girls.[3]

Recombinant growth hormone (GH) therapy (GHT) has been administered to girls with Turner's syndrome, since short stature is almost invariably present[4] and several clinical trials have shown its effectiveness to accelerate the growth rate.[5,6] However, there is a general debate about the possibility that GHT could induce insulin resistance.[7,8] In addition, it is unclear whether these changes in carbohydrate metabolism are related to an increase in GH or insulin-like growth factor-I (IGF-I) levels or to the combination of both. The effect of GH in inducing insulin resistance has been extensively studied, demonstrating a reduction of peripheral glucose utilization and an increase of hepatic glucose release (HGR) both in vitro[3,9] and in vivo.[5,10-12] On the contrary, IGF-I shares many metabolic properties of insulin even if the biological potency of IGF-I is significantly lower than insulin on a molar basis.[13] In particular, it has been reported that acute IGF-I infusions cause inhibition of HGR and an increase in peripheral glucose uptake, although the latter effect was quantitatively more important.[14]

Moreover, although it is well known that administration of exogenous GH stimulates insulin secretion, few results have been produced to understand whether the hyperinsulinemia observed after long-term GHT is related not only to increased pancreatic insulin release (subjected to first-pass liver extraction[15]) but also to changes in insulin clearance, as first postulated by Caprio et al.[8]

Since previous studies evaluating the metabolic effects of GH, estrogen, or oxandrolone treatment[2,16] on insulin resistance were performed in girls with Turner's syndrome of older age, in the present study we focused on a younger population in the absence of any previous treatment. A euglycemic-hyperinsulinemic clamp was performed in girls affected by Turner's syndrome before beginning GHT and at 6 and 12 months of GHT, and in healthy girls as a control. This experimental approach is widely used in children to determine the effects of insulin on glucose fluxes.[1,8,17] To permit calculation of glucose turnover, a stable isotope tracer, dideuterated glucose, was administered during the clamp. Dideuterated glucose allowed us to avoid the ethical problems related to the use of a radioactive tracer in children. Basal and steady-state insulin and C-peptide levels were measured to evaluate insulin clearance and the posthepatic insulin delivery rate as an index of insulin secretion. We found that GHT had a specific effect in decreasing the insulin suppressibility of HGR. In addition, a decrease in insulin clearance and an increase in insulin secretion were observed.

SUBJECTS AND METHODS

Subjects

Clinical characteristics of the subjects are reported in Table 1. The study was performed in six girls with Turner's syndrome and eight healthy girls. Healthy girls were chosen to be of similar age and prepubertal (ie, no evidence of breast or pubic hair development), as it is well known that puberty is responsible for an insulin resistance that can

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Submitted March 7, 1997; accepted May 15, 1997.

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0026-0495/97/4612-0020$03.00/0

Table 1. Clinical Characteristics of the Study Groups

Group	Age (yr)	Tanner Stage	Height (cm)	Weight (kg)	BSA (m^2)	BMI (kg/m^2)	Karyotype
Turner's syndrome							
1	12	I	124	30	1.02	19.5	45X
2	12	I-II	121	25	0.93	17.2	46XX i(xq)
3	13	I	126	27	1.00	16.9	45X
4	10	I	116	27	0.93	20.0	45X/46X del(x) q21
5	8	I	110	20	0.80	16.2	45X
6	10	I	124	27	0.99	17.6	45X
Mean ± SEM	10.8 ± 0.8		120 ± 2.0	26.0 ± 1.4	0.95 ± 0.03	17.9 ± 0.6	
Control							
1	10	I	135	30	1.10	16.5	
2	8	I	126	27	1.01	17.0	
3	9	I	130	28	1.08	16.6	
4	10	I	138	32	1.16	16.8	
5	11	I	137	31	1.16	16.5	
6	10	I	136	30	1.12	16.2	
7	9	I	127	25	0.98	16.8	
8	11	I	140	33	1.18	15.5	
Mean ± SEM	9.8 ± 0.8		133 ± 1.9	29.5 ± 1.0	1.10 ± 0.03	16.5 ± 0.2	

