Use of the Oral Glucose Tolerance Test to Define Remission in Acromegaly

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An oral glucose tolerance test (OGTT) was used to assess growth hormone (GH) secretion in patients with acromegaly prior to (n = 26) and after (n = 71) transsphenoidal adenomectomy as well as in 196 controls. In controls, suppressed concentrations of GH showed a negative relationship both with body mass index (BMI) and with age. Having calculated the reference intervals for suppressed GH concentrations to be expected for any given age and BMI, we compared these individually predicted ranges to GH concentrations actually observed in patients with acromegaly during OGTT. Preoperatively, concentrations exceeded the normal range in all patients. Postoperatively, glucose-suppressed concentrations of GH were less than 2.0 ng/mL in 56 (79%) patients and less than 1.0 ng/mL in 44 (62%). However, only 37 of 71 (52%) patients had glucose-suppressed GH concentrations within the calculated reference intervals (defined by the 95th percentile of normal). Comparing these data with the patient's concentrations of insulin-like growth factor-1 (IGF-1; normal range first established and corrected for age and sex in 494 healthy individuals), congruency of both parameters was found in 59 (77%) patients with an unexplained discrepancy between GH and IGF-1 in the remaining in 16 (23%) patients. Our results confirm that concentrations of IGF-1 must be corrected for sex and age, whereas glucose-suppressed concentrations of GH depend on age and BMI. "Across-the-board" cut-off-values are clearly inadequate and should not be used. Rather, serum GH measurements obtained during an OGTT must be interpreted individually by comparison to control values taking into account both age and BMI.
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ACROMEGALY IS characterized by an enhanced secretion of growth hormone (GH) in the presence of elevated concentrations of somatomedin C (insulin-like growth factor-1 [IGF-1]). Consequently, its cure is defined by a normal concentration of IGF-1 and adequate suppression of GH during an oral glucose tolerance test (OGTT).[1] The definition of "normal" glucose-suppressed serum GH concentrations has become increasingly stringent over the past 20 years. It is now proposed that only a suppression of GH to less than 1.0 ng/mL will set apart patients with active acromegaly from healthy controls.[2] Since GH secretion in healthy subjects decreases with age[3] and body weight,[4] it is remarkable that these 2 factors are in general neglected in the interpretation of glucose-suppressed GH concentrations.[1] Concentrations of IGF-1 are commonly corrected for sex and age, though as a rule not for body mass index (BMI).[1] We recently reported that the interpretation of stimulated GH concentrations in the diagnosis of adult-onset GH deficiency needs to be adjusted for age and BMI.[5] As in GH-deficient patients, age and body weight vary among acromegalics and a similar approach to glucose-suppressed GH concentrations appears appropriate. To this end we first performed OGTTs in a large number of nonacromegalics of different age and body weight. Having calculated reference intervals for GH concentrations to be expected for any given age and BMI, we subsequently compared these individual cut-off values to GH concentrations actually observed in acromegalic patients before and after transsphenoidal surgery.

MATERIALS AND METHODS

Patients

An OGTT was performed in 26 patients with newly diagnosed acromegaly, in 71 acromegalics at least 4 weeks (range, 1 to 78 months; median, 40 months) after transsphenoidal surgery (but otherwise untreated), and in 196 controls. As shown in Table 1 both the control group and patients with acromegaly consisted of men and women with a broad range of age and BMI. Controls were recruited from the endocrine outpatient service and had been referred for evaluation of various suspected disorders (eg, nodular thyroid disease, hypertension, gynecomastia). Patients with diabetes mellitus or impaired glucose tolerance were excluded as were individuals with disorders and/or medications known to interfere with GH secretion. This study was approved by the local ethical committee. The purpose of the investigation was explained to all participants and informed consent was obtained. Written consent was obtained in patients in whom an OGTT was not necessary as part of their routine medical investigation. All patients received written information about their individual results. Following an overnight fast, an indwelling catheter was inserted at 8 AM into an antecubital vein and a baseline blood sample was obtained for the determination of blood glucose, GH, and somatomedin C (IGF-1). The patients then drank 75 g of glucose (Gluco-Drink 75, Roche Diagnostics, Vienna, Austria). Additional blood samples for the determination of glucose and GH were obtained 30, 60, and 120 minutes thereafter.

