The Influence of Body Mass Index on the Growth Hormone Peak Response regarding Growth Hormone Stimulation Tests in Children

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Abstract

Introduction: Several studies have analyzed the association between the maximal growth hormone serum level obtained during a growth hormone stimulation test (GH$_{\text{Max}}$) and the body mass index-standard deviation score (BMI-SDS). However, as sample sizes were quite small, our study aimed to analyze the association between GH$_{\text{Max}}$ and BMI-SDS within a large cohort of 991 children. Further, we investigated other influencing factors, like test type, age, sex, puberty, and preterm birth. Methods: Children with short stature (height <10th percentile) received growth hormone stimulation tests with arginine or glucagon at the Department of Paediatric Endocrinology of the University of Leipzig Medical Center. The study population included a total of 1,438 tests (633 tests on girls, 805 tests on boys), with the majority consisting of prepubertal children (tests = 1,138). The mean age at testing was 7.74 years. Analyses were carried out on the entire cohort as well as stratified by test types.

Results: GH$_{\text{Max}}$ and BMI-SDS were significantly negatively associated with an effect size of $\beta = -1.10$ ($p < 0.001$), independent from the test type. The GH$_{\text{Max}}$ values were significantly ($p < 0.001$) higher for glucagon (mean value: 9.65 ng/mL) than those for arginine tests (mean value: 8.50 ng/mL). Age, sex, premature birth, and puberty were not significantly related to GH$_{\text{Max}}$ values.

Conclusion: We confirmed the negative association between GH$_{\text{Max}}$ and weight status of short children found in previous studies. Therefore, considering BMI-SDS may be helpful in the assessment of growth hormone stimulation tests in short-statured children, but it should not be the determining factor for a treatment decision.

Introduction

In adults, an inverse association between body mass index (BMI) and growth hormone (GH) release has been shown [1, 2]. Therefore, BMI-related cut-off values are recommended in the diagnosis of adult growth hormone deficiency.
deficiency (GHD) [2–4]. Accordingly, the question arises on whether the same relationship can also be observed in children. Several studies investigated this association in children, using GH stimulation tests with, e.g., clonidine, dopamine, or arginine, resulting in mixed findings [5–10]. The majority of studies found a negative association between the maximal GH serum level (GH_{\text{Max}}) and BMI-standard deviation score (SDS). This is reported, e.g., by Lee et al. [8] (test substances: clonidine, insulin, L-dopa), Stanley et al. [9] (test substances: arginine, clonidine, L-dopa/carbidopa, propranolol), and Yau et al. [10] (test substances: arginine with L-dopa). Among others, these studies are included in a recently published meta-analysis by Abawi et al. [5], which confirmed the negative association between BMI-SDS and GH_{\text{Max}}, with focus on overweight/obese children. The authors of this meta-analysis also proposed weight-adjusted cut-off values for the assessment of GHD.

On the other hand, studies by Borges et al. [6] and Lee et al. [7] found no significant association between GH_{\text{Max}} and BMI-SDS in their probands undergoing stimulation tests with clonidine and dopamine, respectively. However, Borges et al. [6] analyzed a cohort that included children with idiopathic short stature and children with GHD as well as normally growing children. Lee et al. [7] also investigated GH tests with clonidine and were able to demonstrate a negative association between BMI-SDS and GH_{\text{Max}} in their cohort of children with short stature.

Although there are already several studies on the association between GH_{\text{Max}} and BMI-SDS, our retrospective study aimed to verify the correlation between BMI-SDS and GH_{\text{Max}} in a larger cohort of children with impaired growth (height <10th percentile), using GH stimulation tests with arginine and glucagon. We focused on the strength of the association between GH_{\text{Max}} and BMI-SDS to identify a new correction factor. This is crucial to evaluate whether and how BMI-SDS should be considered for the interpretation of GH_{\text{Max}} values in daily clinical practice. Furthermore, we investigated associations of GH_{\text{Max}} with age at time of test, type of test, sex, puberty, or premature birth.

