

Adult growth hormone deficiency

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ABSTRACT

Adult growth hormone deficiency (AGHD) is being recognized increasingly and has been thought to be associated with premature mortality. Pituitary tumors are the commonest cause for AGHD. Growth hormone deficiency (GHD) has been associated with neuropsychiatric-cognitive, cardiovascular, neuromuscular, metabolic, and skeletal abnormalities. Most of these can be reversed with growth hormone therapy. The insulin tolerance test still remains the gold standard dynamic test to diagnose AGHD. Growth hormone is administered subcutaneously once a day, titrated to clinical symptoms, signs and IGF-1 (insulin like growth factor-1). It is generally well tolerated at the low-doses used in adults. Pegylated human growth hormone therapy is on the horizon, with a convenient once a week dosing.

Key words: Adult growth hormone deficiency, growth hormone, growth hormone deficiency, hypopituitarism, panhypopituitarism

INTRODUCTION

Adult onset growth hormone deficiency (AGHD) may represent two distinct clinical situations:

1. Children with growth hormone (GH) deficiency transitioning to adulthood **or**
2. GH deficiency acquired during adulthood (structural/trauma or idiopathic).

Over the past decade, there has been an increasing recognition of premature mortality associated with hypopituitarism. There is a two- to three-fold increase in standardized mortality in these patients with hypopituitarism.^[1] The increased mortality is probably related to macrovascular disease (cardiovascular and cerebrovascular).^[2] The fact that these patients with increased mortality were replaced with steroids, thyroxine and a majority were on male hormone replacement, led some experts to believe that GHD may have contributed to the increased mortality.

GH is the first hormone to deplete following any pituitary insult. It was not until 1995 that the concept of growth hormone replacement became popular and recognized.

HISTORICAL REVIEW

In 1922 Evans and Long^[3] injected the beef pituitary extract to animals (rats) and reported excessive growth. Smith,^[4] a few years later, showed the opposite effect of growth cessation following hypophysectomy in rats with re-growth following implantation of pituitary tissue. This suggested the possibility of a substance in the pituitary responsible for growth.

In 1908, it was further thought that this pituitary factor promoting growth might be diabetogenic.^[5] It was only after 1950 that the combined effects were explained by one single substance, growth hormone. Houssay's was awarded the Nobel Prize in 1947 for his extensive work on the hypophysis and carbohydrate metabolism.^[6] Salmon and Daughaday^[7] suggested that GH action was mediated via a factor, named sulfation factor, only later to be identified as somatomedin. This was given a new name: insulin-like growth factor-1 (IGF-1) to indicate its chemical similarity to (pro)insulin. The complete structure with 70 amino acids was reported in 1978.

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In 1944, Li and Evans were the first to claim that bovine GH had been isolated.^[8,9] Berson and Yalow engineered a radioimmunoassay for GH that was later used to determine plasma IGF-1.^[10,11]

The first results of treating children with GH were published in 1932.^[12] The report by Raben^[13] is quoted as the first successful example of the use of GH extracted from human pituitaries. The patient was a young hypopituitary man who responded to GH treatment with an accelerated growth.

As the source of GH (human pituitaries) was limited, in most countries, distribution and use of GH was regulated and supervised by official bodies, for example in the United States by the National Pituitary Agency (NPA). Creutzfeldt–Jakob's disease was a dreaded complication of GH therapy obtained from human pituitary, resulting in death of patients.^[14] In 1979, a commercial company (Genentech) decided to produce GH by inserting the gene controlling GH synthesis into bacteria.^[15] From around 1985, pharmaceutical companies started manufacturing recombinant GH.

