

# Factors that Affect the Dosing Regimen of Growth Hormone Replacement Therapy in Adults with Growth Hormone Deficiency

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## ABSTRACT

Growth hormone (GH) deficiency in adulthood is now widely accepted as a distinct clinical syndrome with significant morbidities. These include abnormal body composition, reduced energy, affective disturbances, dyslipidaemia, and increased cardiovascular risk; all of which can either be improved or ameliorated with GH replacement. It is now over 10 years since recombinant GH has been approved by the United States Food and Drug Administration for use as replacement therapy in GH-deficient adults in the United States; whereas in Europe, it has been used for an even longer period of time. However, despite this widespread clinical experience, there is still a lack of consensus regarding the optimal approach to GH replacement in terms of dose initiation, titration and maintenance in GH-deficient adults. This is because the appropriate dose of GH replacement needs to be determined for each individual patient based on the patient's age, sex, concomitant medications, glucose tolerance, serum insulin-like growth factor I levels, and pregnancy to reduce the rates of adverse events. In this review, data of a retrospective analysis of the GH dosing practices within one institution over a 5-year period is presented to define GH dose requirements during the initiation, titration and maintenance phases of treatment, the frequency of dose adjustments, and the reasons necessitating dose adjustments in young and older GH-deficient adults. Based on these data, this review offers practical recommendations for practicing clinicians involved in managing GH-deficient adults on long-term GH replacement therapy.

**Keywords:** adult; adverse effects; dose adjustment; growth hormone deficiency; safety; treatment

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## INTRODUCTION

### Growth hormone structure

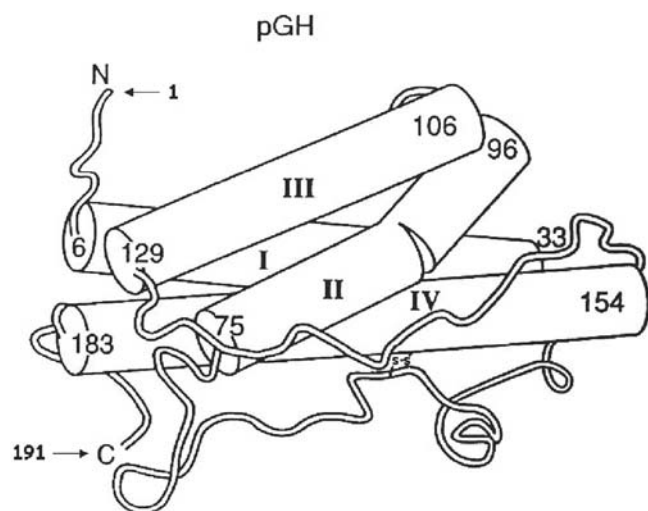
Growth hormone is synthesised and secreted by the somatotroph cells in the anterior lobe of the pituitary gland. The GH molecule itself contains 191 amino acids with two disulfide bonds, and has a molecular mass of approximately 22 kDa. The GH molecule is an elongated molecule with approximate dimensions of 55 X 35 X 35 Å, and contains four helices that are tightly packed as antiparallel bundles aligned in a *up-up-down-down* orientation (Fig. 1). Fifty-four percent of the 191 amino acids are contained within these four helices.

### Composition of circulating GH

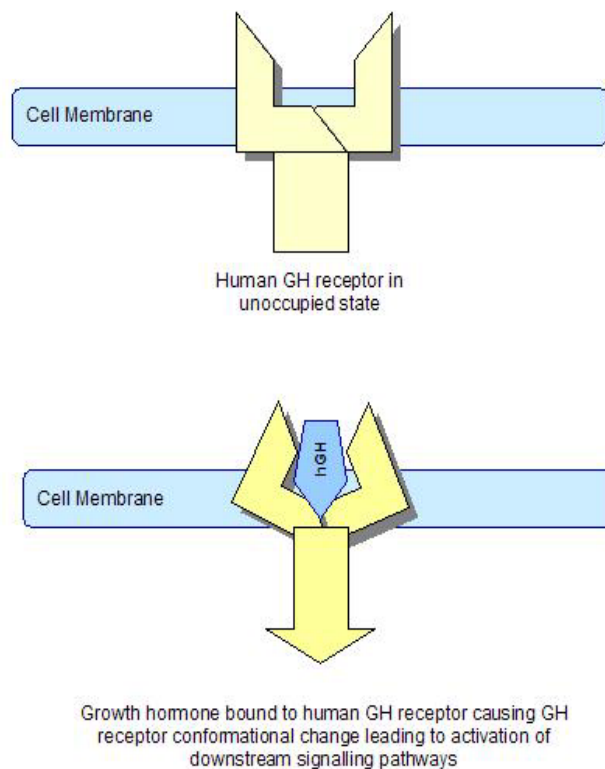
In addition to what is secreted by the pituitary gland, the composition of circulating GH is dependent on the metabolic clearance of GH, interaction with its binding proteins, intravascular aggregation and degradation, recirculating fragments derived from degradation in tissues and spurious non-GH related immunoreactivity.

