Short stature secondary to pituitary growth hormone (GH) deficiency or Turner's syndrome remains the main indication for treatment with GH. However, recombinant human GH is finding other uses in both children and adults, so it is important to understand the effects of GH on metabolic and endocrine function.

Growth hormone (GH) is essential for normal growth in childhood and also exerts metabolic actions in both children and adults. Although it has been believed for many years that GH is not important in adulthood, recent evidence suggests that this may not be the case. Human GH was first used successfully to treat short stature secondary to hypopituitarism in 1958; since then, much knowledge has accumulated about replacement treatment with human GH. The recent availability of recombinant human GH (hGH) has allowed the treatment of more short children, and also encouraged exploration of new uses.

**INDICATIONS FOR GH TREATMENT**

The main indication for GH treatment is short stature secondary to pituitary GH deficiency (from any cause) (Figure 1) or Turner's syndrome. However, the growth-promoting effects of GH are being studied in several conditions including short stature resulting from bone dysplasia, glucocorticoid therapy (for asthma and rheumatoid arthritis) and chronic renal failure or renal transplantation. Other effects of GH include the conversion of catabolic into anabolic states (for example in the postoperative period, or in elderly patients), and in states of malnutrition and the facilitation of ovulation induction by gonadotrophins. GH replacement may have beneficial effects on body composition, well-being and quality of life in adults with GH deficiency.

Potential areas for further study of GH include chronic leg ulceration, wound healing, burns and trauma, spermatogenesis in males and, because of the potent lipolytic actions of GH, the treatment of morbid obesity. GH administration in obese patients treated with diet restriction prevented catabolism of protein stores although it produced no significant acceleration of fat loss. However, although GH may be effective in some or all of these conditions, a major limiting factor in GH usage will be its cost—the average annual cost of treatment of GH deficiency is £6000 (Box 1).

**Box 1. Advantages and disadvantages of growth hormone treatment.**

**Advantages**
- Improved well being and psychosocial performance
- Restoration of a normal muscle/fat ratio by decreasing the volume of adipose tissue and increasing the amount of muscle
- Improvement of muscle strength and exercise capacity
- Improvement in cardiac performance
- Improvement in glomerular filtration and renal plasma flow
- Increase in bone mineral mass, serum calcium and osteocalcin and urinary excretion of hydroxyproline
- Normalization of thermal regulation by increasing sweat secretion
- Normalization of sleep pattern

**Disadvantages**
- Cost
- Long-term effects on glucose metabolism including insulin resistance and increased risk of diabetes
ENDOCRINE EFFECTS OF GH TREATMENT (BOX 2)

Because of the increasing number of real and potential indications for treatment of both children and adults, it is important to be aware of the endocrine and metabolic effects of treatment with human GH (Figure 1). The amount of GH used most often as replacement therapy is 0.05–0.1 mg/kg on alternate days. Most GH deficient patients therefore receive the equivalent of 25–50 µg/kg per day. In normal adults GH is produced at the rate of about 6–17 µg/kg per day, whereas in patients with acromegaly, the production rate varies widely, from 50 to more than 1000 µg/kg per day. The doses of GH used for therapy are, therefore, at or above the total daily GH production in normal individuals and much lower than the amount produced by most patients with active acromegaly. There is, therefore, little risk of the patient developing problems similar to those of acromegalic patients on the dose currently recommended for GH replacement therapy.

Hypothalamic-pituitary-IGF-I axis

The classical concept is that GH induces the production of insulin-like growth factor (IGF-I) in the liver and locally in most tissues, including the epiphyseal growth plate. The growth-promoting activity is then exerted by IGF-I. A more recent view is that GH acts, at least in part, as a dual effector, stimulating both local synthesis of IGF-I and local differentiation of precursor cells to committed IGF-I-sensitive cells. IGF-I itself then acts as an autocrine or paracrine mitogenic agent leading to clonal expansion of the IGF-I-sensitive cells. This concept, the presence of IGF-I in plasma can be considered as a 'leakage' phenomenon that may play a role in the feedback mechanisms regulating GH secretion. GH secretion is inhibited by previous administration of GH in both man and laboratory animals. This

Box 2. Endocrine effects of growth hormone therapy.

negative feedback is probably effected both directly by GH in the acute setting and indirectly through IGF-I in the more chronic setting. IGF-I inhibits GH secretion at hypothalamic level by stimulating hypothalamic somatostatin secretion and also directly at pituitary level. Direct GH effects on GH secretion are also mediated by increased hypothalamic somatostatin secretion (Figure 2). In spite of these potent negative feedback control mechanisms, there is no evidence that long-term therapy with GH leads to persistent suppression of endogenous GH secretion after cessation of therapy, either in short normal children or in those with functional GH deficiency. This suggests that continuous GH therapy to final height may not be necessary in these children. Rapid growth can be induced during the prepubertal years, when growth is predominantly GH modulated, to move the child to a higher centile. The treatment could then be discontinued, allowing the child to resume his or her own growth rate but at a higher centile.

