Aetiology and diagnosis

Specific clinical consequences of adult growth hormone deficiency (GHD) are increasingly recognised. For diagnostic and clinical reasons, it is important to distinguish adult GHD of childhood onset from adult onset.

Childhood onset GHD is usually an isolated phenomenon due to variable deficiency of hypothalamic growth hormone releasing hormone (GHRH): structural causes (eg craniopharyngioma, germ cell tumours or irradiation) occur, but are less common. Isolated GHD in childhood may not persist into adult life, possibly because of maturational deficiency of the hypothalamic-somatotroph axis, so it is essential to reinvestigate young people with childhood onset GHD when linear growth is complete.

In contrast, adult onset GHD is due predominantly to structural pituitary or peripituitary disease and to the effects of surgery and radiotherapy of these lesions. Approximately two-thirds of cases are due to pituitary macroadenomas. Other numerically important causes include craniopharyngioma, parasellar meningioma and cranial irradiation, with the remainder being accounted for by suprasellar germ cell tumours, lymphocytic hypophysitis, Langerhans cell histiocytosis, granulomatous infiltrations including sarcoidosis, haemochromatosis, trauma and post-partum pituitary necrosis. The estimated prevalence of adult onset GHD is about one per 10,000 in European populations. If adult deficiencies persisting from childhood are also included, the prevalence is closer to three per 10,000 population.

GHD occurs early in relation to other hormone deficiencies in structural pituitary disease and after irradiation. It is an almost invariable finding in patients with additional evidence of hypopituitarism and, in contrast to some aspects of pituitary function, is not usually reversible by treatment of primary pituitary mass lesions.

The most widely used diagnostic investigation is the insulin hypoglycaemia test, the sensitivity and specificity of which have been clearly documented in patients with structural pituitary disease; peak GH concentrations below 9 mU/l (3 ng/ml) are diagnostic of GHD. The insulin tolerance test is safe provided that specific precautions are observed; it is essential that this investigation be carried out in appropriate facilities, and it is contraindicated in patients with symptoms or a previous history of ischaemic heart disease or epilepsy. When insulin hypoglycaemia is unsuitable, alternatives include glucagon and arginine stimulation. Clonidine stimulation, although widely used in paediatric practice, is ineffective in adults and has no place in the diagnosis of adult onset GHD. GHRH stimulation alone has been advocated for this purpose but, because it tests GH readily releasable by the somatotroph, it cannot be used to determine the integrity of the hypothalamic-somatotroph axis which is frequently compromised in structural pituitary disease.

Single measurements of serum insulin-like growth factor (IGF)-1 are in the low normal range in 30–50% of patients with adult onset GHD. This is in contrast to the diagnostic value of this measurement in children and adults with childhood onset GHD. As a consequence, measurement of serum IGF-1 alone is insufficient to make the diagnosis — although clearly a low level in a patient with structural pituitary disease who is adequately nourished and does not have liver disease is strongly suggestive of the diagnosis.

Reduced spontaneous GH secretion is a feature of the normal ageing process but this does not usually result in problems in the interpretation of dynamic tests of GH reserve. In contrast, the reduction in GH secretion in morbid obesity, which is reversible with weight loss, may cause diagnostic difficulties; in general, the confirmation of a diagnosis of suspected GHD in an obese patient depends on the presence of supportive features including structural pituitary disease and additional pituitary hormone deficiencies.

Clinical features of adult growth hormone deficiency

Deficiency of GH in the adult is associated with a constellation of symptoms and signs which are increasingly recognised by endocrinologists experienced in the treatment of pituitary disease (Table 1). The establishment of a causal relationship between these clinical features and GHD itself depends substantially on the surrogate evidence of reversibility of individual features by GH replacement therapy and the absence of a relationship with other aspects of hypopituitarism.

The prevalence of these features in the hypopituitary patient are variable, but the derangement of body composition is present in a substantial majority of patients. The psychological symptoms associated with GHD have been evaluated using both generic methods and disease-specific questionnaires (Adult Growth Hormone Deficiency Assessment). GHD has an important association with reduced socioeconomic achievement and adversely affects social interaction.

