

Body Mass Index Determines Evoked Growth Hormone (GH) Responsiveness in Normal Healthy Male Subjects: Diagnostic Caveat for Adult GH Deficiency

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GH secretion is decreased in obese subjects, whereas age-adjusted IGF-I concentrations are normal. This study was undertaken to rigorously delineate the extent of obesity [elevated body mass index (BMI)] associated with decreased somatotrope secretory function resulting in apparent adult GH deficiency. The peak GH response evoked by combined arginine (0.5 g/kg infused iv over 30 min) and GHRH (1 μ g/kg iv bolus) was measured in 59 healthy male subjects with BMIs ranging from normal to obese. BMI correlated with the peak evoked GH response (Pearson $r = -0.59$; $P < 0.01$), and the percentage of subjects exhibiting an abnormal evoked GH response, *i.e.* less than 9 ng/ml, increased from 5% for those

with a BMI less than 25 (normal), to 13% for those with a BMI of 25–26.9 (mildly overweight), to 33% for those with a BMI of 27–29.9 (moderately overweight), and to 64% for those with a BMI of 30 or more (obese). BMI is a major determinant of evoked adult GH response to provocative testing. The diagnosis of adult GH deficiency using the evoked GH response in patients with even mild BMI elevation does not accurately distinguish normal from deficient responses and may result in the erroneous classification of obese subjects as GH deficient and thus unnecessarily requiring GH replacement. (*J Clin Endocrinol Metab* 89: 3397–3401, 2004)

PULSATILE ANTERIOR PITUITARY GH release is stimulated by hypothalamic GHRH and GH secretagogues and is inhibited by hypothalamic somatostatin (1). GH pulse amplitude and frequency are regulated by multiple physiological factors, including age (2), sex (3), sleep (4), body composition (5), stress hormones, and physical activity (6), presumably due to secondary effects on GHRH, somatostatin, and IGF-I levels. GH deficiency may be caused by hypothalamic-pituitary disease, which results in an absolute GH attenuation, or a relative GH deficiency due to alterations in central and peripheral signals that normally modulate GH secretion, such as occur in obesity and aging.

Obesity is associated with diminished spontaneous and stimulated GH secretion in both children and adults (7), and normal somatotrope function is restored by weight loss (8). The pathogenesis of GH insufficiency associated with obesity (9, 10) may be due to increased hypothalamic somatostatin-ergic tone or GHRH hypoactivity, hyperinsulinism, or elevated circulating free fatty acids (11).

The choice of confirmatory tests for diagnosis of adult GH deficiency is undergoing active validation. Measurements of spontaneous GH secretion (12) and IGF-I and IGF-binding protein-3 concentrations are not reliable diagnostic tools reflective of net GH secretory capacity (13–15). Insulin-induced hypoglycemia [determined by insulin tolerance test (ITT)] is the current standard diagnostic test (13, 15, 16) for the diagnosis of adult GH deficiency. Combined arginine-GHRH testing has been proposed (14) for diagnosing adult GH

deficiency and is considered a reliable, reproducible, safe alternative to the ITT (17, 18). The peak GH response is defined as the maximum GH response to arginine-GHRH over the duration of the test.

The aim of this study was to rigorously assess the extent of obesity [elevated body mass index (BMI)] that causes decreased somatotrope secretory function resulting in apparent GH insufficiency. The peak evoked GH response to arginine-GHRH stimulation was measured in 59 healthy male subjects with BMI values ranging from normal to obese.

Subjects and Methods

Study population

Fifty-nine healthy male volunteers, aged 20–60 yr (mean \pm SD, 41 \pm 10), participated in the study after providing institutional review board-approved informed consent. Hormonal abnormalities were excluded by history, physical examination, and measurement of basal TSH, free T_3 /free T_4 , prolactin, gonadal steroids, and IGF-I levels. Subjects were receiving no medications, were eating an unrestricted diet, and had not experienced significant change in body weight for at least 1 month before the study.

Study protocol

Subjects underwent arginine and GHRH testing to evaluate evoked GH responses. After an overnight fast, an indwelling catheter was inserted into a cubital vein that was kept patent by a slow saline infusion, and blood was sampled at the time of catheter insertion (–30 min) and 30 min later (0 min). GHRH (1 μ g/kg) was administered as an iv bolus, and arginine hydrochloride (0.5 g/kg) was infused iv from 0–30 min. Five-milliliter blood samples were drawn at –30 and 0 min, then every 30 min from 0–120 min after the infusion. All samples from an individual subject were assayed in duplicate in the same GH immunoradiometric assay. Serum GH was measured using a chemiluminescent immunometric assay specific for 22-kDa human GH and native sequence GH as standard (Eli Lilly & Co., Indianapolis, IN). Samples were measured

Abbreviations: BMI, Body mass index; ITT, insulin tolerance test.

