

## REVIEW

## Justified and unjustified use of growth hormone

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Growth hormone (GH) replacement therapy for children and adults with proven GH deficiency due to a pituitary disorder has become an accepted therapy with proven efficacy. GH is increasingly suggested, however, as a potential treatment for frailty, osteoporosis, morbid obesity, cardiac failure, and various catabolic conditions. However, the available placebo controlled studies have not reported many significant beneficial effects, and it might even be dangerous to use excessive GH dosages in conditions in which the body has just decided to decrease GH actions. GH can indeed induce changes in body composition that are considered to be advantageous to GH deficient and non-GH deficient subjects. In contrast to GH replacement therapy in GH deficient subjects, however, excessive GH action due to GH misuse seems to be ineffective in improving muscle power. Moreover, there are no available study data to indicate that the use of GH for non-GH deficient subjects should be advocated, especially as animal data suggest that lower GH levels are positively correlated with longevity.

dramatically, with a corresponding increase in quality of life.<sup>1,2</sup> There is also a place for GH in the management of children with other conditions associated with GH deficiency or lack of GH action, such as Turner's syndrome and chronic renal insufficiency.<sup>1,2</sup> Treatment with GH in combination with low dose oestrogens can result in a significant increase in adult height in girls with Turner's syndrome, even if they start the treatment at a relatively late age.<sup>3</sup> Children with hypochondroplasia having severe short stature and disproportion of the body segments owing to the mutation Asn540Lys respond to GH therapy with an increase in spinal length, and in combination with a surgical leg lengthening procedure it is possible for some patients even to achieve an adult height within the normal range.<sup>6</sup> At present, there is no way of predicting which patient with hypochondroplasia will undergo a normal pubertal growth spurt, therefore, all such patients should be monitored during childhood and GH treatment should be only be given to those patients who fail to develop a growth spurt at puberty.<sup>6</sup>

Severe growth retardation can also be observed in children treated with glucocorticoids for conditions such as systemic forms of juvenile chronic arthritis. Studies suggest that GH may partially counteract such adverse effects of glucocorticoids on growth and metabolism in patients with chronic inflammatory diseases, but more long term controlled studies are needed to determine the risks and benefits of GH therapy in this subgroup of GH deficient patients.<sup>7</sup>

The therapeutic use of growth hormone (GH) as replacement in GH deficient adults has been shown to produce a beneficial effect on body composition, serum lipid concentrations, bone mineral density, muscle strength, and exercise endurance. It remains to be determined, however, whether or not chronic GH replacement therapy will indeed have beneficial effects on morbidity and mortality. The benefits of chronic use of GH for other potential indications such as ageing, catabolism, diabetes, and morbid obesity is far from clear.

However, GH is also used for conditions in which no intrinsic disease is present, for example, cosmetic use for slight adiposity and sports use to improve performance. Obviously, the use of GH for these goals is not promoted by the medical profession, and indeed can have significant and potentially dangerous side effects. In the following sections, an overview is given of the accepted indication for use of daily GH injections, as well as an overview on the misuse of this powerful peptide hormone.

## JUSTIFIED USE OF GROWTH HORMONE In children

In paediatrics, there is no doubt that the use of recombinant human GH for short stature has been very successful. The improved final height for these children has been increased

## In adults

The beneficial effects of chronic replacement therapy in GH deficient adult patients have been addressed by many studies. Because of the existence of several large databases, we are able to show beneficial improvements with GH therapy not only in quality of life, cardiac performance, and anthropomorphic parameters such as body composition, but also on many biochemical parameters such as lipid patterns, coagulation, and glucose metabolism.<sup>3,8-16</sup>

Elderly patients with end stage renal disease, who often have protein and/or caloric malnutrition that severely affects general wellbeing and mortality, also benefit from GH therapy. It was reported that GH treatment increased serum insulin-like growth factor-1 (IGF-1), fat free mass, and serum concentration of albumin compared with placebo, while the number of patients with hypoalbuminaemia was reduced by a factor of three in the GH treated group.<sup>3</sup> A

**Abbreviations:** GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP, insulin-like growth factor binding protein

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Growth hormone treatment is recommended for children with proven clinical diagnosis of GH deficiency and for children with Turner's syndrome. It is also recommended for pre-pubertal children with chronic renal failure. (Source: National Institute for Clinical Excellence; *Technology Appraisal Guidance No 42.*)

Growth hormone treatment is recommended for adults with severe growth hormone deficiency, provided that they have a perceived impairment in quality of life and that they are already receiving treatment for any other pituitary hormone deficiencies as required. (Source: National Institute for Clinical Excellence; *Technology Appraisal Guidance No 64.*)

Belgian study reported that GH treatment had a positive effect in short children with renal allografts, even if started in late puberty. However, in the presence of underlying chronic rejection, GH treatment needed careful monitoring to minimise the risk of graft loss.<sup>4</sup>

