

IGF-I and IGFBP 3 in Growth Hormone Deficiency

Role of Insulin Like Growth Factor-I (IGF-I) and IGF Binding Protein 3 in the Diagnosis of Growth Hormone Deficiency: Changing Paradigm

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Abstract

GH stimulation tests are widely used in the diagnosis of GH deficiency (GHD), although they are associated with a high false positive rate. Serum IGF-I levels are monitored during GH replacement treatment in subjects with GH deficiency (GHD) to guide GH dose adjustment and to minimize occurrence of GH-related side-effects. The need for reliance on provocative testing is based on evidence that the evaluation of spontaneous growth hormone (GH) secretion over 24 hours and the measurement of IGF-I and IGFBP-3 levels do not distinguish between normal and GHD subjects. Regarding IGF-I, it has been demonstrated that very low levels in patients highly suspected for GHD (i.e., patients with childhood-onset, severe GHD, or with multiple hypopituitarism acquired in adulthood) may be considered definitive evidence for severe GHD obviating the need for provocative tests. However, normal IGF-I levels do not rule out severe GHD and therefore adults suspected for GHD and with normal IGF-I levels must undergo a provocative test of GH secretion. We hereby review the various literatures at disposal justifying the use of IGF-1 and IGBP3 for diagnosis of growth hormone deficiency.

Data Source: We searched PUBMED and MEDLINE database for relevant articles including key words. References of each article were further reviewed for final synthesis of the manuscript.

Key words: Growth hormone deficiency, Insulin like Growth Factor 1, Insulin like growth factor binding protein 3.

Introduction

Diagnosis of growth hormone (GH) deficiency (GHD) is still a matter of debate. Assuming that no clinical feature can be relied on as a guide, the approach to diagnosis must include a high index of suspicion of hypothalamic-pituitary disease. At present, the insulin tolerance test (ITT) is the diagnostic tool of choice¹, even though this test is contraindicated in patients with electrocardiographic evidence or history of ischemic heart disease or in patients with seizure disorders. Other stimulation tests have proved their usefulness for GHD diagnosis but the maximum response for GH diagnosis

has not been unanimously established in an adult population².

Insulin-like growth factors (IGFs) are polypeptides that act as endocrine mediators of growth hormone (GH)-induced anabolic and mitogenic actions. They also function in a paracrine and autocrine manner to regulate cell growth, differentiation, apoptosis and transformation. The IGF system is a complex network comprised of two growth factors (IGF-I and -II), cell surface receptors (IGF-IR and -IIR), high affinity binding proteins (IGFBP), IGF proteases as well as several

other IGFBP-interacting molecules, which regulate and propagate IGF actions in several tissues³. The clinical use of measurements of IGF-I has been focused primarily on diagnosing or excluding GH deficiency (GHD) and monitoring GH therapy.

IGF-I and IGF-BP3 are being widely used for evaluation of the diagnosis of GHD. Owing to the limitations of GH stimulation tests, there has been a gradual shift from GH-based approaches to those utilizing IGF for the diagnosis of GHD⁴. However, the use of IGF-I or IGF-BP3 in the diagnosis of GHD in children is a matter of controversy^{5,6} because of variable sensitivity and specificity of these tests^{5,7,8}.

Factors influencing levels of IGFs are age, sex, pubertal status, nutritional status, diabetes mellitus, renal failure and liver functions⁹. A reduced IGF-I level may occur in a child with malnutrition¹⁰, hypothyroidism¹¹, hepatic disease, or diabetes mellitus¹², as well as GHD. Pulsatile growth hormone (GH) secretion stimulates GH-responsive tissues to produce IGF-I. IGF-I in plasma is primarily derived from the liver and circulates bound to specific IGF-binding proteins (IGFBPs), six of which (IGFBP 1-6) have been characterized. Most (99%) IGF-I circulates bound to IGFBP-3 in I50-kDa complex. Serum IGFBP-3 concentrations are directly proportional to GH concentrations and nutritional status. IGFBP3 is considered a good marker for the GH-IGF axis.

