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Adult growth hormone deficiency

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Clin Med 2003;**3**:15–19

Growth hormone (GH) has an important physiological role in adulthood.[1–3] Before the 1980s anecdotal reports suggested that patients lacking GH experienced symptoms of increased fatigue and low mood, features that improved with GH replacement.[4] Long-term replacement was not considered because of the lack of availability of cadaveric GH. With the development of recombinant GH in the mid-1980s, interest has been increasing in the consequences of GH deficiency (GHD) and the effects of short- and long-term replacement. Adults with hypopituitarism and GHD are both psychologically and physically less healthy than age-matched controls. This has led to the description of a specific constellation of symptoms and signs, designated the 'adult GHD syndrome'[5] which includes:

- poor self-esteem
- increased levels of anxiety
- lack of social interaction, and
- abnormalities of metabolism, body composition and bone mineralisation.

There has also been considerable interest in the physiological decline in GH secretion with ageing. Integrated GH secretion decreases by approximately 14% per decade in adult life, although peak response to stimulation is still maintained. The effect of GH replacement in older patients has been examined in placebo-controlled trials, but as yet there is little evidence of consistent improvement and this issue will not be considered further here.

Adult-onset growth hormone deficiency

Adult-onset GHD is due to pituitary or peripituitary disease or is a consequence of treatment. The commonest cause (70% of cases) is non-functioning pituitary adenoma. Other causes are shown in Table 1.[6] The prevalence of

Table 1. Causes of growth hormone (GH) deficiency in the first 2,753 adult patients consecutively enrolled into the KIMS* database.[6]

	Patients	
Diagnosis	**No.**	**%**
Non-functioning pituitary adenoma	844	30.7
ACTH-secreting pituitary adenoma	200	7.3
GH-secreting pituitary adenoma	55	2.0
Prolactin-secreting pituitary adenoma	305	11.1
Gonadotrophin-secreting pituitary adenoma	11	0.4
TSH-secreting pituitary adenoma	6	0.2
Pituitary tumour – secretory status unknown	40	1.5
Craniopharyngioma	357	13.0
Surgery**	25	0.9
Irradiation**	54	2.0
Idiopathic	353	12.8
Trauma	55	2.0
Other	448	16.3
Total	*2,753*	

* A pharmaco-epidemiological survey of adult GHD and replacement, which has been running since 1994, with approximately 7,500 patients currently registered.
** The terms surgery and irradiation refer to indications other than pituitary adenoma.
ACTH = adrenocorticotropic hormone; TSH = thyrotrophin.

adult GHD is estimated at one per 10,000, but may be double that if childhood-onset GHD persisting into adulthood is included. Resection of the primary lesion rarely results in recovery of the GH axis, and GH secretion is more susceptible than other pituitary hormones to the effects of mass lesions, surgery or trauma. Radiotherapy in or around the pituitary leads to GHD in approximately 80% of patients after three or more years, even in the absence of other pituitary deficiencies. Importantly for prediction, the more pituitary hormones are deficient the more likely it is that the patient has GHD. The absence of one other hormone gives an 80% chance of GHD, while absence of two hormones increases the likelihood to 90%.[7]

Idiopathic isolated growth hormone deficiency

Idiopathic isolated GHD does not arise *de novo* in adults, but there are adults with idiopathic isolated GHD of childhood who survive into adulthood. Since 30–70% of those with isolated GHD of childhood-onset spontaneously recover GH secretion, it is important for all children with a diagnosis of GHD to be retested once linear growth is complete. The recovery may be a consequence of partial deficiency of growth hormone-releasing hormone (GH-RH) in childhood with subsequent delayed maturation of the hypothalamosomatotroph axis.

Diagnosis of growth hormone deficiency in adults

Diagnosis of adult GHD cannot be made by a single measurement of serum GH or insulin-like growth factor (IGF)-1. GH is secreted in pulses, so a low level may represent a trough in secretion, although a high level due to fortuitous sampling during a secretory peak may rule out deficiency. IGF-1 is at the lower end of the normal age-related reference range in 30–40% of adults with severe GHD, the percentage increasing with advancing years. Therefore, a normal IGF-1 does not exclude GHD, although a low value supports the diagnosis – provided that there is no evidence of liver disease, malnutrition or intercurrent illness which may reduce GH sensitivity.

