Growth hormone – from molecule to mortality

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ABSTRACT – Growth hormone (GH) acts predominantly via insulin-like growth factor-I (IGF-I) expression. Acromegaly is associated with an increased mortality which can be reversed by optimal treatment. Somatostatin analogues are effective adjunctive therapies in patients treated with surgery and/or radiotherapy and result in tumour shrinkage in many patients. Pegvisomant is a GH analogue which inhibits functional dimerization of GH receptors, inhibits GH activity and normalizes IGF-I in over 90% of subjects. Adult GH deficiency is associated with changes in body composition, insulin status, lipid profile and Quality of Life measures. Hypopituitarism is associated with an increased mortality. Replacement with GH has clinically beneficial effects but there are no data on effects on mortality. Taller individuals are at a 20–60 percent increased risk of a range of cancers, an effect that may be mediated via IGFs. These observations suggest that there is an optimal level of circulating GH and IGF-I required to maintain normal health

KEY WORDS: GH receptor antagonist, growth hormone deficiency, growth hormone, hypopituitarism, insulin-like growth factor-I, pituitary tumour, somatostatin analogues

Growth hormone (GH) is a 22 kDa protein secreted from the anterior pituitary gland in an episodic pattern which is central to the regulation of growth. GH exerts its activity indirectly through the induction of insulin-like growth factor-I (IGF-I) expression or directly on tissues such as liver, muscle, bone or fat to induce metabolic changes. The GH receptor (GHR) is a transmembrane protein with an extracellular domain that binds to GH; the intracellular domain interacts with other proteins to regulate cellular functions of the target cell. GH has two binding sites and dimerisation of the GHR is required for signal transduction.

It has become increasingly clear that excess levels of GH are harmful, inducing symptoms as well as resulting in increased mortality in subjects exposed to high levels of GH. This review will outline the current approaches to managing acromegaly, including evidence that mortality rates can now be restored to normal by inhibitors of GH secretion, the development of new agents which will antagonise GH actions, the risks of GH deficiency, and the increasing evidence that GH and IGF-I may be related to morbidity and mortality in a variety of circumstances.

Acromegaly

Acromegaly is caused by GH hypersecretion and resultant elevated circulating IGF-I concentrations. The underlying abnormality in more than 98% of cases is a pituitary GH-producing tumour. The disease is typically diagnosed between 10 and 15 years after the presumed onset of GH hypersecretion because of the slow, insidious progression of the disease and lack of symptoms. The clinical manifestations of acromegaly can be divided into those due to local tumour expansion with compression of surrounding structures – headaches, visual field loss, hypopituitarism – and those due to excess GH and IGF-I secretion. The most common biochemical consequences are impaired glucose tolerance or overt diabetes, and insulin resistance. Cardiovascular disease is an important clinical consequence. The importance of sleep apnoea as a cause of morbidity in acromegaly has become increasingly apparent. The relationship between acromegaly and cancer risk remains controversial. Of all cancers, evidence is strongest for an increased risk of colorectal cancer. Acromegaly decreases life expectancy, with a two- to three-fold increase in mortality, with major causes of death including cardiovascular, cerebrovascular and respiratory disease. The morbidity produced by acromegaly is much more difficult to quantify.

Management of acromegaly

The clinical management of acromegaly has changed dramatically in recent years.[1,2] The two most important advances are:

- the recognition that the increased mortality associated with acromegaly can be reversed by optimal treatment (Table 1)
- the development of effective inhibitors of GH secretion and action as major adjuncts to the traditional approaches of surgery and radiotherapy.

In view of the absence of sensitive clinical parameters, cure has been defined arbitrarily as normalisation of biochemical parameters. There is logic in this approach as there is now increasing and

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convincing evidence that effective biochemical control can reduce mortality to that of the general population. There is general agreement that control of disease is achieved when mean GH levels are <5 mU/l, nadir GH after an oral glucose load is <2 mU/l, and circulating IGF-I is reduced to an age-adjusted normal range. There does remain controversy, however, regarding the relative importance of GH values and IGF-I values in determining post-treatment control status. Virtually all evidence from epidemiological studies has related GH values and not IGF-I values to long-term morbidity and mortality; post-treatment mean GH value <5 mU/l is associated with a mortality no different from the general population.

