Effect of Body Mass Index on Peak Growth Hormone Response to Provocative Testing in Children with Short Stature

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Context: Obesity is associated with decreased spontaneous and stimulated GH secretion, but the effect of body mass index (BMI) on results of GH stimulation testing in children with short stature is not known.

Objective: The aim of the study was to determine the impact of BMI on peak GH to provocative testing in children with short stature.

Design, Setting, and Participants: This was a retrospective review of provocative GH testing performed in 116 children 2–18 yr old in the ambulatory clinic of the Pediatric Endocrinology Unit at the Massachusetts General Hospital from 2004–2008.

Main Outcome Measures: The main outcome measure was peak stimulated GH. Height, weight, IGF-I, and IGF-binding protein 3 were also measured.

Results: In univariate regression analysis, BMI SD score (BMI SDS) was inversely associated with natural log (ln) peak GH to provocative testing ($P = 0.002$), whereas height SDS, ln IGF-I, and IGF-binding protein 3 were not significantly associated with ln peak GH. After controlling for age, gender, BMI, and pubertal status, BMI ($P = 0.002$) remained independently associated with ln peak GH. BMI SDS significantly influenced the likelihood of diagnosis of GH deficiency using peak GH cutoffs of 10, 7, and 5 μg/liter.

Conclusion: In children with short stature, BMI affects peak stimulated GH and should be considered when interpreting GH testing. Higher BMI SDS, even within the normal range, may lead to overdiagnosis of GH deficiency. **(*J Clin Endocrinol Metab* 94: 4875–4881, 2009)**

Adults with obesity have reduced spontaneous (1–3) and stimulated (4–7) GH secretion that may be subsequent to GH suppression by free fatty acids (8, 9). Data in children, although limited, demonstrate that cohorts of obese children and adolescents also have reduced stimulated (10, 11) and endogenous (12, 13) GH secretion compared with normal-weight controls. As in adults, this relative GH deficiency (GHD) of obesity is related to increased visceral adiposity (11) and increased cardiovascular risk markers (14) and is reversible with weight loss or caloric restriction (12, 13). In addition, evidence suggests that reduced GH is not a pathophysiological condition unique to abdominal obesity but instead that there is a continuum of decreasing GH with increasing adiposity, even in normal-weight children. In a cohort of 46 healthy boys, Martha *et al.* (15) demonstrate a significant negative association between body mass index (BMI) SD score (SDS) and several parameters of endogenous GH secretion, including total 24-h GH secretion and secretory burst amplitude. Likewise, in a study of 132 healthy children of normal height and weight, Rose *et al.* (16) show that BMI is negatively associated with mean overnight GH secretion

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Abbreviations: BMI, Body mass index; CV, coefficient of variation; GHD, GH deficiency; IGFBP, IGF-binding protein; MRI, magnetic resonance imaging; SDS, SD score.

as measured by frequent sampling (every 20 min) in girls, although the relationship was not significant in boys. Finally, in 208 healthy children, Albertsson-Wikland *et al.* (17) demonstrate a negative association between weight-for-height SDS and GH secretion rate in pubertal but not prepubertal children.

Whereas these data strongly support a negative impact of BMI on spontaneous GH secretion in children, there is little information to date on the relationship between BMI and peak stimulated GH in children with short stature tested for GHD. This is particularly relevant because children with short stature routinely undergo provocative GH testing, despite its relatively poor reproducibility. In multiple studies, a large percentage of individuals diagnosed with isolated GHD in childhood did not have GHD on retesting in adulthood (18–21), suggesting that provocative testing yields false-positive diagnoses of GHD in many children. Maghnie *et al.* (22) demonstrate that nutritional status may be responsible for some of these false positives. In their cohort, 11 of 17 children with short stature whose provocative testing initially showed GHD had substantially increased peak GH, indicating GH sufficiency, after a 3-d period of hypocaloric diet (22). Given these data, BMI, an integrated measure of long-term nutritional status, is also likely to influence peak stimulated GH. In this study, we aimed to determine the impact of BMI on results of GH stimulation testing in children presenting with short stature.

