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Growth hormone therapy in children and adults

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ABSTRACT Growth hormone is responsible for growth in childhood after the first one to two years, and its deficiency results in short stature. Use of GH has been restricted over the years, initially due to scarcity of supply (human pituitary GH), and thereafter due to expense of the drug (synthetic GH). In the UK, GH is licensed for the treatment of children with GHD, TS, PWS, CRI, and those born SGA who fail to catch up in growth. In some countries GH is used for other indications, and it is also used off-license in the UK for treatment of other conditions (primarily 'short stature syndromes'). Growth hormone plays an important role in determining peak bone mass in adolescence/early adulthood, and has an important metabolic role in adults. Growth hormone deficiency in adults leads to lack of energy, abnormal body composition (reduced lean mass, increased fat mass), adverse cardiovascular factors (elevated cholesterol and triglycerides, abnormal echocardiography, hypertension), and reduced insulin sensitivity. It is thus associated with reduced quality of life and increased cardiovascular risk.

KEYWORDS Adult onset growth hormone deficiency, pituitary disease, short stature, Turner syndrome

LIST OF ABBREVIATIONS Central nervous system (CNS), chronic renal insufficiency (CRI), Creutzfeldt–Jakob disease (CJD), growth hormone (GH), GH deficiency (GHD), insulin tolerance test (ITT), insulin-like growth factor (IGF), isolated GHD (IGHD), low density lipoproteins (LDL), magnetic resonance imaging (MRI), multiple pituitary hormone deficiency (MPHD), myocardial infarction (MI), National Institute of Clinical Excellence (NICE), Prader–Willi syndrome (PWS), small for gestational age (SGA), standard deviations (SD), Turner syndrome (TS) West of Scotland Coronary Prevention Study (WoSCoPS)

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OVERVIEW

GROWTH HORMONE THERAPY IN CHILDREN

In the UK, licensed use of GH therapy is indicated in the following situations:

- Proven GHD
- Turner syndrome
- Prader–Willi syndrome
- Chronic renal insufficiency before puberty
- Short children of at least four years of age who were born SGA

Growth hormone deficiency

Clinical presentation of growth hormone deficiency

Up to the age of one to two years, growth is determined by nutrition, and so the child with GHD will grow normally, and only falter in the second year. Infants with GHD may present with hypoglycaemia, usually in association with other features of congenital hypopituitarism (prolonged neonatal jaundice, micropenis, optic nerve hypoplasia). From the age of two, GHD children show slow growth velocity, as determined by serial measurements of height velocity calculated over a minimum of six months. Growth velocity below the 3rd centile for age and actual height below the 3rd centile (or more than –2 SD) below the mid-parental centile with normal weight gain (patient is often relatively overweight for height) raises the possibility of an endocrine cause for poor growth. Chronic diseases often present with slow growth and poor weight gain. At puberty the GH deficient child may show, in addition to the above, slow growth for pubertal stage, and slow or absent pubertal development.

Causes of GHD

The causes of GHD are:

- Isolated GHD (50–70% of cases) or part of a MPHD
- Congenital GHD: gene mutations, e.g. PROP 1 and PIT1, known association with septo-optic dysplasia and other cranial midline defects
- Acquired GHD: post-radiation to hypothalamic pituitary axis (~80% will be GHD by two years post 30Gy), tumours of the pituitary gland (craniopharyngioma).

Diagnosis of GHD

The guidance produced by NICE on the diagnosis of GHD and GH treatment in childhood highlights that:

- GHD is primarily a clinical diagnosis supported by auxological, biochemical, and radiological findings
- Confirmation of the diagnosis is usually by GH provocation testing
- Two such tests should be used in children with suspected isolated GHD, together with evaluation of other aspects of pituitary function
- The definition of a normal response (and thus of GHD) remains rather arbitrary as there is a continuous spectrum of GH secretory ability in childhood – peak GH concentrations <20 mIU/l (~7 µg/l) have traditionally been used to support the diagnosis.