Both IGF-1 and IGF BP 3 are GH-regulated, but age- and nutrition-dependency often renders interpretation of results difficult, thus making it desirable for each laboratory to have its own normative data matched for age and body mass index (BMI). However, such data are not always available since their collection is expensive, time consuming and requires a high degree of collaboration between clinical and laboratory departments. Thus, it is common practice to make use of reference values provided by commercial assay manufacturers, which include values obtained in a group of control subjects, usually stratified by age and/or sex, but lacking any information on body fatness measurement. Altered body composition, with increased body weight and body fat mass and decreased lean body mass, is a clinical characteristic of GHD and should be taken into account in the matched reference population. Rosenfeld, et al have found that 18% of the putative GH deficient children had serum IGF-1 levels within the normal range for age, and 32% of normal short children had low IGF-1 levels⁴.

The role of IGF-I in the diagnosis of growth hormone deficiency (GHD)

GH secretion can either be measured through investigation of the pituitary or by monitoring markers

that change as a consequence of GH action on its target tissues. The two most widely used and best-validated biochemical parameters are immunoassay measurement of either GH or IGF-I. The first reflects GH secretion while the second reflects GH action. Since GH secretion is pulsatile in nature¹³, GH provocative/stimulation tests are essential.

GH stimulation tests have many fallacies:

1. The insulin tolerance test has been considered the gold standard for the assessment of GH axis¹⁴. However, it has been associated with mortality and morbidity in children due to associated hypoglycemia.
2. There is no consensus as to which of the other agents are most suitable. The sensitivity and specificity of arginine and clonidine stimulation tests are 73% and 85%, and 70% and 85% respectively⁶. There is no agreement on the cut-off GH levels for each assay (i.e., 7 or 10 ng/ mL) to define normality.
3. There is a problem of reproducibility and the tests are associated with a wide coefficient of variation¹⁵.
4. The most significant drawback of these tests has been the lack of normative data. Stimulated GH levels have little resemblance to the growth dynamics of some normal children⁶.
5. Prepubertal children with normal stature may fail to attain peak GH values more than 7 µg/L during GH provocative test⁶. In a study by Marin, et al.¹⁶, there was a high incidence of peak GH concentration consistent with GH deficiency among normal children, i.e. 61 % in the prepubertal children had a GH peak less than 7 µg/L.

With advancing puberty, the percentage of children with normal stature who failed to attain a GH level greater than 7 µg/L in response to arginine, insulin and standardized treadmill exercise declined from 61% at pubertal stage 1 to 44% at stage 2, 11% at stage 3, and 0% at stages 4 and 5. Administration of estrogen to the prepubertal subjects raised the normal range for the peak GH response to the three tests. Thus, both puberty and estrogen administration significantly increase the peak GH response to exercise, arginine, or insulin in normal subjects.

Owing to the limitations of GH stimulation tests, there has been a gradual shift from GH-based approaches to that utilizing IGF for the diagnosis of GHD⁴. The serum level of the major GH-dependent peptide IGF-I is stable during the day, due mainly to the complexing of IGF peptides with a family of IGF-binding proteins (IGFBPs)¹⁷. Thus the potential for assessing GH status with a single estimation of the circulating IGF-I level proved attractive

and gave rise to the hope that eventually dynamic GH provocation tests may become unnecessary. Initially IGF assay problems were caused by interference from the presence of IGFbps^{18,19}. This problem has been overcome by using a variety of approaches including acid size exclusion chromatography before the IGF assay, blocking IGFBP-binding sites with an excess of the unmeasured IGF peptide (excess IGF-II for an IGF-I assay) or IGF analogs that do not bind to IGFbps as radioligands¹⁰.

The sensitivity and specificity of IGF-I in the diagnosis of GH deficiency in children is a matter of controversy because:

1. The liver is the principal source of IGF-I in the circulation
2. Hepatic production of IGF-I is highly influenced by nutritional factors
3. It is possible that decrements in IGF-I expected with GHD are modified by nutritional status and other factors, such that only severe GHD produces a clear segregation of children who are deficient from those who are not.
4. IGF-I levels are not only affected by age and nutritional status but also by thyroid hormones and gonadal steroids. Therefore, the patient should be euthyroid and pubertal staging should be assessed prior to estimation of IGF-I. The IGF-I level is influenced markedly by age and pubertal development^{20, 21, 22}. Particularly low concentrations of IGF-I occur in normal children younger than 5 yr of age. Therefore, the use of IGF-I estimation to distinguish between normal and GH-deficient children is less successful in this age group.

