European Journal of Clinical Investigation (2000) **30**, 771–778

The increased insulin sensitivity in growth hormone-deficient adults is reduced by growth hormone replacement therapy

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Abstract

Background Growth hormone deficiency is associated with increased morbidity and mortality from cardiovascular diseases, which might be related to changes in glucose and lipid metabolism.

Design To assess the influence of long-term growth hormone replacement therapy (GHRT) on glucose metabolism we examined eight growth hormone-deficient (GHD) adults (seven female/one male; age, 46 ± 3 years; body mass index, 31 ± 2 $kg\,m^{-2}$) over a period of 18 months in comparison to an adequate control group consisting of eight obese subjects matched for age, sex, and body mass index. We performed frequently sampled intravenous glucose tolerance tests (FSIGT) with minimal model analysis before the study, and after 12 and 18 months.

Results Following GHRT, insulin-like growth factor-1 (IGF-1) increased significantly from a basal level of 75·9 ± 18·9 to 200·8 ± 31·0 $\mu g\,L^{-1}$ after 12 months of therapy and remained stable, thereafter. GHRT did not affect fasting blood glucose, basal insulin, cholesterol, blood pressure and body weight. However, at 12 months, HbA1c (6·0 ± 0·1 vs. 5·6 ± 0·1% at basal, $P<0·05$) and triglyceride (2·3 ± 0·4 vs. 1·4 ± 0·3 $mmol\,L^{-1}$) significantly increased but returned to pretreatment values at 18 months. Insulin sensitivity was higher in GHD (8·2 ± 3·1) compared to controls ($3·6 \pm 0·53 \times 10^{-4}\,min^{-1}/(\mu U\,mL^{-1})$, $P=0·06$) and decreased significantly after 18 months of GHRT to 5·1 ± 2·6, $P<0·05$. Basal insulin secretion was similar to that in the control group and increased significantly after 12 and 18 months, total insulin secretion only after 12 months. S_G (glucose effectiveness)was lower in GHD patients ($0·0095 \pm 0·001\,min^{-1}$) compared to controls ($0·020 \pm 0·003\,min^{-1}$, $P<0·05$) and increased significantly after 12 and 18 months of GHRT (0·016 ± 0·002, and 0·015 ± 0·001 min^{-1}, $P<0·05$), respectively. Hepatic insulin extraction rate was similar in both groups and remained unchanged following GHRT.

Conclusion We conclude that long-term GHRT induces a significant decrease of the increased insulin sensitivity in GHD patients to levels observed in body mass index-matched control subjects. This is accompanied by an increase in basal and total insulin secretion as well as in glucose effectiveness as a possible compensatory mechanism.

Keywords Growth hormone deficiency in adults, insulin resistance, minimal model analysis, recombinant human growth hormone.

Eur J Clin Invest 2000; 30 (9): 771–778

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Received 31 December 1999; accepted 16 April 2000

Introduction

Growth hormone deficiency (GHD) in adult patients is associated with increased morbidity and mortality from cardiovascular disorders [1–3]. Hypopituitary patients on conventional hormone replacement therapy, i.e. hydrocortisone, thyroxine and sex steroids as appropriate, exhibit a nearly doubled mortality rate due to cardiovascular diseases [1,4], a higher incidence of atherosclerotic plaques in carotid and femoral arteries [5], and a reduced aortic distensibility [6]. Furthermore, smaller hearts [7] and a lower cardiac output [8] have been described. While the exact mechanism for the increased mortality in GHD patients is still unclear, changes in lipid metabolism and carbohydrate tolerance might play a major role. GHD adults are mostly overweight with increased fat mass predominantly located in the abdominal area, accompanied by decreased lean body mass, reduced muscle strength [9–13], elevated plasma total and low density lipoprotein (LDL) cholesterol and increased plasma triglycerides [14,15]. Insulin resistance and hyperinsulinaemia have been described in these patients [16–18], representing the characteristic features of the metabolic syndrome [19]. Furthermore, patients complain of impaired general well-being [20,21] and bone mineral density is reduced [22].