Abbreviations: BSA, body surface area; BMI, body mass index.

confound the results for glucose turnover.[18] Healthy girls were within the 10th and 90th percentiles for height and weight at the time of study. The fact that the body mass index was higher in girls with Turner's syndrome is likely to be related to differences in height rather than in body composition between the two groups. All girls were normoglycemic and normoinsulinemic and had a normal response to a standard oral glucose tolerance test (fasting blood glucose, 4.6 ± 0.2 mmol/L; fasting insulin, 37.8 ± 9.0 pmol/L; 120-minute blood glucose, 5.6 ± 0.3 mmol/L; and 120-minute insulin, 106.2 ± 20.4 pmol/L) in the absence of a family history of diabetes. Moreover, girls with Turner's syndrome had normal fasting GH and stimulated GH values more than 10 μg/L. None had been previously treated with GH, estrogen, or other hormone therapy.

The protocol was approved by the Institutional Ethics Review Board, and the studies were performed after parental informed consent was provided regarding the aims and potential side effects or risks of the study.

Euglycemic-Hyperinsulinemic Clamp Study

Girls with Turner's syndrome were submitted to a euglycemic-hyperinsulinemic clamp before the start of GHT (T0). A similar study was performed in healthy girls as a control. Subsequently, GHT (Saizen; Serono SPA, Roma, Italy) was administered to girls with Turner's syndrome at a dosage of 0.1 U · kg BW^{-1} (0.038 mg · kg BW^{-1}) 6 days per week. An identical euglycemic-hyperinsulinemic clamp was repeated after 6 (T6) and 12 (T12) months of GHT. All patients received their usual dose of GH on the evening before each study day.

All girls were admitted to the hospital at 8 AM after an overnight fast. A 20-gauge Abbocath (Venisystems, Abbot Ireland, Sligo, Ireland) was inserted into an antecubital vein for intravenous infusions. A similar cannula was retrogradely inserted into a vein of the dorsum of the hand, and the hand was placed into a Plexiglas box heated at 55°C to arterialize venous blood samples. The sampling cannula was kept patent by slow saline infusion.

After a basal period of 120 minutes for evaluation of fasting glucose turnover, a euglycemic-hyperinsulinemic clamp that lasted 180 minutes was performed in each girl. A low insulin dose (0.4 mU · kg^{-1} · min^{-1}) was used because we were particularly interested in characterizing insulin inhibition of HGR. During the insulin period, blood glucose was clamped at the baseline level by means of a variable 20% dextrose infusion according to blood glucose measurements obtained every 5 minutes.

Fasting and insulin-stimulated glucose turnover were evaluated by a primed (5 mg · kg^{-1}), continuous (0.05 mg · kg^{-1} · min^{-1}) infusion of [6,6-$^2H_2$]-glucose maintained until the end of the study. After a 2-hour tracer equilibration period, samples were drawn at −20, −15, −10, −5, and −1 minutes for subsequent determination of fasting glucose turnover. After initiation of the insulin infusion, [6,6-$^2H_2$]-glucose was also added to the infused glucose to minimize the changes in atom percent excess during the experiment (hot-glucose infusion technique).[19-20]

Glucose Turnover

In the fasting state, HGR and peripheral glucose disappearance (Rd) were calculated according to the isotopic dilution formula. During the clamp, HGR and Rd were calculated using Steele's non–steady-state equations.[21] A pool fraction of 0.65 and a total glucose distribution volume of 260 mL · kg^{-1} were used. The glucose disposal rate was calculated during the last 30 minutes of the insulin infusion period, ie, between 150 and 180 minutes.

Insulin Clearance and Posthepatic Insulin Delivery Rate

The insulin plasma clearance rate (PCR) was calculated according to the method of Ferrannini et al[15] as the ratio of the exogenous insulin infusion rate (IR) to the steady-state plasma exogenous insulin concentration (which is the difference between total and endogenous plasma insulin levels). Endogenous insulin is obtained by multiplying the basal insulin level by the relative change in C-peptide concentration,

$$\text{PCR (mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = \frac{IRC_b}{(I_{ss}C_b - I_bC_{ss})}, \qquad \text{Eq 1}$$

where I_b and C_b are basal insulin and C-peptide concentrations, respectively, and I_{SS} and C_{SS} are steady-state insulin and C-peptide concentrations, respectively, calculated at the end of the glucose clamp as the mean of values between 150 and 180 minutes.

