Long-Term Monitoring of Insulin Sensitivity in Growth Hormone–Deficient Adults on Substitutive Recombinant Human Growth Hormone Therapy

Claudia Giavoli, Silvia Porretti, Cristina L. Ronchi, Vincenzo Cappiello, Emanuele Ferrante, Emanuela Orsi, Maura Arosio, and Paolo Beck-Peccoz

Since the effects of recombinant human growth hormone (rhGH) replacement therapy on glucose metabolism are still a matter of debate, the aim of the present study was to evaluate the impact of long-term rhGH treatment on insulin sensitivity. Simple indices of insulin resistance (IR) and insulin sensitivity (IS), based on fasting glucose and insulin, such as the homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin check index (QUICKI), were used to estimate the degree of IR and IS in 20 normoglycemic patients (11 men and 9 women; mean age, 44 ± 14 years) with severe adult-onset GH deficiency (GHD). Measurements were determined at baseline and after 1 and 5 years of continuous rhGH therapy. Basal values were compared to those obtained in 20 healthy sex- and age-matched controls. Starting rhGH dose ranged from 3 to 8 μg/kg/d in keeping with sex and age, then doses were titrated according to insulin-like growth factor-I (IGF-I) levels. At baseline all patients had low IGF-I levels (10 ± 5.4 nmol/L), high body mas index (BMI; 27.5 ± 4 kg/m^2), and elevated body fat percentage (BF%; 31.8 ± 9.6). Fasting glucose and insulin levels, as well as HOMA-IR and QUICKI, did not differ significantly from those recorded in the control group. After 1 year of rhGH replacement therapy, normalization in IGF-I levels and a significant reduction in BF% were observed ($P < .001$), and these effects were maintained after 5 years of treatment. Fasting glucose increased from 79 ± 10 to 87 ± 13, and 87 ± 12 mg/dL ($P < .05$) after 1 and 5 years of therapy, respectively. Fasting insulin significantly increased after 1 year, without further modifications in the long-term follow-up. HOMA-IR significantly increased from 2.1 ± 1.7 to 2.5 ± 1.7 ($P < .05$) after 1 year, then decreased to 2.3 ± 1.5 (P = not significant [NS] *v* basal) after 5 years. A specular decrease in QUICKI from 0.37 ± 0.05 to 0.34 ± 0.03 ($P < .01$) occurred after 1 year, with a trend to increase (0.35 ± 0.04; P = NS *v* basal) after 5 years. No patient developed impaired fasting glucose. In conclusion, rhGH therapy determined an increase in fasting glucose and insulin levels, causing in the short-term period a worsening of IS. The sustained reduction in BF%, without further deterioration of IS, suggests that long-term beneficial effects on body composition may overcome the negative influence of GH on glucose metabolism.

GROWTH HORMONE deficiency (GHD) in adults is a well-defined clinical syndrome characterized by several metabolic alterations, such as increased body fat (BF), impaired physical performance, altered lipid profile, and insulin resistance (IR). Recombinant human GH (rhGH) replacement therapy has been shown to reverse many of the above-mentioned alterations. The role of GH as an important regulator of metabolism has been well established.[1,2] However, the effects of rhGH treatment of GHD adults on glucose metabolism are still matter of debate. Short-term studies (<12 months) mainly reported a deterioration of insulin sensitivity (IS).[3-5] Long-term trials (from 30 months to 10 years) mostly showed that, after this initial worsening, insulin sensitivity returned toward baseline values.[6-9] By contrast, some studies reported that IS during rhGH treatment was still lower than at baseline.[10,11] Moreover, all long-term studies examined small numbers of patients (10 to 12 subjects).

The aim of the present study is to evaluate the long-term impact of 5 years of rhGH treatment on IS, using simple and validated indices such as the homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin check index (QUICKI).

MATERIALS AND METHODS

Subjects

Twenty normoglycemic patients (11 men and 9 women; mean age, 44 ± 14 years; body mass index [BMI], 27.5 ± 4 kg/m^2) with adult-onset GHD were studied. The diagnosis of GHD was made on the basis of a peak response of serum GH less than 3 μg/L to a GH provocative test (insulin tolerance test or arginine + growth hormone–releasing hormone [GHRH]) as previously reported.[12] All of the patients showed insulin-like growth factor-I (IGF-I) levels under the lower limit of the age-related reference range. Five patients had a history of clinically nonfunctioning pituitary adenoma, 5 prolactinoma, 9 craniopharyngioma, and 1 meningioma. In all patients, GHD was one of multiple pituitary hormone deficiencies, appropriately substituted. Twenty sex- and age-matched healthy subjects were studied as a control group for basal evaluation of HOMA-IR and QUICKI. Starting rhGH dose ranged from 3 to 8 μg/kg/d in keeping with sex and age, then it was individually titrated according to the combination of serum IGF-I levels and clinical response evaluated after 3 months of therapy. The final dose, after the titration, was 0.3 ± 0.1 mg/d.

