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Research Article

Diagnostic Value of IGF-1 in Growth Hormone–Deficient Children: Is a Second Growth Hormone Stimulation Test Necessary?

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Abstract

Objective: we assessed the diagnostic accuracy of insulin-like growth factor (IGF) 1 measurements with 1 growth hormone stimulation test (GHST) vs performing 2 GHSTs as the standard test to confirm the diagnosis of growth hormone deficiency (GHD) in children.

Methods: We retrospectively analyzed the baseline characteristics, anthropometric measurements, and laboratory data of 703 children with short stature, aged 4-14 years (mean age, 8.46 ± 2.7 years), who had undergone 2 GHSTs. We compared the diagnostic values of IGF-1 levels by using a cut-off value of ≤0 SD score, along with results of a single clonidine stimulation test (CST). We evaluated the false-positive rate, specificity, likelihood ratio, and area under the curve (AUC) of the 2 diagnostic methods. GHD was diagnosed if the peak growth hormone level was <7 ng/mL on 2 GHSTs.

Results: Of the 724 children, 577 (79.7%) had a low IGF-1 level (mean 104.9 ± 61.4 ng/mL), and 147 (20.3%) had a normal IGF-1 level (mean 145.9 ± 86.9 ng/mL). GHD was diagnosed in 187 patients (25.8%), of whom 146 (25.3%) had a low IGF-1 level. An IGF-1 level reflecting ≤0 SDs in combination with results of a single CST had a specificity of 92.6%, a false-positive rate of 5.5%, and an AUC of 0.6088. Using an IFG-1 cut-off level of ≤−2 SDs did not alter the diagnostic accuracy.

Conclusion: Low IGF-1 values of ≤0 SDs or ≤−2 SDs in combination with results of a single CST had poor diagnostic accuracy for GHD.

Key Words: growth hormone deficiency, insulin-like growth factor 1, diagnostic value

Abbreviations: AUC, area under the curve; BMI, body mass index; CST, clonidine stimulation test; GH, growth hormone; GHD, growth hormone deficiency; GHST, growth hormone stimulation tests; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; SD, standard deviation.

Growth hormone deficiency (GHD) is a rare cause of short stature in children and is defined as inadequate secretion of growth hormone (GH) from the anterior pituitary gland. The incidence ranges from 1 per 4000 to 1 per 20 000 of the population [1]. The diagnosis is established through clinical history, physical examination and auxological measurements, biochemical analysis of insulin-like growth factor (IGF) 1 and insulin-like growth factor–binding protein (IGFBP) 3, bone age determination, magnetic resonance imaging features, and results of growth hormone stimulation tests (GHSTs) [1-7].

IGF-1 and IGFBP-3 are GH dependent and help mediate the anabolic and linear growth–prompting effect of pituitary GH [8]. Their levels indicate the status of GH endogenous secretion, exhibit minimal circadian variation [9], and are proposed to be useful tools in evaluating GHD in children [10, 11]. IGF-1 levels are influenced by many factors, including age, pubertal stage, and conditions such as chronic diseases, malnutrition, and GHD. IGFBP-3 is a major carrier protein for both IGF-1 and IGF-11 and has been also used in screening tests for GHD. However, its use in testing has shown no major advantage over the SDs of IGF-1 levels except for its relative high serum concentration in children younger than 8 years; therefore, it is a better identifier of GHD, inasmuch as normal IGF-1 levels are relatively low in this age group [9].

The diagnostic accuracy of IGF-1 level as a valuable screening tool in the evaluation of suspected childhood GHD is questionable because of conflicting data. Furthermore, the standardization of assays and the validation of IGF-1 reference ranges adjusted for age, sex, and pubertal stage are problematic [9, 12]. Multiple studies have demonstrated that IGF-1 level possesses high specificity and low sensitivity, which suggests that a subnormal IGF-1 level is strongly indicative of GHD [13-15]. In contrast, other studies have demonstrated that IGF-1 level has poor diagnostic accuracy. A recent study showed that as a screening test for GHD, IGF-1 level had poor diagnostic accuracy and should not be used alone for GHD screening [16]. In support of those findings, Ibba et al also concluded that IGF-1 measurement had poor accuracy in discriminating children with GHD from those without GHD [17]. However, most studies have demonstrated the usefulness of IGF-1 measurement along with auxological data and results of GHSTs in the diagnosis of GHD [18, 19].