Assessment of GH secretory ability, or a firm diagnosis of GHD, can be difficult because of the pulsatile and predominantly nocturnal nature of GH secretion (Figure 1), variability of GH assays, the complexity of the control of GH secretion, and the GH–IGF-1–growth metabolic pathways. Baseline IGF-1 is often low in GHD, although this is not diagnostic. Diagnosis is based on the clinical features of GHD plus failure to produce sufficient GH during stimulation. Testing should be considered in children with the growth criteria given above, or those at risk of GHD. In suspected isolated GHD, two provocation tests are recommended with an evaluation of other aspects of pituitary function. In children with defined CNS pathology, a history of irradiation, MPHD, or a genetic defect affecting the GH axis, one GH stimulation test is sufficient. Growth hormone response can be blunted in hypothyroidism, so a child with MPHD must be on adequate thyroid hormone replacement. Prior to puberty, it is advantageous to prime children with sex steriods, as GH response is also reduced at this time.

Severe obesity may be associated with marked reduction in GH reserve, and a diagnosis of GHD in markedly overweight patients should be supported by additional pituitary hormone deficiency and/or structural pituitary disease. A poor GH response to stimulation can also be shown in children with psychosocial deprivation.

Magnetic resonance imaging is required in a child with a diagnosis of GHD, to define the anatomy of the pituitary gland and exclude a pituitary tumour.

What are the tests?

Stimulation tests carry risks, and must be carried out by experienced staff in a specialised unit. They are:

- Insulin tolerance test: this is the 'gold standard'. This test provides GH and cortisol response to induced hypoglycaemia. It is contraindicated in a child with epilepsy. There is risk of profound hypoglycaemia, loss of consciousness, and seizure. For the ITT, GHD = peak response <10 mU/L, partial GHD = peak response >10 but <15 mU/L. However, each endocrine unit investigating hypopituitary patients should be aware of different values resulting from assay variations. The NICE definition of GHD peak is <20 mU/L
- Glucagon stimulation test: this carries a risk of delayed hypoglycaemia
- Clonidine test: this carries a risk of profound hypotension
- Arginine test: the extravasation of IV can be painful
- Exercise stress test: often produces a suboptimal response in normal individuals

Performing an overnight GH profile is labour intensive as it involves frequent sampling, admission to hospital, and this disruption may alter normal GH secretion.

Problems with interpreting tests

Growth hormone secretory ability in childhood is a spectrum: how should 'normal' be distinguished from abnormal (GHD)?

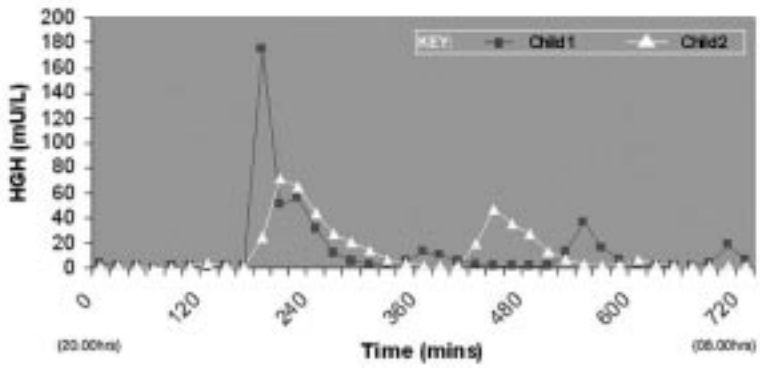

FIGURE 1 Growth hormone secretion. Normal overnight GH profiles (20 minute sampling from 2000 hrs to 0800 hrs) showing the pulsatile nature of GH secretion.