Growth hormone replacement therapy (GHRT) has been shown to improve well-being, body composition and exercise tolerance [23,24]. The findings on the effect of GH replacement on carbohydrate and lipid metabolism, however, are controversial. Following short-time GHRT increased fasting glucose [11], insulin and C-peptide levels have been reported [23] – presumably as a compensatory mechanism to insulin resistance, which is seen in GH excess like acromegaly [25,26], while others could not confirm these findings [27]. In studies on extended GHRT the decrease in insulin sensitivity was reversed after 12 and 26 weeks, respectively [17,28]. While an increased insulin secretion suggesting insulin resistance after 3 months of GHRT has been reported recently [17], the effect of long-term GHRT on insulin sensitivity has not been addressed adequately.

The present study was undertaken to evaluate the influence of long-term GHRT on carbohydrate metabolism during an 18-month period. Insulin secretion, hepatic insulin extraction and insulin sensitivity, as well as glucose effectiveness, were assessed by the minimal model approach employing frequently sampled intravenous glucose tolerance tests (FSIGT) before and after 12 and 18 months of GHRT. Additionally, these parameters were compared to an adequate control group matched for the degree of obesity.

Methods

Patients

Eight patients with GHD, seven females/one male; mean age of 46 ± 3 years (range 28–56); mean body mass index (BMI): 31 ± 2 kg m^{-2} (range 23–43) entered the study after informed consent was obtained. The protocol was approved by the Human Ethics Committee of the University of Vienna. Patients with a history of diabetes, hypertension, or malignancies were excluded. GH deficiency was confirmed by a maximum GH peak less than 3 μg L^{-1} after the intravenous administration of 30 g arginine [29]. GH deficiency was present in each patient for a minimum of 2 years. All patients had additional anterior pituitary deficiencies and were on stable replacement therapy at least 6 months before and during the study period. The clinical characteristics of the eight patients are shown in Table 1. The control group (C) consisted of eight obese, otherwise healthy subjects matched for sex, age and body weight (seven females/one male; mean age: 43 ± 3 years; range: 33–55; BMI 33 ± 2 kg m^{-2}; range: 24–44).

Study design

Patients received 0·125 U (40 μg) kg^{-1} body weight per week recombinant human (rh) GH (Genotropin, Pharmacia, Stockholm, Sweden) for the first 4 weeks and thereafter

Table 1 Patient characteristics

ID	Sex	Age (years)	BMI kg m^{-2}	GH-peak after arginine μg L^{-1}	Diagnosis (year)	Other pituitary dysfunction	Hormone replacement therapy
1	f	48	34	0·5	1988, endocrine inactive pituitary adenoma	gonadotr., thyreotr., corticotr.	E/P, T, H
2	f	55	43	0·5	1984, endocrine inactive pituitary adenoma	gonadotr., thyreotr., corticotr.	T, H
3	f	56	31	1·1	1986, prolactinoma	gonadotr., thyreotr., corticotr.	T, H
4	f	45	26	1·4	1988, prolactinoma	gonadotr.	E/P
5	m	44	31	0	1974, prolactinoma	gonadotr., thyreotr., corticotr.	T/prednisone
6	f	28	25	0	1982, idiopathic GH-deficiency	thyreotr.	T
7	f	43	23	0·5	1989, endocrine inactive pituitary adenoma	gonadotr., thyreotr., corticotr.	E/P, T, H
8	f	49	32	3·0	1988, prolactinoma	gonadotr.	E/P

f, female; m, male; BMI, body mass index; GH, growth hormone; gonadotr., gonadotropic; thyreotr., thyreotropic; corticotr., corticotropic; E, oestradiol; P, progesterone; H, hydrocortisone, T; I-thyroxine.

0·25 U (81 μg) kg^{-1} per week subcutaneously at 20.00 h. Irrespective of body weight the maximum daily dose was not allowed to exceed 4 U. In two patients the rhGH dose had to be reduced because of side-effects due to fluid retention and arthralgias. The lowest dose administered in these patients was 0·07 U (22 μg) kg^{-1} per week.