Subjects and Methods

Subjects in the final analysis included 116 GH naive male and female children with short stature, ages 2–18 yr of age, who presented to our pediatric endocrine unit between 2004 and 2008 and underwent GH stimulation testing, without sex steroid pretreatment, with a combination of at least two of the following: clonidine, arginine, L-dopa/carbidopa, or propranolol. Because our aim was to determine the effect of BMI on provocative GH testing in otherwise healthy children with short stature, children with severe chronic illness or known Turner syndrome were not included in the analysis. In addition, children most likely to be truly GH deficient, including those with central nervous system neoplasms and multiple pituitary hormone deficiencies were excluded. Documentation of technically adequate pituitary magnetic resonance imaging (MRI) scans was available for 83% of patients with peak stimulated GH under 10 μg/liter. Four of these children had abnormal MRI findings and were thus excluded from analysis. Children receiving medications that may affect endogenous GH secretion, including oral or inhaled corticosteroids (23, 24), antipsychotic medications (25, 26), and ondansetron (27), were also excluded. One subject was excluded because complete data were not available from stimulation testing. The Institutional Review Board of Partners HealthCare System approved this study.

Four different stimulation test protocols were used to assess GH secretion: arginine/clonidine (n = 31, arginine 0.5 g/kg, maximum 30 g, iv over 30 min followed by clonidine 100 μg/m^2 at 30 min, with blood sampling every 30 min for 120 min); dopamine/propranolol [n = 7, Sinemet (10 mg carbidopa/100 mg levo-dopa) 150–175 mg/m^2, maximum 250 mg, and propranolol 0.75 mg/kg, maximum 40 mg, with subsequent blood sampling at 30, 45, 60, 90, and 120 min]; clonidine/dopamine/propranolol (n = 63, clonidine at dose above followed by administration of Sinemet and propranolol as above at 150 min, with blood sampling at 30, 45, 60, 75, 90, 120, 150, 180, 195, 210, 225, and 240 min); and arginine/dopamine (n = 15, arginine, Sinemet, and propranolol as above, with subsequent blood sampling at 30, 45, 60, 90, and 120 min).

From review of clinic charts and electronic medical records, height, weight, IGF-I, IGF-binding protein (IGFBP)-3, pubertal status, thyroid function, type of GH stimulation test, and peak GH after stimulation were collected. When data on height, weight, IGF-I, IGFBP-3, and pubertal status were not available from the day of the stimulation test, they were collected from a clinic visit occurring no more than 3 months before the stimulation test; IGF-I and IGFBP-3 were not available during this time frame for 23 and 34 patients, respectively. Pubertal status (Tanner stage for breast development [F] or genital development [M]) was assessed and documented by an attending pediatric endocrinologist; pubertal status was not available for six patients. Bone age was available within 3 months of the stimulation test for 67 patients. BMI was calculated, and BMI and height SDS were calculated using National Child Health Statistics 2000 standards (28). Natural log transformation was used for peak GH and IGF-I because these variables were not normally distributed as determined using the Shapiro-Wilk *W* test.

Assays

Serum GH levels were measured using Immulite 2000, a solid-phase, two-site chemiluminescent immunometric assay with analytical sensitivity of 0.01 μg/liter, intraassay coefficient of variation (CV) ranging from 2.9–4.6%, and interassay CV ranging from 4.2–6.6% (Siemens Healthcare Diagnostics, Deerfield, IL). Serum IGF-I levels were also measured with Immulite 2000, with an analytical sensitivity of 20 μg/liter, intraassay CV ranging from 2.3–3.9%, and interassay CV ranging from 3.7–8.1% (Siemens). IGFBP-3 levels were measured by Esoterix, Inc. (Austin, TX) using competitive binding RIA with a lower limit of 0.3 mg/liter, intraassay CV of 5.1–13%, and interassay CV of 5.5–17%.

Statistical analysis

Statistical analysis was performed using JMP 5.0.1.2 (SAS Institute, Cary, NC). As mentioned, data that were not normally distributed were natural log transformed to approximate a normal distribution. This was required for peak GH levels and IGF-I levels. Univariate analyses were performed using Pearson correlation coefficient for continuous variables and Student's *t* test for categorical variables. Comparisons between multiple groups were performed using 1) ANOVA followed by the Tukey-Kramer test (to adjust for multiple comparisons) for continuous variables and 2) Pearson's χ^2 test or, when cell size was less than n = 5, Fisher's exact test for categorical variables. We used multivariate modeling with stepwise regression to determine independent predictors of peak GH levels. Covariates entered into this model included those known or suspected to impact GH secretion such as age, gender, pubertal status, ln IGF-I, BMI, and the type of stimulation test used. Statistical significance was defined as $P < 0.05$. Results are described as mean ± SD unless otherwise stated.

