CLINICAL STUDY

The effect of body mass index on the diagnosis of GH deficiency in patients at risk due to a pituitary insult

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Abstract

Objectives: Diminished GH response to stimulation has been demonstrated in obesity, leading to erroneous diagnosis of GH deficiency. The aim of this study was to evaluate the influence of body mass index (BMI) on GH responsiveness in patients at risk for pituitary function deficits.

Methods: A total of 59 healthy subjects and 75 patients with a pituitary insult underwent insulin tolerance test or pyridostigmine + GHRH test in order to assess GH secretory reserve. Normal subjects and patients were classified as normal weight (BMI < 24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese (BMI > 30 kg/m²).

Results: All normal individuals with BMI < 24.9 kg/m² demonstrated adequate GH responses, while three of the 21 overweight (14.3%) and nine of the 28 obese subjects (32.1%) did not respond to GH stimulation. Among patients, four of 14 (28.6%) with BMI < 24.9 kg/m², 18 of 22 (81.8%) who were overweight, and 28 of 39 (71.7%) who were obese did not respond to GH stimulation. Of the 46 nonresponder patients with increased BMI, nine (19.6%) had normal insulin-like growth factor 1 (IGF1) values and no other pituitary hormone deficits, raising questions about the accuracy of somatotroph function assessment, while all nonresponders with BMI < 24.9 kg/m² had low IGF1 values and panhypopituitarism.

Conclusions: Our results indicate that BMI > 25 kg/m² has a negative effect on GH response not only in normal healthy subjects but also in patients at risk for pituitary function deficit as well. Parameters such as IGF1 levels and anterior pituitary deficits should be taken into account to accurately assess GH status in these patients.

European Journal of Endocrinology 162 29–35

Introduction

The impact of obesity on GH spontaneous secretion and secretory response to several stimulation tests is well known (1–3). Low GH response to insulin tolerance test (ITT), to GHRH, and to combined arginine + GHRH test (4–6) has been reported. This GH unresponsiveness seems to be functional as it is reversible after weight loss (4–7). Recently, different cut-off GH values according to body mass index (BMI) have been proposed for GHRH + L-arginine test to increase its specificity (8).

The pathogenesis of the phenomenon remains unclear and seems to be multifactorial. Increased hypothalamic somatostatinergic tone, GHRH hypoactivity, and elevated circulating free fatty acids (9, 10) have been implicated. Clinical data support an important role of insulin in obesity-associated GH suppression (11, 12). Pituitary expresses the insulin receptor, and high circulating insulin levels can directly contribute to the suppression of GH synthesis and release in the obese state (13). Reduced dopaminergic neuronal signaling

might also be involved in the pathogenesis of obesity-associated hyposomatotropism (14). Furthermore, the capacity of the kidney to remove GH is affected in obesity, and may in part contribute to decreased GH concentrations (15).

Contrary to GH deficiency (GHD) in children, where low growth velocity is a very characteristic clinical sign, in adults with GHD, specific signs and symptoms are lacking, and the diagnosis is exclusively based on GH response to provocative tests (2, 3). Thus, the diagnosis of GHD in subjects with increased BMI is a challenging task. Although recent data suggest that the evoked GH response in the presence of even a mild BMI elevation does not accurately distinguish normal subjects from GH-deficient subjects (6, 16–18) in the current practice, BMI is not considered in the cut-off points of GH response used in the diagnosis of GHD when patients at high risk for pituitary hormone deficiencies are evaluated (2). Therefore, it is possible that an abnormal GH response in these patients due to adiposity excess will lead to a false diagnosis of GHD and initiation of GH

treatment due to adiposity excess. The aim of our study was to investigate the influence of BMI on evoked GH responsiveness in patients with potential anterior pituitary dysfunction due to diseases (such as pituitary tumors and infiltrative diseases) or therapeutic interventions (transsphenoidal surgery and irradiation) to the hypothalamic–pituitary area, which might harm the anterior pituitary function.

