□ CASE REPORT □

Insulin Resistance in a Patient with Diabetes Mellitus Associated with Turner's Syndrome

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We evaluated insulin resistance and assessed the effect of gliclazide on insulin resistance in a patient with diabetes mellitus associated with Turner's syndrome. Insulin-induced glucose metabolism markedly decreased compared with 12 healthy subjects. The insulin dose-response curve of this patient shifted to the right and down, and recovered somewhat after the administration of gliclazide. This patient had exhibited marked insulin resistance, which seemed to be caused by a defect at the receptor and/or post-receptor levels. Gliclazide reduced her insulin resistance, which suggests that this agent is suitable for treating the insulin resistance in diabetic patients with Turner's syndrome.
(Internal Medicine 33: 560–563, 1994)

Introduction

Diabetes mellitus associated with Turner's syndrome is a cytogenetic disorder, but its etiology has not been clarified (1–3). Turner's syndrome is associated with an increased incidence of carbohydrate intolerance, and aging and obesity increase the incidence of diabetes mellitus associated with Turner's syndrome. We investigated insulin resistance in a patient with diabetes mellitus associated with Turner's syndrome using the euglycemic hyperinsulinemic clamp study technique and assessed the effects of sulfonylurea on insulin resistance.

Case Report

A 39-year-old woman was admitted to our hospital with a hearing disturbance and tinnitus on the right side and vertigo which lasted for 3 days. Turner's syndrome had previously been diagnosed on the basis of a chromosomal study when she was evaluated for short stature and ammenorrhea at the age of 16. Diabetes mellitus was also diagnosed at that time, and she was treated with an oral hypoglycemic agent for several months. Diabetic proliferative retinopathy was identified 7 years ago. She underwent bilateral panretinal photocoagulation, and was started on 52 U of intermediate-acting insulin. The same dose of insulin was administered to her at the start of this admission. Despite therapy, her plasma glucose level was poorly controlled, and symptoms that suggested hypoglycemia were some-

times observed. She had not been receiving estrogen-progesterone therapy. There was no family history of diabetes mellitus. Her height was 134.7 cm, weight 40.2 kg, and body mass index 22.2. Her blood pressure was 126/86 mmHg. She was sexually immature, with stage 3 breast and stage 3 pubic hair development according to Tanner's classification. Skeletal abnormalities included a webbed neck, shield chest, cubitus valgus and brachydactylia.

The patient's urinalysis revealed 3.6 g/day of protein and 2.9 g/day of sugar. Her hematocrit was 0.38, hemoglobin 127 g/L, and white blood cell count 6.3×10^9/L. Blood chemistry tests showed fasting plasma glucose 9.5 mmol/L, BUN 5.7 mmol/L, creatinine 88 μmol/L, total cholesterol 7.42 mmol/L, total protein 52 g/L, and albumin 25 g/L. Creatinine clearance was 1.05 ml/s. and hemoglobin Alc (HbAlc) was 10.0%. Urinary C-peptide reaction (CPR) excretion was 61 μg/day. Urinary excretion of total estrogens was 59 nmol/day, serum progesterone <1 nmol/L. Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were 21 and 164 IU/L, respectively; the LH-releasing hormone (LH-RH) stimulus test produced delayed and hyperresponsive reaction of LH and FSH. Her chromosomal karyotype was 45XO/46XXqi.

