

Growth hormone replacement for adult-onset growth hormone deficiency – What have we learned?

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With the introduction of recombinant growth hormone (rhGH) in 1985, the possibility of replacement therapy for a number of clinical scenarios became possible. Adults with GH deficiency (GHD) exhibit a number of well-recognized clinical and biochemical abnormalities that are currently considered part of a GH deficiency syndrome (Table 1). The diagnosis of GHD and the indications for hormone replacement in this condition are not, however, straightforward and a complete understanding of the potential benefits, as well as the adverse effects of rhGH replacement therapy, is lacking. The purpose of this review is to highlight the issues surrounding the diagnosis of adult GH deficiency and the effects, dosing, and safety of replacement therapy. The discussion will focus on patients with GHD due to pituitary/hypothalamic disease that started in adulthood and not on patients with GHD secondary to child-onset GHD (CO GHD), or cases where GH levels have declined due to normal physiological changes (eg, aging or the so-called "somatopause"), or as part of another disease process.

Who should be screened?

Severe GHD should be considered in individuals who present with features of the GHD syndrome and a history of pituitary/hypothalamic disease. In these cases, the likelihood of GHD increases with the number of pituitary hormone deficits, ranging from 45% if no other deficiency is present to nearly 100% if >3 hormones are being replaced.¹

Making the diagnosis

Markers of GH action

Measurement of insulin-like growth factor-1 (IGF-1) has received the most attention as an alternative means of diagnosing GHD, since it reflects the degree of GH activity and has a long biological half-life. However, in a recent comparison with 6 other diagnostic modalities, Biller et al demonstrated that IGF-1 had the least ability to distinguish between normal patients and those with GHD, given a 44% overlap in values.² This result has been consistent in many other similar studies.³⁻¹¹ Values below a cut-off point of 77.2 µg/L provided 95% specificity in this study, but the authors cautioned that single values are not reliable in confirming a diagnosis due to problems with interassay reliability and the fact that many other conditions can influence IGF-1 levels (eg, malnutrition, hepatic dysfunction, poorly controlled diabetes mellitus, hypothyroidism).¹ As well, alternative markers of GH action, such as IGF binding protein-3 (IGFBP-3), have not been found to be helpful in distinguishing normal versus GHD individuals.⁹

Dynamic tests

The use of any dynamic test for diagnosing GHD is not straight forward, since interassay variability in GH levels can be high and reference ranges must reflect changes in GH levels that are associated with age, obesity, estrogen use, and gender. Current consensus guidelines suggest that the gold standard for adult-onset GHD (AO GHD) is a GH concentration that is <3 to 5 µg/L during an insulin tolerance test (ITT).^{1,12} Over the past several years, numerous efforts have been made to establish alternative dynamic tests (Table 2) to replace the ITT because it is both unpleasant and contraindicated in a substantial number of patients. The majority of these studies have only compared 1 or 2 techniques in a small



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Table 1: Syndrome of GH deficiency

| |
|---|
| Clinical |
| <ul style="list-style-type: none"> • Increased waist/hip ratio • Increased visceral fat mass • Decreased lean body mass • Reduced psychological well-being • Reduced muscle strength and exercise performance • Fatigue • Dry skin |
| Biochemical |
| <ul style="list-style-type: none"> • Altered serum lipids (primarily elevated TC, LDL) |
| Other |
| <ul style="list-style-type: none"> • Reduced BMD • Possible increased fracture risk • Possible increased cardiovascular mortality risk |

TC = Total cholesterol, LDL = Low density lipoprotein, BMD = bone mineral density

number of patients. In contrast, the previously mentioned study by Biller et al was a multicentre comparison aimed at selecting cut-off values to allow 95% sensitivity and specificity in distinguishing GHD patients from normal individuals, after controlling for known modifiers of GH levels (Table 3).² From this analysis, with a cut-off of 5 µg/L, the ITT had a specificity of 92% and a sensitivity of 95%. An improvement in specificity to 95% could be obtained with the ITT if a cut-off of 3.3 µg/L was used, at the expense of sensitivity (89%). This trial also confirmed the finding of Aimaretti et al that the arginine (ARG) plus GH releasing-hormone (GHRH) test was equivalent to the ITT when using a cut-off value of 4.1 µg/L.¹³

Recommendations

Currently, in adult patients, measurement of IGF-1 cannot be advocated as a means of diagnosing or excluding GHD, given its poor sensitivity and specificity. However, in patients with a clinical suspicion of GHD, a value of < 77 µg/L may identify individuals who require dynamic testing to confirm the diagnosis.

The diagnosis of GHD is best supported with an ITT when the patient demonstrates an adequate hypoglycemic response (glucose < 2.2 mmol/L), but has a GH level that is < 3.3 µg/L. The use of an ARG-GHRH test is equivalent to an ITT and can be used as an alternative in those in whom an ITT is contraindicated.