Transsphenoidal surgery remains the most cost-effective and rapid initial treatment of choice for the majority of patients with acromegaly. However, if these rigorous criteria are used for the interpretation of surgical results obtained from an experienced operator in an expert unit, approximately 80% of patients with microadenomas and less than 50% of patients with macroadenomas can be defined as controlled. It is clear therefore that many patients who undergo initial surgery will require additional therapy, such as radiation and/or medical therapy, to alleviate potentially disabling signs and symptoms, and to control GH and IGF-I levels.

Somatostatin analogue therapy

Somatostatin analogue therapy has been proven to be an effective adjunctive therapy in patients who have already been treated with surgery and/or radiotherapy. In addition, several studies in which newly diagnosed acromegalics were given subcutaneous octreotide preoperatively for short time periods of time before surgery report reductions in GH and IGF-I levels to an extent similar to that observed in patients who received octreotide treatment after surgery. Studies of depot somatostatin analogues with prolonged release (Sandostatin LAR, Lanreotide SR and Lanreotide Autogel) have also included patients who have not received pituitary surgery or radiotherapy. Sandostatin LAR has been shown to be effective both as primary therapy and as adjunctive therapy in patients previously treated with surgery and/or radiotherapy.

There is increasing interest in the use of somatostatin analogue therapy to induce shrinkage of tumours produced by growth hormone. The prospective UK Primary Octreotide Therapy Study Group reported on 27 patients with newly diagnosed acromegaly who were treated with sc octreotide and Sandostatin LAR as primary medical therapy for up to 48 weeks.[3] At the end of the study, 73% showed greater than 30% tumour shrinkage. A number of other studies using Sandostatin LAR, Lanreotide SR or Lanreotide Autogel have reported tumour shrinkage in excess of 30% in 20–100% of subjects, although the majority involved small numbers of patients. Substantial tumour shrinkage thus occurs in a significant subset of acromegalic patients.

These observations have led authors to conclude that if the possibility of surgical cure is low, and if there is no visual compromise, then medical treatment with octreotide or lanreotide alone should be as effective biochemically and clinically as the combination of surgery followed by octreotide or lanreotide, and may be a reasonable primary therapeutic modality.[4]

The West Midlands Acromegaly Database (419 patients) was used to determine long-term outcome associated with acromegaly.[5] Mortality was increased in the subgroup of patients with GH levels greater than 4 mU/l (measured either as the mean of a GH day profile or GH values across an oral glucose tolerance test, or a random GH level). IGF-I levels have been proposed as first line investigation for the diagnosis and therapeutic monitoring of acromegaly, but in this large study there was no increase in mortality in the subgroup of patients with raised serum IGF-1 levels. On the basis of these data, serum IGF-1 does not appear to be a reliable marker of long-term risk. This study also reported that this group of patients is subject to reduced life expectancy following pituitary radiotherapy. Treatment with radiotherapy was associated with increased mortality (ratio of mortality rates (RR) 1.67), with cerebrovascular disease the predominant cause of death (standardised mortality ratio (SMR) 4.42).

There is mounting evidence that in a subgroup of patients in whom surgery is unlikely to result in a cure, long-term treatment with depot somatostatin analogues as primary therapy is a safe and effective option. In addition, somatostatin analogues may cause significant tumour shrinkage (Table 2).

GH receptor antagonist (GHRA)

Pegvisomant represents an innovative concept in the medical management of acromegaly.[6] This GH analogue contains nine amino acid substitutions: one which inhibits functional

Table 1. Acromegaly treatment objectives.

1 Reduction or stabilisation of pituitary tumour size
2 Reversal of signs and symptoms to the greatest extent possible
3 Restoration of abnormal biochemistry
4 Prevention of disease recurrence
5 Avoidance of hypopituitarism

Table 2. Conclusions on the treatment of acromegaly.

- Control of GH hypersecretion, and presumably GH action, is a worthwhile objective
- Medical inhibitors of GH hypersecretion and action are effective clinically and biochemically
- Aggressive therapy to normalise GH and/or IGF-I levels should be instituted at diagnosis and during follow-up of all patients
- Radiotherapy may be associated with an increase in mortality
- Tumour shrinkage occurs in a high proportion of patients treated with somatostatin analogues
- Primary medical therapy with somatostatin analogues may be effective for a group of patients with either micro- or macroadenomas

dimerisation of GH receptors and a further eight within the region responsible for receptor binding which give the antagonist a kinetic advantage over native GH, enabling saturation of all GHRs. Because pegvisomant inhibits GH activity and not GH secretion, serum GH concentrations are not a valid marker for treatment efficacy; serum IGF-I concentrations are the only biochemical markers of efficacy in patients treated with pegvisomant. Pegvisomant makes no attempt to control pituitary tumour growth. Its efficacy is not dependent upon the characteristics of the tumour, such as size, and thus feasibility of surgical removal, radiosensitivity, or dopamine and somatostatin receptor density. It is a competitive receptor antagonist and potentially should be effective in all patients, regardless of the nature of the pituitary adenoma.