An otologist diagnosed her auditory disturbance as sensorineural deafness. Therefore, the patient was diagnosed as having diabetes mellitus associated with Turner's syndrome, complicated by sudden deafness on the right side. The sudden deafness was treated with hydrocortisone and improved to
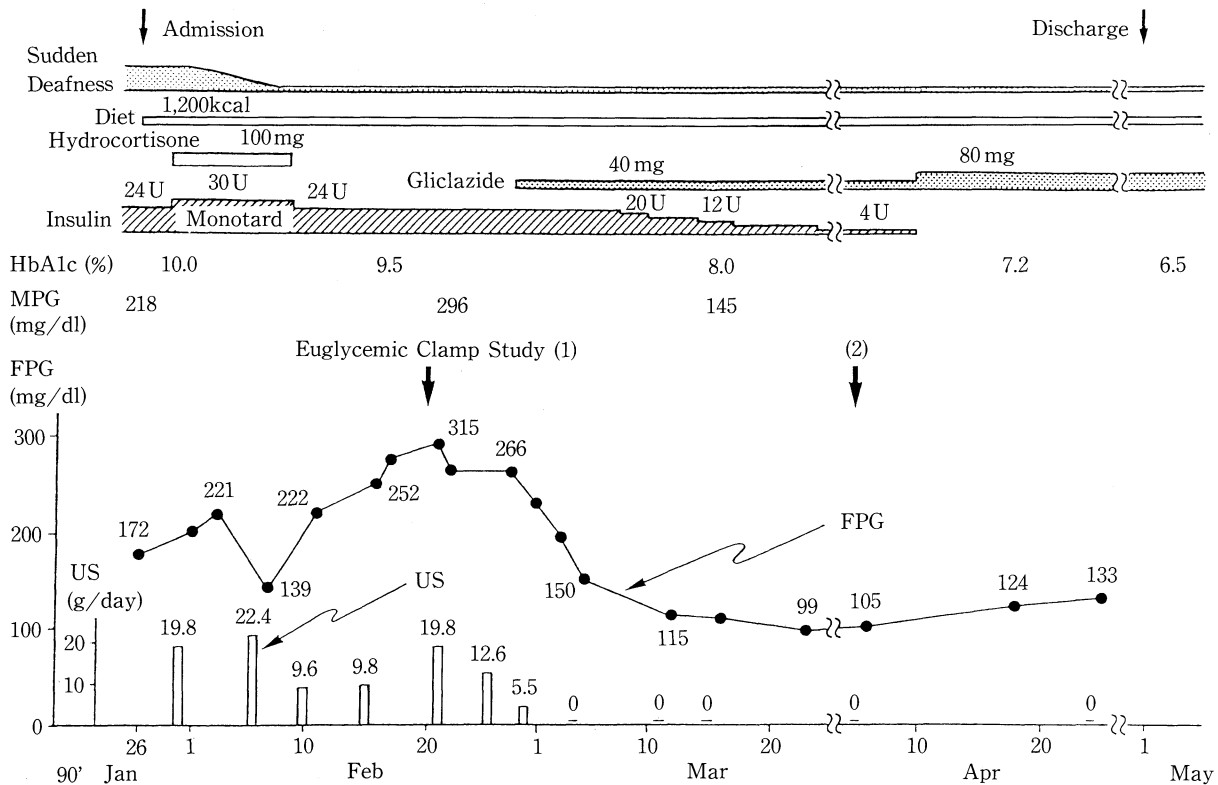
Fig. 1. Clinical course. HbAlc: hemoglobin Alc, MPG: mean plasma glucose, FPG: fasting plasma glucose, US: urine sugar.

some extent. The patient's clinical course on admission is summarized in Fig. 1. At discharge, the patient's body weight of 39.5 Kg had not changed significantly compared to her admission weight, and urinary excretion of CPR was 42 µg/day.