Subjects and methods

Study population

A total of 134 subjects participated in this study. Fifty-nine of them were healthy volunteers (43 females and 16 males, mean age: 53.3 ± 1.7 years, age range: 15–76 years, median: 56 years, BMI: 29.5 ± 0.7 kg/m²). Hormonal abnormalities were excluded by history, physical examination, and measurement of basal hormone levels. No subject suffered from any medical condition (i.e. diabetes mellitus, and liver, renal, or mental diseases) or was under medication known to affect the GH/insulin-like growth factor 1 (IGF1) axis. Seventy-five patients (39 females and 36 males, mean age: 48.9 ± 1.7 years, age range: 18–75 years, median: 51 years, BMI: 29.7 ± 0.7 kg/m²) who presented to our clinical investigation unit for pituitary function assessment after various diseases and therapeutic manipulations that were potentially harmful for the anterior pituitary (Table 1) were also recruited in the study. All were under stable hormone replacement therapy, other than GH, when needed, for at least 6 months before recruitment. More specifically, thyrotrophs deficiency was replaced with thyroxine (T₄) in an appropriate dose to achieve normal free T₄ levels (usually 75–100 µg daily per os), corticotrophs deficiency was replaced with hydrocortisone 20–30 mg daily divided into two to three doses according to serum cortisol levels 2 h post administration and to patients' well-being.

Table 1 Primary diagnosis in patients with a pituitary insult.

	Responders	Nonresponders
Craniopharyngioma	2	5
Gonadotropinoma	1	
Hypophysitis		2
Idiopathic hypopituitarism		5
Infiltrative pituitary disease		1
NFPA	4	10
Pituitary apoplexy		1
Post radiation-induced hypopituitarism	2	2
Post TSS-induced hypopituitarisms	10	16
Prolactinoma	5	4
PROP-1 defect		1
Rathke's cyst	1	1
Sheehan's syndrome		2

NFPA, nonfunctioning pituitary adenoma; TSS, transsphenoidal surgery.

Gonadotrophs deficiency was replaced in males with testosterone enanthate 250 mg i.m. every 20–30 days to achieve normal testosterone levels the day of the next administration and in females with estradiol hemihydrate + norethisterone acetate (HRT). Both patients and controls were on unrestricted diet, and without any significant change in body weight for at least 1 month before the study. All subjects were classified by their BMI as follows: normal weight BMI <24.9 kg/m²; overweight BMI 25–29.9 kg/m²; obese BMI >30 kg/m².

GH reserve was assessed by the ITT or the combined pyridostigmine (PD)+GHRH (PD+GHRH) test as an alternative when ITT was contraindicated (history of coronary heart disease or seizures). Among the 59 normal subjects, 27 underwent the ITT (five with normal weight, nine overweight, and 13 obese), and 32 (five with normal weight, 12 overweight, and 15 obese) underwent the PD+GHRH test. Among the 75 patients, 40 underwent the ITT (eight with normal weight, 12 overweight, and 20 obese), and 35 (six normal weight, 10 overweight, and 19 obese) underwent the PD+GHRH test. After an overnight fast, an indwelling catheter was inserted in all subjects into a vein in the antecubital fossa at 0800 h with the subjects remaining supine during the whole study period. For the ITT protocol, 0.1 U/kg human regular insulin was administered as an i.v. bolus at time 0 to induce a fall in the blood glucose level to 40 mg/dl or less. An additional 0.025 U/kg insulin was given if the glucose level did not reach the goal which was equal to or <40 mg/dl within 30 min, or if the subjects did not demonstrate hypoglycemic symptoms. Blood was drawn at 0 min to obtain the baseline GH, and at 30, 60, 90, and 120 min. Mean glucose nadir levels were similar for normal subjects and patients (19.4 ± 4.8 and 23.6 ± 8.1 mg/dl for patients). Despite the weight-adjusted insulin dose, a positive correlation was noted between BMI and the level of hypoglycemia both in normal subjects ($r=0.57$, $P=0.005$) and in patients with a pituitary insult ($r=0.61$, $P=0.005$). For the PD+GHRH test, 120 mg PD (Mestinon ICN Iberica, Barcelona, Spain) at 0800 h (–60 min) and 100 µg GHRH (Geref, Serono SA) at 0900 h (0 min) were given as an i.v. bolus injection. Blood samples for GH measurements were obtained at –60, 0, 15, 30, 45, 60, and 90 min. At the baseline, sample IGF1 was also measured. No side effects were reported during the study period or for the rest of the day.

The study was approved by the ethical committee of our institution, and informed consent was obtained from all patients.

