Evaluation of the Relationship Between Peak Growth Hormone Response to Growth Hormone Stimulation Tests and Body Mass Index

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ABSTRACT

Objective: A contrary relationship between body mass index (BMI) and growth hormone (GH) secretion has been demonstrated in adults. BMI-specific cutoff levels are suggested for identifying growth hormone deficiency (GHD) in adulthood. However, specific values for BMI and growth hormone stimulation test responses in the childhood age group are not certain. In this research, our purpose was to investigate the relationship between GH peak response and BMI in children who underwent GHST with a prediagnosis of GHD.

Material and Methods: This was a retrospective study of stimulative GH testing with clonidine and L-dopa performed in 150 children 2–18 year-old with short stature (< -2 SDS) in the Pediatric Endocrinology Unit at Bakırçay University Çiğli Training and Research Hospital from the years of 2018 to 2023. Anthropometric measurements, insulin-like growth factor-1 (IGF-1) and IGFBP-3 levels, especially peak-stimulated GH, were evaluated.

Results: A total of 150 patients [98 boys (65.3%) and 52 girls (34.7%)] were included in the study. The mean age of the individuals during testing was 10.26 ± 3.37 years, mean height standard deviation score (SDS) was -2.64 ± 0.89, mean weight SDS was -1.85 ± 1.01 and mean body mass index (BMI) SDS was -0.47 ± 1.07. Ninety-two of the patients (63%) were prepubertal. The mean value for maximum growth hormone serum level (GHmax) clonidine collected during the growth hormone stimulation test was 4.46 ± 2.83 ng/mL, while the mean value in L-dopa test was 3.29 ± 2.57 ng/mL. There was no statistical distinction in terms of both test responses. The correlation between peak GH and BMI-SDS, in terms of clonidine and L-dopa tests, was significantly negative [β = -0.283 (p = 0.004), β = -0.257 (p = 0.010), respectively]. Age, gender and puberty were not significantly associated with peak GH value. In terms of L-dopa peak GH level, the GH level in group 4 (>1 SDS) was revealed to be statistically lower than that in group 1 (< -1 SDS), nevertheless, similar relationship was not detected for clonidine.

Conclusion: In our study, a negative correlation was found between GHmax and BMI-SDS in terms of clonidine and L-dopa tests. Therefore, keeping BMI-SDS in mind when evaluating growth hormone stimulation tests performed in short children may be guiding. Still, future studies are needed to make it a determining factor when deciding on treatment.

Keywords: growth hormone deficiency, growth hormone stimulation test, body mass index.

INTRODUCTION

Growth hormone (GH) is an anterior pituitary hormone that is regulated by hypothalamic GH-releasing hormone (GHRH) and is secreted mainly during REM sleep, following a pulsatile pattern affected by age, gender, sleep, nutrition, physical activity and body weight (1,2). GH effects the liver and stimulates insulin-like growth factor-1 (IGF-1) production. The produced IGF-1 is a protein that exerts anabolic effects and plays a crucial role in linear growth (3). GH secretion occurs in a pulsatile manner, primarily regulated by GHRH and somatostatin or by direct negative feedback from IGF-1 (4). The diagnosis of growth hormone deficiency (GHD) includes auxological parameters (e.g. short stature), laboratory results (e.g. decreased plasma IGF-1 levels), radiological parameters (e.g. delayed bone age), and differentiating from syndromes associated with inadequate growth (e.g. skeletal dysplasias). Recent studies have reported that GH has impacts on some psychological processes.
Children with GHD have been reported to experience sleep disorders, failure to mature psychologically and impaired personality development (5). Failure to thrive, behavioral problems, lack of confidence in social life and depressive symptoms are noteworthy in individuals with GHD (6). Therefore, growth hormone deficiency in children appears as a public health problem that needs to be treated.

