CLINICAL STUDY

Limited utility of oral glucose tolerance test in biochemically active acromegaly

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Abstract

Context: Measurement of GH after oral glucose tolerance test (OGTT) is used for the diagnosis and surveillance of acromegaly. However, there are major discrepancies between glucose-suppressed GH and plasma IGF1 as indices of biochemical activity of acromegaly in patients with relatively mild GH oversecretion. This study was aimed to assess the performance of OGTT in patients with acromegaly and variable GH outputs.

Methods: Forty adults with newly diagnosed, untreated acromegaly (15 with GH >4.3 µg/l and 25 with GH <4.3 µg/l) and elevated IGF1 levels were studied. All underwent Q10 min for 24 h sampling for GH followed by an OGTT.

Results: Postglucose nadir GH (GHn) correlated significantly to 24 h GHn, mean 24 h GH, and baseline GH ($P < 0.001$ for all comparisons). GHn correlated significantly to IGF1 z-scores for the 'low' GH group and for the entire group ($P < 0.0001$ for both comparisons), but not for the 'high' GH group. None of the patients with mean GH >4.3 µg/l had GHn below 1 µg/l. In contrast, 13 out of 25 patients (52%) with GH <4.3 µg/l showed GHn lower than 1 µg/l, and 7 of them (28%) had GHn lower than 0.4 µg/l. These groups did not differ significantly either for average or for maximal GH suppression in OGTT.

Conclusions: Our data show that suppressibility of GH by glucose in acromegaly is a function of the degree of GH hypersecretion and that OGTT has only limited diagnostic value in patients with biochemically active acromegaly but only mildly increased GH output.

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Introduction

Prior to the introduction of insulin-like growth factor 1 (IGF1) assay into clinical practice, measurement of plasma GH after oral glucose tolerance test (OGTT) and repeated GH sampling were the only biochemical means to diagnose active acromegaly. Using RIA procedures, the cut-off for the normal GH response to glucose was conventionally accepted as 2 µg/l (1). Subsequent development of sensitive IRMA and immunoluminometric assays (ILMA) revealed that true GH nadirs (GHn) after oral glucose in healthy controls were much lower in the range of 0.20–0.25 µg/l (2).

Incomplete GH suppression by glucose in the presence of normal IGF1 milieu was proposed to be a potentially predictive sign of future biochemical relapse (3), although other studies did not confirm this conclusion (4, 5). At the same time, it became apparent that active acromegaly with clearly elevated IGF1 concentrations may be present even in newly diagnosed, untreated patients with apparently 'normal' plasma GH concentrations (6). Nowadays, the GHn cut-off currently

most used to define diagnosis and cure of acromegaly has been considered to be 1.0 µg/l (7), although the last consensus has suggested a lower cut-off of 0.4 µg/l (8).

This study aimed to evaluate the performance of OGTT in two different populations of clinically and biochemically active patients with acromegaly (elevated IGF1 concentrations): one with clearly elevated, and another with ostensibly 'normal' mean 24 h GH concentrations, in order to compare and get new insights on the differences of OGTT performance to access biochemical indices of disease. We show here a lack of reliability of OGTT to diagnose active acromegaly with only mildly elevated GH output.

Subjects and methods

Patient data samples were retrospectively collected from prior research protocols approved by the University of Michigan Institutional Review Board and General Clinical Research Center Advisory Committee. Written informed consent was obtained from all subjects prior to

their participation in protocol procedures. Patients were enrolled to this study protocol from March 1996 to January 2002, when Nichols assay was used to assess GH levels in the University of Michigan.

Forty adults with newly diagnosed, untreated active acromegaly (23 males and 17 females) as defined by clinical symptoms (acromegalic features and acral enlargement coupled to other signs and symptoms of acromegaly) and high age-adjusted IGF1 values were studied. Their ages ranged from 18 to 73 years old. All of these patients had been enrolled to other reported protocols coming from the University of Michigan. All underwent frequent (Q10 min for 24 h) blood sampling for GH followed by an OGTT.

A mean 24 h GH value of 4.3 $\mu\text{g/l}$ was taken as the threshold value to assign each patient to the 'high' or the 'low' GH study group, because it was the highest mean 24 h GH found by us in our studies of normal, healthy control adults as published elsewhere (6). This previous publication included 46 normal healthy subjects (27 males and 19 females) divided into subgroups of young and old, and mean 24-h GH of these normal subjects completely overlapped those of low GH output patients whose mean 24 h GH value was $<3.2 \mu\text{g/l}$. However, 5 out of these 46 normal subjects showed higher GH values that reached the maximum value of 4.3 $\mu\text{g/l}$. Therefore, we have chosen this last number to assign patients to each of our present study groups.

