**REVIEW**

Growth hormone and its disorders

J Ayuk, M C Sheppard

Growth hormone (GH) is synthesised and secreted by the somatotroph cells of the anterior lobe of the pituitary gland. Its actions involve multiple organs and systems, affecting postnatal longitudinal growth as well as protein, lipid, and carbohydrate metabolism. GH hypersecretion results in gigantism or acromegaly, a condition associated with significant morbidity and mortality, while GH deficiency results in growth retardation in children and the GH deficiency syndrome in adults. This article, aimed at non-paediatric physicians, examines the clinical features, diagnosis, and current concepts in the management of these conditions.

**ACROMEGALY**

The term acromegaly is derived from the Greek words akron, meaning extremity, and megas meaning great. Acromegaly is a chronic endocrine disease first described by the French neurologist Pierre Marie in 1886. It is caused almost invariably by a GH secreting pituitary adenoma, although rarely it may be attributable to a hypothalamic tumour secreting GHRH or ectopic GHRH secretion from a carcinoid tumour (predominantly of the pancreas or bronchus). It is a rare condition, with an estimated prevalence of around 60 per million and an annual incidence of 3–4 per million, but active acromegaly is associated with significant morbidity and an increase in mortality compared with the general population.

**Molecular pathogenesis**

Pituitary adenomas generally result from dysregulated monoclonal expansion of a mutated cell, pointing to an intrinsic defect as the primary neoplastic event in pituitary tumourigenesis. Tumour formation is most probably the ultimate result of a series of genetic changes involving tumour suppressor gene inactivation and oncogene activation. Stimulatory G protein (Gs) is involved in the mediation of GHRH action and contains an α-subunit; an activating mutation of the α-subunit gene (gsp) leads to persistently activated stimulatory G protein and high intracellular levels of cyclic AMP. This defect mimics stimulation of adenyl cyclase by GHRH receptor activation, resulting in autonomous GH secretion. The gsp mutation has been found in 40% of human GH secreting pituitary adenomas, and is comparatively specific for somatotroph tumourigenesis.

**Clinical features**

The clinical features of acromegaly are attributable to the somatic and metabolic effects of prolonged excess GH exposure or to local effects of an expanding pituitary mass. They often

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**Abbreviations:** GH, growth hormone; IGF, insulin-like growth factor; OGTT, oral glucose tolerance test; IGT, impaired glucose intolerance; GHRH, GH releasing hormone; TRH, thyrotropin releasing hormone; MRI, magnetic resonance imaging; CT, computed tomography; TSS, transsphenoidal surgery
Growth hormone disorders

Growth hormone (GH)

- An anabolic hormone
- Synthesised in the anterior lobe of the pituitary gland
- Acts by binding to two GH receptor molecules
- Responsible for longitudinal growth
- Modulates protein, lipid, and carbohydrate metabolism
- Secretion regulated by the hypothalamus

Acromegaly

- Attributable to GH excess
- Annual incidence 3–4 per million
- Prevalence 60 per million
- Associated with significant morbidity and mortality
- Treatment modalities; surgery, radiotherapy, medical therapy

Clinical features of acromegaly

- Coarse facial features
- Large, spade shaped hands
- Large feet
- Prognathism and macroglossia
- Sleep apnoea
- Goitre
- Colonic polyps

Complications

Musculoskeletal complications

The most significant cause of functional disability in acromegaly is arthropathy. Acromegalic arthropathy affects up to 70% of patients and involves both the axial and peripheral skeleton. The underlying pathophysiology is not entirely understood, but it has been hypothesised that GH excess stimulates local production of IGF1 in cartilage, resulting in thickening of the cartilage, change of the normal joint geometry, and joint hypermobility. Radiological findings include narrowing of the joint spaces, osteophytes, and other features seen in osteoarthritis. Symptomatic carpal tunnel syndrome is also a frequent finding, affecting up to 60% of patients, and is thought to be attributable to oedema of the median nerve in the carpal tunnel, rather than extrinsic nerve compression.