Table 2. Effect of GHT on Fasting Biochemical and Clinical Responses

Parameter	T0	T6	T12	Control
Blood glucose (mmol/L)	4.4 ± 0.1	4.6 ± 0.2	4.4 ± 0.1	4.8 ± 0.2
Serum insulin (pmol/L)	33.0 ± 5.4	81.0 ± 11.4*	69.0 ± 22.8	54.4 ± 8.5
Serum C-peptide (pmol/L)	397.2 ± 33.1	562.7 ± 66.2	595.8 ± 132.4	419.6 ± 51.6
GH (μg/L)	0.6 ± 0.1	1.7 ± 0.4	4.8 ± 1.3*	0.7 ± 0.2
IGF-1 (μg/L)	11.6 ± 1.9†	49.4 ± 6.8*	64.0 ± 8.1*	43.7 ± 1.9
Triglycerides (mg/dL)	35.7 ± 4.5	55.1 ± 8.4*	36.7 ± 2.5	48.8 ± 5.4
FFA (mmol/L)	0.82 ± 0.13	0.72 ± 0.10	0.91 ± 0.16	0.74 ± 0.05
Growth velocity (cm/yr)	3.8 ± 0.4	6.4 ± 2.8*	7.5 ± 0.4*	—

*$P < .05$ *v* T0.
†$P < .05$ *v* control.

The posthepatic insulin delivery rate (IDR), an index related to basal insulin secretion, was derived by multiplying the plasma clearance rate of insulin by the basal insulin concentration[22]:

$$\text{IDR (pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = \text{PCR } I_b. \qquad \text{Eq 2}$$

Analytical Determinations

Plasma glucose was determined by a glucose oxidase method (Beckman Glucose Analyzer II; Beckman Instruments, Palo Alto, CA). Isotopic enrichment of dideuterated glucose was determined using a simple procedure and was analyzed by gas chromatography–mass spectrometry.[23] Serum insulin, C-peptide, GH, and IGF-I were determined by specific radioimmunoassays using commercial kits (Insulin I125 RIA kit, Incstar, Stillwater, MN; C-peptide Double Antibody kit, Diagnostic Products, Los Angeles, CA; SPECTRIA HGH, Farmos Diagnostica, Turku, Finland; and SM-C RIA kit, Technogenetics, Trezzano, Italy). Free fatty acid (FFA) and triglyceride levels were measured using an enzymatic technique on a Cobas Fara II Centrifugal Analyser (Roche, Basel, Switzerland).[24]

Statistical Analysis

Data are presented as the mean ± SEM. A Wilcoxon signed-rank test was used to compare results in girls with Turner's syndrome at T0, T6, and T12, and a two-group Mann-Whitney *U* test was chosen to compare results with the controls.

RESULTS

GH, IGF-I, and Growth Velocity

Fasting biochemical and clinical responses at T6 and T12 are reported in Table 2. GH levels were 0.6 ± 0.1 μg/L in girls with Turner's syndrome at T0, without significant differences versus the control group. At T6 and T12, GH concentrations progressively increased, reaching a statistical difference only at T12. IGF-I levels were significantly lower in girls with Turner's syndrome at T0 compared with the control group ($P < .05$). At T6, IGF-I levels significantly increased, reaching values comparable to those of the controls. These levels slightly increased at T12, but the differences failed to reach statistical significance compared with T6.

During the clamp period, GH levels slightly increased without reaching statistical significance among the different times and compared with the control group. IGF-I levels were superimposable on those found during the fasting period.

Growth velocity showed a concomitant increase at T6 and T12 (Table 2).

