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Growth hormone values after an oral glucose load do not add clinically useful information in patients with acromegaly on long-term somatostatin receptor ligand treatment

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Abstract

The optimal method of assessing GH status in acromegalic patients receiving medical therapy with somatostatin analogs (SSA) has been matter of debate. The aim of the study has been to investigate whether OGTT may add information in patients with discordant random GH (GHr) and IGF values. Moreover, we evaluated the association of GH nadir with the prevalence of co-morbidities observed in acromegalic patients on SSA therapy. We evaluated 130 patients with proven diagnosis of acromegaly on SSA. The patients were subdivided in three groups: patients with controlled disease (both safe random GH and normal IGF-I, group A, 20.0 %), patients with uncontrolled disease (both high random GH and IGF-I, group B, 34.6 %), and patients with discordant random GH and IGF-I values (group C, 35.4 %). A high concordance rate for GH nadir with random GH and IGF-I was observed in group B, while a significant reduced concordance rate has been observed in group A (100 % sensitivity, 64.5 % specificity). By contrast, in group C, we observed concordant results between GH nadir and IGF-I only in 14/59 patients. In group A, the prevalence of diabetes was lower than in group B or C. Safe random GH was the only single criteria associated with a lower prevalence of diabetes. Discrepant IGF-I and either GH nadir or random GH values are frequently observed in acromegalic patients treated with SSA. Concordant IGF-I and random GH may influence the prevalence of metabolic complications. GH nadir measurement may help to interpret discrepancies between random GH and IGF-I data only in few cases.

Keywords

Acromegaly
GH random
GH after OGTT
IGF-I
Somatostatin analogs

Giuseppe Reimondo and Marta Bondanelli have equally contributed to the manuscript.

Introduction

Acromegaly is a disabling disease characterized by GH and growth factor-I (IGF-I) excess, which is associated with increased morbidity and mortality. The therapeutic targets for this condition are to eliminate disease-specific morbidity and to decrease mortality to the expected age- and sex-adjusted rates. Surgery is the first line of treatment, but many patients receive primary medical therapy with somatostatin analogs (SSA) or need adjuvant medical therapy and/or radiotherapy after unsuccessful surgery [1].

The biochemical control is generally defined as a normal IGF-I levels for age and gender, and suppression of serum GH concentrations after OGTT to be less than 1 mcg/L [2] or to be less than 0.4 mcg/L using a sensitive assay [1, 3]. In view of the recently reported discrepancies among different GH assays, individual post-glucose GH nadir (GHn) values for each assay have been proposed [4, 5].

The optimal method of assessing GH status in acromegalic patients receiving medical therapy with SSA has been matter of debate. Retrospective studies indicate that a random GH below 2.5 mcg/L as well as normal IGF-I levels are associated with a normal life expectancy and have been recommended as targets for disease control, both after surgery and during medical therapy [6–8]. More recently, the Consensus on Criteria for Cure of Acromegaly has determined that a optimal disease control is defined by IGF-I level in the age-adjusted normal range and a random GH (GHr) measurement less than 1 mcg/L [3]. GH after glucose load has not been included as a useful parameter, since OGTT has not been extensively used in long-term follow-up of acromegalic patients, being time- and resource-consuming [9].

However, in most patients with treated disease, including those in biochemical remission, the normal pulsatility is not restored and basal GH levels may be raised [9, 10]. Measuring GH level after OGTT reflects the severity of GH hypersecretion after surgery, but its significance and clinical utility during medical therapy with SSA remains to be clarified. Discordant results between GHn after OGTT and IGF-I have been observed in post-operative assessment of acromegalic patients either without medication or receiving medical therapy [11]. A recent paper has confirmed the high discordance rate between IGF-I levels and glucose-suppressed GH [12].

We report the results of a multicentric Italian study analyzing the role of GH nadir after OGTT to predict disease control in 130 acromegalic patients receiving primary or secondary medical therapy with SSA. In particular, we investigated whether OGTT may add information in patients with discordant GHr and IGF values. Moreover, we evaluated the association of GHn with the prevalence of co-morbidities observed in acromegalic patients on SSA therapy.