The various molecular forms undergo differential clearance, which affects their relative proportions in plasma, with oligomeric GH being cleared more slowly than monomeric GH (Baumann *et al.* 1986). This is related to molecular size, which prevents glomerular filtration, and in part to their reduced receptor-binding activity, which reduces receptor-mediated clearance. Thus, oligomers and 20K are present in higher proportions in the circulation than in pituitary extracts (Gorden *et al.* 1973).

Growth hormone is very stable in human plasma (Baumann 1976); hence intravascular degradation is unlikely to occur whilst in circulation. Degradation of GH in peripheral tissues, however, leads to fragments which tend to recirculate (Baumann 1991). Furthermore, certain substances unrelated to GH in plasma may interfere in assays and



**Fig. 1 Computer representation of porcine GH crystal structure.** The four antiparallel  $\alpha$ -helical bundles are represented as *cylindrical rods* labeled I, II, III and IV. The amino and carboxyl termini are indicated with an N and C, respectively. The *numbers* indicate amino acid positions at the N and C termini of each independent  $\alpha$ -helix. Adapted from Abdel-Meguid *et al.* (1987).



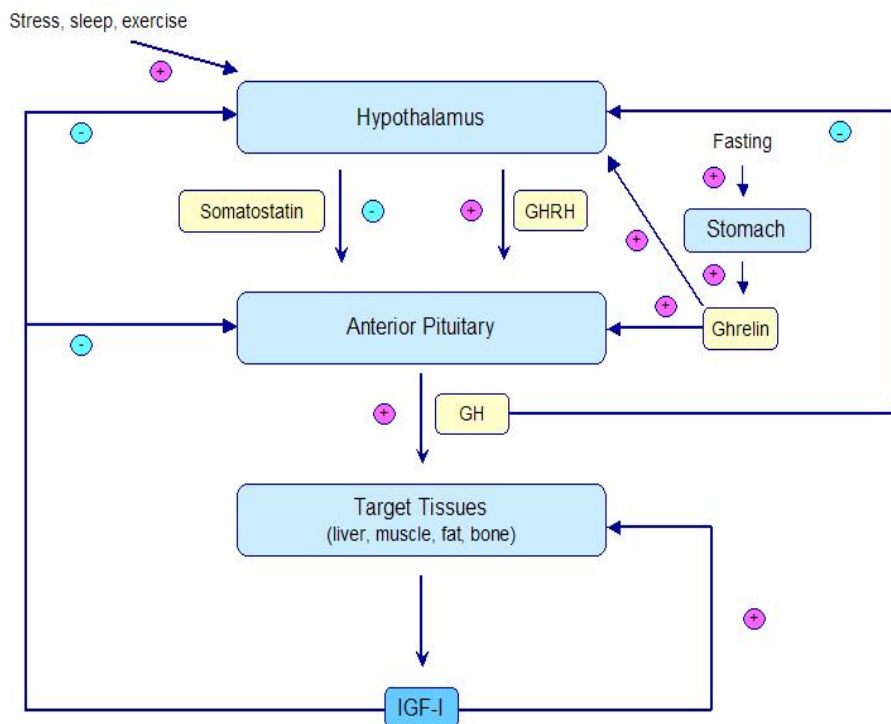
**Fig. 2 Schematic representation of GH receptor activation and signaling.** Top figure: inactive form; bottom figure: GH receptor bound to GH.

thereby masquerade as GH (spurious immunoreactivity). For these reasons, circulating GH is not a fixed mixture of molecular forms, but changes dynamically over time due to association and dissociation from GH binding proteins, differential clearance kinetics, and fragment generation.

### Growth hormone receptor and binding proteins

The actions of GH are mediated by the binding of GH to the transmembrane GH receptor present on the surface of most cells (Mathews *et al.* 1989). The GH receptor consists of a 246 amino acid extracellular domain and 350 amino acid intracellular domain (Leung *et al.* 1987). Each GH molecule contains 2 binding sites, each of which binds to the GH receptor thus forming a dimer (Strobl and Thomas 1994) (Fig. 2).

The GH receptor is subject to a number of post-transcriptional and post-translational modifications during synthesis. The most significant of these is the generation of a soluble GH binding protein (GHBP), comprised of the GH receptor extracellular ligand-binding domain (Strobl and Thomas 1994). It is believed that the primary function of the GHBP is to act as a physiological buffer by stabilising GH in plasma, as high GHBP levels appear to protect the GH molecule from degradation, thus prolonging the half-life of GH from 7 to 27 minutes in the circulation (Baumann *et al.* 1987).



**Fig. 3 Neural regulation of GH synthesis and secretion.** Production of GH is modulated by several factors, including stress, sleep, exercise, and GH itself. The primary hypothalamic regulators of GH release from the anterior pituitary are GHRH and somatostatin, whereas GH secretion is inhibited by IGF-I through a negative feedback mechanism. High serum IGF-I levels decreases GH secretion by suppressing the lactotroph, stimulating the release of somatostatin and inhibiting GHRH secretion. Integration of all the factors that affect GH synthesis and secretion leads to a pulsatile hormone release pattern. Recently, it has been reported that ghrelin, a peptide found predominantly in the stomach, can also stimulate GH secretion.

