Growth Hormone (GH) Treatment in GH-Deficient Adults; Therapeutic and Diagnostic Aspects

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Abstract. Adults with GH-deficiency have increased mortality due to cardiovascular disease and share several clinical signs, such as reduced muscle strength, reduced exercise capacity, reduced sweating ability and thermoregulation, subnormal kidney function, reduced myocardial function, reduced energy expenditure, abnormal thyroid hormone metabolism, impaired psychosocial well-being, decreasing lean body mass and decreased bone mineral content. All studies have unanimously shown that GH replacement therapy in GH-deficient adults have improved all the above reported clinical symptoms.

We conclude that GH-deficiency in adults is associated with a number of subnormal features. GH treatment improves (normalizes) these symptoms and we therefore believe that GH replacement therapy of a GH-deficient individual should be continued after cessation of linear growth. However, treatment of such patients should be carefully monitored since data from follow-up studies are still lacking.

Key words: adult GH deficiency syndrome, GH treatment, diagnosis, bone mineral content, exercise performance, sweating, thermoregulation, lean body mass

Introduction

The potential of growth hormone (GH) treatment to promote linear growth in GH-deficient children is well recognized. Furthermore, pronounced metabolic effects are seen during GH treatment of children with GH-

deficiency in terms of improved bone density, fat distribution and glucose metabolism. Most of these results have been accomplished by the use of extracted pituitary hGH. With the recent advent of biosynthetic human GH wider indications for treatment of children with GH are now possible.

Due to the limited supply of pituitary-derived GH, it has not previously been practicable to continue GH replacement therapy beyond the cessation of linear growth in the adolescent period. Neither has it been well

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examined what the consequences of withdrawal of GH replacement in this critical period might be. During the last five-year period, a substantial amount of data have shown that there are subnormal features in GH-deficient adults that can be normalized if GH replacement therapy is reinitiated.

Normal aging is associated with a gradual decline in GH secretion [1] accompanied by a reduced bone mineral content and lean body mass, and an increased fat mass, a phenomenon referred to as the somatopause. In this respect, there are several resemblances between physiological aging and adult GH-deficiency, and GH treatment has actually been attempted in healthy elderly people [2, 3]. However, these aspects of GH treatment must be clearly segregated from treatment of adults with verified "true" GH deficiency. In this paper we will describe only the typical features of adult patients with "true" GH-deficiency and the potential effects of GH treatment.

Features of the adult GH-deficiency syndrome and effects of GH

Cardiovascular system: GH-deficient patients have myocardial dysfunction [4,5] and increased incidence of atherosclerosis [6, 7] associated with an increased mortality due to cardiovascular disease [8]. GH treatment has increased cardiac output [9] and has been reported to decrease cholesterol and low density lipoprotein concentrations and to increase high density lipoprotein concentrations [10]. GH thus seems to affect cardiovascular function and to regulate lipoprotein metabolism in adults with GH-deficiency.

Renal effects: Glomerular filtration rate and renal blood flow were significantly increased (normalized) after GH treatment [9]. Furthermore, a significant activation of the renin-angiotensin-aldosterone system has been demonstrated in GH-deficient adults [11]. This is in line with the reduction in atrial natriuretic peptide after GH treatment of normal men [12].

Thyroid function: It is now well recog-

nized that GH exerts an important action on peripheral iodothyronine metabolism in terms of stimulation of extrathyroidal conversion of thyroxine (T4) to triiodothyronine (T3). More interestingly, it has been demonstrated that adult GH-deficient patients exhibit subnormal T3 levels (in spite of normal T4 levels), which become normalized with GH substitution [13]. We believe that this action of GH contributes to its overall anabolic effects, especially when keeping in mind that Sato *et al.* [14] have reported a linear correlation between T3 levels and linear growth in GH-treated GH-deficient children.