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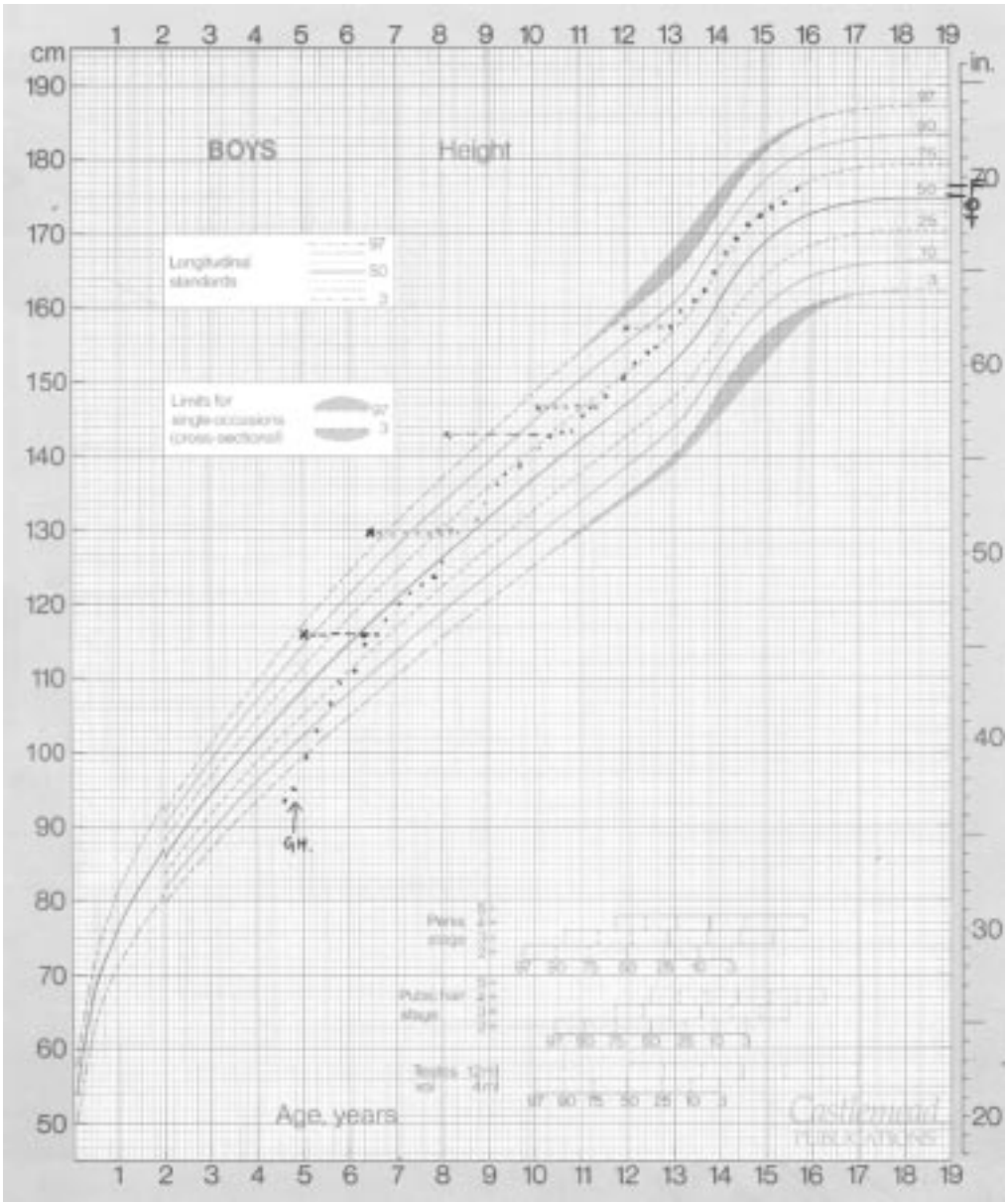

FIGURE 2 Treatment of GHD. In contrast to TS (Figure 3), the response to GH therapy in a child with GHD is more dramatic, with a normal final height achieved on a physiological replacement dose of GH. This boy had a small and abnormally developed pituitary gland on MR scanning.