## Physiology of GH

### Regulation of pulsatile GH secretion

The pulsatile release of GH by the anterior pituitary gland is controlled by GH-releasing hormone (GHRH) and somatostatin released from the hypothalamic median eminence into the hypophyseal-portal circulation. Growth hormone releasing hormone, synthesised in the arcuate nucleus and the ventromedial nucleus, stimulates both GH synthesis and secretion (Fukata *et al.* 1985) via the GHRH receptor (Gaylinn *et al.* 1993). Conversely, somatostatin arising from hypothalamic periventricular and arcuate neurons inhibit GH release without affecting GH synthesis (Lechan *et al.* 1983; Fukata *et al.* 1985) (Fig. 3).

The recently discovered peptide, ghrelin, is released in response to fasting and is mainly produced in the stomach and the hypothalamus (Kojima *et al.* 2001). In addition to its effect on regulating food intake, ghrelin has been shown to stimulate the release of GH secretion through a pituitary and hypothalamic receptor independent from the GHRH receptor (Howard *et al.* 1996) (Fig. 3).

In healthy humans, GH secretion is pulsatile with low basal/trough circulating levels between the peaks (Finkelstein *et al.* 1972). Most of the 24 hour GH release occurs episodically during 8.5 hours as several discrete bursts (Ho *et al.* 1992), which are separated by about 3 hours (Hartman *et al.* 1991). The largest GH peaks occur during phase 3 to 4 of slow wave or delta sleep (Holl *et al.* 1991).

### Regulators of GH secretion and action

The two hypothalamic hormones, somatostatin which inhibits, and GHRH which stimulates pituitary GH release in healthy subjects are regulated by many of the following physiological factors:

#### Gender

Gender has multiple significant influences on the GH-IGF-I axis. Frantz and Rabkin first observed a significant rise in the ambulatory serum GH concentration in women, and the administration of large doses of oestrogen to men evoked a female pattern of markedly amplified GH release (Frantz and Rabkin 1965). Studies by Merimee and Fineberg (Merimee and Fineberg 1971) have further affirmed the gender differences in basal serum GH concentrations, whereas

Thompson *et al.* (1972) demonstrated higher calculated GH secretion rates in oestrogen-replete premenopausal compared to oestrogen-deficient postmenopausal women. Since those studies, basal serum GH (Chapman *et al.* 1994), ambulatory GH concentration (Chapman *et al.* 1994), 24-hour integrated GH concentration (Ho *et al.* 1987) and the pituitary responsiveness to GHRH (Benito *et al.* 1991) and arginine (Merimee and Fineberg 1971) have reported higher GH levels in women compared to men. Premenopausal women secrete 1.5 to 3-fold more GH than men (Ho *et al.* 1987; van den Berg *et al.* 1996), and the pattern of 24-hour GH release is more disorderly in females than males (Pincus *et al.* 1996). Men have larger nocturnal GH pulses with smaller pulses during daytime, whereas women have a more continuous mode of GH secretion with more uniform pulse amplitudes (Jaffe *et al.* 1998).

#### Gonadal steroids

Several studies have shown that the administration of gonadal steroids enhances GH secretion during puberty. Ethinyl oestradiol and testosterone enanthate administration to girls with Turner's syndrome (Mauras *et al.* 1990) and prepubertal boys with constitutional delay of adolescence (Ulloa-Aguirre *et al.* 1990) respectively doubles their 24-hour endogenous GH secretion rates. Oestradiol increases the number of GH secretory pulses per 24 hours and GH secretory pulse amplitudes (Mauras *et al.* 1990), whereas testosterone increases the mass of GH secreted per pulse (Ulloa-Aguirre *et al.* 1990).

When assessed using the approximate entropy statistic, pulsatile GH secretion in boys were more disorderly during mid- to late-puberty (Veldhuis *et al.* 1997) compared to that of young men (Friend *et al.* 1996), indicating a contributory role of rising levels of gonadal steroids in inducing this phenomenon. In men, 24-hour GH secretion correlated with serum testosterone, whereas serum oestradiol positively correlated with GH half-life and inversely correlated to basal GH secretion rates (Veldhuis *et al.* 1995). These data suggest that pulsatile and basal GH secretion may be differentially regulated by testosterone and oestradiol in men.

Androgens have also been implicated to augment the effects of GH at the target site. Blok *et al.* (Blok *et al.* 1997) demonstrated that GH administration in young men with GH deficiency stimulated the growth of androgen-dependent body hair without affecting circulating free testosterone levels. Additionally, GH receptors in lean tissue

are upregulated by testosterone (Sandstedt *et al.* 1994), which partly explains the pronounced anabolic effects of GH in GH-deficient men than in women (Verhelst *et al.* 1997).