### Materials and Methods

#### Subjects

We analyzed clinical data from children aged ≤17 years suffering from short stature (height-SDS <10th percentile). All children with suspected GHD underwent at least one GH stimulation test at the Department of Paediatric Endocrinology of the University of Leipzig Medical Center between January 2004 and August 2019. Data collection was carried out using tools provided by CrescNet, a network of pediatricians and endocrinology treatment centers monitoring growth in health and disease (NCT03072537) [11]. 1,629 GH stimulation tests (730 tests on girls, 899 tests on boys) with the substances arginine or glucagon from 1,127 children (507 girls, 620 boys) were eligible for analyses. Exclusion criteria were syndromic disorders (e.g., Ulrich-Turner syndrome) or severe chronic diseases (e.g., cystic fibrosis, infantile cerebral paralysis, or coeliac disease). We further excluded all tests with gonadal priming. Diagnoses were made applying the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [12]. After applying the exclusion criteria, 991 children (436 girls, 555 boys) contributing 1,438 tests (633 tests on girls, 805 tests on boys, 1,095 tests with arginine, 343 tests with glucagon) were finally included in the analyses (Fig. 1).

Due to the lack of documented testicular volumes in boys or Tanner breast stages in girls [13], the puberty onset was assessed by determining the bone age at the testing date using the radiographic atlas by Greulich and Pyle [14]. Boys with a bone age >13 years and girls with a bone age >11 years were assumed to be pubertal. Otherwise, the children were considered prepubertal [15]. This information was present for 1,226 tests. Children born before 37 weeks of gestation were defined as preterm [16].

#### Study Procedure

Children with a suspected GHD received a first GH stimulation test. Test substances used were either arginine or glucagon. If the maximal test result was lower than the cut-off limit of 8 ng/mL [17], children were retested after 8–12 weeks. 417 children received more than one test.

Tests were carried out using either 0.5 g L-arginine intravenous (max. 30 g) or 50 μg/kg glucagon intramuscular (max. 1 mg). Blood was taken at 0, 30, 60, 90, and 120 min in the L-arginine test and at 0, 30, 60, 90, 120, 150, and 180 min in the glucagon test. Thereafter, the samples were analyzed via chemiluminescent immunoassay [18].

#### Statistics

Statistical analyses were conducted using R version 4.0 [19]. Descriptive statistics were given as mean and standard deviation for continuous variables, and count and percentage for categorical variables. Group differences were assessed by t tests and χ^2 tests, respectively (Table 1). Univariate and multivariate relationships were estimated using linear mixed-effect models as implemented in the lme4 package [20]. The child was included as a random factor to correct for multiple measurements per child. 95% confidence intervals (CIs) are reported for all effects. p values were estimated using normal approximation as implemented in the multcomp package [21]. First, univariate regression analyses were performed to determine the associations of the covariates with GH_{\text{Max}}. In the following multivariate regression analyses, we included the significant covariates (BMI-SDS and test type) as well as age and sex. In addition, we examined the effect of the pubertal stage (derived from bone age) as well as possible interactions of pubertal stage with other independent variables on GH_{\text{Max}}. To calculate R^2 for multivariate models, we used pseudo-R^2 as described in Nakagawa et al. [22]. p values <0.05 were considered to indicate statistical significance.
Table 1. Clinical characteristics of the cohort (mean values: standard deviation)

|                          | Entire cohort, N = 1,438 tests | Arginine, N = 1,095 tests | Glucagon, N = 343 tests | p value |
|--------------------------|--------------------------------|--------------------------|-------------------------|---------|
| Sex, n (%)               |                                |                          |                         |         |
| Male                     | 805 (56.0)                     | 621 (56.7)               | 184 (53.6)              | 0.349   |
| Female                   | 633 (44.0)                     | 474 (43.3)               | 159 (46.4)              |         |
| Gestational age, weeks   | 38.6 (2.79)                    | 38.5 (2.90)              | 38.9 (2.3)              | 0.018   |
| Age, years               | 7.74 (3.50)                    | 7.60 (3.53)              | 8.15 (3.37)             | 0.009   |
| Bone age, years          | 6.30 (3.38)                    | 6.19 (3.40)              | 6.64 (3.30)             | 0.029   |
| GHMax ng/mL              | 8.77 (5.19)                    | 8.50 (4.88)              | 9.65 (6.01)             | 0.001   |
| Height-SDS               | −2.48 (0.55)                   | −2.49 (0.55)             | −2.46 (0.57)            | 0.330   |
| Weight-SDS               | −2.14 (0.99)                   | −2.17 (0.98)             | −2.03 (0.99)            | 0.018   |
| BMI-SDS                  | −0.71 (1.01)                   | −0.74 (1.01)             | −0.59 (0.99)            | 0.016   |

Underweight: BMI < 10th percentile; normal weight: 10th percentile ≤ BMI ≤ 90th percentile; overweight: 90th percentile < BMI ≤ 97th percentile; obese: BMI > 97th percentile. p values describe differences between the test types. Significant association was classified as p < 0.05. SDS, standard deviation score; BMI, body mass index.

