Growth

Disorders of the Growth Hormone (GH) axis such as acromegaly and GH deficiency (GHD) in childhood, adolescence and adulthood, are commonly determined by measuring levels of GH, Insulin-like Growth Factor-I (IGF-I) and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3).[1–3] Over the last decade, several consensus statements have been established describing how to utilise and interpret these parameters in clinical practice.[4–13] However, the ways in which differences between immunoassays can influence the interpretation of these consensus criteria are not always taken into account,[14] despite a number of publications on the implications of the variability in GH[15–18] and IGF-I[19–23] tests. A failure to recognise the impact of those discrepancies can have serious implications for the treatment of a patient.

Physiology

GH secretion by the anterior pituitary gland is pulsatile and diurnal in nature. It is regulated by hypothalamic Growth Hormone Releasing Hormone (GHRH) and somatostatin. GH circulates in various isoforms, namely its monomeric form, as homo- and heterodimers as well as multimers. The main circulating isoform of GH is the 22 kDa isoform (191 amino acids), followed by the 20 kDa isoform (176 amino acids). GH acts via plasma membrane GH receptors. It has direct effects in some tissues, but mainly stimulates production of the insulin-like growth factor IGF-I in liver and other tissues. IGF-I in turn mediates many of the anabolic and metabolic actions of GH. [24–26]

IGF-I secretion is mostly dependent on GH secretion, but nutrition and age also play a role. IGF-I is a polypeptide (7649 Da) with 50 % sequence homology to proinsulin and several biological functions similar to those of insulin. As well as mediating the actions of GH, IGF-I has a negative feedback effect on GH release and inhibits apoptosis. It acts through two transmembrane receptors which are similar in structure to the insulin receptor. The IGFs circulate in blood complexed to six binding proteins (IGFBPs). IGFBP-3 is the main circulating type and it forms a 150 kDa ternary complex which is comprised of an acid labile subunit (ALS), IGFBP-3 and IGF-I or IGF-II. The secretion of IGFBP-3 is GH-dependent, with decreased levels in GH deficiency and increased levels in acromegaly. [27–29]

Measurement of the GH-IGF axis

Due to the variable levels of secreted GH and its short half-life, single measurements of circulating GH are less conclusive in the assessment of growth-related disorders. Diagnosis is usually confirmed by dynamic testing, i. e. a stimulation test with measurement of peak serum GH concentration, or by a suppression test assessing the ability to suppress serum GH following oral glucose load. The levels of GH-regulated substances (e. g. IGF-I and II, IGFBP-2 and -3, and ALS) can also be used as an indirect assessment of GH secretion in the diagnosis of patients with GH disorders. IGF-I and IGBP-3, however, represent the key markers for the evaluation of growth hormone status. [30, 31]

Clinical indications

GH deficiency and excess

The measurement of serum IGF-I and GH is essential in the diagnosis and monitoring of GH deficiency (GHD) and GH excess.

GH secretion is pulsatile and diurnal and may be influenced by exercise and sleep. GH has a short half-life of approximately 20 minutes. Single measurements of serum GH are not usually helpful in assessment of GHD, since levels normally are low in healthy persons who are awake.

The diagnosis of GHD, which is the requirement for GH replacement therapy, is confirmed by GH stimulation tests showing a peak serum GH concentration below a cut-off value [32, 33]. Since no single stimulation test has a sensitivity and specificity of 100 %, at least two tests are recommended. **Various tests are available:**

- **Arginine Stimulation Test / Arginine + GHRH (growth hormone releasing hormone) Test**
- **Insulin Hypoglycaemia Test**
- **Glucagon Stimulation Test**
- **Clonidine Stimulation Test**

The serum values of IGF-I and IGFBP-3 to support the diagnosis of GHD are still under discussion. According to some diagnostic guidelines, however, IGF-I and / or IGFBP-3 concentrations below –1 SD score are sufficient for the strong suspicion of GHD. [34] Because IGF-I is protein-bound, its half-life in serum is much longer than that of GH and it is not subject to pulsatile variability. It has also been shown that age and the time of onset of GHD have a significant influence on IGF-I levels. [35]