Subjects and methods

We evaluated 130 patients with proven diagnosis of acromegaly (90 women and 40 men, median age 55.5 years, range 24–87 years) on SSA referred to five different centers in Italy from 2000 to 2008. The diagnosis of acromegaly was established clinically and confirmed by the following data: (1) high serum GH concentrations (>2.5 mcg/L as the mean of at least five samplings), (2) GH concentrations not suppressed below 1 mcg/L after administration of an oral glucose load (75 mg), (3) circulating IGF-I levels above the upper limit of the age-related reference range developed by the local laboratory of each center, and (4) demonstration of a pituitary tumor at neuroradiological

imaging. SSA was the primary therapy in 39 cases (30 %), whereas it was an adjunctive therapy following surgery in the remainders. At time of the study, 88 patients (67.7 %) were on octreotide long-acting release (8 patients 10 mg/monthly, 36 patients 20 mg/monthly, 44 patients 30 mg/monthly) and 42 patients (32.3 %) on lanreotide slow release (13 patients 60 mg/monthly, 18 patients 90 mg/monthly, 11 patients 120 mg/monthly). All the patients included in the analysis underwent the following endocrine evaluation after at least 6 months of medical therapy (median 28 months, range 6–139 months): measurement of basal GH (GHr) concentration before an OGTT (mean of at least 3 GH values in the morning), measurement of GH concentration after an OGTT (every 30 min for 2 h), and measurement of IGF-I concentration. None of the patients was treated with radiotherapy or had previous or concomitant medical therapy with dopamine agonists. The patients with systolic blood pressure greater than 140 mmHg, or diastolic blood pressure greater than 90 mmHg, or on anti-hypertensive treatment were categorized as hypertensive [13]. Diabetes mellitus was defined when the subject's plasma glucose was greater than 126 mg/dL (7.0 mmol/L) at fasting in at least two samples collected in different days [14]. Impaired fasting glucose (IFG) was defined for fasting plasma glucose between 100 and 126 mg/dL (6.1 and 7.0 mmol/L) in at least two samples collected in different days. Patients with diabetes mellitus who underwent OGTT had optimal disease control (glycosylated hemoglobin <7 %).

Assays

The data presented here derived from several laboratories and hormones were measured in-house at each participating center using commercially available reagents. Serum GH was measured by Immulite 2000, DPC, Los Angeles, CA, USA (Intra- and inter-assay coefficients of variation were: 3.7 and 5.4 %; sensitivity of the methods was 0.01 mcg/L), and by IRMA, DiaSorin, Saluggia, Italy (Intra- and inter-assay coefficients of variation were: 3.9 and 4.1 %; sensitivity of the methods was 0.04 ng/mL). Plasma IGF-I was measured by Immulite 2000, DPC, Los Angeles, CA (Intra- and inter-assay coefficients of variation were: 3.0 and 9.8 %; sensitivity of the methods was 20 mcg/L) and by RIA, Dia-Source, Louvain-La-Neuve, Belgium, after acid-ethanol extraction (Intra- and inter-assay coefficients of variation were: 4.8 and 7.1 %; sensitivity of the methods was 6 mcg/L).

Definitions

Due to the multicentric and retrospective nature of the study and the different assays used for the GH measurement, we adopted different thresholds to reflect the described characteristics of the assays [1–4, 15, 16]: ~~M~~mean basal GH values (GHr) obtained in fasting state were considered safe at less than 2.5 mcg/L and GHn levels were considered controlled at less than 1 mcg/L for GH measured by Immulite 2000 (35 patients), while mean basal GH values (GHr) obtained in fasting state were considered safe at less than 1 mcg/L and GHn levels were considered controlled at less than 0.4 mcg/L for GH measured by IRMA (95 patients). IGF-I concentrations were expressed as percentages of the upper limit of the reference range (IGF %). Specific gender- and age-adjusted reference ranges of IGF-I concentrations were defined at each center in large groups of healthy subjects (center #1: <30 years 400 ng/mL, 31–50 years 315 ng/mL, 51–60 years 270 ng/mL, >60 years 200 ng/mL; center #2: <30 years 440 ng/mL, 31–50 years 318 ng/mL, 51–60 years 252 ng/mL, >60 years 210 ng/mL; center #3: <30 years 415 ng/mL, 31–50 years 320 ng/mL, 51–60 years 260 ng/mL, >60 years 200 ng/mL; center #4: <30 years 400 ng/mL, 31–50 years 315 ng/mL, 51–60 years 280 ng/mL, >60 years 190 ng/mL; center #5: <30 years 400 ng/mL, 31–50 years 320 ng/mL, 51–60 years 250 ng/mL, >60 years 200 ng/mL). The patients were subdivided in three groups: patients with controlled disease (both safe GHr and

normal IGF-I, group A), patients with uncontrolled disease (both high GHr and IGF-I, group B), and patients with discordant GHr and IGF-I values (group C).