Fig. 1. Schematic diagram of patient selection. SDS, standard deviation score.
Results

Cohort Characteristics

Clinical characteristics are summarized in Table 1 and in online supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000526240). Figure 1 shows a diagram of the inclusion and exclusion process. The study population included a total of 991 children (1,438 tests), contributing 1,095 arginine tests and 343 glucagon tests. 56% of the tests were performed in boys. Mean GH_{Max} was 8.77 ng/mL (±5.19 ng/mL), and mean BMI-SDS was −0.71 (±1.01). In most cases, the children were prepubertal (n = 1,138, 92.8%), and only 88 children were tested after the onset of puberty (7.2%). 1,186 tests had been performed in children born term and 183 tests in children born preterm.

Fig. 2. The relationship between BMI-SDS and GH_{Max} in all tests was assessed by univariate linear regression analysis corrected for multiple measurements per child. There is a significantly negative correlation between BMI-SDS and GH_{Max} with $\beta = -1.09$ ($p < 0.001$). $\beta$, estimate (beta coefficient); BMI, body mass index; SDS, standard deviation score.

Fig. 3. The relationship between BMI-SDS and GH_{Max} in arginine tests was assessed by univariate linear regression analysis corrected for multiple measurements per child. There is a significantly negative correlation between BMI-SDS and GH_{Max} with $\beta = -1.10$ ($p < 0.001$). $\beta$, estimate (beta coefficient); BMI, body mass index; SDS, standard deviation score.
Univariate and Multivariate Regression Analysis

Univariate regression analyses showed consistently negative associations between BMI-SDS and GH\textsubscript{Max} values with effect sizes of about $\beta = -1.1$ within the whole cohort ($\beta_{\text{overall}} = -1.09$, $p < 0.001$, Fig. 2), as well as for arginine tests only ($\beta_{\text{arginine}} = -1.10$, $p < 0.001$, Fig. 3) and glucagon tests only ($\beta_{\text{glucagon}} = -1.06$, $p < 0.01$, Fig. 4). These effects persisted after adjustment for age, test type, and sex ($\beta_{\text{overall}} = -1.15$, $p < 0.001$; $\beta_{\text{arginine}} = -1.10$, $p < 0.001$; $\beta_{\text{glucagon}} = -1.11$, $p < 0.01$). Interestingly, neither in the univariate nor in the multivariate analyses could we find significant associations of age or sex with GH\textsubscript{Max} (Tables 2, 3). We also tested for multicollinearity using the variance inflation factor and found no substantial correlation between the independent variables. We found no significant difference in GH\textsubscript{Max} values between term and preterm born children ($\beta_{\text{preterm}} = 0.64$, $p = 0.23$).

Comparison between Arginine and Glucagon Tests

The test type was associated with GH\textsubscript{Max} with higher values for glucagon than arginine tests ($\beta_{\text{glucagon}} = 2.11$, $p < 0.001$). This effect also persisted after adjustment for BMI-SDS, age, sex, and test type as independent variables ($\beta_{\text{glucagon}} = 2.04$, $p < 0.001$) (Table 2). However, as the univariate regression results above implicate, the test type had no impact on the association between GH\textsubscript{Max} and BMI-SDS.

Effect of Pubertal Bone Age Status on GH\textsubscript{Max}

Pubertal and prepubertal children did not differ significantly in their GH\textsubscript{Max} values ($\beta_{\text{puberty}} = 0.7$, $p = 0.39$). Testing for interactions between the independent variables revealed a marginally significant interaction term of $\beta_{\text{BMI-SDS:Puberty}} = -1.40$ ($p = 0.049$) between BMI-SDS and pubertal bone age status. Therefore, the negative association between BMI-SDS and GH\textsubscript{Max} may be

