GH Replacement Improves Quality of Life and Metabolic Parameters in Cured Acromegalic Patients with Growth Hormone Deficiency

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Objective: Effects of GH replacement in patients with GH deficiency (GHD) after a cure for acromegaly so far have been poorly studied, although its prevalence among acromegalic patients may reach the 60%. The aim of the study was to evaluate whether metabolic parameters and quality of life are improved by GH replacement in patients with prior acromegaly and severe GHD.

Design and Methods: This was a prospective study on 42 GHD subjects [22 men, mean age (SD): 48 ± 10]: 10 acromegalics treated with recombinant human GH (group A), 12 acromegalics who refused treatment (group B), and 20 subjects operated for nonfunctioning pituitary adenoma on recombinant human GH (group C). Serum IGF-I levels, lipid profile, glucose levels (fasting and after an oral glucose tolerance test), glycosylated hemoglobin, insulin resistance (homeostasis model assessment insulin resistance index), anthropometric parameters (body mass index, waist circumference, body composition), and quality of life (Questions on Life Satisfaction-Hypopituitarism Z-scores) were evaluated at baseline and after 12 and 36 months.

Results: At baseline, group B showed higher IGF SD score than group A and C, as well as better quality of life and higher post-oral glucose tolerance test glucose levels than group A. After 12-months, similarly in group A and C, the IGF-I SD score significantly increased, and body composition and lipid profile improved, without deterioration of glucose tolerance. Quality of life significantly improved too, and the baseline difference between group A and B disappeared. Results were confirmed after 36 months.

Conclusions: In GHD acromegalic patients, GH therapy improved body composition, lipid profile, and quality of life as in patients with GHD due to nonfunctioning pituitary adenoma, without negative effects on glucose metabolism. GH replacement therapy should be considered in these patients, as in patients with GHD from other causes. **(*J Clin Endocrinol Metab* 97: 3983–3988, 2012)**

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Abbreviations: BF%, Body fat percentage; BMI, body mass index; DM, diabetes mellitus; GHD, GH deficiency; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NFPA, nonfunctioning pituitary adenoma; OGTT, oral glucose tolerance test; QLS-H, Questions on Life Satisfaction-Hypopituitarism; rh, recombinant human; SDS, SD score; TG, triglycerides.

Acromegaly is a disabling disease caused by chronic GH and IGF-I hypersecretion, mostly due to a pituitary tumor, and associated with increased cardiovascular morbidity and mortality (1, 2). Therapeutic options (such as surgery, radiotherapy, and pharmacological treatment) are aimed to reduce the tumor mass and to recover a normal hormonal secretion, thus controlling symptoms related to GH excess and preventing the typical morbidities related to this condition. The biochemical control of the disease is of crucial importance, and efforts to this purpose may be burdened by a great prevalence of pituitary hormone deficiencies, including GH deficiency (GHD).

In a previous paper, we demonstrated in a group of 56 cured acromegalic subjects that the prevalence of GHD reached the 60%, independently from previous type of treatment, being the same in patients treated with surgery alone or with surgery followed by radiotherapy (3). The finding of such a high prevalence of GHD in cured acromegalics raises the question of whether to replace a deficient hormone in patients previously suffering from hypersecretion of the same hormone.

It is well known that GHD in adults is a defined clinical syndrome characterized by several metabolic alterations (increased body fat percentage, impaired physical performance, altered lipid profile, and insulin resistance), most of which reversed by recombinant human (rh) GH replacement therapy (4–7). As recently published, GHD has detrimental effects on body composition and biomarkers of cardiovascular risk in patients with previous acromegaly, too (8). Thus, given both the high probability of GHD in cured acromegalic patients and the long-term consequences of GHD along with the beneficial effects of rhGH replacement, some authors have evaluated the possibility of rhGH replacement in patients with previously active acromegaly. However, published studies are still few, the results so far are conflicting, and long-term data are lacking (9–13).

The aim of the present study was to evaluate the effect of rhGH replacement in a cohort of patients with severe GHD consequent to treatment for active acromegaly. To this purpose a range of selected parameters were monitored at baseline and during a short- and long-term follow-up, and results obtained in this group were compared with those observed in GHD patients operated for nonfunctioning pituitary adenoma (NFPA) on rhGH and in GHD patients with cured acromegaly not treated with rhGH.