Whether or not GH treatment can improve the metabolic state of adult patients with non-pituitary disorders that are characterised by a temporary GH deficient state, for example patients with critical diseases and in perioperative situations, has not been well addressed, although some reports observed dangerous deterioration in patients and increase in morbidity and mortality.<sup>17</sup> However, there are also reports of beneficial effects of supportive GH treatments, for instance, the observation that perioperative GH treatment of younger patients undergoing major abdominal surgery preserved limb lean tissue mass, increased postoperative muscular strength, and reduced long term postoperative fatigue.<sup>18</sup> It was also reported that perioperative GH administration may result in improved cardiac performance during aortic surgery.<sup>19</sup> Studies performed on accidental hip fracture patients were promising but could not be reconfirmed.<sup>20</sup>

Finally, high dose GH treatment increases body weight, lean body mass, and treadmill work output, and appears to be a safe and potentially effective therapy in patients with HIV associated wasting.<sup>21</sup>

### UNJUSTIFIED USE OF GROWTH HORMONE

GH is without doubt a powerful anabolic hormone that affects all body systems and plays an important role in muscle growth. Serum GH levels are variable and are dependent on many factors, such as age, sex, body composition, and exercise itself. The improvements in muscle strength obtained by resistance exercise training in young men or in healthy older men cannot be further enhanced by additional administration of GH. The increases in fat-free mass that can be observed in athletes who use GH for performance enhancement purposes are not due to accretion of contractile protein, but rather to fluid retention or accumulation of connective tissue.<sup>22</sup> In experienced weightlifters and in power athletes, the skeletal muscle protein dynamics are not decreased by short term administration of GH. A placebo controlled study on the efficacy of GH treatment in improving muscle power in power athletes reported no increase in maximum strength during concentric contraction of the biceps and quadriceps muscles, although levels of IGF-1 were doubled.<sup>22</sup> On the other hand, the increased lean mass and improved muscle performance seen in healthy adolescents does not occur in adolescents with GH deficiency, which suggests that GH is of importance for the maturation of lean mass and muscle strength in adolescents and young adults.<sup>23-25</sup>

Despite its potentially serious side effects and lack of evidence for its efficacy, the use of GH for performance enhancement purposes has increased, and the temptation to use GH to improve athletic performance or to enhance appearance is very seductive to adolescents.<sup>22 26-28</sup>

After the summer Olympic Games in Sydney, there were a number of articles in the press that suggested that GH is now

one of the most popular potentially performance enhancing drugs used by athletes. The lack of an official test for GH misuse, together with the widespread rumours of its tremendous beneficial effects seem to make this compound attractive for athletes. Promising methods for detection of GH misuse have been developed, but have yet to be sufficiently well validated to be ready for introduction into competitive sport.<sup>29</sup> There is a further complication; an Italian athlete who won a gold medal at the Sydney Olympic Games was accused of using performance enhancing drugs after the finding of high levels of plasma GH before the Games. Following the accusation, she was studied under stressed and unstressed conditions. Under stressed conditions, GH levels were above the normal range in all blood samples, whereas IGF-1 was normal. Under unstressed conditions, GH progressively returned to accepted normal levels and again IGF-1 was normal. Therefore, the normal range for GH in athletes might have to be reconsidered if used for detection of performance enhancers, as athletes are by definition subject to stress and thus apparently, to wide variations in GH levels.<sup>30</sup>

Interestingly, Coschigano and co-workers observed that mice homozygous for the disruption of the GH receptor lived significantly longer.<sup>31 32</sup> The extension of lifespan in these animals was very large (up to 65%), reproducible, and not limited to any particular genetic background or husbandry conditions. These findings suggest that GH may have an important role in the determination of lifespan. Studies using Ames, Snell, and GH receptor knockout models have concluded that decreased GH and IGF-1 levels are closely correlated with an increased life span.<sup>32-35</sup> Additionally, studies indicating that taller people are more productive than shorter have ignored a wide range of evidence that shorter people live longer.<sup>32 36-44</sup>

Despite this, the assumption that hormonal therapy is a potential "fountain of youth" seems logical, as the diminished secretion of GH is responsible in part for the decrease in lean body mass, the expansion of adipose tissue mass, and the thinning of the skin that occur in old age.<sup>45</sup> At present, however, the effects of GH in healthy elderly men have been studied in only a few randomised placebo controlled trials,<sup>46-48</sup> and the effects of GH therapy on muscle strength, on metabolic and sexual function, and on skeletal homeostasis were not consistent.<sup>46-49</sup> When GH therapy is applied in the elderly as a potential fountain of youth, it must be realised that not only the GH concentration, but levels of IGF-1, insulin, and insulin-like growth factor binding protein (IGFBP)-3 change.<sup>49-55</sup> This is especially important, as some data indicate that high serum IGF-1 levels in combination