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**Table 2. Univariate and multivariate regression analysis of associations with GH\textsubscript{Max} in all tests**

| Parameter               | $\beta$ (univariate) [95% CI] | $\beta$ (multivariate) [95% CI] |
|-------------------------|-------------------------------|---------------------------------|
| BMI-SDS [95% CI]        | $-1.09^{***}$ $[-1.36, -0.83]$ | $-1.15^{***}$ $[-1.42, -0.90]$ |
| Age [95% CI]            | $0.07$ ($p = 0.09$) [0.00, 0.15] | $0.07$ ($p = 0.26$) [0.00, 0.15] |
| Type of test\textsubscript{glucagon} [95% CI] | $2.11^{***}$ [1.54, 2.68] | $2.04^{***}$ [1.47, 2.61] |
| Sex\textsubscript{female} [95% CI] | $-0.30$ ($p = 0.45$) $[-0.86, 0.26]$ | $-0.22$ ($p = 0.92$) $[0.79, 0.34]$ |

Multivariate regression model contained the following independent variables entered into the model: BMI-SDS, age, type of test, and sex. Conditional $R^2 = 0.31$. Significant association was classified as $p < 0.05$. BMI, body mass index; SDS, standard deviation score; $\beta$, estimate (beta coefficient); CI, confidence interval. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$. 

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**Fig. 4.** The relationship between BMI-SDS and GH\textsubscript{Max} in glucagon tests was assessed by univariate linear regression analysis corrected for multiple measurements per child. There is a significantly negative correlation between BMI-SDS and GH\textsubscript{Max} with $\beta = -1.06$ ($p < 0.001$). $\beta$, estimate (beta coefficient); BMI, body mass index; SDS, standard deviation score.
stronger in pubertal children compared to prepubertal children. Neither in pubertal nor in prepubertal children, age and sex had a significant influence on GHMax (Table 4).

**Effect of Applying a Correction Factor for the Diagnosis of GHD on the Number of Individuals within the Cohort**

In our cohort, there were 324 children with the diagnosis “GHD” and 667 children without “GHD” according to a cut-off limit of 8 ng/mL. After applying the correction factor, 103 more children would be below this cut-off and 16 children would be corrected above the cut-off (Table 5; online suppl. Table S2).

**Discussion**

In a large cohort of children with short stature, we were able to confirm the significant negative association between BMI-SDS and GHMax described in previous studies [5, 8–10]. For the entire cohort, as well as in the subcohorts of children tested with arginine or glucagon, we found similar associations between BMI-SDS and GHMax in the univariate as well as in the multivariate regression analyses (β = −1.11). In the meta-analysis by Abawi et al. [5], it was found that for each increase in BMI-SDS of 1, there was a decrease in GHMax of 11.6%. In comparison, we found a similar value of 13.61%. Underlying mechanisms could be (1) increased free fatty acids with increased BMI and their inhibiting effect on the production and release of GH, (2) a dysregulation of ghrelin, a hormone which is reduced in obese children and which...
normally has a positive effect on the release of GH-releasing hormone and on GH, (3) an increase in the activity of somatostatin, whose release is stimulated by leptin produced in adipocytes and which consequently inhibits the GH release [7, 8, 23–25]. In adults, the influence of sleep, nutritional status, exercise, and stress on serum GH concentrations have been described [23]. These results suggest that the patient’s BMI-SDS should be considered in the evaluation of a suspected GHD. Our data suggest a correction factor β of approximately −1.1 (GH_{corrected} = \text{GH}_{measured} − (−1.1) \times \text{BMI-SDS}). This correction would presumably reduce false-positive tests of obese children [24] and therefore also reduce possibly unnecessary GH therapies. Although GH therapy is considered safe and effective, it is still an invasive and often cumbersome treatment for a small child. In addition, even though rare, side effects such as headache, idiopathic intracranial hypertension, or, in more severe cases, epiphysiodesis capitis femoris could be avoided [25, 26]. Finally, reducing false-positive test results minimizes unnecessary healthcare costs, at least in overweight children.

However, further aspects need consideration. As we assume the 50th percentile of BMI as the standard in short children, we consequently would have to correct the GH_{Max} value of probands with a BMI-SDS <0 downward. This would likely have an impact on healthcare costs, as the majority of tested children with short stature in our study had a BMI <0 SDS. Moreover, the officially accepted cut-off levels in GH stimulation tests were set more or less arbitrarily [17, 27], and they differ from country to country [28]. Based on our multivariate analysis of the entire cohort, we could explain about 31% of the variance of GH_{Max} by BMI-SDS. Therefore, other factors such as day-to-day variability or test characteristics have an even higher impact on the release of GH or its detection in serum. Therefore, postulating a general correction of test results according to the probands BMI should not only follow scientific and financial considerations, but also carry an ethical dimension.

