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Research Article

The Role of Insulin-Like Growth Factor-1 (IGF-1) in Diagnosis of Growth Hormone Deficiency from Childhood to Young Adulthood

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Abstract

Objective: To evaluate the accuracy of IGF-1 in diagnosing children with abnormal (low) growth hormone.

Design: A national multicenter cross-sectional study.

Method: Two hundred and seventeen patients with short stature (140 boys and 77 girls), age (5 - 18 years) were evaluated. Anthropometric measurements and pubertal stage evaluations were performed for all children. All patients underwent laboratory tests (CBC, thyroid function, serum IGF-1) and wrist X-rays to determine bone age by using the method of Greulich and Pyle. A provocative GH test was performed with clonidine and glucagon or insulin. Abnormal (low) GH is defined as peak level of GH < 10 µg/T. The patients ts distributed into two groups based on the level of GH. Normal group has normal GH and the abnormal group has low GH response to provocation tests.

Results: A significant difference in BMI ($P < 0.05$), between GHD and ISS groups, BMI was higher in abnormal GH group than normal GH group; however, age ($p = 0.821$) and BA ($p = 0.479$) did not. A significant difference in age means ($P = 0.001$) was found between abnormal and normal IGF-1g groups Sensitivity and specificity of IGF-I were 79% and 38.6%, respectively, using -2SD as cutoff value for IGF-1. The distribution of IGF-1 z scores looks similar for both groups in the range of ± 1SD.

Conclusion: Our study suggests that IGF-1 levels had a poor predicting value for abnormal GH. The presence of abnormal IGF-I levels in a short child with normal GH response to provocative tests and presence of normal IGF-1 in children with abnormal GH response to provocative tests indicate the presence of other strong factors that influence the IG1 levels rather than GH. Increasing cut-off value of IGF = 1 to -1SD as a pilot study did not increase the prediction of children and adolescents with abnormal GH. Our recommendation is that measuring IFG-1 as screening or diagnostic for children with short stature may be of no value, as it is not changing in evaluating or managing children with short stature.

Keywords: *Food and Drug Administration (FDA); Growth Hormone (GH); Growth Hormone Deficiency (GHD); Idiopathic Short Stature (ISS); Insulin-Like Growth Factor-1 (IGF-1)*

Introduction

Food and Drug Administration (FDA) approved growth hormone (GH) therapy for short-stature children due to growth hormone deficiency (GHD), idiopathic short stature (ISS), and others due to specific causes. GHD and ISS are the main causes of short stature, and the only two conditions that recourse GH provocative tests for definite diagnose as the height of individual in both conditions is more than 2 SD below the mean height for a given age, sex, and population group without evidence of nutritional, systemic disease or chromosomal abnormalities [1,2]. But GH is abnormal (low) in children with GHD while normal in children with ISS.

Provocative growth hormone testing is a bit challenging to most of Patric endocrinologists because on, hand, it is still the gold standard to diagnose GH abnormal or normal and on other hands, it has a lot of limitations and poor reproducibility. It is invasive, expensive, lengthy, has side effects some of it very series as hypoglycemia with insulin test, hypotension with clonidine test and in addition to that the cut-off used to define abnormal GH is arbitrary, for children in Saudi Arabia a peak stimulated GH of less than 10 µg/L is the cut-off for diagnosis GHD. Regarding poorly reproducible, a Lee., *et al*. reported that repeating the same provocative test on same subjects with (ISS) after the short period (1 month) gave different results in 18.7% of cases [3]. Loche., *et al*. found that 85% of 33 prepubertal short stature children who diagnosed GHD based on a GH response < 10 µg/L for 2 pharmacologic tests have a normal GH response ≥ 10 µg/L after retesting 1 - 6 months later [4]. This lack of reproducibility requests retesting idiopathic GHD patients after completion of GH treatment as retesting shows that most had normal GH responses [5-12]. We depend on the peak, which varies by the stimulus given [13], assay method [14], nutritional status [15], and BMI [3,16]. Insulin-like growth factor -1(IGF-1) coordinates significantly with GH to promote linear growth. GH stimulates the liver and other tissue to secrete IGF-1, which acts on the proliferation of chondrocytes resulting in bone growth [17]. From Laron., *et al.* studies, we know that IGF-1 is a very important hormone for linear growth, which cannot be normal with low IGF-1 [18]. Serum IGF-1 levels also have some limitations as; they are variable with the age, sex, puberty stage, nutritional status, stress levels, exercise states, insulin levels, and general health status [19]. Most of these limitations can be controlled through proper history and physical examination, using the appropriate growth chart and stander references of normal IGF-1 levels. Several studies were done to evaluate the value of IGF-1 in diagnosis short stature due to growth hormones deficiency or Idiopathic. However, their results are not consistent [20-23]. In the present study, we set up a national multicenter study to evaluate the diagnostic value of serum IGF-1 for short stature children with abnormal or normal growth hormone from 5 - 18 years of age.