Nevertheless the measurement of serum IGF-I is useful since it can be derived from a single blood sample and checked frequently during evaluation, monitoring and treatment of a child with growth failure. Since IGF-I levels vary with ethnicity, it is important to generate population specific normal ranges through childhood and adolescence, incorporating all pubertal stages^{7,8}. There is a paucity of Indian studies on IGF-I and IGF-BP3. Dehiya, et al.¹⁷ have analyzed levels of IGF-I and IGF-BP3 in healthy children and adolescents (from birth to 20 years of age) residing in Mumbai suburbs.

Recently, it has been argued that total IGF-I concentration, in analogy with thyroid and sex steroid hormones, may not reflect IGF bioactivity. Thus, measurement of the serum unbound IGF-I fraction (free IGF-I) might have greater physiological and clinical importance than its total concentration²³. The ratio on a molar basis between IGF-I and the predominant IGF binding protein (IGFBP-3) has been reported to correlate

with free IGF-I²⁴ and has been proposed as an indirect measure of the easily dissociable circulating IGF-I²⁵.

The performance of IGF-I has mostly been evaluated in children diagnosed as GH deficiency on basis of short stature, poor growth velocity and sub-optimal GH levels during 2 provocative tests. Blum, et al.⁷ found sensitivity and specificity of IGF-I to be 92% and 54% respectively, using their normal ranges, when applied to their subjects (mean age 11.2 years) with GH deficiency. The peak GH level was 10 ng/mL (in response to both arginine and insulin). Such a high degree of sensitivity has not been found in other studies. Poor specificity was related to the fact that low IGF-I levels are relatively common in normal prepubertal children. There are still doubts about which is the most appropriate cut-off line for patients with GHD. Moreover, misclassification of subjects may occur, while taking into account false positive and negative results during GH stimulation tests. Different researchers have used cut-off lines based on standard criteria, such as the 5th percentile, the 10th percentile, or 2 SD in relation to the mean. Based on these criteria, a performance of IGF-I has been reported in children in the diagnosis of GHD with a sensitivity ranging from 34-100% and a specificity of 47-99% in different studies^{5,7,8,26-29}. Table 1 summarizes the specificity and sensitivity of IGF-I in various studies.

Table 1: The performance of IGF-1 in the diagnosis of Growth hormone deficiency

Studies	IGF-1		GH Peak level (ng/ml)
	Sensitivity	Specificity	
Granada, et al. (26)	86.2 %	99.3 %	3
Cianfarani, et al (27)	69%	81%	10
Mitchell, et al (28)	62 %	47%	13.5
Tillmann, et al (5)	34%	72%	*
Juul, et al (8)	76%	72%	< 7.5
Hasegawa, et al (29)	100%	82%	6
Blum, et al (7)	92%	54%	< 10

*Children with defined pathology e.g. Septo-optic dysplasia

Using GH testing as the gold standard to distinguish between 155 children with GHD and 219 with normal short stature, an IGF-I estimation at the fifth percentile level of the normal range provided a sensitivity of 95%, specificity of 60%, and accuracy of 75%, while improved figures of 79%, 95%, and 89%, respectively, were associated with an IGF-I cut-off level of 0.1 centile³⁰. The IGF-I results discriminated better in those over 8

yr compared with those under 8 yr of age³⁰. Juul and Skakkebaek³¹ also concluded that measurement of IGF-I was useful in the diagnosis of childhood GHD but, unlike the findings reported by Blum³⁰, more so in younger than older children. They reported accuracy (predictive value) of 88.8% and 52.3% in children aged less than 10 yr and between 10 and 20 yr, respectively³¹. In the latter studies^{30,31} the IGF-I values were corrected for age and sex but not pubertal status.

