

Review**GH deficiency in adults**Dimitrios S Papadogias¹, Polyzois Makras¹, Gregory A Kaltsas^{1,2}, John P Monson²*Departments of Endocrinology, ¹G. Gennimatas General Hospital, Athens Greece, ²St Bartholomew's Hospital, London EC1A 7BE, UK***ABSTRACT**

Until the last decade, the diagnosis of GH deficiency (GHD) in adults was only considered as a marker of hypothalamo-pituitary disease. GHD in adults is now recognized as a specific clinical syndrome associated with a cluster of cardiovascular risk factors such as altered body composition with increased body fat, insulin resistance, adverse lipid profile, reduced physical performance, reduced bone mineral density and impaired quality of life. Several randomized placebo controlled trials have now established that GH replacement can reverse some of these biological changes and improve the overall health status in GHD adults; as a consequence, GH replacement therapy has now been approved in many countries in such patients. With the advent of recombinant technology, there is a virtually unlimited, safe supply of recombinant human GH. Although GH replacement is not administered as commonly as steroid, thyroid and sex hormones in hypopituitary patients, a six-month trial of GH replacement with re-evaluation of well-being, body composition and lipid profile is currently recommended. However, there is marked individual variability in the response to GH replacement, with IGF-I being the most sensitive serum marker of GH action. Questions yet remaining to be answered relate to the role of GH replacement in cases of partial GHD and its use in the elderly population. The safety of long term replacement therapy remains an important issue, particularly in relation to the cardio-vascular system, the incidence of de novo malignant tumours and the recurrence rate of pituitary tumours. In the context of safety, it remains essential to monitor patients by means of longitudinal surveillance databases.

Key words: growth hormone (GH), bone mineral density (BMD), lipoproteins, carbohydrate metabolism, quality of life

INTRODUCTION

GH deficiency in adults, commonly resulting from pituitary or peri-pituitary tumours and/or their treatment, is characterized by a diversity of symptoms and

signs¹. Adults with GH deficiency are less healthy than their age-matched peers, and GHD has been implicated in increased mortality, mainly from cardiovascular disease (CVD) observed in patients with hypopituitarism who receive replacement hormones other than GH^{2,3}. A number of clinical trials have now documented that GH replacement results in sustained benefits in adult patients with GHD^{4,7}. However, GH replacement treatment is not offered to all adult GHD patients; its routine use is still a matter of debate, mainly due to the lack of prospective studies using as

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an end point an overall reduction of cardiovascular mortality. This review will focus on the clinical manifestations and diagnostic confirmation of adult GHD as well as the response to GH replacement treatment. Since the prevalence of adult onset GHD is estimated at approximately 1-3 in 10,000 of the population⁸, it is important to identify the group of patients who will most benefit from this treatment.

CLINICAL AND METABOLIC MANIFESTATIONS

Adults with GHD have altered body composition, with an increase in total body fat as well as an abnormal distribution of fat, mainly abdominal accumulation of excessive adipose tissue, decreased lean body mass, increased LDL-cholesterol, slightly reduced HDL-cholesterol levels and insulin resistance¹. Total body water and circulating extracellular volume are reduced and this together with an increase in subcutaneous fat results in poor venous access⁹. Adult GHD is also associated with decreased muscle strength and reduced physical and cardiac performance^{1,8}. In addition,

patients with adult GHD also have reduced bone mineral density (BMD) and increased incidence of fractures^{10,11} (Table 1). Comparison of data from KIMS (International Pharmaco-epidemiological Survey of the use of GH replacement therapy in adults sponsored by Pfizer Corporation) with data from a control non-GH deficient population showed that prevalence of fractures was 2.66 times higher in KIMS patients over 60 years with hypopituitarism¹². Finally, one of the most striking features of this syndrome is a reduced sense of physical and psychological well-being⁸. Using validated questionnaires based on symptoms most frequently identified by GHD adults, patients report less energy, emotional lability, lower openness, difficulties with memory and attention, low self-confidence and self-esteem, a sense of social isolation and diminished libido¹.

