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Diagnostic Value of Peak-to-Basal Difference or Ratio of Growth Hormone in Children with Growth Hormone Deficiency

Özge Köprülü[1], Elif Gökçe Basa[1], İbrahim Mert Erbaş[1,2], Fatma Yavuzyılmaz Şimşek[1], Özlem Nalbantoğlu[1,2], Hüseyin Anıl Korkmaz[1,2], Behzat Özkan[1,2]

[1]University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Türkiye
[2]University of Health Sciences Türkiye İzmir Faculty of Medicine, Department of Pediatrics, İzmir, Türkiye

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What is already known on this topic?

Growth hormone (GH) deficiency is a relatively rare but important cause of short stature in children, and its diagnosis remains challenging due to the limitations of GH stimulation tests.

What this study adds?

In this study, we evaluated the diagnostic performance of basal-to-peak ratio and basal-to-peak difference derived from L-Dopa and clonidine stimulation tests. Our findings indicate that ΔGH (peak-to-basal difference), particularly in the clonidine test, demonstrated excellent diagnostic performance and may serve as a reliable adjunct to conventional peak GH cut-offs in clinical practice.

ABSTRACT

Objective: Growth hormone (GH) deficiency (GHD) is a rare but important cause of short stature in children. Although GH stimulation tests remain the gold standard for diagnosis, establishing a definitive diagnosis continues to be challenging. Our aim was to evaluate the diagnostic performance of the peak-to-basal ratio and difference for identifying GHD in children.

Methods: Patients with short stature who were evaluated for GHD with GH stimulation tests were retrospectively assessed. ΔGH was defined as the difference between peak and basal GH levels. The GH ratio was calculated as the ratio of peak to basal GH levels.

Results: Data were collected from 265 patients (182 prepubertal) with a median age at presentation of 10.6 years (interquartile range: 6.13-12.42), of whom 46.7% were female. In total, 146 patients met the diagnostic criteria for GHD. ΔGH and GH ratio during the L-Dopa and Clonidine stimulation tests were significantly lower in the GHD group ($p<0.001$). A ΔGH cut-off of ≤7.08 in the clonidine test demonstrated

Corresponding Author: Özge Köprülü, MD, University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Türkiye
E-mail: ozgeguclu@hotmail.com **ORCID:** orcid.org/0000-0002-0598-3494
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excellent discriminative ability, with both sensitivity and specificity above 80%, and an area under the curve close to 0.9, suggesting that this parameter may may provide supportive diagnostic information for GHD.

Conclusion: To the best of our knowledge, ΔGH has been explored only in a limited number of studies. This study investigated diagnostic accuracy of difference (ΔGH) or ratio of peak-to-basal GH on a large cohort of children with short stature. The supportive diagnostic performance observed in our cohort suggests that ΔGH is clinically useful in routine practice.

Keywords: GH ratio, growth hormone deficiency, growth hormone stimulation tests, short stature, ΔGH

Introduction

Short stature is one of the most common reasons for referral to pediatric endocrinology clinics (1). Short stature is defined as a height below -2 standard deviation (SD) scores (SDS) for age and sex (2).

Growth hormone (GH) deficiency (GHD) is one of the most important causes of short stature in children, and accounts for approximately 10% of cases presenting with short stature. Its prevalence ranges from 1/4,000 and 1/10,000 according to reports from around the world (3,4). Although relatively rare, an accurate and early diagnosis of GHD is important, as recombinant human GH (rhGH) replacement therapy is highly effective. Conversely, a misdiagnosis may lead to unnecessary economic costs and expose patients to avoidable adverse effects (5).

The diagnosis of GHD typically relies on evidence from clinical, auxological, radiological, and biochemical assessments and endocrine dynamic tests (1). Although the assessment of spontaneous GH release is considered the best approach, difficulties associated with technicalities and standardization of results make it challenging (6). A diagnosis of GHD requires a failure to respond to two separate stimulation tests (1).

GH stimulation tests are still the gold standard for the diagnosis of GHD, but controversies remain regarding diagnostic criteria (7). One of the major challenges in the diagnostic process is the uncertainty regarding the cut-off values used to define GHD. The limited availability of reference data on GH secretion in normally growing children and the variability in assay methodologies over time both contribute to this uncertainty (6).

With the advent of monoclonal antibody testing and the implementation of newer standards, GH assay results are approximately 40% lower than those obtained with older immunoassay-based methods. Consequently, the diagnostic cut-offs for GHD should be reduced accordingly. However, no universally accepted threshold has yet been established (1).

