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ORIGINAL ARTICLE

Is GH nadir during OGTT a reliable test for diagnosis of acromegaly in patients with abnormal glucose metabolism?

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Abstract

Purpose The growth hormone (GH) nadir during oral glucose tolerance test (OGTT) is the gold standard diagnostic test for acromegaly. The utility of OGTT-GH suppression test in patients with abnormal glucose metabolism (AGM) has not been well established. In this study, we compared the GH nadir during OGTT in patients evaluated for acromegaly in the presence and absence of AGM.

Methods This is a retrospective cohort study of patients with acromegaly (G1, $n = 40$) and a group in whom acromegaly was not confirmed (G2, $n = 53$) who had OGTT-GH suppression test during 2000–2012, using a monoclonal GH immunoenzymatic assay. The patients were categorized as having normal glucose metabolism (NGM) or AGM. GH nadir during OGTT in each group were compared.

Results In G1 and G2, 17 and 19 patients had AGM, respectively. Among 17 patients with diabetes, median HbA1C was 7% (range 5.7–9.6%). All except one patient had HbA1C< 8%. There was no difference in the GH nadir in patients with or without AGM within G1 ($p = 0.15$) and G2 ($p = 0.43$). All G1 patients with AGM had GH nadir > 0.4 µg/L. Four G1 patients with NGM had GH nadir<0.4 µg/L. All G2 patients had GH nadir < 0.4 µg/L, except one with NGM and GH nadir of 0.4 µg/L.

Conclusion Using highly sensitive GH assay, a GH nadir ≥ 0.4 µg/L during the OGTT-GH suppression test may be used for diagnosis of acromegaly in patients with AGM in the absence of poorly controlled diabetes.

Keywords Growth hormone nadir · Acromegaly · Diagnosis · OGTT · Diabetes

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Introduction

Acromegaly is a disorder caused by chronic GH hypersecretion leading to IGF-1 over-production. The measurement of IGF-1 level is recommended as the initial test for patients presenting with clinical features of acromegaly. Some individuals without acromegaly can have elevated IGF-1 levels overlapping that of patients with acromegaly [1]. Patients with mildly elevated IGF-1 levels should undergo oral glucose tolerance test (OGTT) [2]. The 2014 Endocrine Society clinical practice guideline suggests using GH nadir less than 1 µg/L after OGTT to exclude the diagnosis of acromegaly, although lower GH nadir of 0.4 µg/L has been proposed when using highly sensitive GH assay [2, 3].

Despite being considered as the gold standard test for diagnosis of acromegaly, GH suppression test with OGTT is not without pitfalls. Failure of GH suppression can be seen in malnutrition, liver failure, chronic kidney disease, and diabetes mellitus [4]. However, IGF-1 level in most of these

conditions should be either low or normal, and thus acromegaly generally can be excluded when using IGF-1 as a screening test [5].

The diagnosis of acromegaly in patients with diabetes or glucose intolerance can be a challenge due to complex interplay between insulin and GH/IGF-1 regulation. There is little data on GH levels in patients with type 2 diabetes or insulin resistance. Much less is known about the degree of GH suppression in patients with diabetes or impaired glucose tolerance (IGT) compared to patients with acromegaly.

It is suggested that GH suppression by OGTT is not a reliable diagnostic tool in patients with abnormal glucose metabolism (AGM) and diabetes who are suspected to have acromegaly since their GH levels may not suppress normally after OGTT leading to lower specificity and higher false positive results [3, 5]. Early studies have shown paradoxically increased GH levels measured by radioimmunoassay within the first 2 h after glucose load in certain patients with diabetes and IGT [6–8]. Given the high prevalence of type 2 diabetes and IGT in both patients with acromegaly and normal population, diagnostic value of OGTT in patient with prediabetes or diabetes with a GH immunoassay used in current clinical practice should be validated.

The objective of our study is to compare GH nadir between patients with and without acromegaly in the presence and absence of AGM.