DIAGNOSIS OF GH DEFICIENCY

Patients at risk (patients who should be screened)

All patients with evidence of hypothalamic-pitu-

Table 1. Bone mineral density, body composition and lipid profile in adults with growth hormone deficiency

Study	No of patients	Body composition	Bone mineral density	Total Cholesterol	TG	LDL-C	HDL-C
Bing-You et al ⁷⁸	14	NA	Total body 8% decrease	NA	NA	NA	NA
Holmes et al ⁷⁹	26	NA	Changes in z score: lumbar spine, -0.76; femoral neck -0.38	NA	NA	NA	NA
Attanasio et al ⁷²	106	2.4-kg increase in fat mass in men, 3.3-kg increase in fat mass in women	NA	NA	NA	NA	NA
Rutherford et al ⁸¹	11	18–22% increase in fat mass 1 yr after discontinuation of GH therapy	NA	NA	NA	NA	NA
Markussis et al ⁴¹	34	NA	NA	19% increase	NA	23% increase	No change
Kaufman et al ¹¹	30	NA	Total BMD decreased	NA	NA	NA	NA
De Boer et al ²⁵	64	NA	NA	Increased	No change	Increased	No change
Drake WM et al ²⁴	13	NA	Increased in men preserved in women after 5yr of GH replacement	NA	NA	NA	NA

NA denotes not assessed.

itary disease, history of cranial irradiation or childhood onset GHD should undergo evaluation for the presence of adult GH deficiency. The diagnosis is best established with the use of a provocative test of GH secretion¹³. The insulin tolerance test (ITT) is considered to be the test of choice. Using this test, severe GHD is defined as a peak GH response below $3\mu\text{g/L}$ ¹³. In cases where the ITT is contraindicated (patients with coronary heart disease, generalized debility and/or epilepsy), the combined administration of arginine and growth hormone releasing hormone (GHRH) is an acceptable alternative¹³. Another promising diagnostic tool that has to be further validated is the combined administration of GHRH plus Growth Hormone Releasing Hexapeptide (GHRP -6)¹⁴. Tests using arginine alone or glucagon alone are considered less stringent with less diagnostic value. In order to avoid false positive results, particularly in cases of obesity, the diagnosis of isolated adult GHD should be based upon abnormal findings on two dynamic tests¹⁵. Adult patients with hypothalamic-pituitary disease and one or more additional pituitary hormone deficits require only one provocative test to confirm the diagnosis^{8,13}.

GH dependent peptides, such as IGF-I, are used as markers of GH adequacy, although normal IGF-I levels cannot exclude the diagnosis of adult GHD^{8,13}. Conversely, in the presence of structural pituitary disease and/or multiple pituitary hormone deficits, a very low serum IGF-I indicates a high probability of GH deficiency¹³. It should also be noted that serum IGF-I concentration may also be reduced by poor nutrition, hepatic disease, poorly controlled diabetes mellitus and inadequately treated hypothyroidism. Measurement of serum IGF-Binding Protein-3 (IGFBP-3) or acid labile subunit has to date not proven to offer any advantage over the measurement of serum IGF-I¹³.

RESPONSE TO TREATMENT

Body composition

Several studies, using different techniques, have demonstrated that GHD in adult males is associated with a 7% mean increase in total body fat, which is mainly distributed centrally (around the abdomen), and a mean reduction in lean body mass (LBM) of 7-8%¹. In addition, bioimpedance analysis has shown that the hydration state of LBM is lower than normal due to a decrease in extracellular water¹⁵. In these

patients, body muscle mass and plasma IGF-I levels are positively correlated. These changes appear to be reversible following the initiation of GH treatment. Studies have consistently shown a mean increase in LBM averaging between 2-5.5 kg within several months of GH therapy, and this is associated with a similar reduction in fat mass¹. Although the effect on LBM is maintained even for a 10yr period, the reduction in fat mass is not sustained⁴; these changes in body composition appear to be more pronounced in men than in women but this may simply reflect differences in GH sensitivity and IGF-I generation and are not evident when the GH dose is titrated against IGF-I^{16,17}. Interestingly, a recent study examining the changes of fat distribution in male and female GHD adults during the first year of discontinuation of GH therapy showed that the subcutaneous and intrabdominal fat mass increased dramatically in young GHD adults, especially within the first three months¹⁸.

