MINIREVIEW

Beneficial effects of GH replacement therapy in adults

Jens Sandahl Christiansen and Jens Otto Lunde Jørgensen

University Department of Endocrinology and Internal Medicine, Aarhus Kommunehospital, Denmark

Abstract. Growth hormone deficiency in adults is associated with psychosocial maladjustment, reduced muscle strength, and reduced exercise capacity. Body composition is significantly altered, with increased fat and decreased muscle volume as compared with healthy subjects. Kidney function is subnormal. Epidemiological data suggest premature mortality owing to cardiovascular disease in hypopituitary patients. Short-term GH treatment trials have shown improved psychosocial performance, normalization of body composition, increased muscle strength, improved exercise capacity, increased cardiac performance, and normalization of kidney function. Thus GH replacement therapy in GH-deficient adults exhibits potential long-term beneficial effects. A number of important questions have to be addressed before long-term GH replacement therapy in GH-deficient adults can be considered on a routine basis.

Human growth hormone so far has mostly been known for the effect associated with its name – i.e. the action upon skeletal growth in children, and thereby the effect upon the final linear height, and for the clinical acromegalic characteristics seen as a consequence of GH hypersecretion. The clinical interest for GH has therefore mainly been related either to the substitution of the hormone to GH-deficient children, a classic part of pediatric endocrinology, or to the treatment of acromegaly, an area of interest shared by adult endocrinologists and neurosurgeons.

Although a number of different actions of GH, e.g. upon glucose and lipid metabolism and body composition, has been known for many years, until recently the clinical aspects of GH deficiency in adults have received very little attention indeed among endocrinologists, probably mainly owing to the fact that GH substitution in practical terms was out of the question because of shortage of the pituitary-derived hormone.

With the advent in 1979 of biosynthetic human growth hormone described by Goeddel et al. (1), unlimited amounts of natural sequence GH, free of potential pituitary contaminants, have become available. This in itself of course does not justify a more widespread clinical use of the hormone. On the other hand, the introduction of biosynthetic GH not only has made it possible to conduct clinical studies in order to optimize treatment of short stature in GH-deficient children (2), but also to study possible new indications for GH treatment. Until now the large majority of the latter studies has been carried out by pediatric endocrinologists and has focused on the growth promoting effect of GH in a number of conditions associated with short stature, e.g. Turner’s syndrome, uremia in childhood, Prader-Willis’ syndrome, familiar short stature.

Although GH continues to be secreted in normal adults after cessation of skeletal growth (3), the number of published studies dealing with GH therapy in GH-deficient adults is still surprisingly small, a fact probably explained by the lack of tradition and interest for GH as a therapeutic agent within adult endocrinology. However, the studies so far published are strikingly concordant in their results and conclusions. Actually very few, if any, controversies exist on the potential beneficial effects of GH replacement in adult life, although a huge number of questions remains to be answered. The most important of these questions of course is
whether or not the beneficial effects are so prominent that expensive, perhaps lifelong therapy is justified.

This review briefly deals with the present knowledge of GH deficiency in adults from a clinical point of view, and will not deal with the possibility of GH as a drug for alternative indications, e.g. aging, wound healing. Thus we will restrict our consideration to GH replacement therapy.

Mortality

A major consequence of GH deficiency is possibly an increased mortality rate. In a recent paper Rosén & Bengtsson (4) analysed mortality and causes of death retrospectively in more than 300 hypopituitary patients over a 30-year period. A highly significantly increased overall mortality rate of nearly 100% was recorded. It thus seems that life expectancy is reduced in hypopituitary adults in spite of apparent sufficient conventional replacement therapy with cortisone, thyroxine, sex hormones and vasopressin. Mortality risk was increased irrespective of whether hypopituitarism was due to pituitary adenoma or secondary to other diseases. It was suggested that the increased mortality, which was mainly due to a high frequency of cardiovascular disease, might be associated with GH deficiency, which was assumed to be present in all subjects (4). No data dealing with the possible influence of GH replacement therapy on mortality are available.

