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Oral glucose-stimulated growth hormone (GH) test in adult GH deficiency patients and controls: potential utility of a novel test

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Abstract
Context. The diagnosis of adult GH deficiency requires confirmation with a GH stimulation test. Oral glucose (OG) administration affects GH secretion, initially decreasing and subsequently stimulating GH secretion.
Objective. The aim of this study was to investigate the diagnostic efficacy and safety of a long OG test (LOGT) as a stimulus of GH secretion for the diagnosis of adult GH deficiency (AGHD).
Design. Prospective experimental cross-sectional study.
Settings. The study was conducted at the Endocrinology department of the University Hospital of a Coruña, Spain.
Participants and methods. We included 60 (40 women) AGHD patients (15) and controls (45) paired 1:3, of similar age, sex and BMI. The area under the curve (AUC) and peak were calculated for GH. The Mann-Whitney test was used to compare the different groups. ROC curve analyses were used. p-Values < 0.05 were considered as statistically significant.
Interventions. The intervention consisted of orally administering 75 g oral glucose administration; GH was obtained every 30 min for a total of 300 min.
Main outcome measurement. Peak GH area under receiver operating characteristic curve (ROC-AUC) following LOGT.
Results. Peak GH (μg/L) levels were lower in the AGHD patients (0.26 ± 0.09) than in the controls (4.00 ± 0.45), p < 0.001. After LOGT, with the ROC plot analysis the best peak GH cut-point was 1.0 μg/L, with 100% sensitivity, 78% specificity, ROC-AUC of 0.9089 and 81.82% accuracy. There were no relevant adverse events during any of the LOGT.
Conclusions. The LOGT could be a cheap, safe, convenient and effective test for the diagnosis of AGHD.

Keywords
GH; Glucose; Stimulation; Test

1. Introduction

Adults with growth hormone (GH) deficiency (GHD) have increased fat mass and reduced muscle mass, low energy, and reduced quality of life. Although GHD exists as a continuum of deficiency, strict diagnostic criteria exist for severe GHD in adults, which determine replacement strategies in many countries [1–3]. The diagnosis of adult GHD (AGHD) is important given that treatment of this condition, while expensive, has consistently shown improvements in body composition, exercise capacity, endothelial function, inflammatory biomarkers, bone mineral density, lipoprotein metabolism and self-reported quality of life measures [2,4–7]. Adults with a history of childhood-onset GHD or with hypothalamic/pituitary disease, surgery or irradiation to these areas, head trauma, or evidence of other pituitary hormone deficiencies are at risk for AGHD. Diagnosing AGHD is often challenging because of the lack of a single biological end-point, such as growth failure seen in children. Because the symptoms are usually nonspecific, in the absence of pan-hypopituitarism and low serum IGF-I levels the diagnosis of AGHD requires biochemical confirmation with at least one GH stimulation test [8]. The insulin tolerance test (ITT) is considered the "gold standard" test for AGHD having a sensitivity of 96% and a specificity of 92% [8]. However, because it induces hypoglycemia, the test is contraindicated in patients with coronary artery disease, seizures, and in the elderly [8]. Growth hormone releasing hormone (GHRH) combined with arginine has been endorsed by several consensus guidelines [2,3] as the main alternative when the ITT is contraindicated, having a sensitivity of 95% and a specificity of 91% [8]; but the GHRH analog (Geref Diagnostic®) has been withdrawn in the U.S. and Europe [9]. Other currently available tests such as arginine, clonidine, l-DOPA and arginine in combination with l-DOPA have much lower specificity and sensitivity in adults [8]. Recently, alternative tests, including the glucagon stimulation test (GST) have gained acceptance as the alternative to the ITT in the United States [10], however the GST has several disadvantages and is not free of side-effects [11–13]. Therefore, there is an urgent need for alternative tests to the ITT for the diagnosis of AGHD.