Interestingly, glucagon and arginine tests differed significantly in their GH_{Max} values, with glucagon tests being on average about 2 ng/mL higher than arginine tests. We assume that these differences in GH_{Max} occur due to the type of test, which also has been described by Secco et al. [29]. Although only relatively young children aged less than 6 years were examined in this study, it was postulated that test-specific cut-off values should be established to avoid false-positive test interpretations [29–31]. However, in practical terms, the remaining great intraindividual variability of test results again argues against this [32].

In our study, the pubertal and nonpubertal children did not differ significantly in their GH_{Max} values [33]. In contrast to Lee et al. [7] but in line with Loche et al. [34], GH_{Max} and BMI-SDS showed a significant negative association in both the pubertal and prepubertal children. This correlation was stronger in pubertal children. However, tests were performed in a considerably smaller number of pubertal children (88 tests) compared to prepubertal children (1,138 tests). Therefore, the described associations should be re-assessed in an even larger cohort of pubertal children in follow-up studies.

Interestingly, in our analysis of the entire cohort, both sex and age did not show significant influence on GH_{Max} as well as in the analyses stratified by test types, which is in line with results described by Stanley et al. [9] and Lee et al. [7]. Also, we found no significant difference in GH_{Max} values between preterm and term born children, which, to the best of our knowledge, has not been reported yet.

Limitations of our study are its retrospective nature and, for this reason, the assessment of the pubertal stage based on bone age rather than Tanner stages. Bone age is mentioned as a possible method for assessing pubertal status [15], but other studies point out the disadvantages of this method. These are, e.g., the greater variability of bone age in contrast to chronological age [35] or the fact that bone age is more advanced in overweight/obese children [36]. This could lead to a higher misclassification of pubertal and nonpubertal children. On the other hand, overweight/obese children enter puberty earlier, which could be detected by the more advanced bone age in these children [37]. In addition, our cohort consisted mainly of normal-to-underweight children and only a few were overweight or obese (Table 1). Arginine tests were mainly performed as the first stimulation test due to the test protocol at the Department of Paediatric Endocrinology of the University of Leipzig Medical Center. This could have led to the difference in GH_{Max} values between glucagon and arginine tests, as glucagon tests were mainly performed in second intention. However, its strength is the large number of probands and tests performed in a single center with little or no variance in test procedures and laboratory setup.

In conclusion, we showed that GH_{Max} and BMI-SDS are significantly negatively associated, bearing in mind the presence of further influencing factors [7, 8, 27] and the large inter- and intraindividual test differences [28, 31]. However, most of the variability could not be explained, more so as characteristics like sex, age, pubertal bone age status, or prematurity were not significantly associated.
with GH\textsubscript{Max}. The correction equation above may improve the assessment of GHD, as the BMI-SDS explained around 30\% percent of the variability of GH\textsubscript{Max}. By applying the correction factor, especially in the group of underweight-to-normal weight children more individuals would show GH\textsubscript{Max} test values indicating GHD. Overweight-to-obese children would be corrected upward, and therefore, some could not any longer be classified as GH deficient. In our opinion, it seems questionable whether it would be ethically correct to diagnose GHD based on an individual BMI and consequently decide on treatment options. On the diagnostic side, we cannot control or even account for the major part of the variability in the test results caused by different diagnostic agents and/or intra- and inter-assay variability or further unknown/unmeasurable factors [31]. Therefore, in our view, a correction of GH\textsubscript{Max} values on the basis of BMI-SDS or individualized cut-off values should be seen critically.

**Statement of Ethics**

All tests were performed as routine clinical work-up of children with short stature when clinically indicated. In all cases, informed written parental consent was obtained. The registry (CrescNet) was approved by the Federal Data Protection Agency and is registered in the clinical trial database (NCT03072537). The parents/guardians are informed about the registry by their pediatricians and asked for assent. Because CrescNet is a registry study, approval from an Ethics Committee was not required. Parents or children/adolescents had the opportunity to withdraw their assent at any time which leads to complete deletion of all data. There were no agreements concerning confidentiality of the data between the sponsors and the authors or the institutions involved in this study. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

**Conflict of Interest Statement**

The authors declare no conflict of interest.

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**Author Contributions**

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**Data Availability Statement**

All data relevant to the study are included in this article and can be obtained by request. Further inquiries can be directed to the corresponding author.

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