TABLE 1. Clinical characteristics

	All patients (n = 116)	BMI SDS category			
		<−1 (group 1, n = 17)	−1 to <0 (group 2, n = 49)	0–1 (group 3, n = 40)	>1 (group 4, n = 10)
Age (yr)	10.3 ± 3.3	10.9 ± 3.2	10.8 ± 2.5	9.4 ± 3.7	10.4 ± 5.0
Gender (male/female)	79/37	13/4	35/14	24/16	7/3
% prepubertal	76%	76%	78%	76%	67%
Height SDS	−2.4 ± 0.6	−2.7 ± 0.6	−2.4 ± 0.5	−2.3 ± 0.6	−2.1 ± 0.4
BMI SDS[a,d]	−0.2 ± 0.9	−1.7 ± 0.5	−0.5 ± 0.3	0.5 ± 0.2	1.4 ± 0.3
Ln IGF-I (μg/liter)	4.6 ± 0.7	4.5 ± 0.4	4.7 ± 0.7	4.5 ± 0.7	4.7 ± 0.6
IGF-I SDS	−1.4 ± 0.9	−1.6 ± 0.6	−1.3 ± 1.0	−1.4 ± 0.9	−1.20 ± 0.9
IGFBP-3 (mg/liter)	2.6 ± 0.8	2.2 ± 0.8	2.7 ± 0.8	2.5 ± 0.8	2.5 ± 0.4
Ln Peak GH (μg/liter)[a]	2.6 ± 0.6	2.6 ± 0.4	2.8 ± 0.5	2.4 ± 0.6[b]	2.0 ± 0.6[c]

Values are mean ± SD.

[a] ANOVA P value <0.0005; P values for ANOVA for other variables were not significant.

[b] Statistically significant difference ($P < 0.05$) *vs.* group with BMI SDS −1 to <0.

[c] Statistically significant difference ($P < 0.05$) *vs.* BMI SDS <−1 and BMI SDS −1 to <0 groups.

[d] Each BMI SDS group differed significantly ($P < 0.05$) from the other three groups per study design.

Results

Cohort characteristics

Clinical characteristics are shown in Table 1. Of 116 children whose data were included in the final analysis, mean age was 10.3 ± 3.3 yr. Seventy-nine (68%) children were male. The majority of children were prepubertal (n = 84, 76%), with 16 (15%) children at Tanner stage 2, seven (6%) children at Tanner stage 3, two (2%) children at Tanner stage 4, and one (1%) at Tanner stage 5 of puberty. Average height SDS for the cohort was −2.4 ± 0.6. Mean BMI SDS was −0.2 ± 0.9, suggesting a distribution approximating that of the general population for BMI. Median peak GH was 13.3 μg/liter, with interquartile range 9.0–20.0 μg/liter; 36 (31%) children had peak GH below 10 μg/liter.

Determinants of peak GH levels

On univariate analysis, BMI SDS was significantly and negatively associated with ln peak GH (r = −0.28; P = 0.002; Fig. 1). In a subanalysis of 67 children for whom bone age was available within 3 months of the stimulation test, there remained a significant inverse relationship between ln peak GH and BMI SDS when SDS was determined by bone age rather than chronological age (r = −0.45; P = 0.0002). Height SDS was not significantly associated with ln peak GH (Table 2). In contrast, height SDS, but not BMI SDS, was associated with ln IGF-I, IGF-I SDS, and IGFBP-3 (r = 0.36, 0.35, and 0.34; P = 0.0004, 0.001, and 0.002, respectively). Of note, gender and Tanner stage were not significantly associated with ln peak GH (P = 0.60 and 0.51, respectively), nor were age, ln IGF-I, IGF-I SDS, or IGFBP-3 (Table 2). Type of provocative testing protocol was also not significantly associated with ln peak GH using ANOVA (P = 0.36). BMI SDS was not different by type of stimulation test (P = 0.25).