Adiposity is associated with decreased GH secretion [14]. The altered somatotroph function of obesity is not permanent; it can be reversed by a return to normal weight [14]. The most striking secretory capacity appeared when obese subjects were treated with GH-releasing hormone (GHRH) plus GH-Releasing Peptide-6, which resulted in a massive GH response for obese subjects [15]. In obesity, GH secretion is reduced, GH clearance is enhanced, and stimulated GH secretion is reduced, causing a false-positive result. GH stimulation tests should be avoided in obese subjects with very low pretest probability [16]. The effect of obesity on GH levels has been identified as a critical confounder for the diagnosis of GHD in overweight and obese pituitary patients [17,18]. Corneli et al. [19] determined BMI-appropriate cutoffs for the GHRH-arginine stimulation test. Any test for the diagnosis of AGHD has to take into account the critical confounding effect of obesity.

Oral glucose (OG) could be a stimulus for evaluating GH secretion [20]. There is evidence that OG administration affects GH secretion, initially decreasing and subsequently stimulating GH secretion [21,22]. In human obesity, the OG load maintains its late stimulatory effect on somatotrope secretion. However, GH secretion after OG is decreased in obese subjects [23].

The aim of this study was to investigate the diagnostic efficacy and safety of a long OG test (LOGT) as a stimulus of GH secretion for the diagnosis of AGHD.

2. Patients and methods

2.1. Patients and controls

All of the studies were conducted in accordance with the Declaration of Helsinki. The study protocol was approved by our center's ethics committee (University Hospital of A Coruña, Xunta de Galicia), and written informed consent was obtained from all patients and controls. We included a total of sixty patients and controls (forty women) in our study. Fifteen hypopituitary patients with AGHD and forty-five controls were studied. The diagnosis of adult GHD was confirmed by the presence of pituitary disease and a peak GH secretion below 3 μg/L after an insulin tolerance test (ITT), at least 12 months prior to the study. The patients were adequately treated for all pituitary hormone deficits, except for GH. The patients were on stable hormone replacement therapy for pituitary hormone deficits in the form of levothyroxine, hydrocortisone, desmopressin, and sex steroids for at least 3 months before joining the study. The adequacy of hormone replacement was assessed at the beginning of the study. None of the patients received GH therapy within 12 months prior to entering the study. The diagnoses of the patients´ pituitary diseases were nonfunctioning pituitary adenoma (n = 6), craniopharyngioma (n = 5), traumatic brain injury (n = 1), nasopharyngeal carcinoma with previous cranial radiotherapy (n = 1) idiopathic empty sella (n = 1), and hypothalamic sarcoidosis (n = 1). As a control group, we studied forty-five healthy or overweight subjects, selected from a pool of volunteers available to our unit in a 3:1 ratio. Both groups, AGHD and controls, were homogeneous in terms of their BMI. None of the controls had diabetes mellitus or other medical problems, nor were they taking any drugs.

2.2. Study procedure

Between 08.30 and 09.00 a.m., after an overnight fast and while seated, a peripheral venous line was obtained. Fifteen minutes later 75 g of oral glucose (OG) were administered. All of the studies were carried out during the first ten days from the beginning of the menstrual period. We obtained blood samples for glucose, insulin and GH at baseline (fasting) and then at 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min. Basal levels of leptin and insulin-like growth factor 1(IGF-1) were also measured. All blood samples were immediately centrifuged, separated and frozen at − 80 °C. Mid-waist circumference was measured as the midpoint between the iliac crest and the lowest rib, with the patient in the upright position. Total body fat was calculated through bioelectrical impedance analysis (BIA). We studied GH peak and area under the secretory curve (AUC). The primary endpoint was the area under the receiver operating characteristic (ROC) curve for the peak GH following long OG test (LOGT). The basis for the ROC analysis was the patient or control status of the subject. Secondary efficacy endpoints included the calculation of Youden's Index for the cutoff with maximum accuracy.