Despite the promise of these results, multiple studies exist that indicate the serum IGF-I concentration does not correlate perfectly with GH status, as determined by provocative GH testing^{32,33,34}. To improve the diagnostic value of IGF-I measurements, the additional measurement of IGF-II has been recommended³⁵. Despite the fact that IGF-II is less GH dependent than IGF-I, the normal range for IGF-II levels is relatively high in young children and shows little age dependence. Thus, although the accuracy of serum IGF-II measurement alone in detecting GHD is moderate, the combined use of IGF-I and IGF-II improves their value as a diagnostic parameter. In a study of 68 GH-deficient children, 197 normal-statured children, and 44 normal short children, 18% of the GH-deficient children had serum IGF-I levels within the normal range, whereas 32% of normal short children exhibited low IGF-I concentrations. Low IGF-II levels were found in 52% of GH-deficient children but also in 35% of normal short children. Utilizing the results from both IGF assays, however, revealed that 4% of GH-deficient children had normal IGF-I and IGF-II levels but only 0.5% of normal children and 11% of normal short children had reduced concentrations of both IGF-I and IGF-II³⁵. In reality, however, very few paediatric endocrine centres use IGF-II assays in the assessment of children with short stature.

Thus, low levels of IGF-I may be indicative of GHD. The plasma concentrations of the IGF-I could be considered useful indicators of GH bioactivity in children when correlated clinically, and accounting for other confounding factors. However, it is noteworthy that a normal serum IGF-I level does not exclude the presence of GHD.

Role of IGF-BP3 in the diagnosis of GH deficiency (GHD)

Of the six known IGF-BPs, IGF-BP-3 is normally the major serum carrier of IGF peptides³⁶. IGF-BP-3 circulates as part of a ternary complex consisting of IGF-BP-3, an IGF peptide, and an acid-labile subunit^{37,38}. Both acid-labile subunit and IGF-BP-3 are GH dependent. Since IGF-BP-3 determinations reflect combined IGF-I and IGF-II concentrations, age dependency of IGF-BP-3 is less striking than for IGF-I.

Since IGF-BP-3 serum levels are constant throughout the day and are closely GH dependent, it was proposed as a reliable and simple screening test in the work-up of children with short stature and preliminary results were promising. Blum, et al⁷ observed the sensitivity and specificity of IGF-BP3 to be 97% and 95% respectively. Moreover, IGF-BP3 measurement offers several important advantages over IGF-I determination²⁸:

1. No extraction step is required before measurement, thereby improving the precision and facilitating the procedure
2. IGF-BP-3 normally circulates in the serum at high concentrations, so that assay sensitivity is not an issue.
3. IGF-BP-3 serum concentrations, like IGF-I, are age-dependent, but the normal range varies only modestly with age and pubertal status.
4. The impact of nutritional status is not as significant as with IGF-I.

Several studies have addressed the issue of sensitivity and specificity of IGF-BP-3 assessment in the diagnosis of GHD, yielding conflicting results^{5,7,8,26-29,39} (Table 2).

Table 2: Performance of IGF BP 3 in the diagnosis of Growth hormone deficiency

Studies	IGF BP 3		GH Peak level (ng/ml)
	Sensitivity	Specificity	
Granada, et al. (26)	70.4 %	96.7 %	3
Cianfarani, et al (27)	27%	100%	10
Mitchell, et al (28)	14.9 %	98%	13.5
Tillmann, et al (5)	22%	92%	*
Juul, et al (8)	68%	79%	< 7.5
Hasegawa, et al (29)	92%	69%	6
Blum, et al (7)	97%	95%	< 10

* Children with defined pathology e.g. Septo-optic dysplasia

In a more recent evaluation of the usefulness of IGF-BP-3 measurement in the diagnosis of GHD, Juul and Skakkebaek³¹ reported sensitivity and specificity figures of 60% and 97.9% in children less than 10 yr of age and 56.5% and 78.7%, respectively, in those aged between 10 and 20 yr. These results could not be reproduced in other studies^{32,40-43}. Furthermore, the IGF-BP-3 estimation discriminated particularly poorly between GHD and

normality in pubertal children and those with radiation-induced GHD^{32,44}.

Cianfarani et al reported poor sensitivity of IGFBP-3 evaluation, suggesting that proteolysis is likely to affect IGFBP-3 assay results³⁹. Poor sensitivity of IGF binding protein (IGFBP)-3 assessment in the work-up of GH deficiency (GHD) has been ascribed to IGFBP-3 proteolysis¹⁶. On the other hand, specificity of IGF-BP3 for the diagnosis of GHD has been generally reported by various studies to be high^{5,7,8,26-28}.

