Growth Diagnostics: Clinical Significance of Growth Hormone (GH), Insulin-like Growth Factor-I (IGF-I), and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3)

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Growth hormone (GH) is secreted from the pituitary gland. These secretions fluctuate in a circadian pattern over the course of a day, peaking about one hour after the onset of nightly sleep, and are lowest during the day. GH production is stimulated in a pulsatile manner predominantly during sleep under the influence of hypothalamic hormones, but also can be stimulated to a small extent by exercise. As a result of these irregular secretions, the information acquired from a single GH result is very limited. In the past, a series of multiple GH samples collected over a 24-hour period were used to determine GH status.[1] This is not a practical diagnostic procedure in any clinical setting; therefore, current practice usually involves the use of GH provocation testing.

Insulin-like Growth Factor-I (IGF-I) and circulating Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) mediate the growth-inducing functions of GH. Both are regulated by GH but do not exhibit daily fluctuations. IGF-I and IGFBP-3 can be useful serological markers that can aid in the diagnosis of GH dysfunctions, GH deficiencies (GHD), and acromegaly. Both IGF-I and IGFBP-3 can also be used as good surrogate markers for monitoring recombinant human GH (rhGH) and IGF-I replacement therapies. GH provocation testing along with IGF-I and IGFBP-3 baseline measurements assist endocrinologists in diagnosing growth conditions.

Growth Hormone Interactions

Understanding the details of these complex hormone interactions of the Growth Hormone/Insulin-like Growth Factor Axis (Figure 1) is critical in the diagnosis and treatment of growth disorders.[1] Growth hormone releasing hormone (GHRH) is released from the hypothalamus to stimulate the pituitary gland to release GH. Somatotropin release-inhibiting factor (SRIF) is also secreted by the hypothalamus and inhibits the GH release. These two factors constantly up- and down-regulate the release of GH, causing pulsatile secretion throughout the day.[1,2] Deep sleep induces more secretions in higher concentrations, generating a primarily nocturnal secretory pattern.

The up-regulation of GH triggers IGF-I synthesis in the liver and, to a lesser extent, in peripheral cells. IGF-I mediates the growth-promoting actions of GH through both autocrine and paracrine signaling. This accounts for the broad range of physiological actions of IGF-I.[3] IGF-I circulates bound to one of six binding proteins (IGFBPs). IGFBP-3 has a high affinity to IGF-I and it's the most abundant of these binding proteins; therefore, the predominance of IGF-I circulates bound to IGFBP-3.

After the IGF-I and IGFBP-3 complex is formed, it further associates with the Acid-Labile Subunit (ALS). The IGF-I/IGFBP-3 /ALS complex preserves protein conformation and increases the half-life of circulating IGF-I, making it available for future use. IGF-I can also be released from the binding proteins by a specific IGFBP protease reaction.[3]
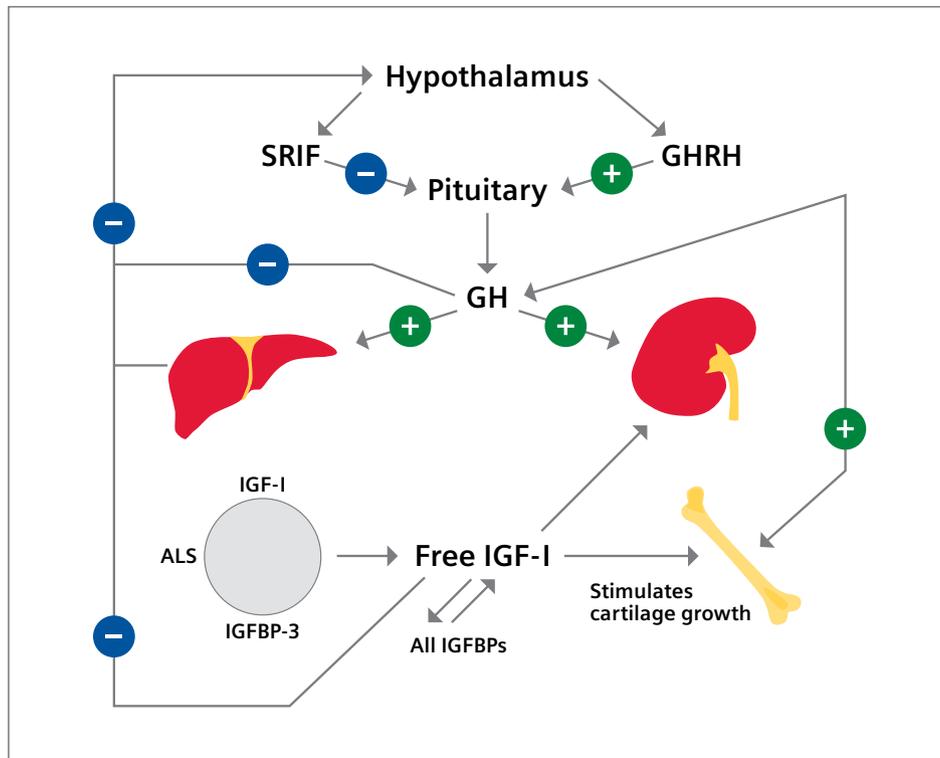