Hormone and Intermediate-Metabolite Levels

In the fasting state, girls with Turner's syndrome before GHT and the control group had similar blood glucose levels. No differences were demonstrated in triglyceride and FFA levels. At T6 and T12, blood glucose and FFA levels were comparable to those found at T0 and in the control group (Table 2). Triglyceride levels increased at T6, reaching a statistical significance compared with T0. No significant differences were observed compared with the control group. At T12, triglyceride returned to pretreatment levels without significant differences compared with the controls (Table 2).

During the clamp period, blood glucose was clamped to fasting levels in all groups, without significant differences among the groups (coefficient of variation <5%). Under insulin action, the rate of FFA inhibition was similar in all groups. Triglycerides remained at values achieved in the fasting period at T0, T6, and T12, whereas they were slightly but not significantly decreased by 20% to 30% in the control group (Table 3).

Glucose Turnover

In the fasting state, HGR and glucose Rd, which are equal under basal steady-state conditions, were similar in girls with

Table 3. Effect of GHT on Biochemical Responses During the Clamp Period

Parameter	T0	T6	T12	Control
Blood glucose (mmol/L)	4.5 ± 0.2	4.4 ± 0.1	4.4 ± 0.1	4.7 ± 0.2
Serum insulin (pmol/L)	109.2 ± 15.6	166.2 ± 4.8*	134.4 ± 12.0	154.5 ± 10.6
Serum C-peptide (pmol/L)	288.0 ± 16.6	208.5 ± 43.0	258.2 ± 46.3	259.8 ± 34.6
GH (μg/L)	1.2 ± 0.5	3.0 ± 1.2	2.6 ± 1.1	1.3 ± 0.3
IGF-I (μg/L)	13.2 ± 3.2	48.9 ± 6.5*	58.6 ± 6.8*	43.2 ± 0.5
Triglycerides (mg/dL)	33.8 ± 6.7	48.4 ± 8.6*	38.3 ± 13.3	40.3 ± 6.9
FFA (mmol/L)	0.22 ± 0.05	0.22 ± 0.06	0.25 ± 0.06	0.18 ± 0.02

*$P < .05$ *v* T0.