PHYSIOLOGY OF GROWTH HORMONE

The 24-h profile of plasma growth hormone levels in normal adults consists of stable low levels interrupted by bursts of secretion. The most reproducible pulse occurs shortly after the onset of sleep associated with the first phase of slow-wave sleep (stages III and IV).^[16]

In men, approximately 70% of the GH pulses during sleep coincide with slow-wave sleep. The GH pulse is generally the largest and often the only pulse observed over a 24-h period. In women, in contrast to the men, GH pulses occur predominantly during daytime contributing to the greater part of the 24-h release of GH. The total amount and the temporal distribution of GH release are strongly dependent on age. As age advances from term infants (tonic GH secretion) to mature infants the frequency and amplitude of the GH pulses decrease, and tonic secretion diminishes. As puberty is reached, the pulsatile pattern of GH release occurs with increased amplitudes during sleep in both boys and girls. Maximal overall GH concentrations are reached in early puberty in girls and in late puberty in boys. The amount of GH secreted daily in healthy men older than 65 years of age is generally less than one-third that in men younger than 30 years.^[17-20]

ETIOLOGY OF GROWTH HORMONE DEFICIENCY

The KIMS database,^[21] which is a multinational

pharmaco-epidemiological surveillance database for adult hypopituitary patients receiving growth hormone therapy, revealed pituitary adenoma and craniopharyngioma as the most important cause for AGHD accounting for 65% of the patients. The HypoCCS study revealed an elegant distribution of possible etiologies of GHD with differences in presentations in the mid-1990s and mid-2000s. In the mid-1990s, pituitary adenoma (50.2%), idiopathic growth hormone deficiency (13.9%), craniopharyngioma (13.3%), non-pituitary intracranial tumors (8.2%), non-common diagnosis (sarcoidosis, empty sella, hypophysitis, pituitary infection, known and unknown genetic abnormalities, and cranial irradiation) (7.4%), pituitary hemorrhage (5.8%), and unspecified diagnosis (1.3%) were reported as common causes. The same authors demonstrated an increase in idiopathic growth hormone deficiency (19.3%), non-common causes (15.8%), and undefined causes (8.6%) by the mid-2000s with a decrease in other causes such as pituitary adenoma (38%), craniopharyngioma (8.4%), and pituitary hemorrhage (2.8%).^[22]

Traumatic brain injury (6–20%) and subarachnoid hemorrhage (12–37%) may result in GHD more frequently than previously suspected.^[23]

CLINICAL FEATURES OF GROWTH HORMONE DEFICIENCY

The symptomatology can be discussed under neuropsychiatric-cognitive, cardiac, metabolic, muscular, and bone symptoms, such as:

- Changes in memory, processing speed and attention
- Lack of well-being
- Depression
- Anxiety
- Social isolation
- Fatigue
- Lack of strength
- Fibromyalgia syndrome
- Neuromuscular dysfunction
- Central adiposity
- Decreased muscle mass
- Decreased bone density
- Impaired cardiac function
- Decreased insulin sensitivity
- Accelerated atherogenesis with increased carotid intima-media thickness
- Increased low-density lipoprotein
- Prothrombotic state
- Decreased sweating and thermoregulation.^[24-32]

Neuropsychiatric-cognitive abnormalities

Patients with GHD frequently complain of low energy

levels, emotional lability, and mental fatigue, resulting in a low perceived quality of life. GH replacement treatment for 6–12 months can lead to significant improvements in body composition, muscle strength, self-esteem scores, energy levels, and emotional reactions.^[33]

Another study demonstrated that up to 70% of patients with the fibromyalgia syndrome exhibited a suboptimal growth hormone response to dynamic testing. Treatment with growth hormone resulted in improvement in perceived energy levels, body image, and pain level^[24] and cognition.^[34]

Cardiovascular morbidity and mortality

Although a matter of much debate, several authors have demonstrated increased cardiovascular mortality.^[1,2,35] GH deficiency and insufficiency are associated with higher levels of plasminogen activator inhibitor-I levels (*prothrombotic*), carotid intima-media thickness, and loss of circulating CD34+ cells, suggesting *endothelial dysfunction*. Some groups have also shown compromised coronary reserved flow.^[36] The degree of GHD is directly related to increased total cholesterol, low-density lipoprotein-C (LDL), truncal fat, waist–hip ratio, and risk of hypertension, all responsible for the proposed increased cardiovascular mortality.^[32,37,38] A meta-analysis on the effects of various cardiovascular parameters were studied in patients treated with GH and it was seen that lean body mass, LDL cholesterol, total cholesterol, and diastolic blood pressure improved significantly with use of GH in GH-deficient adults.^[39]