In contrast, oral but not transdermally administered oestrogen increases the mean 24-hour GH secretion and serum GHBP levels, and decreases serum IGF-I levels in women (Leung *et al.* 2004). The reduction in IGF-I may be due to the increase in local GHBP production, and the exposure of the liver to high portal oestrogen concentrations after intestinal absorption in attenuating hepatic GH-stimulated IGF-I production (Kelly *et al.* 1993). Other studies have indicated that oral oestrogens also attenuate GH/IGF-I actions in peripheral tissues. Nugent *et al.* (Nugent *et al.* 2003) demonstrated the potential use of oral oestrogen as an adjunctive treatment for acromegaly in women, whereas high doses of oestrogens were previously used to alleviate the metabolic effects of acromegaly (Clemmons *et al.* 1980).

In menopausal women, oral oestrogen therapy increases spontaneous and GHRH-stimulated GH release (Weissberger *et al.* 1991). As oral oestrogen decreases serum IGF-I levels (Weissberger *et al.* 1991) possibly by inhibiting GH induction on hepatic IGF-I synthesis (Murphy and Friesen 1988), the reduction of the negative feedback mechanism by IGF-I may also contribute in enhancing GH release by oral oestrogens. Therefore, gonadal steroids appear to regulate and contribute to the gender differences in GH secretion, the increase in GH secretion during puberty and the declining GH levels with ageing.

### Body composition

The anabolic and lipolytic effects of GH on muscle and fat tissue are well documented. In children where GH replacement therapy was first introduced in 1957, it soon became apparent that GH not only affected skeletal growth, but also altered body composition (Tanner and Whitehouse 1967). More recent studies have since substantiated these findings, with GH administration consistently increasing lean body mass and decreasing fat mass (Papadakis *et al.* 1996). Despite these changes in body composition, muscle strength or mass (Lange *et al.* 2002) and daily functional ability (Papadakis *et al.* 1996) remained unchanged. By contrast, discontinuation of GH resulted in a reduction in lean body mass and body weight (Lange *et al.* 2001).

In non-obese boys and adults, increasing relative adiposity is associated with decreased GH secretion (Hartman *et al.* 1992; Martha *et al.* 1992; Weltman *et al.* 1994). As differences in body composition exist between men and women, gender influences should also be anticipated. Weltman *et al.* (Weltman *et al.* 1994) found in 32 women and 12 men significant relationships between 24-hour integrated serum GH levels and age ( $r = -0.79$ ,  $P = 0.002$ ), percentage body fat ( $r = -0.75$ ,  $P = 0.005$ ) and aerobic fitness as measured by peak oxygen consumption ( $r = 0.58$ ,  $P = 0.05$ ), but not body mass index (BMI) ( $r = -0.53$ ,  $P = 0.08$ ). Thus, age, percentage body fat (but not BMI), and fitness are related to 24-hour GH release in young adults.

The mechanism behind the inverse relationship between body fat mass and GH secretion is unclear, and may be mediated through leptin (Gill *et al.* 1997) and insulin (Manglik *et al.* 1998). Leptin receptors are present in the hypothalamus (Erickson *et al.* 1996), and therefore may modulate somatostatin and/or GHRH release; whereas the reduction of serum insulin levels following weight loss has been shown to increase spontaneous GH pulse height (Manglik *et al.* 1998).

### Regional fat distribution

The amount of intra-abdominal visceral fat appears to be closely linked with the metabolic complications of upper body than the waist-hip ratio (Despres *et al.* 1990). Recent studies have shown that increased amounts of intra-abdominal visceral fat are associated with low serum IGF-I concentrations (Rasmussen *et al.* 1994), and diminished GH

responses to pharmacological stimuli (Vahl *et al.* 1996). In stepwise regression models, the amount of visceral fat is a stronger predictor of 24-hour GH secretion than age, gender, percentage body fat or measures of aerobic fitness in non-obese individuals (Vahl *et al.* 1997). Whether abdominal adiposity is a cause or an effect of reduced GH secretion is unclear. Two possible hypotheses could be considered, i.e., increased plasma levels of insulin and free fatty acids (FFAs) associated with abdominal adiposity may result in a negative feedback on GH secretion, or reduced GH secretion might allow for the accumulation of abdominal fat.

