Review

Growth hormone therapy for protein catabolism

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Introduction

Protein catabolism is a common problem in many different patient groups (Table 1). Loss of body protein results in muscle weakness, impaired wound healing, compromised mucosal integrity and a defective immune response. Protein catabolism is accelerated in a variety of conditions, including sepsis, burns, trauma, surgery and organ failure, and when prolonged results in an increase in morbidity and mortality. Nutritional status is an important predictor of outcome in the critically ill and those with cancer and organ failure. Thus, much attention has focused on the use of anabolic therapies, such as growth hormone (GH), to improve the nutritional state of the catabolic patient.

Growth hormone has a well-defined role in promoting childhood growth. Despite a reduction in GH secretion in adulthood, it is now recognized that GH secretion also plays an important role in maintaining normal adult body composition. The actions of GH are predominantly anabolic and the GH-deficient adult has decreased lean body mass and reduced energy levels and exercise capacity. GH treatment reverses these changes and is associated with an improvement in quality of life. The metabolic actions of GH, to promote protein synthesis at the expense of lipolysis (Table 2), make it an attractive anabolic therapy for the patient with protein catabolism. These patients are partially insensitive or resistant to the actions of GH; however, a number of trials using supraphysiological doses of GH have demonstrated improved nutritional status during GH therapy. In this review we discuss the basis for the acquired GH resistance found in catabolic patients and the potential for using GH as an anabolic treatment.

Table 1 Conditions associated with protein catabolism and acquired growth hormone resistance

<table>
<thead>
<tr>
<th>Trauma</th>
<th>Fractures</th>
<th>Burns</th>
<th>Surgical stress</th>
<th>Abdominal surgery</th>
<th>Sepsis</th>
<th>AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Sepsis</td>
<td>Kidney</td>
<td>Fractures</td>
<td>Burns</td>
<td>Sepsis</td>
<td>AIDS</td>
</tr>
<tr>
<td>Organ failure</td>
<td>Kidney</td>
<td>Liver</td>
<td>Fractures</td>
<td>Burns</td>
<td>Sepsis</td>
<td>AIDS</td>
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<tr>
<td>Cancer</td>
<td>Cachexia</td>
<td>Chemotherapy</td>
<td>Fractures</td>
<td>Burns</td>
<td>Sepsis</td>
<td>AIDS</td>
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<tr>
<td>Malnutrition</td>
<td>Anorexia</td>
<td>Short-bowel syndrome</td>
<td>Fractures</td>
<td>Burns</td>
<td>Sepsis</td>
<td>AIDS</td>
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<tr>
<td>Drugs</td>
<td>Malabsorption</td>
<td>Glucocorticoids</td>
<td>Fractures</td>
<td>Burns</td>
<td>Sepsis</td>
<td>AIDS</td>
</tr>
</tbody>
</table>

Table 2 Metabolic effects of GH and IGF-I alone and in combination

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GH</th>
<th>IGF-I</th>
<th>GH and IGF-I</th>
</tr>
</thead>
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<tr>
<td>GH levels</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>IGF-I levels</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>IGFBP-3 levels</td>
<td>↓</td>
<td>or ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Glucose</td>
<td>↓ or ↑</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Lipolysis</td>
<td>↑</td>
<td>→</td>
<td>↑</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td>→ or ↑</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Protein breakdown</td>
<td>↓ or ↑</td>
<td>→</td>
<td></td>
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<tr>
<td>Net protein balance</td>
<td>→</td>
<td>or ↑</td>
<td>↑</td>
</tr>
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Acquired GH resistance

GH is released in a pulsatile fashion from the anterior pituitary, with pulses every 3 to 4 h and maximal secretion occurring at night. Although GH secretion is greatest during puberty, secretion continues throughout life. GH binds to a single high-affinity receptor which is a member of the type 1 cytokine receptor superfamily, and is found in most tissues including muscle and fat, with the greatest number of receptors on the liver. Approximately 40% of GH is bound in the circulation by a high-affinity binding protein which is identical to the extracellular domain of the GH receptor. GH has diverse metabolic actions (Table 2), including the induction of IGF-I which mediates many of the anabolic actions of GH. The majority of circulating IGF-I is derived from the liver, but the contribution of paracrine and endocrine IGF-I in mediating the actions of GH has yet to be established. IGF-I circulates bound to a number of binding proteins (IGFBPs), the most important of which are IGFBP-1 to 3. IGFBP-3 binds approximately 85% of IGF-I and acts as a circulating store. Both GH and IGF-I may feed back to reduce the production of GH (Figure 1).