Gonadal function

GH appears to play an important role in gonadal development and function. GH modulates the local concentration of IGF-I in the ovary and testis, which in turn is important in augmenting the actions of gonadotrophins. Recombinant hGH enhances the effects of gonadotrophin therapy on the ovaries in the human and GH has a direct

Figure 2. Outline of pathways of control and peripheral actions of growth hormone.
stimulatory effect on oestradiol production by human granulosa cells in vitro. 

Thyroid function

Human GH exerts specific effects on the pituitary-thyroid axis. In some patients with hypopituitarism, thyrotropin (TSH) deficiency is present before GH treatment, while others may develop hypothyroidism during treatment.

Metabolic effects of GH treatment (BOX 3)

Carbohydrate metabolism

Although GH exerts both insulin-like and insulin antagonistic effects, it is only the latter that have important physiological or pathophysiological consequences.

In GH-deficient children, hypopituitarism causes a 50% decrease in hepatic glucose production compared to normal children leading to decreased fasting glucose concentrations. This can be reversed by administration of GH, which increases fasting glucose concentrations, hepatic glucose production and insulin levels. Patients with acromegaly show a stepwise deterioration in carbohydrate tolerance as their disease progresses and diabetes mellitus can be induced in animals by chronic treatment with high doses of GH. However, investigators treating thousands of GH deficient children have observed that GH is not diabetogenic when used as replacement therapy to stimulate growth.

This experience has recently been extended to treatment of GH-deficient adults: in a double-blind, placebo-controlled trial involving administration of GH to GH-deficient adults for 6 months, fasting plasma glucose was elevated, as well as insulin and C peptide levels. However, in spite of the higher fasting glucose, the mean haemoglobin A1c did not deteriorate over the treatment period.

In normal subjects, GH administration can increase fasting glucose concentrations and insulin levels and the anti-insulin effects of GH probably occur in both the liver and peripheral tissues. GH has been administered for periods of up to 1 year to children who do not have GH deficiency, and effects on glucose metabolism have been variable. In girls with Turner's syndrome, GH caused no significant change in carbohydrate tolerance, or fasting serum insulin levels. The only evidence that GH antagonized the action of insulin was a significant increase in serum insulin concentrations 60 min after oral glucose loading.

Similarly in normal, short children treated with higher doses of GH than used in GH-deficient children, both oral glucose tolerance and insulin sensitivity were unchanged although insulin and C-peptide responses to oral glucose and intravenous glucagon were increased. It appears that normoglycaemia is maintained at the expense of increased insulin release, but even the elevated fasting insulin levels return to pretreatment values after 2–3 years of continuous GH therapy.

It is likely that most GH recipients are able to compensate for the diabetogenic actions of GH by increasing insulin secretion, and such individuals are unlikely to develop diabetes. Individuals who have pre-existing impairment of insulin secretory reserve may be at higher risk for carbohydrate intolerance and diabetes. It has been suggested that only patients who are obese or have a strong family history of Type II diabetes may develop symptomatic diabetes. It has yet to be determined whether increased insulin secretion in response to GH will have adverse long-term effects.

Lipid metabolism

GH is a potent lipolytic hormone leading to increased levels of free fatty acids (FFA) and ketones. This lipolytic action of GH can be reversed by insulin administration.

As a consequence of its lipolytic action, GH has pronounced effects on body composition. GH-deficient children are relatively obese, and loss of adipose tissue is one of the earliest noticeable changes after starting GH treatment. In one study, limb fat declined rapidly during the first 3 months and reached values normal for body size and bone age at 6 months. GH treatment also promotes redistribution of adipose tissue from an abdominal (android) to a more peripheral (gynoid) distribution and decreases the abdominal adipocyte size and lipogenesis. Similar studies
in adults showed that GH treatment increased lean body mass by about 6 kg and decreased body fat by as much as 20%. Discontinuation of GH treatment in GH-deficient young adults resulted in an increase in body fat.

