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Adult Growth Hormone Deficiency: Current Concepts

Izumi FUKUDA,[1] Naomi HIZUKA,[1] Toko MURAOKA,[1] and Atsuhiro ICHIHARA[1]

[1]*Department of Medicine II, Tokyo Women's Medical University, Tokyo*

Abstract

The clinical syndrome of adult growth hormone deficiency (AGHD) was widely recognized in the 1980s. In this review, we first describe the clinical features and diagnosis of AGHD and then state the effects of growth hormone (GH) therapy for these patients. The main characteristics of AGHD are abnormal body composition, dyslipidemia, insulin resistance, and an impaired quality of life (QoL) due to decreased psychological well-being. For diagnosing AGHD, the international consensus guidelines have suggested that an insulin tolerance test (ITT) is the gold standard, but in Japan, the growth hormone releasing peptide-2 (GHRP-2) test is available and is recommended as a convenient and safe GH stimulating test. The cut-off for diagnosing severe AGHD is a peak GH concentration of 9 g/L during the GHRP-2 test. Since 2006, GH therapy has been approved for Japanese patients with severe AGHD. For adults, GH replacement therapy should be initiated at a low dose (3 g/kg body weight/day), followed by individualized dose titration while monitoring patients' clinical status and serum insulin-like growth factor-I (IGF-I) concentrations. A variety of favorable effects of GH replacement have been indicated; however, it has not yet been established fully whether there is a direct effect of GH treatment on reducing mortality.

Key words: dyslipidemia, growth hormone releasing peptide-2 test, insulin-like growth factor-I, non-alcoholic fatty liver disease

Introduction

Growth hormone (GH) is classically linked with linear growth during childhood. However, in 1962, Raben reported the improvement in the well-being of a 35-year-old woman with hypopituitarism who had been treated with pituitary-derived GH. This suggested that GH might continue to play an important role throughout life in various metabolic actions and influence one's psychological state.[1)] In the 1980s, recombinant human GH (rhGH) became widely available and its effects in adults were extensively studied. The first double-blind, randomized, placebo-controlled study assessing GH treatment in adult GH deficiency (AGHD) was performed in 1989, and various favorable effects of GH replacements were confirmed.[2,3)] Since 2006, GH therapy has been approved for Japanese patients with severe AGHD. In this review, we describe the clinical features, diagnosis, and effects of GH treatment in patients with AGHD.

Causes of AGHD

Table 1 shows the causes of AGHD.[4,5)] GH is usually the first anterior pituitary hormone that is adversely affected by organic lesions in the hypothalamus and/or pituitary. Therefore, the probability of identifying GH deficiency (GHD) is generally higher in patients with multiple pituitary hormone deficiencies and its resultant pathologies. The most common cause of GHD during adulthood is a non-functioning pituitary adenoma and its treatment.[4,5)]

Patients Who Should Be Evaluated for AGHD

An evaluation for AGHD is considered for patients who exhibit evidence of hypothalamic-pituitary disease, and for whom there is an intent to treat.[6)] Testing patients who have other pituitary hormone deficiencies, a history of cranial irradiation, a traumatic brain injury, or a subarachnoid hemorrhage is also recommended by the international guideline from the Growth Hormone Research Society.[6)] It is also recommended for those adults who have experienced childhood-onset GHD, regardless of whether they fulfill the criteria for severe GHD, that they be retested as adults unless they have a known mutation or have acquired irreversible structural pituitary lesions before long-term GH replacement was commenced.[7)]

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Table 1 Causes of adult growth hormone deficiency (AGHD)*

Congenital	Acquired
Genetic	Trauma (peri- or postnatal)
Transcription factor defects:	
PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2	Hypothalamic or pituitary tumors
	Pituitary adenoma
GHRH receptor gene defects	Craniopharyngioma
GH gene defects	Rathke's cleft cyst
	Glioma/astrocytoma
Associated with brain structural defects	Germinoma
Septo-optic dysplasia	Metastatic tumor
Empty sella syndrome	
Encephalocele	Infiltrative /granulomatous disease
Hydrocephalus	Sarcoidosis
Arachnoid cyst	Tuberculosis
	Langerhans cell histiocytosis
	Hypophysitis
	Others
	Surgical
	Cranial irradiation
	Idiopathic

*Table modified in part from Molitch et al.[5] GH: growth hormone, GHRH: GH releasing hormone, HESX-1: homeobox expressed in ES cells 1, LHX3/4: LIM homeobox gene 3/4, PIT-1: pituitary transcription factor 1, PITX-2: paired-like homeodomain 2, PROP-1: prophet of pit-1.