FSIGT

After an overnight fast a FSIGT was performed at baseline, and then after 12 and 18 months of GHRT. A catheter was inserted into an antecubital vein for blood sampling and in a contralateral vein for glucose injection. Basal samples were drawn at − 10 and − 1 min. At time 0 glucose (0·3 g kg^{-1} body weight) was injected within 1 min and additional blood samples were collected at 2, 4, 6, 8, 10, 12·5, 15, 17·5, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 and 180 min for determination of glucose, insulin and C-peptide.

Data analysis

Data analysis was performed by using the minimal modelling technique which, by describing the dynamic relationships between glucose and endogenous insulin and C-peptide, provides parameters which quantify the main individual factors contributing to glucose tolerance. The structure of the models and the meaning of the parameters have been published in detail elsewhere [30–32]. The glucose model [30] quantifies the glucose effectiveness, S_G, i.e. the effect on glucose disposal *per se* without dynamic changes in insulin concentration, and the insulin sensitivity index, S_I. The C-peptide and insulin models [31] provide the time–courses of glucose-stimulated prehepatic insulin secretion, CPS(t), and that of posthepatic appearance of the hormone in periphery, IDR(t). In addition, from C-peptide data, three parameters are estimated which provide the basal insulin release per unit volume (BSR, pM min^{-1}), and the sensitivity to glucose of the first (Φ1) and second (Φ2) phase of the dynamic (suprabasal) insulin release from the beta cell. BSR, Φ1 and Φ2 describe beta cell activity by factoring out the major components of the prehepatic insulin release: the basal and the dynamic phases.

Calculations

Model parameters were estimated using MINMOD [33,34]. The total areas under the concentration curves (AUC) of insulin and C-peptide were obtained by integrating with the trapezoidal rule the concentration time–courses from 0 to 180 min. The total amount of insulin secreted per unit volume (TIS) was calculated by integrating CPS(t). The per cent normalized difference between CPS(t) and IDR(t) gave the time–course of hepatic insulin extraction: its integral over 180 min divided by this time interval allowed the calculation of a weighted mean of the per cent hepatic insulin extraction (HE). The statistical analysis was performed using the Wilcoxon matched pairs signed rank test for differences within the patient group and the non parametric *t*-test (variance analysis) for differences between the groups. All values are given as means ± SEM. A *P*-value $< 0·05$ was considered significant.

Assays

Blood was rapidly centrifuged. Glucose was immediately measured by the glucose oxidase method. Serum for determination of insulin and C-peptide was stored at −20 °C and was analysed later by commercially available radioimmunoassays (Insulin: Biodata, Milano, Italy; C-peptide: C-Pep-CT CIS bio international, GIF-SUR-Yvette CEDEX, France). The intra- and interassay coefficients of variation for insulin and C-peptide assays were less than 10%. Insulin-like growth factor-1 (IGF-1) was measured with a radioimmunoassay method after treatment of serum with acid ethanol to precipitate and neutralize the IGF-I binding proteins [35]. The minimum detectable IGF-1 concentration was 20 $\mu g l^{-1}$, the intra- and interassay coefficients of variation were 3·1 and 10%, respectively. Haemoglobin A1c (HbA1c) was collected in ethylenediaminetetraacetic acid (EDTA) tubes and determined on a Shimadzu high-performance liquid chromatography (HPLC) system (Shimadzu, Kyoto, Japan). The reference range was 4–6%. The inter- and intra-assay coefficients of variation ranged between 1·2 and 2·6%.

Results

Metabolic profile

All patients were GH deficient as documented by a maximum GH response of less than 3·0 $\mu g L^{-1}$ to 30 g arginine and all patients had at least one additional anterior pituitary deficiency (Table 1).

IGF-1 levels increased significantly after 12 months GHRT from 75·9 ± 18·9 $\mu g L^{-1}$ to 200·8 ± 31·0 $\mu g L^{-1}$ ($P < 0·01$). Thereafter, IGF-1 plasma concentrations remained stable throughout the study period (195·4 ± 23·6 $\mu g L^{-1}$ after 18 months; $P = 0·7$ vs. 12 month). IGF-I levels were within 2 standard deviations of those obtained for healthy subjects matched for sex and age.