2.3. Assays and other methods

Serum samples were collected and stored at − 80 °C. Serum GH (μg/L) was measured by a solid-phase, two-site chemiluminescent enzyme immunometric assay (Immulite, EURO/DPC) with a sensitivity of 0.01 μg/L and with intra-assay coefficients of variation of 5.3%, 6.0% and 6.5% for low, medium and high plasma GH levels respectively; and with inter-assay coefficients of variation of 6.5%, 5.5% and 6.6% for low, medium and high GH levels respectively. IGF-1 (ng/mL) was determined by a chemiluminescence assay (Nichols Institute, San Clemente, CA, USA) and with intra-assay coefficients of variation of 4.8%, 5.2% and 4.4% for low, medium and high IGF-1 levels respectively; and with inter-assay coefficients of variation of 7.7%, 7.4% and 4.7% for low, medium and high plasma IGF-I levels respectively. Insulin (μU/mL) was measured with a solid-phase two-site chemiluminescent immunometric assay (Immulite 2000 Insulin, DPC, Los Angeles, CA, USA) and with intra-assay coefficients of variation of 5.5%, 3.3% and 3.7% for low, medium and high plasma insulin levels respectively; and with inter-assay coefficients of variation of 7.3%, 4.1% and 5.3% for low, medium and high plasma insulin levels respectively. Leptin (ng/mL) was measured by radioimmunoassay (Mediagnost, Tubigen, Germany) and with intra-assay and inter-assay coefficients of variation of 5.3% and 13.6% respectively. Plasma glucose (mg/dL) was measured with an

automatic glucose oxidase method (Roche Diagnostics, Mannheim, Germany). All samples from a given subject were analyzed in the same assay run.

2.4. Calculations

The area under the secretory curve (AUC) was calculated with the trapezoidal rule (0–300 min).

2.5. Statistical analysis

Quantitative variables were expressed as mean (standard error) and median (interquartile range). The Mann-Whitney test was used to compare obese and control subjects with respect to their biochemical data, hormonal records and insulin secretion and action indices.

The associations were analyzed using Spearman's Rho correlation coefficient.

ROC curves are constructed by plotting the sensitivity on the ordinate as a function of the complement of specificity for all the possible cut-off values of the diagnostic test. Each point of the ROC curves represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve (ROC AUC) represents the probability of correctly distinguishing between affected and non-affected individuals. A perfect diagnostic test has an ROC curve that passes through the upper left-hand corner (area under the curve = 1), where the true-positive fraction is 1.0 or 100% (perfect sensitivity) and the false-positive fraction is 0 (perfect specificity). Tests with an area under the curve of < 0.5 would not discriminate between affected and non- affected subjects.

Statistical analysis was carried out using the R 3.3.2 software (R Foundation for Statistical Computing, Vienna, Austria) and the Statistical Package for Social Sciences version 19.0 for Windows (IBM, Armonk, NY, USA). All statistical tests were two-sided. Only p-values < 0.05 were considered as statistically significant.

3. Results

The two groups had similar sex, age and BMI distribution as designed by the matching criteria. The age and adiposity indices (Median (interquartile ranges), mean ± SE) of the controls and AGHD/HP patients are shown in Table 1.

Table 1. Age, body mass index (BMI), waist circumference and body fat (Mean ± SE, median, interquartile ranges) in control subjects and adult GH deficiency (AGHD) patients.

	Control subjects		AGHD		p
	Mean ± SE	Median (interquartile ranges)	Mean ± SE	Median (interquartile ranges)	
Age (years)	42.89 ± 1.54	41,00 (34.5–52.0)	40,60 ± 1.79	42,00 (36.0–46.0)	0.561
BMI (kg/m^2)	29,22 ± 0.92	28,00 (24.02–33.45)	27,87 ± 1.63	25,20 (23.8–33.20)	0.357
Waist (cm)	94.09 ± 1.77	92.00 (85.0–103.5)	101.80 ± 3.46	100.00 (90.0–115.0)	0.081
Body fat (%)	33.73 ± 1.45	34.50 (26.3–42.5)	28.73 ± 2.36	27.70 (22.70–36.70)	0.096