Effects of replacement

Body composition

Patients with AO GHD have decreased lean body mass and increased visceral fat mass, resulting in an increased waist-hip circumference.¹⁴⁻¹⁶ These changes can be reversed by rhGH replacement, with an approximate gain in lean body mass that is equal to that lost in visceral fat (2-5 kg). This results in a decreased waist/hip ratio, but no net weight change.¹⁷⁻²¹ This effect is not universal since those with a high initial body mass index (BMI),

Table 2: Dynamic tests for diagnosing GHD

- | | |
|--------------------------|-------------|
| • Insulin tolerance test | • Arginine |
| • Arginine and GHRH | • Glucagon |
| • L-DOPA | • Clonidine |
| • Arginine and L-DOPA | |

GHRH = Growth hormone releasing hormone

the elderly, and women, demonstrate less gain in lean body mass and reduction in body fat.^{22,23}

Cardiovascular system

Recent reports have linked GHD with an increased risk of cardiovascular²⁴ and cerebrovascular²⁵ mortality. These data stem from epidemiological studies reporting a relative risk of 1.5 - 2 for cardiac-related death in hypopituitary patients who had adequate replacement therapy except for GH.²⁶ However, this association has been the subject of debate^{27,28} since it has been suggested that inaccurate thyroid hormone replacement and/or excessive cortisol dosing may be the underlying predisposing factor. It is noteworthy, however, that GHD patients exhibit characteristics that are similar to those associated with the insulin resistance syndrome, which has a clear link to cardiovascular disease.²⁹

The following discussion highlights the main areas of controversy surrounding the possible mechanisms leading to increased cardiovascular risk. GHD patients have been reported to exhibit several important cardiovascular abnormalities including:

- increased waist circumference^{14,15}
- abnormal lipid profiles¹⁶
- increased inflammatory markers³⁰
- elevated blood pressure
- insulin resistance³¹
- premature carotid artery intimal thickening³²
- cardiac remodelling.³³

Unfortunately, there is no evidence in the literature that all of these parameters improve with treatment, nor is there evidence that rhGH prevents cardiac events. For example, although replacement studies ranging from 6 months to 10 years in duration demonstrate persistent improvements in lean body mass, a reduction in fat body mass, and a decrease in waist circumference, improve-

Table 3: GH and IGF-1 cut-off values following dynamic testing to result in a 95% specificity*

| | Cut-off point | PPV(%) | Sensitivity (%) |
|------------|---------------|--------|-----------------|
| ITT | 3.3 µg/L | 96 | 89 |
| ARG-GHRH | 1.5 µg/L | 96 | 68 |
| ARG-L-DOPA | 0.25 µg/L | 96 | 75 |
| ARG | 0.21 µg/L | 97 | 74 |
| IGF-1 | 77.2 µg/L | 94 | 40 |

* Subjects between ages 24-70 yrs; ITT = Insulin tolerance test
ARG = Arginine; GHRH = Growth hormone releasing hormone
IGF=1 = insulin-like growth factor; PPV = Positive predictive value

ment in blood pressure or cardiac systolic/diastolic function has not been consistently documented. It is estimated that this moderate change in central adiposity could lead to a 3% to 4% reduction in cardiovascular events,³⁴ but at present, this remains to be proven.

Although the above findings have been well-replicated, data on glucose homeostasis and lipid profiles in AO GHD are more mixed. There are concerns that both GHD and replacement therapy lead to increased insulin resistance, impaired fasting glucose levels, and new-onset diabetes. In response to these concerns, several long trials of rhGH replacement therapy (3 to 10 years) have not demonstrated an increased incidence of diabetes with rhGH treatment.³⁴⁻³⁶ Instead, these trials have demonstrated that fasting insulin levels remain elevated in non-treated GHD patients³⁴ implying that insulin resistance improves with rhGH.

Several studies have revealed that GHD patients have a mild increase in total cholesterol (TC), low density lipoprotein (LDL), and triglycerides, along with decreased high density lipoprotein (HDL).^{37,38} Replacement over short periods of time (ie, 6 months) appears to improve TC and LDL levels, but these effects are not maintained in patients followed for 36 months to 10 years.³⁴⁻³⁶

Despite its variable effects on traditional cardiac risk factors, it remains clear that GHD is associated with endothelial dysfunction and this alone may contribute to poor cardiovascular health. Specifically, GHD patients have increased carotid intima-media thickness³⁹ and abnormal vascular reactivity.⁴⁰ The mechanism responsible for the endothelial dysfunction is not clear, but it does not appear to be caused by increased oxidative stress.³⁰ Replacement therapy appears to be highly beneficial in restoring vascular reactivity⁴⁰ and reducing non-traditional cardiac risk factors such as c-reactive peptide³⁰ and carotid artery intima-media thickness.³⁵ However, it has yet to be determined if these changes translate into reduced cardiovascular events in the AO GHD patient receiving therapy.

