Treatment of Growth Hormone Deficiency in Adults

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Abstract
Background: The Growth Hormone Research Society held a Consensus Workshop in Sydney, Australia, in March 2007 to review advances in the management of growth hormone (GH) deficiency in adults and to update consensus recommendations. Objective: This short review summarizes key background information presented at the workshop and the consensus recommendations that followed. Conclusions: The benefits of GH replacement in GH-deficient adults are evident throughout life. Clinical response to treatment should be assessed by monitoring biochemistry values, body composition and quality of life. There is no evidence that GH replacement increases the risk of tumour recurrence or de novo malignancy.

Introduction
Growth hormone (GH) deficiency in adults is characterised by perturbations in body composition, carbohydrate and lipid metabolism, bone mineral density, cardiovascular risk profile and quality of life (QOL). It probably contributes to the increase in cardiovascular morbidity and mortality consistently observed in adults with hypopituitarism [1, 2], though this has not yet been proved. The individual response to GH replacement remains highly variable, even after adjusting for the effects of age, gender, body composition and age of onset of GH deficiency. Thus, while the focus of the first decade of GH replacement therapy was on understanding the health benefits of treatment, the second decade of therapy has been characterised by attempts to understand predictors of individual response and to use this information to improve the safety and efficacy of GH replacement [3].

According to the Consensus Workshop, the goal of replacement therapy is to correct the metabolic, functional and psychological abnormalities associated with adult GH deficiency, and therefore all patients with documented, severe GH deficiency should be eligible for GH replacement therapy. Recommendations regarding dosing, hormone interactions, efficacy, safety and disease management for both the young adult after attainment of final height and the elderly were then updated and are discussed herein [4; see also the article by Casanueva et al. in these proceedings].

Therapy
Before initiating GH replacement therapy, treatment of other hormone deficiencies must be assessed as appropriate, the presence and severity of any clinical features

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associated with the deficiency must be identified and GH sensitivity must be assessed. Appropriate evaluation of the hypothalamic-pituitary-adrenal axis is mandatory. GH may attenuate the peripheral action of glucocorticoids by reducing the activity of 11β hydroxysteroid dehydrogenase type 1 [5]. As this enzyme preferably converts inactive cortisone to active cortisol, GH therapy may cause overt adrenal insufficiency in an individual with incipient insufficiency. Moreover, administration of GH probably enhances the peripheral conversion of T₄ to T₃ and may influence the effect of thyroxine replacement therapy [6]. Finally, there are well-known interactions between sex steroids and GH. Oral estrogen administration markedly reduces GH responsiveness [7], and testosterone may potentiate the insulin-like growth factor I (IGF-I) response and the antinatriuretic action of GH [8]. Thus, careful evaluation of other pituitary functions and institution of adequate replacement therapy as needed are mandatory before initiating GH replacement therapy.

**GH Dose Titration**

The observation that males are more sensitive to GH than females is consistent with known GH secretion rates. Johannsson et al. reported a more marked incremental increase in serum IGF-I and a larger gain in total body water in men compared with women receiving the same dose of GH per kilogram of body weight [9]. Burman et al. studied the GH response in 36 GH-deficient adults and reported that males had a higher serum IGF-I level at baseline and exhibited a greater increase in GH response than females given an equivalent dose [10]. In addition, GH dosing that is suboptimal in one patient may lead to overdose in another, and normalisation of serum IGF-I can induce side effects in some [11]. Thus, each patient’s GH dosing regimen should be titrated so that reduction in clinical features of GH deficiency is balanced against evidence of overtreatment as determined by serum IGF-I measurements and the occurrence of side effects. Johannsson et al. compared an individualised GH replacement regimen, in which the GH dose was titrated against serum IGF-I, body composition and clinical response, with a conventional weight-based high-dose regimen [12]. Both groups had similar responses to GH in terms of body composition, glucose homeostasis, lipoprotein (a) and blood pressure, but 30% of subjects receiving individualised doses reported adverse events compared with 70% of subjects in the weight-based, high-dose group.

Subsequently, Drake et al. titrated the GH replacement dose against serum IGF-I concentration with the goal of attaining levels in the upper half of the age-related reference range. Results were compared with retrospective data from subjects treated using a weight-based regimen [13]. The median maintenance doses used were 0.27 mg/day in males and 0.4 mg/day in females, which were significantly lower than the maintenance doses (0.5 mg/day) used in the weight-based regimen. The degree of improvement in quality of life did not differ between regimens. These studies provide important preliminary evidence that an initial low dose of GH followed by individualised dose titration leads to similar beneficial effects, fewer side effects and a lower stable GH dose than a weight-based regimen.