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Various IGF-1 cut-off values have been proposed for the diagnosis of GHD. The Growth Hormone Research Society proposed that an IGF-1 level >0 SDs at any age makes the diagnosis of GHD unlikely [7]. Wit et al proposed the use of a wider range of serum IGF-1 values (between 0 and −2 SDs) in assessing GH levels for GHD [20]. Ibba et al established a cut-off IGF-1 value of −1.5 SD (67.61% sensitivity and 62.62% specificity) for the diagnosis of GHD [17]. Bussieres et al proposed a serum IGF-1 cut-off level below the fifth percentile of the normal values to distinguish idiopathic and organic GHD, which had 84% sensitivity but only 57% specificity [21]. In addition, Guzzetti et al established the most accurate cut-off level for IGF-1, −1.8 SDs, but its sensitivity was moderately low (79.3%), as was its specificity (75%) [22].

A "gold standard" test for diagnosing GHD is lacking. According to current consensus guidelines, an inadequate response in 2 GHSTs with a peak GH level of <7 ng/mL is the cornerstone for the diagnosis of GHD [7]. However, GHSTs have limitations, including the nonphysiological nature of the tests (inasmuch the results do not reflect the status of endogenous GH secretion), the high false-positive rates, the lack of an official cut-off level for the diagnosis of GHD, the arbitrariness of interpretations of GHST results that are based on limited evidence, the use of different assays by different centers [4, 14, 23], poor accuracy and reproducibility, potential risks and side effects, the burden of its lengthy process on the child and parent, and cost [12, 24, 25].

Studies have shown a poor correlation between serum IGF-1 concentration and results of GHSTs and no evidence that a second subnormal GHST is more reliable than low IGF-1 levels in the diagnosis of GHD. In fact, Rosenfeld et al found that in patients with mild abnormalities of GH secretion, the serum concentrations of IGF and IGFBP-3 reflected GH status more accurately than did GHST results and that the poor correlation between IGF-1 and GHST results reflects the inadequacies of the GHST rather than the limitations of IGF assays [26].

Cianfarani et al's findings suggested that a simple assessment of growth velocity and basal IGF-1 level in association with only 1 GHST result may confirm the diagnosis of GH insufficiency in more than half of patients with short stature [14]. Furthermore, Smyczyńska, who compared results of repeated GHST results to IGF-1 levels, observed poor reproducibility of GHST results but a strong correlation between 2 IGF-1 SDs in patients with previously diagnosed GHD who had no other hormonal deficiency or organic abnormalities in the hypothalamic–pituitary region and who were tested twice within 1 year [12]. Those findings reflect the stability and reproducibility of IGF-1 measurements in comparison with the results of GHSTs.

Furthermore, in view of the challenges in diagnosing GHD, the Gulf Cooperation Council published an opinion that a single GH stimulation test combined with IGF-1 measurement and interpreted with clinical auxological results would provide sufficient data to confirm GHD [27]. Additionally, Federico et al, of the Italian Society of Pediatric Endocrinology and Diabetes, proposed an algorithm for the diagnosis of GHD with the measurement of IGF-1 level as the initial step in the laboratory workup for suspected GHD. They proposed that the likelihood of GHD deficiency is high in children with a height ≤−2 SDs, a growth rate of <1.5 SDs, and an IGF-1 level of <−2.0 z-score. Furthermore, in children with normal results of magnetic resonance imaging, Federico et al recommended performing 1 pharmacological test with insulin instead of 2 to diagnose GHD [18].