GH has short half-life, standart direct evaluation is not useful in identifying deficiency. In place of, dynamic GH stimulation tests are preferred as diagnostic tests. These tests include administering a GH releasing agent (e.g., clonidine, L-dopa, insulin, arginine, glucagon) followed by consecutive evaluation of plasma GH values every 30 minutes. ‘Pediatric Endocrine Society and Growth Hormone Research Society’ recommend performing two separate GH stimulation test (7,8). The sensitivity and specificity of these tests vary widely. Shortly after the first publication in 1963 (9), many studies mentioned blunted replies to GH stimulants in adults and children with obesity, while the precise pathophysiology has not been understood (10). Publications describing this response in the obese have been published over the years such as hypothalamic factors (such as somatostatin/GHRH, ghrelin, etc.) and peripheral factors (such as IGF-1, free fatty acids, insulin) (4). Unfortunately, in individuals with overweight or obesity; the unexpected blunted response may lead to overdiagnosis of GHD. However, recent guidelines report unsatisfactory evidence to use BMI-adjusted threshold values in individuals and therefore do not ensure guidance on assessing peak GH values in children with overweight or obesity (7,8). The Pediatric Endocrine Society's 2019 guidelines underline that further research on the influence of obesity on identifying GHD in children is a primary issue (7). Nevertheless, studies in this field are insufficient.

This retrospective study aimed to determine GH's effect on BMI response to clonidine and L-dopa stimulation in 150 children with short stature evaluated at a single center.

**MATERIAL and METHODS**

**Patients**

Medical records were obtained retrospectively from 150 children (Tanner stage 2–5, 98 boys and 67 girls; 94 prepubertal and 56 pubertal) who was performed GH stimulation testing for short stature at Bakırçay University Çiğli Training and Research Hospital between 2018 and 2023. The research was approved by the Bakırçay University Çiğli Training and Research Hospital Ethics Committee (dated 9.13.2023; decision number: 1179). All procedures were applied in accordance with the ethical standards specified in the Declaration of Helsinki. All families of the patients were informed about the purposes of the study and that their medical data could be published, and informed written consent was provided from the parents of the patients. The same pediatric endocrinologist examined all children enrolled in the study for short stature and the laboratory results did not reveal any chronic disease. Summarized clinical characteristics are included in Table 1. Clonidine testing was performed (0.15 mg/m2 orally), before 9.00 am. Blood samples were obtained at 0 minute, and after the ingestion of drug at 30, 60, 90 and 120 minutes for GH levels. IGF-1 was also studied in all individuals at baseline. Individuals with a GH peak response after clonidine <10 mcg/l performed another stimulation test with L-dopa (10 mg/kg orally). L-dopa tests were performed after fasting overnight. The patients did not use any pharmacological agent during stimulation tests.

**Statistical analysis:** SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp. was applied for all statistical analyses. Kolmogorov–Smirnov test was used to analyze the distribution of data. Pearson correlation coefficient was used for univariate analysis. Comparing the two groups were analyzed using the Student t-test. Multivariate linear regression analysis was analysed to determine independent estimators of the peak GH reply to the stimulus. The covariates included sex, age, pubertal stage, BMI-SDS, height velocity-SDS (HV-SDS), height-SDS, target height-SDS, IGF-I, and IGFBP-3. Height-SDS and BMI-SDS were obtained from the Turkish reference data (11). All values are reported as mean ± SD. P < 0.05 (two sided) was evaluated as significant.

**RESULTS**

**Table 1**: Shows that the relationship between L-dopa peak levels. There was no statistically significant distinction between the groups regarding IGFBP-3 levels.