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against GH standard WHO 80/505, and intra- and interassay coefficients of variation were 3.7–14.3% and 5.7–7.5%, respectively. The sensitivity of the assay was 0.05 $\mu\text{g/liter}$. Serum IGF-I levels were measured in duplicate by RIA at baseline. To avoid binding protein interference, samples were treated with acid ethanol. Serum IGF-I was measured using a competitive binding RIA, using native sequence IGF-I (Bachem, Torrance, CA) as standard. The intra- and interassay coefficients of variation were 4.6–20% and 9–10%, respectively. Assay sensitivity was 10 $\mu\text{g/liter}$. IGF-I values were evaluated by comparison with age- and sex-matched individuals.

Normative values for the arginine-GHRH test were established in 326 normal subjects (14) (98 men and 228 women; age range, 20–80 yr) and defined as GH peaks of 16.5 ng/ml and 9.0 ng/liter as third and first lower percentile limits across the life span.

The Pearson correlation coefficient was used to assess relationships between pairs of variables; stepwise linear regression was used to assess the influence of age on the peak GH response after adjustment for BMI. For significance testing, the two-sided 5% level was used.

Normalization of IGF-I values derived for each subject was achieved by subtracting the mean for age decade and then dividing by the SD for age decade to produce a z-score. These z-scores would be expected to have a mean of 0 and an SD of 1.0; thus, the lower 2.5th percentile would be expected to be -2.0 .

BMI was calculated by dividing a subject's weight (in kilograms) by the square of their height (in meters). A BMI less than 25 kg/m^2 is defined as normal, and a BMI of 30 or more is considered obese. A BMI of 27 kg/m^2 or more (overweight) is associated with increased health risks, including hypertension, cardiovascular disease, diabetes, and osteoarthritis (19–21). BMI values ranging from 25–27 kg/m^2 are regarded as acceptable by some, whereas others report that patients within this BMI range incur moderate health risks (19, 20, 22).

Results

Subject characteristics

BMI ranged from 21–40.7 (mean, 26.8 ± 4.0) in 59 healthy subjects, aged 26–60 yr (mean \pm SD, 41 ± 10 ; Fig. 1A). Subjects were from from Caucasian, African-American, and Hispanic ethnic backgrounds. Twenty subjects, aged 23–60 yr, had a BMI less than 25; 16 subjects, aged 33–60 yr, had a BMI of 25–26.9; 12 subjects, aged 21–57 yr, had a BMI of 27–29.9, and 11 subjects, aged 38–60 yr, had a BMI of 30 or more (Fig. 1A).

Peak GH response correlates more closely with BMI than with age

Younger subjects had lower BMI values, whereas older subjects had a wider range of BMI values. Age correlated moderately with both BMI ($r = 0.35$; $P < 0.01$; Fig. 1B) and peak GH response ($r = 0.37$; $P < 0.01$), but did not contribute to the prediction of peak GH response after BMI was entered into the stepwise regression.

IGF-I levels do not correlate with BMI

Normalized IGF-I values did not correlate with BMI ($r = 0.19$; $P > 0.05$), with a minimum z-score for IGF-I of -2.18 . Only a single subject had a z-score more than 2 SD below the expected mean of 0 (-2.18). Furthermore, the IGF-I z-score and peak evoked GH response did not correlate ($r = -0.12$; $P > 0.05$; Fig. 1C).

Peak evoked GH response to arginine-GHRH

BMI correlated with the peak GH response (Pearson $r = -0.59$; $P < 0.01$) after GHRH and arginine administration (Fig. 2). Table 1 depicts the relationship between BMI cate-

