The Relevance of Insulin-like Growth Factor 1 Concentration as a Screening Test for Diagnosis of Growth Hormone Deficiency

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Abstract

Objective: Growth hormone deficiency (GHD) is one of the most important endocrine and treatable causes of short stature. Insulin-like growth factor 1 (IGF-1) concentration is not recommended to establish the diagnosis of GHD. The aim of our study was to analyze the relevance of IGF-1 concentration as a screening test for the diagnosis of GHD.
Materials and Methods: We retrospectively studied patients who were evaluated for short stature at the Endocrinology Department of King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia from January 2015 to December 2018. For IGF-1, laboratory reference ranges were based on age and sex. For all eligible patients, IGF-1 concentration was determined and an ITT was performed. Patients with a peak GH of ≤ 5.0 ng/ml were considered to be GHD and patients with a peak GH of ≥ 5.1 ng/ml were considered non-GHD (nGHD).
Results: We retrospectively included 47 patients for analysis. Mean age was 14.7 ± 1.7 years. There were 38 males (80.9%) and 9 females (19.1%) and mean IGF-1 concentration was 146.4 ± 69.4 ng/dl. Results from the ITT indicated that 27 (57.4%) had GHD. Age was not significantly different between GHD and non-GHD (14.7 ± 1.8 vs. 14.8 ± 1.6 years, P = 0.9). There were non-significantly more males than females in GHD patients (59% vs. 50%, P = 0.7). Mean IGF-1 concentration was not significantly different (146.9 ± 70.4 ng/dl vs. 145.7 ± 69.8 ng/dl, P = 0.9). IGF-1 concentration below the reference ranges for age and gender was non-significantly higher in patients with GHD compared to non-GHD (53.8% vs. 46.2%, P = 0.8). The mean peak for GH concentration was significantly lower in patients with GHD (2.2 ± 1.3 ng/ml vs. 9.9 ± 5.6 ng/ml, P < 0.0001). Peak GH concentration was not significantly correlated with IGF-1 concentration (r = 0.213, P = 0.2). We plotted a ROC curve of IGF-1 concentration according to the diagnosis of GHD as established using ITT. The AUC was 49%. An IGF-1 threshold of 154 ng/dl was selected to emphasize sensitivity rather than specificity. With a threshold of 154 ng/dl, sensitivity was 52% (95% confidence interval (95% CI); 32%, 71%), specificity was 40% (95% CI; 19%, 64%) and the negative predictive value for the diagnosis of GHD was 38% (95% CI; 24%, 54%). With a threshold of 105 ng/dl, the sensitivity was 41% and the specificity was 70%. A threshold of 74 ng/dl, gave a positive predictive value of 60% but a negative predictive value of 43%. 7 of the patients with IGF-1 concentration above the threshold of 154 ng/dl (N = 20) were normal and 13 had GH deficiency. These 13 GHD patients had IGF-1 concentration that differs significantly from those of their GH-sufficient counterparts (105 ± 35 vs. 222 ± 49

ng/dl, P < 0.0001). If IGF-1 was used as a screening test (with a concentration threshold of 154 ng/dl) and ITT as a confirmatory test, 20 (43%) out of 47 ITT would not have been performed, leading to the misdiagnosis of 13 GH-deficient adults. Thus, in our study population, such a procedure would misdiagnose 13 out of 27 GHD patients (48%) and yield a sensitivity of 52%.
Conclusion: *Many reports have already reported that IGF-1 concentration is lower in patients with GHD than in the general population, our study demonstrated the poor negative predictive value of IGF-1 concentration for the diagnosis of GHD, making it the need of the use of the "gold standard" method ITT. This observation remains to be validated by population-based studies.*

Introduction

Growth hormone deficiency (GHD) is one of the most important endocrine and treatable causes of short stature. GHD is associated with altered body composition and with lipoprotein and carbohydrate disorder [1,2]. The interest in the epidemiology of GHD derives from the increasing focus on patients with GHD during the last decades. This interest was spurred on by finding the positive changes in body composition of patients with GHD being treated with growth hormone (GH) [3-6]. Childhood-onset GHD has been estimated to occur in 1 per 30,000 people per year [7]. In adult-onset GHD, an annual incidence of 1.2 per 100,000 adults has been estimated [8].