Bone: A reduced bone mineral content was demonstrated in untreated adults with GH deficiency of childhood or pubertal onset [15,16] as well as in patients with GH deficiency acquired later in life [17], explaining, at least partly, the increased prevalence of osteoporosis in GH-deficiency [7]. There is some controversy on the possible effects of GH replacement therapy on bone in the adult state. Several studies have indicated increased bone turnover in GH-deficient adults during GH replacement therapy, in terms of increments in serum concentrations of bone Gla-protein [18] and procollagens [19] and in urinary excretion of calcium, hydroxyproline and pyridinoline cross-links [20]. However, the effect of GH-induced increase in bone turnover on bone mineral content (BMC) is not clear. Most studies have failed to show an increase in BMC after GH treatment for up to 6 months [21,22,23]. However, a recent open trial reported an increase in BMC after 12 months of GH therapy [24]. This discrepancy we believe is due to the need for longer treatment periods before a beneficial effect on BMC can be seen.

Body composition: GH-deficient adults have a decreased lean body mass and a decreased muscle/fat ratio as demonstrated by various methods, such as cross-sectional CT scan of the thigh [9], bioelectrical impedance [22,25] and total body potassium assessment [22,26]. A decreased extracellular fluid volume has also been reported in these patients

GH treatment of GH-deficient adults

Fig. 1. Mean ($\pm$ SE) levels of circulating iodothyronines, TSH, Tg and T3/T4 ratio in GH-deficient adults not receiving T4 therapy (group I) and receiving T4 therapy (group II) at the end of a 4-month GH treatment period, expressed as percent change from the corresponding levels at the end of a placebo period. Data are derived from reference [13].

[26]. Furthermore, a reduced energy expenditure has been described [27] possibly due to the decreased lean body mass. In all studies, it has been agreed that GH treatment has increased lean body mass and improved the muscle/fat ratio in GH-deficient adults [9,19,21,22,23,24,28,29,39].

Muscular performance: Reduced exercise capacity [28,30] as well as reduced muscle strength [28] was demonstrated in GH-deficient adults, although histological studies of skeletal muscles showed no signs of myopathy [31]. GH treatment improved exercise capacity [9,27,28] as well as muscle strength [9,30].

Reproduction: Male patients with isolated GH-deficiency had moderately reduced semen quality, and short-term treatment with GH did not result in any significant improvement [32]. The potential role of GH and IGFs on reproductive endocrinology is subject to inten-

sive research.

Sweating and temperature regulation: Hyperhidrosis is a classic symptom of acromegaly, and conversely, patients with GH deficiency show reduced sweating, as determined by the pilocarpine iontophoresis method. After 4 months of GH treatment sweating increased significantly towards normal [33]. Sweating is important for maintenance of body temperature during exercise or heat exposure. A report on unexplained hyperthermia in 3 untreated adults with GH deficiency [34] indicates that GH may indeed play a role in sweating and thermoregulation. A recent study revealed that during moderate heat exposure, 6 young adults with GH deficiency had a reduced evaporative heat loss and thereby a greater body heat storage, compared to 6 matched healthy subjects (figure 1). Two of the 6 patients reacted with severe clinical symptoms of heat exhaustion,

Fig. 2. Muscle and fat volume of the high in GH-deficient patients during a short-term GH trial and after more than 1 year of GH treatment, compared to normal subjects, expressed as ml/0.8 cm cross-sectional slice. Bars represent mean (SE). Data are derived from reference [28].

whereas the controls were unaffected. After exercise the patients reached significantly higher core temperatures than the controls [35]. It remains to be seen whether GH treatment can improve thermoregulatory function.

Psychosocial aspects: Follow-up studies of adults treated with GH in childhood have shown a high risk of unemployment and a low marital rate [36,37]. Assessment of psychological well-being in GH-deficient adults revealed that they perceive themselves as having physical and psychological problems [38]. GH treatment improves perception of energy level, mental alertness and mood [38,39]. The mechanisms by which GH exerts its psychological effect are difficult to determine. Improved physical well-being itself might have an effect, or it could be an improved cerebral blood

flow. Finally, a direct cerebral effect of GH or IGF- I cannot be excluded. The latter hypothesis is supported by the improvement of abnormal sleep pattern seen after GH treatment [40].