Materials and methods

This was a retrospective study of 129 patients who underwent GH suppression test with 75g OGTT for acromegaly workup during 2000–2012 at Cleveland Clinic. Among 53 patients with acromegaly, five patients were excluded since they were on medical therapy at the time of OGTT or had OGTT while their disease was in remission and eight patients were excluded since they had inadequate follow up or inconclusive workup. Among the included 93 patients, in 40 patients (18 newly diagnosed acromegaly, 22 known cases of acromegaly) the diagnosis of acromegaly was established; and in 53 patients, acromegaly was not confirmed. Patients were defined as having active acromegaly based on clinical features, elevated IGF-1 levels and growth hormone (GH) levels, positive pituitary imaging for pituitary adenoma, surgical pathology, and subsequent medical therapy when available or clinically indicated. Only two patients in the acromegaly group received medical therapy (octreotide LAR) prior to the testing and both were off medication for at least 3 months at the time of OGTT, had elevated IGF-1 and had a nadir GH > 0.4 μg/L during OGTT.

Subjects were divided into AGM and normal glucose metabolism (NGM) groups. AGM is defined as having either impaired fasting glucose (IFG), IGT, or diabetes mellitus based on OGTT results or a known diagnosis by chart review. BMI data was missing in one patient with acromegaly with NGM. BMI data were missing in two patients in whom the diagnosis of acromegaly was not confirmed (one had NGM and the other had IGT). Among the patients with diabetes, data on hemoglobin A1C (HbA1C) were missing in three and two patients with acromegaly and in the group in which the diagnosis of acromegaly was not confirmed, respectively.

Patients in whom the diagnosis of acromegaly could not be established had GH suppression test done for various reasons including presence of questionable acromegalic features on exam, elevated IGF-1 < two-fold upper limit of normal during workup of pituitary incidentaloma, or discrepant results between 2 IGF-1 assays. These patients either had negative pituitary imaging or the pituitary masses were proven to be from other pathology such as metastatic disease, null adenoma or prolactinoma.

The baseline characteristics of patients with acromegaly and in whom the diagnosis of acromegaly was not confirmed were similar, except for significantly higher IGF-1 in the patients with acromegaly (Table 1). At the time of testing, the patients with diabetes had fasting glucose ranged from 79 to 168 mg/dL and median HbA1C was 7.0% range [5.7–9.6%]. Hgb A1C was <8% in all but one patient. None of the patients had type 1 diabetes. Four patients were on insulin treatment and none of them had active acromegaly. The study was approved by Institutional Review Board at Cleveland Clinic Foundation.

GH suppression by OGTT

Standard 2-h 75g OGTT was performed in each subject after overnight fasting. Blood was drawn at 0, 30, 60, 90, and 120 min after glucose ingestion for plasma glucose and GH levels. IFG is defined as fasting plasma glucose 100–125 mg/dL. IGT is defined as 2-h plasma glucose 140–199 mg/dL after OGTT. Diabetes was defined as having either fasting plasma glucose ≥ 126 mg/dL, 2-h OGTT plasma glucose ≥ 200 mg/dL or ICD-9 diagnosis of type 2 diabetes or HbA1c ≥ 6.5% within 3 months of the GH suppression test date. Because the high sensitivity of the GH assays used and based on our previous extensive experience, normal GH suppression is defined as GH nadir < 0.4 μg/L at any of the time points after the glucose ingestion [1].

Laboratory assay

Serum GH was measured by the automated two-site immunoenzymatic assay on the Tosoh NexIA until 2009, with a detection level of 0.1 μg/L and subsequently on the

Table 1 Demographic summary of patients with acromegaly and patients in whom the diagnosis of acromegaly was not confirmed