Materials and Methods

Patients and study protocol

This was an open-label, prospective study in a cohort of 60 consecutive GHD patients, with a previous diagnosis of acromegaly (n = 22) or nonfunctioning pituitary adenoma (n = 38).

Acromegalics were considered cured according to the current guidelines (14). Patients were studied after a median period of 79 months (range 6–360) after acromegaly remission. Before the beginning of the study, the complete remission of disease was further confirmed by a new 2-h oral glucose tolerance test (OGTT; 75 g) for the evaluation of GH nadir levels and by the measure of serum IGF-I concentrations. In all the patients, a GHRH + arginine test was performed for the diagnosis of GHD (15). This test has been previously validated in the acromegalic population (16, 17). Additional criteria for rhGH eligibility were as follows: IGF-I levels below −1.5 SD score (SDS) and GH peak after a GHRH + arginine less than 4 μg/liter. At the first visit, 10 acromegalic patients accepted to receive rhGH therapy (group A), whereas 12 of them refused treatment and were studied off therapy (group B). The patients with previous NFPA (n = 20) received rhGH and served as treated controls (group C). With respect to pituitary function, 15 patients had isolated GHD (four of 10, seven of 12, and four of 20, in group A, B, and C, respectively), and 27 had multiple pituitary hormone deficiencies variably associated (six of 10, five of 12, and 16 of 20, in group A, B, and C, respectively). None had diabetes insipidus. When necessary, conventional hormone replacement therapy for other pituitary hormone deficiencies was given at stable doses for at least 3 months before beginning rhGH therapy. Moreover, because it is known that rhGH therapy may unmask or worsen a central hypothyroid or hypoadrenal state (18, 19), in groups A and C, both hypothalamic-pituitary-thyroid and hypothalamic-pituitary-adrenal axes were reevaluated no later than 6 months after the start of rhGH, and the other replacement therapy was adjusted, as needed.

An individualized protocol of rhGH dose was used, according to the sex and age of the patients. The initial rhGH dose was 0.2 mg/d for men and 0.3 mg/d for women and then individually titrated according to IGF-I levels. The mean rhGH dose after titration was 0.28 ± 0.15 mg/d and 0.33 ± 0.26 mg/d in group A and C, respectively. All patients (n = 42: 10, 12, and 20 in Group A, B, and C, respectively) were evaluated at baseline and at 12- and 36-month follow-up.

Informed consent was obtained from all participants, and the study was approved by the local ethics committee.

Study parameters and assays

In all the patients, metabolic parameters such as serum glucose levels before and after a 2-h OGTT, insulin, glycosylated hemoglobin (HbA1c), and lipid profile [total and high density lipoprotein (HDL) cholesterol, triglycerides (TG)], were evaluated. Insulin resistance was determined using the homeostasis model assessment (20): homeostasis model assessment insulin resistance index = fasting insulin (milliunits per liter) × fasting glucose (milligrams per deciliter)/22.5. Serum IGF-I levels were measured by a chemiluminescent immunometric assay (Immulite 2000 IGF-I; Siemens Medical Solutions Diagnostics, Los Angeles, CA), with an intra- and interassay coefficient of variation of 2.9 and 7.4%, respectively. The values were compared with those from an appropriate age- and sex-adjusted range. All the other biochemical parameters were measured by standard procedures. The low-density lipoprotein (LDL)-cholesterol levels were calculated by the following formula: LDL-cholesterol = [(total cholesterol − HDL)− TG/5] (21).

TABLE 1. Basal characteristics, short- and long-term rhGH effect, and differences among groups