Changes occur throughout the GH/IGF-I axis in the catabolic patient. Fasting and most catabolic states are associated with an increase in overall GH secretion, decreased circulating IGF-I levels, and a reduced IGF-I response to GH. These changes can be summarized as acquired GH resistance, and the sicker the patient, such as those who are septic, the more severe the resistance. The mechanisms inducing these changes are complex and differ between disease states; the contribution of nutritional status has yet to be established. In animal models, fasting and catabolic states are associated with reduced GH receptor binding, reduced IGF-I gene expression and changes in IGF binding proteins. In the human, GH binding protein is low, which may reflect GH receptor number, and again there are distinct changes in IGF binding proteins with a fall in IGFBP-3 levels and the production of a protease which reduces the affinity of IGFBP-3 for IGF-I.

The changes in IGF-I levels during catabolic illness are open to two opposing interpretations. The low IGF-I levels may represent an adaptive response; switching off the anabolic actions of GH at a time of 'stress'. Alternatively, it may be that IGF-I levels are low due to liberation of IGF-I to the tissues to counteract catabolism. Whichever interpretation is correct, it is clear from the following studies that treatment with pharmacological doses of GH can partially overcome GH resistance in some conditions. It should be emphasized that high doses of GH are needed—up to 10 times the usual replacement dose in adults. Comparison of dose regimens between studies is complicated by the diversity with which dose regimens are reported. As a rough guide, 1 mg GH = 2.5 IU. Thus for an average 70 kg human 10 IU/m²/day = 0.25 IU/kg/day = 0.1 mg/kg/day and the replacement dose of GH used in adults is of the order 1–2 IU/m²/day. In this review we have translated all doses into IU/m²/day.

GH therapy in the catabolic patient

Post-operative

Abdominal surgery results in a period of fasting and marked protein catabolism. In an early study of patients who had undergone major gastrointestinal surgery, GH (10 IU/m²/day) given for 6 days reduced cumulative urinary nitrogen excretion and increased fat oxidation, resting energy expenditure, and IGF-I and glucose levels. When an intravenous feeding regime was added to the GH treatment, nitrogen balance became positive. In a similar patient group, GH (6 IU/m²/day) increased protein synthesis. Muscle biopsies from these patients after surgery showed evidence of increased protein synthesis in those treated with GH. A large, prospective, placebo-controlled, randomized trial of the use of GH after elective cholecystectomy reported spectacular results. GH treatment (8 IU/day, about 5.2 IU/m²/day) for 8 days post-operatively with hypocaloric parenteral nutrition led to positive nitrogen balance from day zero, improved cutaneous cell-mediated immunity, reduced wound infections (from

Figure 1. The growth hormone/insulin-like growth factor-I axis. GHBP, growth-hormone-binding protein; IGFBP, insulin-like-growth-factor binding protein.
Thermal injury leads to a catabolic state with significant morbidity and mortality. Numerous studies have reported the use of GH in thermal injury. 10 IU of GH daily for 7 days decreased urinary nitrogen loss in patients with mean burn size of 54% total body surface area. 12 In contrast, no change in nitrogen balance occurred in patients with 20% burns who received enteral nutrition and a stepped GH dose; 3 IU/m²/day, 6 IU/m²/day and placebo for 5 days. 13 These negative findings may relate to the use of a relatively low GH dose and a higher dose (20 IU/m²/day) was associated with improved whole-body and leg protein synthesis. 14

A number of studies have demonstrated clinical benefits with GH treatment, in addition to the improved metabolic end-points described above. Forty severely burned children were treated with 10–20 IU/m²/day of GH in a double-blind, controlled study. 15 Donor-site healing times decreased with the higher GH dose, and length of admission was shortened from 0.8 to 0.54 days/% total body surface area of burn; for a child with 60% burns this would translate to a reduction from 46 to 32 days. The effects of GH were studied in burned adults who had survived 7 days post-burn and had an expected mortality of over 50%. 16 The patients with slower wound healing were allocated to GH treatment at a mean dose of 11 IU/m²/day. The results were encouraging, showing 11% mortality with GH vs. 37% without, and GH use was an independent predictor of survival. Donor-site healing was faster with GH, despite the allocation of slow-healing wounds to the GH group.

Preliminary metabolic studies of the anabolic effects of IGF-I on burns patients have been reported. IGF-I as a 3-day infusion (20 μg/kg/h) decreased protein oxidation and increased glucose uptake. 17 This was an open, uncontrolled study but beneficial effects were seen without adverse events.