A confident diagnosis of GHD must be based on a subnormal rise in serum GH in response to dynamic stimulation. The gold standard is the insulin tolerance test (ITT) in which, by consensus supported by validation in patients with established structural pituitary disease, severe GHD is defined as a peak response of less than 9 mU/l (<3 ng/ml).[8] This is a safe test when conducted by experienced staff in dedicated units, but is contraindicated in patients with epilepsy or ischaemic heart disease and patients should have adequate replacement of all other deficient hormones before having the test. Obesity (body mass index (BMI) greater than 32 kg/m^2) can lead to a false positive diagnosis of GHD, in part due to increased somatostatinergic tone which reverses with weight loss. If an ITT is contraindicated, alternatives include subcutaneous/intramuscular glucagon, intravenous arginine or combined arginine/GH-RH or GH secretagogue/GH-RH stimulation tests. A similar cut-off of below 9 mU/l (<3 ng/ml) is taken for the glucagon and arginine tests. Higher normative values for the arginine/GH-RH and GH-RH/secretagogue tests are being developed.

Key Points

- **Growth hormone deficiency (GHD) is most commonly caused by pituitary disease or its treatment, or childhood-onset isolated GHD that has persisted into adulthood**
- **GH secretion is the pituitary hormone most sensitive to mass lesions, surgery and irradiation**
- **The gold standard for diagnosis of severe GHD is a peak of less than 9 mU/l (<3 ng/ml) on an insulin tolerance test**
- **The adult GHD syndrome is characterised by reduced quality of life (decreased well-being and energy, increased anxiety and social isolation), abnormal body composition and lipoprotein profiles, atherogenesis and decreased bone mineral density**
- **Recombinant GH replacement reverses these changes**

KEY WORDS: growth hormone, growth hormone deficiency, growth hormone replacement, osteoporosis, pituitary tumour, quality of life

The clinical syndrome of adult growth hormone deficiency

Effects on quality of life

Of the several identified consequences of GHD (Table 2) perhaps the most important from the patient's perspective is the effect on quality of life (QoL), particularly mood, anxiety levels and social interaction. The severity of psychological distress correlates positively with the duration of GHD. Interestingly, the psychological impact is more difficult to demonstrate in adults with childhood-onset GHD. This may be due to adaptation and lack of sensitivity of currently available QoL measures in these patients. Adult GHD is also associated with reduced socio-economic achievement.[9]

Measures of physical and psychological well-being. QoL and psychological well-being deficits have been identified using a variety of measures, including the Nottingham Health Profile (NHP) and Psychological General Well-being Index (PGWBI). In addition, the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire has been developed by documenting the most commonly described symptoms in hypopituitary adults during open interview. It consists of 25 specific questions, with a simple yes/no format, a high score representing

more severe symptoms. These measures are also used to assess longitudinal changes in those patients treated with GH.[10]

Body composition

Clinical and *in vitro* studies have shown that GH has important protein, anabolic, lipolytic and antinatriuretic actions which affect body composition. Patients with GHD have an increase in total fat that accumulates mainly centrally, as determined by computed tomography, dual energy X-ray absorptiometry and waist/hip measurements, even in patients who are not obese by BMI criteria.[11] GHD patients have an increase in median total cholesterol, low-density lipoprotein (LDL) and apolipoprotein B and a modest reduction in high-density lipoprotein. There is a reduction of lean body mass, muscle strength and exercise tolerance in these patients. Total body sodium and extracellular fluid volume are reduced, which may contribute to their reduced muscle strength and exercise capacity.

Cardiovascular effects

Patients with GHD have increased carotid intima-medial thickening, intimal plaque formation and reduced arterial compliance in the carotid artery and aorta. These findings are consistent with enhanced atherogenesis. GHD also results in reduced left ventricular mass and impaired systolic function. These changes improve (but do not normalise) with GH replacement.