Psychological and social aspects

Children with GH deficiency have been reported to be psychologically immature with various degrees of psychosocial maladjustment (5). It is not clear, however, whether these conditions are consequences of GH deficiency per se or due to the variety of endogenous and exogenous abnormalities often associated with GH deficiency in childhood. Long-term follow-up studies of adults previously treated with GH in childhood have shown a low percentage of marriage and a high risk of unemployment (6,7). A small survey dealing with GH-deficient adults never treated with GH, related the high rate of unemployment to the high frequency of physical complaints such as muscle weakness (8).

Very few reports deals with the psychosocial effects of GH therapy in GH-deficient adults. Jørgensen et al. (9) conducted a 4-month placebo-controlled cross-over GH treatment trial in adults who had all been GH-deficient since childhood. Using a rather unsophisticated questionnaire it was demonstrated that GH treatment was preferred to placebo, and that the majority of patients would like to continue GH therapy even if it involved daily injections (10).

McGauley et al. (11) compared psychological well-being in 24 adults who satisfied strict criteria for GH deficiency with matched control subjects. Using well-established health questionnaires it was shown that these GH-deficient adults, most of whom had been rendered GH-deficient in adult life, perceived themselves as being more labile, more socially isolated, and less energetic than did the controls. They furthermore regarded themselves as having a poorer level of general health, less self-control, and less vitality and they experienced more anxiety. The same authors tested the effect of GH replacement therapy in a controlled trial and demonstrated a significant improvement in the self-assessed quality of life in the GH-treated group which also stated significantly higher energy levels as compared with the placebo group (11). Also a recent Swedish study reports a significant improvement in energy levels and well-being during GH treatment in GH-deficient adults (12).

Thus all reported studies support the concept that GH deficiency in adults is associated with a reduction in psychosocial performance and that GH replacement therapy seems to have a beneficial influence on this condition.

Metabolic effects and influence on body composition

The effects of growth hormone upon carbohydrate, protein and lipid metabolism are well known (13,14). In GH-deficient adults, GH therapy prevents the development of hypoglycemia during starvation (13), suggesting that GH plays a role in the normal glucose homeostasis.

The lipolytic effect has been documented both in vivo and in vitro (15). GH has been shown to promote a redistribution of adipose tissue from an abdominal to a more peripheral (from android to gynoid) distribution (16), and to decrease lipogenesis (17).

Nitrogen retention following GH administration
was described in 1958 by Ikkos et al. (18), thereby introducing the so-called "anabolic" action of growth hormone. Likewise, the sodium-retaining effect of acute GH administration was described already in the early fifties (19).

It was soon discovered that, in addition to its effect on skeletal growth, GH treatment had a major effect on body composition. A reduction in subcutaneous fat (skinfold thickness) in hypopituitary dwarfs following GH therapy was originally reported by Tanner & Whitehouse (20). This observation has been repeatedly confirmed, and subsequently it has been demonstrated that the weight gain seen during growth in GH-treated GH-deficient children is associated with an increase in lean body mass as measured by total body potassium (21). Accordingly, the responses of muscle and fat tissue to GH replacement therapy were found to be strikingly dissimilar (22).

Body composition in GH-deficient adults so far has received little attention. Jørgensen et al. (9) studied 22 GH-deficient adults and assessed muscle and adipose tissue volume by means of CT-scanning of the thigh. In the non-GH-treated condition, the distribution of fat and muscle in the thigh was 37 and 63% (as compared with approximately 15 and 85% in healthy subjects). Similarly, Salomon et al. found GH-deficient adults to be overweight (skinfold thickness) and to have decreased lean body mass (total body potassium method) (23).