Fifteen patients were defined as 'high' GH acromegalics (nine males and six females; average age 39.5 ± 3.7 years) and 25 patients were defined as 'low' GH acromegalics (14 males and 11 females; average age 47.4 ± 3.0 years). The higher numbers of the 'low' GH patients as compared to the 'high' GH patients in this protocol are not representative of the prevalence of each of these in acromegaly. It is due to the referral bias whereby the number of patients selected for frequent GH sampling in our studies over the years usually had lower GH values.

All patients had pituitary magnetic resonance imaging (MRI) study performed, and all but one ('low GH' group) had an MRI-identifiable pituitary adenoma. There were 6 patients with a microadenoma and 9 patients with a macroadenoma in the 'high' GH group, whereas the 'low' GH group had 16 patients with microadenomas and 9 patients with a macroadenoma. A GH-secreting pituitary adenoma was histologically and immunochemically identified in all resected cases ($n=38$); one patient with a macroadenoma and 'low' GH refused surgery, and another patient with a microadenoma and 'low' GH was deemed to be medically unfit for general anesthesia.

None of the patients had renal or hepatic impairment, and none were treated with dopamine agonists, somatostatin analogs, GH receptor antagonist, estrogen, or any medication potentially affecting GH secretion.

Participants consumed a standard isocaloric hospital diet consisting of three meals and a bedtime snack during sample collection. Blood sampling for GH was performed at a frequency of every 10 min for 24 h in all patients. Subsequently, 100 g oral glucose was given, followed by GH and glucose measurements every 10 min for 2 h between 0700 and 0900 h while patients were resting in a supine position. We have used 100 g glucose instead of currently recommended 75 g in OGTT studies as both give identical results in terms of GH suppression (9), and many patients had already undergone the 100 g test by the time the guidelines suggesting 75 g to evaluate for both diabetes and acromegaly have been proposed.

Serum GH was measured in duplicate and always by a chemiluminescent assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). GH assay sensitivity reported by the manufacturer and confirmed by our experience was 0.01 $\mu\text{g/l}$. Plasma IGF1 was measured by a two-site IRMA (Diagnostic System Laboratories, Webster, TX, USA) for all samples. Age-adjusted IGF1 values were referenced from a previously published large multicenter study by Brabant *et al.* (10, 11), employing the same assay utilized in this study. Z-score calculation necessitated that age-specific s.d. reference values be averaged, since the reference data existed in a slightly non-Gaussian distribution.

Statistical analysis was performed by Excel 2003 (Microsoft Corporation) and GraphPad Prism 4 (GraphPad Software, San Francisco, CA, USA). All values are shown as means $\pm$ s.e.m. Data groups were compared with the Student's unpaired *t*-test or Mann-Whitney test as appropriate. Relationships between GHn after oral glucose (GHn) levels and other plasma GH parameters and IGF1 z-scores were analyzed by regression analysis, and Spearman *r* was utilized for correlations. A *P* value <0.05 was taken as significant.

Figure 1 Log-log correlation between postglucose nadir absolute GH values (GHn) and spontaneous mean 24 h GH in the entire group of subjects.

Figure 2 Baseline and postglucose nadir absolute GH values for each patient during OGTT. Filled circles represent GH baseline OGTT values, and empty circles represent GH nadir OGTT values.

Results

The two groups studied did not differ significantly for age, although there was a trend for lower age in the 'high' GH group ($P=0.06$). There were no significant differences for gender and body mass index between groups. One patient from the 'high' GH group and two patients from the 'low' GH group showed plasma fasting glucose levels ≥ 126 mg/dl, compatible with the diagnosis of diabetes as defined by American Diabetes Association (12). However, none of them were on any specific therapy for diabetes, and fasting plasma glucose levels were lower than 200 mg/dl by the time of evaluation.

The 24 h individual GH means for the 'high' and the 'low' GH patients varied between 4.66–120.83 and 0.64–3.95 $\mu\text{g/l}$ respectively ($P<0.0001$). The GHn of both groups strongly correlated to 24 h GHn, defined as the lowest 5% of all GH values, i.e. the lowest seven samples within the 24 h array ($r=0.97$ and 0.94 for the 'high' and the 'low' GH groups respectively, $P<0.0001$ for both) as well as for the entire group ($r=0.97$, $P<0.0001$). Furthermore, there were significant correlations of GHn and mean 24 h GH

($r=0.91$ and 0.63 for the 'high' and the 'low' GH groups, $P<0.0001$ and $P<0.001$ respectively) as well as for the entire group ($r=0.88$, $P<0.0001$). Likewise, GHn correlated significantly with the baseline GH from OGTT for both the studied groups ($r=0.96$ and 0.79 for the 'high' and the 'low' GH groups respectively, $P<0.0001$ for both comparisons) as well as for the entire group ($r=0.93$, $P<0.0001$). Figure 1 shows regression analysis of the logarithm-transformed GHn versus mean 24 h GH in all subjects.