In this study, we aimed to evaluate the diagnostic performance of the peak-to-basal ratio and peak-to-basal difference for identifying GHD in children.

Methods

Study Design and Patients

We retrospectively analyzed patients with short stature who were evaluated for GHD with GH stimulation tests at the University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital between December 2022 and August 2025. All patients were followed up in our pediatric endocrinology clinic at a tertiary referral hospital in western Türkiye. A structured questionnaire was used to systematically evaluate all clinical, hormonal and radiological data. The SDS for weight, height, body mass index (BMI), and midparental height were measured according to Turkish children's reference values (8).

Patients with chronic systemic illnesses, chronic conditions affecting growth, untreated or inadequately treated hypothyroidism or other endocrine disorders were excluded from the study. Mild, well-controlled hypothyroidism was allowed if thyroid function had been normalized before testing. In addition, patients with incomplete data regarding GH stimulation tests or biochemical parameters were also excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Non-Interventional Research Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 2025/15-07, date: 02.10.2025). Informed consent was obtained from all subjects and parents involved in the study. Written informed consent has been obtained from the patients and parents to publish this paper.

Hormonal and Biochemical Measurements

Serum GH concentrations were measured by chemiluminescent immunoassay, using Siemens Healthineers IMMULITE 2000 xpi Immunoassay System (Siemens Healthineers USA, 40 Liberty Blvd, Malvern, PA 19355, US). Results were expressed in ng/mL. After an overnight fast, L-Dopa was administered orally at a dose of 10 mg/kg (maximum 500 mg), and blood samples were obtained at 0, 30, 60, 90, and 120 minutes for GH measurement. Following overnight fasting, clonidine was administered orally at a dose of 0.15 mg/m² (maximum 300 mg) body surface area between 08:00 and 09:00 and blood samples were collected at baseline and at

30, 60, 90, and 120 minutes. The highest GH value obtained during the test was defined as the peak GH concentration. Children with peak GH value <10 ng/mL in the first stimulation test underwent a second stimulation test on a separate day. GHD was diagnosed when the peak GH concentration was <10 ng/mL in at least two different stimulation tests. ΔGH was calculated as the difference between peak and basal GH levels in the L-Dopa and Clonidine stimulation tests. The GH ratio was calculated as the ratio of peak to basal GH levels during the L-Dopa and Clonidine stimulation tests.

Statistical Analysis

Statistical analyses of the data were performed using SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Distribution of data was evaluated using the Kolmogorov-Smirnov test. For numerical comparisons, the Student's t-test or Mann-Whitney U tests were used to assess differences between the two groups according to the normal distribution of the measured parameters. Categorical variables were analyzed with the chi-square test. Receiver operating characteristic (ROC) curves were used to define the cut-off values for the ratios and delta of GH levels in clonidine and L-Dopa tests that yielded the highest sensitivity and specificity. Data are presented as mean±SD or median and interquartile range (IQR, 25th-75th percentile). In all statistical tests, p values <0.05 were considered as statistically significant.

Results

A total of 317 patients with short stature who underwent GH stimulation testing were included in the analysis. Fifty-two patients with a peak GH >10 ng/mL in the first stimulation test were excluded from the study. Data were collected from the remaining 265 patients, of whom 182 were prepubertal and 46.7% were girls, with a median age at presentation of 10.6 years (IQR: 6.13-12.42). In total, 146 (55.1%) patients met the diagnostic criteria for GHD.

The cohort with GHD consisted of 146 children, including 79 (54.1%) male and 67 female, with a median age of 10.3 years (IQR: 6.3-12.6). These children had a median height SDS of -2.64 (IQR: -3.02– -2.37) and a mean BMI SDS of -0.55±1.07. The GH peak responses to L-Dopa and Clonidine stimulation were 3.09 and 5.14 ng/mL, respectively.