Figure 1: Growth Hormone/Insulin-like Growth Factor Axis[2]

Diagnostic Growth Assays

The irregular GH production cycle makes a single, random measurement ineffective in diagnosing GHD. The most useful GH measurements are associated with GH provocation tests for diagnosing GHD. Numerous pharmacological agents are used in the GH provocation tests, such as insulin, arginine, and GHRH. The GH provocation tests require that the patient fast for 10 to 12 hours prior to administering the provocative agent. Afterward the GH is sampled for several hours to monitor the change in GH. These tests are expensive, time-consuming, do not have well-established intervals or cutoffs, and introduce additional risk to the patient. Despite these shortcomings the GH provocation tests are a direct means of probing GHD.

IGF-I and IGFBP-3 levels show only minor fluctuations throughout the day, in contrast to the circadian variations that GH displays. The stable serum readings of IGF-I and IGFBP-3 can be thought of as an integrated measurement of GH secretions. GHD and GH-resistance patients typically have low IGF-I and IGFBP-3 concentrations. These measurements should be compared to the age-based reference intervals that have been determined for these assays[4] (Figures 2 and 3).

An overproduction of GH is most frequently caused by a GH-secreting pituitary tumor, and may present clinically as acromegaly or gigantism. When a GH excess is suspected, an oral glucose tolerance test is the best means of directly measuring GH. This is an expensive and time-consuming test that requires the patient to fast and have multiple samples drawn. However, cutoffs for diagnosing acromegaly and gigantism are more established using this method. Elevated IGF-I and IGFBP-3 levels are also indicative of GH overproduction. It is important to compare the IGF-I and IGFBP-3 results against the established reference intervals,[4] as shown in Figures 2 and 3.

IGF-I is produced in the liver and mediates many of the GH biological functions. It serves as an important signal, transmitting the GH secretion and nutritional status to various cells. Additional stimuli of IGF-I should be taken into consideration as they could significantly alter a patient's results and lead to falsely reduced or elevated values. Table 1 lists confounding conditions that may increase or decrease IGF-I levels.

Table 1: Confounding conditions that affect IGF-I levels.[5]

Reduced IGF-I Levels	Increased IGF-I Levels
Malnutrition/malabsorption	Precocious puberty
Hypothyroidism	Obesity
Liver disease	Kidney disease (dialysis)
Untreated diabetes mellitus	
Chronic inflammatory disease	
Malignant disease	
Multiple injuries	

Reference Intervals

Under normal conditions, diurnal fluctuation of IGF-I and IGFBP-3 is minimal. The establishment of sex- and age-based reference intervals allow a single, random measurement to assist in the evaluation of the patient's growth status and monitoring of their treatment.

Age-based reference intervals for IGF-I and IGFBP-3 were established[4] and are depicted in Figures 2 and 3.