Cardiovascular complications

Acromegaly is characterised by a high incidence of cardiovascular disease, which contributes significantly to morbidity and mortality. Hypertension occurs in around a third of all patients, ranging in some series up to 60%. The mechanisms underlying the development of hypertension in acromegaly remain unclear although experimental and clinical studies suggest possible roles for the anti-natriuretic action of GH, changed sympathetic tone, and direct effects of vascular growth factors. Acromegalic cardiomyopathy is caused by the effects of chronic GH excess on the heart. It is characterised by biventricular concentric hypertrophy, with thickened ventricle walls but normal sized chambers. The cardiac hypertrophy is associated with functional changes (decreased ejection fraction in response to exercise), valve abnormalities, and a high incidence of arrhythmias. The incidence and severity of the abnormalities increase in elderly patients with long disease duration.

Metabolic complications

GH counteracts the effects of insulin on glucose and lipid metabolism, resulting in metabolic complications in patients with acromegaly. The most frequent of these is changed glucose metabolism. The prevalence of overt diabetes mellitus ranges from 19% to 56% in patients with active acromegaly, with impaired glucose tolerance (IGT) occurring in up to 46%. Studies investigating the pathogenesis of changed glucose metabolism in acromegaly suggest GH excess induces insulin resistance by impairing the ability of insulin to suppress gluconeogenesis, decreasing peripheral glucose utilisation, and reducing insulin receptor numbers and binding affinity.

Neoplastic complications

The association between the GH/IGF1 axis and neoplasia such as breast, prostate, and colon cancer has been the subject of basic and clinical research for many years. Data linking IGFs to tumourigenesis and neoplastic growth have been extensively reviewed by Khandwala et al. However, epidemiological studies exploring the link between acromegaly, cancer incidence, and mortality have given rise to conflicting data, leading to significant debate. Early studies suggested an increased incidence of neoplasia overall, particularly of the breast and colon, in patients with acromegaly. Evidence from more recent studies, however, has failed to confirm these findings, and suggests overall cancer incidence is not increased in acromegaly.

What has emerged is that patients with acromegaly have an increased risk of developing colorectal cancer, although the exact magnitude of this risk and the role of screening programmes remain the subject of much debate. In addition, recent epidemiological studies found cancer death rates in cohorts of patients with acromegaly were similar to those in the general population, suggesting malignancy is not a significant cause of mortality in patients with acromegaly.

Diagnostic investigations

Biochemical diagnosis

The clinical features of acromegaly are outlined above, but as it often develops insidiously, few patients present immediately at the time of onset of symptoms and the most common mode of presentation is as an incidental finding by a healthcare professional. Biochemical confirmation relies on the demonstration of excessive GH secretion. Baseline biochemical assessment includes a fasting or random GH and
### Complications of acromegaly

- Musculoskeletal; orthopathy, carpal tunnel syndrome
- Cardiovascular; hypertension, cardiomyopathy, arrhythmias
- Metabolic; impaired glucose and lipid metabolism
- Neoplastic; colorectal cancer

IGF1 measurement, with a random GH level less than 0.4 μg/l (0.8 mU/l) and a normal age and sex matched IGF1 excluding the diagnosis of acromegaly. However, as GH is secreted in a pulsatile manner, single GH measurements provide inadequate information regarding GH increase and therefore if either of these levels is not achieved or index of suspicion is high, an oral glucose tolerance test (OGTT) should be performed with 75 g oral glucose and subsequent measurements of glucose and GH every 30 minutes over two hours. Failure of GH suppression to less than 1 μg/l (2 μU/l) during an OGTT suggests the diagnosis of acromegaly, but the results should always be considered in conjunction with an IGF1 measurement as other conditions (for example, diabetes mellitus, renal disease) can cause discordantly increased GH levels. Twenty four hour mean GH levels can also be used in the diagnosis of acromegaly (mean 24 hour GH less than 2.5 μg/l (5 μU/l) excludes acromegaly), but 24 hour sampling is time consuming and less cost effective than an OGTT, and is now usually reserved for research purposes or for patients with equivocal OGTT or IGF1 results. Thyrotropin releasing hormone (TRH), GHRH, or gonadotrophin releasing hormone (GnRH) stimulation tests and measurement of IGF binding protein 3 offer no additional information for the diagnosis of acromegaly.