Because of uncertainties in the clinical diagnosis and the lack of a "gold standard" test for diagnosing GH—specifically, the lack of evidence that a second subnormal GHST result is more reliable than low IGF-1 levels in the diagnosis—a simple reproducible measurement of serum IGF-1 seems more reasonable than the burden of a second GHST. Hence, the aim of this study was to assess the diagnostic accuracy of measuring IGF-1 level with 1 GHST vs performing 2 GHSTs as the standard test to confirm the diagnosis of GHD in children.

Materials and Methods

This retrospective study included 724 children aged 4-14 years (mean age 8.5 ± 2.7 years) who were referred to the endocrine clinic for assessment of short stature between January 2014 and January 2021 at King Abdul Aziz University Hospital, Jeddah, Saudi Arabia. Children were included based on the following criteria: (1) height below ≤2 SDs or (3rd percentile), or (2) poor growth velocity below the 25th percentile, or (3) or a decrease in height of at least 0.3 SDs/year, or (4) height that is below the parental target height potential that had undergone 2 GHSTs. The following data were documented from the patients' charts: baseline characteristics (age at assessment and sex), main auxological characteristics (height, weight, and body mass index [BMI], all plotted on World Health Organization growth charts and expressed as *Z* scores for chronological age and gender), height velocity over 1 year before and the first year post GHST including those diagnosed with GHD, first year delta height velocity SDs, and Tanner stage according to Marshall and Tanner [28, 29], biochemical results (IGF-1 and IGFBP-3 levels), and bone age, as well as GHST results. We excluded all children younger than 3 years because IGF-1 levels remain low for the first 15-18 months of age [30] and no reference values for IGF-1 SDs have been established that could be determined by the IGF-1 calculator used in this study. In addition, the normal range of IGF-1 values may include the lower limit of detection of the assay, and there maybe overlap when comparing children with and without GHD [7].

IGF-1 levels were measured by an enzyme-labeled chemiluminescent immunometric quantitative assay (IMMULITE 2000; Siemens Medical Diagnostics, Germany), and we used the IGF-1 SD calculator for IMMULITE 2000 to calculate the IGF-1 *Z* score according to chronological age and gender [31]. The patients were divided into 2 groups, those with IGF-1 levels ≤0 SDs and those with IGF-1 levels >0 SDs.

Bone age was estimated according to the Greulich and Pyle method [32]. Bone age was considered delayed if it differed from norms for age and gender by at least 1 year. GHSTs with clonidine and glucagon were performed on the same day after an overnight fast. Children in the peripubertal period are not primed with sex steroids prior to GHST. Initially, a baseline GH level was obtained (the 0-minute time point), and then clonidine was administered orally at 150 μg/m^2 of body surface area up to a maximum dose of 250 μg, and blood samples were obtained at the 30- and 60-minute time points. At 75-minute time point from the start of clonidine test, a dose of 15 μg/kg glucagon was then administered intramuscularly up to a maximum dose of 1 mg, and new GH blood samples were obtained thereafter at the 90-, 120-, 150-, 180-, and 210-minute time points after clonidine administration. To

quantify serum GH levels, we used a Siemens IMMULITE 2000 Systems analyzer 2-site chemiluminescent immunometric assay (Diagnostics Products Corporation, Germany). A GH peak of <7 ng/mL in response to 2 different stimuli tests (clonidine and glucagon) confirmed the diagnosis of GHD.

Statistical Analysis

The anthropometric measurements, including weight and height, and BMI percentiles and SDs, were calculated with AnthroCal, a child growth assessment app in which *Z* scores are calculated based on the World Health Organization's growth charts. Data for each child were dichotomized according to the baseline IGF-1 level. An IGF value representing less than 0 SDs was considered a low level. Demographic data are expressed as means and SDs for normally distributed continuous variables and as number of patients (and percentages) for dichotomous variables. $P \leq .05$ defined the level of statistical significance.