Lean body mass has also been found to be the single predictor of basal metabolic rate (BMR) and resting energy expenditure (REE). In GHD adults, REE is lower than predicted after correction for age, height and weight¹. GH replacement rapidly increases REE, an effect that can be attributed not only to the increase in LBM, and therefore to increased protein synthesis, but also to increased cellular metabolism, increased fat oxidation and increased peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) which is mediated by GH¹⁹.

Bone Mineral Density (BMD)

Patients with adult onset GHD have lower BMD compared to normal subjects and the degree of osteopenia is directly correlated with circulating IGF-I levels²⁰. Increased bone loss and decreased bone remodelling may be involved in the pathogenesis of reduced bone mass in patients with adult onset pituitary deficiency. Biochemical markers of bone turnover in adult GHD are associated with a decreased remodelling rate. Several studies have shown no difference in BMD between patients with isolated GHD and those with multiple pituitary hormone deficiency of childhood onset, suggesting that GHD may be a key factor for reduced bone mass in these patients, probably as a consequence of failure to achieve peak bone mass¹¹. Low BMD is associated with a doubling of the fracture rate compared to healthy controls²¹.

GH is regarded as an osteo-anabolic hormone and when given to GHD adults exerts a biphasic effect: following an initial net increase of bone resorption, stimulation of bone formation leads to a net gain in bone mass after 12-24 months of treatment¹. In a placebo controlled study, GH treatment in GHD adults was associated with a 5% increase of BMD in the spine and 2% in the femoral neck⁵. In this study, BMD increased at sites composed mostly (lumbar spine) or partially (femoral neck) of trabecular bone but not at

a site composed of cortical bone (proximal radius), suggesting that beneficial effects of GH therapy occur primarily in trabecular bone (Figure 1). The improvement in BMD persisted for 18 months after discontinuation of the treatment²². Furthermore, analysis of data from patients enrolled in KIMS has provided the first evidence from a large-scale survey that patients with hypopituitarism and GHD have a higher prevalence of fractures than the general population and that GH substitution therapy reduces frac-