**Glucocorticoid-induced catabolism**

High-dose glucocorticoid treatment is complicated by protein catabolism. This was studied in a group of normal adults treated with a 7 day course of high-dose prednisone (0.8 mg/kg/day) with or without GH (10 IU/m²/day). 18 Prednisone treatment produced negative protein balance, which was abolished by the addition of GH. Leucine kinetics indicated that GH increased the rate of protein synthesis whereas prednisone increased proteolysis. In four patients treated with long-term prednisone for lung disease, a 7-day course of GH (12.5 IU/m²/day) improved whole-body nitrogen balance by increasing protein synthesis. 19 Both of the above two studies noted insulin resistance in the GH-treated groups; this is unsurprising in view of the well-recognized anti-insulin actions of GH, but is of particular relevance in patients taking glucocorticoids. IGF-I rather than GH has been used in an attempt to avoid diabetogenic side-effects whilst preserving the anabolic benefits. Fifteen healthy volunteers received prednisone (0.8 mg/kg/day) and either IGF-I (100 μg/kg twice daily) or placebo for 5 days. 20 IGF-I treatment increased protein synthesis and nitrogen retention without affecting protein breakdown. Glucose concentrations were unchanged with IGF-I treatment despite markedly reduced insulin concentrations.

**Human immunodeficiency virus (HIV) infection**

Wasting is a prominent feature of the acquired immunodeficiency syndrome (AIDS) and is not reversed by nutritional supplementation. 21 Six wasted HIV-positive men were treated with GH at 10 IU/m²/day for 7 days. 22 Over this short period, they gained weight, retained nitrogen and increased resting energy consumption—probably using fat as substrate and sparing protein oxidation. However, a
single GH injection leads to significantly less IGF-I production in men with AIDS than in healthy men,23 and to bypass this resistance IGF-I has been used. Two doses of IGF-I (4 or 12 μg/kg/h) were used for 12 h daily over 10 days. The results were disappointing, again possibly due to IGF-I feedback reducing GH production. A theoretical way around this problem is to use combination therapy with GH and IGF-I, and early results have been favourable.24 A 4-week study randomized 16 patients with AIDS to either placebo or combined GH and IGF-I therapy; positive nitrogen and potassium balance and a 2.5% increase in lean body mass resulted from combination therapy.

Cancer
Cachexia is a consequence of many cancers; it is partly due to malnutrition, but even when total parenteral nutrition is used the response may be poor, suggesting that metabolic factors are also involved.25 GH has been used with mixed results in an attempt to reverse this catabolic process. Twenty-eight patients with solid tumours received either GH (10–20 IU/m²/day) or placebo for 3 days.26 GH increased both protein synthesis and breakdown with synthesis predominating, leading to improved net protein balance. GH (12.5 IU/m²/day) for 3 days in patients with incurable cancer increased GH, IGF-I and insulin concentrations whilst urinary nitrogen excretion decreased.27 When the subjects were analysed according to nutritional status, improvements in nitrogen economy were predominantly seen in the patients who were within 90% of their ideal body weight. It was concluded that the more malnourished cancer patients were the most resistant to the anabolic effects of GH.

Overall, GH may be useful as a palliative treatment in cancer patients although higher doses may be needed in severely malnourished individuals. GH excess (acromegaly) is associated with an increased risk of neoplasia, particularly colonic carcinoma, and its use in patients with cancer could theoretically promote tumour growth, although this has not been seen following GH treatment of children with cancer.28

Pulmonary disease
Patients with severe chronic obstructive airways disease (COAD) are often malnourished, which is associated with a poorer prognosis and may contribute to respiratory muscle weakness.29 An uncontrolled pilot study examined the effect of 3 weeks GH treatment (5 IU/m²/day) in seven patients with COAD who were below 90% of their ideal weight.30 Nitrogen balance improved in all subjects and a sustained weight gain of 2.03 kg occurred. There was a significant 27% increase in maximal inspiratory pressure, suggesting improved respiratory muscle function. A second study used GH as an adjunct to total parenteral nutrition (TPN) in six malnourished patients with COAD.31 The patients received 12 days of TPN and GH at two doses—3 IU/m²/day on days 8–11 and then 6 IU/m²/day on days 12–15. GH treatment led to doubling of IGF-I concentrations, positive nitrogen balance, increased fat oxidation and increased resting energy expenditure. In contrast to the previous study, no significant changes were seen in respiratory function.

The very long clinical course of many pulmonary diseases may prohibit GH use on cost grounds alone. Short courses of GH may have a role to cover periods of increased catabolism during intercurrent infections or concomitant glucocorticoid treatment.