Table 2 shows the metabolic parameters for the controls and patients before and after 12 and 18 months of GHRT. In summary, BMI, waist-to-hip ratio, fasting blood glucose, basal insulin concentration, cholesterol and blood pressure did not change significantly during GHRT. HbA1c and triglyceride levels increased significantly after 12 months ($P < 0·05$), but were not different from basal levels at 18 months ($P = 0·15$). C-peptide levels were significantly higher after 18 months of GHRT ($P < 0·02$). The control group compared to the GHRT group had

Table 2 Metabolic parameters of controls and patients on growth hormone replacement therapy (GHRT)

Variable	Controls	GHRT basal	GHRT 12 months	GHRT 18 months
n (men/women)	8(1/7)	8(1/7)		
Age (years)	43 ± 3	46 ± 3		
Body mass index ($kg\,m^{-2}$)	33 ± 2	31 ± 2	32 ± 2	32 ± 2
Waist-to-hip ratio	0·90 ± 0·33	0·89 ± 0·04	0·88 ± 0·04	0·90 ± 0·04
SBP (mmHg)	138 ± 5	116 ± 6[a]	118 ± 6	116 ± 6
DBP (mmHg)	83 ± 2	78 ± 4	82 ± 2	83 ± 3
Triglycerides ($mmol\,L^{-1}$)	1·7 ± 0·1	1·4 ± 0·2	2·3 ± 0·4[b]	1·9 ± 0·5
Cholesterol ($mmol\,L^{-1}$)	6·1 ± 0·4	6·1 ± 0·5	6·6 ± 0·5	6·2 ± 0·5
Glucose ($mmol\,L^{-1}$)	4·2 ± 0·2	4·6 ± 0·2	4·5 ± 0·1	4·6 ± 0·1
HbA1c (%)	4·9 ± 0·2	5·6 ± 0·1[a]	6·0 ± 0·1[b]	5·8 ± 0·2
Basal insulin ($pmol\,L^{-1}$)	60 ± 9	49 ± 15	52 ± 11	62 ± 22
C-peptide ($nmol\,L^{-1}$)	0·68 ± 0·02	0·51 ± 0·01	0·63 ± ·01	0·76 ± 0·02[c]

GHRT, growth hormone replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a] $P<0·05$, C vs. GHRT basal.
[b] $P<0·05$, GHRT basal vs. GHRT 12 months.
[c] $P<0·02$, C vs. GHRT 18 months.

significantly lower basal HbA1c levels and significantly higher systolic blood pressure.

FSIGT tests and minimal model parameters

Figure 1 shows the basal and dynamic values of glucose, insulin and C-peptide following intravenous glucose injection in patients before (Fig. 1a) after 18 months GHRT (Fig. 1b) and of controls (Fig. 1c). The values after 12 months GHRT are not shown in the figure for the sake of clearness. AUC for glucose was not different between GHD and controls and did not change following GHRT (not shown). AUC for C-peptide was significantly higher in controls compared to GHD at basal ($P<0·05$). AUC of insulin was also higher in controls vs. the patients but the difference did not reach statistical significance. After 18 months of GHRT AUC for insulin and C-peptide increased significantly ($P<0·02$) when compared to the basal state.

Table 3 reports the model-derived parameters. S_I was initially higher in GHD vs. controls ($P=0·06$) but decreased significantly following GHRT after 18 months ($P<0·05$). Glucose effectiveness (S_G) was lower in GHD compared to control at baseline ($P<0·01$) and increased after 12 ($P<0·05$) and 18 months ($P<0·03$). Basal insulin secretion (BSR) was not different between GHD and controls and increased after 12 months ($P<0·01$) and 18 months ($P=0·05$), respectively. Total insulin secretion (TIS) was not different between GHD and controls at basal and increased significantly after 12 months of GHRT. Hepatic insulin extraction was not different between

Table 3 Model-estimated and calculated parameters from frequently sampled intravenous glucose tolerance tests for controls and patients on growth hormone replacement therapy