All predictive provocation tests have limited (<80%) sensitivity and specificity (resulting in false-positives and false-negatives) and repeat tests show concordance only 50–70% of the time. Specificity can be maximised by requiring that two tests should be positive (i.e. avoids falsely labelling normal children as GHD), however, this approach misses many treatable individuals; sensitivity can be maximised by requiring that both tests should be negative (i.e. minimises missed diagnoses) although doing so can lead to many normal children being falsely labelled as GHD.

Thus diagnosing GHD remains problematic. Some children with a degree of GH insufficiency are denied GH therapy that might benefit their growth and are labelled as 'idiopathic short stature' whilst some receive GH but are probably entirely normal. The growth response to GH therapy is ultimately the best clinical marker for GHD (Figure 2).

Turner syndrome

Short stature in TS is not due to GHD, but a short stature homeobox defect probably accounts for about 75% of the growth deficit. Studies suggest that GH therapy improves final height by 5–10 cm, but variable trial designs make examination of the evidence difficult.

Management of TS also includes oestrogen therapy to induce puberty, followed by combined hormone replacement towards the end of puberty. Figure 3 shows an example of the use of GH for TS.

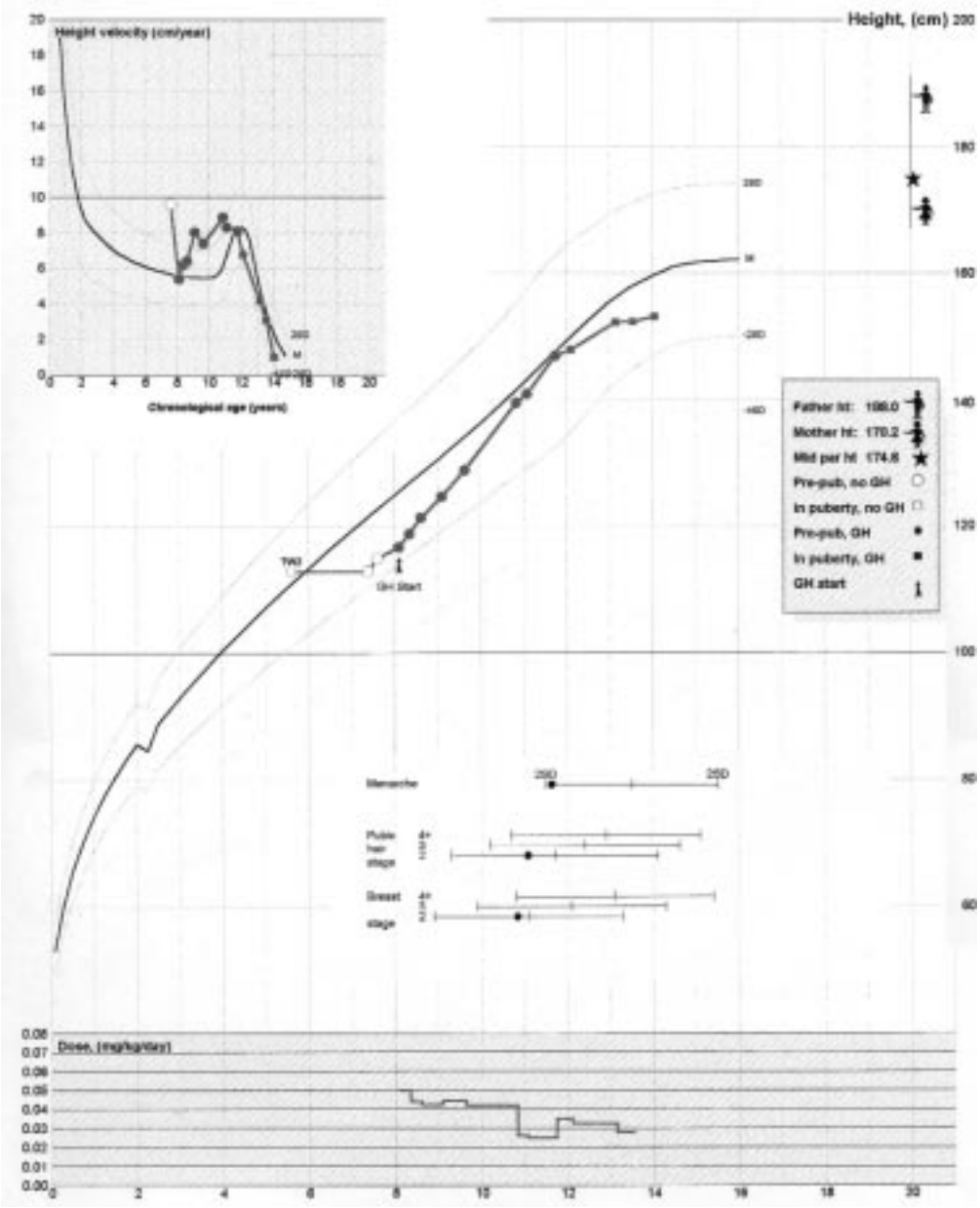

FIGURE 3 Growth charts for TS. The final height achieved by this girl with TS is about 10 cm taller than the mean for the UK TS population. However, the height that she would have reached without GH therapy is unknown as she may have inherited her single X chromosome from her 'tall' father or her 'short' mother. In the latter case her height gain would have been even more impressive, but studies in large numbers of TS girls treated with GH would suggest that the height gain is of the order of 5–10 cm indicating that the former situation is more likely. Growth hormone is being used in high doses pharmacologically to achieve an improvement in final height in a girl who is not GH deficient but who has bones that respond suboptimally to (normal) endogenous GH secretion (GH resistance).

Prader-Willi Syndrome