	Group A (n = 10)			Group B (n = 12)			Group C (n = 20)		
	Basal	12 months	36 months	Basal	12 months	36 months	Basal	12 months	36 months
Age (yr)	46 ± 11			51 ± 9			47 ± 13		
Sex (F/M)	6/4			8/4			8/12		
BMI (kg/m^2)	28 ± 2.8	27.9 ± 4.2	28.1 ± 4.5	27.8 ± 4.0	26.8 ± 3.7	26.0 ± 3.9	27.1 ± 4.4	27.6 ± 5.0	27.0 ± 3.9
BF (%)	35.7 ± 5.2	31.7 ± 2.4[a]	30.9 ± 2.6[a]	32.8 ± 9.6	34.9 ± 6.1	34.4 ± 3.1	36.9 ± 9.9	33.5 ± 9.7[a]	31.6 ± 9.2[a]
Waist (cm)	100 ± 17	99 ± 15	99 ± 15	94 ± 14	92 ± 9	92 ± 9	93 ± 14	93 ± 14	93 ± 14
IGF-I (SDS)	−2.2 ± 0.5	0.0 ± 0.9[a]	0.0 ± 0.5[a]	−1.6 ± 0.8[b]	−1.7 ± 0.5[b]	−2.2 ± 0.5[b]	−2.3 ± 0.5	0.0 ± 0.5[a]	0.0 ± 0.6[a]
Glucose (mg/dl)	79 ± 8	82 ± 11	79 ± 3	84 ± 13	87 ± 15	89 ± 12	83 ± 6	86 ± 6	82 ± 9
2-h glucose (mg/dl)	90 ± 32	106 ± 26	105 ± 22	128 ± 34	136 ± 34	139 ± 42	110 ± 35	122 ± 33	122 ± 23
Insulin (mU/liter)	6.4 ± 4.2	7.4 ± 4.4	10.3 ± 3.8	6.3 ± 4.0	10.2 ± 9.9	8.6 ± 6.0	9.6 ± 6.8	8.9 ± 7.6	9.1 ± 8.6
HOMA-IR	1.1 ± 0.8	1.6 ± 1.0	2.0 ± 0.7	1.4 ± 1.0	2.4 ± 2.0	1.9 ± 1.5	2.0 ± 1.5	2.1 ± 1.8	1.9 ± 1.8
HbA1c (%)	5.5 ± 0.1	5.5 ± 0.4	5.6 ± 0.3	5.4 ± 0.4	5.7 ± 0.4	5.5 ± 0.3	5.3 ± 0.5	5.4 ± 0.4	5.4 ± 0.4
TC (mg/dl)	231 ± 19	208 ± 14[a]	199 ± 39[a]	188 ± 35[b]	197 ± 36	191 ± 36	216 ± 29	199 ± 33[a]	200 ± 34[a]
HDL (mg/dl)	59 ± 18	52 ± 17	46 ± 13	56 ± 27	61 ± 25	53 ± 19[a]	52 ± 26	52 ± 16	58 ± 16
LDL (mg/dl)	150 ± 16	130 ± 14[a]	118 ± 38[a]	112 ± 29[b]	112 ± 32	119 ± 15	140 ± 39	118 ± 30	120 ± 25
TG (mg/dl)	122 ± 50	134 ± 57	141 ± 63	90 ± 36	118 ± 67[a]	100 ± 38	109 ± 39	131 ± 47	125 ± 38
SBP (mmHg)	119 ± 11	125 ± 11	127 ± 11	126 ± 14	126 ± 16	122 ± 20	119 ± 14	119 ± 13	116 ± 12
DBP (mmHg)	79 ± 11	82 ± 7	82 ± 9	83 ± 11	81 ± 9	73 ± 11	77 ± 8	78 ± 5	78 ± 9

Group A: Acromegalics on rhGH; group B: nontreated acromegalics; group C: NFPA on rhGH. M, Male; F, female; 2-h glucose: post-OGTT glucose levels; TC: total cholesterol; SBP/DBP: systolic blood pressure/diastolic blood pressure.

[a] $P < 0.018$ *vs.* basal.

[b] $P < 0.018$ group B *vs.* groups A and C.

Anthropometric measurements

Body weight, height, and waist circumference were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Body composition [body fat percentage (BF%)] was evaluated by dual-energy x-ray absorptiometry (Hologic 4500; Hologic Inc., Waltham, MA).

Quality of life

Quality of life was assessed with validated Questions on Life Satisfaction-Hypopituitarism (QLS-H) self-administered questionnaire (22). Results are expressed in z-scores. The z-scores are defined by the following equation: z-score = [QLS-H score-mean(age)]/SD (age) for a given general population. SD is the SD for data sets that did not require transformation to obtain normal distribution. Lower scores are indicative of a poorer quality of life.

Statistics

Calculations were performed by SPSS for Windows, version 17.0 (SPSS, Paris, France). Data are expressed as mean ± SD. Normal distributed variables were compared using a Student's *t* test among the groups of patients and within each group at 0, 12, and 36 months. After Bonferroni's correction for multiple comparison tests (three groups), a two-tail $P < 0.018$ was considered statistically significant.