Methods

Plasma glucose was measured in venous plasma by the hexokinase method. GH was determined with a time-resolved fluoroimmunoassay kit (Delfia, Wallac Oy, Turku, Finland) using an automated AutoDelfia system. This kit is calibrated against the World Health Organization (WHO) First International Reference Preparation 80/205 (1 ng/mL = 2.6 mU/mL). The minimal detection limit of this assay was 0.01 ng/mL and its inter- and intra-assay coefficients of variation were less than 5%. Concentrations of IGF-1 were determined after acid ethanol extraction by an enzyme-linked immunosorbent assay (Diagnostic Systems Laboratory, Webster, TX). Inter- and intra-assay coefficients of variation of this method were less than 10%. The normal range of IGF-1 was established in 494 individuals (194 men and 300 women) of various age groups.

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Table 1. Age, Sex, BMI, and Glucose-Suppressed Concentrations of GH in Patients With Acromegaly and in Controls

	Patients With Acromegaly		
	Before Surgery	After Surgery	Controls
No. of subjects	26	71	196
Male/female	17/9	32/39	69/127
Mean age (yr)	52 (29-70)	53 (20-77)	50 (16-90)
Mean BMI (kg/m^2)	27 (21-34)	28 (17-45)	30 (15-52)*‡
BMI < 20 (n)	0	1	13
BMI 20-25 (n)	8	16	41
BMI 25-30 (n)	14	37	58
BMI 30-35 (n)	4	10	34
BMI 35-40 (n)	0	5	28
BMI > 40 (n)	0	2	22
GH/OGTT (ng/mL)	2.6-221.0§	0.1-65.4†	0.1-3.8†

NOTE. Values are means and respective ranges.
*$P < .05$ *v* acromegalics before surgery.
†$P < .01$ *v* acromegalics before surgery.
‡$P < .05$ *v* acromegalics after surgery.
§$P < .01$ *v* acromegalics after surgery.

Statistical Analysis

To compute adjusted 95% and 99% reference intervals of both GH and IGF-1 for healthy subjects, linear regression analysis was used, considering BMI, age, and sex as independent variables. Because of nonnormal distributions, GH was transformed as $t(GH) = g \times \log(GH)$, where g is the geometric mean of the GH distribution (Box-Cox transformation). Furthermore, BMI was log-transformed. Quadratic effects of log(BMI) and age and interactions of log(BMI), age, and sex were taken into account. Nonsignificant terms were removed from the regression equations. From those final regression models we obtained reference intervals for individual prediction. For each patient we computed if his/her GH or IGF-1 value lay outside the reference intervals by comparing the GH and IGF-1 values with the reference distribution at the respective values of the independent variables of the final model. Patients were classified as "outlying" if their GH or IGF-1 concentration was greater than the 95% quantile of the adjusted reference distribution. This procedure could be automated for the evaluation of future patients. A chi-square test was used to assess the correlation of outliers with respect to the reference GH distribution and outliers with respect to the reference distribution of IGF-1. To compare variables between groups, analysis of variance (ANOVA) and Duncan's post-hoc test were used. *P* values less than .05 were considered to indicate statistical significance. The SAS System V8.1 (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Somatomedin C (IGF-1)

The influence of sex, age, and BMI on concentrations of IGF-1 was investigated in 494 individuals (300 women and 194 men). Regression analysis confirmed age, squared age, and sex as independent predictors for IGF-1. Table 2 shows the relationship between serum concentrations of IGF-1 and both age and sex. There was a significant ($P < .05$) effect of BMI on IGF-1, which, however, became insigificant when adjusting for the patients' age in the regression model (Table 2). BMI was therefore eliminated from the final model. Normal values for IGF-1 for the various age groups are summarized in Table 3.

Table 2. Fitted Model on Controls to Establish the Normal Range of IGF-1

Independent Variable	Parameter Estimate	Standard Error	*P* Value
Intercept	$\beta_0 = 418.52$	22.43	<.0001
Age	$\beta_1 = -6.34$	0.95	<.0001
Age^2	$\beta_2 = 0.0357$	0.0092	<.0001
Sex (male = 1, female = 0)	$\beta_3 = 26.70$	6.22	<.0001
Log (BMI)	(not used in the final model)*		.4381

*Significance of log (BMI) if it was added to the final fitted model as an independent variable.

GH During OGTT

In controls there was a negative relationship between serum GH concentrations following oral glucose and both age and BMI, but not sex. Figure 1 depicts these relationships as a 3-dimensional plot. Having thus calculated the 95% and 99% reference intervals for serum GH concentrations to be expected from our statistical model for any given age and BMI we compared these predicted values to GH concentrations actually observed in patients with acromegaly following oral glucose. Thereby all serum GH concentrations in newly diagnosed patients with acromegaly were outside the reference intervals calculated for their age and body mass. Postoperatively (Table 4) glucose-suppressed concentrations of GH were less than 2.0 ng/mL in 56 of 71 (79%) patients and less than 1.0 ng/mL in 44 of 71 (62%). In 37 of 71 (52%) patients, glucose-suppressed GH concentrations were within the calculated reference intervals (defined by the 95th percentile of normal); 46 o f 71 (65%) were within the 99th percentile.