Hormone measurements

Samples were collected and centrifuged, and serum was stored in aliquots at –20 °C until assayed. Serum GH concentrations were determined using a commercially available IRMA kit (CIS Bio International,

Gif-sur-Yvette, France). The detection limit was 0.04 µg/l. The intraassay coefficient of variations (CV) were 2.4 and 2.8% at concentrations of 3.5 and 17 µg/l respectively. Serum IGF1 was measured using a commercially available RIA kit (Mediagnost, Reutlingen, Germany). The detection limit was 0.1 µg/l. The intraassay CV was 7.4%.

The diagnostic cut-off point for adult GHD was a GH response of <3 µg/l following the ITT (2). For the PD+GHRH test, a GH response of <12.8 µg/l was considered indicative of GHD as this cut-off value was defined by Hoeck *et al.* (19) using the same GH IRMA assay that was used in our study.

Statistical analysis

Variables were expressed throughout as mean $\pm$ S.E.M., except where noted otherwise. The statistical analysis was performed by the SPSS for Windows statistical package (version 10.0; SPSS, Inc., Chicago, IL, USA). Statistical analysis to identify differences between two groups was performed by *t*-test, Mann–Whitney rank sum test when data distribution was not normal, or by χ^2 test. For multiple comparisons, one-way ANOVA was used, followed by Student–Newman–Keuls test or one-way ANOVA on ranks followed by Dunn's method (when data distribution was not normal). Pearson's correlation or Spearman rank order (when data's distribution was not normal) and linear regression were also used. Logistic regression was used to identify factors that had a significant effect on GH responsiveness. The odds ratio of an event is defined as the ratio of the probability that an event occurs to the probability that it fails to occur. The odds ratio indicating the effect of one unit change in each factor was calculated. The level of significance was set at 0.05 for all statistical tests.

Results

GH response in normal subjects

Individual GH_{max} responses during ITT and PD+GHRH test according to BMI are shown in Fig. 1. Normal weight subjects exhibited higher GH_{max} levels than overweight and obese subjects during the ITT (16.5 ± 1.4 , median 14.8, range 21.0–13.0 vs 10.7 ± 1.2 , median 11.6, range 14.1–2.1 and 7.5 ± 1.2 , median 9.1, range 13.0–2.3 µg/l, $P < 0.05$ respectively) and than obese subjects (64.7 ± 21.9 , median 42.9, range 142.0–18.3 vs 15.8 ± 2.1 , median 15.9, range 37.9–5 µg/l, $P < 0.05$) during the PD+GHRH test (Table 2).

Forty-seven of the normal subjects in this study demonstrated normal GH response, but 12 of them did not respond to GH stimulation testing. The percentage of responders was significantly higher in the normal weight group than in the overweight (100 vs 85.7%,

Figure 1 Individual GH_{max} levels in normal weight (N/w), overweight (O/w), and obese normal subjects (NS) or patients (P) during (A) PD+GHRH test and (B) ITT. Horizontal solid lines denote the median of GH_{max} levels for each group, and horizontal lines indicate cut-off values for normal GH response: 12.8 µg/l for PD+GHRH (A) and 3 µg/l for ITT (B).

$P = 0.049$) and the obese groups (100 vs 67.9%, $P = 0.029$, Table 3). As shown in Table 3, among the nonresponders in this group, three subjects were overweight and nine were obese, while all subjects with normal BMI exhibited normal GH response. Overall, three of the 21 overweight subjects (14.3%) and nine of the 28 obese subjects (32.1%) did not respond to GH stimulation. Statistical analysis also revealed that responders were significantly younger, and had lower BMI than those who did not respond to GH stimulation (age: 50.9 ± 1.9 vs 63.1 ± 2.4 years, $P = 0.001$, and BMI: 28.5 ± 0.8 vs 32.9 ± 1.3 kg/m², $P = 0.0095$, Table 4). No difference in weight and waist/hip ratio was noted between responders and nonresponders.

Table 2 Peak GH responses during insulin tolerance test (ITT) and pyridostigmine (PD)+GHRH test in normal subjects and patients.