### Radiological investigation

Magnetic resonance imaging (MRI) is now considered the gold standard for investigating pituitary adenomas, providing invaluable information about tumour size and extension, and permitting accurate delineation of parasellar structures. The information obtained is improved if this is performed at a centre specialised in examination of the pituitary fossa. For patients in whom it is not possible to perform MRI, computed tomography (CT) offers a reasonable alternative.

### Other investigations

Visual field defects occur in up to 20% of patients with acromegaly, predominantly in those with larger tumours, suprasellar extension, and higher GH levels. A bitemporal hemianopia is the most common defect but other forms may also be seen. Visual fields should be tested by confrontation during initial assessment, and if necessary this should be followed by formal documentation using Goldman perimetry.

Over 50% of patients with acromegaly have pituitary dysfunction affecting the secretion of at least one other anterior pituitary hormone, therefore basal pituitary function should be assessed by measuring serum prolactin, gonadotrophins, testosterone/oestradiol, thyroid stimulating hormone (TSH), free T₃, free T₄, and serum cortisol, although dynamic testing of the hypothalamo-pituitary-adrenal axis may be necessary.

In rare cases where a GHRH secreting tumour is suspected, serum GHRH levels can be measured.

### Management

Several retrospective studies have shown a twofold to threefold increased mortality in acromegalic patients compared with age and sex matched controls, with death predominantly attributable to vascular disease, respiratory disease and, in the earlier studies, malignancy. However, results from the more recent studies also showed that the increased mortality associated with acromegaly can be diminished if treatment is successful in reducing GH hypersecretion to less than 2–2.5 μg/l (4–5 mU/l), whether this is measured as the mean of a growth hormone day profile or as a random growth hormone level. This has resulted in the publication of a consensus statement defining the criteria for cure of acromegaly as a normal age matched serum IGF1 level and a GH nadir of less than 1 μg/l (2 μU/l) during an oral glucose tolerance test.

The main aims of treatment of acromegaly are reversing the symptoms and signs of the disease, treating the underlying cause, preventing disease recurrence, and improving long term survival. This entails the use of surgery, radiotherapy, and/or medical therapy.

### Surgery

Transsphenoidal surgery (TSS) is still considered first line treatment for acromegaly in most patients. Based on strict biochemical criteria (mean GH less than 2.5 μg/l (5 μU/l), suppressed GH during an OGTT and/or normal IGF1), the overall remission rate after TSS ranges from 55% to 70%. A number of factors have emerged as crucial in determining outcome after TSS, including tumour size, extrasellar extension, dural invasion, and pre-treatment GH levels. Remission rates for microadenomas are around 80% to 90%, while those for macroadenomas are around 50%. The expertise of the pituitary surgeon also plays a key part in determining outcome, as has been illustrated by data from our centre in Birmingham; surgical outcome improved significantly when surgery was performed by a single dedicated pituitary surgeon rather than eight different surgeons, as had been the case previously.

Surgical complications such as cerebrospinal fluid (CSF) leaks, diabetes insipidus, and development of new hypopituitarism are infrequent, occurring in less than 7% of cases, while recurrence after initial surgical remission occurs in around 6%.

### Radiotherapy

Radiotherapy has been used in the management of acromegaly for nearly a century, with conventional fractionated radiotherapy lowering GH levels over 20 years to less than 5 μg/l (10 mU/l) in 70% to 90% of patients. Radiotherapy is also effective at controlling tumour growth as shown by Brada et al, with progression free survival of 94% at 10 years and 88% at 20 years in patients with pituitary adenomas treated with external beam radiotherapy. However, a number of factors have led to a re-evaluation of the role of radiotherapy in the management of acromegaly. Apart from the long lag time to clinical effect, during which the patients continue to suffer the effects of GH hypersecretion, a number of studies have shown that IGF1 levels remain raised in a significant proportion of patients whose GH levels are reduced to 2–2.5 μg/l (4–5 mU/l) after treatment with radiotherapy. Hypopituitarism, which itself has been linked to
premature mortality.\textsuperscript{44} is a significant problem, and at 10 years, around half of all patients treated with radiotherapy will have developed new anterior hormone deficiencies.\textsuperscript{35} In addition, it is now well recognised that patients treated with radiotherapy have a significantly increased risk of cerebrovascular events and cerebrovascular mortality compared with the general population.\textsuperscript{44} \textsuperscript{46} \textsuperscript{47} Radiation induced visual deterioration and the development of second brain tumours occur in a small proportion of patients,\textsuperscript{35} and although cognitive dysfunction is listed as a side effect of radiotherapy, recent evidence suggests it occurs in patients with pituitary tumours regardless of treatment modality.\textsuperscript{36}

