

CLINICAL STUDY

Insulin sensitivity in Turner's syndrome: influence of GH treatment

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Abstract

Objective: Excessive GH secretion may lead to secondary diabetes mellitus, while prolonged GH treatment may accelerate the onset of type 2 diabetes mellitus in predisposed individuals. Turner's syndrome (TS) patients are a population at risk since they have reduced glucose tolerance (GT) spontaneously and because they are usually treated with high doses of GH.

Design and methods: The aim of the study was to evaluate insulin sensitivity (IS) and glucose tolerance (GT) in a group of TS patients treated with GH for a period of 6 years. Forty-seven TS girls were included in the study. GH was administered at a mean weekly dosage of 0.35 mg/kg, injected subcutaneously over 6–7 days. GT was assessed according to the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. IS was evaluated with the quantitative insulin sensitivity check index (QUICK-I).

Results: No significant increase of impaired GT was observed in the patients during the follow-up period, while a reduced IS was detected. IS in TS patients was already lower than in prepubertal controls ($P < 0.001$) before starting treatment and further decreased during the first year of therapy ($P < 0.05$), and then remained stable over the following years. No correlation was found between QUICK-I, body mass index, years of treatment, onset and duration of puberty. One patient became diabetic during the course of treatment.

Conclusions: GH treatment in TS girls does not significantly increase the prevalence of impaired GT or type 2 diabetes mellitus, while it does, however, decrease IS.

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Introduction

Height prognosis in girls with Turner's syndrome (TS) has significantly improved following the introduction of growth hormone (GH) treatment, in particular when started early and if higher doses of GH are given (1–4). This kind of treatment approach raises, however, some concern about the potential diabetogenic effect of excessive GH concentrations (5–7). An impaired glucose tolerance has been seen in TS subjects before starting GH treatment (8) and also in TS adults who had never been treated with GH (9, 10). Previous studies have shown that GH treatment does not worsen glucose tolerance in TS girls, while inducing insulin resistance (11–14). Even if insulin returns to close to pretreatment levels after GH withdrawal (12), it is not yet known whether such a long period of insulin resistance could influence carbohydrate tolerance in adulthood. In this paper, we report our experience with regard to the influence of GH treatment on glucose tolerance and insulin sensitivity in TS girls, evaluated by the quantitative insulin sensitivity check index (QUICK-I) (15).

Subjects and methods

Subjects

We evaluated 47 TS girls who were treated with GH and regularly followed-up at the Department of Paediatrics of the Regional Hospital of Bolzano (12 patients) and at the Department of Paediatrics, University of Padua (35 patients). At the beginning of treatment the chronological ages were 8.2 ± 2.8 years, height standard deviation score (SDS) -2.25 ± 0.77 and body mass index (BMI) SDS 0.8 ± 2.0 . At the end of the study, 6 years later, the chronological ages were 12.6 ± 3.1 years, height SDS -1.58 ± 3.13 and BMI SDS 0.79 ± 1.59 . Forty-seven TS patients were examined during the first 2 years of treatment and 35, 27, 23 and 20 of them during the 3rd, 4th, 5th and 6th year respectively. Their clinical characteristics at the beginning of GH treatment and at the end of the study are summarized in Table 1. Chromosomal analysis showed a 45,X karyotype in 40% of the subjects, structural abnormalities in 44% and a mosaicism in 16%. Three patients had one diabetic parent and

another one had a father and grandfather who were both diabetic. Five (10.7%) of them suffered from Hashimoto's thyroiditis; only three of them, however, were on L-thyroxine. Eighteen (39.3%) were affected with cardiac anomalies such as aortic coarctation, bicuspid valves and ventricular septal hypertrophy. Puberty started spontaneously in 14 (29.7%) girls and was pharmacologically induced with low doses of ethinylestradiol (Amsa, Italy) (5 µg daily) in 13 (27.6%) girls at a mean age of 12.4 ± 1.6 8 years. At the end of the study 11 girls were pubertal (either spontaneously or pharmacologically); the mean period from the appearance of breast development was 2.0 ± 1.4 years. The treatment regimen with GH was the same in both centres, i.e. 0.35 mg/kg per week, given subcutaneously over 6–7 days. All patients had a regular auxological follow-up every 6 months. Forty girls, 20 prepubertal and 20 pubertal, mean age 10.4 ± 4.4 years, of normal height and body weight, were selected as controls and matched with the patients, according to chronological age and pubertal status. The ethical committee of the hospital approved the study and informed consent was obtained from the parents.