The first major study of pegvisomant in the treatment of acromegaly reported on 112 patients treated for 12 weeks. Normalisation of IGF-I was reported in up to 89% of patients. In a more extensive study of 90 patients treated for over 12 months, normal serum IGF-I concentrations were achieved in 97% of patients.[7] Significant improvements in overall well-being, symptom scores for perspiration, fatigue and paraesthesiae, and improvements in soft tissue swelling were noted. Metabolic parameters also improved with decreases in fasting insulin and glucose concentrations. The risk of any treatment of acromegaly that does not attempt to control tumour size is that there will be a gradual increase in tumour size or that the blockade of GH action could induce negative feedback mechanisms to stimulate tumour expansion, analogous to Nelson's syndrome following bilateral adrenalectomy in Cushing disease. There is thus a need for high quality IGF-I assays with robust age- and gender-matched reference ranges and careful follow-up of all patients with regular imaging of tumour size.

Adult growth hormone deficiency

Adult growth hormone deficiency (GHD) can result from onset during childhood or adulthood. The most common type of deficiency with onset in childhood is idiopathic; the commonest cause of acquired GHD in adults is a pituitary adenoma and its treatment (surgery or radiotherapy). GH deficiency may occur in isolation or in association with other pituitary hormone deficiencies. GH is usually the first anterior pituitary hormone to be lost in patients with large non-functioning adenomas following surgery or radiotherapy. Unlike the poor growth associated with GH deficiency in childhood, none of the features of GH deficiency in adults is pathognomonic for the condition. It is necessary therefore to define GH deficiency in adults using biochemical criteria, which is now generally agreed to be a peak GH response of less than 3 ug/l during an insulin tolerance test in patients with existing hypothalamo-pituitary disease or who received GH during childhood.

In adult life, GHD is associated with significant changes in biological variables, such as body composition, physical performance, insulin status, bone mineral density (BMD), lipid profile and Quality of Life (QoL) measures.[8] A range of studies have documented increased cardiovascular risk factors in patients

Key Points

The increased mortality associated with acromegaly can be reversed by optimal treatment

Effective inhibitors of GH secretion and action have been developed as major adjuncts to the traditional approaches of surgery and radiotherapy for acromegaly

Adult GH deficiency is associated with significant changes in biological variables which are improved by replacement with GH

There appears to be an association between height and cancer risk, an effect that may be mediated by IGFs

These observations indicate that there is an optimal level of circulating GH and IGF-I needed to maintain normal health

with hypopituitarism, including visceral obesity, glucose intolerance, insulin resistance, hyperlipidaemia, vascular endothelial dysfunction, and, in some studies, hypertension. These risk factors have been attributed to growth hormone deficiency. Decreased BMD has been reported in GHD and hypopituitary patients have an increased risk of fracture; this situation is complicated by the presence of gonadal steroid deficiency and the appropriateness of glucocorticoid therapy. Adults with GHD have a lower perceived QoL and higher levels of psychological distress than healthy controls. Characteristic features are depressed mood, increased anxiety, lack of energy, social isolation and impaired well-being. Replacement therapy with GH has shown beneficial effects on body composition (reducing fat mass and increasing muscle mass), bone quality, cardiovascular risk factors and QoL, but there are no data on the effects of growth hormone treatment on mortality.

Hypopituitarism, GHD and mortality

Four retrospective studies have examined mortality in patients with hypopituitarism and all have confirmed increased mortality compared with age-matched controls. A prospective study examined total and specific-cause mortality in more than 1,000 patients with a diagnosis of hypopituitarism, and attempted to identify factors contributing to the excess mortality.[9] The West Midlands Hypopituitary Database was established in 1990 and comprises patients with underlying pituitary disease from 16 referral centres across the West Midlands region in the UK (population about 5.5 million, representing about 10% of the UK population).