It has been proposed that the measurement of the IGFBP-2 concentration adds to the value of IGF-I and IGFBP-3 assays in the diagnosis of GHD⁴⁵. IGFBP-2 values are usually elevated in patients with GHD^{45,46}. Despite the fact that in most patients there is agreement between the IGFBP-2/ IGF-I ratio, IGFBP-3 measurements, and the results of GH testing, the IGFBP-2/IGF-I ratio was discordant from thigh response in 21% of 80 patients (57 GHD and 23 idiopathic short stature), and IGFBP-3 results were discordant in 18%⁴⁵.

The proponents of IGF-I and IGFBP-3 estimations as the best choice of initial investigations in a child with possible GHD point out that in individuals with genetic forms of GH insensitivity (GHI), all have a low IGFBP-3 and most have a low IGF-I concentration^{47,48}. By definition, these individuals have elevated GH concentrations associated with a mutation or deletion of the gene for the GH receptor, which renders them insensitive to GH action. Furthermore, despite the universally low IGFBP-3 concentrations and the characteristically severe growth failure, serum IGFBP-3 concentrations still correlate significantly with the height SDS^{47,49}.

Thus, low levels of IGF-BP3 are very specific for the diagnosis of GHD, indicating its clinical utility. However, due to poor sensitivity of IGFBP3, normal serum level does not exclude GHD.

IGF-1 and IGF-BP3 in the diagnosis of Adult GHD

The changes in IGF-I levels throughout life are similar to those of GH. With the onset of puberty there is a 2 to 3-fold rise in serum IGF-I concentrations followed by a decline such that average adult levels are reached by the early twenties²². There follows a gradual decline with advancing age²². Similar to IGF-I but less age-dependent, serum IGFBP-3 levels rise to a peak during the pubertal years and then slowly decline in adulthood⁴⁹. Thus, in the adult patient with potential GHD, serum IGF-I and IGFBP-3 measurements can only be interpreted if decade-based normative data are available. The usefulness of an IGF-I estimation in the diagnosis of adult GHD is a matter

of contention although it has become clear that at least some of the disparity between studies is explained by the timing of the onset of GHD. Hoffman et al.⁵⁰ found that 70% of IGF-I and 72% of IGFBP-3 values in adult-onset GHD patients, mean age 45 yr, were within the range of normal subjects even allowing for the effects of age. Holmes⁵¹, in a subsequent study of 65 adults, mean age 35 yr, with GHD defined by a peak GH response of less than 3.8 ng/ml to a provocative test, and associated with other evidence of pituitary disease, found that 70% had an IGF-I SDS below 22. In the latter study, however, the 65 adults consisted of a mixture of childhood-onset and adult-onset GHD⁵¹.

DeBoer et al.⁵² focused on childhood-onset GHD and reevaluated GH status in 89 young adult males who had previously received GH replacement in childhood. Approximately 93% of the patients had an IGF-I level below the normal range with a similar number of subnormal IGFBP-3 levels among the patients (Fig. 1). Attanasio et al.⁵² pursued the same theme in a large study of 74 childhood-onset and 99 adult-onset GHD patients. They concluded that there are profound differences between these two forms of GHD⁵³. With group data they observed that the serum IGF-I levels were below normal in both groups of GH-deficient patients but were significantly lower in childhood-onset than adult-onset GHD patients⁵³. Other authors have made similar observations^{54,55}. In these studies, however, it is not clear whether sufficient decade-based normative data were available or whether the severity of GHD was equal in the childhood-onset and adult-onset groups. Thus, apart from the potential impact of the timing of onset of GHD, it is possible that the severity of GHD influences the interpretation of IGF-I results.

To pursue this question further, Shalet et al⁵⁶ have analyzed the IGF-I SDS results of the mixed population of 65 adults with childhood- and adult-onset GHD studied by Holmes⁵¹ in the context of the severity of GHD. A direct comparison of the IGF-I SDS with peak GH response was impossible due to the multiplicity of GH provocative tests used in that study⁵¹. Therefore, the IGF-I SDS data was stratified, in the context of additional pituitary hormone deficits, into those with GHDO, GHD1, GHD2, and GHD3 (Fig. 2). In each of the latter categories, there was a mix of adult-onset and childhood-onset GHD patients, thereby allowing a comparison of IGF-I status among groups with tightly defined degrees of GHD. The numbers were sufficient for statistical comparison in the GHDO, GHD1, and GHD3 groups and, in each category, the median childhood-onset IGF-I SDS is lower than the median adult-onset IGF-I SDS, reaching significance in two of the three groups (GHDO, 23.83 vs. 22.69, P 50.239; GHD1, 25.75 vs. 22.03, P 5 0.022; GHD3, 26.28 vs. 22.09, P 50.0003)⁵¹. These observations suggest that for a given