Relationship Between GH and IGF-1 in Operated Acromegalics

When age- and BMI-adjusted glucose-suppressed serum concentrations of GH were compared with sex- and age-adjusted concentrations of IGF-1 in 71 operated patients with

Table 3. Concentrations of Somatomedin C (IGF-1) in 494 Individuals (194 men, 300 women) of Various Ages

Age (yr)	Men			Women		
	No.	Mean	95% Quantile	No.	Mean	95% Quantile
20-25	7	333	446	18	306	419
25-30	6	309	422	27	282	395
30-35	16	287	400	25	260	373
35-40	11	267	380	26	240	353
40-45	21	249	361	29	222	318
45-50	15	232	345	28	208	303
50-55	23	218	330	21	191	303
55-60	21	205	317	21	178	290
60-65	28	193	306	23	167	279
65-70	15	184	297	15	157	270
70-75	11	177	289	23	150	262
75-80	13	171	284	31	144	257
80-85	7	167	280	13	140	253

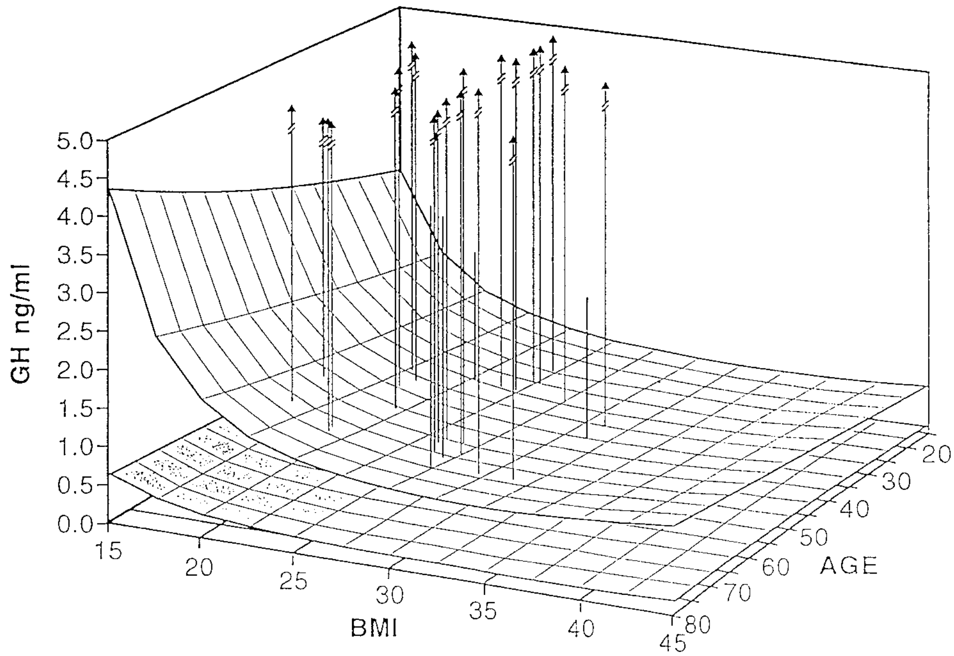

Fig 1. Impact of age and BMI on glucose-suppressed serum concentrations of GH (ng/mL) in 26 patients with newly diagnosed acromegaly. The 95% and 99% percentiles of normal controls (n = 196) are also indicated.

acromegaly, normal concentrations of both GH and IGF-1 were seen in 29 (41%) (Table 5). In 8 patients (11%), IGF-1 was normal in the presence of supranormal glucose-suppressed concentrations of GH, whereas 8 other patients presented supranormal concentrations of IGF-1 although glucose-suppressed GH was in the normal range. In 4 of these patients, these results were obtained 5 months, 3 years, 4 years, and 19 years after their transsphenoidal operation. The remaining 4 patients were investigated within 2 months of their transsphenoidal operation. Since then, the results were reproduced in 2 of these 4 patients at a later time. In 1 patient IGF-1 was normal when the test was repeated at a later time. One patient of this group was lost to follow-up. Finally, 26 (37%) patients had supranormal concentrations of both IGF-1 and glucose-suppressed GH. Thus, concentrations of IGF-1 and glucose-suppressed GH were congruent in 55 (77%) patients.