### Obesity

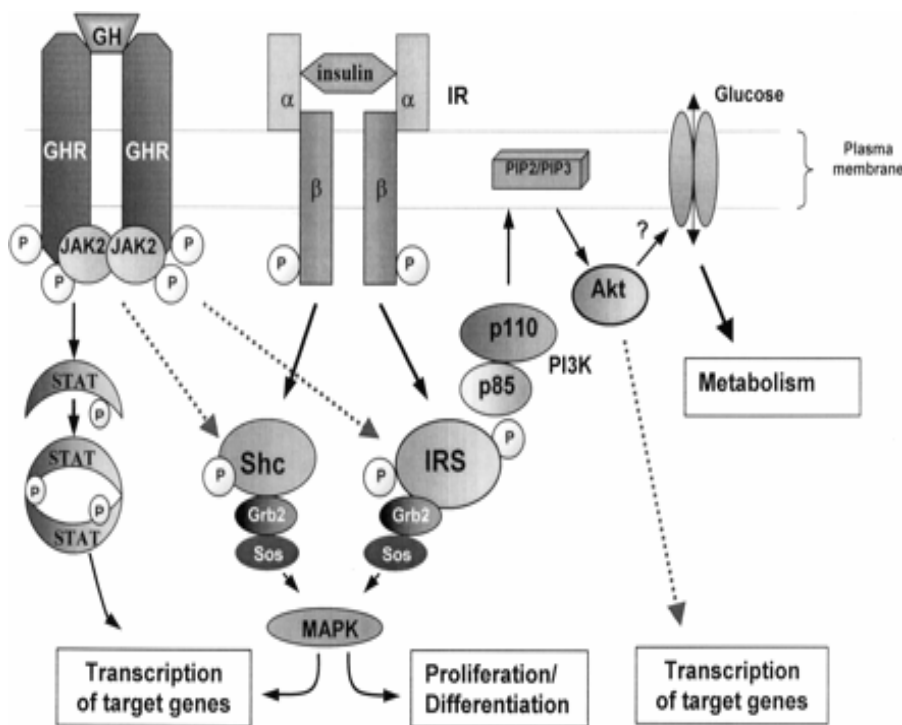
Obese patients display impaired spontaneous GH secretion and somatotroph responsiveness to provocative stimuli such as insulin-induced hypoglycaemia, GHRH, arginine, clonidine and various combinations of these pharmacological agents (Cordido *et al.* 1990; Tanaka *et al.* 1990; Maccario *et al.* 1997). However, Cordido *et al.* (Cordido *et al.* 1993) showed that GHRH increased serum GH levels, thus demonstrating that the pituitary in obese subjects retains significant GH secretory capacity. The GH insufficiency in obese subjects is reversible after marked weight loss (Williams *et al.* 1984). Despite lower 24-hour integrated GH concentrations resulting from both reduced pulsatile GH secretion and accelerated metabolic clearance, the circadian rhythmicity remains preserved (Veldhuis *et al.* 1991). Recent studies using more sensitive GH assays have consistently reported that with increasing body fat, the amplitude of GH pulses and mass of GH secreted per pulse decreases without any changes in GH pulse frequency (Rasmussen *et al.* 1995a, 1995b; Veldhuis *et al.* 1995). Among the metabolic aberrations associated with obesity, chronic elevation of FFA levels (Cordido *et al.* 1996) and hyperinsulinism (Clemmons and Underwood 1991; Chapman *et al.* 1998) probably play a role in causing GH insufficiency. Hyperinsulinaemia decreases serum IGF-BP-1 and increases free IGF-I levels, thereby inhibiting GH release without altering total IGF-I levels (Chapman *et al.* 1998). Increased hypothalamic somatostatin secretion may also reduce GH secretion in obese subjects following reports of enhanced GH response to GHRH after the administration of arginine, which inhibits somatostatin release (Cordido *et al.* 1990; Maccario *et al.* 1997).

### Growth hormone action

The major physiological function of GH in humans is growth promotion. In children, GH deficiency causes short stature, whereas increased GH secretion in pre-pubertal children and in adults lead to gigantism and acromegaly, respectively. Recombinant GH administration stimulates longitudinal bone growth and skeletal muscle growth, and has a more robust effect than IGF-I on longitudinal bone growth in animals, although the effects of GH and IGF-I may also be additive (Fielder *et al.* 1996).

In healthy adults, GH exerts several metabolic effects, including effects on carbohydrate, protein and fat. Growth hormone is also an anabolic hormone, inducing positive nitrogen balance and protein synthesis in muscle (Manson and Wilmore 1986). Muscle size is increased in GH-deficient individuals undergoing GH replacement therapy at all ages (Manson and Wilmore 1986; Rudman *et al.* 1990). Because GH enhances amino acid uptake into skeletal muscle, it has been suggested that this tissue is the primary target of the physiological effects of GH (Fryburg and Barrett 1993).

Growth hormone therapy increases lean body mass by enhancing protein synthesis, with little effect on protein degradation (Wolf *et al.* 1992). Concomitant with the increase in lean body mass, nitrogen balance is shifted toward retention (Horber and Haymond 1990), with the reduction in urinary urea excretion, urea fluxes and urea production rates (Manson and Wilmore 1986; Lundberg *et al.* 1991). It is particularly noteworthy that when endogenous GH action is partially blocked under conditions of fasting, urea produc-



**Fig. 4 Convergence between insulin and GH signalling.** The insulin receptor phosphorylates IRS proteins, resulting in the activation of p110. The lipid products of PI 3-kinase activation (PIP2 and PIP3) recruit protein kinase B (Akt) to the plasma membrane. Engagement of Grb2/Sos by tyrosyl-phosphorylated IRSs proteins and Shc is expected to activate p21<sup>ras</sup> and the downstream MAP kinase cascade. Growth hormone induced dimerization of the GH receptor leads to activation of JAK2 and phosphorylation of Shc and the IRS proteins. This signaling cross-talk (shown in dotted lines) is thought to be important for the insulin-like and anti-insulin like effects of GH. Fig. 1 from Dominici and Turyn (2002) *Experimental Biology and Medicine (Maywood)* **227**, 149-157, with kind permission by the Society for Experimental Biology and Medicine.

tion rates rise by more than 50%, strongly affirming the importance of GH as a protein-conserving agent during fasting (Norrelund *et al.* 2001).

