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Review Article

Adult Growth Hormone Deficiency and Replacement Therapy: Current Approaches

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Abstract

Background: Adult Growth Hormone (GH) deficiency is a significant clinical condition affecting 2-3 per 10,000 individuals, characterized by metabolic, cardiovascular, and quality of life impairments.

Objective: To provide a comprehensive review of adult GH deficiency epidemiology, diagnosis, and replacement therapy approaches.

Methods: Review of current literature on adult GH deficiency, including epidemiology, clinical manifestations, diagnostic methods, and treatment protocols.

Results: Adult GH deficiency presents with central obesity, decreased muscle mass, cardiovascular risk factors, reduced bone density, and impaired quality of life. Pituitary adenomas (57%) and craniopharyngiomas are the leading causes. The insulin tolerance test remains the gold standard for diagnosis, with peak GH <3 µg/L indicating severe deficiency. Re-evaluation is critical for childhood GH deficiency patients, as 30% - 70% may normalize in adulthood. GH replacement therapy, initiated at 0.2 mg/day and titrated based on IGF-1 levels, significantly improves body composition, cardiovascular risk profile, and quality of life. Treatment is generally safe with manageable side effects, including arthralgia and fluid retention.

Conclusion: Adult GH deficiency requires individualized diagnosis and treatment approaches. GH replacement therapy is safe and effective when properly monitored, with no increased malignancy risk. Transition period management from pediatric to adult care is crucial for optimal outcomes.

Introduction

Adult Growth Hormone (GH) deficiency was previously considered a relatively insignificant clinical condition. However, studies beginning in the late 1980s demonstrated that adult GH deficiency has significant adverse effects on quality of life, cardiovascular health, bone metabolism, and body composition [1]. With the production of recombinant human growth hormone, treatment of adult GH deficiency became possible and has now become an accepted endocrinological treatment modality. Recent economic analyses have demonstrated that adults with confirmed Adult GH Deficiency (AGHD) have healthcare costs more than twice those of adults without GH deficiency, highlighting the clinical significance of this condition [1].

Epidemiology and etiology

Although the true prevalence of adult GH deficiency is not precisely known, recent large-scale studies estimate it to be between 0.2 (confirmed) and 37.0 (confirmed + at-risk) per 100,000 in the general population [2]. The wide range reflects challenges in diagnosis and underdiagnosis of the condition. Among 54,310 individuals at risk for AGHD and 268 with confirmed AGHD in recent US real-world data, only 3.1% and 9.7% received GH treatment, respectively, suggesting significant undertreatment [1].

The most common causes of GH deficiency include pituitary adenomas (57%) and craniopharyngiomas (2%). Other causes include cranial radiotherapy, head trauma, subarachnoid hemorrhage, Sheehan syndrome, hypophysitis, and pituitary

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apoplexy. Sheehan syndrome, characterized by postpartum pituitary necrosis, has been associated with elevated atherosclerotic cardiovascular disease risk, with approximately one-fourth of patients showing coronary artery plaques [3]. Normal GH response can be achieved in adulthood in 30% - 70% of patients with childhood GH deficiency; therefore, re-evaluation is necessary in these patients after completion of linear growth.

Clinical presentation and diagnosis

Adult GH deficiency is characterized by nonspecific symptoms, and multiple symptoms are usually seen together. Clinical findings vary according to age, time of disease onset, and severity of deficiency.

Physical and metabolic findings

Body composition changes: The most characteristic findings include central obesity, increased visceral adipose tissue, decreased muscle mass, and muscle weakness. Patients show increased total body fat percentage while lean body mass decreases. These changes particularly create a "metabolic syndrome"-like picture. Recent studies have shown that GH replacement therapy can lead to significant reductions in tissue fat percentage within 6 months of treatment initiation [4].