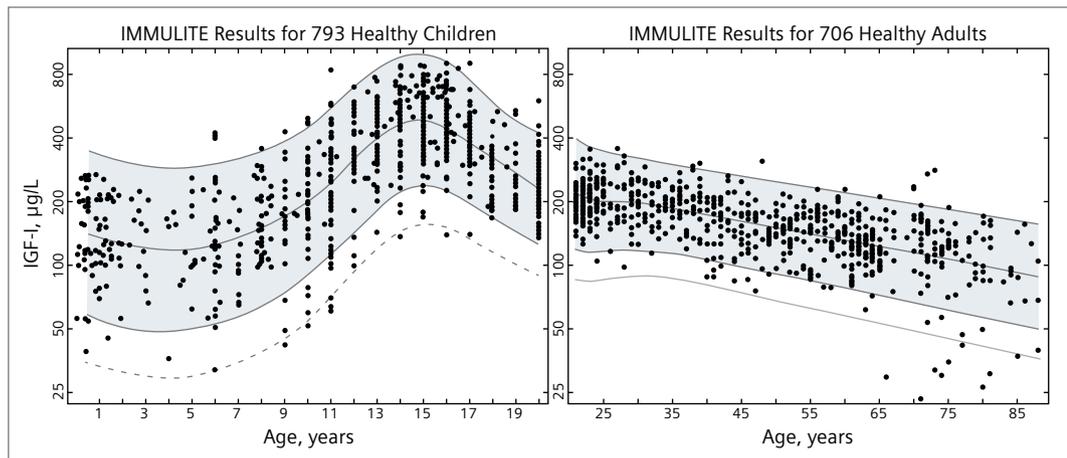Figure 2: IGF-I Reference Interval (a) for patients <20 yrs. and (b) for patients > 20 yrs.
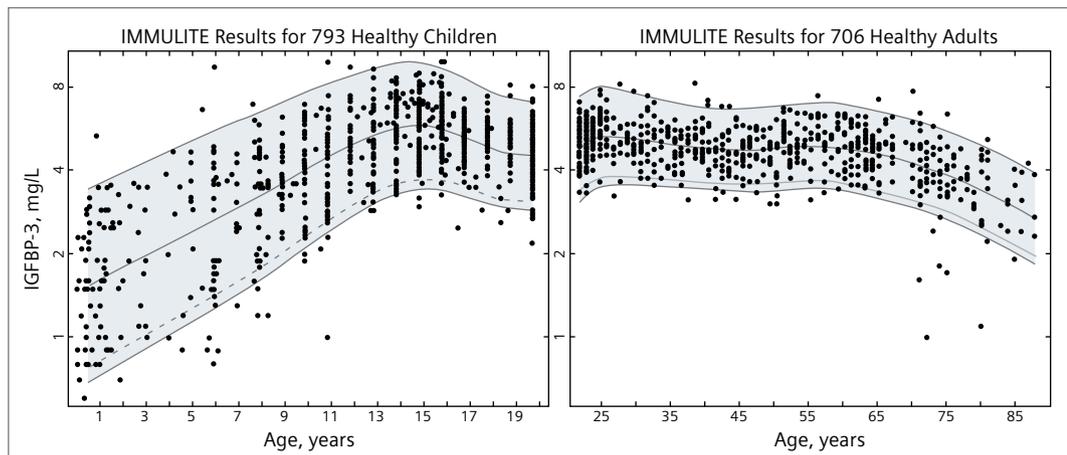

Figure 3: IGFBP-3 Reference Interval (a) for patients <20 yrs. and (b) for patients > 20 yrs.

Excessive Growth

Excessive action of IGF-I while epiphyseal growth plates are open causes gigantism,[5] which occurs very rarely. Children and adolescents with gigantism stand > 2 standard deviations above the mean height for their gender and age. Acromegaly is also caused by hypersecretion of IGF-I.[6] In contrast to gigantism, it occurs in adolescence and adults after their epiphyseal growth plates have fused. Acromegaly in adults is the most common disorder of GH excess, with an estimated prevalence of between 45 and 120 per million.[7] Visible signs of acromegaly and gigantism are enlarged hands and feet, in addition to larger and broader facial features. These conditions are most often caused by a GH-secreting pituitary adenoma, or less frequently by ectopic causes of GH-release, and are commonly treated by surgery, radiation therapy, and the use of a GH receptor antagonist.