Variable	Controls	GHRT basal	GHRT 12 months	GHRT 18 months
Glucose				
S_I ($10^{-4}\,min^{-1}\,\mu U^{-1}\,mL^{-1}$)	3·6 ± 0·5	8·2 ± 3·1	7·1 ± 2·8	5·1 ± 2·6[c]
S_G (min^{-1})	0·020 ± 0·003	0·0095 ± 0·001[a]	0·016 ± 0·002[b]	0·015 ± 0·001[c]
Insulin secretion				
BSR ($pmol\,L^{-1}\,min^{-1}$)	37·5 ± 6·4	33·3 ± 6·0	50·4 ± 9·0[b]	52·0 ± 13·7[c]
Φ_1 ($[nmol\,L^{-1}]\,min^{-1}/[mmol\,L^{-1}]$)	2·7 ± 0·6	0·9 ± 0·1[a]	1·0 ± 0·1	1·2 ± 0·1
Φ_2 ($[pmol\,L^{-1}]\,min^{-2}/[mmol\,L^{-1}]$)	0·74 ± 0·11	0·36 ± 0·05[a]	0·40 ± 0·05	0·34 ± 0·07
TIS ($nmol\,L^{-1}$ in 180 min)	15·6 ± 3·3	12·1 ± 2·5	15·4 ± 2·1[b]	17·0 ± 3·5
TOT CP AREA ($pmol\,L^{-1}$ in 180 min)	32·6 ± 13·7	17·6 ± 3·1[a]	23·1 ± 3·2	28·9 ± 7·3[c]
TOT INS AREA ($nmol\,L^{-1}$ in 180 min)	23·9 ± 3·7	20·4 ± 6·1	25·7 ± 5·3	30·8 ± 9·3[c]
HE (%)	85 ± 2	86 ± 2	84 ± 4	80 ± 4

C, controls; S_I, insulin sensitivity index; S_G, glucose effectiveness; BSR, basal insulin secretion rate per unit volume; Φ_1, first-phase B-cell sensitivity to glucose; Φ_2, second-phase B-cell sensitivity to glucose; TIS, total amount of secreted insulin per unit volume; TOT INS AREA, total area under insulin concentration curve; TOT CP AREA, total area under C-peptide concentration curve; HE, hepatic insulin extraction rate; values are mean ± SEM.
[a] $P<0·05$, C vs. GHRT basal.
[b] $P<0·05$, GHRT basal vs. GHRT 12 months.
[c] $P<0·05$, GHRT basal vs. GHRT 18 months.