Bone metabolism

Investigations of bone metabolism in purely AO GHD populations are limited. The vast majority of studies of bone mineral density (BMD) in GHD adults have included individuals with child-onset (CO) disease, a distinction that is important because the observed osteopenia in adults with CO GHD is thought to reflect abnormalities in bone mass formation during childhood.⁴¹ In studies examining AO GHD, there is strong evidence that these individuals have reduced BMD that improves with replacement by 12 months.⁴² These changes are accompanied by increased markers of bone remodelling and histomorphometric evidence of cortical bone thickening.⁴² Of the 3 published papers on fracture rates in AO GHD, 2 were not powered to assess this question, although a three-fold increase of vertebral fractures was suggested.^{43,44} The third trial examined data from 264 patients selected from a pharmaco-epidemiological survey of GHD patients, and demonstrated a 2.7 fold

increase in fracture rates. Replacement therapy in this trial reduced fracture risk only in those >50 years and in men <30 years.⁴⁵ These positive findings have not yet been confirmed by randomized controlled trials.

Quality of life

Quality of life is a difficult parameter to assess due to its subjective nature and sensitivity to numerous influences. In general, the GHD patient does seem to experience a decreased sense of well-being,⁴² however, debate over this still exists.⁴⁶ Most of the criticism stems from the acknowledgement that the GHD patient's quality of life can be affected by other factors including other hormonal imbalances, radiation to the frontal lobes, and transcranial surgical approaches. Replacement trials have demonstrated improvements in many areas of well-being including reduced healthcare utilization.^{35,47} Although the mechanism behind this improvement is not clear, it may involve improved exercise performance⁴⁸ and improved cardiac function.²³

Evaluation of replacement therapy

Unlike the pediatric population where growth can be monitored, AO GHD patients have limited objective markers of efficacy. It is not recommended to use IGF-1 levels as a marker of successful therapy since they are not always decreased before starting therapy⁶ and they do not correlate with changes in body composition or metabolism.^{49,50} Notwithstanding, IGF-1 levels should be assessed from a safety point of view with the aim of keeping the levels in the appropriate age and gender reference range to prevent over-replacement. Effects on waist circumference, lipid levels, BMD, and well-being are also important to follow, since the decision to continue treatment should be determined by these parameters. The side effects most commonly reported with replacement therapy include edema, arthralgias, and headaches. All of these can be minimized by slow dose adjustments, particularly in the elderly, in women, and in those with higher BMIs, the groups that appear to be more prone to these effects.⁵¹⁻⁵³

Recommendations

Replacement schedules should be instituted in a slow and stepwise manner in order to minimize side effects. Dosing should be increased gradually until IGF-1 levels are within the appropriate reference range (approximately a 6-month process). At 1 year, it is reasonable to reassess the benefit of continuing replacement therapy since most trials demonstrate improvement by this time. Reassessment can be done by evaluating biochemical parameters (ie, lipids, glucose), body composition (ie, waist circumference, lean body mass, BMD) and well-being (ie, exercise endurance, psychological questionnaires).

Dosing

Dosing schedules should be adjusted to maximize benefits in a manner that minimizes side effects. As there are clear age and gender differences, the current consensus

guidelines correctly suggest a low initial therapy of rhGH (0.15-0.3 mg/d or 0.45-0.9 IU/day) that is not weight-adjusted.¹ Interestingly, two recent trials have demonstrated that alternative dosing may be appropriate. In the first, Amato *et al* demonstrated that thrice weekly injections can reduce side effects with slightly fewer benefits in lipids, body composition, and bone mineral density.⁵⁴ Kehely *et al* subsequently reported that a low daily dose (3 µg/kg per day) may be a particularly effective way of initiating therapy in those prone to adverse effects (eg, females and AO GHD patients) so that adverse effects are minimized, but some improvement in body mass composition is achieved.⁵⁵

Recommendations

Daily dosing (0.15-0.3 mg/d or 0.45-0.9 IU/day) of rhGH is the currently recommended schedule for replacement therapy. An initial low dose of either 0.15 mg/d or 3 µg/kg per day can be used to minimize adverse side effects, particularly in those at higher risk (eg, women, the elderly, and those with increased BMIs).

Safety

Safety concerns associated with rhGH treatment include:

- common side effects (myalgias, arthralgias, edema) thought to be due to increased fluid retention
- possible glucose intolerance
- thyroid/cortisol hormone homeostasis
- increased malignancy risk.