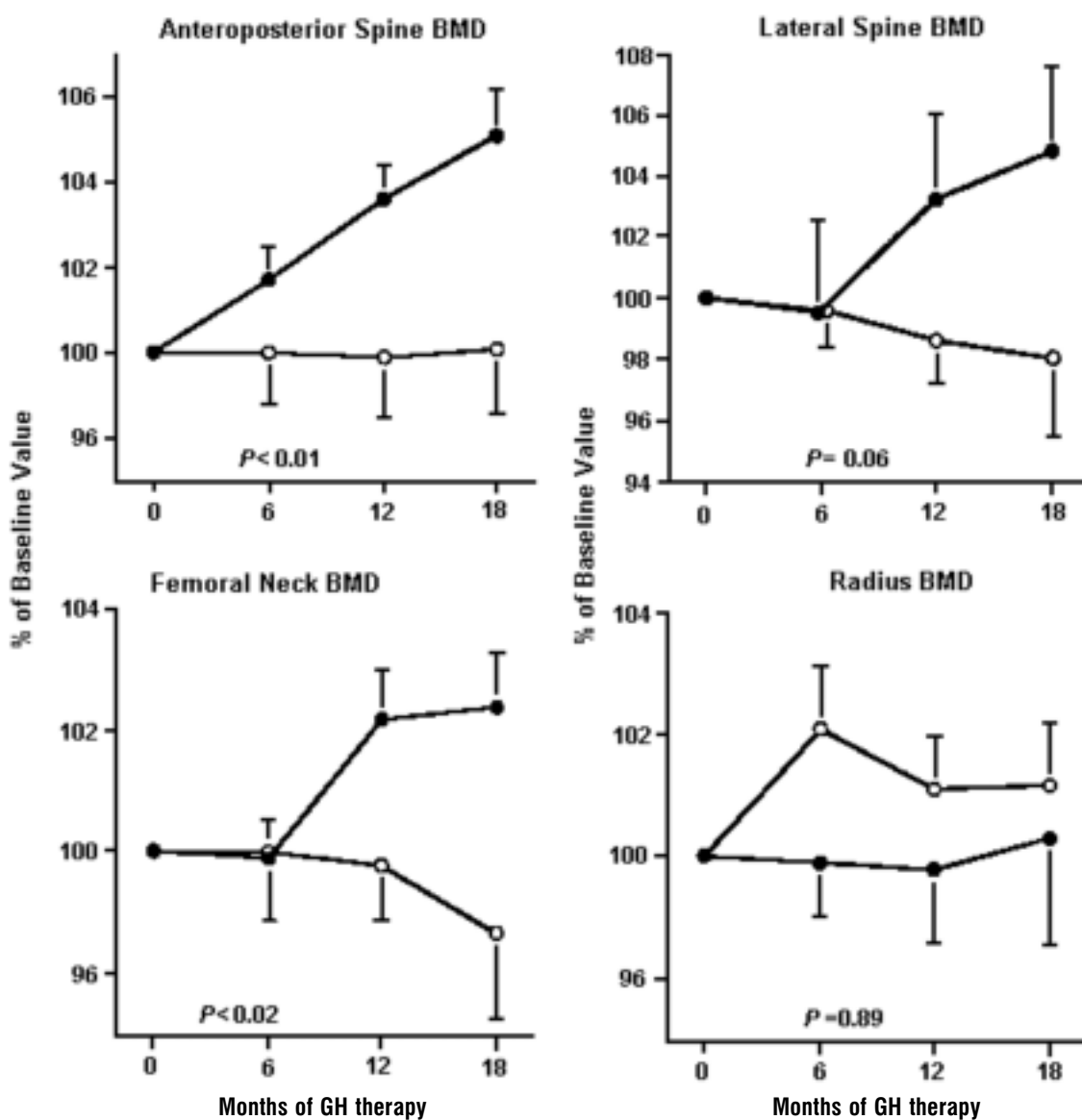


Figure 1. Bone mineral density (BMD) of the lumbar spine in the anteroposterior projection, lateral projection, femoral neck and of the one third distal radius in patients with growth hormone deficiency receiving growth hormone (●) or placebo (○). Values are percentages of the baseline values, and error bars represent ± 1 SE. P values are for comparisons of rates of change between the two groups. (Reproduced with permission from *Annals of Internal Medicine*, 1 December 1996, 125:883-890).

ture risk^{12,23}. Longitudinal data from a 5-year study confirmed that long-term GH treatment in hypopituitary adults with GH deficiency results in an increase in BMD in males and stabilization of BMD in females both at lumbar spine and femoral neck²⁴.

Muscle strength

Decreased LBM in GHD adults results in mild to moderate reduction in muscle strength. Skeletal muscle force may be reduced due to altered muscle mass, contractile elements and/or muscle fibre, anaerobic energy supply, neural recruitment of fibres, or a combination of these²⁵. The administration of growth hormone to GHD adults increases LBM, muscle volume and maximum voluntary isometric muscle strength but not local muscle endurance or dynamic muscle strength^{6,26}.

Lipid profile

GH affects lipoprotein metabolism by increasing both lipoprotein production and secretion from the liver and their clearance from the circulation by up-regulating expression of hepatic LDL receptor²⁷. Patients with GHD have mild hypercholesterolemia due to increased LDL-cholesterol and apolipoproteins B levels while LDL-cholesterol levels are inversely related to GH secretory status²⁸. Compared with age, weight and sex-matched controls, adult GHD patients have higher serum triglyceride and lower high-density lipoprotein (HDL) cholesterol levels²⁹. GH treatment results in a less atherogenic profile, with a significant reduction in LDL cholesterol levels, which has

been maintained over a 10-year period⁴. The adverse lipid profile in GHD adults and its attenuation with GH replacement is more pronounced in women⁸. Observational data from patients who had completed 3 years of GH treatment showed an overall increase of HDL-cholesterol and a significant decrease in the LDL/HDL ratio, which is considered a strong discriminator for the risk of coronary heart disease³⁰. Of note, these changes were greater in the older and middle age groups of patients but not in patients younger than 40 years³⁰. In addition, GH therapy increase Lipoprotein a (Lp(a)) levels and this effect is not influenced by the apolipoprotein (a) phenotype^{31,32}. Effects of GH replacement therapy on body composition and lipid profile in adults with GHD are outlined in Table 2.