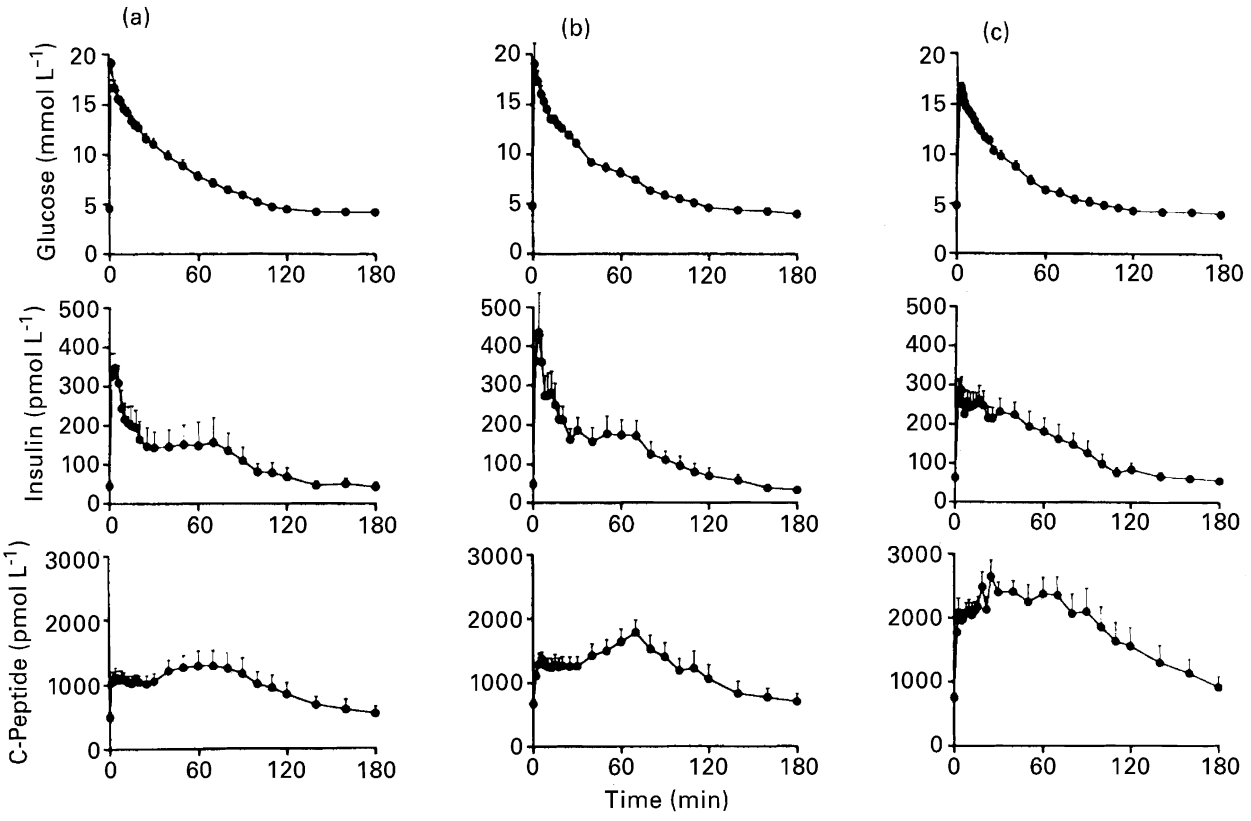

Figure 1 Line graphs show average time–courses of glucose, insulin and C-peptide as mean ± SEM of patients on GHRT (a) before ($n=8$) and (b) after 18 months of therapy ($n=8$) and of control subjects (c) ($n=8$) during intravenous glucose tolerance tests. Glucose injection ($0{\cdot}33\,g\,kg^{-1}$) was started at 0 min and lasted for 1 min.

GHD and controls and did not change following GHRT. B-cell sensitivities to glucose of first (Φ1) and second phase (Φ2) were significantly higher in controls compared to the patient group at basal, but did not change during 18 months GHRT.

Discussion

In this study we could demonstrate elevated insulin sensitivity in patients with GHD compared to BMI-matched control subjects. Long-term GHRT induced a significant decrease in insulin sensitivity and an increase in basal and total insulin secretion. Glucose effectiveness, however, improved after 12 and 18 months of GHRT. These changes were accompanied by a transient worsening of glycemic control after 12 months, which was reversed at the end of the observation period. All patients in the present study were severely GH deficient as confirmed by a maximum GH response $<3\,\mu g\,L^{-1}$ after arginine stimulation. The dose of GHRT was physiological as confirmed by IGF-1 levels in the normal range during therapy [35] which does not suggest an iatrogenic GH excess interfering with our results.

In the present study we have employed the FSIGT test to simultaneously evaluate insulin sensitivity, insulin secretion and hepatic insulin extraction. As regards the estimation of insulin sensitivity this approach has been validated against the glucose clamp method [36] and has been widely used in different nondiabetic populations [37]. Despite their obesity GHD adults displayed a higher degree of insulin sensitivity when compared to healthy controls matched for the degree of obesity. In fact, when compared with the values for SI obtained by the same method in healthy lean controls in another study [38], the GHD subjects exhibit a normal degree of insulin sensitivity. The explanation for this finding remains speculative. While the waist-to-hip ratio was not different between the respective groups, systolic blood pressure was significantly higher in controls, however, on average still within the normal range, whereas diastolic blood pressure was not different between the groups. Although hypertension might be associated with insulin resistance, this relatively small difference for systolic blood pressure is very unlikely to be responsible for the pronounced difference in insulin sensitivity. A more likely explanation seems to be the absence of GH, which is a potent insulin antagonistic hormone [39], which could counteract the effect of obesity on insulin sensitivity in

GHD adults. Our finding of increased insulin sensitivity due to GH deficiency has also been observed by other investigators [40,41]. In those studies reporting insulin resistance in GHD subjects [17,18], the GHD subjects were more obese than the healthy controls. Thus, the insulin resistance in these patients might rather be attributed to obesity and fat distribution *per se* than to GH deficiency.