Body composition and metabolic abnormalities

GHD adults have reduced lean body mass and increased abdominal adiposity. In a study of 15 healthy adult women, the authors showed that GH secretion was much reduced in patients with high truncal fat compared to those with low truncal fat.^[40] Truncal obesity is associated with metabolic syndrome and insulin resistance. Although the truncal fat improves (reduces) as early as 3 months of GH replacement, the antagonistic actions of GH on insulin, mediated by hepatic effects and increased plasma free fatty acids, cause further decline in insulin sensitivity that improves only after 1 year of GH therapy.^[28,41,42] GH deficiency is associated with hypertriglyceridemia, hypertension,^[33] and low levels of high density lipoprotein (HDL) which has shown to improve following recombinant GH replacement.^[43] A meta-analysis of 37 blinded, randomized, placebo-controlled trials found an overall beneficial effect of GH replacement therapy on LDL cholesterol and total cholesterol profiles, however did not show consistent benefits on HDL cholesterol or triglyceride levels.^[39]

Muscular abnormalities

GH deficiency has been associated with reduced lean

muscle mass and impaired neuromuscular function.^[44,45] There was an improvement of lean mass, neuromuscular function (isometric knee flexor strength) that was sustained over a 10-year period while of GH replacement. In a very interesting study of patients with the fibromyalgia syndrome, up to 70% of patients were shown to have GHD which showed a marked improvement in symptomology following growth hormone replacement.^[24]

Bone abnormalities

Although GH may act directly on skeletal cells, most of its effects are mediated by IGF-I, which is present in the systemic circulation and is synthesized by peripheral tissues. AGHD causes low bone turnover osteoporosis with high risk of vertebral and nonvertebral fractures, and the low bone mass. GH replacement reverses this situation rapidly, resulting in increases in markers of bone formation (e.g. osteocalcin and bone-specific alkaline phosphatase) and bone resorption (e.g. urine deoxypyridinoline). This increase in bone metabolism eventually results in an increase in bone mineral density (BMD), but it is only after 18 months of therapy that it becomes evident.^[46-48]

Diagnosis

There are consensus guidelines for the diagnosis and management of GHD in adults. Recombinant GH therapy got approved by the U.S. Food and Drug Administration (FDA) in 1996.

Dynamic testing forms the mainstay of diagnosis. Patients with childhood-onset GHD should be retested for GHD as adults, unless they have known mutations, embryopathic lesions, or irreversible structural lesions/damage, as reversal of diagnosed GHD is known to occur. Adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, or other pituitary hormone deficiencies should be considered for evaluation for acquired GHD.

Available dynamic testing options are:

1. The insulin tolerance test (GH peak measurement of 3 µg/l or less is indicative of severe AGHD)^[49] for an optimal cutoff of GH of 5.1 µg/l (96% sensitivity and 92% specificity).^[49,50] This remains the gold standard.
2. The glucagon stimulation test.
3. Combined growth hormone releasing hormone (GHRH) and the arginine test (95% sensitivity and 91% specificity at a GH cutoff of 4.1 µg/l).^[50,51]
4. Levodopa.
5. Arginine plus levodopa.
6. Clonidine.
7. Growth-hormone-releasing peptide 2.^[52]

A cutoff of 3 µg/l defines severe GHD, whereas a cutoff value of 5 µg/l defines GHD. A balance between high sensitivity and high specificity can be achieved with a cutoff level of GH 5.1 µg/l.^[50] Amongst all the dynamic tests, the Insulin tolerance test and combined GHRH and arginine test have the best sensitivity and specificity.