	Acromegaly ($n=40$)	Patients in whom acromegaly was not confirmed ($n=53$)	*P*-value
Age	49 [20 to 80]	45 [17 to 73]	0.44[a]
Male gender	21 (52.5%)	22 (41.5%)	0.3[b]
BMI	29 [22.31 to 48.24]	31 [20.40 to 53.01]	0.48[a]
IGF-1 (SDS)	4.23 [−0.27 to 17.04]	2.46 [−1.76 to 5.97]	<0.001[a]
Glucose metabolism			
NGM	23 (57.5%)	34 (64%)	0.67[b]
IFG	4 (10%)	3 (5.7%)	0.46[b]
Fasting glucose (mg/dL)	101 [100, 112]	106 [101 to 124]	0.34[a]
IGT	5 (12.5%)	7 (13.2%)	0.99[b]
2-h post-prandial glucose (mg/dL)	151 [142 to 168]	148 [140 to 181]	0.72[a]
DM	8 (20%)	9 (17.1%)	0.9[b]
HbA1C (%)	6.5 [5.7 to 7.5]	7.4 [6.5 to 9.6]	0.06[a]

Data is reported as Median [Min, Max]

BMI body mass index, *SDS* standard deviation score (see text), *NGM* normal glucose metabolism, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance test, *DM* diabetes mellitus

[a]Wilcoxon Rank Sum test

[b]Fisher's Exact Test

immunoemzymatic assay by Beckman Coulter DxI 600 with a detection level of 0.05 µg/L. There was a very good correlation between the two GH assays which was demonstrated by in-house laboratory study with correlation slope 0.914, $r = 0.99$. The intra-assay and inter-assay coefficients of variation were <4 and <6% for the NexIa assay and <5 and <7% for the Beckman Coulter assay, respectively.

Plasma IGF-1 was measured by a two-site chemiluminescent immunoassay by Nichols Advantage with a lower limit of detection of 17 ng/mL from 2000 to March 2006, and Siemens Immulite 2500 with a detection level of 25 ng/mL thereafter. There was a very good correlation between the 2 IGF-1 assays, as demonstrated by in-house laboratory study (correlation slope 0.83, $r = 0.987$). As the IGF-1 data were derived from different labs with multiple reference ranges, we made the assumption that the reference range represented –2 standard deviations (SD) to +2 SD in order to enable comparison across different assays and normal ranges. On the basis of this assumption, the mean (μ) was calculated as the value corresponding to 0 SD, along with the corresponding SD for each IGF-1 result (X). The following formula for each IGF-I result was used to derive a standard deviation score (SDS): $SDS = (X-\mu)/SD$ [1].

Statistical analysis

Data were shown using medians (ranges) for continuous measures and frequencies and percentages for categorical factors. GH nadir was calculated for each patient across 30, 60, 90, and 120 time point measures. Data were not normally distributed, so Kruskal–Wallis tests were performed when three or more groups were present and Wilcoxon rank sum tests were used when two groups were present. Sensitivity and specificity measures between groups were estimated and compared using Fisher exact test. Analysis was performed using R software (version 2.15; Vienna, Austria).

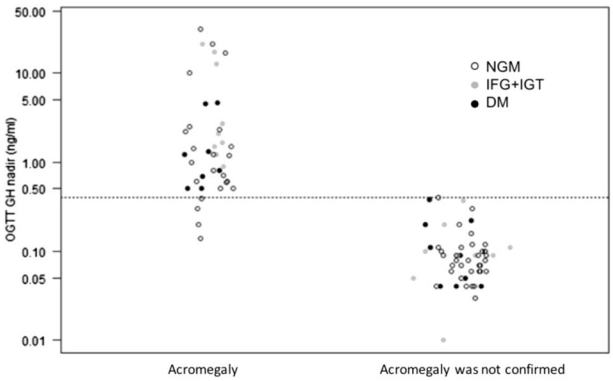

Fig. 1 Nadir GH during OGTT in patients with acromegaly and patients in whom the diagnosis of acromegaly was not confirmed

Results

GH suppression in whom acromegaly was not confirmed

GH nadirs in all subjects were illustrated in Fig. 1. In subjects in whom acromegaly was not confirmed, OGTT was able to suppress GH to less than 0.4 µg/L in all except one patient who had a GH nadir level of 0.4 µg/L. This particular patient presented with large heterogenous sellar