BMI (kg/m ²)	ITT			PD + GHRH test		
	<24.9	25–29.9	>30	<24.9	25–29.9	>30
Normal subjects (<i>n</i> =59)						
Mean GH _{max} ± S.E.M.	16.5 ± 1.4	10.7 ± 1.2*	7.5 ± 1.2*	64.7 ± 21.9	24.3 ± 4.3	15.8 ± 2.1*
Median	14.8	11.6	9.1	42.9	20.5	15.9
Range	21.0–13.0	14.1–2.1	13.0–2.3	142.0–18.3	64.0–9.0	37.9–5.0
<i>n</i>	5	9	13	5	12	15
Patients (<i>n</i> =75)						
Mean GH _{max} ± S.E.M.	8.6 ± 2.2	2.9 ± 1.7	3.7 ± 1.0	23.8 ± 6.8	9.7 ± 2.3	5.3 ± 1.2*
Median	8.4	1.3	1.9	25.6	6.1	4.1
Range	18.0–0.5	21.4–0.1	17.0–0.1	48.0–4.1	22.0–3.3	18.0–0.1
<i>n</i>	8	12	20	6	10	19

*Statistical significant difference ($P < 0.05$) from normal weight subjects within the same group.

A statistically significant negative correlation was found between GH_{max} response to ITT and BMI ($r = -0.52$, $P = 0.0059$) and GH_{max} response to PD + GHRH test and BMI ($r = -0.64$, $P = 0.0001$). Logistic regression analysis showed that both age and BMI are important factors for determining the responsiveness of GH to stimulation in normal subjects. More specifically, the odds ratio for age was 0.85 ($P = 0.006$, 95% confidence interval (CI): 0.76–0.95); thus, the odds for a positive response decreased by 15% with each year of age. The odds ratio for BMI was 0.80 ($P = 0.012$, 95% CI: 0.67–0.95); the odds for a positive response decreased by 20% with each increase in one unit in BMI.

GH response in patients with a pituitary insult

Individual GH_{max} responses in patients with a pituitary insult during ITT and PD + GHRH test according to BMI are shown in Fig. 1. Statistical analysis revealed that GH_{max} levels during PD + GHRH test were significantly lower in obese patients than in normal weight patients (23.8 ± 6.8 median 26.6, range 48.0–4.1 vs 5.3 ± 1.2 , median 4.1, range 18.0–0.1 µg/L, $P < 0.05$, Table 2).

Of the 75 patients at risk for GHD due to a pituitary insult in the past, 50 did not respond to GH stimulation testing. The percentage of responders was significantly higher in the normal weight patients than in the overweight (71.4 vs 18.2%, $P = 0.002$) and the obese patients (71.4 vs 28.3%, $P = 0.01$; Table 3). The

percentage of responders was significantly higher in overweight and obese normal subjects than in patients within the same BMI group (85.7 vs 18.2%, $P = 0.000$ in the overweight subjects and 67.9 vs 28.3%, $P = 0.004$ respectively). No statistically significant difference in age, weight, waist/hip ratio, and BMI was noted between responders and nonresponders (Table 4). Furthermore, no correlation was found between age or BMI and GH_{max}, and logistic regression analysis revealed that neither age nor BMI was a significant determining factor for GH responsiveness.

As expected, no responders had a higher probability to receive hormone replacement treatment. Thus, three among the responders were on HRT replacement, and four on testosterone, while among the non-responders 33 patients received T₄, 37 hydrocortisone, eight HRT, and five testosterone, usually in a combination depending on the extent of the anterior pituitary deficit.

In order to validate the probability for GHD in this cohort, we considered age-adjusted IGF1 levels and anterior pituitary function. Of the 25 patients with normal GH response, 10 had a normal BMI, four were obese and 11 were overweight (Table 3). All patients in this group had no other pituitary hormone deficiencies and demonstrated normal age-adjusted IGF1 levels. Among the nonresponder patients ($n = 50$), four patients had normal BMI, while 18 were overweight and 28 were obese (Table 3). All nonresponder patients with normal BMI exhibited low age-adjusted IGF1 levels

Table 3 Effect of body mass index (BMI) in GH response of normal subjects and patients.

BMI (kg/m ²)	<24.9		25–29.9		>30	
	<i>n</i> (%)	<i>P</i>	<i>n</i> (%)	<i>P</i>	<i>n</i> (%)	<i>P</i>
Normal subjects (<i>n</i> =59)						
Responders (<i>n</i> =47)	10 (100%)	0.053 ^a	18 (85.7%)	0.049 ^b /0.000 ^a	19 (67.9%)	0.029 ^b /0.004 ^a
Nonresponders (<i>n</i> =12)			3 (14.3%)		9 (32.1%)	
Patients (<i>n</i> =75)						
Responders (<i>n</i> =25)	10 (71.4%)		4 (18.2%)	0.002 ^b	11 (28.3%)	0.01 ^b
Nonresponders (<i>n</i> =50)	4 (28.6%)		18 (81.8%)		28 (71.7%)	

^aCompared to patients within the same BMI group.