We used the euglycemic hyperinsulinemic clamp technique to assess insulin sensitivity and responsiveness, as previously described (4, 5). We also assessed insulin resistance in 12 non-obese healthy subjects (7 men, 5 women, 35.2±6.6 yr), including a woman with the same age, height and weight as the patient. Briefly, human insulin was administered at rates of 40, 80, 140, 200, and 400 mU/m^2 body surface area/min for 90 minutes. The plasma glucose concentration was maintained at approximately 4.5 mM by a variable infusion of exogenous glucose in a concentration of 20%. The glucose disposal rate needed to maintain euglycemia was determined as the mean value observed every 10 minutes of the last 30 minutes. The following parameters were estimated by measuring the levels of plasma-free insulin by radioimmunoassay: glucose disposal rate (GDR) [mg/Kg/min], GDR/steady-state insulin level (GDR/I) ratio, metabolic clearance rate of insulin (MCRI) [ml/m^2/min], and metabolic clearance rate of glucose (MCRG) [ml/Kg/min]. The first clamp study was performed while the patient was receiving 24 U/day of intermediate-acting insulin. The second clamp study was performed about 40 days later while she was receiving 4 U of insulin and 40 mg a day of oral gliclazide. The anti-insulin antibody test was negative, and the results of an insulin receptor assay, using insulin binding to erythrocyte receptors

(6), were 2.9% and 3.2% in the first and second clamp studies, respectively (normal 3.0% to 8.5%).

Results

During both euglycemic clamp studies, the plasma glucose was kept between 4.2 and 5.0 mM, and the maximal infusion of exogenous insulin caused plasma-free insulin levels of more than 1,000 µU/ml (Fig. 2). The insulin dose-response curve in the first clamp study shifted to the right and downward compared with the control curve, indicating a low sensitivity and responsiveness to insulin in present patient. Sulfonylurea caused a shift toward the normal pattern. In the first clamp study, GDR, GDR/I ratio and MCRG were markedly low in the patient (Table 1). Although these parameters increased slightly in the second clamp study, they remained below normal. MCRI was above normal in both studies. The GDR at 200 mU/m^2/min of insulin infusion, which nearly expressed the maximal GDR, improved from 3.9 mg/kg/min in the first clamp study to 7.3 mg/kg/min in the second clamp study (normal 12.0±1.6).

The HbAlc level improved to 6.5% with the administration of 80 mg of oral gliclazide alone.

Discussion

Although the prevalence of glucose intolerance and diabetes increases with age in individuals with Turner's syndrome, overt
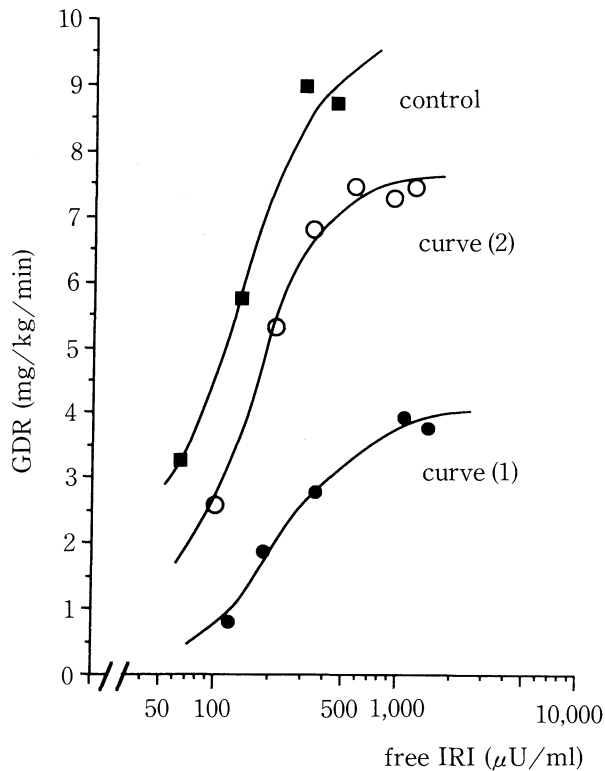
Fig. 2. Insulin dose-response curve. 1) The insulin dose-response curve before gliclazide administration in the patient and a control subject matched in age and stature. 2) The insulin dose-response curve after administration of gliclazide. GDR: glucose disposal rate, IRI: immunoreactive insulin.