When the relationship between clonidine GH peak response and clinical parameters was examined by multivariate regression analysis, a significant negative correlation was detected with BMI SDS (p = 0.010), but no significant correlation was detected with other parameters (Table 2). When the relationship between L-dopa GH peak response and clinical parameters was examined by multivariate regression analysis, a significant negative correlation was detected with BMI SDS (p = 0.004) and a significant positive correlation with IGF-1 level (p = 0.007). No significant correlation was detected with other parameters (Table 3).
**Table 1. Clinical characteristics of the individuals (Values are mean ± SD)**

<table>
<thead>
<tr>
<th>Features</th>
<th>All patients (n=150)</th>
<th>Group 1 (-&lt;1) (n=43)</th>
<th>Group 2 (-1 to 0) (n=55)</th>
<th>Group 3 (0 to +1) (n=41)</th>
<th>Group 4 (&gt;1) (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)*</td>
<td>10.26 ± 3.37</td>
<td>12.34 ± 2.10</td>
<td>10.60 ± 2.97</td>
<td>7.98 ± 3.27</td>
<td>8.94 ± 4.18</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>98/52</td>
<td>31/12</td>
<td>33/22</td>
<td>26/15</td>
<td>8/3</td>
</tr>
<tr>
<td>Prepubertal %</td>
<td>63 %</td>
<td>41.4 %</td>
<td>57.4 %</td>
<td>85 %</td>
<td>90.9 %</td>
</tr>
<tr>
<td>Weight SDS*</td>
<td>-1.85 ± 1.01</td>
<td>-2.81 ± 0.63</td>
<td>-1.88 ± 0.60</td>
<td>-1.15 ± 0.74</td>
<td>-0.47 ± 1.08</td>
</tr>
<tr>
<td>Height-SDS</td>
<td>-2.64 ± 0.89</td>
<td>-2.78 ± 0.72</td>
<td>-2.73 ± 0.86</td>
<td>-2.39 ± 1.03</td>
<td>-2.58 ± 1.00</td>
</tr>
<tr>
<td>BMI SDS*</td>
<td>-0.47 ± 1.07</td>
<td>-1.82 ± 0.58</td>
<td>-0.44 ± 0.29</td>
<td>0.41 ± 0.32</td>
<td>1.33 ± 0.22</td>
</tr>
<tr>
<td>Target height SDS</td>
<td>-0.99 ± 0.96</td>
<td>-0.85 ± 0.60</td>
<td>-1.10 ± 0.76</td>
<td>-1.06 ± 1.60</td>
<td>-1.09 ± 0.44</td>
</tr>
<tr>
<td>HV-before treatment (cm/year)</td>
<td>4.32 ± 1.52</td>
<td>4.03 ± 1.44</td>
<td>4.33 ± 1.34</td>
<td>4.45 ± 1.75</td>
<td>4.71 ± 1.61</td>
</tr>
<tr>
<td>IGF-1 (mcg/L)</td>
<td>112.6 ± 61.4</td>
<td>136.1 ± 65.4</td>
<td>111.4 ± 49.3</td>
<td>97.7 ± 63.6</td>
<td>82.1 ± 67.3</td>
</tr>
<tr>
<td>IGF-BP3 (mg/L)</td>
<td>3.97 ± 1.74</td>
<td>4.36 ± 1.12</td>
<td>4.11 ± 2.18</td>
<td>3.66 ± 1.41</td>
<td>3.05 ± 1.78</td>
</tr>
<tr>
<td>Clonidine-GH peak (mcg/L)</td>
<td>4.46 ± 2.83</td>
<td>4.81 ± 2.68</td>
<td>4.35 ± 2.73</td>
<td>4.80 ± 3.11</td>
<td>2.42 ± 2.08</td>
</tr>
<tr>
<td>L dopa-GH peak (mcg/L)</td>
<td>3.29 ± 2.57</td>
<td>3.80 ± 3.10</td>
<td>3.29 ± 2.32</td>
<td>3.27 ± 2.36</td>
<td>1.45 ± 1.32</td>
</tr>
<tr>
<td>HV-first year of the treatment</td>
<td>10.53 ± 3.65</td>
<td>9.76 ± 3.64</td>
<td>9.79 ± 3.46</td>
<td>11.7 ± 3.43</td>
<td>13.06 ± 4.05</td>
</tr>
</tbody>
</table>

BMI: body mass index, SDS: standard deviation score, HV: height velocity

* Each BMI SDS group varied significantly (p < 0.05) from the other three groups per study design

b Statistically significant variation (p < 0.05) vs. BMI SDS 0 to +1 and BMI SDS > 1 groups.

c Statistically significant variation (p < 0.05) vs. group with BMI SDS < -1.