There is evidence that GH influences plasma cholesterol and triglyceride concentration. GH administration in large doses for 1 week lowers cholesterol levels and raises triglycerides. In a 6-month study of GH treatment in hypopituitary adults, fasting plasma cholesterol levels were reduced whereas plasma triglyceride levels were unchanged. GH might stimulate the excretion of cholesterol from the body, as GH administration increases biliary excretion of cholesterol and bile acids.

**Protein metabolism**
GH is an anabolic hormone, causing a decrease in urinary nitrogen excretion and in the plasma urea concentration when administered both to GH-deficient children and normal subjects. Increases in insulin and IGF-I induced by GH may mediate some of the anabolic effects of GH on protein metabolism.

Several studies have demonstrated the beneficial effects of the anabolic actions of GH. Treatment with GH for 6 months in GH-deficient adults resulted in an increase in lean body mass and thigh-muscle cross-sectional area. This increase in muscle mass is accompanied by increased strength of limb girdle muscles and improved exercise performance. Psychosocial performance is also improved.

**Sodium metabolism**
A sodium retaining effect of GH was first demonstrated in rats in the 1950s. In vitro studies support the hypothesis that the antinatriuretic action of GH is a tubular effect, and that GH acts by increasing the sodium pump activity. In consequence, the blood volume is increased in patients with active acromegaly and returns to normal when the disease is treated successfully. In addition, 20–30% of acromegalic patients develop hypertension. Acute sodium retention also occurs when GH is administered to both normal and GH-deficient adults. However these effects disappear spontaneously during the first 2 or 3 months of therapy.

There are potential adverse consequences of fluid retention caused by GH treatment, particularly in older patients or those who have pre-existing cardiopulmonary disease. Although the link between sodium and water retention and hypertension in patients who have acromegaly is not firmly established, it is probable that the former contributes to hypertension and might be significant in GH-treated patients who have a predisposition to hypertension.

**Mineral metabolism**
GH is known to have effects on mineral metabolism causing calcium and phosphorus retention. GH excess in acromegalics is associated with increased serum levels of 1, 25-dihydroxy vitamin D and 24, 25-dihydroxy vitamin D and the possibility of a direct effect of GH on the renal 1a-hydroxylase has been suggested. Acute elevation of GH to supraphysiological levels in GH-deficient patients causes reduced urinary phosphate excretion and a slight increase in calcium excretion. Recent studies suggest that the effect on phosphate metabolism is mediated by IGF-I, possibly via a direct effect of IGF-I on renal phosphate handling. However prolonged therapy led to reduced urinary calcium excretion and increased serum calcium above basal levels but still within the normal range. GH treatment induces a rise in markers of bone formation like osteocalcin, type 1 procollagen and alkaline phosphatase, as well as urinary hydroxyproline excretion, suggesting a higher rate of bone resorption.

**Tumour formation or growth**
Rats treated with 0.4–2.5 mg GH for 305–346 days develop tumours of lymphoid tissue, adrenals and other organs at a high rate. Furthermore in acromegaly, the incidence of polyposis and carcinoma of the gastrointestinal tract is increased. In a survey of 48 acromegalic patients, 7 were found to have had malignancies, producing ratios of observed/expected incidence for gastrointestinal malignancies of 4.45. There is no evidence, however, that GH treatment of children with short stature or GH-deficient adults is associated with an increased risk of malignancy, although studies in adults thus far have been limited in duration.

**CONCLUSION**
GH has been used to promote linear growth in GH-deficient children for more than two decades and treatment is discontinued after epiphyseal fusion. In hypopituitary adults, replacement therapy has not traditionally included GH but this policy is being re-evaluated because of the availability of recombinant GH and the probable beneficial effects of treating adult GH deficiency.

There have been no controlled studies to establish the precise dose required in adults with GH deficiency. In view of possible side-effects, it would be advisable to use the lowest effective dose as measured by IGF-I with the least side-effects as indicated by repeated measurements of blood pressure, weight and HbA1c.

The increasing number of indications for GH treatment has raised concern regarding the long-term safety of GH, especially in short normal children. However the risk of carbohydrate intolerance is limited to those with pre-existing impairment of insulin secretory reserve and long-term data indicate that recombinant human GH treatment is both safe and effective in children and adults.

**LEARNING POINTS**
- GH replacement therapy in selected GH deficient adults has definite physical and psychological benefits.
- GH replacement therapy is both safe and effective in children and adults.
- It is important to be aware of the various endocrine and metabolic effects of GH when using GH treatment in GH deficient subjects or other conditions.

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