Growth hormone also has lipolytic actions on fat and muscle. This effect is mediated by the inhibition of lipoprotein lipase, an enzyme involved in the lipid accumulation in adipocytes (Ottosson *et al.* 1995). Long-term effects of GH include decreased fat deposition and increased fat mobilization. Growth hormone also causes mild reductions in low-density lipoprotein (LDL) cholesterol levels and small elevations in high-density lipoprotein (HDL) cholesterol (Asayama *et al.* 1984). Acute administration of GH to fat and other tissue explants causes a temporary insulin-like effect on glucose uptake. In contrast, chronic excessive exposure to GH leads to insulin resistance associated with hyperinsulinemia (Rosenfeld *et al.* 1982). Prolonged high doses of GH administration ultimately results in hyperglycemia that is associated with enhanced hepatic gluconeogenesis and glycogenolysis, and may also be indirectly caused by the lipolysis induced by GH; the so-called 'lipotoxic' effect (Randle *et al.* 1963).

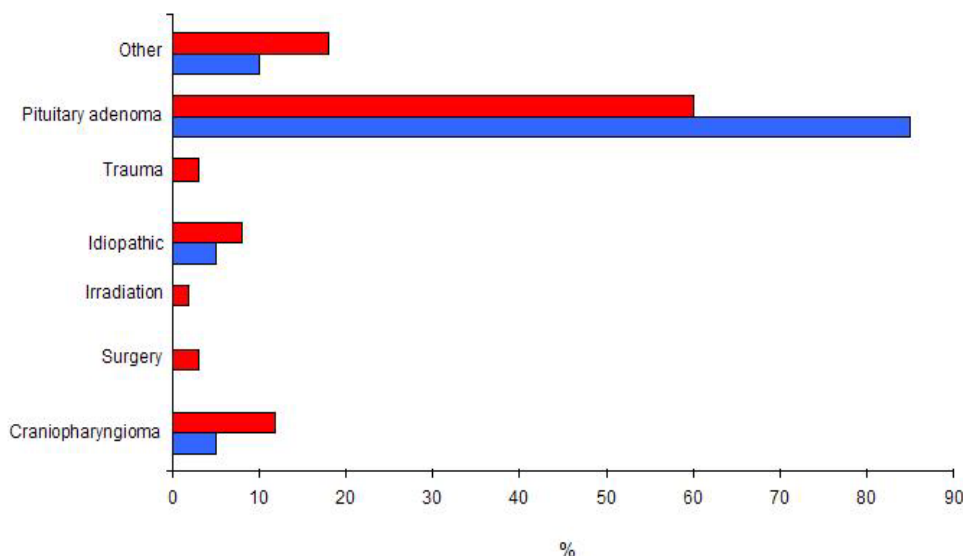
### Mechanism of GH action

The GH receptor utilises the janus kinase (JAK)-signal transducer and activator transcription pathway (Carter-Su and Smit 1998). The binding of the GH molecule induces conformational changes to the GH receptor, and the activated GH receptor associates with JAK2 (Fig. 2). Upon activation by GH, JAK2 phosphorylates multiple intracellular GH receptor tyrosine residues (Carter-Su and Smit 1998), thus activating several different signalling pathways. Additionally, GH receptor activation induces tyrosine phosphorylation of the insulin receptor substrate (IRS) proteins IRS-1 and IRS-2, which subsequently associate with phosphatidylinositol (PI)-3'-kinase in various GH-responsive cell types (Argetsinger *et al.* 1996; Souza *et al.* 1994). The PI-3'-kinase pathway requires the IRS molecules, which are likely to be phosphorylated by JAK2 (Souza *et al.* 1994; Argetsinger *et al.* 1996). Activation of the IGF-I receptor also stimulates the phosphorylation of the IRS family of signalling proteins (le Roith and Butler 1999), thus providing a mechanism for cross-talk between GH and IGF-I at the level of signal transduction, and therefore explains the ability of GH to exhibit insulin-like activity (Argetsinger *et al.* 1996; Ridderstrale and Tornqvist 1996) (Fig. 4).