Both groups have reported results from controlled trials on the effect of GH replacement therapy on body composition (9,23). The details of design and patients in these two studies are shown in Table 1. It is noteworthy that both studies, despite distinct differences in design, methods and category of patients, showed that GH therapy induced highly significant changes in body composition with decreasing volume of adipose tissue and increasing amounts of muscle, although neither study reports total normalization of these parameters within the study period. The results of 4 months GH therapy as compared with placebo on muscle volume measured by CT scanning (9) are shown in Fig. 1. Sim-

### Table 1.
Controlled trials on the effect upon body composition of GH replacement therapy in adults.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>N</th>
<th>Age (years)</th>
<th>Design</th>
<th>Methods for evaluation of body composition</th>
<th>Treatment period (months)</th>
<th>GH-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarhus/Copenhagen (9)</td>
<td>GH-deficient since childhood</td>
<td>22</td>
<td>24 (18-39)</td>
<td>Placebo-controlled cross-over</td>
<td>CT-scanning, skinfold thickness</td>
<td>4</td>
<td>2 IU/m² daily sc.</td>
</tr>
<tr>
<td>London (23)</td>
<td>GH deficiency acquired in adult life (except 2)</td>
<td>24</td>
<td>39 (21-54)</td>
<td>Placebo-controlled parallel</td>
<td>Total body potassium, skinfold thickness</td>
<td>6</td>
<td>0.07 IU/kg daily sc.</td>
</tr>
</tbody>
</table>

Fig. 1.
Volume of thigh muscle expressed as ml/8 mm cross-sectional CT-scan in GH-deficient adults after 4 months of treatment with GH (□) and placebo (■), respectively. Mean ± SEM.
ilar results have recently been published by Whitehead et al. (24).

Thus, the data so far available support the concept that GH has distinct and important actions in the maintenance of normal body composition, and that the abnormal muscle/fat ratio in GH-deficient adults can be normalized by GH replacement therapy.

Muscle strength and exercise capacity

Some GH-deficient patients complain of lethargy, and muscle fatigability may be one of the reasons for the low employment rate of these patients (8). The exact knowledge of muscle function status in GH deficiency is, however, scarce. In a recent study Cuneo et al. (25) compared skeletal muscle function in adults with long-standing GH deficiency and normal subjects. The 24 patients, who also participated in the subsequent GH treatment trial (23), were all strictly GH-deficient hypopituitary patients on stable hormonal replacement therapy apart from GH substitution. Muscle strength was examined by a dynamometer. Whether expressed per quadriceps area or body weight, quadriceps force was found to be significantly lower in the GH-deficient adults than in the normal subjects. Cuneo et al. conclude that muscle force is reduced in GH deficiency predominantly in proportion to the reduced muscle mass. But, in addition, a reduction in force/muscle area is found to contribute to the reduced muscle strength (25).

Jørgensen et al. (9) measured quadriceps strength in GH-deficient adults during GH replacement therapy and placebo administration. A small but only marginally significant increase in muscle strength was recorded in the 4-month GH treatment period. In agreement with Cuneo et al. (25), a significant correlation between muscle mass and muscle strength was found (9). It was subsequently demonstrated that GH replacement for more than one year further improved muscle function, as compared with the results after only 4 months of therapy (26). Also these results have recently been confirmed (24).

In addition, exercise capacity was evaluated by a standard ergometer test using increments in workload until exhaustion. Exercise capacity was significantly improved during GH treatment as compared with placebo (9), but values were still far below those obtained in matched control subjects (Fig. 2).

At present, it can be concluded that GH deficiency in adults is characterized by a subnormal muscle strength, probably mainly owing to reduced muscle mass, and a low exercise capacity. It is tempting to associate these findings with the low employment rate of these patients. Short-term trials indicate a beneficial effect of GH replacement therapy upon these parameters.

Specific organ effects

Heart

In healthy subjects, GH administration increases heart rate, cardiac output, and myocardial contractility (27). In adult GH deficiency, GH therapy for 4 months was associated with small but significant increments in cardiac performance (9). One anecdotal communication has reported a beneficial effect of GH therapy on terminal heart failure in a GH-deficient patient (28). As mentioned above cardiovascular mortality has been found to be highly increased in supposedly GH-deficient hypopituitar
Glomerular filtration rate (iothalamate clearance) in GH-deficient subjects as compared with healthy controls.