Table 1 summarizes the demographic, clinical, and laboratory findings of the patients, comparing those diagnosed with GHD to those without GHD. Chronological age, age by height, bone

Table 1. The demographic, clinical, and laboratory findings of the patients

	GH deficiency (n=146)	Normal (n=119)	p value
Gender (male/female)	79/67	63/56	0.846
Prepubertal/Pubertal	102/45	80/38	0.781
Chronological age (years)	10.3 (6.3-12.6)	9.0 (5.9-12.3)	0.398
Age by height (years)	7.59 (4.45-9.98)	6.84 (3.83-9.45)	0.321
Bone age (years)	8.0 (4.0-11.0)	7.0 (3.5-11.0)	0.468
Weight, SDS*	-1.89±1.04	-2.19±0.88	0.008
Height, SDS	-2.64 (-3.02–-2.37)	-2.69 (-3.16–-2.29)	0.863
BMI, SDS*	-0.55±1.07	-0.83±0.88	**0.020**
MPH, SDS*	-1.26±0.98	-1.39±0.91	0.342
IGF-1, SDS	-1.61 (-2.27–-1.15)	-1.46 (-2.21–-0.79)	0.121
IGFBP-3, SDS	-0.41 (-1.05-0.27)	-0.22 (-0.63-0.34)	0.051
L-Dopa			
Peak GH, L-Dopa	3.09 (1.79-4.60)	6.49 (4.11-11.25)	**<0.001**
ΔGH, L-Dopa	2.37 (0.53-3.77)	5.15 (2.21-10.70)	**<0.001**
GH ratio, L-Dopa	7.78 (1.69-28.19)	16.6 (5.2-91.6)	**0.001**
Clonidine			
Peak GH, Clonidine	5.14 (3.20-7.11)	13.05 (11.4-15.70)	**<0.001**
ΔGH, Clonidine	4.59 (2.34-6.44)	11.79 (9.59-14.40)	**<0.001**
GH ratio, Clonidine	12.77 (4.10-38.8)	26.15 (8.80-68.5)	**0.006**

*Normal distribution (Student's t-test). Data are given as mean ± SD or median (IQR 25-75 percentile).
ΔGH: peak GH-basal GH in the L-Dopa and Clonidine provocation tests.
GH ratio: ratio of peak-to-basal GH in the L-Dopa and Clonidine provocation tests.
SDS: standard deviation score, GH: growth hormone, BMI: body mass index, MPH: midparental height, IGF-1: insulin-like growth factor 1, IGFBP-3: insulin-like growth factor binding protein 3

age, weight SDS, height SDS, mid-parental height SDS, insulin-like growth factor-1, SDS, and IGF-binding protein-3 SDS were similar between the groups.

As expected, peak GH responses during both the L-dopa and clonidine stimulation tests were significantly lower in patients with GHD compared with those without GHD. ΔGH (the difference between peak and basal GH levels) in the stimulation tests were significantly lower in the GHD group ($p<0.001$). GH ratio (the ratio of peak-to-basal GH levels) during the L-Dopa and Clonidine stimulation tests were significantly lower in the GHD group ($p<0.001$).

ROC analysis revealed that the cut-off value of GH ratio in the L-Dopa stimulation test ≤9.98 supported good diagnostic prediction with 57.2% sensitivity and 63.3% specificity [area under the curve (AUC)± standard error (SE), 0.627±0.038; $p=0.001$] (Figure 1). ROC curve analysis also identified a cut-off value of ≤4.04 for the ΔGH in the L-Dopa stimulation test which yielded 82.2% sensitivity and 60.9% specificity (AUC±SE, 0.735±0.036; $p=0.001$) (Figure 2).

ROC curve analysis showed that a GH ratio cut-off value of ≤27.4 in the Clonidine stimulation test provided good diagnostic performance, with 66% sensitivity and 49.4% specificity (AUC±SE, 0.610±0.039; $p=0.001$) (Figure 3). ROC curve analysis demonstrated that a cut-off value of ΔGH ≤7.08 in the clonidine stimulation test also provided good diagnostic accuracy, with 81.3% sensitivity and 86.2% specificity (AUC±SE, 0.892±0.029; $p<0.001$) (Figure 4).

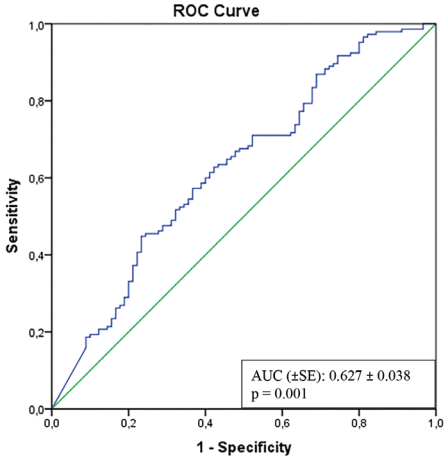

Figure 1. ROC curve analysis of the GH ratio in the L-Dopa stimulation test
ROC: receiver operating characteristic, AUC: area under the curve, SE: standard error, GH: growth hormone

Discussion

In this study, we investigated the diagnostic performance of the GH ratio and ΔGH on L-Dopa and clonidine stimulation tests for identifying GHD in children. Our findings demonstrated that ΔGH and GH ratio may provide additional supportive evidence, particularly ΔGH in the clonidine test.

