Effects of growth hormone therapy on exercise performance in men

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Although growth hormone is considered to have anabolic benefits and abuse is widespread, there is little evidence that it actually improves exercise performance.

This summer the world’s top athletes will dream of Olympic glory, and for the few who achieve professional success there are notable financial rewards. It is perhaps unsurprising that there is a strong temptation to enhance performance pharmacologically in both professional and amateur sports, and growth hormone (GH) is well recognised as a drug of abuse. This is particularly the case among weightlifters, where it is typically used in combination with androgenic steroids.1

The advocates of GH are keen to highlight its reputation as a potent anabolic compound that improves lean muscle mass, burns fat and enhances physical performance, as well as having the potential to avert age-related decline. These publicised qualities, in combination with the technical difficulties surrounding detection, mean that GH abuse is thought to be widespread. Therefore the question is: ‘Does GH actually improve exercise performance?’

PHYSIOLOGY OF GH SECRETION
Growth hormone has many different functions, but is particularly important during adolescence to achieve final height. It is secreted in pulses from the anterior pituitary gland, where the dominant stimulatory factor for its release is GH-releasing hormone, which is produced by the hypothalamus (Figure 1). A variety of other factors play a less influential role (Box 1).

After achieving peak GH pulses during the adolescent growth spurt, pulse amplitudes gradually decline with age,2 though the

Figure 1. The growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis. Hypothalamic release of GH-releasing hormone (GHRH) triggers release of GH from the anterior pituitary gland into the general circulation. Peripheral GH can have direct effects on target tissues, although most of its actions are mediated through the production of IGF-1 in the liver.
BOX 1. Factors influencing growth hormone (GH) secretion

FACTORS STIMULATING GH RELEASE
- Sleep
- Exercise
- Met-enkephalins (GH-releasing peptides-6, -2)
- Ghrelin
- Androgens
- Acute glucocorticoid exposure
- High protein diet

FACTORS INHIBITING GH RELEASE
- Somatostatin, which is mediated by:
  - GH-releasing hormone
  - Hypoglycaemia
  - Hyperthyroidism/hypothyroidism
  - Chronic glucocorticoid exposure

The frequency of release continues to be increased during sleep and exercise. GH release during exercise is proportional to the level of intensity and activity repetition, with the levels achieved being lower in men than in women.3

Peripheral effects of GH are mediated both directly and indirectly via the production of insulin-like growth factor-1 (IGF-1) in the liver. Measurement of GH and IGF-1 levels is complicated by patterns of release, diet, age, gender and obesity; in addition to the lack of assay standardisation; expertise and experience are therefore essential when interpreting results.4

GH EXCESS AND SUPPLEMENTATION
Prolonged excessive GH secretion leads to acromegaly, which is associated with adverse features typically evolving over several years of exposure (Box 2). In patients with GH deficiency, evidence strongly favours GH replacement to improve body composition and muscle mass.5,6 and to increase exercise and aerobic capacity.5 GH deficiency is also associated with a higher rate of cardiovascular mortality, and replacement may return these rates to baseline in men.5,7

To achieve the appropriate GH replacement, both clinical and IGF-1 responses are monitored and doses are titrated to achieve the desired therapeutic goals. Complications of GH replacement include progression of diabetic retinopathy and potentially growth promotion of malignant tumours, while reports of iatrogenically inducing acromegaly are rare.8

The perception that GH is beneficial in promoting strength and exercise capacity in individuals without GH deficiency extrapolates from the growth effects seen in adolescents; the benefits observed in treatment of GH deficiency, and the proposed anabolic actions. It is assumed, therefore, that similar benefits will be restored in post-adolescent adults. There are relatively few recognised side-effects of GH supplementation in people with a normal GH/IGF-1 axis aside from carpal tunnel syndrome,9 but concerns exist regarding other potentially severe effects such as hypertension or impaired glucose tolerance.

GH AND METABOLISM
GH affects the metabolism of lipids, protein, and glucose. Boluses of GH at physiological doses activate lipolysis and increase circulating non-esterified fatty acids (NEFA).2 This suggests conversion from carbohydrate to lipid energy sources and may generate some of the reductions in total body fat and increased lean body mass observed following prolonged treatment.

The effects on carbohydrate metabolism depend on the duration of GH exposure2 and levels of circulating NEFA. These include increased hepatic glucose production (gluconeogenesis), impaired peripheral glucose uptake, inhibition of hepatic and skeletal muscle glycogen storage,3 promotion of peripheral insulin resistance and impaired glucose tolerance.

Protein synthesis is increased in skeletal muscles through the amplification of intracellular signalling and transcription, with a reduction in protein oxidation following exercise, suggesting a net anabolic effect on whole body protein metabolism.2 Finally, there is inactivation of the renin-angiotensin system leading to salt and water retention, which increases total body water and extracellular fluid.

GH AND SKELETAL MUSCLE
In spite of recognised improvements in strength following replacement in GH deficiency states,5 it is contentious whether these benefits occur in the presence of a normal GH/IGF-1 axis.