In stepwise multivariate regression analysis including age, gender, type of stimulation test, pubertal status (prepubertal *vs.* pubertal), BMI, and ln IGF-I as independent variables tested in the model and ln peak GH as the dependent variable, BMI, type of stimulation test, and ln IGF-I were the only

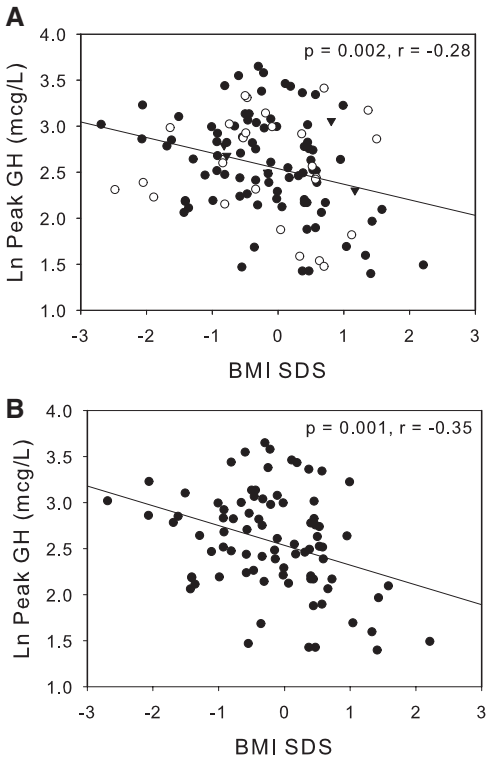

FIG. 1. A, Univariate correlation between ln peak GH and BMI SDS in all children: ●, prepubertal children; ○, pubertal children; ▼, children with unknown pubertal status. B, Univariate correlation between ln peak GH and BMI SDS in prepubertal children.

TABLE 2. Univariate analysis of associations with ln peak GH

	r	*P* value
Age (yr)	0.06	0.49
Height SDS	−0.04	0.70
BMI SDS	−0.28	0.002
Ln IGF-I (μg/liter)	0.10	0.34
IGF-I SDS	−0.02	0.84
IGFBP-3 (mg/liter)	0.08	0.49

significant predictors of ln peak GH (Table 3). This model explained 19% of the variance in ln peak GH.

Interestingly, when we divided our subjects based on pubertal stage (prepubertal *vs.* pubertal), the univariate association between BMI SDS and ln peak GH was even stronger (r = −0.35; $P = 0.001$) within prepubertal children (Fig. 1), whereas the univariate association was no longer significant within pubertal children (r = −0.07; *P* not significant). When controlling for other possible determinants of GH in the pubertal subgroup using multivariate modeling, however, BMI emerged as a negative predictor of ln peak GH. In stepwise multivariate regression analysis including bone age, gender, type of stimulation test, BMI, and ln IGF-I as independent variables and ln peak GH as the dependent variable, BMI ($P = 0.02$), bone age ($P = 0.02$), and type of stimulation test ($P = 0.03$) were significantly associated with ln peak GH in the pubertal subgroup; this model explained 48% of the variance in ln peak GH.

Impact of BMI on diagnosis of GHD

To determine the impact of BMI on the diagnosis of GHD, we divided patients into four BMI SDS categories: group 1, BMI SDS less than −1 (n = 17); group 2, BMI SDS −1 to less than 0 (n = 49); group 3, BMI SDS 0–1 (n = 40); and group 4, BMI SDS more than 1 (n = 10). BMI category was significantly associated with ln peak GH ($P = 0.0005$); ln peak GH was significantly lower in group 4 compared with groups 1 and 2, and ln peak GH in group 3 was significantly lower than in group 2 (Table 1). In separate subanalyses excluding patients most likely to have true isolated GHD, the association between BMI category and ln peak GH remained significant when eliminating patients with peak GH under 5 μg/liter ($P = 0.03$), patients with IGF-I SDS less than −2 ($P = 0.02$), or patients with height SDS less than −2.5 ($P = 0.02$). IGF-I and IGFBP-3 values were not different between BMI groups. A scatter plot of peak GH, IGF-I, and IGFBP-3 according to BMI category is shown in Fig. 2.

TABLE 3. Multivariate analysis of associations with ln peak GH

Parameter	Estimate	F ratio	*P* value	Cumulative R^2
Intercept	2.86			
Type of stimulation test	−0.18	9.6	0.003	0.08
BMI (kg/m^2)	−0.07	10.6	0.002	0.15
Ln IGF-I	0.19	4.5	0.04	0.19

Stepwise regression model contained the following independent variables entered into the model: age, gender, type of stimulation test, pubertal status (prepubertal *vs.* pubertal), BMI, and ln IGF-I.