The abnormality of lipoprotein profiles is variable but may additionally be associated with a reduction in high-density lipoprotein (HDL) cholesterol. Furthermore, in addition to the predictable deficit in the counterregulatory response to hypoglycaemia, there is a paradoxical reduction in insulin sensitivity and an increased incidence of impaired glucose tolerance. The latter phenomenon may be at least partly explained by the abnormal fat distribution which is evident in hypopituitary
Table 1. Clinical and laboratory features of adult growth hormone deficiency.

| Symptoms and signs                        | Test results                                                                 |
|------------------------------------------|-----------------------------------------------------------------------------|
| Decreased energy                         | Decreased bone density                                                      |
| Decreased muscle strength                | Increased low-density lipoprotein cholesterol and apolipoprotein B          |
| Decreased muscle mass                   | Decreased cardiac muscle mass (especially childhood onset)                 |
| Increased body fat                       | Impaired cardiac function                                                  |
| (especially central adiposity)           |                                                                             |
| Accelerated atherogenesis                | Decreased total and extracellular fluid volume                             |
| Decreased sweating and impaired thermoregulation | Decreased insulin sensitivity                                           |
| Lack of positive well-being             | Increased plasma fibrinogen and plasminogen activator inhibitor-1          |
| Depressed mood                           |                                                                             |
| Increased anxiety                        |                                                                             |
| Social isolation                         |                                                                             |

patients regardless of body mass index (BMI)9. Obesity (BMI>30kg/m²) is found in approximately 30% of hypopituitary adults on conventional replacement in comparison with less than 10% in European population studies9.

Additional features of adult GHD include a reduction in total and extracellular fluid volume and an overall reduction in bone mineral density (BMD) involving both cortical and trabecular bone. The adverse effects on BMD are particularly evident in childhood onset patients, probably because of failure to achieve peak bone mass, and in young and middle-aged patients with adult onset disease. Recent studies in a large cohort of hypopituitary patients have demonstrated increased risk of fracture compared with an age-and sex-matched control population10.

The effects of GHD on body composition, lipid profile, blood pressure and insulin sensitivity would predict an increased risk of macrovascular disease. Two retrospective studies from Sweden2,11 suggest that hypopituitary adults have an approximately twofold increased rate of death from cardiac and cerebrovascular disease, with a decreased death rate from malignancy in males2. A further study from the UK12 has confirmed excess mortality in GHD, but has not documented an increase in cardiovascular disease against the background incidence – although it should be borne in mind that the latter is higher in the UK than in Sweden so the numbers required to demonstrate significant differences are greater. Increased atherogenesis has been documented ultrasonographically in both adult13 and childhood onset GHD14, and hypopituitarism on conventional replacement is associated with increased serum fibrinogen and plasminogen activator inhibitor type 1. Whereas childhood onset GHD may be associated with a relative lowering of blood pressure, adult onset disease appears to precipitate or exacerbate hypertension in a proportion of patients. In addition, in both childhood and adult onset GHD left ventricular ejection fraction and diastolic relaxation are impaired, which might contribute to the reduced exercise tolerance in GHD and also further compromise cardiac function in patients with ischaemic heart disease.

The efficacy of growth hormone replacement

Patients selected for GH replacement on the basis of specific criteria (see below) almost invariably demonstrate a significant improvement, especially in body composition, fat distribution and parameters reflecting well-being and quality of life. The improvement in body composition occurs relatively early (within 3 months), and the reduction in central fat is easily followed clinically by the simple procedure of waist measurement. In my own practice, this decreases by an average of 6 cm over the first six months of treatment, with improvement maintained thereafter.

The antinatriuretic effects of GH explain the symptoms of fluid retention which were a common feature of early trials of GH replacement in which we now know the body weight-based dosing regimens to have been excessive. Careful titration of GH dose normalises total and extracellular fluid volume with very few adverse symptoms. Despite the improvement in central adiposity, insulin sensitivity declines further during the first six months of GH therapy8,15, but returns to baseline by 12 months15.

The improvement in body composition is paralleled by favourable changes in total, low-density lipoprotein and HDL cholesterol. However, some studies have demonstrated minor increments in serum lipoprotein (a) in patients who have otherwise demonstrated an improvement in lipoprotein profiles8,16.