Other ancillary diagnostic tests include:

1. IGF-1 (Insulin like growth factor-1).
2. IGF-BP3 (IGF-binding protein 3).

Having normal levels of IGF-I and IGFBP-3 does not exclude a diagnosis of GHD in adults.^[49,50,53] IGF-I can be of some diagnostic assistance if levels are below the age-adjusted normal range. Although IGF-1 can be very useful in diagnosis of AGHD, appropriate population based cutoffs, expressed as a IGF-1 standard deviation score (IGF-1 SDS), can prove to be more useful as an isolated diagnostic marker in adults. IGF-BP3, although useful, does not provide any further diagnostic accuracy over IGF-1.^[54]

Treatment

Once the diagnosis of GHD is established, an ideal replacement regimen should be instituted and titrated to a clinical response and serum IGF-1 level. Several quality of life questionnaires have been used to assess clinical response, e.g. adult growth hormone deficiency assessment (AGHDA) score, Nottingham Health Profile (NHP); Psychological General Well Being Scale (PGWB) and disease-specific questionnaires like {Questions on Life Satisfaction Hypopituitarism (QLS-H)}.^[55]

GH therapy can affect the metabolism of other hormones. GH is known to affect 11βHSD-1 (11-beta-hydroxydehydrogenase-1), hence initiation of GH may lead to partial cortisol deficiency.^[56] GH may also interact with the TSH axis. Patients on thyroxine replacement frequently require an increase in their dose^[57] probably because of enhanced peripheral conversion of T₄ to T₃ mediated via GH. It may also have a central inhibitory effect on TSH. Women require a higher GH dose than men to achieve a similar increment in IGF-I. GH sensitivity is blunted in females on oral estrogen.^[58] Therefore, a thorough assessment of the pituitary gland in its entirety is required before considering isolated GH therapy.

Dosing regimens have evolved from weight-based dosing to individualized dose-titration strategies. In general, women require higher doses of GH to achieve the same IGF-I response.^[48] GH secretion normally decreases with age. GH dose requirements are lower in older patients. For patients aged 30–60 years, a starting dose of 300 µg/day is reasonable and is usually not associated with any side

effects. Daily dosing should be increased by 100–200 µg every 1–2 months titrated to the IGF-1, which should generally be kept in the upper half of the reference range, although no published studies offers specific guidance in this regard. Clinical benefits may not become apparent for 6 or more months of treatment. Older (>60 years) patients should be started on lower doses (100–200 µg/day) and increased more slowly. Younger (<30 years) patients may benefit from higher initial doses (400–500 µg/day); for patients transitioning from pediatric treatment, even higher doses may be appropriate.^[49] Pegylated long-acting human growth hormone is on the horizon, which has been found to be efficacious, safe, well-tolerated, once-weekly treatment of adult patients with GHD.^[59]

Most *adverse effects* include fluid retention (5–18%), hypertension, paresthesias, joint stiffness, peripheral edema, arthralgia, and myalgias, carpal tunnel syndrome (2%). Adult patients who are older, heavier, or female are more prone to develop these complications.^[60] Most of these adverse reactions improve with dose reduction. Insulin resistance and type 2 diabetes^[61] can occur or worsen in patients with pre-existing diabetes. Retinopathy, benign intracranial hypertension, and gynecomastia are rare.^[62-64]

Although there might have been some concern with respect to the risk of cancer with the use of GH therapy, an increase in the recurrence rates of either intracranial or extracranial tumors has not been demonstrated in AGHD.^[65,66]

CONCLUSIONS

GHD (isolated or as part of multiple hormone deficiencies) is being increasingly recognized as a cause of premature mortality. Over the last decade or two, much of our understanding on various clinical presentations of GHD has improved. The documented benefits of replacement therapy have helped improve the quality of life of many patients lives with AGHD. Replacement is well tolerated. The long-term fears of tumor recurrence or re-growth have not been confirmed by most observational studies, and until proven otherwise, GH therapy should be routinely prescribed and titrated to reap clinical benefits.

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