Growth Hormone–Deficient Adults Are Insulin-Resistant

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Patients with growth hormone deficiency (GHD) have traditionally been described as having increased insulin sensitivity with a tendency toward fasting hypoglycemia, at least in children. In other studies, impaired glucose tolerance has been found. To evaluate basal insulin sensitivity, a hyperinsulinemic, normoglycemic clamp was performed with an insulin infusion rate of 40 mU/m²/min after an overnight fast. Fifteen patients (four women and 11 men aged 20 to 62 years) with GHD for at least 1 year were compared with 15 healthy controls matched for sex, age, and body mass index (BMI). Thirteen patients had complete pituitary deficiency and were being treated with conventional hormone replacement therapy. Two men had isolated GHD since childhood. Four men were being treated with bromocriptin. There were no significant differences between fasting blood glucose (4.4 ± 0.1 *v* 4.7 ± 0.2 [mean ± SEM] mmol/L) or fasting plasma insulin (9.5 ± 1.4 *v* 8.8 ± 1.1 mU/L) in patients and controls, respectively. Fasting free fatty acid (FFA) levels were lower in patients (444 ± 35 *v* 796 ± 94 μmol/L, *P* < .01). Blood glucose levels during the clamp were similar (4.6 ± 0.1 *v* 4.9 ± 0.1 mmol/L), as were insulin levels (81 ± 4 *v* 93 ± 4 mU/L). A decrease in glucose infusion rate (GIR) was seen during the clamp in GHD subjects (3.9 ± 0.5 *v* 9.9 ± 0.7 mg/kg body weight/min) as compared with controls (*P* = .001). Even if corrections were made for body fat, there was a significant difference (GIR corrected per lean body mass, 5.8 ± 0.8 *v* 13.9 ± 0.9 mg/kg lean body mass/min, *P* < .001). The results suggest that adults with GHD are insulin-resistant. Despite this finding, normal fasting plasma insulin levels were seen.

THE IMPORTANCE of pituitary hormones, including growth hormone (GH), in terms of glucose homeostasis has been known for many years.[1] Children with GH deficiency (GHD) are prone to fasting hypoglycemia,[2] possibly due to a decrease in hepatic glucose production, which is lower than glucose utilization and normalizes during GH replacement therapy.[3] In lean adults with GHD, fasting plasma glucose and insulin concentrations have been found to be normal and hypoglycemia is a rare phenomenon. However, the glucose response to prolonged fasting is altered with decreased blood glucose and plasma insulin levels as compared with controls.[4] Hypoglycemic responsiveness to intravenous insulin is normal in adults with GHD, but the return of plasma glucose toward basal concentrations is delayed.[5] The cause of this delay is probably that GH is of importance to glucose counterregulation after hypoglycemia.[6]

Merimee et al[7] found that during an oral glucose load, glucose tolerance was impaired and patients displayed hypoinsulinemia. Similar results have been observed by others.[8] During GH treatment, the insulin response to glucose was augmented, and a direct insulinotropic effect of GH has been suggested.[7]

We have previously described the effect on glucose homeostasis during 6 months of treatment with recombinant human GH (rhGH) in patients with GHD.[9] However, information about glucose metabolism in untreated adult patients with GHD is limited. We therefore studied basal insulin sensitivity in patients with chronic GHD as compared with matched controls.

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SUBJECTS AND METHODS

Subjects

Fifteen patients (four women and 11 men) aged 20 to 62 years who regularly visited the outpatient clinic at the Division of Endocrinology were asked to participate in the study. Thirteen patients had adult-onset complete pituitary deficiency involving thyroid, adrenal, and gonadal function, which had been present for at least 1 year before this study. Two men had isolated GHD since childhood, and one had been treated with GH from the ages of 5 to 17 years. This treatment had ended 3.5 years before our study. The other patients were being treated with replacement therapy involving glucocorticoids (cortisone acetate 25 mg/d), thyroid hormones (L-thyroxine 0.10 to 0.15 mg/d), and sex hormones. Four men were being treated with bromocriptin (2.5 to 10 mg/d). GHD was defined as a maximum GH response of less than 5 mU/L after insulin-induced (0.1 IU/kg body weight) hypoglycemia. All patients displayed clinical signs of hypoglycemia and had blood glucose levels less than 2.2 mmol/L. Two patients had plasma insulin-like growth factor-I (IGF-I) levels in the low-normal range, and the remaining 13 patients had levels less than the normal range (mean ± SEM, 79.3 ± 11.2 μg/L for all patients). Characteristics of the subjects are listed in Tables 1 and 2.