Accurate measurement of IGF-I and IGFBP-3 is widely established in the monitoring of GH replacement therapy. Titration of the GH dose to maintain the concentrations of IGF-I and IGFBP-3 within the respective age-related normal ranges is recommended by the consensus guidelines.[36] IGFBP-3 testing is particularly useful in young children, in whom serum IGF-I levels are in a similar range in GHD and non-GHD.[37] In a recently published systematic review and meta-analysis of 12 studies investigating the diagnostic values of serum IGF-I and IGFBP-3 for GHD, it was stated that they are useful to support the diagnosis of GHD and that they can be utilised as auxiliary diagnostic indexes for provocative testing. Taking into account all analysed studies, the sensitivity and specificity values to support the GHD diagnosis were 0.66 and 0.69 for IGF-I and 0.50 and 0.79 for IGFBP-3.[38]

Hypersecretion of GH, commonly due to a pituitary adenoma, leads to gigantism if acquired before epiphyseal closure and in acromegaly thereafter.

The majority of patients with acromegaly have GH concentrations above 5 ng/ml in basal fasting samples drawn at bed rest. However, a single elevated GH value cannot verify the diagnosis of acromegaly. Serum IGF-I levels are a useful tool to assess integrated GH secretion and for screening and diagnosis. If the level is elevated, diagnosis is usually confirmed by functional testing.

If the body is not able to suppress serum to below a defined value after an oral glucose load, this is considered the diagnostic criterion for acromegaly (oral glucose tolerance test, OGTT).

In healthy individuals, GH levels fall to less than 0.2–0.3 ng/ml one or two hours after glucose load.[39, 40]

Patients should be monitored following onset of treatment for acromegaly to assess the effectiveness of the therapy. Monitoring of serum IGF-I and GH levels in acromegaly patients is essential. Elevation of IGF-I is considered a sensitive and specific indicator that the disease persists after therapy.[36]

Although IGFBP-3 measurement is not a useful addition to IGF-I testing for the diagnosis and follow-up of acromegaly and gigantism, some studies suggest that IGFBP-3 measurements may be helpful in confirming the diagnosis of acromegaly with coexisting uncontrolled diabetes and distinguishing it from high GH levels attributable to poor control of diabetes.[41]

Some disorders with symptoms similar to those of GHD

- **Turner syndrome:** multiple factors of impaired growth, including abnormalities in the GH/IGF-I and IGFBP axis
- **Prader-Willi syndrome:** associated with reduced GH secretion and low IGF-I levels
- **Silver-Russell syndrome**: characterised by growth retardation and occasionally associated with GH deficiency
- **Laron syndrome:** characterised by insensitivity to GH and very low levels of IGF-I and IGFBP-3
- **Small for Gestational Age (SGA) without catch-up growth:** GH Therapy with IGF-I and IGFBP-3 monitoring
- **SHOX-D (Short stature homeobox gene deficiency):** GH Therapy with IGF-I and IGFBP-3 monitoring
- **Primary IGF-I deficiency (IGFD):** normal GH secretion in the presence of low IGF-I and low IGFBP-3

Chemiluminescence immunoassay product portfolio

Product name	Information	Code
Human Growth Hormone (hGH)	100 tests, calibrators included	IS-3700
Insulin-like Growth Factor-I (IGF-I)	100 tests, calibrators included	IS-3900
Insulin-like Growth Factor-I (IGF-I) Control Set	Control 1–3 (3 × 1 ml of each)	IS-3930
Insulin-like Growth Factor Binding Protein-3 (IGFBP-3)	100 tests, calibrators included	IS-4400
Insulin-like Growth Factor Binding Protein 3 (IGFBP-3) Control Set	Control 1–3 (3 × 1 ml of each)	IS -4430

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