Importantly, studies in the UK and Sweden have demonstrated a two- to threefold increase in the standardised mortality ratio (SMR) in hypopituitarism, especially from macrovascular disease.[12] These patients have had other deficient hormones replaced, so it has been hypothesised that GHD may be responsible for the observed increased mortality. This is supported by the increase in cardiovascular risk factors identified in GHD patients, but also assumes that other hormones are optimally replaced. The latter may not be the case, especially in the context of gonadal steroid deficiency, but there is strong circumstantial evidence linking GHD to increased risk of vascular disease.

Carbohydrate metabolism

Central adiposity in GHD is associated with insulin resistance. Fasting insulin levels are increased and there is a greater prevalence of diabetes mellitus and impaired glucose tolerance (which may be partly explained by increased central adiposity). However, paradoxically, GH replacement initially decreases insulin sensitivity, although this substantially returns to baseline by 12 months.[13] There is no evidence that GH replacement increases the risk of developing *de novo* diabetes mellitus over and above that conferred by underlying generalised obesity as manifest by increased BMI.

Table 2. Symptoms and clinical features of adult growth hormone deficiency (GHD).

Symptoms	Clinical features
Lack of positive well-being	Increased body fat (esp central adiposity)
Depressed mood	Decreased muscle mass
Increased anxiety	Decreased bone density
Social isolation	Increased LDL cholesterol and apoB
Decreased energy	Decreased cardiac muscle mass (esp childhood-onset GHD)
Decreased muscle strength	Impaired cardiac function
	Decreased total and extracellular fluid volume
	Decreased insulin sensitivity
	Increased plasma fibrinogen and PAI-1
	Accelerated atherogenesis
	Decreased sweating and thermoregulation

apoB = apolipoprotein B; esp = especially; LDL = low-density lipoprotein; PAI = plasminogen activator inhibitor.

Bone mass

Adult GHD patients have a reduced bone mass involving cortical and trabecular bone compared with age-matched healthy controls. This is of particular importance in childhood-onset GHD because it may result in failure to achieve peak bone mass. Adults with GHD have a two- to threefold higher risk of osteoporotic fractures.[14] Gonadal steroid deficiency of variable duration is probably an additional factor in compromising bone mass in patients with adult-onset GHD.

Growth hormone replacement

In most endocrine units a decision to replace GH is based not only on biochemical proof of GHD, evidence of hypothalamic-pituitary disease (unless persisting childhood-onset) and full replacement of other deficient pituitary hormones, but also on demonstrable clinical consequences for the patient, perhaps the most important being reduced QoL. Replacement therapy should also be considered for those with adverse cardiovascular risk profile, osteopenia or osteoporosis. GH replacement is contraindicated only in patients with active malignant disease, advanced diabetic retinopathy or pregnancy.

Administration of growth hormone

Recombinant GH is given by daily subcutaneous injection. The current approach in most units is to titrate the dose gradually until serum IGF-1 is between the median and upper end of the age-related reference range; this usually takes 4–12 weeks.[15] Maintenance doses are higher in women than men (because of oestrogen-mediated reduction in IGF-1 generation) but, apart from the effects on bone mineral density (BMD) (see below), there are no gender differences in the effects of GH provided that serum IGF-1 is targeted in this way.

Patients are usually assessed after six months on treatment, although most patients report a benefit after three months on maintenance GH doses. There are occasional side effects of myalgia, arthralgia and carpal tunnel

syndrome due to GH-induced antinatriuresis, but these are uncommon if the dose is titrated slowly – and much less common than with weight-based dosing which resulted in excessive doses, particularly in men and obese subjects. These effects rapidly resolve with dose reduction.

Quality of life

Placebo-controlled trials have shown contradictory results on QoL improvement, perhaps because the criteria in some studies have excluded patients with the greatest baseline QoL deficit. In fact, those with the greatest psychological morbidity benefit most from replacement. Our experience is that over 80% of selected patients with the greatest psychological morbidity demonstrate subjective benefit.