Carbohydrate metabolism and insulin sensitivity

Adults with GHD are insulin resistant due to an increase in total and visceral fat and the development of central obesity³³. The degree of insulin resistance depends on the extent of the obesity and probably the duration of GH deficiency¹. GH replacement therapy during the first year of therapy results in relative hyperinsulinemia with further deterioration in insulin sensitivity and increases of glucose concentrations. Subsequently, glucose concentrations return towards baseline, probably due to the beneficial changes of GH replacement in body composition^{1,8}. In a placebo controlled study, insulin sensitivity remained unchanged after 7 years of GH replacement and showed a tendency to remain higher at the end of the study than at baseline in the treated compared to the un-

Table 2. Effects of growth hormone replacement therapy on body composition and lipid profile in adults with growth hormone deficiency

Study	Number of patients	Duration of Therapy	Lean Body Mass	Adipose mass	Total Cholesterol	LDL-C	HDL-C	TG	Lp(a)
Whitehead ⁶	14	6 mo	7% ↑	10% ↓	no change	no change	no change	no change	NA
Cuneo ²⁶	24	6 mo	-	-	12% ↓	24% ↓	no change	24% ↓	NA
Attanasio ⁸⁰	AO 52 CO 32	6 mo	AO:3.5kg ↑ CO:3.7kg ↑	AO:4.9% ↓ CO:5.5% ↓	AO:8% ↓ CO:5% ↓	AO:11% ↓ CO:5% ↓	AO:23% ↑ CO:12% ↑	NA	NA
Bengtsson ⁷	9	6.5 mo	3.9kg ↑	6 kg ↓	no change	NA	NA	no change	NA
Salomon ³³	11	6 mo	5.5 kg ↑	5.7 kg ↓	12% ↓	NA	NA	no change	NA
Baum ⁵	16	1.5 yr	4% ↑	11% ↓	NA	NA	NA	NA	NA
Eden ²⁸	9	6 wk 26wk	NA	NA	↓ no change	↓ no change	↑ ↑	no change no change	↑ ↑
Rosen ⁸²	25	1 yr	4% ↑	8% ↓	no change	NA	12% ↑	no change	NA
Weaver ⁸³	22	1yr	NA	1.8 kg ↓	↓	NA	NA	no change	↑

NA denotes not assessed, AO: Adult onset, CO: Childhood onset.

treated patients³⁴. The overall risk of developing diabetes mellitus is not increased during GH replacement therapy, although GHD patients with low baseline insulin sensitivity are at increased risk^{8,34}. In a two year study, GH replacement therapy given at a low titrated dose resulted in modest increment in mean fasting glucose and mean glycated haemoglobin, both of which remained within the reference range³⁵. In this study a weak but significant correlation was found between the increment in HbA1c and pretreatment BMI.

Cardiovascular function

Patients with hypopituitarism receiving conventional hormonal replacement therapy excluding GH have a mortality rate twice that of age and sex-matched normal subjects, a difference attributable to an increased number of cardiovascular events and implicating GHD as an etiological factor³. Loss of GH secretion is an early event in the development of pituitary deficiency and it can therefore be assumed that the majority of patients with hypopituitarism are also GH deficient. Both GH and IGF-I receptors are expressed in the heart and these hormones may be involved in the developmental growth and maintenance of the structure of the heart^{36,37}. Their effects can be either direct, acting on the endothelial cells, or indirect modifying established risk factors linked to atherosclerosis^{38,39}. GHD in adults is associated with a disturbed lipoprotein pattern, higher incidence of hypertension, abnormal body composition, impaired glucose homeostasis, hypercoagulability, increased intima-medial thickening and arterial intimal plaque formation, premature atherosclerosis, impaired cardiac function and a decrease in exercise capacity³⁹⁻⁴¹. Patients with GHD also have increased sympathetic nerve activity, probably of central origin, leading to hypertension, contributing further to the increased cardiovascular mortality⁴². Nitric oxide generation has been found to be low and endothelium dependent vasodilatation is impaired in GHD adults and improves with GH replacement therapy^{43,44}. These changes result in an increased atherogenic propensity and may contribute to premature cardiovascular mortality¹. Interestingly, in one study treatment with GH normalized the intima-media thickness of the common carotid artery within 6 months and that of the carotid bifurcation within 3 months⁴⁵. Factors that accelerate atherosclerosis in GHD adults are outlined in Table 3.