Results

Basal evaluation

At baseline, group B showed higher IGF-I levels evaluated as SDS and lower total cholesterol levels than groups A and C (Table 1), better QLS-H scores (−0.4 ± 0.1 *vs.* −1.9 ± 0.9, $P = 0.012$) (Fig. 1), and higher post-OGTT glucose levels than group A, even though these values were not statistically significant (128 ± 34 *vs.* 90 ± 32 mg/dl, $P = 0.026$). In particular, impaired glucose tolerance (IGT) was found in one of 10, five of 12, and three of 20 subjects in groups A, B, and C, respectively. No patients had diabetes mellitus (DM), and no difference among groups was recorded for other parameters. Regarding cardiovascular risk factors, one of 10, one of 12, and two of 20 patients were on lipid-lowering drugs in groups A, B, and C, respectively, whereas one of 10, two of 12, and one of 20 were on antihypertensive medications, in groups A, B, and C, respectively.

Twelve-month follow-up

After 12 months, IGF-I levels significantly increased in both groups A and C, reaching normal values in all patients (0.0 ± 0.9 and 0.0 ± 0.5 SDS, respectively, $P <$

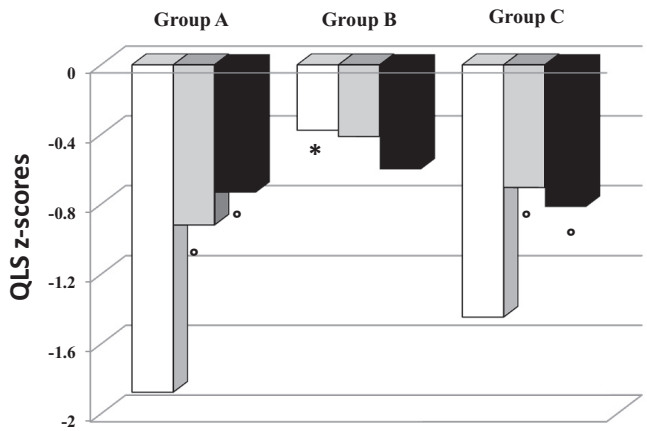

FIG. 1. Quality of life scores, as evaluated by QoL-AGHDA in different groups at baseline (*white columns*) and after 12- (*gray columns*), and 36-month (*black columns*) rhGH therapy. Group A: acromegalics on rhGH; Group B: not treated acromegalics; Group C: NFPA on rhGH. *, $P < 0.018$ *vs.* groups A and C; °, $P < 0.018$ *vs.* basal.

0.001 *vs.* baseline, $P = 0.017$ *vs.* group B). In treated patients, a decrease in BF% (from 35.7 ± 5.2 to 31.7 ± 2.4 and from 36.9 ± 9.9 to 33.5 ± 9.7 in groups A and C, respectively, $P = 0.014$), total cholesterol (from 231 ± 19 to 208 ± 14 and from 216 ± 29 to 199 ± 33 mg/dl in groups A and C, respectively, $P = 0.001$), and LDL cholesterol (from 150 ± 16 to 130 ± 14 and from 139 ± 33 to 120 ± 27 mg/dl in groups A ($P = 0.017$) and C, $P = 0.017$ and $P < 0.001$, respectively) was observed. QLS-H scores also significantly improved on rhGH (from −1.9 ± 0.9 to −0.9 ± 1.2 and from −1.5 ± 1.1 to −0.7 ± 1.4, in groups A and C, $P = 0.003$ and $P = 0.004$ respectively), as shown in Fig. 1. In groups A and C, fasting and post-OGTT glucose levels, glycosylated hemoglobin, and homeostasis model assessment-insulin resistance index did not change on rhGH. Moreover, subjects of group B still showed higher post-OGTT glucose levels than those of group A, even though these values were not statistically significant. The percentage of IGT among groups was the same as basal, even though in group C one patient developed DM and one patient switched from normal glucose tolerance to IGT. The percentage of patients on lipid-lowering or antihypertensive medications did not change.

Thirty-six-month follow-up

Results obtained after 12 months were fully confirmed in the long-term evaluation. In particular, the reduction of total and LDL-cholesterol was maintained and BF% further decreased. Patients in group B still showed post-OGTT glucose levels slightly higher than those of group A.

The proportion of patients with IGT still remained unchanged among groups, but one patient of group B showed DM. Moreover, in the long-term evaluation, patients not treated with GH showed a significant decrease in HDL-cholesterol and an increasing trend in BF%. Improvement in quality of life was sustained in the long term. In particular, in group A, QLS-H scores showed an increasing, although not significant, trend *vs.* 12-month evaluation (Fig. 1). No other differences between treated and untreated subjects were found, likely due to the small number of subjects in each group.