Therefore, the Consensus Workshop agreed to the following [4]:

- The objectives of treatment are to maximise benefit and minimise side effects.
- GH secretion is greater in younger than older individuals and in women than men. Based on extensive clinical experience, the recommended starting dose of GH should be 0.2 and 0.3 mg/day in young men and women, respectively, and 0.1 mg/day in older individuals.
- Dose determination based on body weight is not recommended due to large interindividual variation in absorption and GH sensitivity and the lack of evidence that heavier adults require a larger replacement dose.
- Dose escalation should be gradual, individualised and guided by clinical and biochemical response. This means that the aim of treatment should be to achieve a normal serum IGF-I level. Most published trials showing beneficial effects of GH have achieved a mean serum IGF-I level of +1 SDS, but for the individual patient, determination of the level of IGF-I SDS to be obtained should be guided by other biochemical response markers and the clinical response.

**Goals of GH Treatment**

**For Young Adults during the Transition Period**

The goal of GH therapy is not limited to maximising final height. After completion of linear growth, withdrawal of GH in adolescents who remain severely GH deficient results in loss of lean body mass (LBM) and increases in total body fat and abdominal fat mass [14–16]. Adults with childhood-onset GH deficiency who are taken off GH replacement for a long period of time have more severe metabolic disease consequences than do patients with adult-onset GH deficiency [17]. Ironically,
adults with childhood-onset GH deficiency have a near-normal self-perception of well-being and QOL both before and after discontinuation of GH therapy at final height [18, 19].

Cross-sectional studies indicate that peak muscle strength in normal adults occurs between 20 and 30 years of age [20, 21]. Indirect evidence suggests that GH may be of importance in developing muscle strength because young adults with GH deficiency have reduced muscle mass and strength [22]. Moreover, there is an association between the increases in LBM and bone mass in children [23]. Discontinuation of GH replacement therapy after attaining final height may arrest further maturation of muscle mass and strength [24].

Prospective studies have assessed changes over time in adolescents with severe GH deficiency that persists into adulthood for those continuing, as well as those discontinuing, GH replacement therapy. Danish investigators studied 19 adolescents with childhood-onset GH deficiencies who were treated with either GH or placebo for 1 year after reaching final height. Results showed an increase in percent body fat and insulin sensitivity after 1 year in those who stopped GH therapy, but no changes in those who continued GH treatment [25, 26]. In another study, 24 patients received a paediatric dose of GH during a lead-in period, then 12 patients remained on GH for 12 months and 12 patients stopped treatment [27]. LBM increased by 6% in patients who continued treatment but was unchanged in those who discontinued treatment. Drake et al. [28] reported a greater percentage of bone mineral density accrual with GH treatment in GH-deficient adolescents during transition. A large prospective multinational study investigated the role of GH replacement at two different doses in 147 young adults who had discontinued GH treatment after attaining final height [29]. Treated patients demonstrated a significantly larger increase in total and lumbar spine bone mineral content compared with untreated patients. There was no dose dependency in treatment response. However, Mauras et al. could not reproduce these results in 58 GH-deficient adolescents at the completion of linear growth who were randomised to either daily GH or placebo for 2 years [30]. At final height, the adolescents on GH treatment had normal BMD, body composition, cardiac function, muscle strength, carbohydrate and lipid metabolism and QOL; this finding was the same regardless of whether they were randomised to GH or placebo during the 2-year period.

Based on these findings, the Consensus Workshop agreed to the following recommendations regarding the transition period [4]:

- The goal of GH treatment after cessation of linear growth is to achieve full somatic development, including accrual of maximal bone and muscle mass.
- GH treatment should be continued in all young adults with persistent GH deficiency after attaining final height.
- GH-deficient adolescents who decline continued therapy should be monitored closely. Evidence of body composition abnormalities is a strong indicator of the need to restart GH therapy, and such a finding should prompt discussion with the patient regarding the advantages of treatment.
- During the transition period, the paediatric endocrinologist should arrange for the patient’s transition to an adult endocrinologist to ensure continuity of care.