Adult GHD, particularly of childhood onset, leads

Table 3. Risk Factors For Atherosclerosis Associated With Adult Growth Hormone Syndrome

Increased visceral fat
Increased insulin resistance
Increased LDL-cholesterol and ApoB
Decreased HDL-cholesterol
Higher incidence of hypertension
Increased carotid intima-medial thickness
Decreased nitric oxide generation – Impaired endothelium dependent vasodilatation
Hypercoagulability (↑ plasminogen activator inhibitor, ↑ fibrinogen)
Increased inflammatory markers of vascular disease (↑ CRP)

to a reduction in the mass of both ventricles and impaired cardiac performance with low heart rate (hypokinetic syndrome)⁴⁶. These alterations are particularly evident during physical exercise and may contribute to the reduced exercise capacity of GHD patients, in addition to the reduced muscle mass and strength⁴⁷. A short term placebo controlled study demonstrated that GHD adults had significant cardiac impairment (reduced left ventricular mass index, reduced left ventricular systolic function associated with decreased fractional shortening and rate-adjusted mean velocity of circumferential fibre shortening)⁴⁸. Treatment with recombinant GH for 6 months resulted in normalization of echocardiographic findings, while six months after cessation of therapy, cardiac function had returned to pretreatment levels⁴⁸. In another study of thirty adults with acquired GHD, cardiac output increased by 30 to 40% and total peripheral resistance decreased by approximately 30% during GH therapy⁴³. Six months of GH replacement have been shown to increase left ventricular mass, stroke volume and cardiac output, and reduce peripheral vascular resistance in GHD adults⁴⁹. A sustained effect on cardiac performance has been reported to be maintained up to 3 years after commencement of GH therapy¹. It is important, however, to monitor the long-term cardiovascular effects of GH replacement as the correct physiological GH replacement regimen is not known, whereas persistently elevated IGF-I levels are related to excess cardiovascular mortality in acromegalic patients⁴⁶.

Quality of life (QoL) and well-being

GHD in adults causes distress and poor well-being⁵⁰. Patients with adult GHD feel less energetic and

less healthy than normal subjects of the same age (alterations of sleeping pattern, greater emotional lability, more difficulties with sexual relationships, greater sense of social isolation, poor concentration and memory difficulties)^{26,50}. Although methods evaluating and monitoring physical and emotional well-being carry inherent limitations, recent developments have provided more sensitive scoring systems, such as the adult GHD assessment (QoL-AGHDA) score⁵¹. This is a questionnaire comprising 25 items based on the symptoms most frequently reported by GHD adults. Questions regarding energy, physical and mental drive, concentration, memory, personal relationships, social life, cognition and emotions are included and a single score is obtained (Table 4). Initial placebo controlled trials (which did not use the QoL-AGHDA score) have documented statistically significant

improvements in quality of life after the initiation of GH replacement therapy^{1,7,52}. This effect of GH replacement therapy is seen within 3 to 6 months of treatment and is sustained throughout the duration of GH replacement^{1,8}. The speed of onset of improvement before any expected increase in muscle strength and cardiac performance and the fact that this occurs despite only small increments in serum IGF-I levels suggests a direct GH effect on the brain^{1,51}. In addition, GH replacement therapy resulted in a significant decrease in the number of days of 'sick leave', the number of days in hospital and the number of visits to the doctor⁵³. In current clinical practice, a 6-month course of GH replacement should be undertaken to assess clearly QoL benefits in GHD adults⁸.

Who's to be treated

All patients with documented severe GHD are eligible for GH replacement, the goal being to correct abnormalities associated with GHD¹³. Lack of well-being and abnormal body composition remain the most common reasons to consider a trial of GH replacement therapy in adults, and they represent the most useful clinical markers of GH efficacy during replacement⁵⁴. Recently, GH has also been approved by the FDA for use in human immunodeficiency virus (HIV) associated wasting states in adults⁵⁵. Absolute contraindications for GH replacement therapy are active malignancy, benign intracranial hypertension and proliferative or pre-proliferative diabetic retinopathy¹³. Well controlled diabetes mellitus is not a contraindication; however, as GH antagonizes insulin effects, careful monitoring is required⁵⁶. Stable background retinopathy should not lead to discontinuation of GH replacement⁵⁶. Early pregnancy is not a contraindication, but GH should be discontinued in the second trimester as GH is produced by the placenta¹³.