Procedures

Investigations were performed at baseline and after 1 and 5 years of therapy. Evaluated parameters included: IGF-I, body fat percentage (BF%), and fasting blood glucose and insulin for the determination of HOMA-IR and QUICKI. Serum IGF-I was measured by a radioimmunoassay (RIA) method supplied by Mediagnost, Tübingen, Germany, sensitivity 0.01 nmol/L, and the intra- and interassay coefficients of variation were 3.2% and 7.4%, respectively. Body composition was evaluated by whole body bioelectrical impedance analysis (BIA), using

From the Institute of Endocrine Sciences, University of Milan, Ospedale Maggiore IRCCS; and the Unit of Endocrinology, Ospedale San Giuseppe-Fatebenefratelli, A.Fa.R., Milan, Italy.

Submitted August 4, 2003; accepted November 10, 2003.

Supported in part by research grants (9906153187-00) from the Ministero dell'Università and Ricerca Scientifica (MURST, Rome) and from the Ospedale Maggiore IRCCS (Milan).

Address reprint requests to Paolo Beck-Peccoz, MD, Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, Pad. Granelli, Via F. Sforza, 35, 20122-Milano, Italy.

0026-0495/04/5306-0041$30.00/0

doi:10.1016/j.metabol.2003.11.025

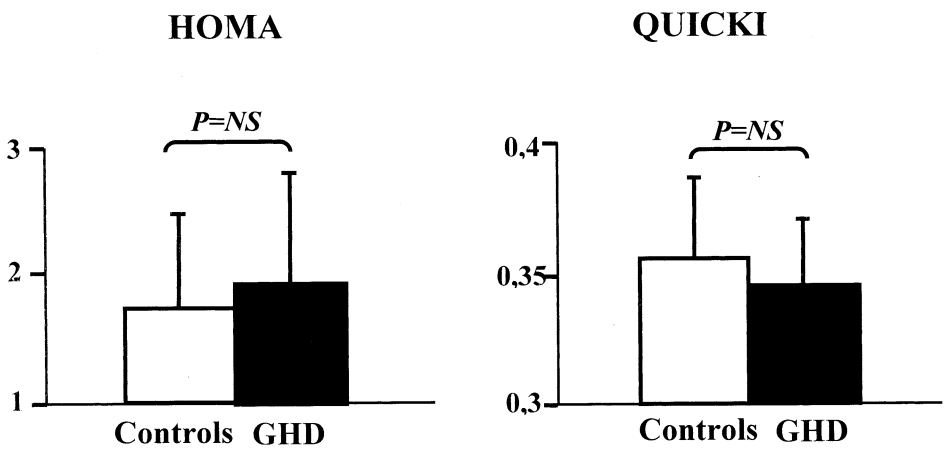

Fig 1. Basal comparisons: parameters of IR (HOMA) and IS (QUICKI) in 20 controls and 20 patients with GHD.

a portable impedance analyzer (RJL Systems, Detroit, MI), following the manufacturer's instructions. BF% was calculated using Segal's regression equation[13] and the results were compared with those reported by Pichard et al[14] in normal subjects matched for age and sex. Fasting glucose was measured with standard technique. Insulin concentration was assessed with an immunoenzymatic one-step assay (Medgenics Diagnostics, Fleurus, Belgium; sensitivity, 0.15 mU/L). IR was determined using the HOMA-IR and QUICKI methods, computer-solved indices based on fasting serum insulin (FI) and glucose concentrations (FG). The formulae are as follows: HOMA-IR = FI (mU/L) × FG (mmol/L)/22.5 and QUICKI = 1/[log FG (mg/dL) + log FI (mU/L)].[15,16] HOMA-IR can be used to predict the degree of IR, while QUICKI is an index of IS.

Statistical Analysis

Basal comparisons between GHD patients and controls were performed using Student's *t* test for unpaired data. Differences before and after treatment values (1 and 5 years of therapy) were sought using 1-way repeated-measures analysis of variance (ANOVA). After checking the Gaussian distribution of the data, the level of significance was then determined using Student's paired *t* test. $P < .05$ was considered significant. Data are expressed as the mean ± SD.