Table 2 Comparison of nadir GH (μg/L) during OGTT in patients with acromegaly and patients in whom acromegaly was not confirmed by glucose metabolism subtypes

	NGM		AGM (IFG + IGT + DM)		IFG or IGT		DM		p-value[a]	p-value[b]
	Median [Min, Max]	N	Median [Min, Max]	N	Median [Min, Max]	N	Median [Min, Max]	N		
Patients with acromegaly	1 [0.14, 31.6]	23	1.5 [0.5, 21.4]	17	2.10 [0.9, 21.4]	9	1.00 [0.5, 4.6]	8	0.15	0.071
Newly diagnosed	1.65 [0.14, 31.6]	8	3.6 [0.5, 21.4]	10	7.65 [1.2, 21.4]	6	2.55 [0.5, 4.8]	4	0.35	[c]
Established cases	0.8 [0.3, 16.7]	15	1.2 [0.68, 2.1]	7	1.5 [0.9, 2.1]	3	2 [0.68, 1.3]	4	0.42	[c]
Patients in whom acromegaly was not confirmed	0.08 [0.03, 0.4]	34	0.09 [0.01–0.38]	19	0.10 [0.01, 0.37]	10	0.09 [0.04, 0.38]	9	0.43	0.64

[a]Compares GH nadir in patients with NGM and AGM (Wilcoxon rank sum test with continuity correction)

[b]Compares GH nadir in patients with NGM, IFG/IGT and DM (Kruskal–Wallis rank sum test)

[c]Results comparing the three groups in patients with acromegaly at initial diagnosis and during follow up were not performed because the groups were too small to allow for statistical testing

mass with slightly elevated IGF-1 and later found to have Hodgkin Lymphoma with sellar dissemination. In this group, the GH nadir was not different in subjects with NGM and AGM (Table 2). Further analysis on GH suppression in NGM, IFG/IGT, and diabetes did not demonstrate statistically significant difference.

GH suppression in patients with acromegaly

Majority of patients with acromegaly (36 out of 40 patients) had GH nadir above 0.4 μg/L. All four acromegalic patients in whom GH suppressed less than 0.4 μg/L with OGTT belonged to NGM group (0.39, 0.3, 0.2, and 0.14 μg/L). All of them had elevated IGF-1 levels (2.53–5.73 SDS). Three of them were newly diagnosed with positive GH staining on pathology. The 4th one was a known case of acromegaly with residual tumor after transsphenoidal surgery and radiation therapy (Table 3). Similarly, in patients with acromegaly, GH nadir was not significantly different in patients with NGM and AGM regardless of glucose metabolism subtypes or whether the patients were previously treated surgically (Table 2).

When using a GH nadir cut-off of <0.4 μg/L to define the absence of active acromegaly, the sensitivity of GH suppression test was 82.6% in patients with NGM, as compared to 100% in patients with AGM. The specificity was 97.1% in patients with NGM compared to 100% in those with AGM including IFG/IGT, and diabetes.

Discussion

Insulin enhances hepatic IGF-1 production by inducing expression of GH receptors on hepatocytes and/or exerting a permissive effect at post-receptor level [9–12]. Accordingly, it is hypothesized that portal hypoinsulinemia leads to low IGF-1 levels through decreased liver GH receptors, thus creating a state of GH resistance and resulting in elevated GH as a compensatory mechanism [13]. Insulin treatment has been shown to increase IGF-1 production in type 1 diabetes [9]. The administration of insulin directly to portal circulation results in a greater increase in serum IGF-1 compared to subcutaneously injected insulin, supporting the role of hepatic insulinization for adequate IGF-1 production [14]. Patients with uncontrolled type 1 diabetes were shown to have higher basal GH, while their IGF-1 levels are lower than normal subjects in the same age and sex group [10, 15].