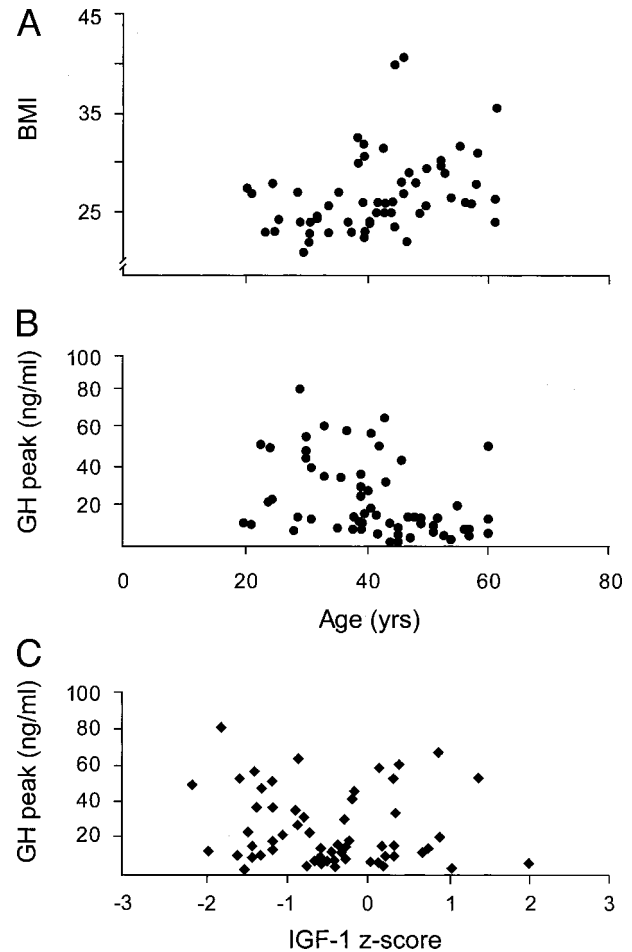


FIG. 1. Scatterplot of peak GH responses after arginine-GHRH administration in 59 subjects, aged 20–60 yr. A, BMI (kilograms per meter squared) plotted against age (years). Each point represents one subject. BMI increases with age (Pearson $r = 0.35$). B, Peak GH response (nanograms per milliliter) during 30–120 min after stimulation with arginine-GHRH plotted against each subject's age. C, Peak GH response (nanograms per milliliter) during 30–120 min after stimulation with arginine-GHRH, plotted against each subject's IGF-I z-score (Pearson $r = -0.12$; $n = 58$).

gories and percentage of subjects classified as abnormal, *i.e.* evoked GH values less than 9 ng/ml (23). As BMI increased, the percentage of subjects with an evoked GH response less than 9 ng/ml increased from 5% for subjects with a BMI less than 25 to 64% for subjects with a BMI greater than 30.

Time course of mean GH response

The peak GH response (maximum observed) occurred at 30 min in 28 subjects, at 60 min in 31 subjects, at 90 min in three subjects, and at 120 min in one subject. The mean GH peak was 24.2 ng/ml. Figure 3 shows the mean GH response at each time point during the test in normal, overweight, and obese subjects. As the BMI increased, there was a progressive reduction in the mean GH response.

Discussion

This study evaluated the influence of BMI on the utility of provocative arginine-GHRH testing for GH deficiency in

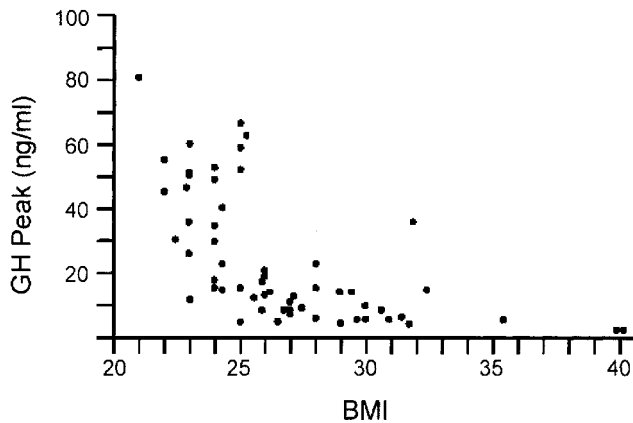


FIG. 2. Peak GH response (nanograms per milliliter) after arginine-GHRH administration correlates with BMI (kilograms per meter squared; Pearson $r = -0.59$). Each point represents peak GH response of one subject plotted against the subject's BMI value.

TABLE 1. BMI correlates with peak GH responses in 59 normal subjects

BMI	<25	25–26.9	27–29.9	>30
n	20	16	12	11
Subjects with evoked GH <9 ng/ml (%)	1 (5)	2 (13)	4 (33)	7 (64)

healthy male subjects. The results demonstrate that BMI is a major negative determinant of evoked GH response to provocative testing. The pathogenesis of GH insufficiency in obesity is unclear. Possible mechanisms include disordered hypothalamic tone and altered somatotrope cell function. A functional compensatory somatotrope response to the complex altered afferent pituitary signals that occur in obesity may be present. Peak GH responses are significantly suppressed in normal subjects with even very mildly elevated BMI (*i.e.* slightly overweight subjects). These subjects would have been erroneously diagnosed as GH deficient and would have qualified for GH replacement therapy.

The evoked GH response to insulin-induced hypoglycemia (determined by ITT) has been the standard GH provocative test (13, 15, 16). Because the test has contraindications, has serious potential risks in some patients, and is labor intensive, alternative sensitive and specific tests have been evaluated (24). Arginine-GHRH has been proposed as a useful, reproducible, age-independent alternative provocative test to the ITT (17, 24, 25).