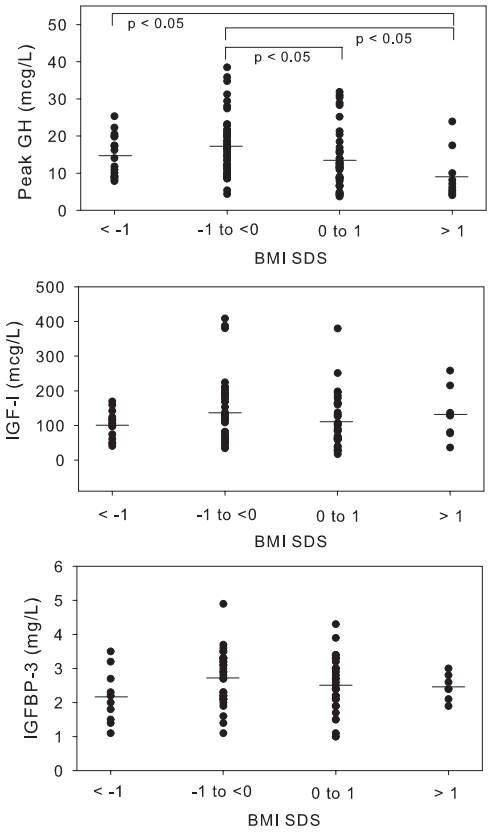

FIG. 2. Scatterplot for peak GH to provocative testing (*top*), IGF-I (*middle*), and IGFBP-3 (*bottom*) levels according to BMI category: BMI less than −1 (group 1, n = 17), BMI −1 to less than 0 (group 2, n = 49), BMI 0–1 (group 3, n = 40), and BMI more than 1 (group 4, n = 10). *Solid horizontal lines* represent the mean for each group.

Using a common pediatric cutoff of peak GH under 10 μg/liter to diagnose GHD, 70% of patients in group 4 received a diagnosis of GHD, whereas only 38% of patients in group 3, 18% of patients in group 2, and 29% of patients in group 1 were diagnosed with GHD (*P* value for Pearson $\chi^2 = 0.009$, Fig. 3). Results were similar using lower diagnostic peak GH cutoffs of less than 7 μg/liter (50% in group 4, 23% in Group 3, 4% in group 2, and 0% in group 1 with GHD, *P* value for Fisher's exact test = 0.0002) and less than 5 μg/liter (30% in group 4, 15% in group 3, 2% in group 2, and 0% in group 1 with GHD, *P* value for Fisher's exact test = 0.007) (Fig. 3).

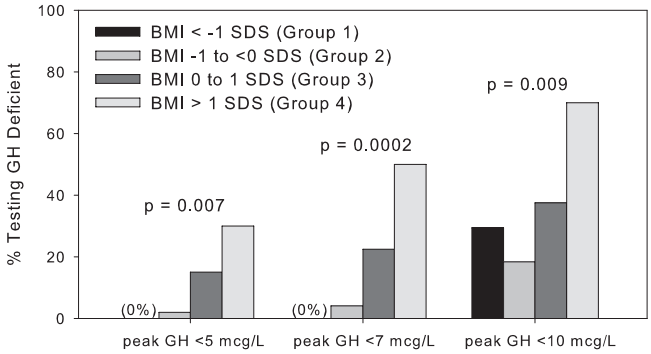

FIG. 3. Percentage of patients testing GH deficient by BMI category for three different peak GH cutoffs: less than 5, less than 7, and less than 10 μg/liter. *P* value is shown for each cutoff.

Discussion

Our data demonstrate that peak GH response to provocative testing decreases with increasing BMI SDS in a relatively large cohort of otherwise healthy children with short stature. Because our cohort included children with a range of BMI that approximated a normal distribution (mean BMI SDS of −0.2 and SD of 0.9), our data suggest that the relationship between BMI and peak GH is not unique to obesity but rather persists in the normal-weight pediatric population. Analysis of peak GH response according to BMI SDS category demonstrates the clinical significance of this finding; children with higher BMI SDS are more likely to fail provocative GH stimulation testing, but this may not be an indicator of true GHD. In fact, in our cohort, ln IGF-I, IGF-I SDS, and IGFBP-3 were positively associated with height SDS, whereas ln peak GH was not.