While the pattern of changes in GH and IGF-1 regulation has been well-described in type 1 diabetes, such pattern is not uniform in type 2 diabetes or insulin resistance. A cross-sectional study in adult Danish population (3354 subjects, 520 of whom with insulin resistance defined by increased

Table 3 Characteristics of the four patients with active acromegaly but GH nadir during OGTT less than 0.4 µg/L

Study ID	Age	Gender	Tumor size (cm)	Pathology report	GH nadir (µg/L)	IGF-1 (normal range, ng/mL); SDS
69	54	M	0.5	Positive staining with antibodies to GH and focal staining to TSH	0.39	435 (87–267); 5.73
94	35	F	1.4 × 2.1 × 1.8	Not available, known case of acromegaly treated previously with surgical resection and radiation therapy	0.3	357 (117–329); 2.53
111	36	M	0.8	Positive staining with antibodies to TSH and GH	0.2	409 (117–329); 3.51
124	52	M	0.5	All cells were labeled positively with antibodies to prolactin. Rare cells were labeled positively with antibodies to GH	0.14	341 (87–267); 3.64

F female, *M* Male, *SDS* standard deviation score (see text)

homeostasis model of insulin resistance) revealed both low and high IGF-1 levels were related to insulin resistance, suggesting U-shape relationship between IGF-1 levels and insulin resistance [16]. The wide range of IGF-1 levels in type 2 diabetes is probably due to multiple factors interacting to control IGF-1 concentrations such as hepatic insulin resistance, increased inflammatory cytokines, effect of obesity on IGF-1 production, and changes in IGF binding proteins [17].

Little data is available on the degree of GH suppression in patients with diabetes or IGT compared to patients with acromegaly. By using area-under-the curve ratio of GH and glucose during OGTT, Anderwald et al. [18] demonstrated that circulating glucose had at least 50% less suppressive action on GH release in insulin-resistance non-diabetic patients compared with insulin-sensitive non-diabetic patients.

In this study the GH suppression was not affected by the presence of AGM when using highly sensitive GH assay. All patients with acromegaly with AGM had GH nadir above the proposed <0.4 µg/L cut-off [2, 3]. Only four patients with acromegaly had GH nadir below 0.4 µg/L and all of them had NGM. One subject with NGM in whom acromegaly was not confirmed had borderline GH nadir at 0.4 µg/L, while the rest of the subjects in whom acromegaly was not confirmed had GH nadir below 0.4 µg/L regardless of their glucose metabolism status. It should be noted that patients with diabetes in our study were relatively well-controlled, as only one patient had HbA1C above 8% at the time of the study. Accordingly, the performance of OGTT in patients with poorly controlled diabetes may need further studies.

Suppressed GH level after glucose loading is most likely due to inhibition of GH-releasing hormone and/or stimulation of somatostatin release [19]. Lack of GH suppression during OGTT has been reported in patients with insulin resistance and abnormal glucose tolerance [6, 7]. However, GH measurement in these early studies were done by conventional radioimmunoassay which has limited sensitivity and is no longer used in current practice. Later studies have tried to address the degree of GH suppression with OGTT in patients with diabetes and glucose intolerance. However, the results were conflicting. Using polyclonal enzyme immunoassay for GH measurement, Hattori et al. did not detect difference in GH response during OGTT among normal subjects and patients with IGT or diabetes. In fact, all patients with IGT and diabetes had GH nadir ≤1 µg/L [20]. In contrast, a study by Kayath et al. using monoclonal enzyme immunoassay showed lack of GH suppression in approximately 70% of IGT patients. However, the authors used a very low cut-off of 0.1 µg/L to define GH suppression and did not include patients with acromegaly in the study to compare GH nadir using the same assay [21]. It is

difficult to compare the results of these studies due to different nature of GH assay, different amount of glucose used in OGTT, and the use of different method-specific cut-off values to define GH suppression. Therefore, it is important to establish assay specific cut-offs for different commercially available GH assays.