The 15 healthy control subjects were recruited by advertisement in the local newspaper. The criteria for being healthy, in addition to subjective well-being, were a history of no hospital visits, no diabetes or hypertension, and no medical treatment for any disease during the past 2 years. Of 255 answers in the 40- to 60-year age group, 207 fulfilled criteria for healthy controls. Eleven men and four women were anthropometrically matched groupwise against the patients for age, sex, and body mass index (BMI).

Informed written consent of all subjects was provided, and the study was approved by the Ethics Committee of the Medical Faculty at the Göteborg University.

Body Weight, Body Height, and BMI

Body weight was measured in the morning to the nearest 0.1 kg using a 6800 Digital Indicator (Detecto Scale, Webb City, MO), after subjects had voided. Body height was measured to the nearest

Table 1. Age and Anthropometric Data in GHD Patients and Healthy Controls

Characteristic	Patients (n = 15) Mean	Patients (n = 15) Range	Controls (n = 15) Mean	Controls (n = 15) Range	P
Age (yr)	48	20-62	52	42-60	NS
Sex (M/F)	11/4		11/4		NS
Height (cm)	175	153-191	176	146-192	NS
Weight (kg)	83.9	53-118	84.5	68-100	NS
Body fat (kg)	26.8	11-55	24.7	14-38	NS
Lean body mass (kg)	57.1	28-77	59.8	38-72	NS
BMI (kg/m^2)	27.5	19.2-35.5	27.3	21.8-35.6	NS
FFA (μmol/L)	444	281-704	796	290-1,460	<.01

0.5 cm with subjects barefoot. BMI was calculated using the formula BMI = body weight/height^2 (kilograms per meter squared).

Infusions

All experiments were begun at 8 AM after an overnight fast. Patients were given their hormone replacement after the clamp had been performed. Infusions were administered via a catheter placed in a cubital vein, and arterialized blood samples were drawn from a dorsal hand vein in the contralateral arm. Insulin (Actrapid Human; Novo-Nordisk, Copenhagen, Denmark) was dissolved in NaCl (154 mmol/L) to a concentration of 40 mU/mL, with albumin 4 mg/mL added to prevent adhesion, and infused at a rate of 40 mU/m^2/min during the euglycemic clamps. Glucose 200 mg/mL (Baxter Chemicals, Oslo, Norway) was infused at variable rates in the same catheter as the insulin. Potassium chloride (100 mmol/L) was infused at a rate of 7 mmol/h to prevent hypokalemia during clamps.

The euglycemic clamp was initiated with a primed insulin infusion for 10 minutes followed by a constant infusion during the following 2 hours, as reported previously.[10] The infusion rate was adjusted to keep glucose level constant at 4.5 mmol/L. During the clamp, arterialized venous blood samples were drawn every 5 minutes to measure blood glucose levels with glucose test strips (BM-test glycemie 1-44; Boehringer, Mannheim, Germany) and a reflectometer (Reflolux II; Boehringer). Glucose levels measured with the reflectometer correlated closely with levels measured with both the YSI glucose analyzer (Yellow Springs, OH; N = 91, r = .99) and the glucose-6-phosphatase dehydrogenase technique (N = 1,410, r = .99). Glucose levels were also measured using the glucose-6-phosphatase dehydrogenase technique (Beckman, Fullerton, CA) before and every 20 minutes during the clamps. Glucose levels presented in the results were measured using this technique.

Table 2. Characteristics of 15 Patients (11 men and 4 women) With GHD

Characteristic	No. of Patients Men	No. of Patients Women
Diagnosis		
Chromophobe adenoma	3	2
Meningioma	1	0
Prolactinoma	5	1
Sheehan's syndrome	0	1
GHD since childhood	2	0
Replacement treatment		
Corticosteroids	9	4
Thyroxine	9	4
Gonadal steroids	9	1
Desmopressin	3	0

Analytic Procedures

Insulin levels were determined using a radioimmunoassay (Phadeseph Insulintest; Pharmacia, Uppsala, Sweden). Triglyceride concentrations were determined using a fully enzymatic method (Boehringer). Free fatty acid (FFA) levels were determined using an enzymatic colorimetric method (NEFAC; Wako, Neuss, Germany). IGF-I concentrations were determined using a hydrochloric acid–ethanol extraction radioimmunoassay (Nichols Institute Diagnostic, San Juan Capistrano, CA). GH levels in serum were determined using a polyclonal immunoradiometric assay method (Pharmacia). Glucose infusion rate (GIR) was calculated from the steady state during the last 30 minutes of the 2-hour clamp. Lean body mass and body fat were estimated using bioelectric impedance analysis (BIA-101; RJL System, Detroit, MI).