Table 1. Euglycemic Clamp Study*

| Parameter | Patient | | Controls |
	First	Second	(n=12)
GDR	0.8	2.5	6.3±0.5
GDR/I ratio	0.6	2.3	10.9±1.0
MCRG	0.7	2.5	8.9±0.9
MCRI	909.1	879.1	763.8±29.9

GDR: glucose disposal rate (mg/kg/min), GDR/I ratio: GDR/steady-state insulin level, MCRG: metabolic clearance rate of glucose (ml/kg/min), MCRI: metabolic clearance rate of insulin (ml/m^2/min), Control data are mean±SD, *Insulin infusion 40 mU/m^2/min.

diabetes is not commonly associated with this syndrome. The 46XXqi karyotype structural abnormality contributes to the susceptibility of diabetes mellitus in Turner's syndrome (3). Diabetes mellitus has also been observed in patients with Klinefelter's syndrome (7), suggesting that glucose intolerance may be linked to an abnormality on chromosome X.

Abnormal carbohydrate metabolism in Turner's syndrome is caused by a diminished beta cell function and peripheral insulin resistance (1, 2). However, impaired glucose tolerance in Turner's syndrome is believed to be caused by Turner's

syndrome itself, as an abnormal oral glucose tolerance test and impairment of insulin-stimulated glucose uptake are more common in nondiabetic children with Turner's syndrome than in normal children (3, 8). However, the precise mechanism of insulin resistance in Turner's syndrome has not been clarified. Caprio et al (8) recently reported that insulin resistance was related to an early metabolic defect that may be restricted to the nonoxidative pathways of intracellular glucose metabolism. Stoppoloni and colleagues reported that insulin resistance resulted from a defect in a muscular insulin receptor (9). In the present study, the downward and rightward shift in the insulin dose-response curve indicated a marked decrease in insulin-induced glucose utilization, although the possibility cannot be ruled out that the intermediate-acting insulin used the morning previous to the clamping day exerted influence on the insulin resistance to some extent (10). During these clamp studies, the insulin-induced glucose utilization seemed to reflect the peripheral glucose utilization, because the plasma-free insulin levels were high enough to suppress the hepatic glucose production (11).

In Turner's syndrome the number of insulin receptors in red blood cells has been found to have been decreased (12). Olefsky (13) reported that when the distribution of insulin receptors is below 10%, the maximal insulin action is decreased. However, in the present diabetic Turner's syndrome patient, receptor binding to the insulin receptors on red blood cells was much greater than 10%. Therefore, the decrease in GDR in the present patient cannot be explained only by a decrease in insulin receptors.

Gliclazide has been found to increase the number of insulin receptors and to modify the affinity of insulin receptors on monocytes, in addition to stimulating beta cells (14, 15). Potentiation of post-binding insulin-induced glucose utilization in tissues has also been observed. In the present study, low-dose gliclazide caused an upward shift in the insulin dose-response curve, indicating an improvement in insulin sensitivity and responsiveness. This observation suggests that gliclazide increased insulin action at both receptor and post-receptor levels. The number of insulin receptors did not increase markedly after gliclazide therapy, indicating that the increase in insulin sensitivity and responsiveness seemed not to be related to a change in the number of insulin receptors. Moreover, to confirm the effect of gliclazide on insulin resistance, if we have the opportunity to discontinue gliclazide, we would like to observe the insulin resistance mechanism.

Marked obesity has been found to reduce insulin sensitivity, but in Turner's syndrome, impaired insulin-stimulated glucose metabolism is not correlated with the body mass index (8), suggesting that insulin resistance in Turner's syndrome is independent of the severity of obesity. In the present case, the incomplete recovery of maximal responsiveness may have been related to a genetic defect of glucose metabolism that is specific to Turner's syndrome.

The present results suggest that gliclazide therapy reduces insulin resistance in diabetes mellitus associated with Turner's syndrome, although its precise mechanism remains to be clari-

fied.

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