Statistical analysis

Database management and all statistical analyses were performed by using the Statistica for Windows software package (Statsoft Inc., Tulsa, OK, USA). Rates and proportions were calculated for categorical data, and means and standard deviations for continuous data. Normality of data was assessed by the Kolmogorov–Smirnov test. For continuous variables, differences were analyzed by means of the two-tailed Student's *t* test when data were normally distributed and by using the Mann–Whitney *U* test for nonparametric data. Bonferroni adjustment for multiple comparisons was performed when appropriate. For categorical variables, differences were analyzed by means of the χ^2 test and Fisher's exact test. Levels of statistical significance were set at $p < 0.05$.

Results

Controlled IGF-I values were observed in 47.6 % of all patients, and safe GHr were observed in 36.2 % of subjects and GHn in 21.5 %.

In all patients, mean GHn levels were significantly lower in patients with controlled IGF-I levels as compared with uncontrolled IGF-I levels (2.1 ± 1.5 vs. 5.1 ± 5.3 ng/mL, $p = 0.02$ for GH measured by IRMA; 1.7 ± 1.2 vs. 3.5 ± 5.6 ng/mL, $p = 0.04$ for GH measured by Immulite); the same figure for GHn was observed in patients with safe GHr levels when compared with uncontrolled GHr levels (0.6 ± 0.2 vs. 3.8 ± 4.0 ng/mL, $p = 0.01$ for GH measured by IRMA; 1.1 ± 0.7 vs. 4.1 ± 5.5 ng/mL, $p = 0.01$ for GH measured by Immulite). Moreover, considering the three criteria GHn, GHr, and IGF-I, we observed concordant controlled values (IGF-I and both GHn and GHr) in 16/130 (12.3 %) and concordant uncontrolled values in 46/130 (35.4 %). By using the established criteria of disease control that included the presence of concordant IGF-I and GHr levels, 26 patients (20.0 %) resulted controlled (group A), 45 patients (34.6 %) uncontrolled (group B), and 59 patients (45.4 %) had discordant results (group C). In group C, normal IGF-I levels were observed in 36 patients and 22 subjects had safe GHr.

Mean age and treatment duration did not significantly differ among the 3 groups; mean IGF-I levels were significantly higher in group B compared with both group A and C ($p < 0.001$), as well as in group C compared with group A ($p < 0.02$) (Table 1).

Table 1

Comparison of demographic and clinical characteristics among the three groups

	Group A	**Group B**	**Group C**	***p***
Age (years)	57.4 ± 11.7	55.2 ± 14.0	53.9 ± 12.5	NS
IGF-I (% ULN)	−31.4 ± 21.5	79.4 ± 96.9	5.5 ± 49.2	<0.001 B versus A and C

				0.02 A versus C
Duration of treatment (months)	45.9 ± 32.2	36.5 ± 31.4	38.2 ± 34.5	NS

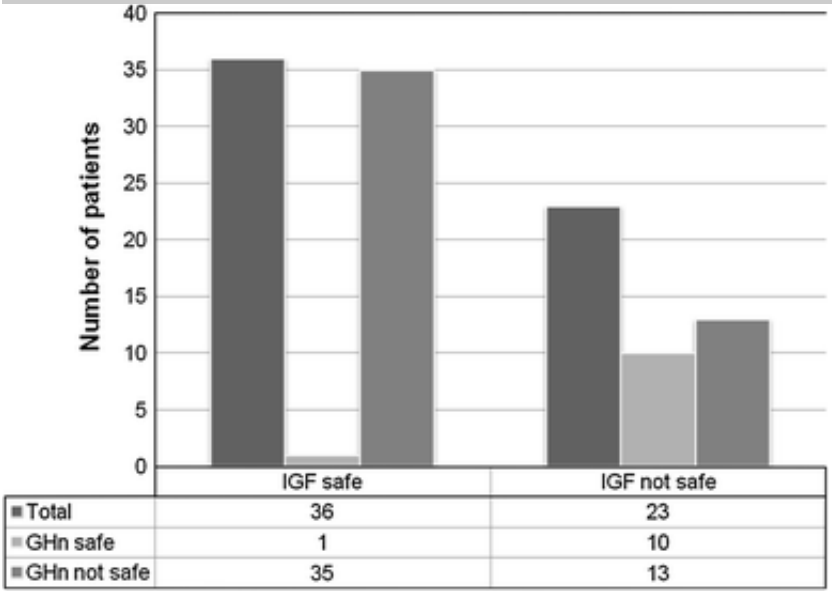
Data are expressed as mean and SD

ULN upper limit of normality

An high concordance rate for GHn with GHr and IGF-I was observed in group B (100 % of uncontrolled patients had GHn not safe), while a significant reduced concordance rate was observed in group A (17/26 patients, 65.4 % of controlled patients had GHn safe, $p < 0.001$ vs. group B), resulting in a 100 % sensitivity (95 % CI 0.93–1) and 65.4 % specificity (95 % CI 0.53–0.76) with a 83 % positive predictive value and 100 % negative predictive value. In group C, a good concordance rate was seen between GHn and GHr (77.9 %), whereas concordant results between GHn and IGF-I was observed only in 14/59 (23.7 %) patients (Fig. 1).

