

# The Laboratory Assessment of Growth Disorders

Acromegaly



# Diagnostic Testing for Growth Disorders

## Growth Hormone Deficiency and Stimulation Tests

In children, short stature for their age, delayed development, and lower than average bone density and muscle strength could all signify GH deficiency (GHD).<sup>3</sup> In adults, GHD can manifest as a decrease in bone density, less muscle mass, and altered lipid levels.

GH stimulation tests are used to diagnose hypopituitarism and GHD.<sup>4</sup> In the most frequently used stimulation tests, a sample of blood is drawn after a period of fasting (usually 10-12 hours). Insulin or arginine is then given intravenously to stimulate GH production. GH levels are tested at timed intervals and the results compared to cut-off values to see if the pituitary gland was stimulated by the insulin (or arginine) to produce the expected levels of GH.

Disorder	Diagnosis	Treatment	Monitoring
<b>GHD</b>	GH stimulation test and IGF-I measurement	rhGH	Regular IGF-I and IGFBP-3 measurements
<b>GH Excess</b> Gigantism (Children) Acromegaly (Adults)	GH suppression test and IGF-I measurement  IGFBP-3 if suppression and IGF-I are discordant	Surgery Radiotherapy  GH Antagonists  Somatostatin analogs	IGF-I measurement
<b>GH Receptor Defects</b> eg. Laron Syndrome	IGF-I measurement	rhIGF-I eg. IMPLEX (rhIGF-1/IGFBP-3)	IGF-I measurement

## Growth Hormone Excess and Suppression Tests

GH hypersecretion is most often due to the presence of a GH-secreting adenoma.<sup>5</sup> Excess GH in children can cause gigantism in which growth continues after puberty to reach heights of 7 or more feet tall. Other symptoms of GH excess include thickening of facial features, general weakness, delayed puberty, and headaches. Excess GH in adults is termed acromegaly and involves bone thickening. If untreated, it can lead to enlarged hands and feet, enlarged facial bones, carpal tunnel syndrome, and abnormally enlarged internal organs.

GH suppression testing is used to detect GH excess in children and adults.<sup>6</sup> A fasting baseline blood sample collection is followed by a second draw after the patient drinks a glucose solution. GH is suppressed by the glucose in normal individuals, and not suppressed in acromegalic and gigantism patients.

# Consensus Statement on the Standardization and Evaluation of GH and IGF-I Assays

Representatives of the Growth Hormone Research Society, the IGF Society, and the International Federation of Clinical Chemistry (IFCC) convened an international workshop at Keswick Hall, Virginia, USA in 2009 to review factors affecting GH and IGF-I immunoassay testing and reporting of results.

These factors included standardization, assay comparability, variables that affect assay interpretation, technical factors affecting assay performance,

assay validation criteria, and the development and use of normative data. Recommendations for each of these variables were made for measurements of each peptide. The consensus statement concludes that major improvements are necessary in the areas of assay performance and comparability.

*This groups main recommendations are tabulated below.*

## Standardization Obstacles

### Current Obstacles

**Different Standards: GH**

Not all GH assays are calibrated to a common IRP

**Value Assignment: IGF-I**

IGF-I WHO IS 87/518 has an incorrectly assigned concentration

**Heterogeneous Analytes: GH**

e.g. circulating GH consists of monomers, dimers, post translationally modified forms. Detection of each varies among assays

**Reporting of Results: GH**

e.g. GH assays have been expressed in mass units and international units

**Interference: GH and IGF-I**

Matrix effects and GHBP and IGFBP's interfere with assays

## Standardization Recommendations

### Recommendations for Manufacturers

**Adopt a single universally accepted standard:**

**GH:** 2nd IS for Somatropin 98/574 (>96% purity, 22 kDa GH)

**IGF-I:** WHO IS 02/254, normative interval should be re-established

**GH**

**Assay Performance:** specific for 22kDa isoform (high affinity and specific antibodies) and accurate measurements at low end (LoQ of 0.05 µg/L) with a CV of <20%.

**GHBP Interference:** degree of interference should be specified as well as cross-reactivity with 20 kDa GH, placental GH, GH analogs

**IGF-I**

**IGFBPs Interference:** IGF-I assay without any interference with IGFBPs is ideal. Dissociation method and prevention of re-association recommended.

**Normative Data:** should include a random selection of all ages and be reported in mass units. Must include: 2.5 to 97.5 percentiles, 3 year intervals for children and adolescents, Tanner Stages and sex-specific intervals between 6 and 18 years

**GH and IGF-I**

**Calibrator Matrix:** should mimic human serum



For laboratory professionals  
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## Understanding the GH/IGF-I Axis

Growth hormone (GH) is released from the pituitary gland into the bloodstream where it acts, via GH receptors, to promote growth and maintain protein synthesis in bone, muscle and cartilage. The majority of GH effects are mediated by IGF-I. GH stimulates IGF-I and IGFBP-3 release from the liver and other tissues. GH itself is regulated by the hypothalamus which produces two factors: growth hormone-releasing hormone (GHRH) which stimulates GH secretion, and Somatostatin which suppresses GH secretion. The interactions of these hormones form a system termed the GH/IGF-I axis.<sup>1</sup> (Figure 1)

GH has a very short half life and is released in a pulsatile manner throughout a 24 hour period with most secretion occurring during periods of sleep.<sup>2</sup> Therefore, random GH measurements are not useful in clinical diagnosis of growth-related disorders. Growth hormone stimulation and suppression tests are more useful in investigating GH abnormalities. Testing of IGF-I levels, which reflect GH secretion, has also become essential in diagnosis and management of growth disorders.

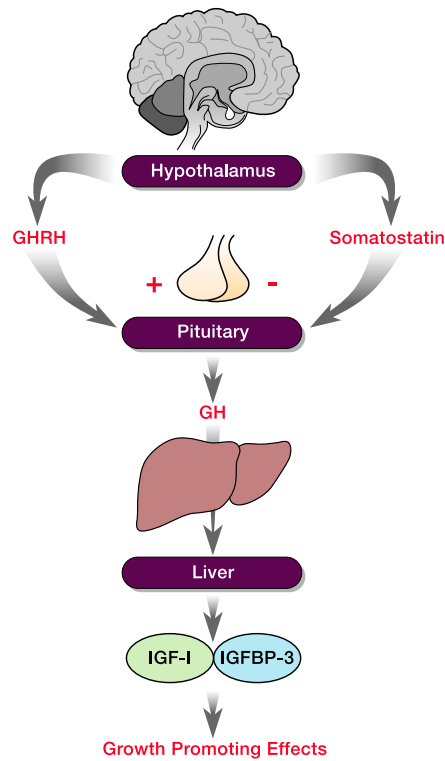


Figure 1



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