Gamma knife radiosurgery, which permits a highly precise circumscribed delivery of radiation to a target in a single session, has also been used to treat acromegaly.\textsuperscript{44} In a recent study, around 25% of patients treated with gamma knife radiosurgery achieved GH less than 2.5 µg/l (5 mU/l) and IGFI normalisation within five years, with significant tumour shrinkage.\textsuperscript{47} However, more long term follow up data are required to fully assess its role in the management of acromegaly.

At present, radiotherapy should be reserved for patients in whom satisfactory control of tumour growth, GH, and IGFI has not been achieved by surgery and/or medical therapy.

**Medical therapy**

Traditionally, TSS and/or radiotherapy have been considered first line treatment for acromegaly, but despite recent advances in both these forms of treatment, the overall surgical cure rate remains around 60% and radiotherapy is characterised by delayed effect and a high incidence of hypopituitarism, as discussed above. This means medical therapy is necessary in a significant proportion of patients, and current options include dopamine agonists, somatostatin analogues, and more recently GH receptor antagonists.

**Dopamine agonists**

The dopamine agonist bromocriptine was the first effective medical treatment for acromegaly, but it lowers GH secretion to the desired levels in less than 20% of cases and is associated with a number of side effects including nausea, dizziness, and headaches.\textsuperscript{48} Newer dopamine agonists like cabergoline are better tolerated and more efficacious, lowering GH levels to less than 2 µg/l (4 mU/l) in up to 46% of cases, with greater responses in patients with tumours co-secreting GH and prolactin.\textsuperscript{49} This is not uncommon, as up to one third of these adenomas are plurihormonal acidophil cell derived tumours and co-secrete both hormones.\textsuperscript{49}

**Somatostatin analogues**

The use of dopamine agonists has largely been superseded by the introduction of somatostatin analogues, which exert their biological effects by activating somatostatin receptors (predominantly sub-receptor types 2 and 5) in the pituitary.\textsuperscript{50} Octreotide, a long acting synthetic somatostatin analogue, has been used to treat acromegaly for two decades, and since the mid-1990s, three slow release depot preparations have been introduced; Sandostatin LAR (Novartis), Lanreotide LA (Ipsen), and Lanreotide Autogel (Ipsen). These have been shown to be both effective and safe, suppressing GH levels to less than 2–2.5 µg/l (4–5 mU/l) and normalising serum IGFI levels in 50%–70% of cases.\textsuperscript{51} \textsuperscript{52} In addition, tumour shrinkage by 20%–50% has been reported in around 30% of patients pre-selected for octreotide responsiveness.\textsuperscript{53} \textsuperscript{54} \textsuperscript{55}

Although somatostatin analogues have traditionally been used as an adjunct to surgery and radiotherapy, they are increasingly being used as first line therapy in the treatment of acromegaly. Several studies in which somatostatin analogues were given to previously untreated (de novo) patients showed suppression of GH and IGFI to a similar extent to that seen in patients who received the drugs after surgery.\textsuperscript{56} \textsuperscript{57} \textsuperscript{58} These findings have led the authors to conclude that if the possibility of surgical cure is low, and if there is no visual compromise, then medical treatment with somatostatin analogues alone is as effective biochemically and clinically as the combination of surgery followed by medical therapy, and offers a reasonable primary therapeutic modality.

