

SOMATROPIN

Disease diagnosis and treatment



Synthesis

- GH is the most abundant anterior pituitary hormone, and GH-secretion somatotrope cells constitute up to 50% of the total anterior pituitary cell population.
- The pituitary GH gene produces two alternatively products that give rise 22-kDa GH (191 amino acids) and a less abundant, 20-kDa GH molecule, with similar biologic activity.

Secretion

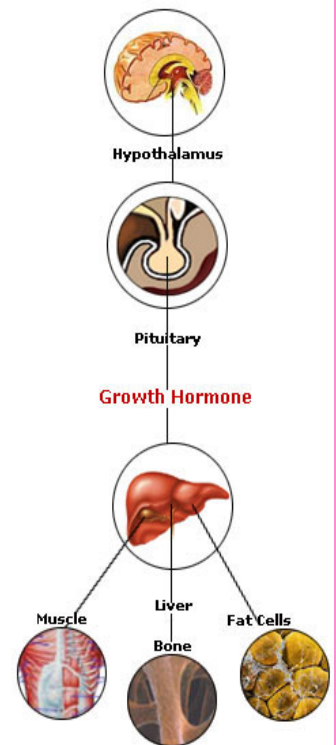
- GH secretion is controlled by complex hypothalamic and a peripheral factor:
 - ▶ GHRH stimulates GH synthesis and release Ghrelin or gastric-derived peptide, as well as synthetic agonists of the GHRP receptor stimulate GHRH and also directly stimulate GH release.
 - ▶ GHRH is secreted as discrete spikes that elicit GH pulses whereas SRIF sets basal GH tone.
 - ▶ Somatostatin "Somatotropin Release Inhibiting Factor (SRIF)" is synthesized in the medial preoptic area of the hypothalamus and inhibits GH secretion.
 - ▶ IGF-I, the peripheral target hormone for GH, feeds back to inhibit GH, estrogen induces GH, whereas glucocorticoid excess suppresses GH release.

Insulin-like growth factors:

Through GH exerts direct effects in target tissues, many of its physiological effects are mediated indirectly through IGF-I, a potent growth and differentiation factor. The major source of circulating IGF-I is hepatic in origin. Peripheral tissue IGF-I exerts local paracrine actions that appear to be both dependent and independent of GH. Thus, GH administration induces circulating IGF-I as well as stimulating IGF-I expression in multiple tissues.

Physiology

- ▶ Though IGF-I is not an approved drug. Investigational studies provide insight into its physiologic effects. Injected IGF-I (100µg/Kg) induces hypoglycemia and lower doses improve insulin sensitivity in patients with severe insulin resistance and diabetes. In IGF-I infusion enhances nitrogen retention and lowers cholesterol levels. Bone turn over may also be stimulated by IGF-I.
- ▶ IGF-I side effects are dose-dependent, and overdose may result in hypoglycemia, hypotension, fluid retention, temporomandibular jaw pain and increased intracranial pressure. All of which are reversible.



*"Better
Growth....Change
the Future."*

Disorders of growth and development

Skeletal maturation and somatic growth:

The growth plate is dependent on a variety of hormonal stimuli including GH, IGF-I, sex steroids, thyroid hormones, paracrine growth factors. The growth-promoting process also requires caloric energy, amino acids, vitamins and trace metals and consumes about 10% of normal energy production.

Bone age is delayed because of:

- ▶ GH deficiency
- ▶ Hypogonadism
- ▶ Thyroid hormone deficiency
- ▶ Elevated pubertal sex steroid levels.

GH deficiency in children:

GH deficiency isolated GH deficiency is characterized by:

- ▶ Short stature
- ▶ Micropenis
- ▶ Increased fat
- ▶ High-pitched voice

GHRH receptor mutations:

Recessive mutations of the GHRH receptor gene in subjects with severe proportionate dwarfism are associated with low basal GH levels that can't be stimulated by exogenous GHRH, GHRP or insulin-induced hypoglycemia.



Growth hormone insensitivity

This is caused by defects of GH receptor structure or signaling. homozygous or heterozygous mutations of the GH receptor are associated with partial or complete GH insensitivity and growth failure (laron syndrome) this diagnosis is based on normal or high GH levels.

Nutritional short stature:

Caloric deprivation and malnutrition, uncontrolled diabetes and chronic renal failure represent secondary causes of GH receptor function. Children with these conditions typically exhibit features of acquired short stature with elevated GH and low IGF-I levels. Circulating GH receptor antibodies may rarely cause peripheral GH insensitivity.

Psychosocial short stature:

Emotional and social deprivation lead to growth retardation accompanied by delayed speech, discordant hyperphagia and attenuated response to administered GH.



Children GH deficiency (CGHD):

Presentation and diagnosis:

- Short stature should be comprehensively evaluated if a patient's height is < 3SD below the mean for age or if the growth rate has decelerated. Skeletal maturation is best evaluated by measuring a radiological bone age, which is based mainly on the degree of growth plate fusion.

Laboratory investigation:

GH deficiency is best assessed by examining the response to provocative stimuli including exercise, insulin-induced hypoglycemia and

Adult GH deficiency (AGHD):

- This disorder is usually caused by hypothalamic or pituitary somatotrope damage. Acquired pituitary hormone deficiency follows a typical sequential pattern whereby loss of adequate GH reverse foreshadows subsequent hormone deficits. The sequential order of hormone loss is usually:
GH→FSH/LH→TSH→ACTH

Presentation and diagnosis:

- The clinical features of AGHD include changes in body composition, lipid metabolism and quality of life and cardiovascular dysfunction.

Impaired quality of life

- Decreased energy and drive, poor concentration, low self-esteem, social isolation.

Body composition changes:

- Increased body fat mass, central fat deposition, increased waist-hip ratio, decreased lean body mass.

Reduced exercise capacity Cardiovascular risk factors:

- Impaired cardiac structure and function, abnormal lipid profile, decreased fibrinolytic activity, atherosclerosis, omental obesity.

Laboratory investigation:

Testing should be restricted to patients with the following predisposing factors:

- Pituitary surgery.
- Pituitary or hypothalamic tumor or granulomas.
- Cranial irradiation.
- Radiological evidence of a pituitary lesion.
- Childhood requirement for GH replacement therapy.

The most validated test is insulin-induced (0.05 to 0.1U/Kg) hypoglycemia, and peak GH release occurs at 60min, and remains elevated for up to 2hr. About 90% of healthy adults exhibit GH responses > 5µg/L; AGHD is defined by peak GH response to hypoglycemia of < 3µg/L

Treatment

In children:

With growth hormone deficiency, the usual dose in the U.K is 0.5 to 0.7 units/Kg body-weight or 12to20 units\m2 body-surface weekly. This weekly dose may be given by intramuscular injection in 3 divided doses or by subcutaneous injection, usually in 6 or 7 divided doses.

In adults:

With growth hormone deficiency lower doses are recommended. A suggested initial dose is 0.125 units\Kg weekly, divided into daily subcutaneous injection, and increased according to requirements up to a max. of 0.25 units\Kg per week.

Somatropim

Recombinant human growth hormone (rhGH), is a polypeptide with a sequence of 191 Amino Acid residues and a molecular weight of about 22, 125D.

The amino acid sequence of (rhGH) is identical to that of the naturally occurring pituitary gland hormone.