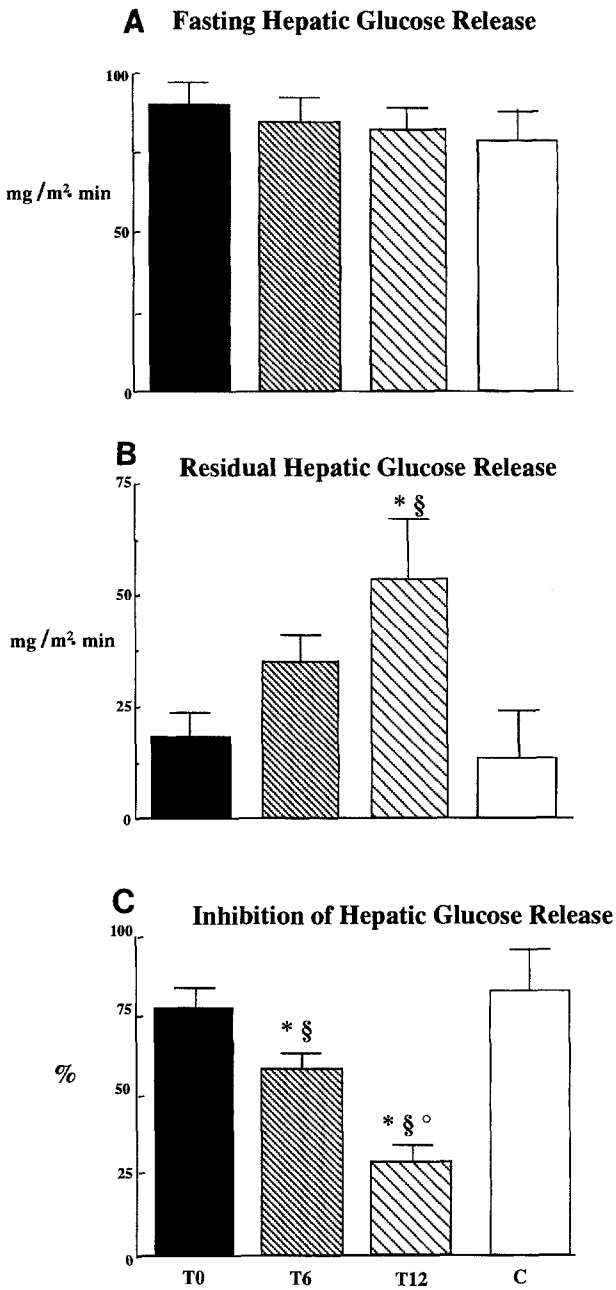

Fig 1. Fasting HGR (A), residual HGR at the end of the clamp (B), and % inhibition of HGR by insulin (C) in girls with Turner's syndrome at T0, T6, and T12 and in control girls (C). *$P < .05$ *v* T0, §$P < .05$ *v* C, °$P < .05$ *v* T6.

Turner's syndrome before treatment and in control girls. GHT did not affect fasting HGR and Rd both at T6 and T12 (Fig 1A).

At the end of the clamp period at T0, HGR decreased to a similar extent, achieving values of 19.63 ± 4.70 in girls with Turner's syndrome and 16.03 ± 13.69 mg/m² · min in the control group. The effect of GHT was to progressively and significantly increase HGR, which doubled at T6 and achieved a threefold increase at T12 (Fig 1B). This was even better represented when the percent inhibition of HGR was considered (Fig 1C). In fact, about 80% inhibition of HGR was achieved in girls with Turner's syndrome before treatment and in the control group, a value expected at the insulin levels achieved during the clamp period. On the contrary, the percent suppression of HGR was about 60% at T6 and decreased to about 30% at T12, suggesting that GHT produced a profound state of hepatic insulin resistance.

The Rd was 144.6 ± 14.7 mg/m² · min at T0, without significant differences compared with the control group (123.4 ± 26.3 mg/m² · min). At T6, Rd was slightly decreased (131.9 ± 2.8 mg/m² · min, NS *v* T0 and controls), whereas it increased at T12 compared with T6 and the control group (143.8 ± 13.5 mg/m² · min, NS).

Insulin and C-Peptide Levels, Insulin Clearance, and Posthepatic Insulin Delivery Rate

Insulin and C-peptide levels measured in the fasting state are reported in Table 2. In the fasting state, girls with Turner's syndrome before GHT and the control group had similar C-peptide levels. Insulin levels were slightly but not significantly lower than those found in the controls. At T6 and T12, C-peptide levels were slightly but not significantly higher than those found at T0 and in the controls. Serum insulin was significantly increased at T6 to levels similar to those found in the controls. These levels were maintained at T12.

Insulin and C-peptide levels measured at the end of the clamp period are reported in Table 3. The exogenous insulin infusion resulted in peripheral insulin levels of 109.2 ± 15.6, 166.2 ± 4.8, 134.4 ± 12.0, and 154.5 ± 10.6 pmol/L at T0, T6, and T12 and in the controls, respectively ($P < .05$, T6 *v* T0). C-peptide levels were similar in all the Turner's groups and in the controls. In particular, the percent inhibition of C-peptide levels was 35.3% ± 14.4% at T0 compared with 48.6% ± 5.9% in the controls (NS). At T6 and T12, the percent inhibition of C-peptide levels was 67.3% ± 2.2% and 62.0% ± 6.3% (NS *v* T0 and controls).