**Elderly Persons with GH Deficiency**

Normal aging is associated with clinical features similar to those seen in untreated GH-deficient patients, though the magnitude of the changes may differ. Toogood et al. reported that GH response to arginine, GH area-under-the-curve during 24-hour GH profiling and serum IGF-I concentration are lower in elderly hypopituitary patients than in elderly healthy controls [31]. Furthermore, untreated elderly GH-deficient adults have an abnormal increase in body fat and pathological fat distribution compared with normal elderly subjects [32]. The finding of increased relative amounts of body fat in elderly GH-deficient adults has been confirmed in other studies [33, 34]. There are no major differences between GH-deficient and normal elderly subjects in lean mass and bone mass [35, 36], but muscle strength is reduced in elderly GH-deficient adults.

Short-term GH replacement in elderly patients increases LBM and decreases fat mass [32, 34]. One study found that GH replacement in elderly GH-deficient patients induced a transient increase in physical capacity [37]. GH therapy also improved QOL similarly in elderly GH-deficient patients and younger counterparts [38].

A study of the effects of 2 years of GH replacement therapy had elderly GH-deficient adults (>65 years of age) receive a lower dose than younger patients who were comparable in terms of body mass index (BMI) and gender [33]; results agreed with those of an earlier study [39]. After statistical correction for the lower dose in the elderly patients, responses to 2-year GH replacement were similar for nearly all variables studied. The exceptions were that the waist circumference, waist:hip ratio and serum low-density lipoprotein cholesterol responses were
more clinically favourable among the elderly than the younger patients [33].

The Consensus Workshop agreed to the following recommendations regarding elderly GH-deficient patients [4]:

- The age-related decline in the GH–IGF-I status does not warrant GH supplementation, but patients with proven GH deficiency should be treated.
- Elderly GH-deficient patients require lower GH doses because of the physiological decrease in GH secretion.
- The elderly are more sensitive to GH and prone to side effects; thus, GH doses should be adjusted carefully in them.

Safety

**Diabetes Mellitus (DM)**

To date there is no evidence that GH increases the risk of DM in adults [40], but data suggest that it may do so in children. A study using data from the Pfizer International Growth Database (KIGS) reported that GH treatment in children induced a very modest increase in the incidence of type 2 DM [41]. In addition, an analysis performed on data from 5,120 patients (2,706 men) included in Pfizer International Metabolic Database (KIMS) found that 26 men and 17 women developed de novo DM during follow-up [40] and 16 patients developed DM during the first year of GH replacement therapy. Notably, the mean age and BMI of patients who developed DM was 44.0 years and 34.0 kg/m² for women and 49.2 years and 32.8 kg/m² for men. Results of statistical calculations suggested that the incidence of type 2 DM in GH-treated hypopituitary patients with normal BMI is not increased compared with that in the background population. Furthermore, a high BMI may pose the same risk for development of type 2 DM in GH-deficient adults as it does in any other population.

Based on these findings, the Consensus Workshop agreed to the following recommendations regarding glucose metabolism and GH replacement therapy:

- GH replacement therapy is not associated with an increased incidence of either type 1 or type 2 DM. However, it does increase insulin resistance and may lead to decreased glucose tolerance.
- Individuals predisposed to type 2 DM, such as those with a positive family history, who are obese or who are older, require careful monitoring.
- GH-deficient patients diagnosed with type 2 DM should be managed in the same manner as all other patients with the disease, and GH replacement therapy should be continued.

**Tumour Regrowth/Recurrence**

Progression-free survival rates for patients with pituitary tumour have been reported to range from 12 to 69% after surgery, and from 72 to 92% following surgery and radiotherapy [42]. These results are based on data collected before GH was added to the replacement therapy regimen for hypopituitarism. While available data on tumour recurrence and regrowth during GH replacement therapy are limited, they are still reassuring.

In a prospective study of 100 patients with pituitary and peripituitary tumours (91% received external radiotherapy) who were treated with GH replacement therapy, only one case of slight intracellular enlargement was reported after 1–4 years of follow-up [43]. A retrospective study of patients with craniopharyngioma compared 32 patients on GH replacement for a mean period of 6.3 years with 53 untreated patients with similar tumour and treatment characteristics after a similar follow-up. During the observation period, 4 GH-treated patients and 22 untreated patients developed tumour recurrence [44]. A recent retrospective case-controlled study compared the effects of GH treatment in patients with hormonally inactive pituitary adenomas undergoing tumour surgery. Of the 55 matched pairs followed for at least 5 years, 16 tumour progressions were noted in the treatment group and 12 in the control group [45]. Statistical analysis revealed no significant increase in either the rate of recurrence (p = 0.317) or progression (p = 0.617) within the follow-up period when GH was adequately replaced.