3.1. Fasting serum levels

Fasting glucose, hormones, lipids and C-reactive protein results (Median (interquartile ranges), mean ± SE) are shown in Table 2. Fasting GH levels were lower in the AGHD group than in healthy controls; 0.16 ± 0.04 vs. 1.35 ± 0.30 for the AGHD and control group, respectively. Fasting IGF-I levels were lower in the AGHD group than in the healthy controls; 94.87 ± 14.82 vs. 137.59 ± 7.21 for the AGHD and control group, respectively. Fasting cortisol levels were lower in the AGHD group than in the healthy controls; 5.17 ± 1.46 vs. 17.99 ± 0.65 for the AGHD and control group, respectively. Fasting TSH levels were lower in the AGHD group than in the healthy controls; 0.86 ± 0.54 vs. 2.68 ± 0.29 for the AGHD and control group, respectively. Fasting C-reactive protein levels were higher in the AGHD group than in the healthy controls; 1.12 ± 0.34 vs. 0.43 ± 0.05 for the AGHD and control group, respectively.

Table 2. Biochemical and Hormonal data (Mean ± SE, median, interquartile ranges) in control subjects and adult GH deficiency (AGHD) patients.

	Control subjects		AGHD		p
	Mean ± SE	Median (interquartile ranges)	Mean ± SE	Median (interquartile ranges)	
Fasting glucose (mg/dL)	98.42 ± 2.22	96.00 (91.00–103.00)	94.20 ± 3.48	93.00 (81.0–103.0)	0.317
Fasting insulin (μIU/mL)	8.32 ± 0.96	6.60 (3.58–11.10)	19.49 ± 6.68	8.20 (2.0–23.6)	0.411
GH (μg/L)	1.35 ± 0.30	0.40 (0.06–1.78)	0.16 ± 0.04	0.10 (0.05–0.20)	**0.025**
IGF-1 (μg/L)	137.59 ± 7.21	139.0 (93.55–173.5)	94.87 ± 14.82	80.0 (60.0–97.0)	**0.004**
Cortisol (μg/dL)	17.99 ± 0.65	17.80 (15.2–20.65)	5.17 ± 1.46	2.20 (1.20–10.20)	< **0.001**
Free T4 (ng/dL)	1.14 ± 0.03	1.20 (1.00–1.20)	1.13 ± 0.06	1.15 (0.98–1.33)	0.973
TSH (μU/mL)	2.68 ± 0.29	2.39 (1.59–3.34)	0.86 ± 0.54	0.07 (0.01–0.96)	**0.001**
Leptin (ng/mL)	31.82 ± 4.21	22.80 (12.45–45.10)	20.49 ± 6.16	12.35 (5.68–30.98)	0.078
Triglycerides (mg/dL)	132.09 ± 24.48	86.00(66.50–150.50)	134.8 ± 29.97	96.0 (64.0–217.0)	0.838
Total-cholesterol (mg/dL)	201.93 ± 5.55	195.0 (173.50–229.5)	209.0 ± 5.48	211.0 (185.0–227.0)	0.365
LDL-cholesterol (mg/dL)	124.88 ± 5.27	122.0 (95.0–155.0)	128.33 ± 7.00	131.0 (108.0–149.0)	0.484
HDL-cholesterol (mg/dL)	56.53 ± 2.27	54.0 (46.0–66.50)	55.6 ± 5.24	52.0 (42.0–57.0)	**0.602**
C-reactive protein (mg/dL)	0.43 ± 0.05	0.29 (0.18–0.58)	1.12 ± 0.34	0.58 (0.30–1.22)	**0.014**

3.2. Serum levels after oral glucose

The post-oral glucose serum GH, glucose and insulin levels (Median (interquartile ranges), mean ± SE) are presented in Table 3.

Table 3. After oral glucose GH, glucose and insulin secretion (Mean ± SE, median, interquartile ranges) in control subjects and adult GH deficiency (AGHD) patients. $AUC_{0–300}$, area under the secretory curve between 0 and 300 min.