The GHn also correlated significantly with IGF1 z-scores for both the 'low' GH group ($r=0.75$, $P<0.0001$) and to the entire group ($r=0.73$, $P<0.0001$). However, there was no significant correlation of GHn with IGF1 z-scores for the 'high' GH group.

The baseline and nadir absolute GH values for each patient during OGTT are shown in Fig. 2. In the 'high' GH group, none of the patients had GHn below 1 $\mu\text{g/l}$. On the other hand, 13 out of 25 patients (52%) in the 'low' GH group had GHn below 1 $\mu\text{g/l}$, and 7 patients (28%) had GHn below 0.4 $\mu\text{g/l}$. Six patients in the 'low' GH group (24%) had baseline GH (immediately before OGTT) levels below 1 $\mu\text{g/l}$. The clinical data for patients suppressing GH under 0.4 $\mu\text{g/l}$ are shown in Table 1. Four out of these seven patients were cured by transsphenoidal surgery and normalized IGF1 levels. GH-secreting adenoma was identified immunochemically in all of them.

In Fig. 3, the average percent suppression for each 10 min time point during the entire 120 min of OGTT is shown for the two studied groups. No statistical differences could be observed between groups at any time point. The maximal overall percent suppression for the 'high' GH group was observed at 120 min ($13.6 \pm 8.6\%$). Likewise, the maximal average GH percent change was detected at 110 min ($16.1 \pm 12.2\%$) in the 'low' GH group.

The maximal GH suppression at any time point during OGTTs for both groups (Fig. 4) was similar between the 'high' and the 'low' GH groups of patients (-31.8 ± 5.7 vs $-42.9 \pm 5.3\%$, $P>0.05$).

Table 1 Clinical data for the seven acromegalic patients suppressing to lower than 0.4 $\mu\text{g/l}$ in oral glucose tolerance tests.

Patient	Gender	Age (years)	BMI (kg/m^2)	Adenoma	GH ^a ($\mu\text{g/l}$)	GH nadir ^b ($\mu\text{g/l}$)	IGF1 (ng/ml) (upper limit)
01	Female	38	17.58	Micro	0.29	0.13	309 (239)
02	Female	30	30.00	Micro	0.08	0.07	561 (257)
03	Male	25	26.98	Micro	1.59	0.21	348 (309)
04	Female	22	22.04	Macro	0.78	0.13	361 (294)
05	Female	49	25.15	Micro	0.28	0.16	281 (208)
06	Female	25	27.18	Micro	0.06	0.03	398 (294)
07	Male	40	22.98	Micro	0.91	0.19	493 (228)

BMI, body mass index; Micro, microadenoma; Macro, macroadenoma; IGF1, insulin-like growth factor 1.

^aBaseline GH in oral glucose tolerance test.

^bGH nadir in oral glucose tolerance test.

Figure 3 Average GH percent suppression for each 10 min time point during the entire 120 min of OGTT for the 'high' and the 'low' GH groups.

Discussion

Several studies have recently attempted to define the normal postglucose GHn as an indicator of biochemical remission of acromegaly. While some of them have suggested that the 1 µg/l cut-off level was satisfactory (4, 5, 7, 13, 14), others have suggested that lower cut-offs should be utilized to better define remission of acromegaly (8, 9, 15–18). We show here that the utility of OGTT is determined by the degree of endogenous GH hypersecretion: 100% of clinically and biochemically active acromegalic patients with 'high' GH profiles have postglucose GHn higher than 1 µg/l, while over 50% of the active 'low' GH acromegalic patients have ostensibly normal GH suppressibility by the same criterion. Moreover, in the 'low' GH group, postglucose GH values below 0.4 µg/l, i.e. normal according to the proposed contemporary criteria (8), were achieved in almost 30% of the patients.