Fig. 1

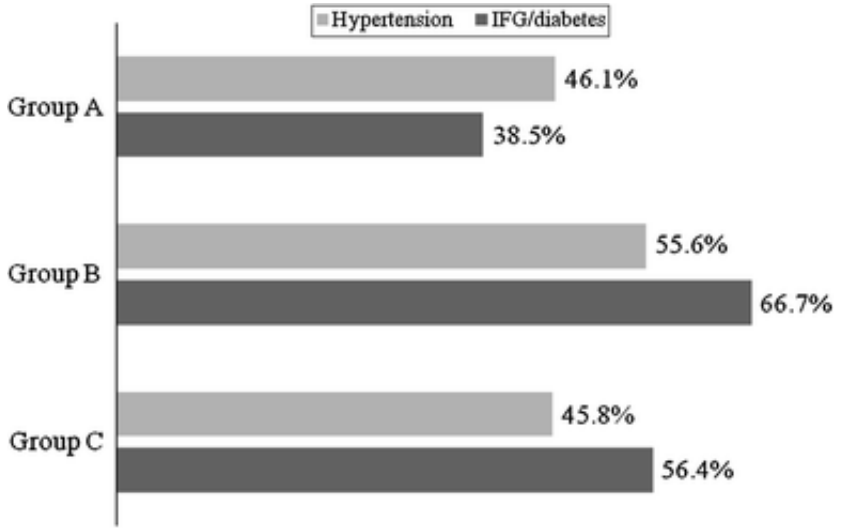
Concordance and discordance between GHn versus IGF-I in group C



In group A, the prevalence of IFG/diabetes was statistically lower than in group B but not than in group C (38.5 vs. 66.7 %, $p = 0.03$; 38.5 vs. 56.4 %, p = NS), whereas the prevalence of hypertension was similar among the 3 groups (Fig. 2). Interestingly, considering the single criteria (IGF-I, GHr, or GHn), only the GHr was able to indicate differences of IFG/diabetes frequency between patients with safe GHr compared to those with not safe GHr (60.2 vs. 44.7 %, $p = 0.04$).

Fig. 2

Prevalence of hypertension and IFG/diabetes in the different groups



Discussion

The present study has investigated whether GHn after OGTT may add information in patients with discordant GHr and IGF values in acromegalic patients on SSA therapy. Moreover, we evaluated the association of GHn with the prevalence of co-morbidities. We found controlled IGF-I levels in 47.6 % of patients, controlled GHr in 36.2 %, and GHn in 21.5 %. Concordance among the three criteria was found in 47.7 % of patients, with concordant controlled values only in 12.3 % (n = 16) and a high rate of discordance especially in patients with normal IGF-I. The use of concordant IGF-I and GHr as criteria of disease control showed a good positive predictive value (83 %) and negative predictive value (100 %), because almost 2/3 of controlled patients had GHn safe and all uncontrolled patients had GHn not safe. A good concordance rate between GHn and GHr (77.9 %) has also been observed in patients with discordant GHr and IGF-I levels. Although different GH assays has been used, we have not observed significant differences in results among the centers, in particular respect to their agreement. Moreover, the prevalence of IFG/diabetes was lower only in patients with concordant IGF-I and GHr, suggesting that concordance between these two criteria may be satisfactory to define disease control in patients treated with SSA.

The question of how we should biochemically monitor disease activity after surgery or during medical therapy still requires a satisfactory answer. Monitoring of GH levels is a key to this process. A recent meta-analysis shows that attainment of random serum GH levels below 2.5 ng/mL are associated with a normalization of mortality [6]. However, OGTT is considered the most rigorous method for GH assessment, and it should be preferred to a random GH measurement after surgery, even if it is unknown whether GH nadir may predict mortality [9]. The role of OGTT during SSA therapy remains to be fully appreciated.