Cardiovascular risk factors: Increased total cholesterol and LDL-cholesterol levels, and decreased HDL-cholesterol levels are observed. There is an increased incidence of insulin resistance and glucose intolerance. Blood pressure tends to increase. Recent research has demonstrated that GH deficiency elevates high-sensitivity C-reactive protein (hs-CRP) levels, an inflammatory marker, which significantly decreases following GH replacement therapy [5].

Decreased exercise capacity: Significant decreases in maximal oxygen uptake, muscle strength, and endurance are observed. Patients have difficulty maintaining daily activities.

Bone metabolism disorders: Decreased bone mineral density and increased fracture risk are observed. Bone formation and resorption markers are found to be low. This condition is more pronounced, especially in childhood-onset GH deficiency.

Neurological and psychiatric findings

Cognitive function disorders: Attention deficits, concentration difficulties, memory problems, and slowing of processing speed may be observed. These findings may be more pronounced, especially in childhood-onset GH deficiency. In patients with traumatic brain injury, GH deficiency is often the cause of persistent post-concussive symptoms, with loss of libido, reliance on sleep aids, and feeling overweight being strong predictors of GH deficiency [6].

Psychiatric symptoms: Depressive mood, anxiety, irritability, a tendency toward social isolation, and general mood deterioration are common. These findings may be among the earliest and most prominent symptoms of the disease.

Quality of life effects

Impairment in social and occupational functions: Patients may experience decreased work performance, reduced participation in social activities, and problems in family relationships. Increased sick days and higher early retirement rates have been reported.

Sexual function disorders: Loss of libido and erectile dysfunction, especially in men; sexual disinterest in women may be observed. These findings significantly affect quality of life and have been identified as strong predictors of GH deficiency in clinical assessment tools [6].

Gastrointestinal manifestations

Recent recognition of gastrointestinal involvement in hypopituitarism has revealed that GH deficiency can lead to nausea, vomiting, constipation, malabsorption, intestinal pseudo-obstruction, and hepatic dysfunction. GH deficiency specifically impairs gut motility and mucosal integrity, contributing to these symptoms [7].

Diagnostic methods

Growth hormone stimulation tests are required for the diagnosis of adult GH deficiency. Recent consensus from the Growth Hormone Research Society indicates that the insulin tolerance test (ITT) remains the gold standard in adults, with consensus to recommend the macimorelin test [8]. For diagnosis, a peak GH response of <3 µg/L in ITT is accepted as the criterion for severe GH deficiency.

However, there are ongoing controversies about diagnostic criteria. Recent Delphi survey results show that consensus on GH deficiency diagnosis was lower in pediatric practice (59% agreement on statements) compared to adult practice (88% agreement), mainly with respect to choice and interpretation of GH stimulation tests [8]. IGF-1 levels can be used supportively for diagnosis, but they may be in the normal range in 30-40% of patients with adult-onset GH deficiency.

In β-thalassemic patients, who are at increased risk for GH deficiency due to iron overload, the marked variability in GH deficiency diagnoses highlights the need for multiple diagnostic tests to improve accuracy and avoid unnecessary interventions [9].

Status of patients with childhood GH deficiency in adulthood

Transition period and re-evaluation: Normal GH secretion may be observed in adulthood in 30-70% of patients diagnosed with GH deficiency in childhood; therefore, re-evaluation after completion of linear growth is of critical importance. This situation is more common, especially in patients with idiopathic isolated GH deficiency.

Re-testing indications: Re-testing must be performed in patients with isolated idiopathic GH deficiency without organic pituitary disease. However, re-testing is not necessary in the following situations:

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- Known genetic mutations (PROP1, POU1F1, etc.)
- More than 3 pituitary hormone deficiencies
- Severe organic pituitary disease (craniopharyngioma, severe pituitary aplasia)
- Hypothalamic-pituitary structural anomalies

Recent studies have shown that sex steroid priming before GH testing enhances spontaneous nocturnal GH secretion and reduces the frequency of divergent results between spontaneous and stimulated values [10]. This approach is particularly recommended when evaluating children in prepuberty or early puberty for suspected GH deficiency.