RESULTS

At baseline, all patients showed IGF-I levels under the normal range for age, high BMI, and elevated BF%. Fasting glucose and insulin values, as well as HOMA-IR and QUICKI, did not significantly differ from those recorded in the control group (Fig 1). None of the 20 patients showed adverse reactions or side effects during rhGH therapy. Baseline and post-treatment values are listed in Table 1.

After 1 year of rhGH replacement therapy IGF-I levels significantly increased, normalizing in all patients, and BF% significantly decreased ($P < .01$). Fasting blood glucose and insulin significantly increased, along with a significant increase of HOMA-IR and a specular and significant decrease of QUICKI. No patient developed impaired fasting glucose.

At the fifth year, IGF-I levels were still in the normal range for age and BF% further decreased. Fasting glucose was still significantly higher than at baseline, while fasting insulin showed a trend to decrease and was not significantly different form baseline. Again, no patient showed impaired fasting glucose. Consistently with the sustained reduction in BF%, both HOMA-IR and QUICKI showed a trend to return towards basal values (Fig 2).

DISCUSSION

The results of the present study demonstrate that rhGH therapy, at the doses used to achieve normal IGF-I levels, does not cause IR. In fact, despite the transient worsening of IS, in the long-term, along with a further reduction of BF%, both HOMA-IR and QUICKI tended to return to baseline.

The problem of IR during rhGH therapy in adult patients is still open and relevant. rhGH treatment of GHD adults is now well indicated and widely used, and patients have to undergo life-long therapy; thus, the importance of surveillance of adverse events is manifest. Many studies have been performed to establish the effect of rhGH on glucose metabolism in GHD adults, but there is no agreement, with some reports showing increased and other unchanged IR. The reasons for these discrepancies may be related to either the different rhGH doses employed or different study protocols or the various methods used to evaluate glucose tolerance. Moreover, long-term trials examined small groups of patients (no more than 10 to 12 subjects).

The present report evaluates the long-term effects (5 years) of rhGH therapy on glucose metabolism in a considerable number of subjects (20 patients). Our results are in agreement with those reported in the literature, describing a short-term deterioration of IS, followed by a subsequent return to baseline. In fact, in short-term studies, rhGH replacement therapy has

Table 1. Metabolic Parameters Before and After 1 and 5 Years of rhGH Therapy

	Basal	1 Year	5 Years
IGF-I (nmol/L)	8.4 ± 4.4	24.8 ± 9.6*	22.2 ± 8.0*
BF%	34.4 ± 10.9	32.3 ± 9.2*	29.9 ± 9.4*
BMI (kg/m^2)	27.5 ± 4.0	27.9 ± 4.4	27.2 ± 4.5
FBG (mg/dL)	76.6 ± 9.9	86.8 ± 12.7*	87.3 ± 12*
FI (mU/L)	9.5 ± 8.7	11.4 ± 7.5*	11.1 ± 7.4

Abbreviations: BF, body fat; FBG, fasting blood glucose; FI, fasting insulin.

*$P < .05$ *v* basal.