Several previous reports studied the limits of GH suppressibility by glucose and suggested different normalcy criteria for men and women or correction for the body mass index in patients with acromegaly (17). These questions, while unquestionably valid scientifically, would be very difficult to implement in clinical practice especially when GH assay heterogeneity is so wide. Thus, the most recent consensus statement (8) intentionally chose to provide a strict but uniform 0.4 µg/l criterion. In our study, plasma GH suppression by glucose to below 0.4 µg/l occurred in both males and females, in both lean and overweight acromegalic patients, and in both macro- and microadenomas. In the majority of cases, baseline GH levels (prior to administration of oral glucose) were lower than 1.0 µg/l, corroborating the notion that GH suppressibility by glucose in naive acromegalic patients is a function of the magnitude of spontaneous GH hypersecretion.

The distinction between the 'high' and the 'low' GH groups as used in this analysis is likely to be artificial, and both groups represent different parts of the continuum of GH output in patients with acromegaly. Indeed, percent GH suppression by glucose did not differ between the two groups, and there was high degree of linear correlation between the magnitude of spontaneous GH output and the glucose-suppressed GH level across the entire group. It is noteworthy to point that if a lower cut-off value such as 3.2 µg/l had been taken (6), two patients would move from the 'low' to the 'high' GH group. Interestingly, these two patients showed GHn higher than 1.0 µg/l, which means that there would be even higher percentage of normal suppressibility in the 'low' GH group, exacerbating the problem even further. The rest of the data would not change materially.

Several studies have recently addressed the frequent discrepancies between GHn and IGF1 levels during the follow-up of acromegalic patients (19–21). While it has been suggested that data from OGTT can effectively substitute the GH day curve (20), the degree of increased IGF1 levels and GHn was correlated with subtle abnormalities of daytime GH secretion (19). However, these studies have addressed the role of OGTT in previously treated patients, whereas patients in our study were all newly diagnosed and treatment-naïve.

Present investigation also shows that while maximal average GH suppression was usually achieved at about 120 min after glucose overload, as suggested by others (22), the timing of the nadir varied for each patient between 60 and 120 min. Therefore, although the 120 min has been advocated as the sole point in OGTT to be measured (12, 22), our data suggest that adherence to this recommendation or the use of relatively infrequent GH sampling may actually miss the time of maximal GHn. Perhaps, this might at least in part explain the combination of normal IGF1 and incompletely suppressed GH described by other investigators (5, 22–24).

The physiological meaning of GHn is uncertain. OGTT might conceivably serve as an inexpensive and

Figure 4 Maximal GH suppression at any time point during OGTT for the 'high' and the 'low' GH groups.

easily performed test to assess the spontaneous baseline GH secretion, i.e. the 'growth-defining' parameter of the total GH output (25, 26). However, GHn was perfectly normal in almost 30% of the patients with relatively low GH output but with clinically active disease and clearly elevated IGF1 concentrations. This is, to the best of our knowledge, the first study to show that, although GHn correlates significantly with mean 24 h GH, baseline OGTT values, and to 24 h GHn in acromegalic patients irrespective of GH output, the maximal suppressibility observed with GHn cannot serve as an exclusion of active disease in the 'low' GH acromegalic group of patients. It had been suggested recently that, in the presence of discordant serum IGF1 and GHn levels, IGF1 is more predictive than GHn in terms of insulin sensitivity and clinical symptom score (27). Likewise, studies have recently addressed the limited usefulness of GHn in the assessment of patients previously subjected to radiotherapy, when GH and IGF1 may be discordant (28), or during the use of somatostatin analogs (21, 23). In agreement with those studies, our data also show the limited utility of OGTT in the diagnosis of naïve acromegalic patients with low GH output. However, IGF1 measures are also subjected to several pitfalls and, as shown by our data, the correlation of GHn with IGF1 is usually lost at higher GH values, possibly due to saturation of hepatic GH receptors (29).

This study utilized the Nichols GH ILMA that is no longer commercially available. Taking into account the heterogeneity of assay performance (9, 17, 30, 31), our estimates of the false-negative rate of GHn value in patients with relatively low spontaneous GH output may not be numerically applicable to the currently used GH assays. Similar studies utilizing GH assays currently in clinical and research use are needed.

In conclusion, previous studies have shown that OGTT is of little predictive value in patients with treated acromegaly and normal plasma IGF1 concentrations (4). We show here that GH suppressibility by glucose in acromegaly is a function of the magnitude of spontaneous GH hypersecretion in naïve acromegalic patients. It is predictably abnormal and, thus, superfluous, in patients with clearly elevated GH concentrations, but may have very high false-negative rate in patients with relatively low GH output, i.e. in the very group requiring heightened diagnostic scrutiny. The false negativity of ~50% using the conventional criterion of 1 µg/l, or ~30%, when using Nichols ILMA and the criteria recommended by the most recent consensus statement (8) draw attention to the potential limitation of this test as a diagnostic tool to the low GH output acromegalic patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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