Growth hormone stimulation has also been shown to regulate gene expression of IGF-I and many of the IGF-binding proteins (IGFBPs), including the acid labile subunit (ALS) (Jones and Clemmons 1995). *In situ* hybridization studies show that the messenger ribonucleic acids (mRNAs) encoding IGF-I, IGFBP-3, and ALS are not co-localised within the same cells in the liver (Chin *et al.* 1994). Hepatocytes express mRNAs encoding IGF-I and ALS, whereas IGFBP-3 mRNA is exclusively expressed in adjacent endothelial cells of the hepatic sinusoids. Unlike hepatocytes, sinusoidal endothelial cells of the liver do not express detectable levels of GH receptor mRNA. Thus, the regulation of IGFBP-3 levels by GH is presumably indirect and likely to be mediated by IGF-I, as demonstrated by the marked reduction in circulating IGFBP-3 levels in liver-specific IGF-I gene-deleted mice despite elevated GH levels and the reversal of this effect following rhIGF-I administration (Yakar *et al.* 2001). In contrast, hepatocytes do not express detectable levels of IGF-I receptor mRNA, indicating that IGF-I presumably does not act on hepatocytes directly, but rather relies on the inhibition of GH to complete the feedback circuit.

### Modes of GH exposure and biological efficacy

Studies examining the pharmacological aspects of rhGH therapy have shown that daily evening subcutaneous GH therapy improved linear growth response in prepubertal GH-deficient children compared to thrice weekly injections despite using similar GH doses (MacGillivray *et al.* 1996). However, less consistent results have been shown in GH-deficient adults. Amato *et al.* demonstrated that daily *versus* thrice weekly rhGH injections were equally effective in GH-deficient adults in increasing serum IGF-I levels and improving lipid and bone metabolism, bone mineral density and body composition (Amato *et al.* 2000). Similarly, alternate day GH administration to GH-deficient adults induced a sustained increase in protein synthesis and lipolysis (Lucidi *et al.* 2000). The timing of administration of rhGH injections is also an important factor. Evening subcutaneous GH injections appear to mimic endogenous GH secretion more closely by inducing higher circulating GH levels during the early hours of the night (Jorgensen *et al.* 1990b). Reduced elimination rates of GH administered in the evening may possibly account for these findings, as the half-life of exogenous and endogenous GH have been shown to be



**Fig. 5 Aetiology of GH deficiency in patients > 65 years (red bars) and < 65 years (blue bars).** X-axis represents the % of patients with various causes of GH deficiency derived from the Pharmacia International Metabolic Database (KIMS). Adapted from Feldt-Rasmussen *et al.* (2002).

prolonged in the evening compared to the morning (Holl *et al.* 1993).

### Growth hormone pharmacokinetics and pharmacodynamics

The serum profile following subcutaneous GH injections is intermediate between a pulsatile and continuous GH pattern, characterised by protracted absorption and disappearance of GH (Jorgensen *et al.* 1990a). Maximal absorption after a subcutaneous GH injection is 4 to 6 hours (Jorgensen *et al.* 1990a), whereas the half-life of GH after subcutaneous administration is 5.3 hours (Laursen *et al.* 1993) reflecting not only elimination but also distribution and absorption of GH. Following continuous subcutaneous GH infusion, steady state serum levels were reached after 16 hours (Laursen *et al.* 1996). In contrast, the bioavailability after subcutaneous administration ranges from 50% to 63%, which is lower compared with intravenous (iv) administration (Laursen *et al.* 1996). The reduction in bioavailability of GH following subcutaneous administration might be caused by local degradation of GH at the injection site (Jorgensen *et al.* 1988), impaired ability of some assays to recognise the GH molecule due to the alteration of the immunoreactivity of the molecule during its passage through subcutaneous tissues (Jorgensen *et al.* 1988), and possibly the disappearance of small amounts of GH into the lymphatic system (Charman *et al.* 2000). However, the reduction of the bioactivity of subcutaneous compared with iv GH administration was apparently of a smaller magnitude (15 to 20%) than bioavailability (Laursen *et al.* 1996), which may be due to degraded but still bioactive GH molecules. Thus, daily evening subcutaneous injections appear to provide an approximated physiological GH administration regimen with acceptable bioavailability and without appreciable reductions in bioactivity.

## ADULT GROWTH HORMONE DEFICIENCY

### The syndrome of growth hormone deficiency in adults

Prior to its characterization over 20 years ago, adult growth hormone (GH) deficiency was not regarded as a clinical syndrome as it was thought that GH did not play a physiologic role in adulthood. The first anecdotal evidence that GH replacement may have a role in adults came from a case report where a 35 year-old woman with hypopituitarism given GH subsequently reported improved vigour and well-being (Raben 1962). Adult GH deficiency is now a recognized clinical syndrome (Cuneo *et al.* 1992) with abnormalities in body composition, physical and affective disturbances, and increased rate of malignancies and cardiovas-

cular risk even when all other pituitary hormones are intact or adequately replaced (McCallum *et al.* 2002; Svensson *et al.* 2004; Abs *et al.* 2006).