Statistical Analysis

The mean ± SEM for results were calculated using conventional methods. Differences between groups were tested using Wilcoxon's signed-rank test. Values of P less than .05 were considered significant.

RESULTS

Patients and controls were matched for age, sex, and BMI (Table 1). Body fat was higher and lean body mass lower in the GHD group versus controls, although differences were not statistically significant.

There was no significant difference in fasting blood glucose (4.4 ± 0.1 *v* 4.7 ± 0.2 mmol/L) or fasting plasma insulin (9.5 ± 1.4 *v* 8.8 ± 1.1 mU/L) between patients and controls, respectively.

Blood glucose during the steady state of the clamp was similar in patients and controls (4.6 ± 0.1 *v* 4.9 ± 0.1 mmol/L), as were plasma insulin levels (81 ± 4 *v* 93 ± 4 mU/L). The mean plasma insulin concentration during the clamps was similar during the first and second hour (87 ± 9 *v* 86 ± 6 mU/L) for everyone, including controls, as was blood glucose (5.0 ± 0.3 *v* 4.7 ± 0.2 mmol/L). GIR was lower during the first hour versus the second hour, as would be expected in a non–steady-state situation (5.9 ± 0.6 *v* 6.9 ± 0.6 mg/kg body weight/min).

Fasting triglyceride concentrations were not significantly different in patients versus controls (1.63 ± 0.27 *v* 1.31 ± 0.13 mmol/L).

Fasting FFA levels were lower in the GHD group (444 ± 35 *v* 796 ± 94 μmol/L, P < .01; Table 1). At the end of the clamp, FFA levels were lower in the GHD group (53 ± 10 *v* 121 ± 18 μmol/L for controls; P = .001). However, the decrease from the fasting level was similar in the two groups (87% ± 2.6% and 84% ± 1.7%, respectively).

A decrease in GIR was seen in GHD patients (3.9 ± 0.5 *v* 9.9 ± 0.7 mg/kg body weight/min) as compared with controls (P = .001; Fig. 1a), as well as after corrections for body fat (GIR per lean body mass, 5.8 ± 0.8 *v* 13.9 ± 0.9 mg/kg lean body mass/min, P < .001; Fig 1b).

DISCUSSION

The present study indicates that GHD patients are insulin-resistant. GIRs were less than half those of controls, both when calculated according to body weight and when corrected for body fat. The results show a decreased

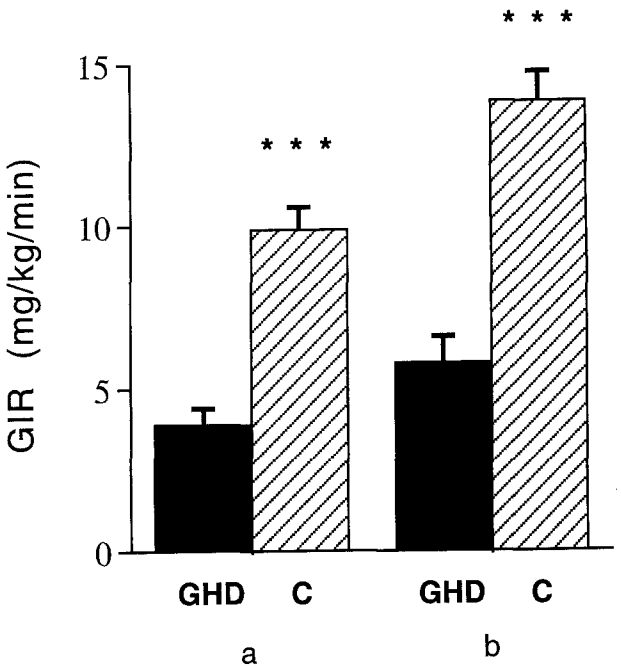

Fig 1. GIR in adult patients with GHD as compared with matched controls (C). (a) GIR per body weight; (b) GIR per lean body mass.

sensitivity to insulin in peripheral tissues in adults with GHD. However, FFA levels were equally suppressed by insulin during the clamps, thus suggesting that the antilipolytic action of insulin is preserved and that the insulin resistance is "selective."

