

## **Insulin like Growth Factors and Growth Hormone Deficiency**

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Insulin-like growth factors (IGFs) are polypeptides that act as endocrine mediators of growth hormone (GH)-induced 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), IGFBP proteases as well as several other IGFBP-interacting molecules, which regulate and propagate IGF actions in several tissues(1). 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 GHD(2). However, the use of IGF-I or IGF-BP3 in the diagnosis of GHD in children is a matter of controversy(3,4) because of variable sensitivity and specificity of these tests(3,5,6).

Factors influencing levels of IGFs are age, sex, pubertal status, nutritional status, diabetes mellitus, renal failure and liver functions(7). Pulsatile growth hormone (GH) secretion stimulates GH-responsive

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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 a 150-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.

### **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 nature(8), 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 axis(9). 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% respectively(4). 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 variation(10).
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 children(4).

5. Prepubertal children with normal stature may fail to attain peak GH values more than 7 µg/L during GH provocative test(4). In a study by Marin, *et al.*(11), 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 GHD(2). 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.

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(5,6). There is a paucity of Indian studies on IGF-I and IGF-BP3. Dehiya, *et al.*(12) 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.

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.*(5) 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(3,5,6,13-16). *Table I* summarizes the specificity and sensitivity of IGF-I in various studies.

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)

Since IGFBP-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 al.*(5) 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 determination(14):

1. No extraction step is required before measurement, thereby improving the precision and facilitating the procedure
2. IGFBP-3 normally circulates in the serum at

high concentrations, so that assay sensitivity is not an issue.

3. IGFBP-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 IGFBP-3 assessment in the diagnosis of GHD, yielding conflicting results (3,5,6,13-16,17). (Table II). Cianfarani et al reported poor sensitivity of IGFBP-3 evaluation, suggesting that proteolysis is likely to affect IGFBP-3 assay results(18). Poor sensitivity of IGF binding protein (IGFBP)-3 assessment in the work-up of GH

**TABLE I**—The Performance of IGF-I in the Diagnosis of Growth Hormone Deficiency

	IGF-I		GH peak level
	Sensitivity	Specificity	
Granada, <i>et al.</i> (13)	86.2%	99.3%	3 ng/mL
Cianfarani(14)	69%	81%	10 ng/mL
Mitchell, <i>et al.</i> (15)	62%	47%	13.5 mU/I
Tillmann, <i>et al.</i> (3)	34%	72%	*
Juul, <i>et al.</i> (6)	76%	72%	<7.5 ng/mL
Hasegawa (16)	100%	82%	≥ 6ng/mL
	50%	82%	5-10 ng/mL
Blum, <i>et al.</i> (5)	92%	54%	<10 ng/mL

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

**TABLE II**—The Performance of IGF-BP3 in the Diagnosis of Growth Hormone Deficiency

	IGF-BP3		GH peak level
	Sensitivity	Specificity	
Granada, <i>et al.</i> (13)	70.4%	96.7%	3 ng/mL
Cianfarani(14)	27%	100%	10 ng/mL
Mitchell, <i>et al.</i> (15)	14.9	98%	13.5 mU/I
Tillmann, <i>et al.</i> (3)	22%	92%	*
Juul, <i>et al.</i> (6)	68%	79%	<7.5 ng/mL
Hasegawa (16)	92%	69%	≥ 5 ng/mL
	39%	69%	5-10 ng/mL
Blum, <i>et al.</i> (5)	97%	95%	<10 ng/mL

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

### What this Study Adds

- Measurements of IGF-I and IGFBP3 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.

deficiency (GHD) has been ascribed to IGFBP-3 proteolysis(14) On the other hand, specificity of IGF-BP3 for the diagnosis of GHD has been generally reported by various studies to be high (3,5,6,13-15).

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

#### 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 IGFBP-3 measurements suggests that while a combination of a low IGF-I and low IGFBP-3 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.*(15) 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 IGFBP-3 alone is a surrogate marker for GHD and even when analyzed in combination, they cannot be used as surrogate markers for GHD.

Tillmann, *et al.*(3) 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 IGFBP-3 levels. A high score was highly indicative of GHD, but was achieved by few patients. A normal IGFBP-3 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 GHD(4). However, in a study by Cianfarani, *et al.*(18), 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-BP-3 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 GHD(19). 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 tests(20).

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