degree of GHD, the serum IGF-I concentration is lower in adults with childhood-onset compared with adult-onset disease. The explanation for this latter observation is unclear; however, it supports the notion that an IGF-I estimation is more likely to be of diagnostic use in childhood-onset than in adult-onset GHD.

An additional observation needs to be made in the patients with adult-onset isolated GHD. Toogood et al.⁵⁷ had shown previously that 24% of GHDO patients had a peak GH response of less than 1.9 ng/ml to an ITT. In the data of Holmes⁵¹, there are 11 patients in the GHDO group with adult onset disease, eight of whom have an IGF-I SDS below 22. Therefore, any therapeutic strategy to decide which GH deficient patients warrant a trial of GH therapy must allow for patients with isolated GHD, who on an individual basis may show as severe a degree of GHD as a patient with panhypopituitarism.

Rational approach to the diagnosis of GHD

Normal levels of IGF-I and IGF-BP3 do not exclude a diagnosis of GHD. The high specificity of IGF-I and IGF-BP3 measurements suggests that while a combination of a low IGF-I and low IGF-BP3 would be highly suggestive of GHD, significant number of children with GHD will have normal values for either of these two markers. Mitchell, et al.²⁸ have observed that, if, for a diagnosis of GHD, the requirement were for both these tests to be positive, then 99% of children without GHD would be correctly identified; however, the sensitivity of this test was only 15%. Hence, neither IGF-I nor IGF-BP3 alone is a surrogate marker for GHD nor even when analyzed in combination, they cannot be used as surrogate markers for GHD.

Tillmann, et al.⁵ devised a scoring system for diagnosis of GH deficiency based on the positive predictive value of the GH stimulation test, and the IGF-I and IGF-BP3 levels. A high score was highly indicative of GHD, but was achieved by few patients. A normal IGF-BP3 level, however, did not exclude GHD. GH stimulation test with a peak level more than 10 ng/mL was the most useful single investigation to exclude a diagnosis of GHD.

Peak GH response to two different provocative tests less than 7 or 10 ng/mL has been considered previously as essential for the confirmation of GHD⁶. However, in a study by Cianfarani, et al.⁵⁸, a simple assessment of height velocity (HV) and basal IGF-I in association with only one GH stimulation test, has been shown to confirm the diagnosis of GHD in a majority of patients.

It is useful to schedule IGF-I and IGF-BP3 to study abnormalities of GH-IGF axis, and as part of initial screening and diagnostic workup in short children. This

should be followed by GH provocative tests for making a definitive diagnosis of GHD⁵⁹. Thus a rational diagnostic approach to the diagnosis of GH deficiency should emphasize good history and auxologic measurements, evaluation of IGF-I and IGF-BP3 levels to identify GH-IGF axis abnormalities, and finally confirmed by GH provocative tests⁶⁰.

Conclusion

Thus, low IGF-I and IGF-BP3 concentrations are reliable guides to the diagnosis of severe GHD, provided the investigator considers the alternative possibilities of malnutrition, hypothyroidism, liver disease, and GHI. Discrepancies between IGF-I and IGF-BP3 results compared with the GH responses to dynamic tests exist, however, in those children believed to have lesser degrees of GHD. The inadequacies of dynamic provocative tests of GH release, outlined previously, may explain the discrepancies in the GH status defined by the GH and IGF axis results. Alternatively, it may be that IGF-I and IGF-BP3 estimations are less useful than the peak GH response to provocative testing in children with GH insufficiency.

We conclude that measurements of IGF-I and IGF-BP3 are useful as screening tests for the diagnostic work up of short children. These screening tests should be followed by GH provocative test for making the definitive diagnosis of GH deficiency. GH provocative test still remains the single most useful investigation for the diagnosis of GHD.

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