DISCUSSION

Serum concentrations of GH fluctate over a wide range in normal individuals[6,7] and are not precise enough for the biochemical diagnosis of active acromegaly and its cure. Hence, suppression of GH concentrations following an oral glucose load has, for many years, remained the fundamental procedure to this end.[8,9] However, due to improved technology, the definition of a "normal" GH response to oral glucose and hence the definition of cure in acromegaly has changed in recent years. Whereas glucose-suppressed GH concentrations of less than 2.5 ng/mL were considered normal in 1985,[10] it has been shown more recently by means of a chemiluminescence assay with enhanced sensitivity[8] that glucose induces a suppression of GH to less than 0.5 ng/mL in normal individuals. Serum concentrations of IGF-1 reflect an integrated effect of GH secretion and may also be used to define active and cured acromegaly. They decline with age.[11] The relationship between GH and somatomedin C (IGF-1) is linear for GH values up to 20 ng/mL.[12] Thus, cure of acromegaly is currently defined by a normal concentration of IGF-1 and by a suppression of GH during an OGTT to less than 1.0 ng/mL.[1,2]

The secretion of GH decreases with age[3] and body weight[4] and these 2 variables must be taken into account in the diagnosis of adult-onset GH deficiency.[5] Since the majority of patients with acromegaly are neither young nor non-obese, we reasoned that the same approach should apply to the interpretation of glucose-suppressed GH concentrations in the diagno-

Table 4. Distribution of Glucose-Suppressed Serum Concentrations of GH and of IGF-1 Among 71 Patients With Acromegaly Following Transsphenoidal Surgery Demonstrating the Impact of Different Cut-Off Values for GH

GH	GH > 2.0 ng/mL	GH < 2.0 ng/mL	GH < 1.0 ng/mL	GH Within 95% RI*	GH Within 99% RI*	IGF-1† Normal	IGF-1† Elevated
>2.0 ng/mL	15/71 (21%)			0/15 (0%)	0/15 (0%)	0/15 (0%)	15/15 (100%)
<2.0 ng/mL		56/71 (79%)		37/56 (66%)	45/56 (80%)	37/56 (66%)	19/56 (34%)
<1.0 ng/mL			44/71 (62%)	37/44 (84%)	44/44 (100%)	33/44 (75%)	11/44 (25%)
All patients				37/71 (52%)	46/71 (65%)		

*Reference intervals of GH adjusted for age and BMI.

†Concentrations of IGF-1 were adjusted for age and sex.

Table 5. Relationship of Glucose-Suppressed Serum Concentrations of GH and of IGF-1 Among 71 Patients With Acromegaly Following Transsphenoidal Surgery

	IGF-1 Normal (<95% RI)	IGF-1 Elevated (>95% RI)	Total
GH normal, n (<95% RI)	29 (41%)	8 (11%)	37 (52%)
GH elevated, n (>95% RI)	8 (11%)	26 (37%)	34 (48%)
	37 (52%)	34 (48%)	71

sis of acromegaly,[13] although this is not commonly done or even recommended.[1] As shown by the results of the present investigation, the definition of normal concentrations of GH and hence their interpretation in acromegalics is influenced by the 2 variables, age and BMI. In the present series this was of no consequence for newly diagnosed patients since serum concentrations of both GH and IGF-1 by far exceeded the normal range in each case irrespective of the applied definition. It should be pointed out, however, that the number of newly diagnosed acromegalics included in our study was comparatively small and that the precise definition of the normal range may well be of importance for future patients since GH concentrations after glucose may be less than 1.0 ng/mL in some acromegalics with active disease.[14]