Markers of bone remodelling (serum bone-specific alkaline phosphatase and osteocalcin for bone formation; urine and serum pyridinoline and deoxypyridinoline for bone resorption) increase within four months of commencement of GH replacement, and these changes are sustained at 12 months17. BMD has been shown to increase after 12–24 months of continued GH replacement18.
The early higher-dose placebo-controlled trials suggested that a proportion of patients demonstrated a significant improvement in quality of life, as determined by generic questionnaires, including the Nottingham Health Profile, and a desire to continue treatment in the long term. This was evident in many patients within three months of commencing GH, but was delayed for more than six months in a significant number. The greatest improvement was shown in patients who had severe GHD and the greatest deficit in energy and vitality prior to commencing GH. More recent experience using lower doses indicates improvement in quality of life in over 80% of patients.

Criteria for selecting patients for growth hormone replacement and dosing strategies

Proposed minimum criteria are listed in Table 2. Patients should satisfy diagnostic criteria and demonstrate one or more of the recognised clinical features of GHD.

Doses used in almost all the published work to date have been based on body weight or surface area. This approach, which is essentially an adaptation of paediatric practice, results in much higher doses in obese patients, a high incidence of side effects related to sodium and water retention and supraphysiological levels of serum IGF-1, and ignores gender differences in susceptibility to GH. To eliminate these problems, we have adopted a dose-titration approach with increments based on serum IGF-1 measurements, with the aim of achieving a serum IGF-1 between the median and upper end of the age-related reference range. This approach has successfully reduced maintenance doses without loss of efficacy, and is associated with a very low incidence of adverse symptoms during initiation of therapy. In many GH deficient patients with essential hypertension, GH replacement improves blood pressure, probably because of a reduction in peripheral vascular resistance.

Long-term benefits of growth hormone replacement therapy

The major issues for consideration with respect to long-term benefits of GH replacement therapy are:
- increased cardiac morbidity
- osteoporosis (increased fracture risk)
- reduced quality of life and work capacity (burden on social services).

The effect of GH replacement on long-term cardiac morbidity will emerge only from very long-term surveillance of treated patients; physician-managed, multinational databases have been established for this purpose. GH replacement has been shown to reduce total

Table 2. Minimum criteria for commencement of growth hormone (GH) replacement in adults (patients should demonstrate 1, 2, 3 and one other clinical feature).

| Criterion | Confirmatory finding |
|-----------|----------------------|
| 1. Hypothalamic-pituitary disease in adult onset GHD or persisting GHD in childhood onset | |
| 2. Defined GHD on insulin tolerance, glucagon or arginine testing | Peak GH <9 mU/l |
| 3. Full replacement of other hormone deficiencies | |
| 4. Decreased quality of life | Score >6 on AGHDA questionnaire |
| 5. Reduced bone mineral density | T score <1.0 |
| 6. Adverse cardiovascular risk profile | Hyperlipidaemia, central adiposity |
| 7. Reduced exercise tolerance, cardiac decompensation | |

AGHDA = Adult Growth Hormone Deficiency Assessment
GH = growth hormone deficiency
T score = 5D score applied to young adult reference range
cholesterol by approximately 15%. By analogy with the effects of other lipid-lowering therapies, this would be predicted to reduce the incidence of symptomatic ischaemic heart disease by 30%. Cardiac disease carries the cost of acute and chronic treatment and loss of productivity.

Prolonged GH replacement therapy (>4 years) increases BMD by approximately 12%. This would be expected substantially to reduce fracture rate and the concomitant costs of immediate and long-term management.

Preliminary studies from Sweden indicate that hypopituitary adults are more likely to be unemployed, retire early or be in receipt of long-term invalidity benefit. These factors, together with the associated loss of productivity, constitute an important component of cost-benefit analysis.

Long-term surveillance (2,500 patient years on the KIMS Pharmac and Upjohn International database of adult GHD patients) has thus far not demonstrated any untoward consequences of GH replacement; in particular, there is no evidence for increased incidence of regrowth of residual pituitary tumour. Clearly, continued monitoring is mandatory.

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