Sepsis
Patients with sepsis have received GH as part of larger heterogeneous groups in a number of studies, but relatively few studies have focused exclusively on the use of GH in sepsis. A study using a massive dose of GH (60 IU/m²/day) for 5 days was limited by the death of 9/20 patients.32 However, an increase in IGF-I and a decrease in the urea production rate (as an indirect measure of decreased protein breakdown) were seen. Similarly, 20 septic patients received 10 IU/m²/day GH or placebo for 3 days and during GH treatment nitrogen production was reduced.33

Trauma
Nitrogen wasting following trauma has been recognized since the work of Cuthbertson in 1931, and a number of studies have examined the role of GH in reversing this process. Twenty victims of multiple trauma receiving total parenteral nutrition (TPN) were randomized to receive a 7-day course of 15 IU/m²/day GH or placebo.34 Metabolic studies, before and after treatment, revealed that GH reduced daily nitrogen losses from 121 mg/kg/day to 41 mg/kg/day, and increased calculated protein synthesis rates by 28%. The same group also reported that in the patients treated with GH, there was a reversal of the hypoaminoacidaemia seen following trauma,35 and IGFBP-3 levels were significantly increased.36 In contrast, use of a higher dose of GH (20 IU/m²/ day) in more severely catabolic patients (240–260 mg/kg/day nitrogen loss) did not produce a nitrogen-sparing effect, although IGF-I, albumin and transferrin levels increased.37
Renal failure

Growth failure occurs in children with renal failure and GH therapy promotes linear growth in these children. Therefore, an anabolic effect of GH may be anticipated in adult patients with renal failure. Adult patients given GH (12.5–25.0 IU post-dialysis) for 2 weeks had a reduction in urea generation and protein catabolic rate, and increased IGF-I levels. Similarly, GH (7 days of 12.5 IU/day) decreased nitrogen excretion and protein catabolic rate in patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. There were no side-effects, although glucose levels rose. The same dose of GH was used for 6 weeks in seven malnourished patients who were already receiving parenteral nutrition between haemodialysis sessions. A rise in albumin and IGF-I occurred accompanied by a fall in the protein catabolic rate. Initial studies using IGF-I as an anabolic agent in renal failure have shown a reduced IGF-I half-life and resistance to its effects compared to normal subjects.

Short-bowel syndrome

Patients whose bowel can no longer adequately absorb nutrients receive parenteral nutrition at great expense and inconvenience. In a group of patients with severe short-bowel syndrome who were dependent on TPN, GH was used either alone or in combination with a glutamine-enriched or high carbohydrate diet for a 3-week period with the aim of maximizing residual bowel function. The combination of GH (14 IU/m²/day), glutamine and a high carbohydrate diet produced a 29% increase in protein absorption, 36% increase in carbohydrate absorption and no change in fat absorption. Sodium and water absorption also increased with the net effect of stool output falling from 1.8 kg/day to 1.3 kg/day. The same investigators then proceeded to use this combination in 47 patients for a 28-day period followed by discharge on glutamine and a high carbohydrate diet alone. At an average follow-up of one year, 40% no longer required TPN, and 40% had reduced their TPN requirements.

Cardiac failure

Cardiac hypertrophy is commonly seen in patients with acromegaly who are exposed to chronic high GH concentrations and this provided the rationale for the use of GH in patients with idiopathic dilated cardiomyopathy. Seven patients received GH (2 IU/day) for 3 months in an open, uncontrolled study. The results were encouraging—improvements occurred in left ventricular ejection fraction, left ventricular muscle mass, exercise capacity, symptomatology and quality of life. Controlled and blinded studies are now required to confirm these observations and to explore the duration of benefit.

Summary

GH and IGF-I have shown remarkable consistency of effect in a wide range of catabolic conditions. Doses of around 10 IU/m²/day of GH and 80 μg/kg/day of IGF-I over short periods of time can improve net protein synthesis and preserve lean body mass. Most studies have reported metabolic endpoints, but favourable clinical effects have included decreased hospital stay and mortality in burns, improved respiratory muscle function in COAD, preserved grip strength post-operatively, and improvements in cardiac and bowel failure.

Adverse effects of GH treatment are uncommon and usually related to glycaemic control. GH and IGF-I have differential effects on insulin concentrations—increasing or decreasing concentrations, respectively. The hypoglycaemic effects of IGF-I are dependent on route of administration and are avoided by subcutaneous delivery. Occasional patients have needed to discontinue GH treatment due to hyperglycaemia, although the anabolic action of GH may be partially mediated by increased insulin levels.

The co-administration of GH and IGF-I has theoretical advantages by both increasing IGF binding-protein concentrations and balancing glycaemic control. An initial study with combination therapy in calorically-restricted volunteers has shown anabolic effects greater than with either agent alone. This approach requires further study in catabolic patients. There is a need for large, well-designed trials with clinical rather than purely metabolic end-points, and some of these are already underway. Should these studies confirm the early findings, financial considerations will become paramount, although it remains possible that treatment may be self-financing if lengths of hospital admissions are shortened.

Acknowledgements

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References