^bCompared to normal weight (BMI <24.9 kg/m²) within the normal subjects or the patients group.

Table 4 Somatometric data of normal subjects and patients with a pituitary insult.

	Normal subjects		Patients	
	Responders	Nonresponders	Responders	Nonresponders
Age (years)	50.9 ± 1.9	63.1 ± 2.4*	45.9 ± 3.4	50.4 ± 1.9
BMI (kg/m ²)	28.5 ± 0.8	32.9 ± 1.3*	28.5 ± 1.3	30.3 ± 0.8
Weight (kg)	73.2 ± 2.3	83.3 ± 3.8	77 ± 4.1	82 ± 2.80
W/H	0.9 ± 0.01	0.96 ± 0.08	0.88 ± 0.02	0.95 ± 0.01

*Statistically significant difference from responders, $P < 0.05$.

and had more than three anterior pituitary hormone deficiencies. On the contrary, nine of the 46 non-responder patients (19.6%) with increased BMI (three overweight, 16.7%, and six obese, 21.4%) had no other pituitary hormone deficiencies and had normal age-adjusted IGF1 levels.

To further examine the effect of BMI on the GH response in patients with a pituitary insult, we classified them using the BMI-stratified GH_{max} range of the normal subjects (Table 2). Thus, for the ITT the cut-off GH_{max} levels were defined to 13.0, 2.1, and 2.3 µg/l for normal weight, overweight, and obese subjects respectively (Fig. 1 and Table 2). With this approach, five normal weight, ten overweight, and ten obese patients exhibited GH_{max} below the cut-off limit. From this cohort, one patient with normal weight (GH_{max} 9.2 µg/l), two overweight patients, and three obese patients had no other pituitary hormone deficiencies and normal age-adjusted IGF1 levels. For the PD + GHRH test, the cut-off GH levels were defined as 18.3, 9.0, and 5.0 µg/l for normal weight, overweight and obese subjects respectively (Fig. 1 and Table 2). With this approach, two normal weight, seven overweight, and 16 obese patients exhibited GH_{max} below the cut-off limit. From this cohort, one overweight patient and three obese patients had no other pituitary hormone deficiencies and normal age-adjusted IGF1 levels. Overall, 10 of the 50 (20%) patients did not reach the BMI GH_{max} for the respective provocative test.

Discussion

Previous studies have shown that subjects with an increased BMI demonstrate a decreased GH response to stimulation tests (4–6, 20–22), which is at least partially restored with weight loss (5, 7). In addition, it has been reported that GH response is negatively correlated with indices of central adiposity (20, 22). Interestingly, there is a controversy in the published literature on the degree of adiposity above which GH under-responsiveness becomes apparent. While some (6, 8, 18, 22) have demonstrated that GH response is suppressed even in subjects with a mildly elevated BMI, others have shown that BMI < 35 kg/m² has no effect (21). We have shown in the present study that 14.3% of the overweight subjects and 32.1% of the

obese normal subjects did not respond to GH stimulation in accordance with the reports (6, 18, 22) that even a mildly elevated BMI has a negative effect on GH response.

However, in clinical practice the real diagnostic challenge appears in the assessment of the GH status in overweight or obese individuals at risk for GHD due to diseases or therapeutic modalities of the hypothalamic–pituitary area (6). In the present study, we have provided evidence that increased BMI may affect GH responsiveness not only in healthy subjects but also in the above-mentioned patients as well. To assess more accurately GH status in these patients, in our present study we considered not only GH provocative testing results but also the age-adjusted IGF1 levels and the co-existence of other anterior pituitary hormone deficiencies. Low IGF1 is the most specific marker of GHD (23), but normal values do not exclude the diagnosis of GHD, as a significant overlap of IGF1 levels between normal subjects and GHD patients has been noted (24). However, the development of percentiles of IGF1 s.d. scores, above which the likelihood of GHD is very low (25), enables us to use a normal age-adjusted IGF1 together with the lack of other pituitary hormone deficits to safely exclude GHD in our patients. The presence of other pituitary hormone deficiencies, especially in the presence of low IGF1, has been demonstrated to increase the probability of GHD (26, 27). Very recently, Gibney *et al.* have demonstrated that GH reserve can be accurately and cost-effectively investigated using age-adjusted IGF1 s.d. scores and the presence of other pituitary hormone deficiencies in ~50% of patients with organic pituitary disorders (28).