The finding of decreased stimulated peak GH with increasing BMI in a largely prepubertal cohort with a normal weight distribution adds to the literature suggesting that results of pharmacological GH stimulation may depend on numerous physiological variables, only one of which is sufficiency of GH secretion. Marin *et al.* (29) have demonstrated that peak stimulated GH increases significantly with pubertal stage and with estrogen pretreatment in a cohort of normal children, with prepubertal children significantly more likely to test GH deficient compared with children in puberty unless estrogen pretreatment is administered. In addition, the GH secretion pattern immediately before the stimulation test can affect peak GH response, such that peak stimulated GH may be lower if an endogenous peak has occurred just before testing (30, 31). Finally, both short-term (22) and, as our study demonstrates, long-term nutritional status affects peak GH. These numerous determinants of peak stimulated GH likely account for the poor reproducibility of provocative GH testing, even when the period between test and retest is only on the order of months (32).

Of note, our regression model explained only 19% of the variability in peak stimulated GH levels. We anticipate that an important determinant of peak GH response is pituitary somatotrope reserve, which should account for much of the variability not explained by our model. In addition, peak GH likely varies according to pubertal stage (29), although we did not demonstrate a significant relationship in our cohort, probably because the majority of our cohort was prepubertal. Other possible predictors include levels of gonadal steroids (particularly in pubertal children) and other hormones with a potential impact on GH secretion such as cortisol, leptin, and ghrelin (33–36) as well as nutritional status in the days preceding the stimulation test (22).

Given the clear relationship between BMI and peak stimulated GH demonstrated in adult cohorts (4–7), the lack of univariate relationship between BMI and peak GH in our pubertal subgroup was surprising, but may be a consequence of small sample size. It is also likely that the heterogeneity of our pubertal subgroup with respect to levels of sex steroids confounded the relationship between stimulated GH and BMI, because we did see a significant inverse association between ln peak GH and BMI after controlling for bone age and ln IGF-I, both of which are strongly affected by estrogen, as well as gender and type of stimulation test.

Our data have many limitations. First, in this retrospective, cross-sectional study, we cannot determine causality, and we cannot exclude the possibility that patients with true GHD had higher BMI, thus driving our results. To reduce this possibility, we excluded patients with multiple pituitary hormone deficiencies, abnormal pituitary MRI, or history of central nervous system neoplasm from our cohort. In addition, height SDS scores were not different between BMI groups and actually tended to be higher in the group with BMI more than 1 SDS, suggesting that this group may not have been uniquely GH deficient. Furthermore, in three separate subanalyses excluding patients based on either peak GH lower than 5 μg/liter, IGF-I SDS less than −2, or height SDS less than −2.5, the association between BMI and peak GH persisted.

Second, because these are retrospective clinical data, four different provocative testing protocols were used, and our sample size was not large enough to analyze each subgroup separately. Different GH stimulation tests are known to have different potencies with respect to GH stimulation. Although type of test was not significantly associated with ln peak GH stimulation in univariate regression analysis, type of test was related to peak GH in multivariate modeling. BMI was not significantly different by type of test, and BMI remained a significant predictor of ln peak GH when controlling for the type of testing

protocol in multivariate analysis. It is certainly possible, however, that BMI has a larger impact on peak GH after some provocative agents and less of an impact with other agents. For instance, if increased somatostatin tone plays a role in the relationship between increased BMI and peak GH, BMI may be less of a factor in protocols that employ arginine, an inhibitor of somatostatin secretion. Larger studies with consistent provocative testing protocols will be needed to confirm the effect of BMI on peak GH in children.

Third, we did not have data on anthropometrics or body composition (such as waist circumference or waist to hip ratio), which appear to have a larger influence on GH dynamics than BMI (11, 37). Although recent studies in children and adolescents demonstrate that BMI may be as strongly associated with overall body fatness as waist circumference (38, 39), BMI may be a rough surrogate for more specific measures of visceral abdominal adiposity, which may be stronger correlates of GH secretion than BMI. Finally, we do not have data on lipids, serum inflammatory markers, or other cardiovascular risk parameters, so we cannot determine whether there is any association in this cohort between reduced GH and cardiometabolic risk. In obesity, relative GHD appears to contribute independently to markers of cardiometabolic risk in both children and adults (14, 40), but it is unclear whether this association would persist in a normal-weight cohort.

Despite these limitations, our data highlight the need to consider BMI when interpreting the results of provocative GH stimulation testing in children. Although larger studies are clearly needed to determine the causative factors and metabolic consequences of reduced GH with increasing adiposity in the pediatric age group, our data demonstrate that even in a normal-weight cohort, children with higher BMI are disproportionately overdiagnosed with GHD.

Acknowledgments

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