Kidneys
GH is known to increase glomerular filtration rate and renal plasma flow in healthy subjects (29). In GH-deficient adults, both parameters (expressed per 1.73 m² of body surface area) were reported significantly reduced as compared with normal subjects (9) (Fig. 3), in agreement with the original observation by Falkheden (30). Four months of GH replacement therapy completely normalized kidney function (9) (Fig. 4).

Current questions
Although GH deficiency in adults is associated with a number of abnormal conditions and symptoms most likely caused by the lack of GH, and although GH therapy has repeatedly been shown to have beneficial effects upon these conditions, there are still a number of crucial questions to be answered in connection with GH replacement therapy in these patients.

Undesirable effects
Since we are dealing with replacement of a lacking hormone and therefore in principal can argue that all the effects seen are the desired actions of the hormone, we must, however, realize that replacement of GH in the strict sense, with restoration of pulsatile secretion into the vascular bed around the pituitary gland, is not possible. We need more experience with long-term treatment in GH-deficient adults in whom modern GH therapy, i.e. daily sc injection, has been instituted. In particular, the long-term effects upon glucose metabolism, including plasma insulin levels, and upon body fluid homeostasis should be monitored.

Diagnosis
Defining GH deficiency is not simple, not even in children in whom reduction in growth velocity is a "sine qua non" in the diagnosis (31). In adults we will have no support from auxological data, but will
have to rely on clinical data, laboratory measurements, and stimulation tests. A very important area for research in the next few years will be to attempt to characterize GH secretory status better, e.g. by means of IGF-I, IGF-II, IGF-binding proteins, GH receptor status, and body composition, in order to help us diagnose GH deficiency in adults. This is even more important if we consider the possibility that in the future we will take interest not only in total GH deficiency, but also in various degrees of partial GH deficiency or relative insufficiency. Present knowledge does not allow such a differentiation.

**Epidemiology**

Once we agree upon the diagnosis of GH deficiency and insufficiency, epidemiological data on prevalence and incidence rates, and the association to other clinical endocrinological conditions must be obtained.

**Clinical management**

Whom shall we treat? How long should they be treated? What is the optimal treatment regimen? What dose of GH should we use? Should the dose be calculated according to weight or body surface? Will the dose be the same in men and women, and should we consider reduction of dose with increasing age?

Are some conditions associated with GH resistance? and how do we define GH resistance?

**Psychosocial aspects**

Long-term evaluation of the impact of GH treatment on psychosocial parameters, especially quality of life assessments, is certainly needed. What are the consequences of introducing long-term daily injection therapy? Can the positive results so far reported be reproduced?

**Economic aspects**

At present, GH therapy is very expensive. The concept of introducing GH therapy to new categories of patients has often been questioned for simple economic reasons. This question is of course important and relevant, but premature. First of all, it can be foreseen beyond reasonable doubt that the cost of GH will be reduced considerably within the next few years. This will be the inevitable consequence of the reduced production costs and the increased competition on the GH market. Secondly, and even more important, a cost-benefit analysis of GH replacement therapy cannot be performed before we know the benefits. Arguments that GH deficiency in adults so far has been no clinical problem, and that the patients apparently have done well without GH replacement, are of course insufficient and should be considered irrelevant. Present knowledge neither permits the conclusion that GH-deficient adults show no or only minor clinical signs of GH deficiency, nor justifies a general recommendation for GH substitution to anyone at any age.

We are just at the beginning of a very important and exciting era of clinical endocrinological research.

**References**

10. Pedersen SA, Jørgensen J0, Christiansen JS, Skakkebæk NE. Psychosocial effects of growth hormone treatment in growth hormone deficient adults. A double-blind cross-over trial. International Sympo-