We then calculated and compared the diagnostic value of IGF-1 levels by using a cut-off of ≤0 SDs (for age and gender) in combination with results of a single clonidine stimulation test (CST), including the true-positive, true-negative, and false-positive results (probability of labeling children as having GHD based on IGF-1 level + CST while testing negative for GHD on 2 GHST); specificity; and likelihood ratio for the diagnosis of GHD in children. The area under the curve (AUC) was used to determine the discriminatory ability, wherein the acceptable level was >0.7. The false-positive rate for a single GHSTs in combination with an IGF-1 measurement reflecting ≤0 SDs was compared with the results of the standard 2 GHSTs. To analyze the data, we used STATA version 22.0 for Mac (StataCorp, College Station, TX, USA).

Results

The mean age of the 724 children was 8.5 years (± 2.7 years), and GHD was diagnosed in 187 (25.8%) based on 2 GHST results (a peak GH level of <7 ng/mL). Table 1 lists the children's baseline characteristics. The children with low IGF-1 levels were older and had a lower height SD and BMI percentile than those with normal IGF-1 levels; 67.9% were prepubertal, and the IGF-1 and IGFBP-3 levels were significantly lower than in those with normal IGF-1 levels. The proportions of GHD in both groups were similar.

Table 2 lists the diagnostic values of the GHSTs, which consisted of the IGF-1 level and results of a single CST. The false-positive rate was 5.5% in children with IGF-1 levels reflecting ≤0 SDs and 5.4% in those with IGF-1 levels >0 SDs, which was statistically significant with $P < .001$. The combination of a single CST result and a low or normal IGF-1 level had a specificity of ~92.5%. Interestingly, using an IGF-1- cut-off value to ≤−2 SDs did not change the diagnostic value for diagnosing GHD, with potentially mislabeling 6.6% of children as having GHD.

Table 1. Baseline characteristics

Characteristics	Total cohort (n = 724)	IGF-1 ≤0 SD (n = 577)	IGF-1 >0 SD (n = 147)	*P* value
Age (years)	8.5 ± 2.7	8.6 ± 2.7	8.0 ± 2.6	.02
Sex (male), n (%)	422 (58.3)	346 (60)	76 (51.7)	.07
Height (cm)	115.5 ± 15.3	116.0 ± 14.8	113.9 ± 17.0	.1
Height (SD)	−2.2 ± 1.2	−2.3 ± 1.2	−1.9 ± 1.2	.01
Weight (kg)	22.4 ± 10.6	22.4 ± 10.7	22.3 ± 10.3	.9
BMI (kg/m^2)	15.8 ± 3.4	15.7 ± 3.5	15.9 ± 3.2	.4
BMI (percentile)	33.7 ± 31.9	32.2 ± 31.3	39.3 ± 33.6	.02
Tanner stage (n)				
I	492	382	110	.08
II	151	127	24	
III	60	50	10	
IV	16	16	2	
V	1	1	0	
Height velocity (cm/year)				
Prior to GHST	4.2 ± 1.7	4.2 ± 1.7	4.3 ± 1.8	.5
1st year post GHST	6.4 ± 2.4	6.35 ± 2.4	6.6 ± 2.4	.35
1st year delta HV	1.92 ± 2.7	1.91 ± 2.7	1.93 ± 2.5	.96
Bone age, years	7.0 ± 2.9	7.0 ± 2.9	6.7 ± 2.8	.2
Delayed bone age, n (%)	288 (39.7)	229 (39.6)	59 (40.1)	.077
IGF-1 level (ng/mL)	113.4 ± 69.3	104.9 ± 61.4	145.9 ± 86.9	<.001
IGF-1 (SDs)	−0.90 ± 1.25	−1.35 ± 0.94	0.81 ± 0.67	.000
IGFBP-3 level (ng/mL)	3407.7 ± 1234.4	3407 ± 234.4	3770 ± 194.7	.002
Growth hormone deficiency[a], n (%)	187 (25.8)	146 (25.3)	41 (27.8)	.5

All values are mean ± SD unless indicated otherwise.
Abbreviations: BMI, body mass index; GHST: growth hormone stimulation test; HV: height velocity; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor–binding protein 3.
[a]GH level < 7 ng/mL.