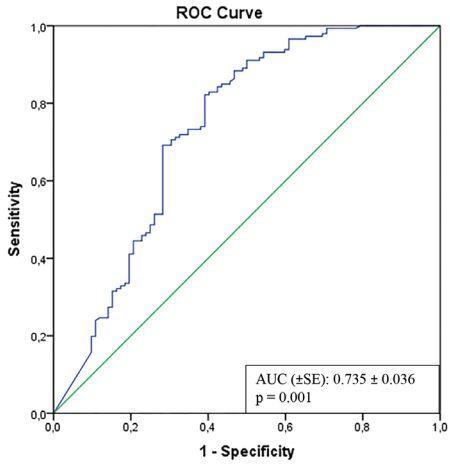

Figure 2. ROC curve analysis of the ΔGH in the L-Dopa stimulation test
ROC: receiver operating characteristic, AUC: area under the curve, SE: standard error, GH: growth hormone

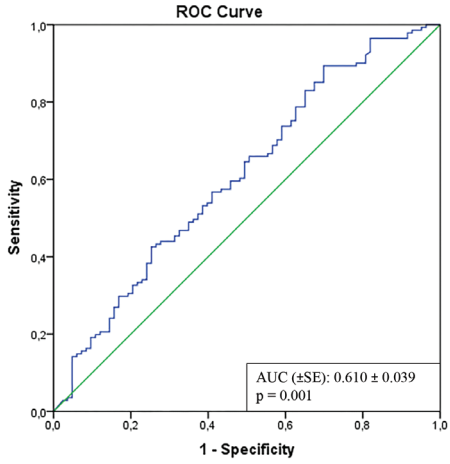

Figure 3. ROC curve analysis of the GH ratio in the Clonidine test
ROC: receiver operating characteristic, AUC: area under the curve, SE: standard error, GH: growth hormone

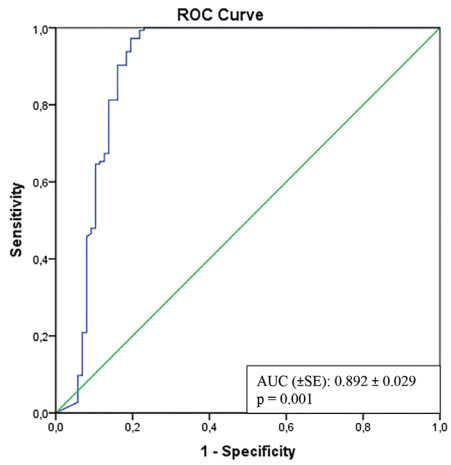

Figure 4. ROC curve analysis of the ΔGH in the Clonidine stimulation test
ROC: receiver operating characteristic, AUC: area under the curve, SE: standard error, GH: growth hormone

A diagnosis of GHD is established when peak GH responses are subnormal in at least two independent stimulation tests (4,9). As expected, in our cohort, the peak GH levels were lower in children with GHD than in non-GHD.

GHD accounts for only a small proportion of children with short stature, but misdiagnosis is common and may expose children to unnecessary treatment (6). Despite the dramatic changes in GHD treatment since the 1960s, diagnosing GHD remains challenging (6,10). Previous studies have also reported the challenges of GH stimulation tests. Furthermore, GH secretion may be influenced by factors such as obesity, undernutrition, sex, age and puberty (1,6,11). In fact, due to the inherent limitations of GH stimulation tests, the Pediatric Endocrine Society guidelines recommend against using GH stimulation test results as the sole diagnostic criterion for GHD in children and emphasize the importance of integrating auxological, biochemical, and imaging findings in the diagnostic process (12).

GH stimulation tests remain controversial, due to their low sensitivity and specificity, which further reduce their diagnostic reliability (13). Traditionally, a peak GH cut-off of <10 µg/L has been used in children. However, some experts have proposed lowering this threshold to <7 µg/L. Although diagnostic guidelines have been revised over the past decades and peak GH cut-off values have been modified accordingly, these thresholds remain largely arbitrary, particularly in pediatric populations (14).