In both healthy young adults9 and experienced weightlifters10 treated with GH versus placebo for up to 12 weeks, no additional increase in skeletal muscle size, strength or protein synthesis was observed. However, the perception that GH is beneficial in promoting muscle mass is supported by the consistent finding of increased lean body mass observed following prolonged treatment in healthy adults9 and experienced weightlifters10 treated with GH versus placebo for up to 12 weeks. GH supplementation in patients with GH deficiency states leads to improved body composition, increased muscle mass and improved exercise capacity.11

In summary, GH supplementation seems to have a number of potential therapeutic applications in GH deficiency states and in patients with GH resistance. In healthy adults, GH supplementation does not increase muscle mass or strength. However, in patients with GH deficiency states, GH supplementation leads to improved body composition, increased muscle mass and improved exercise capacity.

BOX 2. Long-term adverse effects of acromegaly

CARDIOVASCULAR EFFECTS
- Insulin resistance (impaired glucose tolerance and diabetes mellitus)
- Hypertension
- Hypertriglyceridaemia
- Increased total body water (weight gain, heart failure)
- Cardiomyopathy

MUSCULOSKELETAL EFFECTS
- Coarse facial features
- Enlarged feet, hands and tongue
- Carpal tunnel syndrome
- Osteoarthritis
- Sleep apnoea
- Prognathism
- Increased interdental spacing

OTHER EFFECTS
- Organomegaly
- Colonic polyps
- Cancer (colon, breast, thyroid)
- Body odour
- Sweating
- Skin thickening

ENDOCRINOLOGY
demonstrated, irrespective of whether this was combined with resistance training. There were, however, significant improvements in lean body mass, suggesting possible enlargement of non-skeletal muscle tissues, such as viscera, ligament and soft tissues.

Furthermore, histological features of skeletal muscle in healthy individuals following GH administration for two weeks have shown increases in tendon and muscle collagen protein synthesis but no influence on skeletal muscle myofibrillar protein synthesis. Greater skeletal muscle collagen content could increase overall muscle mass, and theoretically it is possible that the higher levels of structural collagen could strengthen the tissue matrix, potentially making these tissues more resistant to injury without impacting on strength. However, this is yet to be proved.

In acromegaly there is no associated skeletal muscle hypertrophy, but visceral and soft tissue enlargement are observed. Furthermore, these individuals have muscle weakness and histologically there is evidence of myopathic features, which may impair strength.

**GH AND EXERCISE CAPACITY**

Treatment with GH in patients with GH deficiency produces significant improvements in maximal power output, oxygen uptake and ability to mount an appropriate cardiac rate response, which all act to improve overall exercise capacity. The explanations for improved exercise capacity in treated GH deficiency include normalisation of lipolysis, increased cardiac output, increased extracellular fluid volume and improved sweating ability; the latter potentially leads to improved regulation of core temperature.

However, studies comparing GH treatment with placebo in individuals with a normal GH/IGF-1 axis for up to six weeks have shown no differences in muscle strength, or torso and limb circumference, in spite of measurable increases in lean body mass and total body water. In non-professional athletes treated with GH for four weeks, no improvements in aerobic exercise performance in terms of maximal power output, oxygen uptake or cardiovascular adjustment (as measured by blood pressure, heart rate and electrocardiography) were observed during aerobic bicycle exercise. The lack of physiological benefit from GH treatment was also compounded by increases in circulating glucose, NEFA and lactate, all of which may hamper exercise performance. The lack of positive findings in these studies is unsurprising given that in acromegaly exercise capacity and ventricular ejection fraction improve following suppression of GH release with octreotide treatment.

All the same, there remains some difficulty with study interpretation and cross-study comparison because of the small numbers of subjects, short treatment times and vastly different testing conditions. Finally, these studies do not reflect real-world dosing practices in sports, where there is a perception that benefits of GH are apparent only after the first three months of treatment. This is an important consideration, as rates of skeletal muscle protein turnover are relatively slow, and additional strength benefits in patients with GH deficiency may be observed after two years of GH replacement therapy.

**GH EFFECTS IN AGEING MEN**

Levels of GH attenuate with age and it is recognised that the ageing process carries many similarities with GH deficiency in terms of lean body mass and metabolic changes. This has led to interest as to whether GH supplementation could be used to reverse some of the features of age-related decline. GH supplementation in men aged over 60 years has shown potential benefits in lean body mass and possibly bone mineral density, although results for muscle strength or exercise capacity have been conflicting, particularly as studies have combined GH and testosterone replacement. However, concerns have been raised regarding potential aggravation of heart failure and deteriorations in glucose regulation.

Interestingly, animals with GH and IGF-1 deficiency or resistance have a longer life expectancy, which may be related to mitogenic and anti-apoptosis activity. This suggests that GH may actually accelerate the ageing process.

**CONCLUSIONS**

In the athletic arena, GH doping is considered to be widespread and used in combination with other agents, and regimes vary depending on individual preferences and cost implications. GH is considered to be anabolic because of the extrapolation of effects seen in
adolescence and GH deficiency, net increases in protein synthesis and improvements in lean body mass. However, it must be recognised that the effects of GH administration in adults with a normal GH/IGF-1 axis are not comparable to those in GH deficiency and that the complexity of processes influencing GH release and peripheral actions means that overall performance should be considered as opposed to isolated effects.

Although studies to date have been small in both subject numbers and treatment times, they have demonstrated measurable changes in GH and IGF-1 levels, as well as possible deleterious effects on exercise performance that should be taken seriously. In summary, when considering the balance between potential benefits and risks of GH administration in the presence of a normal GH/IGF-1 axis, there is sufficient evidence that GH does not provide desired improvements to aid training and may actually lead to potential harm.

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REFERENCES