Insulin-like growth factor 1 (IGF-1) is the metabolic effector of GH. It is produced by the liver and is mainly controlled by GH [9]. IGF-1 concentration is not recommended to establish the diagnosis of GHD, mainly due to the overlap of IGF-1 concentrations between normal and GH-deficient subjects [10]. Dynamic tests are currently recommended for the diagnosis of GHD: the insulin tolerance test (ITT) is considered as the reference test [10-14].

Poor diagnostic accuracy of the IGF-1 concentration in patients suspected of having GHD is in keeping with reports that IGF-1 concentrations show considerable overlap between normal and GH-deficient adults. Hence, a normal IGF-1 concentration does not rule out GHD. However, the presence of a low IGF-1 level in patients with hypopituitarism associated with three or more pituitary hormone deficiencies is considered highly indicative of GHD [15,16].

In our knowledge, there have been no nationwide studies using uniform diagnostic criteria. Thus, we tried to improve the simplicity and safety of the diagnosis of GHD. The use of diagnostic strategy with IGF-1 as the first screening step and the ITT as the second confirmatory step has not been studied in a population admitted on routine endocrinological practice for short stature. The aim of our study was to analyze the relevance of IGF-1 concentration as a screening test for the diagnosis of GHD.

Materials and Methods

We retrospectively studied patients who were evaluated for short stature at the Endocrinology Department of King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia from January 2015 to December 2018. For IGF-1, laboratory reference ranges were based on age and sex. For all eligible patients, IGF-1 concentration was determined and an ITT was performed. The ITT consisted of the IV injection of 0.1 units of insulin/kg body weight. Blood samples were collected 0 (baseline), 30, 60, 90, and 120 mins for GH. Blood glucose concentration was also determined to ensure that the patients were hypoglycaemic if blood glucose concentration was < 2.2 mmol/l. Patients with a peak GH of ≤ 5.0 ng/ml were considered to be GHD and patients with a peak GH of ≥ 5.1 ng/ml were considered non-GHD (nGHD). Peak GH secretion during provocative testing was used to assess the capacity of the pituitary to release GH [17]. Blood was centrifuged, and serum was frozen with dry ice until analysis by an independent laboratory. Blood glucose was determined using a glucose oxidase method. GH concentration was determined using a radioimmunometric test, with IS 80/505 as the international standard. This kit was specific for 20 KD and 22 KD human GH. The detection limit was 0.2 ng/ml. At 1.70 ng/ml, intra and inter assay coefficients of variation are 3.9% and 2.3%, respectively. IGF-1 concentration was determined using an immunoradiometric method (Unilabs Company, Germany). At 310 ng/dl, inter and intra assay coefficients of variation were 1.3 and 3.3%, respectively.

Statistical analysis

Data has been presented as means ± standard deviation or numbers (%). Quantitative variables were compared between the two groups by using the Student's t-test. Differences in categorical variables were analysed using the chi-square test. The relationship between continuous variables was assessed using coefficients of correlation. The ability of IGF-1 concentration to discriminate between normal and GH-deficient patients was evaluated by receiver operating characteristic (ROC) curve analysis. The cut-off for optimal clinical performance measures was determined from the ROC curve. Sensitivity, specificity and positive and negative predictive values were calculated for IGF-1 and for the cascade test strategy. The optimal sensitivity and specificity using different IGF-1 cut-off values to predict the presence of GHD were examined by the receiver operating characteristic curve (ROC) analysis. A greater area under the curve (AUC) indicates better predictive capability. An AUC = 0.5 indicates that the test performs no better than chance, and an AUC = 1.0 indicates perfect discrimination. An ideal test is one that reaches the upper left corner of the graph (100% true positives and no false positives). To determine the optimal IGF-1 cut-off points, we computed and searched for the shortest distance between any point on the curve and the top left corner on the y-axis. The distance was estimated at each one-half unit of IGF-1 according to the equation: Distance in ROC curve = $(1\text{-sensitivity})^2 + (1\text{-specificity})^2$ [18,19]. Diagnostic performance of IGF-1 in predicting GHD was assessed by calculating AUC, sensitivity, specificity, positive and negative predictive values. P value < 0.05 indicates significance. The statistical analysis was conducted with SPSS version 23.0 for Windows.