Insulin clearance results are reported in Fig 2. The plasma clearance rate of insulin was significantly higher in girls with Turner's syndrome before GHT than in the control group. It decreased at T6, remaining in the normal range at T12. The

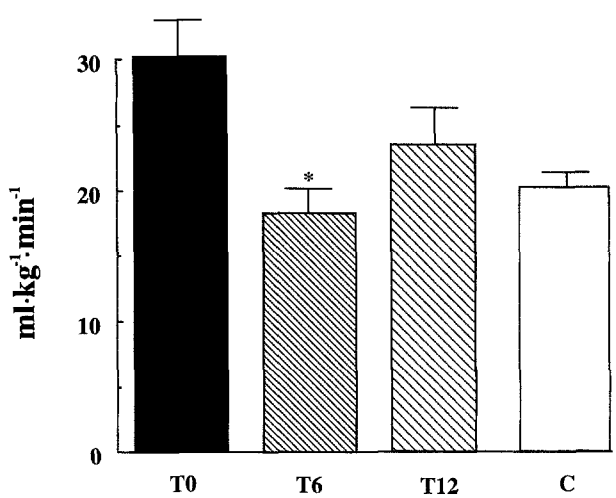

Fig 2. Insulin clearance in girls with Turner's syndrome at T0, T6, and T12 and in control girls (C). *$P < .05$ *v* T0.

posthepatic insulin delivery rate was similar at T0 and in the controls (0.99 ± 0.24 *v* 1.11 ± 0.24 pmol · kg^{-1} · min^{-1}, NS). At T6 and T12, it was significantly increased compared with T0 (1.31 ± 0.17 and 1.59 ± 0.13 pmol · kg^{-1} · min^{-1}, $P < .05$ *v* T0 and NS *v* controls), suggesting an increased insulin secretion after GHT.

DISCUSSION

The results of the present study are consistent with a normal insulin activity on glucose metabolism along with an increased insulin clearance in previously untreated girls with Turner's syndrome. GHT progressively decreased insulin's ability to suppress HGR without an appreciable influence on insulin stimulation of peripheral glucose Rd, thus suggesting a preferential hepatic insulin resistance. Moreover, at T6, a complete normalization of insulin clearance was associated with an increase of the posthepatic insulin delivery rate, both maintained after 1 year of GHT.

The presence of insulin resistance in girls with Turner's syndrome has been debated for a long time. In a previous study, Caprio et al[1] demonstrated that insulin resistance is a very early defect in girls with Turner's syndrome that may be restricted to nonoxidative pathways of intracellular glucose metabolism. On the contrary, in the present study, no defects of glucose turnover were observed before GHT. A possible explanation is related to the different insulin levels achieved during the clamp in our study and theirs.[1] In this study, we chose a low-dose insulin infusion achieving insulin levels of 150 pmol/L to study primarily hepatic insulin sensitivity; Caprio et al[1] used a high-dose insulin infusion achieving insulin levels of about 400 pmol/L to totally suppress HGR and focus on peripheral insulin sensitivity only. It cannot be excluded that, by using elevated insulin levels, Caprio et al were able to magnify a defect that is not detectable at lower insulin levels.

Interestingly, GHT caused a progressive impairment in the insulin suppression of hepatic glucose production that was manifest during low-dose insulin infusion but not in the fasting condition. No peripheral insulin resistance was present at T12 as compared with levels found in the control group. The preferential effect of GH on HGR found in the present study is consistent with previous studies showing hepatic receptors for GH[25-27] and the presence of a direct inhibition of GH on insulin binding in the liver[25,27] but not in muscle.[28] These data are well in accordance with previous short-term studies showing that hepatic glucose suppressibility by insulin is significantly decreased after 4 to 12 hours of continuous intravenous GH infusion.[29-32] The fact that no peripheral insulin resistance is observed in the present study after 1 year of GHT is probably related to the opposite effects of GH and IGF-I on glucose utilization in skeletal muscle. In fact, whereas GH induces a change in the glucose-carrier system leading to a restriction of glucose transport,[33,34] both acute and chronic increases in IGF-I levels increase the basal rate of glucose utilization in skeletal muscle with an effect independent of insulin levels in the rat.[35] Thus, the likely compensation between the opposite peripheral effects of GH and IGF-I might explain why only the effects of GHT on HGR were detected in the present study.