Many of the clinical features of PWS suggest abnormal hypothalamic function. Growth hormone deficiency has also been demonstrated. In PWS, although GH was initially introduced to treat short stature, GH is now primarily used to improve body composition (reduce fat and increase lean body mass). Parents often report that the child has more stamina (e.g. can walk further). Growth hormone improves height velocity in the short term and possibly improves final height. It also improves lipid profile and bone mineral density.

Chronic renal insufficiency

Chronic renal insufficiency in childhood is associated with poor growth and short stature. Growth hormone increases height velocity in the short term by about 4 cm/year, but there is insufficient evidence to be certain whether this improves final height. Growth hormone therapy is discontinued just before, and for a year after, renal transplantation (increased risk of transplant rejection). Some centres resume GH therapy thereafter, if growth is poor.

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Short stature in the child born SGA

Around 90% of children born SGA catch up in height by two years of age, although those born prematurely may take up to four years to do so. For those that do not catch up, GH has been shown to improve final height. Because of theoretical increased risks of a metabolic syndrome in later life (type 2 diabetes, cardiovascular disease, dyslipidaemia), some studies of GH therapy have included measurements relating to these aspects during treatment, although no long-term outcomes will be available for some time. Growth hormone therapy increases IGF-1 levels and insulin resistance, both of which reverse when therapy is discontinued.

Administration/dosage/monitoring of GH therapy

In the UK, treatment is initiated and monitored by a paediatric endocrinologist, but usually under a shared-care protocol with the general practitioner. Dosages are:

- for GHD: 0·025–0·035 mg/kg/day (15 IU/m^2/week)
- for PWS and SGA children: 0·035 mg/kg/day
- for TS and CRI: 0·045–0·05 mg/kg/day (30 IU/m^2/week)

Growth hormone is given as daily subcutaneous injections, at home. All children should have careful monitoring of growth and maturation, and in many centres bone age and blood biochemistry are also monitored (e.g. HbA1C, IGF-1).