Optimal GH dose

In the initial studies, a weight or surface area based dosing regimen was employed^{6,57,58}. This was based on experience gained from treatment of GHD children and resulted in GH daily doses of approximately 25 µg/kg that were associated with supranormal levels of serum IGF-I levels and high rates of side effects¹⁷. Adults with GHD are more susceptible than children to side effects, especially at the initiation of therapy⁵⁵. Subsequent studies have shown that GH replacement

Table 4. Quality of life assessment of GH deficiency in adults (AGHDA score)

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1. I have to struggle to finish jobs.
 2. I feel a strong need to sleep during the day
 3. I often feel lonely even when I am with other people
 4. I have to read things several times before they sink in
 5. It is difficult for me to make friends
 6. It takes a lot of effort for me to do simple tasks
 7. I have difficulty controlling my emotions
 8. I often lose track of what I want to say
 9. I lack confidence
 10. I have to push myself to do things
 11. I often feel very tense
 12. I feel as if I let people down
 13. I find it hard to mix with people
 14. I feel worn out even when I've not done anything
 15. There are times when I feel very low
 16. I avoid responsibilities if possible
 17. I avoid mixing with people I don't know well
 18. I feel as if I am a burden to people
 19. I often forget what people have said to me
 20. I find it difficult to plan ahead
 21. I am easily irritated by other people
 22. I often feel too tired to do things I ought to do
 23. I have to force myself to do all the things that need doing
 24. I often have to force myself to stay awake
 25. My memory lets me down.
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should be commenced using a dose titration regimen based on measurements of serum IGF-I¹⁷. Recombinant human GH is administered as subcutaneous injection once a day, usually in the evening. Since it is not possible to recreate normal physiology with a single subcutaneous injection of GH, the goal of treating GHD adults is correction of the associated clinical syndrome. Therapy should start at a low dose of 0.15–0.30 mg/day (0.45–0.9 IU/day) with gradual increase thereafter¹³. Peak level is reached at approximately 4–6 hours after an injection, with a length of disappearance of 20–24 hours⁵⁹. Based on clinical and biochemical responses, the dose is reviewed every 2–4 weeks. Women require a higher dose than men; elderly patients tolerate GH less than young adults, but are more sensitive to GH treatment^{13,55}.

Measurement of IGF-I levels represents the best single test to monitor the adequacy of GH treatment⁶⁰. The aim is to achieve a serum IGF-I level between the median and the upper end of the age-related reference range for the patient by using the minimum dose of GH⁸. Serum IGF-I levels increase and then plateau at 2 weeks after an alteration in GH dose and measurements at this time reliably reflect GH activity for titration purposes¹⁷. The dose should be increased gradually on the basis of clinical and biochemical responses and no more frequently than at monthly intervals¹³.

Side effects and surveillance during therapy

The most common side effects of GH treatment in adults with hypopituitarism are arthralgia, myalgia, carpal tunnel syndrome and paresthesias which are related to the antinatriuretic actions of GH⁵¹. These symptoms are more frequent with higher doses and subside following dose reduction¹. Benign intracranial hypertension occurs more frequently in children and improves with the cessation of therapy¹⁹. Furthermore, GH induces transient resistance to the actions of insulin and in patients with limited insulin reserve glucose intolerance may result^{34,61}. Side effects of GH replacement are more likely to occur in older patients, in those with a peak serum GH response to provocative testing of greater than 1 mU/l, in those with a greater increment in serum IGF-I whilst receiving GH replacement, and in those with greater weight and BMI⁶².

Although the risk of certain malignancies (e.g. colon cancer) is increased in patients with acromegaly,

it would have been inappropriate to extrapolate that GH replacement in adults will have similar consequences. Importantly, analysis of data from patients enrolled in KIMS indicate no increased risk of cancer recurrence or de novo malignancies after GH replacement, and mortality rates appear no different from age, sex and country adjusted mortality rates⁶¹. Based on the limited data available, there is no evidence that GH treatment increases either the risk of a second malignancy in subjects who have already had a malignancy or de novo cancer or leukemia⁵⁶. Although patients with a pituitary tumour or craniopharyngioma are at risk of tumour recurrence, there is no evidence that GH replacement therapy increases this risk⁶¹. Although GH replacement titrated against serum IGF-I is not associated with early increase in the recurrence rate or re-growth of hypothalamo-pituitary tumours, a baseline scan is recommended in all patients before instituting GH replacement therapy⁶³.