	Control subjects		AGHD		p
	Mean (SE)	Median (interquartile ranges)	Mean (SE)	Median (interquartile ranges)	
Peak GH (μg/L)	4.00 ± 0.45	3.88 (1.74–6.04)	0.26 ± 0.09	0.10 (0.05–0.48)	< **0.001**
$AUC_{0–300}$ GH (μg/L·min)	298.13 ± 34.42	259.35 (101.8–409.1)	42.64 ± 14.74	21.70 (15.0–63.4)	< **0.001**
Peak glucose (mg/dL)	175.42 ± 7.14	174.00 (135.0–202.0)	170.5 ± 15.00	155.5 (126.0–221.5)	0.844
$AUC_{0–300}$ glucose (mg/dL·min)	32,423.3 ± 1361.12	31,605.0 (28,342.5–34,912.5)	34,225.0 ± 3552.85	31,605.0 (26,268.8–39,017.5)	0.844
Peak insulin (μU/mL)	86.84 ± 8.23	65.40 (49.4–114.5)	123.2 ± 18.31	119.5 (86.8–185.5)	0.074
$AUC_{0–300}$ insulin (μU/mL·min)	10,422.4 ± 925.01	8892.0 (6569.4–13,152.8)	50,859.5 ± 33,953.33	16,829.4 (8566.3–33,163.5)	**0.026**

GH was lower in the AGHD patients than in the healthy control group after the LOGT (Table 3 and Fig. 1).

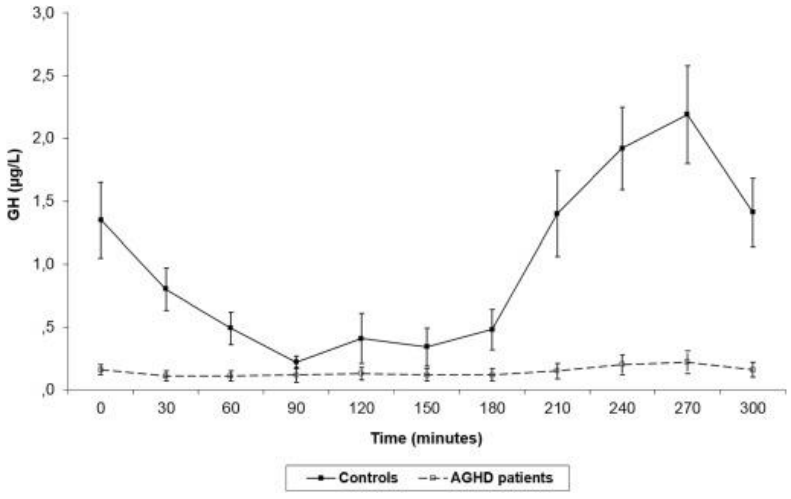

Fig. 1. Mean ± SE plasma GH (μg/L) in control subjects and adult GH deficiency (AGHD) patients during the prolonged oral glucose tolerance test.

The AUC of GH (μg/L·min) between 0 and 300 min was lower in the AGHD patients than in the controls; 42.64 ± 14.74 vs. 298.13 ± 34.42, for the AGHD patients and controls respectively (Table 3). Peak GH (μg/L) levels were lower in the AGHD patients than in the healthy controls, 0.26 ± 0.09 vs. 4.00 ± 0.45, for the AGHD patients and healthy controls respectively (Fig. 2).