Safety

From 1963 to 1985 patients were treated with GH extracted from human pituitaries. In 1985, it was recognised that three recipients of human GH had developed CJD (since when over 100 treated patients have developed CJD worldwide), and from this time only synthetic GH has been used, which, combined with the surveillance of children treated with GH by the Pfizer International Growth Database (KIGS) and the National Cooperative Growth Study, has provided reassuring data on safety.

More recently, deaths in markedly obese, GH-treated children with PWS have been reported, and a possible contribution from GH has not yet been excluded. There is no evidence that GH treatment in children causes malignancy.

Side-effects include fluid retention and headaches (benign intracranial hypertension). With rapid catch-up growth, slipped femoral epiphysis may occur and hypothyroidism can be unmasked. There is a risk of glucose intolerance.

Management of GHD at final height

Final height is determined by growth velocity of <1 cm/year. The licence for GH treatment requires that GH should be stopped and the individual should be retested to determine whether they fulfil the criteria for GHD as a young adult.

Unlicensed use of GH

The range of conditions for which GH is licensed is growing and in many of these GH is used pharmacologically to stimulate growth. The quality of the evidence behind benefit from GH in a number of licensed indications is not necessarily better than in other situations and diagnoses. Outcome needs to be considered not just in terms of final height and centimetres gained, but in psychological and quality of life terms, and few such data are available. Situations where GH could be considered 'unlicensed' or 'off-label' include idiopathic short stature (which is an approved indication in the USA), skeletal dysplasias, Noonan's syndrome and other 'short stature syndromes' (of which there are over 850 of varying degrees of rarity in the London Dysmorphology Database), and glucocorticoid use.

GROWTH HORMONE THERAPY IN ADULTS

Although it is best known for its effects on growth and development, GH is an important metabolic agent that continues to have a role throughout the human life span. Adults with GH deficiency suffer a large number of symptoms and pathophysiological abnormalities (Table 1).

Patients perceive an abnormal quality of life, characterised by reduced energy, tiredness, and an increased feeling of social isolation. Body composition is abnormal; lean mass is reduced, and fat mass is increased, with a propensity towards central obesity and intra-abdominal fat deposition. Skeletal metabolism is abnormal, with reduced bone turnover and reduced bone mineral density, particularly in adults below the age of 50 years. Adults with GHD have an adverse cardiovascular risk profile with elevated cholesterol (total and LDL) and triglycerides, and reduced insulin sensitivity. Other markers, including carotid intima-media thickness, interleukin 6, and C-reactive protein, are also adversely affected. This has led to the suggestion that GHD is implicated in the twofold increase in mortality from cardiovascular disease observed in patients treated for hypopituitarism with conventional endocrine replacement therapy, but who do not receive GH replacement.

Benefits of GH replacement therapy in adults

Treatment with GH replacement results in a rapid improvement in quality of life; patients report less tiredness and more energy. The body composition changes are reversed and exercise capacity increases. The cardiovascular risk profile improves with a fall in serum cholesterol similar to that seen in the WoSCoPS, which reported a 32% reduction in relative risk of death from MI. Despite this, it

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TABLE 1 The reported effects of GH deficiency in adults.

Effect	Features
Impaired quality of life	
Abnormal body composition	Increased fat mass Decreased lean mass Decreased total body water Increased central fat deposition
Decreased bone mineral density*	
Reduced exercise capacity	
Abnormal echocardiography*	Reduced cardiac size Reduced left ventricular wall thickness
Serum lipid abnormalities	Raised total and LDL cholesterol Raised triglycerides High density lipoprotein cholesterol reduced in some studies
Hypertension	
Reduced insulin sensitivity	
Abnormal cardiovascular risk factors	Raised C-reactive protein Raised interleukin-6 Impaired fibrinolysis Increased carotid intima media thickness
Thin skin	
Decreased sweating	
Reduced red cell mass	
Reduced glomerular filtration rate	

**more pronounced in young adults*

is not yet known whether GH replacement therapy will reduce the increased risk of death from cardiovascular disease observed in this patient cohort. Longer term benefits of GH replacement therapy include increased bone mineral density. This is particularly important during the transition from adolescence to early adulthood when GH plays an important role in determining peak bone mass.