The first two concerns have already been discussed. Physicians should be aware that the common side effects due to fluid retention are mainly limited to the first 6 months of therapy, that they are dose-related, and that they usually resolve. If these side effects occur, therapeutic doses can be reduced and subsequently, gradually increased, unless the symptoms are severe or life-threatening (eg, in the case of decompensated congestive heart failure). With glucose intolerance, it should be noted that diabetes itself is not currently considered a direct contraindication for therapy, since there are poor data supporting a significant worsening of glucose homeostasis.¹ It is prudent to screen patients with diabetes for preproliferative/proliferative retinopathy, because this would be an indication for withholding or discontinuing rhGH therapy, according to current consensus guidelines.^{1,56}

Awareness that GH therapy alters other hormonal systems is necessary, because most patients are on thyroid and glucocorticoid replacement. GH increases extrathyroidal conversion of T4 to T3, as well as possibly reducing total cortisol levels by reducing cortisol binding protein.⁵⁶ Thus, these

systems should be monitored periodically and the treating physician should be aware that GH therapy can theoretically unmask adrenal insufficiency in patients with borderline adrenal function.

The concern about increased cancer risk stems from several sources. First, the association of colon neoplasia with GH excess is well-recognized in the acromegaly patient population. In the general population, it has also been demonstrated that prostate⁵⁷ and breast⁵⁸ cancer risk are proportional to IGF-1 levels, although a cause and effect link has never been proven and, as previously mentioned, several other important confounding factors (eg, nutritional status) can influence IGF-1 levels.¹ Further, given that many AO GHD patients have a history of pituitary adenomas or craniopharyngiomas, the administration of a growth factor is a concern.

Despite these issues, the cancer safety data for replacement therapy in adult populations is limited and difficult to interpret. In the 2001 evaluation of rhGH therapy, the Growth Hormone Research Society⁵⁶ considered this therapy safe, but recommended that pretreatment pituitary imaging was necessary, along with ongoing surveillance for new or recurrent malignancy. This recommendation is supported by the recent cohort study of 1848 patients registered with the United Kingdom's national registry, and followed over 41 years after treatment with human GH, that demonstrated an increased mortality from colorectal cancer and Hodgkin's disease.⁵⁹ As these were primarily CO GHD patients possibly treated with higher doses than would be used in adults, it is difficult to extrapolate this data to AO GHD patients treated with rhGH. Thus, until similar studies are repeated in this population, caution is still warranted.

Recommendations

The safety aspects of GH therapy are controversial and thus, the potential risk/benefit ratio should be evaluated for each patient. Close supervision of each patient on therapy is recommended, with monitoring for fluid retention, glucose intolerance, thyroid dosing, adrenal insufficiency, and new/recurrent malignancy. The presence of an active malignancy is considered an absolute contraindication to therapy.^{1,56}

Summary and recommendations

The decision to initiate rhGH replacement therapy in AO GHD patients should not be taken lightly given its possible adverse effects, cost, and route of administration. In the properly selected patient, however, rhGH can improve well-being, body composition, and bone density, with theoretical reductions in fracture risk and cardiovascular death. Therefore, this decision should be individualized and include the patient's input. Similarly, continuation of

therapy must involve frequent re-evaluations of patient response to therapy, using both objective and subjective parameters, in order to ensure that the benefits of therapy are maintained.

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Abstract of Interest

Growth hormone therapy for hypopituitary adults: time for re-appraisal.

BARKAN AL, CLEMMONS DR, MOLITCH ME, STEWART PM, YOUNG WF JR.

The advent of the production of large quantities of recombinant growth hormone (GH) has made it possible to have sufficient material to assess its efficacy in adult growth hormone deficiency (GHD). Although some studies have shown that patients who are severely deficient benefit from GH therapy, the spectrum of GHD is broad, and the degree of deficiency at times is very difficult to define. In some cases, benefit is not easily quantified, and some studies have claimed benefits that, although statistically significant, are either not clinically important or are so marginal as to be questionable in terms of cost, difficulty of administration and potential risks. The purpose here is to identify the current problems in the diagnosis of GHD, to discuss the rationale for GH therapy and to assess the potential effects of GHD as well as the benefits of GH therapy in GHD adults. We will include a commentary as to which effects appear more robust than others and which are likely to result in the greatest patient benefit. Finally, some attention will be paid to long-term safety issues that should be monitored to ensure that this medication is safe even for the patients with the greatest need.

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Upcoming Meetings

2-5 October 2002

Canadian Diabetes Association and the Canadian Society of Endocrinology Metabolism Professional Conference and Annual Meetings

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5-9 October, 2002

1st Joint Symposium: The Growth Hormone Research Society and The International Society for Insulin-like Growth Factor Research

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