The initial tests for GH excess are a fasting or random GH and IGF-I. According to the Acromegaly Consensus Group statement,[8] acromegaly can be excluded if either of the following sets of tests results are observed:[8]

1. Random GH < 0.4 µg/L and IGF-I is normal; or

2. Oral glucose tolerance test results of < 1 µg/L in addition to normal GH and IGF-I values.

The consensus statement[8] clearly points out that the IGF-I value needs to be compared to a reference interval that is age and gender appropriate for the patient.

The publication also defines criteria for treatment outcomes (controlled, inadequate control, and poor control) based on GH, IGF-I, and MRI data. As an example, the controlled treatment outcome criteria are as follows:

1. Nadir GH < 1.0 µg/L

2. IGF-I normal (vs. age-gender reference interval)

3. No clinical activity observed by MRI

Growth Hormone Deficiency (GHD) in Children

Often when a child is taken to a doctor for evaluation of growth hormone deficiency, the family is concerned about the child's lack of size and physical development. Two terms that are commonly used in treating patients that have not met their growth targets are growth failure and short stature. Short stature is defined by the child's height being < 2 standard deviations below the mean (or approximately the 3rd percentile). Many children with short stature actually have normal growth velocity. Growth failure, however, describes a growth rate below the appropriate growth velocity for age based on normal growth rates.[9,10]

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Table 2: GH-IGF disturbances that cause short stature or growth failure.

Clinical Presentation	Site of Disturbance	GH-IGF Axis
Idiopathic GHD w/reduced GHRH	Hypothalamus	GH ↓
Hypothalamic tumor	Hypothalamus	IGF-I ↓
Pituitary tumor	Pituitary gland	GH ↓
Abnormal GH variant	Pituitary gland	IGF-I ↓
Laron syndrome (GH receptor defect)	IGF-I local production	GH ↑, IGF-I ↓
Pygmies	IGF-I local production	GH N, IGF-I ↓
Glucocorticoid-induced GHD	Cartilage	GH N, IGF-I N
IGF-I resistance	Cartilage	GH N, IGF-I ↑

↑ = increased, ↓ = decreased, N = normal

When a child presents with a history of slow growth that suggests GHD, the physician should evaluate the patient for other causes of growth failure, such as hypothyroidism, chronic systemic disease, Turner syndrome, and skeletal disorder.[11] After these conditions have been ruled out, the child should be screened for a GH/IGF-I deficiency. The consensus document on GH therapy for children and adolescents[11] calls for a single GH provocation test when the patient presents with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiencies (MPHD), or a genetic defect (Table 2). If isolated GHD is suspected, it is recommended that two GH provocation tests be conducted.

In practice, IGF-I and IGFBP-3 are often measured initially, so the possibility of GHD can be evaluated before subjecting children to GH provocation testing. Provocation tests are not only costly and time-consuming, but some can also put children in jeopardy. Additionally, provocation tests do not have well-established assay-specific reference values and cutoffs.

Child Dosing and Maintenance Guidelines

In children, the principle measure of successful GH therapy is the increase of the patient's height and growth velocity. IGF-I and IGFBP-3 levels are monitored routinely during therapy to confirm GH dosage is sufficient; serological monitoring can also help assess patient compliance. Additional patient monitoring is essential to check for potential negative side effects, such as intracranial hypertension. The 2000 consensus guideline states that the GH dose should be 25 to 50 µg/kg/day delivered intramuscularly, with dose adjustments made for obese children.[11] Recently, Cohen et al.[12] published a randomized, controlled study that achieved improved growth response by titrating individualized GH dose. This type of dosing requires that the initial dose be adjusted based on the IGF-I and IGFBP-3 levels.

Adult Growth Hormone Deficiency (AGHD)

The diagnosis of AGHD is often difficult because the patient is fully grown and height is no longer an indication of the condition. Therefore, the physician needs to rely on biomarkers to identify adults who have GHD. The most common causes of AGHD are:

• hypothalamic-pituitary disorders,

• childhood-onset GHD,

• previous cranial ablation, and

• traumatic brain injuries.

The suspicion of GHD is heightened when other pituitary hormone deficiencies are present.[13] These patients often have a higher incidence of cardiovascular disease and reduced bone mass, which increases their risk of fractures. AGHD is also associated with reduced lean body mass with concomitant decreased physical strength and increased fatty tissue (especially central obesity), which can lead to metabolic disease, reduced quality of life, anxiety, and depression.