Test protocol: Re-evaluation is performed with an insulin tolerance test or alternative tests at least 1-3 months after discontinuation of GH treatment. IGF-1 levels should also be measured during this period.

Predictors of persistent GH deficiency

Factors predicting continuation of permanent GH deficiency from childhood to adulthood include:

- Severe short stature (height SDS <-3)
- Multiple pituitary hormone deficiencies
- Low IGF-1 levels
- Structural anomalies on pituitary MRI
- Organic causes (craniopharyngioma, genetic mutations)
- Very low response in childhood GH stimulation tests

Problems in the transition period

Adverse effects of GH treatment discontinuation: Discontinuation of GH treatment after completion of linear growth in patients with permanent GH deficiency leads to:

- Increase in BMI and development of central obesity
- Decrease in muscle mass, increase in fat mass
- Decrease in bone mineral density
- Deterioration in lipid profile (HDL-cholesterol decrease)
- Increase in cardiovascular risk factors
- Deterioration in quality of life

Challenges in transition process: Studies show significant problems in the transition between pediatric and adult endocrinology [10]:

- 40% - 50% of patients are transferred to adult services without re-evaluation
- Male patients particularly tend to drop out of follow-up
- Practice differences exist between centers

Growth hormone replacement therapy

Treatment indications: GH replacement therapy is indicated in adult patients with a confirmed diagnosis of severe GH deficiency [3,7,8]. When making treatment decisions, factors such as the patient's quality of life impairment, cardiovascular risk factors, and bone metabolism problems should be considered. In some countries (such as the UK), criteria for being below a certain threshold in quality of life scores are required to initiate treatment [2].

Treatment protocol and dose adjustment: GH replacement therapy is started at a low dose and gradually increased by monitoring IGF-1 levels [2,7,8]. The starting dose is usually 0.2 mg/day, with the target IGF-1 level being between the mean and upper limit of the normal range for age [2]. Women, especially those using oral estrogen, may require higher doses than men. Lower doses are preferred in elderly patients [2].

Side effects and safety

The most common side effects of GH replacement therapy are arthralgia, myalgia, edema, and carpal tunnel syndrome due to fluid retention [6,7]. These side effects are usually dose-dependent and resolve when the dose is reduced. Benign intracranial hypertension is a rare but serious side effect [6].

Regarding effects on carbohydrate metabolism, GH treatment may cause a temporary increase in insulin resistance, but it has been shown not to adversely affect glucose homeostasis in the long term [2,6].

Malignancy risk and safety

Large-scale surveillance studies on malignancy risk show that GH treatment does not increase the risk of de novo tumor development or tumor recurrence [1,6]. GH treatment in patients with a history of cancer is generally considered safe, but individual risk-benefit analysis is required.

Use in patients with cancer history: GH deficiency is common in patients who received childhood cancer treatment, and remission status should be evaluated before starting GH treatment in these patients. Meningioma risk may increase in patients who received head-neck radiotherapy, but this is thought to be related to radiotherapy rather than GH treatment.

Monitoring and treatment duration

Patients receiving GH replacement therapy should be monitored at 3-6 month intervals. Monitoring should evaluate IGF-1 levels, quality of life scores, body composition, cardiovascular risk factors, and bone metabolism [2]. Treatment is usually continued lifelong, but discontinuation may be considered in case of side effect development or change in benefit/risk ratio.

Conclusion

Adult GH deficiency is a clinical syndrome that leads to significant health problems. With appropriate application of diagnostic criteria and individualized treatment approach, GH

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replacement therapy is a safe and effective treatment option. Treatment started at low doses and titrated by monitoring IGF-1 levels significantly improves patients' quality of life and reduces cardiovascular risk factors.

Re-evaluation of patients with childhood GH deficiency during the transition period is of critical importance. Considering the adverse effects of treatment discontinuation in these patients, early recognition of those with permanent deficiency and continuation of treatment is necessary. Long-term follow-up studies support the safety of treatment and show no increase in malignancy risk.

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