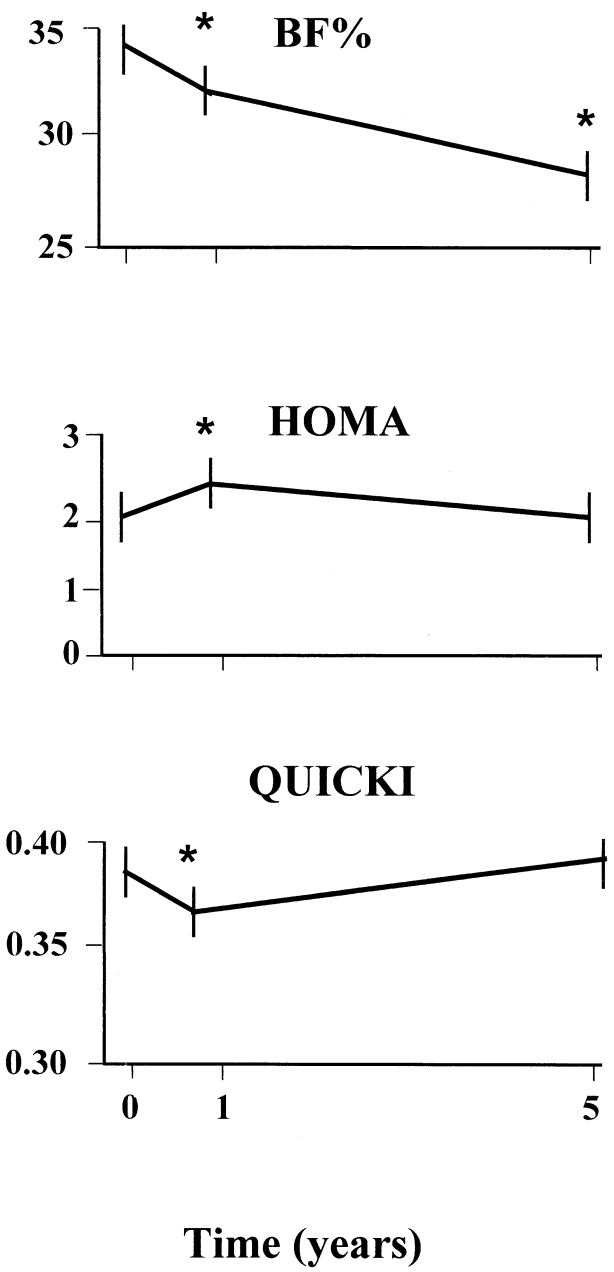

Fig 2. Modifications of BF%, HOMA, and QUICKI during rhGH replacement therapy. *$P < .05$ *v* basal values.

induced an increase in fasting blood glucose and insulin[4,10,17,18] and a reduction in IS.[4,10,11] This short-term deterioration in glucose tolerance may be partly due to the relatively high doses used in previous studies, still based on body weight (from 7 to 12 μg/kg/d). Hence, the reported short-term increase of IR may be a consequence of supraphysiological rhGH treatment. This hypothesis is well supported by at least 2 interesting studies. The first, by Yuen et al,[19] compared the effect of 2 physiological rhGH doses (intermediate: 3.3 μg/kg/d; low: 1.7 μg/kg/d) with a standard replacement dose (8 μg/kg/d) in healthy adults. This study was conducted over 7 days, and IS and beta-cell function were calculated by HOMA. The authors demonstrated that the lower the rhGH dose was, the less IS was impaired, with an improvement of IS, especially in males, with lower doses. The second study, by Bülow and Erfurth,[20] examined the effect of a low individualized GH dose ($\sim$6 μg/kg/d) in young patients with childhood-onset GHD, and found that 9 months rhGH treatment caused no significant deterioration of glucose tolerance.

Few long-term studies (>12 months) evaluating glucose tolerance have been published. Estimated by the oral glucose tolerance test (OGTT) and the insulin clamp technique, unaltered glucose tolerance has been demonstrated after 3 to 7 years of treatment[6,8,9,21] and unaltered fasting glucose and insulin after up to 10 years of treatment.[7] In all of these studies no more than 10 to 12 subjects received long-term rhGH replacement therapy. There is also a report describing a small but significant improvement in IS after 12 months of GH replacement therapy. However, the selected patients were lean (mean BMI, 22.8 kg/m^2) and young (mean age, 29.5 years), and thus less prone to develop IR.[22]

The initial worsening of IS observed in long-term trials may be partly due to the supraphysiological doses used in the titration period.

The mechanisms by which rhGH therapy induces IR are complex and not yet fully understood; they may be at least partially explained by its lypolitic action. GH increases lipid oxidation and free fatty acids (FFA) availability. According to the glucose-FFA cycle postulated by Randle et al,[23] these increased FFA concentrations may decrease the uptake of glucose in skeletal muscle. Later studies have confirmed the inverse relationship between circulating FFA and IS in GHD adults using a blocker of FFA release, acipimox.[24,25]

The long-term improvement of IS may reflect the beneficial effects of rhGH on body composition. In fact, rhGH replacement therapy has been shown to induce a sustained increase in lean mass and a sustained decrease in fat mass. In our series of patients the reduction in BF% was significant and progressive during the whole study period.

In conclusion, long-term rhGH replacement therapy, at the doses used to achieve IGF-I levels in the middle of the normal range, does not determine IR, suggesting that the positive and persistent effect of rhGH in reducing BF% may overcome the negative influence of GH on glucose metabolism. The present data, obtained in a large group of patients, are encouraging about the safety of long-term rhGH replacement therapy.

ACKNOWLEDGMENT

The authors gratefully acknowledge Dr Giuseppe Ivan Vaghi, Antonia Maffini, and Sofia Galofaro for their excellent technical assistance. We also thank Deriu Rita for her irreplaceable nursing assistance.