Given the recognised efficacy of somatostatin analogues in improving biochemical parameters and reducing tumour size, a number of studies have investigated the impact of pre-treatment with these drugs on surgical outcome. While some have shown no clear benefits, others have found improvements in terms of remission rates and clinical conditions, including preoperative blood pressure, cardiac function, glucose metabolism, and shorter hospital stays.\textsuperscript{59} \textsuperscript{60}

There are a number of side effects associated with somatostatin analogue therapy, but these are rarely severe and in general do not limit treatment. Around 50% of patients experience gastrointestinal symptoms including diarrhoea, nausea, and abdominal discomfort, but these are usually transient.\textsuperscript{61} New gallstone formation (usually asymptomatic) occurs in 10%–20% of patients and a small number develop impaired glucose metabolism.\textsuperscript{62}

**GH receptor antagonists**

Pegvisomant is a novel, genetically engineered GH receptor antagonist that, in contrast with dopamine agonists and somatostatin analogues, inhibits GH action rather than secretion. It exerts its biological actions by preventing functional dimerisation of the GH receptor.\textsuperscript{63} Clinical studies have shown that pegvisomant is remarkably effective, improving clinical symptoms and signs and resulting in IGFI normalisation in over 90% of patients.\textsuperscript{64} \textsuperscript{65} The drug seems to be safe and well tolerated. Because pegvisomant works by blocking the actions of GH, efficacy is independent of tumour characteristics, such as the density of somatostatin receptors. Despite normalised IGFI levels, GH levels remain raised in these patients, albeit with minimal or neutralised bioactivity because of receptor block. Concerns of the raised GH concentrations being reflected in tumour growth need to be clarified by additional long term monitoring studies.

There is now overwhelming evidence that the clinical outcome in patients with acromegaly can be improved substantially by means of earlier diagnosis, better surgical expertise, a multidisciplinary approach to management, and effective medical therapies used in a flexible manner. The factors that are important in choosing an optimal strategy

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**Figure 1** U shaped curve showing the optimal level of circulating GH required to maintain normal health. Both GH excess and GH deficiency seem to be associated with an increase in mortality. AGHD, adult growth hormone deficiency; SMR, standardised mortality ratio.
GROWTH HORMONE DEFICIENCY

Growth hormone deficiency in adulthood can result from onset during childhood or later in life. Idiopathic GH deficiency is the most common cause of GH deficiency in children. It is a poorly defined and often reversible condition that presents with short stature and low growth velocity for age. In contrast, adult onset GH deficiency generally presents as part of a combined pituitary hormone deficiency phenotype (hypopituitarism) and is commonly attributable to a pituitary adenoma and/or treatment with surgery or radiotherapy. GH is usually the first anterior pituitary hormone to be affected in patients with large pituitary adenomas or after pituitary surgery and radiotherapy. Other causes of GH deficiency are listed in the box.

Growth hormone deficiency syndrome

There is no single symptom or sign that is pathognomonic of GH deficiency in adult life, but a well defined constellation of symptoms and signs has been identified in adults with GH deficiency, leading to the recognition of a “GH deficiency syndrome”. In adult life, GH deficiency is associated with changed body composition, changed metabolism, reduced exercise capacity, and impaired quality of life. Adults with GH deficiency have reduced skeletal muscle, reduced lean body mass and increased fat mass, particularly distributed in the truncal region, mostly in visceral tissue. In addition, these patients have reduced bone mass compared with matched healthy controls, and are at increased risk of sustaining osteoporotic fractures.

Adult GH deficiency and hypopituitarism have been associated with a number of risk factors for cardiovascular disease, including vascular endothelial dysfunction, dyslipidaemia, and insulin resistance. Reduced left ventricular mass, impaired cardiac systolic function, and impaired response to peak exercise have also been reported. These findings, along with the reduced lean body mass, result in reduced muscle strength and exercise capacity.

Using validated questionnaires, several studies have reported reduced self perceived psychological wellbeing and quality of life in adults with GH deficiency. Characteristic features include depressed mood, anxiety, lack of energy, social isolation, and impaired wellbeing.

Diagnosing GH deficiency in children is straightforward, as it is associated with growth retardation. However, diagnosis of adult onset GH deficiency is much more challenging, as none of the features associated with the condition are pathognomonic. Although GH response to a number of pharmacological stimuli including clonidine, glucagon, arginine, and GHRH have been used to diagnose GH deficiency, the insulin tolerance test is currently considered the diagnostic test of choice, with a peak GH response of less than 3 μg/l confirming the diagnosis. This test can, however, be unpleasant for patients and is contraindicated in those with epilepsy and ischaemic heart disease, resulting in an ongoing search for newer and safer tests to diagnose GH deficiency. Recently developed strategies include the combined arginine and GHRH stimulation test and the combined GHRH and GH releasing peptide 6 stimulation test.