Table 2. Diagnostic value of the GH stimulation test based on basal IGF-1 level and single clonidine stimulation test in comparison to 2 GH stimulation testing

Test	True-positive result n (%)	True-negative result n (%)	False-positive result n (%)	Specificity (95% CI)	*P* value	Positive LR	Negative LR
IGF-1 ≤0 SDs + clonidine n = 577	146 (25.3)	399 (69.2)	32 (5.5)	92.6 (89.7, 94.9)	<.001	13.5	0
IGF-1 >0 SDs + clonidine n = 147	41 (27.9)	98 (66.7)	8 (5.4)	92.5 (85.7, 96.7)	<.001	13.3	0
IGF-1 ≤−2 SDs + clonidine n = 121	35 (28.9)	78 (64.5)	8 (6.6)	90.7 (82.5, 95.9)	<.001	10.8	0
IGF-1>−2 SDs + clonidine n = 603	152 (25.2)	419 (69.5)	32 (5.3)	92.9 (90.1, 95.1)	<.001	14.1	0

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor 1; LR, likelihood ratios.

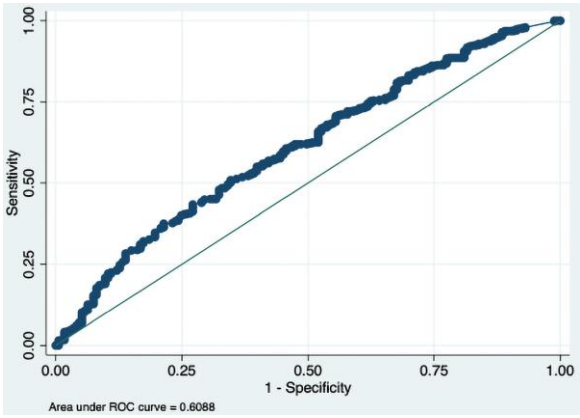

Figure 1. Insulin-like growth factor 1 level of accuracy in diagnosing growth hormone deficiency, with an area under the receiver operating characteristics (ROC) curve of 0.6792.

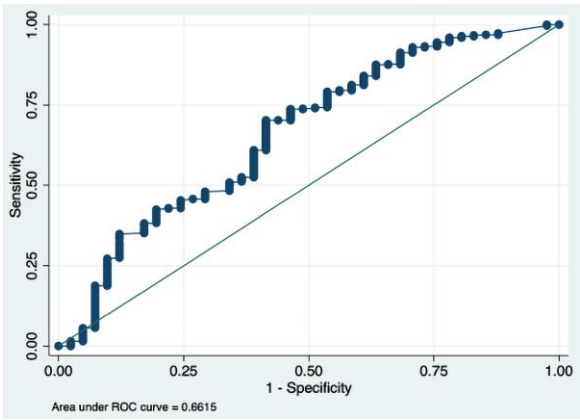

Figure 2. Insulin-like growth factor 1 level of accuracy of ≤−2 SD in diagnosing growth hormone deficiency, with an area under the receiver operating characteristics (ROC) curve of 0.6615.

The IGF-1 level of accuracy in diagnosing GHD choosing different cut-off levels of 0 and ≤−2 was demonstrated by the AUC in Figs. 1 and 2 respectively.

Discussion

The results indicate that if only children with low IGF-1 levels were tested, the diagnosis of GHD would have been missed in 41 (27.8) who had a normal IGF-1 and who tested positive for GHD on the CST. Furthermore, an IGF-1 at a cut-off level reflecting ≤0 SDs in combination with a single CST had poor diagnostic accuracy in diagnosing GHD, as evidenced by its low specificity (92.6%) and incorrect diagnosis of GHD in 5.5% of children, with an AUC of 0.6088.