**Figure 1:** Variation of mean clonidine peak GH response according to BMI-SDS

**Figure 2:** Variation of mean L-dopa peak GH response according to BMI-SDS

GH: growth hormone
BMI: body mass index
SDS: standard deviation score
DISCUSSION

Our findings show that the peak GH response to stimulation tests with clonidine and L-dopa reduces with an increment of BMI SDS in a cohort of short, otherwise healthy children. Analysis of peak GH response by BMI SDS category revealed that individuals with higher BMI SDS may be more likely to have an unsatisfactory reply on the GH stimulation test. Additionally, in our cohort, in terms of L-dopa peak GH level, the GH level in group 4 (>1 SDS) was statistically lower than that in group 1 (< 1 SDS).

Our data indicate many similarities with those promulgated by Stanley et al. They reported a negative correlation between BMI-SDS and GH peak in 116 short children who underwent GH stimulation tests using four different secretagogues (arginine, clonidine, L-dopa/carbidopa, propranolol) (12). In our study, a similar relationship was observed in two stimulation tests (clonidine, L-dopa). Stanley et al. also revealed that the correlation between BMI-SDS and GH peak was substantial solely in prepubescent individuals, whereas in our research, the correlation was substantial in the entire cohort (12).

Studies conducted in adult subjects have revealed a contrary relationship between BMI and GH provocation tests. In the study of Dichtel et al., which enrolled 108 overweight/obese patients, it was revealed that while BMI significantly influenced L-Dopa tests, they were not affected by the arginine test (13). Similarly, in our study, in terms of L-dopa peak GH level, the GH level in group 4 (>1 SDS) was reported to be statistically lower than that in group 1 (< -1 SDS), nevertheless, similar relationship was not detected for clonidine.

Even though GH treatment is revealed as reliable and effective, it is considered an invasive and usually costly therapy for young children. Yang et al. included 460 children who underwent GH provocation test in their retrospective study. They classified participants according to their BMI. Obese children with GHD have a significantly better reply in height increment and BMI reduction pending two years of GH therapy compared to non-obese children with GHD.

There were no differences between peak GH and GH stimulation test (GHST) type, except for the clonidine test, which showed a much lower peak GH in obese GHD children (Peak GH: 0.86 [Obese] vs. 5.49 [Normal/Overweight], p = 0.008)(14). It showed that the threshold value for the obese group was significantly lower than that for the normal/overweight group. Considering these findings, obesity alters with the sort of challenge test but significantly influences the peak stimulated GH value. Loche et al. described the contrary influence of BMI on the GH reply to the clonidine stimulation test (15). In the study by Thieme et al., the GH response was found to be approximately 2 ng/mL higher on average than arginine tests (16). It was assumed that these distinctions in the GH peak value were owing to the sort of test used by Secco et al (17). Lowering the GHST cut-off value should be considered in stimulation tests applied in the obese GHD group, including the most commonly used clonidine and L-dopa tests in the childhood age group.

The limitations of our study were its retrospective pattern, and the absence of control group. Additionally, the fact that the study was conducted in a single center may have resulted in limited data.

CONCLUSION

In conclusion, BMI significantly influences the peak GH response in short GHD patients, contributing substantially to the variability in peak growth hormone levels. Therefore, it is essential to consider BMI when evaluating responses to stimulation tests. This highlights the need for novel and more effective stimulation agents.

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Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study.

REFERENCES