REFERENCES

1. Davidson MB: Effect of growth hormone on carbohydrate and lipid metabolism. Endocr Rev 8:115-131, 1987

2. Press M: Growth hormone and metabolism. Diabetes Metab Rev 4:391-414, 1988

3. Salomon F, Cuneo RC, Hesp R, et al: The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321:1797-1803, 1989

4. Fowelin J, Attval S, Lager I, et al: Effects of treatment with recombinant human growth hormone on insulin sensitivity and glucose metabolism in adults with growth hormone deficiency. Metabolism 42:1443-1447, 1993

5. O'Neal D, Kalfas A, Dunning P, et al: The effects of 3 months treatment with growth hormone (GH) therapy on insulin and glucose-mediated glucose disposal and insulin secretion in GH-deficient adults. A minimal model analysis. J Clin Endocrinol Metab 79:975-983, 1994

6. Al-Shoumer K, Gray R, Anyaoku V, et al: Effects of four years' treatment with biosynthetic human growth hormone (GH) on glucose homeostasis, insulin secretion and lipid metabolism in GH-deficient adults. Clin Endocrinol 48:795-802, 1998

7. Gibney J, Wallace JD, Spinks T, et al: The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. J Clin Endocrinol Metab 84:2596-2602, 1999

8. Chrisolidou A, Beshyah S, Rutherford O, et al: Effects of seven years of growth hormone replacement therapy in hypopituitary adults. J Clin Endocrinol Metab 85:3762-3769, 2000

9. Svensson J, Fowelin J, Landin K, et al: Effect of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. J Clin Endocrinol Metab 87:2121-2127, 2002

10. Weaver JU, Monson JP, Noonan K, et al: The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity and cardiovascular risk factors in hypopituitary adults. J Clin Endocrinol Metab 80:153-159, 1995

11. Rosenfalk A, Maghsoudi S, Fisker S, et al: The effect of 30 months of low-dose replacement therapy with recombinant human growth hormone (GH) on insulin and C-peptide kinetics, insulin secretion, insulin sensitivity, glucose effectiveness, and body composition in GH-deficient adults. J Clin Endocrinol Metab 85:4173-4181, 2000

12. Ghigo E, Aimaretti G, Giannotti L, et al: New approach to the diagnosis of growth hormone deficiency in adults. Eur J Endocrinol 134:352-356, 1996

13. Segal KR, Van Loan M, Fitzgerald PI, et al: Lean body mass estimation by bioelectrical impedance analysis: A four-site cross validation study. Am J Clin Nutr 47:7-14, 1988

14. Pichard C, Kyle UG, Bracco D, et al: Reference values of fat-free and fat masses by bioelectrical impedance analysis in 3393 healthy subjects. Nutrition 16:245-254, 2000

15. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentration in men. Diabetologia 28:412-419, 1985

16. Katz A, Nambi SS, Mater K, et al: Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 85:2402-2410, 2000

17. Binnerts A, Swart GR, Wilson JH, et al: The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. Clin Endocrinol 37:79-87, 1992

18. Beshyah SA, Henderson A, Niththyananthan R, et al: The effect of short and long term growth hormone in hypopituitary adults on lipid metabolism and carbohydrate tolerance. J Clin Endocrinol Metab 80: 356-63, 1995

19. Yuen K, Ong K, Husbands S, et al: The effects of short-term administration of two low doses versus the standard GH replacement dose on insulin sensitivity and fasting glucose levels in young healthy adults. J Clin Endocrinol Metab 87:1989-1995, 2002

20. Bülow B, Erfurth EM: A low individualized GH dose in young patients with childhood onset GH deficiency normalized serum IGF-I without significant deterioration in glucose tolerance. Clin Endocrinol 50:45-55, 1999

21. Whitehead HM, Boreham C, Mcllrath EM, et al: Growth hormone treatment of adults with growth hormone deficiency: Results of a 13-month placebo controlled cross-over study. Clin Endocrinol 36: 45-52, 1992

22. Hwu CM, Kwock CF, Lai TY, et al: Growth hormone (GH) replacement reduces total body fat and normalizes insulin sensitivity in GH-deficient adults: A report of one-year clinical experience. J Clin Endocrinol Metab 82:3285-3292, 1997

23. Randle P, Garland P, Hales P, et al: The glucose fatty-acid cycle: Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785-789, 1963

24. Segerlantz M, Bramnert M, Manhem P, et al: Inhibition of the rise in FFA by acipimox partially prevents GH-induced insulin resistance in GH-deficient adults. J Clin Endocrinol Metab 86:5813-5818, 2001

25. Nielsen S, Møller N, Christiansen JS, et al: Pharmacological antilipolysis restores insulin sensitivity during growth hormone exposure. Diabetes 50:2301-2038, 2001