Currently there are only a few studies using modern GH assays to evaluate GH suppression during OGTT in patients with AGM and diabetes. A small study using commercial enzyme immunoassay (detection limit 0.05 µg/L) demonstrated appropriate GH suppression with OGTT in all patients with uncontrolled diabetes ($n = 10$, mean HbA1C 10 ± 0.5%) with mean GH nadir 0.20 ± 0.04 µg/L, while GH in patients with acromegaly ($n = 10$) with similar HbA1C were clearly elevated and not suppressed after OGTT. Repeated GH suppression test in patients with diabetes after intensive glycemic control therapy (HbA1C improved to 6.9 ± 0.1%) showed no difference in GH levels during OGTT [22]. Another study on GH suppression in patients with diabetes using sensitive chemiluminescence assay showed almost all patients had GH nadir <1 µg/L. All men with diabetes were able to achieve GH nadir less than 0.4 µg/L, but only 64 and 80% of premenopausal and postmenopausal patients had nadir GH less than 0.4 µg/L. The study did not include any patients with acromegaly, and none of the patients had HbA1C more than 10% [23].

Our study is in agreement with these recent studies that at least in the absence of poorly controlled diabetes, and when GH is measured with modern sensitive assays, OGTT may be used to evaluate patients suspected to have acromegaly. Our study included a larger pool of patients with acromegaly. In addition, we had a control arm so we were able to compare GH nadir between patients who had acromegaly and those in whom the diagnosis could not be established with different type of glucose metabolism (NGM, IFG, IGT, and diabetes). GH nadir in subjects with NGM and AGM within acromegaly group and no-proven acromegaly group were not different. We also demonstrate that insulin resistant state such as IFG or glucose intolerance does not prevent normal suppression of GH with OGTT either.

Despite modern noncompetitive immunometric GH assays have higher sensitivity and result in lower serum GH levels compared to older polyclonal radioimmunoassays, the endocrine society recommends a cut-off GH nadir <1 µg/L to exclude the diagnosis of acromegaly due to concern of assay inaccuracy at low level [2]. However, several studies have shown that patients with mild acromegaly may have nadir GH lower than 1 µg/L [1, 3, 24]. A cut-off GH nadir <0.4 µg/L has been proposed to improve sensitivity of disease detection, as most healthy subjects were able to suppress GH to less than 0.4 µg/L after glucose load [25–28]. According to some studies, GH nadir were even less than 0.2 µg/L in healthy adults [3, 28].

The GH < 0.4 µg/L cut-off appears to perform well in AGM at our institution. We are aware that defining a universal GH nadir cut-off is challenging as different methodology of various immunoassays and patient factors including age, sex, and BMI have impact on GH nadir [27]. As it has been shown in some other studies, there were four patients with active acromegaly who had GH nadir suppressed below 0.4 µg/L. Faje et al. [29] proposed the concept of "micromegaly" hypothesizing that the baseline GH (even as low as 0.2 µg/L) rather than the pulses determines the IGF1 level and using a GH nadir <1 µg/L would miss some of the acromegaly cases.

Patients with acromegaly who have severe hyperglycemia may have normal IGF-1 level due to hepatic GH resistance [30] and their biochemical profile may be similar to patients with poorly controlled diabetes (non-suppressed GH with OGTT and normal IGF-1) [31, 32]. However, clinical manifestations of acromegaly should be quite obvious if GH hypersecretion is severe enough to result in extreme hyperglycemia. If diagnosis of acromegaly is questioned in patients with poorly controlled diabetes, repeated OGTT and IGF-1 level may be considered after diabetes is better controlled.

Our study is limited by its relatively small sample size and retrospective nature. We were not able to use the same GH assay over the study period. However, there were good correlation between the GH assays used with low inter-assay coefficients of variation. None of our subjects had poorly controlled diabetes. Therefore, interpretation of OGTT in the setting of uncontrolled diabetes should be with caution as failure of GH suppression in such cases may need to be further studied.

In conclusion, GH nadir ≥ 0.4 µg/L during OGTT may be used to diagnose acromegaly in patients with IFG, IGT, and in patients without poorly controlled diabetes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethicall approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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