



# Laboratory approach to disorders of Growth Hormone secretion

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## Physiology of Growth Hormone

Growth hormone (GH) is produced by the pituitary gland. It is released in a pulsatile manner, and exhibits diurnal variation. Peak secretion occurs within an hour after the onset of deep sleep. Physical activity, trauma and sepsis increase GH levels. There is a complex interaction of nutritional factors, and hypothalamic appetite regulating peptides that control GH secretion. GH levels are increased in fasting, malnutrition, with ingestion of high protein meals and in hypoglycaemia. Hormones also impact on secretion – for example, oestrogen and dopamine stimulate release, whilst cortisol excess inhibits GH secretion.

GH and related growth factors regulate a variety of metabolic processes. These include protein synthesis, lipid oxidation, lipolysis, antagonism of insulin action, and sodium, water and phosphate retention.

GH stimulates insulin-like growth factor 1 (IGF1) and IGF binding protein 3 (IGFBP3) production in the liver. Some of the actions of GH affect the peripheral somatic cells directly, but many are mediated via IGF1.

IGF1, also called somatomedin, is similar in structure and function to insulin. IGF1 production is stimulated by GH, and IGF1 has a negative feedback effect on release of GH from the pituitary gland. IGF1 is released into the bloodstream from the liver, and acts as an endocrine hormone in peripheral tissues. It is a potent growth and differentiation factor.

Circulating IGF1 is bound to a carrier protein (IGFBP3) which is the most abundant member of the IGF binding protein family. IGFBP3 transports IGF1 and controls its bioavailability. The control and secretion is similar to that of IGF1. It is a more stable index of the actions of GH than a random measurement of GH.

## Growth Hormone Deficiency

Growth hormone deficiency (GHD) may be congenital or acquired. The single most important clinical manifestation is growth failure (height velocity < 25<sup>th</sup> percentile for age). Careful documentation of growth rate is essential in making the correct diagnosis. In neonates with congenital GHD, neonatal morbidity may include prolonged jaundice and hypoglycaemia. Children with acquired GHD present with severe growth failure, delayed bone age and other clinical features related to infantile fat distribution.

GHD may occur in isolation, or in association with other pituitary hormone deficiencies. When combined with adrenocorticotrophic hormone (ACTH) deficiency, the hypoglycaemia may be severe. Other causes of GHD include head injury, previous cranial surgery or irradiation, pituitary tumours or infiltrative pathology. Some genetic defects have also been described in a small percentage of patients. The cause of GHD in paediatric patients is often idiopathic.

The definitive diagnosis of GHD can be challenging, and once a child is investigated for short stature, a methodical approach is required. The first step is to evaluate for other causes of growth failure, including chronic systemic disease, hypothyroidism, Turner syndrome, and skeletal disorders. If there is no evidence of these disorders, then document bone age, and request IGF1 and IGFBP3. If these are abnormal, follow with provocative GH testing, and a MRI of the hypothalamic-pituitary region.

In some circumstances, a GH stimulation test may be indicated. These include clonidine GH stimulation tests in children, and glucagon or insulin hypoglycaemic stimulation tests in adults.

## Growth Hormone Excess

Excess growth hormone secretion presents clinically as gigantism in children or acromegaly in adults. In both these scenarios there is often a strong clinical suspicion.

Measurement of all three biomarkers (GH, IGF1 and IGFBP3) demonstrate increased levels in these patients. Random GH tests alone are not useful for the diagnosis, as secretion is pulsatile, diurnal, and stimulated by a variety of factors as noted above.

The best single test for the diagnosis of acromegaly is IGF1. Serum IGF1 levels are increased in virtually all patients with acromegaly, and provide excellent discrimination from normal individuals. GH suppression tests may be required to demonstrate subtle abnormalities of increased GH secretion. The oral glucose tolerance test (OGTT) is the most specific test for establishing the diagnosis of acromegaly. Inadequate suppression of serum GH after a glucose load confirms the diagnosis of acromegaly. It is also the gold standard for determining control of GH secretion after surgery, but is not as helpful in assessing biochemical control in patients treated with somatostatin analogues.

## Growth Hormone Insensitivity

Growth hormone insensitivity is uncommon. The primary cause in children is a genetic defect, usually at GH receptor level. The commonest described in the literature is Laron syndrome. Growth hormone secretion is normal but the actions of GH are absent due to receptor or post-receptor genetic defects.

## Summary of laboratory approach

- Current literature suggests that the evaluation of GH status must include IGF1 and IGFBP3 as they are more stable and have minimal diurnal variation.
- IGF1 and IGFBP3 are almost always low in children with severe GHD. Low IGF1 and IGFBP3 together with decreased height velocity may be diagnostic for GHD. In patients with borderline results, GH stimulation tests may be necessary to demonstrate subtle or moderate GHD.
- The decision about whether to perform provocative GH tests depends on individual patient characteristics, including the severity of growth failure, degree of bone age delay, and whether the low levels of IGF1 and IGFBP3 can be explained by other factors such as poor nutrition.
- GH insensitivity may also occur as a result of chronic illnesses (e.g. malnutrition or chronic kidney disease). In patients with GH insensitivity, GH levels are normal or increased, but they have low levels of IGF1 and IGFBP3.
- The best single test for the diagnosis of acromegaly is IGF1.
- A normal serum IGF1 concentration is strong evidence that the patient does not have acromegaly.
- If the IGF1 concentration is high or equivocal, serum GH should be measured after an OGTT.

**Table 1. Guide to interpretation of laboratory results**

Clinical Status	GH	IGF1	IGFBP3
Normal	Normal	Normal	Normal
GH deficiency (dwarfism)	Low	Low	Low
GH excess (acromegaly)	High	High	High
GH insensitivity	High	Low	High

- All three tests (GH, IGF1 and IGFBP3) are available at Lancet Laboratories.  
Sample type: Serum (Gold/SST)
- For dynamic testing (GH stimulation or suppression tests) kindly contact one of the Chemical Pathologists at Lancet Laboratories

References are available on request

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Polokwane | (015) 294 0400

Cape Town | (021) 673 1700

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Rustenburg | (014) 597 8500

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