Iwayama et al demonstrated that the best diagnostic accuracy of IGF-1 was at a cut-off of −1.493 SD, with a specificity of 0.471 and an AUC of 0.571; these results corroborate our findings of the poor accuracy of IGF-1 level in diagnosing GHD, with an AUC of 0.679 [16]. Similarly, Ibba et al demonstrated poor diagnostic accuracy of IGF-1 in discriminating patients with GHD from those without GHD with a best cut-off of −1.5 SDs for which the specificity was 62.62% and the AUC was 0.69 [17]. In contrast, in a systematic review and meta-analysis of the diagnostic accuracy of IGF-1 in GHD, the AUCs were reported to be 0.78 and 0.8 in different studies [19], which implied an acceptable rate of accuracy in GHD diagnosis. Furthermore, according to Ali et al, the diagnostic value of combined IGF-1 and IGFBP-3 measurements had 69.35% sensitivity, 83.33% specificity, a positive predictive value of 86%, a negative predictive value of 64.81%, and 75% accuracy [33]. In addition, Guzzetti et al showed a specificity of 98.4%, when using CST in combination with an IGF-1 level reflecting −1.8 SDs [22].

Poor diagnostic accuracy might be related to confounding factors that lead to changes in the IGF-1 levels, including characteristics of the cohort tested, nutritional status, the underlying etiology, difference in the severity of GHD, IGF-1 immunoassay used, its interpretation and validation of reference ranges, and variations in assay performance and comparability as shown by other studies [4, 9, 12, 34].

GHSTs with 2 different GH stimulants remain the "gold standard" test for the diagnosis of GHD in children [3, 7]. However, because of the nonphysiological nature of this testing, its cost, amount of time required, and potential side effects, we explored whether a single CST and an IGF-1 level ≤0 SDs could replace the need for a second GHST in the diagnosis of GHD in children. The Growth Hormone Research Society stated that a serum IGF-I levels >0 SDs at any age makes GHD unlikely. While the Gulf Cooperation Council chose a cutoff of −2 SDs to indicate a relatively likelihood of GH deficiency. Hence, when we explored the diagnostic values of both cut-off levels 0 SDs and −2 SDs and compared it to normal IGF-1 levels, we found no statistical difference between both cut-off level among both groups, as shown in Table 2.

Of interest is that 27.8% of GHD children in our cohort had normal to >0 SDs of IGF-1 concentrations, which are lower

than those reported in other studies despite using higher IGF-1 cut-off levels. Ibba et al reported that in their experience, 40% of patients with severe GHD had IGF-1 concentrations higher than −2 SDs, which overlapped with values found in children without GHD [17]. Similarly, Zelazowska-Rutkowska et al found that mean serum IGF-1 concentration were normal in 41.7% of children with suspected pituitary dwarfism who had abnormal GHST results [35]. In contrast to our study, Codner et al and Ibba et al, using IGF-1 levels reflecting −2.0 and −1.5 SDs, respectively, found that IGF-1 levels were significantly lower in children with GHD than in those without GHD [10, 17]. Furthermore, Juul and Skakkebaek concluded that subnormal IGF-1 and IGFBP-3 levels are highly predictive of a subnormal GHST result in children younger than 10 years in whom GHD is suspected [15]. Additionally, other studies showed that the high specificity of serum IGF-1 levels (>90%) strongly supports their use in the diagnosis of GHD and may decrease the need for further testing in children with idiopathic short stature [36, 37].

This study had several limitations, mainly related to factors that might have affected the IGF-1 levels. We did not elaborate on the underlying etiology of GHD, and we did not exclude children with failure to thrive who underwent GHSTs because they were among the patients being tested in our institution for GHD. In addition, we chose a cut-off of 0 SDs to discriminate low from normal IGF-1 levels in accordance with the cut-off proposed by the Growth Hormone Research Society [7], even though lower cut-offs have been used in other studies, as mentioned previously. However, our study did demonstrate poor diagnostic accuracy even at lower cut-off levels of ≤−2 SDs.