The results of this study are well in accordance with previous studies in which GH was administered at similar doses. In fact, using GH replacement at a dose of 0.2 IU/kg/wk in nondiabetic hypopituitary subjects, Weaver et al[36] observed changes in basal glucose homeostasis predominantly related to increased HGR, whereas reduced peripheral glucose uptake was quantitatively less relevant. Similarly, with GHT at a dose of 0.3 IU/kgBW/d, they observed no changes in glucose levels and basal glucose turnover. In addition, after a euglycemic clamp, dose-response curves for glucose disposal were comparable before and after GHT.[37] Moreover, in a survey of 5 years, Saenger et al[38] did not find alterations of glucose metabolism during GHT in girls with Turner's syndrome. In fact, mean fasting and postprandial glucose remained unchanged and hemoglobin A_{1c} remained in the normal range. However, at substantially higher doses, GHT increased HGR and markedly reduced peripheral glucose uptake, causing a higher degree of glucose intolerance.[39]

Before GHT, fasting C-peptide concentrations were similar in the two groups, whereas fasting insulin concentrations in girls with Turner's syndrome tended to be lower, albeit not significantly, than in the control group, the latter group having values comparable to those previously reported.[17,40,41] Of note is that an opposite trend was demonstrated in a previous study by Caprio et al[1] in which fasting insulin levels were slightly but not significantly higher in girls with Turner's syndrome than in normal controls. Since it has been suggested that fasting insulin levels are inversely related to insulin sensitivity,[37,42] the different trend for fasting insulin levels found in our study and the study by Caprio et al[1] is in keeping with the different degrees of insulin sensitivity found in girls with Turner's syndrome in the two studies.

After GHT, fasting C-peptide concentrations slightly increased, albeit not significantly, and fasting insulin concentrations increased to levels similar to those observed in the control group. The increase in insulin levels after GHT is in all likelihood the result of an increased insulin secretion and a concomitant reduction in insulin clearance. In fact, even if we were not able to demonstrate significantly higher C-peptide levels after GHT as previously observed,[8] the finding that the posthepatic insulin delivery rate significantly increased after GHT is highly suggestive of an increased insulin secretion related to GHT. On the other hand, insulin clearance in girls with Turner's syndrome was higher than in the controls before treatment, but progressively and significantly decreased during GHT to achieve normalization at T12. Interestingly, when insulin clearance was correlated with insulin sensitivity before and during GHT, a significant positive correlation was found ($r = .59$, $P < .05$). This result, which needs to be interpreted with caution because of the small number of patients, is nevertheless in accordance with previous reports.[43,44] In particular, Haffner et al[44] speculated that the association between insulin sensitivity and insulin clearance could be an autoregulatory mechanism to compensate for insulin resistance. Increased insulin secretion would manifest when the latter mechanism is no longer sufficient, thereby increasing the risk of clinical diabetes. In addition, in previous studies reporting on patients with insulin resistance, decreased insulin action always coexisted with decreased insulin clearance.[45-48] In line with these findings, Walker et al[37] found increased insulin concentrations but no changes in basal glucose turnover in children treated for 1 year with GH. They hypothesized that the children may have

developed a subtle form of insulin resistance, since they needed to increase insulin levels to maintain similar glucose metabolism. Based on all of these previous observations, we speculate that the increase in the posthepatic insulin delivery rate and the normalization of insulin clearance observed in girls with Turner's syndrome during GHT may be an attempt of the glucose-insulin system to counteract hepatic insulin resistance to maintain fasting normoglycemia.

In conclusion, we found that both insulin-stimulated glucose Rd and insulin inhibition of HGR were normal in girls with Turner's syndrome at a very early stage of the disease and before therapy. One year of GHT was successful in stimulating the growth rate but significantly decreased the insulin suppressibility of HGR with only slight changes in peripheral insulin sensitivity. In addition, an increase in the insulin posthepatic delivery rate and a normalization of insulin clearance were present, probably to counteract hepatic insulin resistance. These metabolic alterations were observed in the presence of fasting normoglycemia and normoinsulinemia and have to be carefully considered by the physician as a counterpart to achieving a successful increase in growth rate during GHT in Turner's syndrome. Moreover, it may be desirable for the physician to use the lower dose of GH able to increase the growth rate, to attenuate the effects of GH on glucose metabolism.

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