The study was approved by the Institutional Medical Research Center of the two participating centers, and informed consent was obtained from the patients or their parents or guardians

Materials and Methods

The study took place at the endocrinology clinic of the pediatric department in King Abdulaziz Medical City and Fakeeh Hospital in Jeddah, Saudi Arabia. Short-stature subjects were recruited from referred children aged 5 to 18 years who presented there from March 2010 until March 20017. The inclusion criteria included subjects with a height below -2 standard deviations (SD) from the mean for their age and sex, those free of chronic disorders or genetic diseases, and those with a normal karyotype for female subjects. The exclusion criteria involved subjects with hypothyroidism.

chronic disease, on or received growth hormone, liver or renal problem, drugs that could affect height as cortisol, spine or lower limb deformity. Two hundred and seventeen patients with short stature (140 boys and 77 girls) were evaluated. Anthropometric measurements and pubertal stage evaluations were performed for all children, according to standards [24,25]. All patients underwent laboratory tests (CBC, thyroid function, serum IGF-1) and wrist X-ray to determine bone age by using the method of Greulich and Pyle [26]. A provocative GH test was performed with clonidine and glucagon or insulin. GHD is defined as peak level of GH < 10 µg/mL. Clonidine (100 mcg/m^2 body surface area, orally), insulin (0.10 IU/kg iv), and glucagon (30 µg/kg body weight up to a maximum of 1 mg/ml. All subjects were

tested in fasting conditions in each participating center. The patients were distributed into normal group that has normal GH and the abnormal group has low GH response to provocation tests.

Data collected from study patients were analyzed using the statistical package SPSS (v23), different methods of analysis were conducted including descriptive statistics in terms of means and standard deviations, Odds ratio, cross tabulations-and Chi squared test and t test.

Hormone assays

Serum concentrations of IGF-1and GH were determined by chemiluminescence immunoassay (CLIA), using LIAISON® XL which is a fully automated chemiluminescence analyzer. For the IGF-1 assay, a monoclonal antibody is linked to an isoluminol derivative (isoluminol-antibody conjugate) and another monoclonal antibody is used for coating magnetic particles (solid-phase) after separation of IGF-I from binding proteins and the level < -2 standards of normal considered low.

Results

The two hundred and seventeen patients with short stature have been distributed to two groups according to the status of growth hormone with 146 abnormal GH and 71 normal GH. The Demographic and clinical characteristics of both groups are summarized in table 1.

Variable	Abnormal GH (N = 146)	Normal GH (N = 71)	P value
Age	12.0 ± 3.1	12.0 ± 2.9	0.957
Weight (kg)	29.2 ± 12.7	27.1 ± 8.1	0.175
Height (cm)	127.8 ± 15.9	128.7 ± 13.7	0.665
Height SDS	-2.7 ± 1.1	-2.6 ± 1.0	0.483
BMI	17.3 ± 4.6	16.0 ± 2.5	0.025*
IGF-1 (ng/ml)	161.6 ± 107.3	173.4 ± 116.4	0.464

Table 1: *Demographic and clinical characteristics of patients with low and normal growth hormone.*

**Significant at 0.05 levels.*

A significant difference has been found in BMI between abnormal GH and normal GH groups. IGF-1 using ± 2 SD was not significantly different between abnormal and normal GH group, however, those children with normal GH had a higher level of IGF-1 compared to low GH patients (Table 1). According to Chi squared test results, growth hormone test was found to be not significantly associated with sex. The IGF-1 result was significantly associated with sex; the Odds Ratio indicated that females were less likely to had low IGF-1 result compared to males (Table 2).

