Journal of Endocrinology, Diabetes and Metabolic Complications (JEDMC)

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Review Article

Growth Hormone Deficiency in Children: An Analysis Pediatric Endocrinology

Losa R, Rossini T *, Karavitaki R, Bengtsson W, Boguszewski R, Corneli T
Department of Medical Sciences, Bilkent University, Turkey.
*** Corresponding Author**: Rossini T,Department of Medical Sciences, Bilkent University, Turkey.

Citation: Losa R, Rossini T,Karavitaki R, Bengtsson W, Boguszewski R, Corneli T,Growth Hormone Deficiency in Children: An Analysis Pediatric Endocrinology V1(1),2025

Received date: June 28, 2025**: Accepted date:** July 18, 2025**: Published date:** July 29, 2025

Keywords: pituitary gland, hypothalamus, hypothalamic-pituitary tumors, GH stimulation

Abstract
Growth hormone (GH) deficiency is caused by congenital or acquired causes and occurs in childhood or adulthood. GH replacement therapy brings benefits to body composition, exercise capacity, skeletal health, cardiovascular outcomes, and quality of life. Before initiating GH replacement, GH deficiency should be confirmed through proper stimulation tests, and in cases with proven genetic causes or structural lesions, repeated GH stimulation testing is not necessary. The dosing regimen of GH replacement therapy should be individualized, with the goal of minimizing side effects and maximizing clinical improvements.

Introduction
The fundamental importance of growth hormone (GH) during adulthood to help maintain proper metabolism, body composition, and quality of life may be underappreciated because GH is primarily recognized for promoting linear growth during childhood and adolescence. Adult GH deficiency (AGHD) is a rare condition that affects approximately 2 to 3 in 10 000 individuals and can be caused by genetic mutations, developmental abnormalities, traumatic brain injury, pituitary or hypothalamic tumors, or surgical or radiologic treatments for these or other nearby tumors. AGHD can be classified as either childhood-onset (CO-AGHD) or adult-onset (AO-AGHD), which have estimated incidence rates of 2 in 100 000 and 1 in 100 000 cases per year, respectively.

Growth hormone (GH) is released from somatotrophs in the anterior pituitary gland in a pulsatile manner due to opposing actions of growth hormone releasing hormone (GHRH) which has a stimulatory effect, and somatostatin (also known as somatotropin release-inhibiting factor or SRIF) which has a inhibitory effect. There are numerous factors that affect GH section. Hypothyroidism as well as adiposity are associated with a decrease in GH secretion, while undernutrition leads to over secretion of GH (however with low levels of insulin-like growth factor-1 (IGF-1) levels indicating GH resistance). The majority of GH is found in the 22-kDa form (75%), however, smaller amounts of 20-kDa (5–10%) and 17.5-kDa (1–5%) peptides are also present. Once released into circulation, GH stimulates fat breakdown and promotes protein synthesis. Although GH can exert its effect directly at the cellular level, it primarily acts on the liver to synthesize IGF-1 which exerts peripheral growth promoting effects. IGF-1 circulates bound to IGF-binding proteins (IGFBPs), which extend the serum half-life of IGFs. IGFBP-3 is the major IGFBP in humans and transports the majority of circulating IGF-1.

Molecular Genetics
GH is a peptide encoded by the GH1 gene, which is part of a 65-kb cluster of five genes located on chromosome 17q22-24. Four forms of familial isolated growth hormone deficiency (IGHD) have been described: autosomal recessive (type IA and IB), autosomal dominant (type II) and X-linked recessive (type III). IGHD Type 1A classically occurs with homozygous 6.5–45 kb deletions in GH1, which prevent synthesis or secretion of GH. Affected individuals present with severe growth failure before 6 months of age, including a height less than 4.5 standard deviations below the mean. Serum levels of GH are undetectable, and upon initiation of GH replacement therapy, anti-GH antibodies often develop. IGHD Type IB is a less severe autosomal recessive form of GHD resulting from splice site, frameshift, missense, and nonsense mutations in GH1. IGHD Type II is commonly due to single base deletions from the first six nucleotides of intron 3. This

mutation results in the increased production of a 17.5 kDa form of GH. Phenotypic presentations vary as affected individuals may range from having a normal height to exhibiting severe short stature. Other pituitary hormone deficiencies may also develop when splice site mutations are present, including adrenocorticotropic hormone (ACTH), prolactin, thyroid-stimulating hormone (TSH), or gonadotropin deficiencies. A hypoplastic anterior pituitary gland may be detected on MRI in approximately 38–50% of individuals. IGHD Type III may be associated with X-linked mutations, such as SOX3, a transcription factor located at Xq27 and involved in pituitary development.

Diagnostic Approach

The diagnostic workup should begin with a thorough history and physical examination. Birth history (maternal health during pregnancy, birth difficulties, mode of delivery, birth weight and length, postnatal complications), review of general health, significant medical and surgical history, and family history (consanguinity, familial heights and age at onset of puberty, medical problems) should be obtained. Clinical information obtained from the history including neonatal hypoglycemia, prolonged neonatal jaundice, or prior cranial irradiation increase suspicion for GHD.

Treatment

Treatment of GHD is accomplished by administration of recombinant human growth hormone (rhGH). Treatment can be given in children whose epiphyses are open. Historically, treatment has required daily subcutaneous injections typically administered in the evening to more closely match the release pattern of endogenous GH. However, no difference in effectiveness has been observed based on the timing of medication administration. Sustained-release preparations of rhGH are also now available in the United States and a few other countries. In a 52-week randomized study in prepubertal children with GHD, patients using once weekly lonapegsomatropin had an annualized height velocity (AHV) of 11.2 ± 0.2 cm/year, while patients treated with equivalent doses of aqueous rhGH administered by daily subcutaneous injection had an AHV of 10.3 ± 0.3 cm/year.

Conclusion

Although it remains controversial whether GH treatment reduces cardiovascular mortality in patients with hypopituitarism, GH treatment in patients with GH deficiency has more benefits than harm. It is important to accurately diagnose GH deficiency through GH stimulation tests before starting GH treatment. The GH dose should be individualized to minimize side effects and to maximize clinical efficacy.

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