Growth hormone deficiency and mortality

A number of studies have examined mortality in patients with hypopituitarism and all have confirmed increased mortality compared with age matched controls, predominantly attributable to respiratory, cardiovascular, and cerebrovascular disease. The extent to which GH deficiency influences this increased mortality remains unclear and has been the subject of much debate. Although adult GH deficiency has been implicated as having a vital role in mediating increased vascular mortality in hypopituitarism, the largest study examining mortality in hypopituitarism reported that the only hormone deficiency that was conclusively implicated in the excess mortality was untreated gonadotrophin deficiency. Furthermore, evidence is lacking that GH replacement in GH deficiency patients leads to improved survival. In fact, untreated patients with isolated GH deficiency due to GH gene deletion, patients with multiple pituitary hormone deficiency due to PROPI gene mutation, and patients with isolated IGF1 deficiency due to GH receptor gene mutation (Laron syndrome) can survive to an advanced age, reaching ages of 80–90 years. By contrast, a recent study of 11 subjects living in a Swiss valley with isolated GH deficiency due to deletion of the GH1 gene reported a significantly reduced life span in comparison with siblings, as well as with the normal population living in the valley.

GH replacement

Replacement therapy with GH has consistently been shown to have beneficial effects on body composition, bone turnover, cardiovascular risk factors, and quality of life. In studies investigating the effects of GH replacement on body composition, lean body mass increased by 2 to 5.5 kg, while (predominantly abdominal) fat mass was reduced by 4 to 6 kg after six months. Longer term treatment (12 months or more) led to increases in bone mineral density and biochemical evidence of bone remodelling.

The effects of GH replacement on cardiac morphology and function are well described, with a number of studies showing a significant increase in left ventricular mass and stroke volume. This results in improved cardiac performance.

GH therapy leads to an improvement in vascular risk due to a number of factors including changed nitric oxide...
availability and changes in lipid fractions and inflammation mediators. However, most studies to date do not show a beneficial effect on insulin resistance.45

Several studies assessing the impact of GH replacement on psychological wellbeing in patients with GH deficiency have shown significant improvements in mood and quality of life, especially in those patients with greatest psychological morbidity.46

Despite the beneficial effects of GH therapy outlined above, to date no data exist on the effects of GH replacement on mortality.

GH replacement is associated with few side effects, the most common being fluid retention, arthralgia, and myalgia. Reassuringly, data from long term studies suggest there is no significant risk of tumour development or recurrence.47

CONCLUSION

GH is essential for growth, but also modulates protein, lipid, and carbohydrate metabolism. There is clear evidence that GH excess is associated with reduced survival, and suggestions that GH deficiency may play a vital part in the increased mortality seen in patients with hypopituitarism. These clinical findings suggest that there probably is an optimal level of circulating GH required to maintain normal health, represented in figure 1 as a U shaped curve; in disorders of GH excess or deficiency, restoration of GH levels to normal reduces mortality risk to that of the normal population.

QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

1. Growth hormone
   (A) Is synthesised in the posterior lobe of the pituitary gland
   (B) Is responsible for intrauterine and postnatal growth
   (C) Modulates protein, lipid, and carbohydrate metabolism
   (D) Effects are mediated predominantly via IGF1
   (E) Binds to two GH receptor molecules

2. Acremegaly
   (A) Is most commonly caused by a GH secreting pituitary adenoma
   (B) Is diagnosed by showing increased GH and reduced IGF1 levels
   (C) Is always associated with tall stature
   (D) Is associated with reduced survival
   (E) Is associated with a reduction in GH levels when treated with pegvisomant

3. Adult onset growth hormone deficiency
   (A) Results in short stature
   (B) Is associated with increased mortality that can be reversed by GH replacement
   (C) Leads to impaired quality of life
   (D) Is often associated with deficiencies in other anterior pituitary hormones
   (E) Can occur after a head injury

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ANSWERS  
I. (A) F, (B) F, (C) T, (D) T, (E) T.  
2. (A) T, (B) F, (C) F, (D) F, (E) F.  
3. (A) F, (B) F, (C) T, (D) T, (E) T.
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