Some concern has been raised recently by reports associating high-normal IGF-I levels with prostate cancer risk and breast cancer risk in premenopausal women^{64,65}. However, it is difficult to interpret these findings since neither prostate nor breast cancer appears with increased incidence among acromegalic patients⁶⁶.

Monitoring of thyroid function should be conducted in all patients since GH increases extrathyroidal conversion of T4 to T3 and may unmask incipient hypothyroidism⁵⁶. Finally, by inhibiting 11 β -hydroxysteroid dehydrogenase type I activity, GH results in enhanced net conversion of cortisol to inactive cortisone; this might hypothetically precipitate adrenal insufficiency in patients with borderline ACTH deficiency or those receiving a relatively low dose of hydrocortisone replacement^{54,67}. Moreover, relatively high dose GH may decrease serum total cortisol concentrations by decreasing circulating cortisol binding protein (CBP)^{52,68}.

FUTURE PROSPECTS

Growth hormone therapy is beneficial in adults and children primarily as a replacement therapy. The wide-ranging physiological effects of endogenous GH have led to the use of GH therapy in a range of other conditions⁶⁹. So far the use of GH has also been studied in small numbers of adults with burn injuries, respira-

tory failure, congestive cardio-myopathy and renal failure, after liver transplantation and during recovery from surgery. To date no consistent benefit has been demonstrated⁷⁰. Furthermore, in a double blind, placebo controlled trial involving severely ill patients necessitating intensive care, administration of high doses of GH was associated with increased morbidity and mortality (42% mortality in the GH-treated group compared to 18% of placebo)⁷¹. GH stimulates bone remodelling activity, opening up the possibility that GH can be added to antiresorptive agents in the treatment of osteoporosis. In a study designed to test this hypothesis, GH given cyclically with or without calcitonin for 2 yrs increased BMD at the lumbar spine and selected areas of the hip in postmenopausal women, but improvements were less marked than those achieved with estrogen or bisphosphonates and were associated with a relatively high incidence of adverse experiences⁷². GH therapy has been studied in men with features of the metabolic syndrome and is associated with an early improvement in insulin sensitivity and a beneficial effect on diastolic blood pressure and lipid profile^{69,73}.

Of special interest is the use of GH during the transition period from adolescence to adulthood because this period involves the achievement not only of adult height but also of peak bone mass, adult body composition and reproductive maturity⁷⁰. Peak bone mass is attained some years after final height while discontinuation of GH therapy in adolescents with severe GHD may lead to detrimental changes in body composition, lipid profiles and cardiac structure^{74,75}. However, not all patients with childhood onset GHD will remain growth hormone deficient as adults, as a significant proportion of patients with idiopathic childhood onset GHD produce GH responses within the normal range when retested as adults^{76,77}. Thus, a stimulation test in patients who have achieved their final height should be undertaken to identify the patients who may be at risk of developing the adult GHD syndrome. Patients with a GH response less than 5µg/L on ITT are most likely to develop GHD in adulthood if GH treatment is stopped at final height⁷⁷. Other uses of GH are under investigation and an area of special interest is the development of orally active GH secretagogues for those patients who might benefit from GH therapy and in whom hypothalamic-pituitary function is intact⁷⁶.

SUMMARY

Growth hormone deficiency (GHD) in adults is now recognized as a specific clinical syndrome, commonly resulting from pituitary or hypothalamic disease associated with unfavourable effects on body composition, lipid metabolism, bone mass and quality of life. Untreated GHD has been regarded as a factor implicated in the increased cardiovascular mortality observed in patients with hypopituitarism. So far, an extensive array of clinical trials and longitudinal studies have documented that GH replacement therapy provides both physical and psychological benefits. Diagnosis of GHD in adults should be based on provocative testing of GH secretion and the dose of GH replacement therapy should be titrated against serum IGF-I in place of weight-based dosing regimens. The appearance of secondary malignancy does not appear to be increased, but longer surveillance studies are needed to monitor the safety of GH treatment.

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