The number of observed deaths was 181 compared with the 96.7 expected (SMR 1.87). Univariate analysis indicated that mortality was higher in women (2.29) than men (1.57), in younger patients, in patients with an underlying diagnosis of craniopharyngioma (9.28), and in the 353 patients treated with radiotherapy (2.32 vs 1.66). Excess mortality was attributed to cardiovascular, respiratory and cerebrovascular causes, with a marked increase in cerebrovascular deaths in patients who underwent radiotherapy (4.36 vs 1.64). There was no effect of

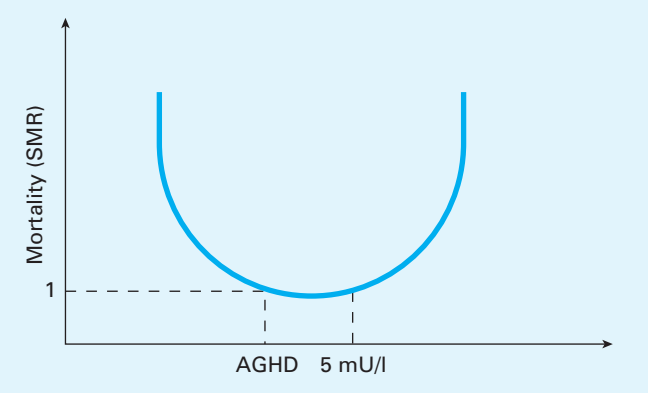

Fig 1. U-shaped curve. Clinical observations and literature reports suggest that there is an optimal level of circulating GH and IGF-I required to maintain normal health. Excess levels of GH and GH deficiency appear to be associated with an increase in mortality. AGHD = adult growth hormone deficiency; SMR = standardised mortality ratio.

hormonal deficiency on mortality, except for gonadotropin deficiency which, if untreated was associated with excess mortality. Adult growth hormone deficiency has been implicated as having a vital role in mediating increased vascular mortality in hypopituitarism. Although growth hormone replacement is known to have beneficial effects, there are no data on the effects of growth hormone treatment on mortality. Risks of radiotherapy must be balanced against the undoubted efficacy of treatment in reducing recurrence rate of non-functioning pituitary tumours.

Height, leg length, cancer risk and IGF-I

A large body of literature supports the existence of an association between height and cancer risk.[10] Taller individuals appear to be at a 20–60% increased risk of a range of cancers. Associations have been reported for a range of cancers particularly for breast, prostate, colorectal, thyroid and haematopoietic. The component of height most often associated with increased risk is leg length. Leg length is a marker for growth before puberty. The three main environmental factors influencing childhood growth are nutrition, ill health and psychological well-being. Nutritional status before puberty may be most important. Height per se clearly does not cause cancer but simply acts as a biological marker for some other exposure. Confounding factors such as social class, smoking and body mass index (BMI) have been ruled out. A proposed link is to circulating levels of growth hormones and factors. IGFs have been implicated as having a role in the development of cancer, and height may act as a marker for levels of these growth factors. Cross-sectional studies of children demonstrate that IGF-I levels are associated with stature. Recent research has demonstrated that raised levels of IGF-I or low levels of IGF-BP3 are associated with increased risks of prostate cancer, pre-menopausal breast cancer and colorectal cancer. It is interesting that height-cancer associations are found for these same cancers. The biological link with IGF-I includes protection of damaged cells from apoptosis and thus increasing potential to become cancerous, potent stimulation of cell turnover, and amplification of effects of DNA-damaging agents. Finally, there is considerable evidence for the important role of nutrition in regulating IGF-I.

IGF-I and heart failure

Several experimental investigations have emphasised the favourable effects of IGF-I on left ventricular remodelling, partly through its anti-apoptotic effects. A community-based study followed 717 elderly people without known myocardial or heart failure for 5 to 9 years.[11] Subjects with higher levels of IGF-I developed heart failure less often than those with lower levels. If confirmed, these data suggest that maintenance of optimal levels of IGF-I in the elderly may reduce the risk of heart failure.

These extensive clinical observations and literature reports suggest that there is an optimal level of circulating GH and IGF-I required to maintain normal health. Excess levels of GH and GH deficiency appear to be associated with an increase in mortality (U-shaped curve; Fig 1); restoration of GH levels to normal reduces mortality risk to that of the normal population.

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