The mechanism by which GH affects mood is unclear. GH crosses the blood-brain barrier and alters cerebrospinal fluid levels of vasoactive intestinal polypeptide, β-endorphin and the dopamine metabolite, homovanillic acid. However, the effect of GH in restoring normal hydration and increasing exercise capacity may play a major role in improving general well-being.

Fat mass

There is a mean reduction in fat mass of up to 4 kg within six months; these changes are sustained for up to 10 years after treatment. GH replacement also increases lean body mass within six months and total body water, particularly extracellular water and plasma volume, within 3–5 days. GHD is associated with increased activity of 11β-hydroxysteroid dehydrogenase type 1, which catalyses net conversion of inactive cortisone to cortisol. This may partially explain the central adiposity of GHD, and this accumulation in central adiposity is reversed by GH replacement. LDL cholesterol decreases by an overall median of approximately 0.4 mmol/l on GH replacement, in addition to the effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Exercise capacity improves, probably due to a combination of restoring circulating volume, improving lean body mass and improving psychological well-being.[16]

Bone mineral density

There is a biphasic effect of BMD. It is initially unaltered or even decreased as activation of bone remodelling is initiated. This is supported by increases in measures of bone formation (eg osteocalcin, bone-specific alkaline phosphatase) and of resorption (eg deoxypyridinolone) within weeks of starting GH. In the longer term (1–5 years), BMD increases. This is most evident in men who show an increment in BMD -Z score of 0.5–1.0 standard deviation over five years. The impact of this increase in BMD on fracture rates remains to be determined.

Activities of daily life

Recent studies from the KIMS database have shown significant reductions in both the number of patients requiring assistance with daily living and hospital inpatient stays over 24 months of treatment,[17] and similar SMRs to background populations. In the future, GH may become a standard replacement therapy for all patients with GHD, particularly if long-term data confirm the favourable effect on the previously demonstrated increased mortality of hypopituitarism.

Cost benefit

Cost benefit analysis of adult GH replacement should consider not only cost (average £3,500 per patient per year) and subjective benefit to patients but also the potentially favourable impact on the future cost burden of increased incidence of cardiovascular disease, osteoporosis and fractures, and reduced work capacity. These patients are more likely to be unemployed, which places an increased cost burden on social services.

Conclusion

The last decade has led to major advances in the understanding of adult GHD and the benefits of treatment. Replacement is well tolerated and can make a dramatic difference to people's lives. No long-term adverse effects have been reported; initial fears of tumour recurrence have not been confirmed but close follow-up continues. Long-term follow-up of large patient cohorts should provide meaningful data on the effects of GH on fracture rates and overall mortality.

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Hypercalcaemia

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Clin Med 2003;**3**:19–22

Hypercalcaemia is one of the more common metabolic abnormalities seen in hospital practice; it occurs in approximately 5% of hospital inpatients.[1] Hypercalcaemia results from an imbalance between the amount of calcium entering the plasma from the gastrointestinal tract or as a result of bone resorption and the amount being lost from the circulation through the urine or into newly formed bone. The overall fluxes in each of these systems are of a similar magnitude (Fig 1), but the net loss of calcium in the urine is the result of most of the filtered calcium being reabsorbed within the tubules. The level of calcium in the blood is therefore exquisitely sensitive to changes in both renal function and tubular handling of calcium.[2]

In most cases of hypercalcaemia a new steady state is reached in which calcium entering the circulation is balanced by that leaving it; this results in a stable situation in which the plasma calcium remains at a relatively constant level. However, when the hypercalcaemia is sufficient to impair renal function, either directly or as a result of dehydration, calcium excretion is impaired and the plasma calcium level increases. This results in further worsening of renal function, with consequent elevation of plasma calcium. This vicious circle is termed 'disequilibrium hypercalcaemia' and can rapidly lead to circulatory collapse if not treated with the appropriate degree of urgency.

Causes of hypercalcaemia

Most cases of hypercalcaemia in clinical practice will be the result of either primary hyperparathyroidism or malig-

Fig 1. Diagram indicating normal daily calcium fluxes in an adult.