Results

We retrospectively included 47 patients for analysis. Mean age was 14.7 ± 1.7 years (Table 1). There were 38 males (80.9%) and 9 females (19.1%) and mean IGF-1 concentration was 146.4 ± 69.4 ng/dl. Results from the ITT indicated that 27 (57.4%) had GHD (Table 2). Age was not significantly different between GHD and non-GHD (14.7 ± 1.8 vs. 14.8 ± 1.6 years, P = 0.9). There were non-significantly more males than females in the GHD patients (59% vs. 50%, P = 0.7). Mean IGF-1 concentration was not significantly different (146.9 ± 70.4 ng/dl vs. 145.7 ± 69.8 ng/dl, P = 0.9). IGF-1 concentration below the reference ranges for age and gender was non-significantly higher in patients with GHD compared to non-GHD, (53.8% vs. 46.2%, P = 0.8). The mean peak for GH concentration was significantly lower in patients with GHD (2.2 ± 1.3 ng/ml vs. 9.9 ± 5.6 ng/ml, p < 0.0001). Peak GH concentration was not significantly correlated with IGF-1 concentration (r = 0.213, P = 0.2) (Figure 1). IGF-1 concentrations according to GH deficiency status have been demonstrated (Figure 2).

We plotted a ROC curve of IGF-1 concentration according to the diagnosis of GHD as established using ITT (Figure 3). The AUC was 49%. An IGF-1 threshold of 154 ng/dl was selected to emphasize sensitivity rather than specificity. We tested the diagnostic accuracy of several thresholds (Table 3). With a threshold of 154 ng/dl, sensitivity was 52% (95% confidence interval (95% CI); 32%, 71%), specificity was 40% (95% CI; 19%, 64%) and the negative predictive value for the diagnosis of GHD was 38% (95% CI; 24%, 54%). With a threshold of 105 ng/dl, the sensitivity was 41% and the specificity was 70%. A threshold of 74 ng/dl, gave a positive predictive value of 60% but a negative predictive value of 43%.

Parameters		Total
Numbers		47
Age (years)		14.7 ± 1.7
Gender	Male	38 (80.9)
	Female	9 (19.1)
IGF-1 (ng/dl)		146.4 ± 69.4

Table 1: Demographics [mean ± standard deviation or number (%)].

| Parameters		GHD	nGHD	P value
Numbers		27 (57.4)	20 (42.6)	
Age (years)		14.7 ± 1.8	14.8 ± 1.6	0.9
Gender	Male	23 (59.0)	16 (41.0)	0.7
	Female	4 (50.0)	4 (50.0)	
IGF-1(ng/dl)		146.9 ± 70.4	145.7 ± 69.8	0.9
GH (Peak) (ng/ml)		2.2 ± 1.3	9.9 ± 5.6	< 0.0001