How to Diagnose AGHD

I. Clinical signs and symptoms of AGHD

In adults suspected of having GHD, there is no specific clinical sign that offers the same measure of diagnostic "certainty" as the growth retardation that occurs in children. Patients with AGHD can exhibit a variety of clinical signs including increased fat mass, particularly fat distributed in the abdominal region, decreased lean body mass, osteopenia, dyslipidemia, insulin resistance, and/or glucose intolerance. AGHD may also be associated with altered cardiac structure and function, and reduced physical performance. As a result of such symptoms, patients can subsequently experience and report a reduced quality of life (QoL).

Several epidemiological studies have indicated an associated increased mortality risk in patients with hypopituitarism, particularly when all pituitary hormones except GH were replaced; however, the increase in mortality may in part be attributed to the inappropriate replacement of other pituitary hormones, or a history of radiotherapy localized to the hypothalamic-pituitary region. The standardized mortality rate for individuals with AGHD has been shown to be about 1.8 compared to the general population,[8,9] and the mortality linked to cardiovascular complications appears to be increased.[8]

II. GH stimulation test

International consensus guidelines have suggested that the insulin tolerance test (ITT) is the gold standard test for diagnosing AGHD.[6] The reliability of the ITT, as a provocative test with a cut-off diagnostic concentration of 5.1 g/L, was demonstrated by results indicating 96% sensitivity and 92% specificity when evaluated by the receiver operator characteristic (ROC) curve analysis.[10] According to the current guidelines, the cut-off for a biochemical diagnosis of AGHD during an ITT is a peak GH concentration that is equal to or less than 3 g/L.[6] However, the ITT must be performed under careful medical management in an experienced endocrine unit and is contraindicated for several clinical conditions including a history of seizures and/or ischemic heart disease. It should also be noted that false-positive results may occur in patients who are severely obese.

In Japan, Chihara et al. proposed the usefulness of the GH-releasing peptide-2 (GHRP-2) test for evaluating GH secretory status.[11] For diagnosing AGHD, a GH cut-off value of 15 g/L with a GHRP-2 test corresponded with a value of 3 g/L for the ITT, whereas severe AGHD was diagnosed using a cut-off value of 9 g/L for the peak GH level in GHRP-2 test. The GHRP-2 test is considered to be a convenient and safe diagnostic test for AGHD. Among other classical provocative tests, the arginine test and glucagon test have been considered as alternatives, although they have less discriminatory power than the ITT.[5] The clonidine test and Levodopa test, which are useful for children, are however regarded as poor tests for adults.

III. Serum IGF-I levels

A considerable overlap has been shown to exist between circulating insulin-like growth factor-I (IGF-I) concentrations in healthy subjects, matched for age and sex, and IGF-I concentrations in patients with AGHD, even in those patients classified as having severe AGHD which was confirmed by a GH stimulating test.[12] Therefore, normal IGF-I levels cannot be excluded from a diagnosis of AGHD, and GH stimulating test should be considered for patients who have an evidence or a strong clinical suspicion of hypothalamic-pituitary disease, even if circulating

IGF-I levels are within the normal range. On the contrary, the presence of low IGF-I levels in patients with hypopituitarism, which is associated with more than three pituitary hormone deficiencies, is highly indicative of the existence of GHD.

Treatment Aims for AGHD

The aim of GH replacement therapy is to treat the signs and symptoms of GHD by correcting the metabolic abnormalities and impaired QoL associated with AGHD.

GH Dosing Titration

Determining an appropriate GH replacement dose is a relatively more challenging task when treating adults with GHD as opposed to children with GHD because the efficacy of administered GH is overtly reflected in linear growth in children. The tolerance of adults for GH is lower than that of children, and the individual responsiveness to GH varies according to many factors such as age, age at onset of GHD, sex, and adiposity. In general, women require more GH per kilogram of body weight than men, younger patients require more GH than older patients, and adult patients who had childhood-onset require more GH than adult-onset GHD to obtain an equivalent clinical response.

In healthy subjects, similar IGF-I levels depend on a higher GH secretion in women. By a similar mechanism, the sex-related differences in GH dose requirements occur because estrogen modulates hepatic IGF-I generation in women more than it does in males. Taking these things into consideration, the GH dosing guidelines issued by the Growth Hormone Research Society recommend the following:[6]

- GH replacement therapy should start with a low dose, especially in older individuals (0.1 mg/day), administered as daily subcutaneous injections in the evening.
- GH dosages should be increased gradually and individualized, on the basis of clinical and biochemical responses, no more frequently than at monthly intervals.
- Incremental dose increases should be between 0.1 mg/day and 0.2 mg/day.
- Clinical status and serum IGF-I levels should be monitored.
- The GH maintenance dose should seldom exceed 1.0 mg/day.