Patients and controls were matched for BMI, suggesting that other factors besides body weight per se have an important effect on insulin resistance. We have previously shown that GHD patients have a higher waist to hip ratio than BMI-matched controls, thereby indicating an abdominal fat distribution in GHD.[11] Abdominal fat distribution is associated with insulin resistance,[12] and the abdominal body fat distribution in GHD may play an important role in the insulin resistance of these patients. Other factors such as differences in muscle fiber types and less physical activity in GHD may also be of importance. Other possible explanations for this insulin resistance are low IGF-I levels and a deterioration in IGF-I–stimulated glucose transport in muscle[13] or a change in the transcription of insulin-responsive genes such as the glucose transporter gene, GLUT4.[14]

Serum triglyceride levels are higher in adults with GHD,[11,15] with a tendency also in the present GHD patients. An increased concentration of FFA could thus be expected in patients with GHD. However, decreased fasting concentrations of FFA were found instead in the present study. Children with GHD have lower FFA levels,[3] as do GHD patients with diabetes.[16] A likely mechanism for decreased FFA levels could be a decrease in the lipolytic effect in the absence of GH. However, there are also studies indicating higher concentrations of FFA in patients with GHD.[4]

Abdominal fat distribution is a well-known risk factor for cardiovascular disease.[17-18] Adult patients with hypopituitarism receiving conventional replacement therapy but not GH have an increased mortality from cardiovascular disease.[19] Untreated GHD could explain this increase in mortality. Interestingly, there are several similarities between the so-called metabolic or insulin-resistance syndrome and untreated GHD in adults. Both are characterized by premature atherosclerosis and increased mortality from cardiovascular diseases, central and visceral obesity, high triglyceride and low high-density lipoprotein cholesterol concentrations, increased prevalence of hypertension, elevations of fibrinogen and plasminogen activator inhibitor-1 activity, and insulin resistance.[11,20-22]

Hyperinsulinemia is a common feature in all other states involving insulin resistance, such as obesity, hypertension, and non–insulin-dependent diabetes mellitus.[12,20] Despite the marked insulin resistance in GHD patients in the present study, no significant compensatory increase in fasting plasma insulin was found and fasting glucose levels were normal, possibly as a result of a decrease in hepatic glucose production.[3] In vitro studies have shown that FFAs augment gluconeogenesis, and low levels of FFA may cause a decrease in gluconeogenesis. Thus, decreased FFA concentrations might explain our previous observations of decreased fasting blood glucose in patients with GHD.[11]

Randle et al[23] postulated a glucose–fatty acid cycle in which FFAs compete with glucose as a physiologic substrate. It is now generally accepted that FFAs compete with glucose as an oxidative fuel,[24] and this has been shown to reduce skeletal muscle glucose uptake in man.[25] It seems likely that patients with GHD and decreased fasting FFA levels do not have the same competition with glucose as an oxidative fuel, which might in turn explain the lack of increase in fasting plasma insulin in GHD. The low fasting insulin concentration may also be explained by the lack of GH, which has been suggested to be an insulinotropic hormone.[7,26]

The vast majority of patients with adult-onset GHD also have other pituitary deficiencies. It has therefore been questioned as to whether the changes observed in adults with GHD are due to the lack of GH or are the result of imperfect hormone replacement therapy. No data are available on the changes in insulin sensitivity induced by cortisol, thyroid, and sex-steroid replacement therapy. However, it is unlikely that the replacement doses used in this study for deficient adrenal, thyroid, and gonadal function induce changes in insulin sensitivity of the magnitude observed in these patients. A control group consisting of pituitary-deficient patients who had received the same treatment but did not have GHD would be extremely difficult to find, since GH is one of the first hormones to disappear in the event of pituitary failure. The best way to evaluate insulin resistance of GHD patients is to replace GH, while keeping the other hormone therapy constant and using the same subjects as their own controls.[7,9]

It is known that insulin sensitivity can deteriorate during rhGH treatment, but this could be a transient phenomenon. In a previous study, we showed that rhGH treatment induced a markedly worsened insulin resistance after 6 weeks, due to a decrease in the effect of insulin on glucose

utilization. However, after 6 months of rhGH treatment, insulin sensitivity was restored to baseline values.[9] It is likely that the favorable changes in body composition, such as an increase in lean body mass and a decrease in abdominal and visceral adipose tissue, induced by rhGH treatment counteract the insulin-antagonistic effect of GH. Hypothetically, a further improvement in insulin sensitivity is possible, since exercise capacity and physical activity continue to improve beyond the first 6 months of rhGH treatment.[27]

Hepatic glucose production has been shown to be almost suppressed with insulin levels similar to those in the present study.[9] We have not investigated whether insulin clearance differs between GHD patients and controls. However, this seems unlikely, since steady-state insulin concentrations were similar in the two groups. To our knowledge, it is not known whether GHD patients experience a change in the number of insulin receptors or insulin affinity. However, a diminution in erythrocyte insulin receptors has been described after short-term hGH administration in GHD children.[28]

In conclusion, the data suggest that adult patients with GHD are insulin-resistant. A compensatory increase in fasting plasma insulin was not observed.

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