Our patients with normal BMI who did not respond to GH provocative testing exhibited low age-adjusted IGF1 levels and panhypopituitarism, validating thus the diagnosis of GHD. However, 16.7% of the overweight nonresponders and 21.4% of our obese nonresponders had no other pituitary hormone deficiencies and normal age-adjusted IGF1 levels, raising questions about the accuracy of diagnosis of GHD in these two groups of patients. Thus, GH stimulation in patients with a history of insult in the hypothalamic–pituitary area and increased BMI does not accurately distinguish normal response from inadequate response, and may result in the erroneous classification of overweight and obese patients as GH deficient, requiring thus GH

replacement. It is well known that GHD precedes deficiency of other pituitary hormones in patients in whom pituitary dysfunction emerges over years, as in the case of patients after radiotherapy (29). Interestingly, none of the nine nonresponder patients in our study with increased BMI, normal IGF1, and anterior pituitary function had a history of pituitary irradiation, and thus the possibility that GHD could be the first and only anterior pituitary deficiency in this cohort is rather unlikely (29).

Most of the investigators who have attempted to study the influence of BMI on GH responsiveness have studied only normal subjects (6, 18, 20, 22). On the contrary, in studies on hypopituitary patients, the BMI effect on GH dynamic testing is not considered (16, 21). In a variable percentage of patients in these studies, abnormal BMI ($> 25 \text{ kg/m}^2$) is reported and thus their results should be interpreted with caution. Kelestimur *et al.* (21) have used the GHRH+GHRP-6 test in 366 controls and 176 GHD patients with different degrees of hypopituitarism, and demonstrated that the cut-off value of this test has to be diminished for the controls with BMI $> 35 \text{ kg/m}^2$. However, they did not question whether among the 50 patients with BMI $> 30 \text{ kg/m}^2$ some were falsely classified as GHD due to their increased BMI. More recently, Murray *et al.* (30) have evaluated the GH status in 54 patients with a putative insult to the hypothalamic–pituitary axis. Although they did not consider the degree of adiposity to classify their patients as severely or partially GH deficient, they had noted that GH peak is negatively correlated with body fat mass, and they concluded that obesity is potentially a major confounder for an accurate diagnosis. Interestingly, 33 of their 54 patients had no other pituitary hormone deficits (30).

Interestingly, when we tried to classify our patients according to the BMI-stratified GH response range retrieved from our normal subjects cohort, we found the same percentage of questionable GH stimulation results, indicating that other factors except BMI may contribute to the low specificity of GH testing in this cohort. As expected, more patients with a poor GH response were on replacement treatment for one or multiple pituitary hormone deficiencies. Whether subtle over- or under-replacement in these patients interferes with GH responsiveness is not known. Indeed, to arrive at firm conclusions on the specificity of GH testing in patients with increased BMI, larger studies are needed.

With this study, we would like to draw attention toward a potential overdiagnosis of GHD in some overweight and obese patients at risk for GHD due to insults of the hypothalamic–pituitary area. How is it possible to overcome this problem? Some investigators have proposed BMI-adjusted GH cut-offs in several provocative tests (8, 18, 21), but this approach is not widely accepted so far. In this study, we have proposed to carefully consider age-adjusted IGF1 levels and the anterior pituitary function.

In conclusion, we have provided evidences that increased BMI has a negative effect on GH response to provocative stimulation not only in normal subjects, but also in patients at risk for GHD due to insults of the hypothalamic–pituitary area. In this last cohort, BMI $> 25 \text{ kg/m}^2$ may result in the erroneous diagnosis of GHD in 19.6% of the patients. Thus, parameters such as age-adjusted IGF1 values or the presence of other pituitary hormone deficits should be taken into account in order to accurately assess secretory GH reserve in these patients.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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Received 16 August 2009

Accepted 31 August 2009