There is no justification for the use of growth hormone in non-GH deficient subjects. This includes use in ageing, but otherwise healthy subjects, and the misuse of GH in subjects in an attempt to improve muscle mass and (or) strength. The use of GH in severely diseased patients in an intensive care setting has been shown to be dangerous.

with low serum IGFBP-3 concentrations might increase the risk of cancer.<sup>53-56</sup>

## CONCLUSIONS

Growth hormone replacement therapy for children and adults with proven GH deficiency due to a pituitary disorder has become an accepted therapy with proven efficacy. In children with short stature due to other conditions, GH therapy is also often successful. In GH deficient adults with increased body fat and reduced muscle mass, and consequently reduced strength and exercise tolerance, GH therapy has also proven to be a successful method to improve quality of life, and to reverse many anomalies. GH has also been considered for the therapeutic treatment of frailty, osteoporosis, morbid obesity, cardiac failure, and various acute and chronic catabolic conditions. However, the available placebo controlled studies have not reported many significant beneficial effects. Furthermore, after a report on an increase in mortality in critically ill patients receiving large doses of GH, the official use of GH in non-GH deficient adult patients has been reduced to almost zero.

GH can induce changes in body composition that are considered to be advantageous to ageing subjects and sportsmen. However, there are no results that indicate that the use of GH for these individuals should be advocated, because of the lack of any proven efficacy for improved performance. Moreover, animal data suggest that higher GH levels are negatively correlated with longevity.

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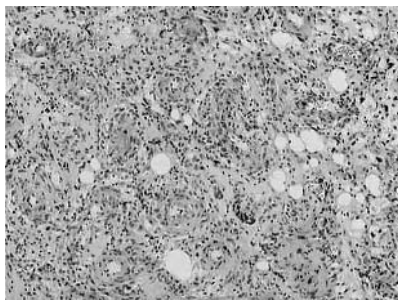
## IMAGES IN MEDICINE.....

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### Tuberous sclerosis associated with giant bilateral bleeding angiomyolipomas



**Figure 1** Abdominal computed tomogram showing giant bilateral renal masses consisting predominantly of fat tissue, and a retroperitoneal haematoma.



**Figure 2** Histological specimen showing a typical renal angiomyolipoma (haematoxylin and eosin  $\times$  200).



**Figure 3** Abdominal computed tomogram showing a giant bleeding right renal angiomyolipoma.

**T**uberous sclerosis is a systemic disorder characterised by benign hamartomatous tumours that involve multiple organ systems. Angiomyolipomas are found in about two thirds of the kidneys of patients with tuberous sclerosis at necropsy.<sup>1</sup>

A 29 year old woman with tuberous sclerosis presented with diffuse abdominal pain, gross haematuria, and hypotension. At the age of 22 the patient had been admitted to our hospital with acute upper abdominal pain and gross haematuria. Physical examination had revealed bilateral massive abdominal masses with no tenderness. Computed tomography had confirmed the presence of giant bilateral renal masses with the typical appearance of an angiomyolipoma, and a huge retroperitoneal haematoma extending to the pelvis and the left side of the abdomen (fig 1). After arterial embolisation, left radical nephrectomy was performed. The pathological diagnosis was angiomyolipoma without malignant findings, and the patient was discharged two weeks after the operation (fig 2).

During the latest admission, computed tomography of the abdomen showed a giant right renal angiomyolipoma (fig 3). An attempt for selective arterial embolisation failed, and right radical nephrectomy was performed as the patient was becoming haemodynamically unstable. The patient has been started on haemodialysis, and renal transplantation is planned.

Kidneys can be involved in three different ways in tuberous sclerosis: angiomyolipomas, cystic disease, and renal cell carcinomas.<sup>1</sup> The typical angiomyolipoma is a mixture of smooth muscle, fat, and abnormal blood vessels, the relative proportions of which vary widely.<sup>1</sup> Although angiomyolipomas were previously considered to be hamartomas, they have been recently recognised as clonal neoplasms, and it has been proposed that the perivascular epithelioid cell is the progenitor cell.<sup>2</sup> From the clinical point of view, angiomyolipomas are usually silent, but they can rarely cause life threatening haemorrhage. Patients with tuberous sclerosis and angiomyolipomas greater than 4 cm have a high risk of developing symptoms and may require surgery.<sup>1</sup> Because of its sensitivity in detecting small amounts of fat, computed tomography is the imaging modality of choice, although the typical appearance may be altered in predominantly non-fatty angiomyolipomas or in tumours in which haemorrhage has occurred. Long term follow up results of patients with angiomyolipomas treated with selective arterial embolisation have been reported recently.<sup>3</sup> Selective arterial embolisation seems to be ideal in the case of acute haemorrhage in selected patients with renal angiomyolipoma but its indication, safety, and efficacy require further evaluation.

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