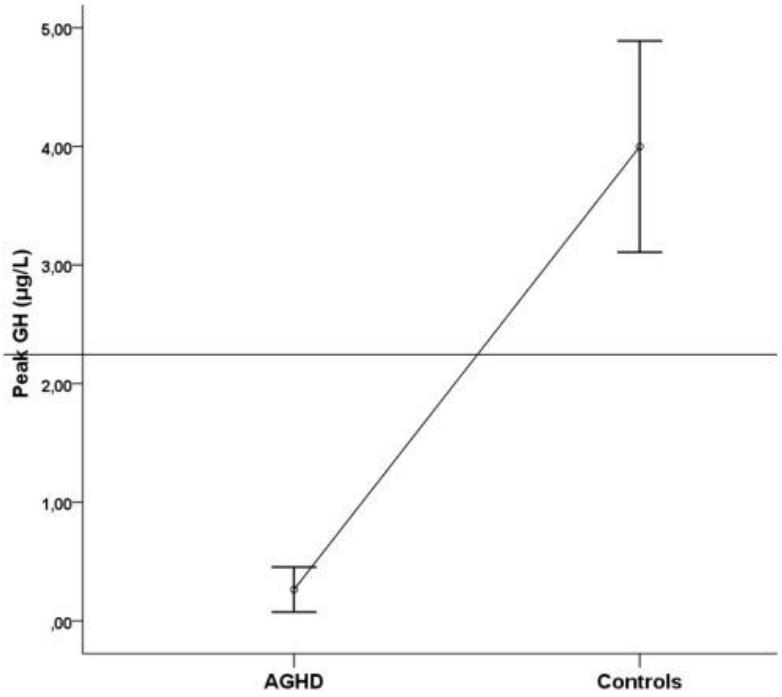

Fig. 2. Peak GH (Mean ± SE) in control subjects and adult GH deficiency (AGHD) patients.

3.3. Correlations

There were significant negative correlations between peak GH secretion and waist circumference in the control group; Rho = − 0.331, p = 0.027, and a borderline significant negative correlation between peak GH secretion and BMI in the control group; Rho = − 0.268, p = 0.075. No correlation was found in the AGHD patients.

3.4. Receiver operating curve (ROC) analysis

With the ROC plot analysis for the entire group the best peak GH cut-off point was 1.0 μg/L, with 100% sensitivity, 78% specificity, ROC AUC of 0.9089 and 81.82% accuracy (Fig. 3).When BMI-specific cut-off points were used on subgroup analyses, the ROC analysis improved slightly. In the lean population the best pair of values for the highest sensitivity, 100.0%, and the highest specificity, 84.0%, was found using a peak GH cut-off point of 1.3 μg/L, ROC AUC 0.9200, with a good accuracy as 87.1%. In the obese population the best pair of values for the highest sensitivity, 100.0%, and the highest specificity, 75.0%, were found using a peak GH cut-off point of 0.7 μg/L, ROC AUC 0.9000, with a good accuracy of 79.17%.

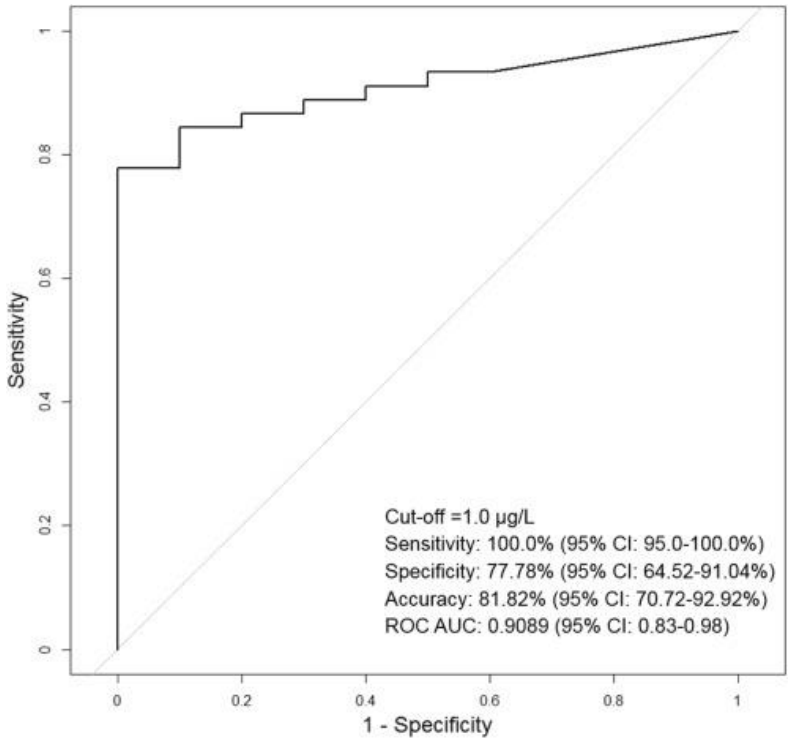

Fig. 3. ROC curves for peak GH responses to the long oral glucose test in the entire group of control subjects and adult GH deficiency (AGHD) patients.

3.5. LOGT side effects

There were no serious adverse events requiring medical intervention during any of the 60 OG tests. Nausea was the most common side effect in 5 (8%) subjects out of the whole group. None of the subjects vomited. There were no instances of symptomatic hypoglycemia or hypotension.