Not all adults receiving GH replacement therapy perceive benefit in terms of quality of life. Patients that are most severely affected perceive the greatest benefit. The recent NICE guidelines restrict the initiation of GH to those patients that have moderately to severely impaired quality of life, and in order to continue GH therapy the patient must demonstrate significant benefit using a quality of life questionnaire. Despite the compelling evidence that GH improves cardiovascular risk, this indication was excluded because there was a lack of long term outcome data.

Diagnosis of GH deficiency in adults

It is evident from the list of signs and symptoms that none are specific to GHD so the diagnosis is made biochemically and only in the presence of known hypothalamic-pituitary disease. Growth hormone deficiency is defined as a peak GH response below 9 mIU/L (3 µg/L) during an ITT. The ITT is contraindicated in patients over 60, or who have a history of ischaemic heart disease (patients should have a normal electrocardiogram), or seizures. Given the risks associated with the ITT it should only be performed in specialist units by experienced staff. Other tests may be used but the diagnostic criteria must be determined locally for each test. The diagnosis of adult-onset, idiopathic, isolated GH deficiency is not recognised by endocrinologists.

Dose of GH in adults

The dose of GH used in adults is determined by age and gender. Higher doses are required in younger patients and women, particularly those on oral oestrogen therapy. Patients are started on a low dose (0·1–0·3 mg/day) and the dose is titrated against the serum IGF-1, aiming for a level in the upper part of the normal range. Maintenance doses can range from 0·2 to 1·0 mg/day.

Other indications for GH therapy

At the present time GH therapy in adults is only licensed for use in those with severe GHD. Growth hormone has been used experimentally as an anabolic agent in the elderly, in patients with HIV, and in patients on critical care. Although there are consistent improvements in body composition, there is very little evidence that suggests GH produces a functional benefit in the elderly. The studies in patients on critical care were discontinued as the death rate was higher in the treatment group.

In some countries GH is promoted as an anti-ageing compound. It may also be abused by athletes.

Side-effects of GH replacement therapy

In the short term side-effects from GH include peripheral oedema, paraesthesia and carpal tunnel syndrome, headaches, and arthralgia. These are dose-dependent and are rare now that patients start at a low dose which is titrated against IGF-1.

Long term GH replacement therapy appears to be safe in adults with severe GHD. The main concerns are glucose intolerance and malignancy. Blood glucose and glycosylated haemoglobin should be monitored regularly. Epidemiological data suggest a link between GH exposure and malignancy; however, current data from long term surveillance studies do not suggest that this risk is increased in adults receiving GH replacement therapy.

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HIGHLIGHTS

- Up to the age of one to two years, growth is determined by nutrition, and so the child with GHD will grow normally, and only falter in the second year
- Growth velocity <3rd centile for age and actual height <3rd centile or >–2SD below mid-parental centile, with normal weight gain (often relatively overweight for height) raises the possibility of an endocrine cause for poor growth
- Stimulation tests carry risks, and must be carried out by experienced staff in a specialised unit
- Magnetic resonance imaging is required in a child with a diagnosis of GHD, to define the anatomy of the pituitary gland and to exclude a pituitary tumour
- Growth hormone treatment in children is only licensed in the UK for: growth hormone deficiency, Turner syndrome, Prader–Willi syndrome, chronic renal insufficiency before puberty, and short stature in children from four years of age who were born SGA
- Adults with GHD have an adverse cardiovascular risk profile with elevated cholesterol
- The diagnosis of adult onset, idiopathic, isolated GHD is not recognised by endocrinologists

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