Regarding cardiovascular risk factors, one of 10, one of 12, and three of 20 patients were on lipid-lowering drugs in groups A, B, and C, respectively, whereas two of 10, three of 12, and one of 20 were on antihypertensive medications, in groups A, B, and C, respectively. No side effects were recorded throughout the study period.

Results and comparisons among groups are summarized in Table 1.

Discussion

In this study we evaluated the short- and long-term effects of rhGH therapy on several parameters in GHD patients previously treated for acromegaly. The originality of the present report is that the selected cohort had an extremely severe GHD. Treated acromegalic patients were compared with patients with previous NFPA on rhGH and with untreated acromegalic subjects. We also provide the longest follow-up so far described in the literature.

The main result of the present study is that rhGH therapy in patients with previous acromegaly induced a persistent improvement in quality of life and metabolic parameters as in patients with previous NFPA. Even though GHD in previously acromegalic patients is the same syndrome affecting adults with GHD from other etiologies (9, 10), rhGH replacement experience in these patients is still limited, few reports have been so far published, and long-term data are lacking.

The results of the present study are in agreement with those previously reported, mainly regarding rhGH effects on body composition, lipid profile, and quality of life (9, 10, 12, 13). As far as quality of life, our results are supported by a recent study reporting an improvement after 6 months of rhGH in women with GHD and a previous history of acromegaly, improvement that was even greater than that observed in women with GHD due to other hypothalamic-pituitary disorders (13*)*. However, there is no full agreement on this topic. Namely, the study by van der Klaauw *et al.* (11) did not find any marked beneficial effect of rhGH replacement. The authors supposed that higher rhGH doses, pharmacological and not substitutive, could result in more detectable changes in evaluated parameters. Indeed, in our study, rhGH doses used in previous acromegalics were fully similar to those used in patients with NFPA, starting with a minimal dose of 0.2 or 0.3 mg/d, according to sex, and then titrated on the basis IGF-I levels, as suggested by current guidelines (7). The finding of normal IGF-I levels for the age- and sex-related reference range both at the 12- and 36-month follow-up supports the substitutive nature of rhGH replacement. A possible explanation of this discrepancy between our results and those previously reported may be driven from the basal characteristics of the present cohort. Indeed, using the above-mentioned additional inclusion criteria, we collected a group of patients with particularly severe GHD, as defined by GH peak less than 4 μg/liter after a combined stimulus as GHRH + arginine and by IGF-I SDS lower than −1.5. Thus, as generally observed in GHD patients and also in subjects with previous acromegaly, the more severe the GHD, the better the response to rhGH replacement.

In the comparison between treated and nontreated acromegalics, the cross-sectional design of the present study may be a pitfall in the interpretation of results. Indeed, a randomized placebo-controlled study on short-term ef-

fects of rhGH replacement in acromegalic patients has been published in 2010 (12), reporting a positive effect of rhGH therapy both on body composition and quality of life. In the present study, even though acromegalic patients were not randomized but divided on the basis of their choice to receive or not receive rhGH therapy, we decided to evaluate also patients off therapy, thus providing a long-term follow-up not yet reported in literature. At baseline, patients refusing treatment had not only better QLS-H scores but also higher IGF-I SDS than patients in the treatment group. Therefore, one may hypothesize that these characteristics may reflect a less severe GHD syndrome, not essentially identified by the magnitude of response to stimulation tests, but actually defined by a better perceived quality of life and a higher IGF-I SDS. Moreover, patients with normal quality of life may be disinclined to start a potential life-long lasting treatment based on daily sc injections. During follow-up, a significant decrease in HDL-cholesterol along with a decreasing trend of QLS-H scores was observed in untreated GHD acromegalics, thus suggesting an initial worsening of metabolic and clinical condition of these patients.

In conclusion, in GHD acromegalics rhGH therapy improved body composition, lipid profile and quality of life as in patients with GHD and previous nonfunctioning pituitary adenoma. Quality-of-life status may be either a determinant in patient's choice to start rhGH and a valid parameter to monitor efficacy of rhGH replacement. Long-term follow-up in wide groups of patients is necessary both to confirm efficacy and safety of rhGH and eventually to find any clinical or metabolic deterioration in untreated patients, suggesting the opportunity to start rhGH substitution.

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