This can be seen in patients with operated acromegaly. Roughly 80% of this group had post-glucose GH concentrations of less than 2.0 ng/mL and would formerly have been considered[10,15] to be cured. Applying the more recently proposed cut-off value for glucose-suppressed GH concentrations of less than 1.0 ng/mL,[1] the percentage of our patients in remission after transsphenoidal surgery is 62%. However, this comparatively[16] favorable outcome of surgery is biased due to the exclusion of patients already receiving any form of medical (eg, octreotide) therapy, since these patients, by definition, had not been cured by surgery alone. Comparing glucose-suppressed concentrations of GH in operated patients with acromegaly with the 95% reference intervals to be expected for any given age and BMI according to the used statistical model, the percentage of our patients cured by transsphenoidal surgery is reduced to 52%. As shown in Table 2, all patients who had serum GH concentrations within their individual control range (95% percentile, corrected for age and BMI) had serum GH concentrations of less than 1.0 ng/mL. On the other hand, 7 of 44 (16%) patients with a GH concentration of less than 1.0 ng/mL were outside this individual control range. To lower this figure to 0% in our 71 patients with treated acromegaly would require that the the threshold of (uncorrected) GH concentrations be lowered to 0.5 ng/mL. In accordance with recent suggestions by others,[14] this indicates that an (uncorrected) glucose-suppressed serum GH concentration of less than 1.0 ng/mL is still too high to exclude active acromegaly. On the other hand, a threshold value of 0.5 ng/mL would have labeled 22 of 196 (11%) subjects in our control group as "acromegalics," indicating that in the recognition of residual acromegaly no threshold value of glucose-suppressed serum GH concentration will combine 100% sensitivity with 100% specificity. Such a separation may be achieved, however, by correcting the determined concentrations for age and BMI.

Serum concentrations of somatomedin C (IGF-1) have been used in the assessment of acromegaly for more than 20 years.[17] The determination of insulin-like growth factor binding protein-3 (IGFBP-3) levels and of leptin does not increase accuracy achieved by age-adjusted concentrations of IGF-1.[18] Although the relationship between GH and IGF-1 is linear for GH concentrations of less than 20 ng/mL and there is a strong correlation with glucose-suppressed concentrations of GH,[17,19] IGF-1 concentrations are regarded by some investigators to be of limited value in the follow-up of acromegalic patients.[2,19]

Correction of concentrations of IGF-1 for age and sex[11] is generally recommended.[1,20-22] The data obtained in our healthy control group confirm that both age and sex have an impact on the concentration of IGF-1. BMI also appears to influence IGF-1 when a univariate analysis is used; however, using a more complex multivariate analysis and taking into account the additional variables age and sex, a direct impact of BMI on IGF-1 is no longer apparent. Thus, BMI is a function of age.[20] Since serum IGF-1 concentration depends primarily on the secretion of GH, the difference in the impact of BMI on concentrations of GH and of IGF-1 is surprising and may indicate the modulation of hormone clearance. As to age- and sex-dependence of serum IGF-1 we have determined concentrations in a large group of men and women to establish the respective normal ranges for different decades of life. This approach appears to suffice for practical purposes, although from a puristic point of view it must be acknowledged that the relationship between age and BMI is smooth from 20 to 80 years. Applying these age- and sex-corrected normal ranges of IGF-1 on postoperative acromegalics it becomes apparent that serum concentrations of IGF-1 and of glucose-suppressed GH are congruent in about 77% of these patients. In 8 patients (11%), IGF-1 was normal in the presence of supranormal glucose-suppressed concentrations of GH. Conversely, IGF-1 (corrected for age and gender) was above normal in 8 patients with normal GH concentrations. The latter phenomenon has previously been reported by others[23,24] in up to 20% to 30% of patients with treated acromegaly, albeit using less stringently defined normal ranges of GH and IGF-1. Patients receiving medical therapy were not included in our study and hence treatment with long-acting analogs of somatostatin does not explain these relatively elevated concentrations of IGF-1.[25] The protracted clearance of protein-bound IGF-1 may interfere with the postoperative determination of IGF-1 in some acromegalics.[26] In one of our patients, who was investigated within 2 months after transsphenoidal surgery, this may explain the observed discrepancy between postoperative concentrations of IGF-1 and glucose-suppressed GH. The relationship between GH and IGF-1 in acromegalics has recently been described to be gender-specific,[27] which could be in keeping with a relative resistance to GH[28] in women. The same authors[27] also confirmed,[29] in their acromegalic patients, age-related changes in GH/IGF-1 relationship compatible with a relative GH resistance in older individuals. The possibility of such sex- and/or age-related differences in the relationship between GH and IGF-1 would, however, be of no consequence in the interpretation of our data, which were carefully controlled not only for these variables but also for BMI. Clinical criteria are not sensitive enough to solve the discrepancy between glucose-suppressed concentrations of GH and (carefully calibrated) concentrations of IGF-1. The clinical consequence of this discrepancy must, at this point, remain open for discussion.

We conclude from our data that concentrations of IGF-1 must be corrected for sex and age, whereas glucose-suppressed concentrations of GH depend on age and BMI, while across-the-board cut-off-values are clearly inadequate and should not be used. Appropriate nomograms should help to better interpret clinical data on serum GH and IGF-1 concentrations in patients with acromegaly.

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