It is recommended that GH replacement dose should not be based on body weight; individualized dose titrations should follow to optimize the potential for beneficial effects with a minimum of side effects.[13]

Serum IGF-I is the most useful biological marker for monitoring GH dose titration. To adjust a dose of GH, several authors recommend aiming for IGF-I concentrations in the upper half of the reference range,[14,15] but it is suggested to not exceed the upper limit of the normal range by more than two standard deviations (SDs).

In female patients receiving estrogen replacement therapy, a higher dose of GH is typically required when oral versus transdermal estrogen is administered.[16] Oral estrogen more prominently impairs the modulatory effect of GH on hepatic IGF-I production than does transdermal estrogen, primarily because a higher concentration of estrogen passes though the liver after oral administration.

Effects of GH Replacement

I. Body composition

GH and IGF-I play a key role in maintaining normal body composition in adults. Adult patients with untreated GHD have an abnormal body composition with an increase in their total and visceral fat mass, and a decrease in their lean body mass and total body water. Compared to age-matched subjects, the body fat mass of adult patients with GHD was shown to be about 7% higher and was associated with insulin resistance and an increased risk for cardiovascular complications.[17] According to more than 50 randomized and controlled trials that compared the effects of GH to a placebo treatment in adults with GHD, GH replacement was associated with a significant reduction in both body weight (2.3 kg) and body fat (2.6 kg), and an increase in lean body mass without significant changes in their body mass index.[17] A systematic review of the effects of long-term GH replacement (> 5 years) on body composition in patients with AGHD confirmed an associated consistent increase in lean body mass and a decrease in body fat mass; however, the effects on body mass index (BMI) were conflicting.[18]

II. Bone metabolism

Severe AGHD has been associated with low bone mineral density (BMD) and low bone mineral content (BMC), likely attributable to low bone turnover and delayed mineralization, which has been shown to improve following GH treatment.[19,20] The BMD of older adult patients with GHD seems to be less adversely affected. Toogood et al. reported that there was no difference in the BMD of patients with AGHD who were older than 60 years compared to age-matched subjects without AGHD.[21] The effects

of GH replacement on bone metabolism have been shown to vary depending on the duration of GH therapy. According to the results of four studies that analyzed the effects of long-term GH therapy on bone metabolism in more than 300 patients with AGHD, BMD declined after the initiation of GH as a result of increased bone resorption. However, these same studies all reported a subsequent increase in BMD within the first year of treatment; the increase reached a plateau phase that was maintained according to observations made after 5 years.[18]

III. Lipid metabolism, inflammatory markers, and atherosclerosis findings

Low-density lipoprotein-cholesterol (LDL-C) and triglyceride levels increase in patients with AGHD. Similarly, serum markers of inflammation, such as interleukin 6 (IL-6) and C-reactive protein (CRP), become elevated in patients with AGHD.[13] Carotid intima-media thickness (IMT), which is a biomarker for the risk of myocardial infarction and stroke, also increased in patients with AGHD. GH replacement was associated with a significant improvement in LDL-C and high-density lipoprotein-cholesterol (HDL-C), but no change in triglyceride status was evident.[20] A study has investigated whether GH therapy can provide a benefit to patients with severe AGHD by lowering LDL-C. This study assessed whether any additional benefit could be derived when GH therapy was added to statin (HMG-CoA reductase inhibitors) therapy versus the benefit achieved by administering statins alone.[19,22] The study results revealed that GH administration achieved a significant additional improvement in LDL-C, suggesting that not only statins, but also statins in combination with GH therapy, can provide clinically meaningful benefits in the management of patients with AGHD and associated dyslipidemia. Evidence also exists to show that carotid IMT is rapidly improved with GH replacement; it decreased up to 18% after long-term therapy, and circulating IL-6 and CRP concentrations also decreased.[18] It is not clear whether the reduction in inflammation markers is due to a direct effect of GHs on the immune system, or if inflammation is indirectly mediated by an improvement in body composition.[13]

IV. Quality of life

Reduced QoL and well-being resulting from low energy levels, social isolation, and increased emotional stress are well-known psychological effects of AGHD.[19] In general, QoL seems to improve during long-term GH therapy. The positive effects on QoL have been observed within the first year of treatment and have been maintained thereafter.[18] Japanese patients with AGHD reported a decreased QoL, as evaluated by the Short Form (36) Health Survey (SF-36), but significant effects of 24 weeks of GH replacement on QoL were not observed.[23]

V. Fatty liver disease

Several clinical studies have suggested that non-alcoholic fatty liver disease (NAFLD), or its progressive condition referred to as non-alcoholic steatohepatitis (NASH), is frequently observed in patients with AGHD.[24] These co-morbidities have been improved by GH therapy, suggesting that the deficit of GH contributes to steatosis and fibrosis in the liver.[24] Recently, Nishizawa et al. reported that a GH-deficient rat model developed NASH, and not only the administration of GH, but also IGF-I prevented the development of liver disease in this rodent model. It was presumed that IGF-I plays an essential role in the liver by improving mitochondrial function and reducing oxidative stress.[25]