The difficulties in performing GH stimulation tests, the potential adverse effects, reference data for GH secretion in normally growing children, the high false-positive rates and the uncertainty of consensus on cut-off values have led researchers to explore new diagnostic strategies (4,7,11,15,16).

The rationale for using ΔGH or GH ratio lies in their ability to capture dynamic responsiveness rather than relying on a single stimulated peak, which may be influenced by pre-test conditions, body composition, or assay variability. In our cohort, ΔGH improved the discrimination of the tests, supporting the concept that such dynamic indices may offer supplementary information rather than serving as independent diagnostic tools.

One possible explanation for false-negative results in GH stimulation testing is the occurrence of a spontaneous physiological GH peak shortly before the test (9,17), which may blunt the stimulated response. In such cases, considering the increase relative to the basal value may provide a better reflection of the pituitary reserve and secretory capacity than absolute peak concentrations alone.

In children with peak GH responses <5 ng/mL, the diagnosis of GHD is clearer (2,7,9,12). However, when peak GH values is in the range of 5-10 ng/mL, the diagnosis becomes more challenging and requires additional values and supportive criteria. Our study extends previous findings by identifying a ΔGH cut-off of ≤7.08, although its clinical utility remains dependent on the reference peak GH threshold used to define GHD. In our cohort, a ΔGH value of ≤7.08 in the clonidine stimulation test demonstrated reasonable discriminative performance, with sensitivity (81.3%) and specificity (86.2%) both exceeding 80% and an AUC approaching 0.9. These results suggest that ΔGH may provide supportive diagnostic information, particularly when evaluating children within the borderline peak GH range of 5-10 µg/L. However, although ΔGH showed discriminative ability in this subgroup, it did not confer a clear diagnostic advantage over conventional peak GH criteria. Therefore, ΔGH should be interpreted as an adjunctive rather than a primary diagnostic parameter.

To the best of our knowledge, ΔGH has rarely been investigated in the diagnostic work-up of pediatric GHD. Borges et al. (18) addressed this parameter and reported that both GH peak concentrations and ΔGH were significantly lower in children with GHD compared to non-GHD groups. Our study extends these findings by identifying a ΔGH cut-off (≤7.08) with supportive performance, thereby providing novel evidence that this parameter may serve as a reliable criterion.

Study Limitations

This study has certain limitations. First, the retrospective, single-center design inherently restricts the generalizability of our findings, as patient characteristics, clinical approaches, and stimulation protocols may differ across institutions. Second, only L-Dopa and clonidine stimulation tests were used; the proposed ΔGH and GH ratio thresholds were not validated against more reliable reference tests, such as the insulin tolerance test (ITT).

Third, subgroup analyses by pubertal stage, sex, BMI and magnetic resonance imaging (MRI) characteristics were limited. Another limitation of our study is that GHD was defined based on stimulation test results rather than structural or genetic confirmation. However, this definition is consistent with most clinical studies in the field, as the ITT or MRI-based criteria are not routinely available for all patients. Finally, longitudinal outcomes, particularly growth response to rhGH treatment, were not available. Prospective, multicenter studies are needed to examine whether baseline ΔGH and GH ratio predict rhGH treatment response.

Conclusion

The strong supportive diagnostic performance observed in our cohort suggests that ΔGH is clinically useful in routine practice. However, validation in larger, multicenter studies with other supporting diagnostic data, such as cranial MRI and/or ITT, is needed before it can be widely adopted.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Non-Interventional Research Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 2025/15-07, date: 02.10.2025).

Informed Consent: Informed consent was obtained from all subjects and parents involved in the study. Written informed consent has been obtained from the patients and parents to publish this paper.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Özge Köprülü, Concept: Özge Köprülü, İbrahim Mert Erbaş, Behzat Özkan, Design: Özge Köprülü, İbrahim Mert Erbaş, Behzat Özkan, Data Collection or Processing: Özge Köprülü, Elif Gökçe Basa, Fatma Yavuzyılmaz Şimşek, Özlem Nalbantoğlu, Hüseyin Anıl Korkmaz, Analysis or Interpretation: Özge Köprülü, Elif Gökçe Basa, Literature Search: Özge Köprülü, Writing: Özge Köprülü, İbrahim Mert Erbaş, Behzat Özkan.

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