GH excess in acromegalic patients [25,26] as well as experimental short-time GH administration in pharmacological doses in men [42] and in dogs [43] have been shown to induce insulin resistance and hyperinsulinaemia. Most studies investigating glucose metabolism following short-time GHRT reported either unchanged [27] or decreased insulin sensitivity [17,28,44,45]. The insulin resistance, however, was mostly reversed following an extended treatment period up to 12 months. In our study, however, long-term GHRT decreased insulin sensitivity after 12 and 18 months to an extent seen in healthy control subjects matched for the degree of obesity. An inadequate high glucocorticoid substitution causing the decrease of insulin sensitivity as a potential explanation is unlikely since the corticotropic-insufficient patients were on a stable cortisol replacement dose before and throughout the study. In addition, it has been reported, that the bioavailability of orally administered hydrocortisone is reduced in GH-substituted patients [46]. Despite our patients becoming insulin resistant they did not exhibit the profile of the metabolic syndrome in terms of hypertension and worsening of lipid metabolism, although a transient increase in triglyceride levels was observed after 12 months.

In nondiabetic subjects insulin resistance is compensated for by hyperinsulinaemia to maintain normal glucose levels. Accordingly, our patients exhibited increased insulin levels in response to decreased insulin sensitivity at 12 and 18 months following GHRT, which confirms the observation of Salomon et al., who described increased basal insulin levels after 6 months GHRT [23]. The insulin hypersecretion could be divided into its components by the minimal model technique. While basal insulin secretion rate increased significantly after 12 and 18 months, total insulin secretion rate was significantly elevated only at 12 months, whereas hepatic insulin extraction rate remained unchanged. The amount of dynamic first-phase releasable insulin as response to the glucose injection and second-phase insulin release, which represents the capacity to synthesize newly releasable hormone, remained unchanged after 18 months GHRT, indicating that the basal insulin secretion is responsible for the increase of secreted insulin as also reflected by the elevated basal C-peptide level. Whether GH *per se* stimulates insulin secretion, as shown in *in vitro* studies [47], and hyperinsulinaemia causes insulin resistance, or decreased insulin sensitivity causes hyperinsulinism cannot be answered with the minimal model approach. Furthermore, GH-induced changes in protein [48] and lipid metabolism and on body composition [9,23] can influence carbohydrate metabolism. However, no significant increase of BMI, body fat content and waist-to-hip ratio during GHRT in our patients was observed.

HbA1c was significantly higher in GHD patients at baseline compared with obese controls. HbA1c as a measure of glucose control is influenced by insulin sensitivity as well as insulin secretion. While insulin sensitivity was essentially normal in GHD patients, we could observe a decrease in B-cell sensitivity to glucose of first and second phase in GHD patients, suggesting impaired insulin secretion. Since it is well known that GH stimulates insulin secretion [47] GH deficiency might at least in part be responsible for the elevation of the HbA1c in GHRT patients via impairment of insulin secretion.

The ability to dispose of glucose is dependent on the combined abilities of glucose *per se* and secreted insulin to stimulate net glucose disposal. As our patients all had adequate beta cell function, the increased insulin secretion in response to insulin resistance could maintain fasting glucose levels and HbA1c levels in reference ranges. Additionally, the observed increase in glucose effectiveness, the importance of which has been reported recently [49–51], could be another compensatory mechanism to maintain glucose levels in the physiological range.

In conclusion, when compared to an appropriate BMI-matched control group, we could demonstrate increased insulin sensitivity in GHD patients before GHRT which decreased following GHRT. This was accompanied by insulin hypersecretion and an elevated glucose effectiveness as potential compensatory mechanisms. The induction of insulin resistance by GHRT would be hard to reconcile with the expected benefits of GHRT on overall survival of GH-deficient patients. Thus, further studies on GH-related effects on other known risk factors for cardiovascular disease and over even longer periods of observation are necessary. We conclude that patients on GHRT with compromised beta cell function or a family history of diabetes deserve special attention and careful monitoring of glucose metabolism.

Acknowledgements

G. Pacini has been supported in part by a Progetto Bilaterale grant from the Italian National Research Council, Comitato 07 (responsible: Dr K. Thomaseth of LADSEB).

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