Table 2: Comparison between patients with growth hormone deficiency (GHD) and non-GHD (nGHD) [mean ± standard deviation or number (%)]. GH: growth hormone; IGF-1: insulin-like growth factor 1.
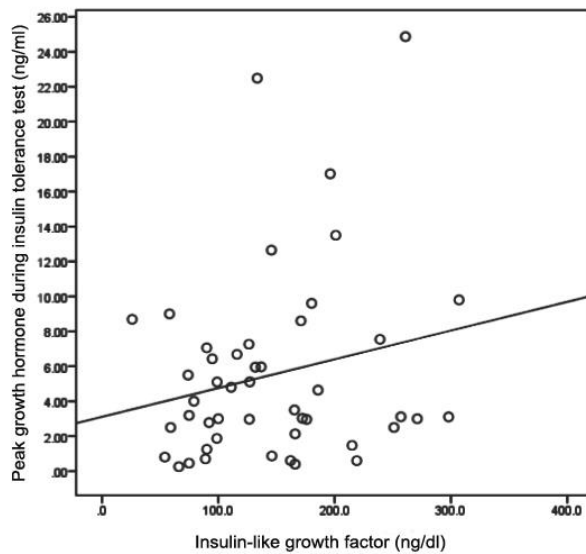
Figure 1: Correlation of insulin-like growth factor 1 concentration and growth hormone peak during insulin tolerance in the study population.
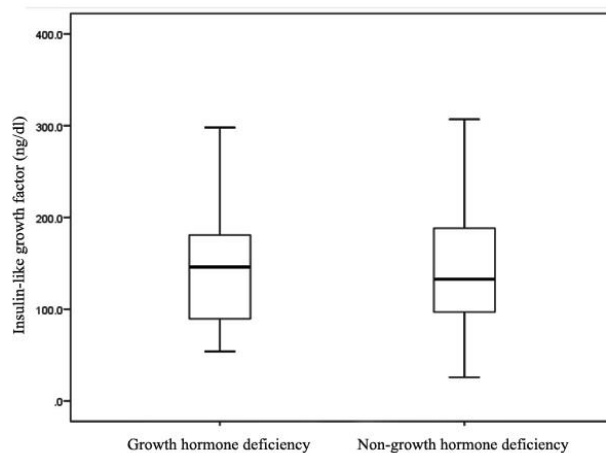
Figure 2: Insulin-like growth factor 1 concentration in patients with and without growth hormone deficiency: crosses represent individual data. Boxes represent 25th and 75th percentiles, split by median, with error bars representing 5th and 95th percentiles.
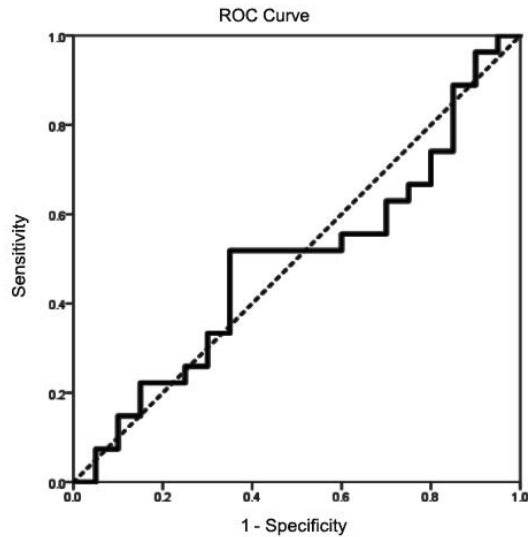
Figure 3: Receiver operating characteristic curve (ROC) of insulin-like growth factor 1 concentration, according to the diagnosis of growth hormone deficiency established using insulin tolerance test.

Statistic	IGF-1		
	154 ng/dl	105 ng/dl	74 ng/dl
True positives	14	11	3
True negatives	7	14	18
False positives	13	6	2
False negatives	13	16	24
Sensitivity	52 (32 - 71)	41 (22 - 61)	11 (2 - 29)
Specificity	35 (15 - 59)	70 (46 - 88)	90 (68 - 99)
Positive Predictive Value	52 (40 - 64)	65 (45 - 80)	60 (22 - 89)
Negative Predictive Value	35 (21 - 52)	47 (36 - 57)	43 (38 - 48)
Accuracy	45 (30 - 60)	53 (38 - 68)	45 (30 - 60)

Table 3: Diagnostic performance of IGF-1 in detecting growth hormone deficiency.

7 of the patients with IGF-1 concentration above the threshold of 154 ng/dl (N = 20) were normal and 13 had GH deficiency. These 13 GHD patients had IGF-1 concentration that differs significantly from those of their GH-sufficient counterparts (105 ± 35 vs. 222 ± 49 ng/dl, P < 0.0001).