4. Discussion

The main result of this study is that we have found that after the LOGT and with ROC plot analysis we obtained a peak GH cut-off point of 1.0 µg/L for the diagnosis of AGHD, with 100% sensitivity, 78% specificity and 81.82% accuracy. The present study suggests that LOGT is both safe and accurate in diagnosing AGHD. The peak GH response after LOGT makes it possible to establish the diagnosis of AGHD with good sensitivity and specificity. Furthermore, this test was well tolerated by the patients, and does not require parenteral administration.

There are many pharmacological GH stimulation tests for the diagnosis of AGHD; however, none of them fulfill the requirements for an ideal test having high discriminatory power; being reproducible, safe, convenient, and economical; and not being dependent on confounding factors such as age, gender and nutritional status [16]. Although the ITT is considered as the standard reference test for diagnosing AGHD, alternative tests are needed, because this test is often contraindicated due to the risks associated with hypoglycemia. In addition, performing an ITT may be challenging in some settings since it requires trained personnel, monitored facilities and other resources that may not be available to every clinician [9]. The arginine-GHRH test had emerged as the best alternative, but unfortunately Geref Diagnostic® was removed from the U.S. and Europe [8]. In recent years different new tests have been evaluated. Garcia et al. have found that oral macimorelin is safe, convenient and effective in diagnosing AGHD with a comparable accuracy to the arginine-GHRH

test [24]. The main limitation of this test is that a new drug has to be administered, which is largely unavailable, and the absence of large-scale studies. Gasco et al. [25] have found that testing with acylated ghrelin is a reliable diagnostic tool for the diagnosis of AGHD, in lean and overweight subjects, if appropriate cut-off limits are assumed, but obesity strongly reduces GH response to ghrelin and the diagnostic reliability of the test. Interestingly Hawkes et al. [26] have found that some children will not have a sufficient GH response to pharmacological stimuli but will have a robust response to intravenous line placement. In the US trends in GH stimulation testing in AGHD patients has been carried out with the Answer program [10]. The most commonly used GH stimulation test was arginine + l-DOPA (27%; mostly a single center) and glucagon (25%; most frequent test after 2009). The glucagon stimulation test (GST) has gained acceptance as the alternative to the ITT in the United States [10]. Most prior studies that examine the diagnostic use of the GST for AGHD either omit BMI information or only include controls with normal BMI [8,11,27,28]. Several recent studies have also questioned the diagnostic accuracy of the GST when the GH cut-off point of 3 μg/L is used in obese/overweight adults [29,30]. The advantages of the GST are its reproducibility, safety, and lack of influence by gender and hypothalamic GHD [9], whereas its disadvantages include the lengthy duration of the test (3–4 h), and the fact that an intramuscular injection is required that may not appeal to some patients. Commonly reported side-effects include nausea, vomiting, and headaches ranging from < 10% [11] to 34% [12]. The side effects of the GST seem to be more pronounced in elderly subjects, where severe symptomatic hypotension, hypoglycemia and seizures have been reported [13]. We believe that in addition to the GST the LOGT could be a reliable alternative to the ITT. The LOGT presents several advantages over other current alternatives such as the GST or the macimorelin test. The specific advantages of this new test are that no preparation is required, it is not associated with vomiting or symptomatic hypoglycemia, the stimulus is administered orally, and it is a nutrient, not a drug. Due to its high sensitivity the LOGT could be used in a two-step approach; if there is an adequate response to the LOGT, the AGHD can be excluded, and it will only be necessary to carry out a second, more cumbersome test like the ITT in the few patients with a high suspicion of GHD with an inadequate response to the LOGT. In addition, the LOGT could simultaneously determine the glucose tolerance status.