We found controlled GHr in 36.2 % of patients, whereas suppressible GH after OGTT was found only in 21.5 % of the patients; therefore, controlled GHr levels were frequently (44.6 %) associated with non-suppressible GH after OGTT. More than half of these patients, with non-suppressible GH after OGTT and normal GHr, also showed high IGF-I levels suggesting an inadequate control of GH-IGF-I axis by SSA.

Monitoring of serum IGF-I levels in acromegaly is also essential: ~~W~~when measured properly and compared with a well-characterized, age-adjusted normative database, elevation of the IGF-I level is a sensitive and specific indicator of persistent or uncontrolled disease [1, 9, 17]. Single IGF-I estimation is easier to perform than GH levels measured throughout an OGTT or a GH day curve,

and it has been shown to better correlate than GH levels with clinical disease activity and patients outcome. However, there are discrepant views on the possibility that IGF-I may correlate with patient outcome [6].

In our series, we have observed concordant results between GHr and IGF-I in almost half of patients (54.6 %). In this cohort, GHn levels after OGTT did not fail to recognize the patients with uncontrolled disease. By contrast, in the group with conflicting results between GHr and IGF-I values, GHn values have demonstrated a good concordance rate with GHr, while the concordance with IGF-I has been shown only in a limited number of patients.

The most recent guidelines suggest that both GH and IGF-I should be measured to assess the biochemical response to medical treatment, because discrepancies between GH and IGF-I levels are observed in approximately 30 % of patients. Interestingly, the patients with discordant results are exposed to significant morbidity [1, 3]. The present study reports a high degree of discordance between both GHr and GHn levels and IGF-I levels in patients treated with SSA, in agreement with recent series of patients on SSA therapy [18, 19].

In our patients on SSA, IGF-I resulted normal in 43.1 % of patients with abnormal GHn and in 44.6 % of those with elevated GHr. Using IGF-I solely, these patients could be considered to have controlled disease, despite persistently secreting GH excess in some cases. A direct suppression on peripheral GH-dependent IGF-I levels by SSA may be in part responsible for the normal IGF-I, despite the persistence of an increased GH secretion [20]. The D3 polymorphism of the GH receptor may play a role in determining such a discrepancy [21].

Regarding the discordance between IGF-I and GHn, it has also been suggested that SSA therapy may alter the physiological response to glucose load [11]. Moreover, it cannot be excluded that GHn levels may also appear to be “abnormal” if the cut-off is inaccurate or has not been properly adjusted for the population and assay methods [4, 5, 22]. In our study, GH was measured by different immunometric assays which have a sensitivity of around 0.2 mcg/L or higher; therefore, we choose to apply different cut-offs for GH measured by IRMA or Immulite to reflect the described characteristics of the assays. Moreover, also the available assays for IGF-I presents some limits since a recent safety notice has been provided for IGF-I Immulite assay for a negative bias, and there are no age- and gender-adjusted data for IGF-I measured by RIA. However, we have calculated age-adjusted values for IGF-I measurement in each center, and all the patients have been diagnosed and followed by the same methods available during the study period. Due to the GH and IGF-I assays limits, we have focused our study on discrepancies between the adopted tests.

The present study confirms the importance of achieving concomitantly controlled IGF-I and GH values, because we observed a lower prevalence of IFG or diabetes in patients with concordantly controlled parameters when compared to patients with concordantly abnormal parameters or discordant results, in agreement with the literature [1, 23, 24]. Because GHr has been demonstrated to be superior to GHn to predict less comorbidity (IGF-I was at limit of the statistical significance) and most of the patients with concordant IGF-I and safe GHr levels had also safe GHn levels, it may be concluded that the presence of normal IGF-I associated with normal GHr levels may be associated with less comorbidity in patients treated with SSA, either as primary or secondary therapy.

In conclusion, discrepant IGF-I and either GHn or GHr values are frequently observed in

acromegalic patients treated with SSA, as primary and adjunctive therapy. Concordant IGF-I and GHr are associated with a reduced prevalence of metabolic complications, and in particular, the presence of safe GHr is associated with a lower prevalence of IGT/diabetes. GHn measurement may help to interpret discrepancies between GHr and IGF-I data only in few cases. Therefore, performing an OGTT, by using specific cut-off of GH suppression for each assays, in acromegalic patients on primary or adjunctive SSA therapy does not seem advisable in everyday practice. The helpful availability of future better assays and adequate cut-offs for the measurement of GH and IGF-I should reduce the discrepancies between the tests and the difficulties in the interpretation of the data particularly in patient followed during medical therapy.

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The authors declare that they have no conflict of interest.

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