Study design

At the beginning of GH treatment and yearly thereafter, the patients were admitted to hospital after an overnight fast for the evaluation of glucose tolerance and bone age. BMI (kg/m^2) was calculated and expressed as SDS (16). Height measures were also converted to SDS for chronological as well as for bone age (17). Bone age was assessed according to Greulich & Pyle (18). All patients underwent a standard oral glucose tolerance test (OGTT): 1.75 g glucose/kg body weight up to 75 g with blood samples taken at 0, 30, 60, 90 and 120 min, in order to evaluate glucose and insulin levels.

Glucose tolerance and diabetic status were defined according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (19): impaired glucose tolerance: 2-h level above 7.8 mmol/l (140 mg/dl) and below 11.1 mmol/l (200 mg/dl); diabetic status: 2-h level above 11.1 mmol/l (200 mg/dl).

Insulin sensitivity was evaluated with QUICK-I = $1/[\log(I_0) + \log(G_0)]$, where I_0 is the fasting insulin and G_0 the fasting glucose (15).

Table 1 Clinical findings of the TS girls at the beginning of GH treatment and at the end of the study.

	Chronological age (years)	Bone age (years)	Height (SDS)	BMI (SDS)
Beginning	8.2 ± 2.8	6.9 ± 2.7	-2.25 ± 0.77	0.8 ± 2.05
End	12.6 ± 3.13	11.2 ± 2.46	$-1.58 \pm 1.05^*$	0.79 ± 1.59

* $P < 0.0001$.

Assay

Serum glucose was measured with automatic analyzers, using a hexokinase catalysed glucose oxidase method. Serum insulin was measured with an immunoradiometric assay (Immulite 2000 Insulin; DPC, Los Angeles, CA, USA) which has intra- and interassay coefficients of variation of 8.3% and 8.6% respectively.

Statistical analysis

Data are expressed either in absolute values (means \pm s.d.) or as a percentage. Paired Student's *t*-test was used for the statistical analysis of the data. A χ^2 test was used to verify differences between frequency of impaired glucose tolerance. One-way analysis of variance was used to compare differences in insulin sensitivity between patients and control subjects. The correlation between variables was sought by calculating the Pearson coefficient. A *P* value of less than 0.05 indicates statistical significance.

Results

Auxology

Following treatment with GH a significant increment in height SDS ($P < 0.0001$) was observed, while BMI SDS remained stable (Table 1).

Glucose tolerance

During the study period no significant increase in the number of cases with impaired glucose tolerance was observed. Impaired glucose tolerance was present in 4.2% of the subjects before starting treatment and in 10% of the 20 girls at the end of the survey (Fig. 1). Seven patients with an impaired glucose tolerance at some point during treatment subsequently normalised their glucose tolerance, without suspending treatment but following only dietary advice. Only one case of diabetes was recorded in a patient who did not have any risk factors such as obesity, familial or impaired glucose tolerance before starting GH therapy. At the onset of diabetes, fasting plasma glucose was 7.1 mmol/l (128 mg/dl) and the 2-h glucose level on OGTT was 13.2 mmol/l (238 mg/dl). Fasting insulin level was 28 mU/l and the 2-h insulin level on OGTT was 175 mU/l. The patient had also glycosuria (210 mg/dl; 11.6 mmol/l) and showed an hemoglobin (Hb)A1c of 6.8% (normal value $< 5.4\%$). Markers of humoral islet cell autoimmunity, such as antibodies against islet cells, glutamic acid decarboxylase, insulin and tyrosine phosphatase, were absent. GH treatment was therefore stopped and 6 months later the patient had only an impaired glucose tolerance (2-h glucose level on OGTT was 10.9 mmol/l (196 mg/dl)) while HbA1c decreased to 5.6% and the patient no longer had any glycosuria.

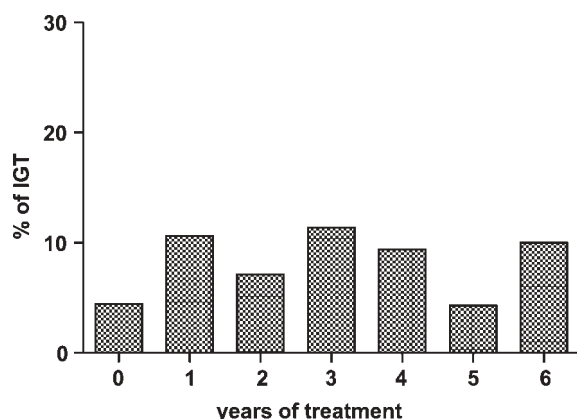


Figure 1 Prevalence of impaired glucose tolerance (IGT) in TS girls on GH therapy.