Several factors, including gender, age, body composition, and nutritional status, affect GH secretion and responsiveness to provocative testing (26–28). Obesity diminishes GH responses (7) and is associated with decreased pulsatile GH secretion, increased metabolic clearance, and resultant decreased GH concentrations (29). Twenty-four-hour GH levels in obese men are reduced by 75% compared with those in age-matched normal weight males (29). For each unit increase in BMI, 24-h GH secretion decreases by 6% (30). Abdominal visceral fat is a stronger predictor of 24-h GH release than total percentage body fat (31), and BMI relates inversely to peak GH responses to ITT and arginine-GHRH (24). IGF-I levels have been reported as high, normal, or low in obese subjects (32–36). Furthermore, normal IGF-I levels are also

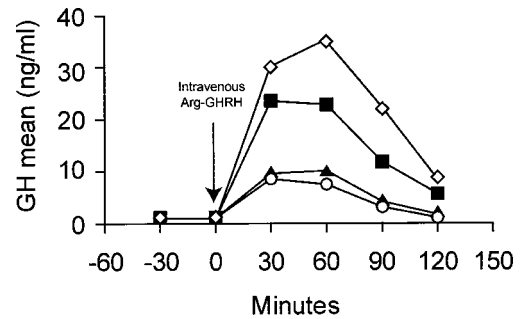


FIG. 3. Mean GH concentrations (\pm SE) at each time point during the provocative test in normal subjects (BMI, <25; $n = 20$), slightly overweight subjects (BMI, 25–26.9; $n = 16$), moderately overweight subjects (BMI, 27–29; $n = 12$), and obese subjects (BMI, >30; $n = 11$). Each point represents the mean GH response of the subjects in the group. \diamond , Normal; \blacksquare , slightly overweight; \blacktriangle , moderately overweight; \circ , obese.

found in approximately 30% of hypopituitary patients (37–39).

In light of the clear reduction in both spontaneous and stimulated GH secretion in obese subjects, BMI must be evaluated when the diagnosis of GH deficiency is being considered. This study establishes the importance of careful consideration of the influence of even modest BMI changes on peak GH responses to arginine-GHRH. The influence of BMI has been controlled with varying degrees of rigor in reported studies (17, 23, 24, 40–43) and has not been uniformly considered in the evaluation of GH responsiveness to adult arginine-GHRH testing.

When pyridostigmine-GHRH and arginine-GHRH tests and IGF-I measurement were evaluated for diagnosis of adult GH deficiency, BMI in control subjects (normal $\pm 15\%$ ideal body weight) was as high as 29 in some subjects (40). Furthermore, BMI values in the hypopituitary group varied from 18–27, and the potential suppressive effects of these elevated BMI levels were not considered for data analysis. In a study to validate the reproducibility of arginine-GHRH testing in healthy subjects, the young and elderly groups had BMI values less than 25; however, the hypopituitary group had BMI values greater than 25 (17). In comparing GH responses to an abbreviated arginine-GHRH test in children and adolescents with those in young or middle-aged healthy adults, BMI values were not provided (43). The utility of five different stimulation tests to define test-specific GH cut-off points was assessed to improve their diagnostic accuracy (24). Patients with adult-onset hypothalamic-pituitary disease and multiple (two or more) additional (other than GH deficiency) pituitary hormone deficiencies were compared with control subjects matched for age, sex, and BMI and also to subjects with hypothalamic-pituitary disease and not more than one additional pituitary hormone deficiency (24). Although BMI was carefully matched between hypopituitary and control subjects, the average BMI was markedly elevated in both groups (24). The validity of reported normal GH responses (and cut-off points established) in these studies should therefore be interpreted with caution.

Furthermore, published arginine-GHRH protocols are not standardized. Some researchers evaluate GH levels every 15 min from 0–90 min (23, 40, 42), some evaluate GH levels

every 15 min for 120 min (17, 43), and one study evaluated GH levels every 20–30 min for 2.5 h (24). Computed peak values will be lower for tests with wider time spacing and fewer measurement time points. In addition, GH assay variability should be considered when comparing study results. In comparison with two prior studies aimed at establishing GH cut-off points for arginine-GHRH testing (14, 24), the assay used here was similar to that used by Maccario *et al.* (23), but differed from that used by Ghigo *et al.* (14).

This study indicates that provocative testing for diagnosis of GH deficiency in patients with any degree of BMI elevation above normal will not accurately distinguish normal from deficient responses. BMI should be measured, and GH results appropriately interpreted for all adult subjects undergoing GH testing for adult GH deficiency. The arginine-GHRH test cannot be used to evaluate GH deficiency in subjects with even mildly elevated BMI values. Large population studies are required to establish appropriate GH cut-offs for subjects with elevated BMI values. The presence of obesity must be taken into account before concluding that a patient is truly GH deficient and therefore an appropriate candidate for GH replacement.

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