The benefits of GH therapy in patients with AGHD are listed in Table 2.[26] The cost of GH treatment is

Table 2 Clinical features and benefits of GH replacement therapy in patients with AGHD*

Clinical features of AGHD		Benefits of GH replacement
Abnormal body composition		
Increased fat mass	→	Decreased fat mass
Decreased lean body mass	→	Increased lean body mass
Decreased BMD	→	Increased BMD following an initial < 6 month decrease
Atherosclerosis risk factors		
Dyslipidemia	→	Decreased LDL-C
	→	Increased HDL-C
	→	Unchanged triglycerides
Increased inflammatory markers		
IL-6, CRP	→	Decreased IL-6 and CRP
Carotid IMT	→	Decreased carotid IMT
Development of NAFLD/NASH	→	Improved fatty liver disease
Decreased QoL	→	General improvement in QoL
Increased mortality	→	Unknown effect on mortality

*Table modified in part from Hoffman.[26] AGHD: adult growth hormone deficiency, BMD: bone mineral density, CRP: C-reactive protein, GH: growth hormone, HDL-C: high-density lipoprotein-cholesterol, IL-6: interleukin 6, IMT: intima-media thickness, LDL-C: low-density lipoprotein cholesterol, NAFLD: non-alcoholic fatty acid disease, NASH: non-alcoholic steatohepatitis, QoL: quality of life.

relatively high. Therefore, long-term survey of efficacy and safety of GH replacement therapy including whether GH improves cardiovascular complications throughout the life and reduce mortality in adults with GH deficiency might be required in order to clarify more about cost-effectiveness of GH therapy.

Side Effects of GH

The most common side-effects of GH therapy are edema and arthralgia caused by GH-associated fluid retention. At present, there is insufficient evidence to suggest that GH replacement increases the risk of developing diabetes mellitus, at least in patients in the normal weight BMI category of 18.5–24.9 kg/m^2; however, a reasonable strategy may be to start patients with AGHD on a low dose of GH if they present with a higher than normal BMI.[27] Based on the observation of more than a thousand patients with AGHD, the likelihood of an increased risk for the recurrence and re-growth of hypothalamus-pituitary tumors was not determined in adults.[28] In this report, Abs et al. also reported that there was no recurrence in 127 GH-treated adult patients with craniopharyngioma.[28] Recently, several studies were performed whether GH replacement therapy affects on a tumor recurrence or increase in size of pituitary or central nervous system tumors. In 2005, Chung et al. reported a case of a 54-year-old patient with a germ cell tumor who required a suspension of GH therapy because of tumor recurrence.[29] Hatrick et al. reported that there was no statistically significant differences in pituitary adenoma re-growth rate between GH treated group and controls.[30] Olsson et al. investigated tumor progression in craniopharyngioma. The 10-year tumor progression free survival rate (PFSR) was 85% for the GH treatment group and 65% for the control group and they concluded that GH replacement did not affect the PFSR in patients with craniopharyngioma.[31] Regarding an effect of long-term GH therapy on tumor recurrence, two studies[32,33] reported 11 cases of tumor recurrence among 23 prospective studies with GH therapy duration ranging from 5 years to 15 years that were reviewed by Appelman-Dijkstra et al.[18] One of those study concluded that the recurrence rate appeared to be no higher compared to control group,[32] though, there was a lack of control data in the other study.[33]

Because of its growth promoting effect, the influence of GH administration on cancer risk has been extensively studied. To date, children and adults treated with GH do not appear to have an increased cancer risk compared to general population.[34] Of course, long-term surveillance of a large population is required continuously and it is important to maintain serum IGF-I levels during GH therapy within age-matched normal range for avoiding GH excess.

Conclusion

In this review, the clinical features and the diagnosis of AGHD are discussed, as well as the GH treatment guidelines that included a reference to their efficacy and safety. A severe GH deficit causes various metabolic abnormalities in addition to an impaired QoL due to decreased psychological well-being. GH dosing regimens should be individualized because of the distinct individual differences in terms of patients' responsiveness to GH. GH therapy has proven to be beneficial for many patients with AGHD. The long-term clinical efficacy of GH replacement, including such factors as its ability to reduce cardiovascular events and its potential effects on the mortality of patients with AGHD are still largely unknown, and therefore the long-term clinical efficacy of GH replacement remain issues deserving future attention.

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Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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Address reprint requests to: Izumi Fukuda, MD, PhD, Department of Medicine II, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
e-mail: izumif@endm.twmu.ac.jp