Insulin sensitivity

Before recombinant human GH treatment, insulin sensitivity in TS girls was clearly lower than in prepubertal controls as expected (0.370 ± 0.05 vs 0.405 ± 0.04 ; $P < 0.001$). Insulin sensitivity significantly decreased during the first year of therapy (0.370 ± 0.05 vs 0.344 ± 0.02 ; $P < 0.05$), with no further reduction over the following 6 years (Fig. 2). After 6 years of treatment, however, insulin sensitivity was still significantly lower in TS subjects than in pubertal controls (0.325 ± 0.02 vs 0.355 ± 0.04 ; $P < 0.05$).

Correlations

No correlation was found at any time between QUICK-I, BMI, years of treatment, onset and duration of puberty.

Discussion

The results of this survey have shown that GH treatment leads to a significant catch-up growth in TS girls

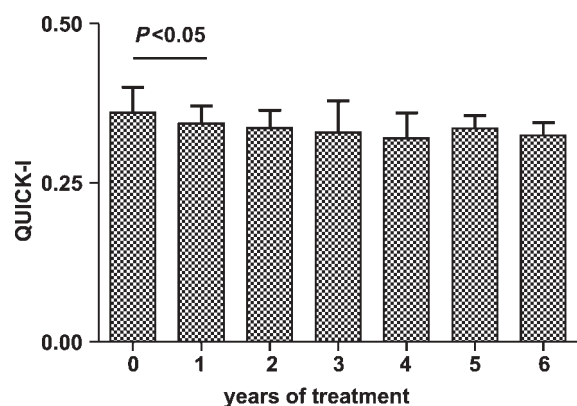


Figure 2 Mean \pm s.d. insulin sensitivity (QUICK-I) in TS girls on GH therapy.

without further worsening glucose intolerance in the great majority of them. Insulin sensitivity which, in agreement with another report (20), was already lower than in controls before starting GH treatment, decreased significantly over the first year of treatment. No further reduction was observed over the following years however, probably because of the beneficial effect of GH on body composition leading to a reduction of body fat. Insulin sensitivity always remained lower than in the control group. Furthermore, one patient, without any family history of diabetes, showed a diabetic response to OGTT, which turned to impaired glucose tolerance 6 months after GH treatment was suspended.

Our findings agree with two other studies concerning short normal children (21) and children with Prader-Willi syndrome (22), similarly showing a reduced insulin sensitivity shortly after the beginning of GH treatment. There is some debate as to whether a reduced insulin sensitivity is only a transient phenomenon (22–24) or a persistent one (25, 26) as shown in this study. Differences in patient selection, body composition and different doses of GH treatment among various studies probably account for such discrepancies.

In our patients, the reduced insulin sensitivity could have been caused by changes in body weight, by a puberty-related increase of sex hormones and/or by treatment with GH. However, since no correlation between QUICK-I, BMI and puberty was found, GH should be considered the main factor responsible for the decrease in insulin sensitivity. GH therapy in fact, by increasing lipid oxidation and thus circulating free fatty acids levels (23, 24), may reduce the uptake of glucose in skeletal muscle (26, 27).

As a consequence, higher serum insulin levels were observed during long-term GH treatment (12) which, however, return towards pretreatment values after the discontinuation of GH therapy. Serum insulin levels, on the other hand, only partly reflect tissue insulin sensitivity and different degrees of sensitivity can thus be observed for a given amount of insulin (28). In order to better evaluate tissue responsiveness to insulin we therefore used the QUICK-I which is a simple, accurate and reproducible method, correlating very well with the hyperinsulinaemic euglycaemic glucose clamp and the minimal model analysis (15), and is thus suitable for population studies.

The main finding of this study is that, apart from the only one patient who became diabetic, glucose tolerance did not worsen in TS patients during GH treatment, while a significantly reduced insulin sensitivity was detected. Insulin resistance is an established risk factor for the development of type 2 diabetes mellitus (29), atherosclerosis, dyslipidaemia and hypertension (30, 31) and, thus, even if an improvement is reported when GH is no longer administered, we consider that a longer follow-up is needed to verify whether such a long period of insulin resistance could influence carbohydrate tolerance in adulthood.

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