Obesity is the most important confounding factor for the diagnosis of AGHD. National data on obesity prevalence among U.S. adults show that more than one-third are obese [31], with similar, although slightly lower, results in Europe [32] and worldwide [33]. Hormone deficiencies, glucocorticoid replacement, and hypothalamic damage may all be potential contributors to obesity in patients with pituitary conditions. In fact, it has been found that the mean BMI of 349 consecutive patients who underwent a GST at two institutions was in the obese range at 32 kg/m^2[29]. Obesity has been shown to be a state of relative GH deficiency [15,34]. Physiological studies have demonstrated reduced GH half-life and fewer GH pulses, longer intervals between GH pulses, and one-quarter of the GH production of normal-weight men. Free fatty acids have been implicated in the pathophysiology of this relative GH deficiency in obesity [35]. Insulin resistance may also be a mechanism of reduced GH levels in obesity, although the published data are somewhat contradictory [36]. Iranmanesh et al. [34] demonstrated that each BMI unit increase was associated with a 6% decrement in the rate of daily GH secretion within each age tertile. The Veldhuis group studied GH secretion during 6 h after OG in men [20]. They found that glucose-suppressed nadir GH concentrations and post glucose rebound-like peak GH release in men are strongly determined by selective metabolic surrogates, especially including adipose visceral fat, adiponectin, leptin and sex hormone binding globulin. Recent data have suggested that an important contributor to rebound GH secretion after glucose ingestion is delayed endogenous ghrelin drive under waning somatostatin restraint [22]. These data confirm that BMI should be considered when testing pituitary patients for AGHD in the clinical setting. Prior studies have reported decreased peak GH levels on GHRH-arginine testing with increasing BMI, which has resulted in the establishment of BMI-specific cutoffs for this test in the diagnosis of GH deficiency in pituitary patients [19]. Biller et al. [8] noted a 1.4-ng/mL decrease in peak GH level for every 1 kg/m^2 BMI in a control population. A few studies have addressed the impact of increasing BMI on GST results, including Gomez et al. [37] and Yuen et al. [30]. Dichtel et al. [29] have found that a large proportion of healthy overweight/obese individuals (45%) failed the GST using the standard 3 ng/mL GH cutoff. A 1-ng/mL GH cutoff may reduce the overdiagnosis of AGHD in overweight/obese patients. Similar results have been found by Hamrahian et al. [38] in a group of patients with pituitary disease and sex, age and BMI matched controls. The American Association of Clinical Endocrinologists and the American College of Endocrinology [39]

have proposed that in order to reduce overdiagnosing AGHD in overweight/obese patients with the GST, a lower GH cut-off point of 1 μg/L should be used in these subjects. However, this lower GH cut-point still requires further evaluation for diagnostic accuracy in larger patient populations with varying BMIs. In the present study, our control and AGHD patients were specifically BMI-matched in order to avoid the confounding effect of obesity.

The limitations of our study include the relatively small sample size, which did not allow for the stratification of BMI subgroups (overweight vs. obese) in the analysis. Also, the limited number of patients did not allow for a cause-specific (hypothalamic vs. pituitary) analysis of the data or for further analyses based on other patient features (i.e., hormone deficiencies number). Subjects with diabetes, renal or hepatic dysfunction also were also excluded from the control group. Further studies including a larger number of these patients will be needed in order to determine the sensitivity and specificity of this test in these scenarios. The GH cut-off point was developed using the Immulite EURO/DPC assay, and may not be generalized to other GH assays due to inter-assay variation [40]. Additionally, we were not able to assess the reproducibility of the LOGT, as the test was only performed once per subject. There are several strengths to our study. AGHD was confirmed in the patients with the "gold standard" ITT test. The study was prospective with the use of BMI-, sex- and age-matched controls to decrease the chances of misclassifying individuals due to variability in these variables. Remarkably, our control group was BMI-matched. ROC analysis was used to calculate the GH cut-off points. The same laboratory was utilized to measure GH levels. Obese controls were included in the analysis.

In conclusion, this study shows that LOGT is safe and effective in diagnosing GH deficiency in adults, with a comparable sensitivity and specificity to other provocative tests. This novel oral test could be a safe, rapid, convenient and cheap alternative, especially for patients for whom ITT is contraindicated in establishing the diagnosis of AGHD that could be performed in most outpatient settings.

Disclosure

The authors have nothing to disclose related with this article.

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