Tests to diagnose GHD include measurement of GH using provocation tests and measurement of IGF-I. As with children, the GH provocation tests do not have well-established cutoffs and can cause some risk to the patient. One consensus document[13] outlines the limitations of these tests. Consensus documents also recommend that IGF-I is a good initial screening test when GHD is suspected for patients who are over 40 years old and have a body mass > 25 kg/m.[11,13]

As stated in a 2007 consensus document,[13] "Not all patients suspected of having GHD, however, require a GH stimulation test for diagnosis. Patients with three or more pituitary hormone deficiencies and an IGF-I level below the reference range have > 97% chance of being GHD, and therefore do not need a GH stimulation test."[13] This is further supported in a publication by Kwan et al.,[14] in which an algorithm for AGHD testing is proposed (Figure 4).

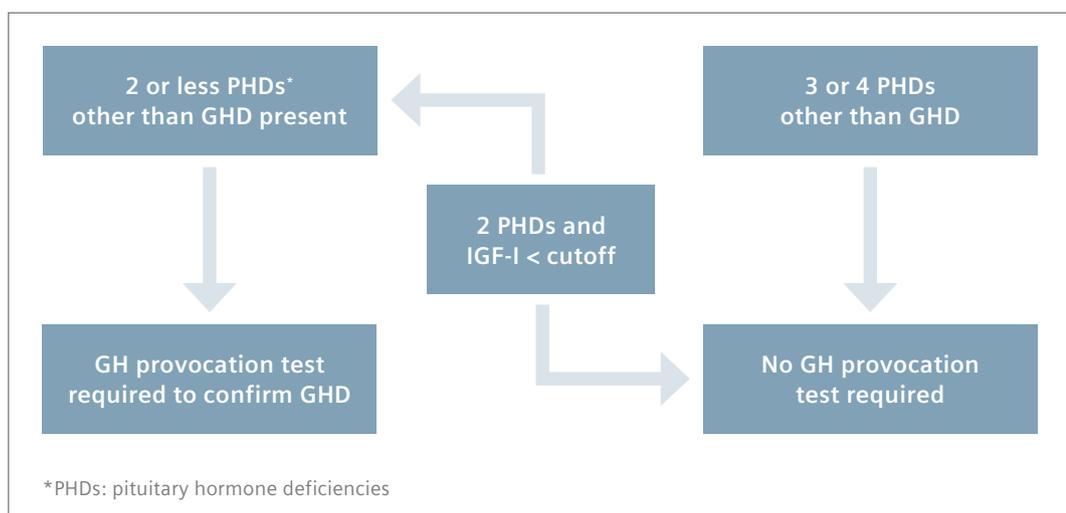| 2 or less PHDs* other than GHD present		3 or 4 PHDs other than GHD
	2 PHDs and IGF-I < cutoff	
GH provocation test required to confirm GHD		No GH provocation test required

*PHDs: pituitary hormone deficiencies

Figure 4: Algorithm used to determine what screening is necessary to diagnose AGHD.[13]

Adult Dosing and Maintenance Guidelines

IGF-I and IGFBP-3 are useful markers for titrating an individual patient's dose. Normally, the initial dose is 0.1 mg GH/day for older patients, 0.2 mg GH/day for younger men, and 0.3 mg GH/day for women. After six weeks, IGF-I and IGFBP-3 are measured to optimize the therapy; the dose is adjusted so the IGF-I and IGFBP-3 concentrations are slightly below the age- and gender-related upper limit of the reference interval.[13] Once the individual's dose is established, monitoring needs to take place annually, or if changes in dosing are made.

Importance of Growth Hormone Assays

GH, IGF-I and IGFBP-3 results are essential when diagnosing and treating growth disorders. The Siemens GH assay is very specific and sensitive that requires only a small volume of sample. Siemens IGF-I and IGFBP-3 assays have established sex- and age-based reference intervals that are crucial in assessing the patient's growth condition. All three of these growth assays are analyzed on all IMMULITE® systems, facilitating timely and accurate results.

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