Test	Chi square value	P value	OR
Growth Hormone	1.325	0.249	0.709
IGF-1 result	3.890	0.048*	0.537

Table 2: *Gender difference in GH and IGF-1 levels.*

**Significant at 5%.*

The t-test for the mean difference between the IGF-1 result and selected continuous variables of the study was found a significant difference in age means between low and normal IGF-1 groups (Table 3). IGF-I concentrations were below the age- and sex-related range for 57 of 146 (39%) of patients with abnormal GH and 15 of 71 (21%) patients with normal GH. The commercial kit we used provides a reference in the form of centiles (2.5^{th} to 95.5^{th} centiles) according to age and sex, taking the 2.5 centiles as a threshold value (−2SD). The results of GH and IGF-1 of both groups using ± 2SD and ± 1SD are summarized in table 4 and 5 respectively.

Variable	Low	Normal	P value
Age	13.1 ± 2.7	11.5 ± 3.2	0.001*
Height	131.1 ± 14.5	128.7 ± 15.8	0.266
Weight	29.6 ± 10.9	29.4 ± 13.2	0.898
BMI	16.8 ± 3.9	17.0 ± 4.2	0.741
Bone age	10.1 ± 3.3	9.4 ±3.5	0.196

Table 3: *IGF-1 differences among selected variables.*

**Significant at 5%.*

	GH result		
IGF-1 result	**Normal**	**Abnormal**	**Total**
Normal	56	89	145
Low	15	57	72
Total	71	146	217

Table 4: *Results of GH and IGF-1 (using ± 2SD) results.*

217 subjects had result in GH and IGF-1, 56 had both normal results, 57 had both (abnormal and low) results, 89 had normal IGF-1 result, but abnormal GH result, 15 had normal GH result, but IGF-1 result.

	GH result		
IGF-1 result	**Normal**	**Low**	**Total**
Normal	51	79	130
Low	20	67	87
Total	71	146	217

Table 5: *Results of GH and IGF-1 (using ± 1 SD) results.*

217 Subjects had result in GH and IGF-1, 51 had both normal results, 67 had low results, 79 had normal IGF-1 result, but low GH result, 20 had normal GH result, but IGF-1 result.

The ability of the IGF-1 to identify correctly those who have low GH result is 79.2%. (Sensitivity) and the ability of the IGF-1 to identify correctly those who have normal GH result is 38.6%. (Specificity) using ± 2SD as the threshold value. The test statistic of McNemar χ^2 p-value was (p-value = 0.000). The result indicated that the two tests produce different results. Analyzing the frequencies of 89 and 15, we see that many cases had low IGF-1 result compared with few cases of abnormal GH result. If ± 1SD (rather than ± 2SD) range is used, the

Sensitivity found to be 71.8%, and Specificity 45.9%. The test statistic of McNemar χ^2 p-value was (p-value = 0.000). The result indicated that the two tests produce different results. Analyzing the frequencies of 79 and 20, we see that many cases had low IGF-1 result compared with few cases of abnormal GH result. The distribution of IGF-1 z scores looks similar for both groups in the range of ± 1SD (Figure 1).

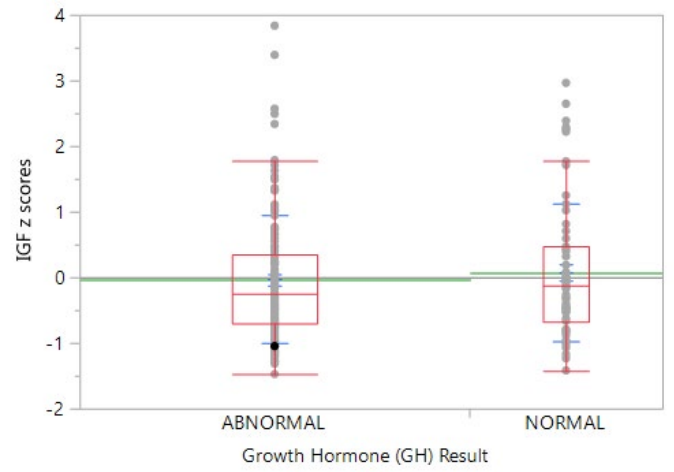

Figure 1: *Distribution of IGF-1 z scores.*

The points represent z score for IGF-1 measures for each group, the green horizontal bars represent the means of IGF-1 z scores for each group, the blue horizontal bars represent ±1SD range of IGF-1 z scores, the red horizontal bars represent (from top to bottom) maximum usual value, 75th centile, median, 25th centile and minimum usual value and the points above the maximum usual bar represent the outliers (values > 2 SD).