In addition, 60 subjects who had survived childhood brain tumours and were receiving adult GH replacement therapy were studied prospectively. Sixteen patients had residual tumours, and three had secondary neoplasia (meningiomas) demonstrated on baseline scans. Of the 16 residual tumours, only one incurable ependymoma and one residual menigioma progressed in size over a mean period of 7.7 years were reported [46]. Follow-up scans also revealed continued growth of the three meningiomas detected at baseline, and three additional cases were detected during GH replacement therapy. All secondary neoplasia occurred 17–37 years after radiotherapy. Results of these studies do not indicate that GH replacement increases tumour recurrence or tumour regrowth. However, these studies were small and the follow-up periods were limited. Therefore, vigilance and
long-term surveillance are indicated for patients previously treated for tumours, particularly those at increased risk of secondary tumour, as is the case for survivors of childhood brain tumours.

**Malignancy Risk**

The mitogenic and growth-promoting effects of GH and IGF-I and their impact on neoplasia provide a theoretical basis for concern that GH treatment could increase cancer risk and promote tumour growth. Thus, subjects with hypopituitarism secondary to genetic or tumour-related causes might have an inherently higher risk of neoplasia compared with normal subjects. Furthermore, some treatment modalities including radiotherapy also may increase the risk of secondary neoplasia. Two retrospective studies found increased rates of neoplasia and mortality from neoplasia in patients with pituitary adenomas, suggesting that increased risks are either inherent in GH treatment or due to increased surveillance of this patient population [47, 48]. Another study assessed the risk of secondary brain tumour in 426 patients with pituitary adenomas who received radiotherapy between 1962 and 1994 [49]. Patients were followed for 5,749 patient-years, and the median follow-up was 12 years (range, 0–38.4 years). Most tumours were treated with a radiation dose of 40–50 Gy in 20–30 fractions. The cumulative risk of secondary brain tumour was 2.0% after 10 years and 8.5% after 30 years. Moreover, the relative risk of a secondary brain tumour was increased in a biphasic manner: 24.2 (95% CI, 4.8–43.5) after 5–9 years and 28.6 (95% CI, 0.6–57) after 20–29 years of follow-up. Importantly, all 11 secondary tumours occurred within the radiation field. Therefore, estimations of the additional risks posed by GH replacement therapy must be derived using adequate comparative patient cohorts.

Of greater concern is the report of a small but statistically significant increase in the number of patients who survived childhood cancer but subsequently developed secondary neoplasms [50]. Survivors of childhood cancer treated with GH for a median treatment duration of 6.2 years had a 2.15-fold greater risk of developing a secondary neoplasm – mostly meningiomas – than non-GH-treated survivors. The investigators concluded that the increased risk associated with GH use appeared to decrease over time because a previous report from the same cohort demonstrated a relative risk of secondary neoplasia of 3.12 after a median treatment duration of 6.2 years [51]. However, these data should be interpreted with caution given the small number of events. Further studies of the long-term safety of GH replacement therapy and continuing surveillance of this particular group of childhood cancer survivors are warranted.

Based on these findings, the Consensus Workshop agreed to the following recommendations regarding malignancy risk and GH replacement therapy:

- There is no evidence that hypothalamic or pituitary tumour recurrence is influenced by GH replacement therapy.
- There is no evidence that GH replacement in adults increases the risk of de novo malignancy or recurrence.
- Pituitary imaging should be performed before GH replacement therapy is initiated.
- For survivors of childhood cancer, GH treatment slightly increases the relative risk of developing a second neoplasia. However, there are no comparable data in adults.
- GH therapy should be stopped in all patients with active malignancy until the underlying condition is controlled.

**Summary and Conclusions**

GH replacement therapy is well tolerated in adults with a diagnosis of severe GH deficiency when doses are titrated and serum IGF-I levels and clinical efficacy of treatment are carefully monitored. Before initiating GH replacement therapy, clinical features of GH deficiency should be assessed, the optimal route and dose of other hormone replacement therapy should be ensured and patient sensitivity to GH should be estimated. This evaluation should guide the decision of when to start GH therapy, when and how much to titrate and what clinical variables are most useful for monitoring efficacy. Although all data support the safety and efficacy of GH replacement in adults, patients receiving long-term treatment should be monitored for safety.

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