Conclusions

A low IGF-1 level (reflecting ≤0 or ≤−2 SDs) in combination with results of a single CST has poor accuracy in diagnosing GHD in children. Hence, IGF-1 levels in the diagnostic work-up showed no value in the population of this study. Subnormal responses to 2 GHSTs remain the mainstay for the diagnosis of GHD, but new diagnostic modalities are needed.

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Disclosures

T.F. has nothing to declare.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

References

1. Charles GDB, Dattani MT. *Handbook of Clinical Pediatric Endocrinology*. 2nd ed. John Wiley & Sons Ltd, 2012.
2. Nielsen J, Jensen RB, Juul A. Growth hormone deficiency in children. *Ugeskr Laeger*. 2014;176(25):V12130706.
3. Grimberg A, DiVall SA, Polychronakos C, *et al*. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr*. 2016;86(6):361-397.
4. Chinoy A, Murray PG. Diagnosis of growth hormone deficiency in the paediatric and transitional age. *Best Pract Res Clin Endocrinol Metab*. 2016;30(6):737-747.
5. Ranke MB, Mullis PE. *Diagnostics of Endocrine Function in Children and Adolescents*. 4th ed. Karger, 2011.
6. Stanley T. Diagnosis of growth hormone deficiency in childhood. *Curr Opin Endocrinol Diabetes Obes*. 2012;19(1):47-52.
7. Collett-Solberg PF, Ambler G, Backeljauw PF, *et al*. Diagnosis, genetics, and therapy of short stature in children: a Growth Hormone Research Society international perspective. *Horm Res Paediatr*. 2019;92(1):1-14.
8. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. *Mol Pathol*. 2001;54(5):311-316.
9. Blum WF, Alherbish A, Alsagheir A, *et al*. The growth hormone-insulin-like growth factor-I axis in the diagnosis and treatment of growth disorders. *Endocr Connect*. 2018;7(6):R212-R222.
10. Codner E, Mericq V, Ugarte F, *et al*. Usefulness of the measurement of insulin-like growth factor (IGF-I) and IGF-1 binding protein-3 (IGFBP-3) for the diagnosis of growth hormone (GH) deficiency in children. *Rev Med Chil*. 1999;127(7):807-813.
11. Cianfarani S, Liguori A, Germani D. IGF-I and IGFBP-3 assessment in the management of childhood onset growth hormone deficiency. *Endocr Dev*. 2005;9:66-75. https://doi.org/10.1159/000085757
12. Smyczyńska J. Inclusion and withdrawal criteria for growth hormone (GH) therapy in children with idiopathic GH deficiency—towards following the evidence but still with unresolved problems. *Endocrines*. 2022;3(1):55-75.
13. Obara-Moszyńska M, Kedzia A, Korman E, Niedziela M. Usefulness of growth hormone (GH) stimulation tests and IGF-I concentration measurement in GH deficiency diagnosis. *J Pediatr Endocrinol Metab*. 2008;21(6):569-579.
14. Cianfarani S, Tondinelli T, Spadoni GL, Scirè G, Boemi S, Boscherini B. Height velocity and IGF-I assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? *Clin Endocrinol (Oxf)*. 2002;57(2):161-167.
15. Juul A, Skakkebaek NE. Prediction of the outcome of growth hormone provocative testing in short children by measurement of serum levels of insulin-like growth factor I and insulin-like growth factor binding protein 3. *J Pediatr*. 1997;130(2):197-204.
16. Iwayama H, Kitagawa S, Sada J, *et al*. Insulin-like growth factor-1 level is a poor diagnostic indicator of growth hormone deficiency. *Sci Rep*. 2021;11(1):16159.
17. Ibba A, Corrias F, Guzzetti C, *et al*. IGF1 For the diagnosis of growth hormone deficiency in children and adolescents: a re-appraisal. *Endocr Connect*. 2020;9(11):1095-1102.
18. Federico G, Street ME, Maghnie M, *et al*. Assessment of serum IGF-I concentrations in the diagnosis of isolated childhood-onset GH deficiency: a proposal of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED). *J Endocrinol Invest*. 2006;29(8):732-737.
19. Shen Y, Zhang J, Zhao Y, Yan Y, Liu Y, Cai J. Diagnostic value of serum IGF-1 and IGFBP-3 in growth hormone deficiency: a systematic review with meta-analysis. *Eur J Pediatr*. 2015;174(4):419-427.
20. Wit JM, Bidlingmaier M, de Bruin C, Oostdijk W. A proposal for the interpretation of serum IGF-I concentration as part of