Diagnosis of GH-deficiency

Children: There are many problems in diagnosing GH deficiency in poorly growing children. In a recent paper it was demonstrated that 33 of 63 children previously diagnosed as GH-deficient by means of classic pharmacological and sleep tests did not have a true deficiency when retested, and 13 of these (21%) were considered to have a normal GH response. However, the children who appear-

GH treatment of GH-deficient adults

Fig. 3. Sweating secretion rates determined by the pilocarpine iontophoresis method, after 4 months of GH treatment in GH-deficient adults, compared to healthy subjects. Median values are shown. Data are derived from reference [33].

ed to be normal when retested did not grow differently from those who were still GH-deficient [41]. Therefore, the diagnosis does not *per se* indicate which children will benefit from GH treatment, and very strict criteria for subdividing poorly growing children according to their maximal GH response to a provocative test may not be justified. However, this is not the case for adults. We strongly believe that, in the present era of adult GH treatment, very strict criteria for diagnosing adults with GH deficiency should be put forward.

Adults: Obviously, some of the potential candidates for adult GH replacement therapy have been diagnosed in childhood due to growth deficit and have subsequently been treated with GH. When diagnosing adults with GH deficiency or confirming the diag-

nosis in adult patients with GH deficiency of childhood onset, we have to rely on clinical data (specific features of GH deficiency), laboratory measurement and provocative tests, since auxological data do not support the diagnosis in adults, as they do in children. This suggests some potential pitfalls, which have to be dealt with in the future:

1. Provocative test:

a. Definition of specific cut-off value following a GH provocative test for each laboratory.

Due to the heterogeneity of circulating GH forms, each GH assay may proserect with these GH forms to a different extent, and therefore it is of the outmost importance that each laboratory construct its own normal cut-off value [42].

b. Age-dependence of endogenous GH secretion.

Normal aging is associated with a gradual decline in integrated 24-hour GH secretion [1]. Therefore, the use of a fixed cut-off level in a classical GH provocative test is thought to be inadequate.

c. GH responsivity to provocative test during the menstrual cycle.

GH responsivity to a provocative test is strongly dependent on sex steroids, and the GH response is very dependent on the time of the menstrual cycle [43].

Basal serum IGF-I and IGFBP-3:

Serum levels of IGF-I and IGFBP-3 reflect the integrated 24-hour GH secretion and have proven to be reliable indices of GH secretion and linear growth in children. Less is known about the diagnostic value of these parameters in adults. Serum levels of IGF-I exhibit, like integrated serum GH concentrations, a gradual decline with increasing age in healthy adults [1] as do serum levels of IGFBP-3 [44]. This implicates that a hypothetical IGF-I concentration of $150\mu\text{g/L}$ is below the normal range for a 20-year-old patient but in the middle part of it if the patient is 70 years old. It emphasizes the

Fig. 4. Heat calculations and temperatures after 90-minute heat exposure (40°C) in 6 GH-deficient adults (P1-P6) compared to matched control subjects (C1-C6). a) Heat storage, b) evaporation, c) rectal temperature and d) skin temperature. Data are derived from reference [35].

importance of a large reference material, when using serum concentrations of IGF-I and IGFBP-3 as diagnostic tools in adults.

We therefore propose that a definition of the adult GH deficiency syndrome should at least include:

1. Insufficient response to classical stimulation tests (taking into account age, stage in

menstrual cycle, and assay-specific cut-off values)

2. Serum IGF-I and IGFBP-3 below the normal range for age (large reference material required) and
3. GH deficiency since childhood or
4. If GH deficiency acquired in adulthood, additional deficiency of at least one of

ACTH, LH/FSH or TSH, or known reason for GH-deficiency (intracranial tumour).

Concluding remarks

GH deficiency in adults is associated with a number of clinical symptoms. GH treatment improves or normalizes these symptoms. Therefore, we believe that GH treatment should be continued in adulthood in GH-deficient patients. However, the results of ongoing, long-term GH studies of GH-deficient adults should be obtained before a final decision can be made.

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