If IGF-1 was used for screening test (with a concentration threshold of 154 ng/dl) and ITT for confirmatory test, 20 (43%) out of 47 ITT would not have been performed, leading to the misdiagnosis of 13 GH-deficient adults. Thus, in our study population, such a procedure would have misdiagnosed 13 out of 27 GHD patients (48%) and yield a sensitivity of 52%.

Discussion

In this 3-year retrospective study, we found that IGF-1 concentration was not significantly correlated with peak GH concentration during ITT. We confirmed that IGF-1 has a poor positive predictive value for the diagnosis of GHD. However, IGF-1 thresholds at 154, 105 and 74 ng/dl were associated with a poor negative predictive value. Thus, the measurement of IGF-1 concentration, followed by a confirmatory dynamic test ITT for patients with an IGF-1

concentration lower than 154 ng/l, proved to be a valid approach. We also observed a non-significant negative correlation between age and IGF-1 concentration, as in many reports (r = -0.1, P = 0.5) [11,20,21].

The diagnostic procedure we propose here was developed to limit the use of ITT which can result in adverse reactions typical of symptomatic hypoglycemia. We chose a very feasible method with large access: IGF-1 determination. It has been shown, in large groups of patients with adult GHD, that IGF-1 concentration (adjusted for age and sex) is low in a very high proportion of GHD cases [20-22]. This is in disconcordance with our findings: only 13 out of 27 subjects with GHD had an IGF-1 concentration higher than the threshold we selected.

The clinical relevance of our diagnostic strategy is of clinical importance. This approach could not distinguish individuals with GHD from individuals without GHD which affects therapeutic options, as GHD patients can be treated with recombinant GH, which may improve the height and quality of life [23,24]. We were concerned by the imperfect diagnostic performance of the cascade test; it misdiagnosed 13/27 patients, meaning that these 13 patients would have been denied for recombinant GH treatment. However, the titration of recombinant GH treatment aims to obtain normal IGF-1 concentrations, which is already the case for these patients. Furthermore, these patients could be the least likely to benefit from recombinant human GH treatment as suggested by their normal IGF-1 concentration although this is disputed by others [25-27].

Interestingly, the diagnostic procedure using a very low threshold for IGF-1 is associated with a 60% positive predictive value [16]. With this threshold, 2 out of 5 patients would have been misclassified as GHD in our study population. We believe that our diagnostic procedure (i.e. IGF-1 threshold of 154 ng/ml) is safer than that with the low threshold (74 ng/ml) because even if some patients would not have access to GH, despite being potential candidates for this treatment, all candidates for GH treatment identified by the cascade test approach had effective GHD. Conversely, with the low threshold procedure, some patients with normal GH function would receive GH therapy, which is not indicated currently.

Some limitations must be acknowledged. This is a single center study, with a small number of patients. However, the study population is not selected at variance with other reports on the same topic similar to those studied in other large-scale cohorts [28]. We had to rely on IGF-1 concentration and not on IGFBP-3, which has been reported to be of greater diagnostic value by some, but not all authors [29-32]. A second limitation is that the IGF-1 threshold concentration (154 ng/dl) did not take age and sex into account. Thirdly, IGF-1 concentration could vary greatly as shown in normal volunteers [33]. Thus, the threshold of 154 ng/ml could be crossed due to this variability. However, this drawback can be overcome if IGF-1 is assessed regularly (i.e. yearly). Coupled with ITT in a diagnostic strategy such as what is proposed here, this variability will not lead to inappropriate GH therapy, but simply to a possible delay of active treatment.

In conclusion, many reports have already reported that IGF-1 concentration is lower in patients with GHD than in the general population, our study demonstrated the poor negative predictive value of IGF-1 concentration for the diagnosis of GHD, making it the need for the use of the "gold standard" method ITT. This observation remains to be validated by population-based studies.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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