Discussion

Short stature is an easy medical condition to diagnose; however to know exactly the case of short stature in healthy children is challenging. GH provocation tests are currently the goldstone to diagnose GH deficiency [27]. However, these tests carry many limitations [27,28]. First it is non-physiological provocative tests, which have a high rate of error in the diagnosis of GH deficiency [29-32], second a limited reproducibility [28], third the cut off value of GH concentration suggested to diagnose GH deficiency is arbitrary [27,28], Therefore, the insulin-like growth factor has been studied as a diagnostic test for growth hormone deficiency [33-35].

Our data showed a clear overlap of IGF-1 values for patients with growth hormone deficiency and patients with normal growth hormone. Such overlapping has been reported with other authors, patients with GH deficiency and normal IGF-1 levels [33,36-38], as well as patients with normal GH and low IGF-1 [33,36,39-41]. The current study found that low IGF-1 levels in only 57 (39%) of the patient with GH deficiency and 15 (21%) of patients with normal GH. The ability of the IGF-1 to identify correctly those who have low GH result (Sensitivity) is 79.2%. And the ability of the IGF-1 to identify correctly those who have normal GH result (Specificity) is 38.6%. Raising the cut-off value for low IGF-1 levels to -1SD, as a pilot study did not significantly change the Sensitivity 71.8% or Specificity 45.9%. Which indicates that IGF-1value cannot be used as a diagnostic marker for GH deficiency, however the establishing cut-off value of IGF-1 in the used commercial kit may be different in our patients. The measurement of serum IGF-1 levels is expensive and add coast to the evolution of short stature children without defiant benefit as we cannot depend on it soul to diagnose GHD, low and normal results don't exclude GHD. Also, it takes time for processing the serum sample that may delay diagnosis.

The findings of this study demonstrated that IGF-l doesn't reflect the GH status and cannot be use to exclude GH deficiency or replace GH provocation tests. Therefore, measuring IGF-1, as screening test for short stature children may be not necessary.

Concentration of IGF-1 has a number of significant limitations. It is influence by many factors such as under-nutrition, renal failure, hepatic failure, chronic illness, diabetes mellitus and hypothyroidism [42-44] which have been excluded in our subjects before measuring IGF-1. The IGF-1 concentrations are also age dependent as proven in our study and markedly low in children under 5 years of age, [45] make the distinguish between normal and abnormal concentration difficult. Therefore, all of our subjects were above 5 years of age. However, IGF-1 concentration may be affected also by intrinsic factors such as genetic factors [46] and biological variability in the same subject [47]. Which cannot be excelled in this study. Furthermore, IGF-1 was measured 1-3 months before growth hormone provocation tests. This fact may contribute to the low prediction. However, 1-3 months between GH and IGF-1 measurement is short to influence the range of IGF-1 concentrations through pubertal maturation or age.

Conclusion

The IGF-1 to identify correctly those who have low GH result (Sensitivity) is 79.2%. And the ability of the IGF-1 to identify correctly those who have normal GH result (Specificity) is 38.6%. Raising the cutoff value for low IGF-1 levels to -1SD, as a pilot study did not significantly change the Sensitivity 71.8% or Specificity 45.9%. Which indicates that IGF-1value cannot be used as a diagnostic marker for GH deficiency, however the establishing cut-off value of IGF-1 in the used commercial kit may be different in our patients. The measurement of serum IGF-1 levels is expensive and add coast to the evolution of short stature children without defiant benefit as we cannot depend on it soul to diagnose GHD if low and normal results don't exclude GHD. Also, it takes time for processing the serum sample and this may delay diagnosis.

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