laboratory screening in children with growth failure. *J Clin Res Pediatr Endocrinol*. 2020;12(2):130-139.
21. Bussieres L, Souberbielle JC, Pinto G, Adan L, Noel M, Brauner R. The use of insulin-like growth factor 1 reference values for the diagnosis of growth hormone deficiency in prepubertal children. *Clin Endocrinol (Oxf)*. 2000;52(6):735-739.
22. Guzzetti C, Ibba A, Pilia S, *et al*. Cut-off limits of the peak GH response to stimulation tests for the diagnosis of GH deficiency in children and adolescents: study in patients with organic GHD. *Eur J Endocrinol*. 2016;175(1):41-47.
23. Boguszewski MCS. Growth hormone deficiency and replacement in children. *Rev Endocr Metab Disord*. 2021;22(1):101-108.
24. Ali M, Casey A, Kirk J, Dias RP. Overcoming the need for a second test: an evaluation of anthropometric, biochemical, and radiological parameters in the diagnosis of GH deficiencyPresented at Society for Endocrinology BES 2015, Harrogate, UK. Endocrine Abstracts; 2015.
25. Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Arch Dis Child*. 2016;101(1):96-100.
26. Rosenfeld RG, Albertsson-Wikland K, Cassorla F, *et al*. Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. *J Clin Endocrinol Metab*. 1995;80(5):1532-1540.
27. Al Herbish AS, Almutair A, Bin Abbas B, *et al*. Diagnosis and management of growth disorders in Gulf Cooperation Council (GCC) countries: current procedures and key recommendations for best practice. *Int J Pediatr Adolesc Med*. 2016;3(3):91-102.
28. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45(239):13-23.
29. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44(235):291-303.
30. Ibba A, Loche S. Diagnosis of GH deficiency without GH stimulation tests. *Front Endocrinol (Lausanne)*. 2022; 13:853290. https://doi.org/10.3389/fendo.2022.853290
31. Nutrition SSoEa. Tools/SDS IGF-1 calculator/SDS IGF-1 determined by immulite 2000 (Siemens) new standard IS 02/254; 2022. https://www.seen.es/portal/calculadoras/sds-igf-1/siemens
32. Greulich W, Pyle S. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford University Press; 1959, p. 272. Accessed February 14, 2023. http://www.sup.org/books/title/?id=2696
33. Ali A, Hashim R, Khan FA, *et al*. Evaluation of insulin-like growth factor-1 and insulinlike growth factor binding protein-3 in diagnosis of growth hormone deficiency in short-stature children. *J Ayub Med Coll Abbottabad*. 2009;21(3):40-45.
34. Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. *Clin Chem*. 2011;57(4):555-559.
35. Zelazowska-Rutkowska B, Trusiak M, Bossowski A, Cylwik B. Diagnostic usefulness of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 in children with suspected pituitary dwarfism. *Clin Lab*. 2018;64(5):759-765.
36. Nunez SB, Municchi G, Barnes KM, Rose SR. Insulin-like growth factor I (IGF-I) and IGF-binding protein-3 concentrations compared to stimulated and night growth hormone in the evaluation of short children–a clinical research center study. *J Clin Endocrinol Metab*. 1996;81(5):1927-1932.
37. Inoue-Lima TH, Vasques GA, Scalco RC, *et al*. IGF-1 assessed by pubertal status has the best positive predictive power for GH deficiency diagnosis in peripubertal children. *J Pediatr Endocrinol Metab*. 2019;32(2):173-179.