A major reason for overlooking the potential role of GH in treating adult hypopituitary patients with GH deficiency was the limited supply of pituitary-derived GH as the preparation was extracted from human cadaver pituitaries (Raben 1958). Extracted preparations of GH were used for the treatment of children with GH deficiency until 1985, when its use was discontinued worldwide because of its association with cases of Creutzfeldt-Jakob disease. Since the mid-1980s, when all GH in clinical use has been recombinant DNA-derived biosynthetic human GH that is free of the Creutzfeldt-Jakob prions, many studies have been performed resulting in a major reappraisal of its physiologic role in adult life and confirming the importance of treating this syndrome; similar to deficiencies in thyroid hormone, cortisol, and sex steroids that are routinely replaced.

Growth hormone as replacement therapy for GH-deficient adults was approved by the United States Food and Drug Administration in 1996. Subsequently, the introduction of recombinant GH replacement therapy for the treatment of GH-deficient adults has opened up new treatment avenues and great progress has been achieved in our understanding of GH physiology in adults with GH deficiency. Although treatment appears to be safe overall, there have also been theoretical concerns in certain areas necessitating long-term surveillance, including risks of glucose intolerance, pituitary/hypothalamic tumor recurrence, and cancer (Society 2001). Thus, it is now apparent that GH dosing is not a simple process that lends itself to the use of a chart or formula, and that an experienced endocrinologist should be involved in initiating GH therapy and monitoring responsiveness, using appropriate laboratory and imaging studies to follow these patients.

### Aetiology

Adult GH deficiency most commonly results from pituitary or peripituitary tumours and their treatment, and the commonest tumours being benign pituitary adenomas (Fig. 5). The incidence of adult GH deficiency is not known, but indirect estimates based on the incidence of pituitary tumours suggest an incidence of 10 people per million per year, with childhood-onset GH deficiency being the most common idiopathic cause, and not necessarily associated with other pituitary hormone deficiencies. In 1998, KIMS (Pharmacia International Metabolic Database), a pharmaco-epidemiological survey of adult GH-deficient patients receiving GH replacement therapy, reported a total of 2084 GH-deficient patients from 16 countries have been recruited into the database (Feldt-Rasmussen *et al.* 2002).

## Consequences of GH deficiency

In 1990, it was first suggested that hypopituitary patients had increased cardiovascular mortality (Rosen and Bengtsson 1990), and it was postulated that this excess mortality was related to cardiovascular and cerebrovascular (Svensson *et al.* 2004) mortality. In addition, GH-deficient adults suffer from a range of metabolic, body compositional and functional abnormalities (Table 1).

### Features of untreated adult GH deficiency versus healthy controls

#### Carbohydrate

Growth hormone deficient adults exhibit many features such as central obesity, dyslipidaemia, insulin resistance and glucose intolerance (Carroll *et al.* 1998) that resemble those observed in patients with the metabolic syndrome. In keeping with the increase in central adiposity, studies have reported that GH-deficient adults have higher fasting insulin levels (Cuneo *et al.* 1992) and increased prevalence of abnormal glucose tolerance (Beshyah *et al.* 1995b) than carefully matched controls. However, despite higher integrated insulin responses to these glucose levels, frank diabetes was not commonly observed in these patients. Previous studies have used a variety of techniques to assess insulin sensitivity in GH-deficient adults, and these studies report strikingly similar results. O'Neal *et al.* (1994) and Fedou *et al.* (1996) using the iv glucose tolerance test and Bergman's minimal model analysis respectively demonstrated almost 50% reduction in whole-body insulin sensitivity, whereas Johansson *et al.* (1995) and Hew *et al.* (1996) reported reductions in insulin sensitivity by more than 50% in GH-deficient adults with the hyperinsulinaemic euglycaemic clamp technique compared to carefully matched controls. Similarly, insulin sensitivity was reduced using the homeostasis model assessment (Weaver *et al.* 1995) and the modified insulin suppression test (Hwu *et al.* 1997). However, these studies also suggest that insulin resistance is not only confined to overweight GH-deficient adults and is not related to the number of deficient pituitary hormones (Hew *et al.* 1995), but more so to the duration and severity of GH deficiency (Hew *et al.* 1996). Hew *et al.* also demonstrated, using the muscle biopsy technique, a 64% reduction in insulin-mediated glucose uptake associated with reduced glucose disposal and glycogen synthesis in GH-deficient adults (Hew *et al.* 1996). These data, thus, indicate that the insulin resistance seen in patients with GH

deficiency may be part explained by the inhibition of the glycogen synthase pathway.

However, the mechanisms of insulin resistance in GH deficiency compared to GH excess may be different. The diabetogenic properties of chronic supraphysiological GH exposure is characterised in active acromegalic patients with virtually all studies describing a 2- to 3-fold increase in basal insulin levels (Bolinder *et al.* 1986) and small increments in circulating glucose levels (Hansen *et al.* 1986; Moller *et al.* 1992). The reduction in insulin sensitivity in acromegalic patients is confirmed by hyperinsulinaemic glucose clamp studies, where the impairment in insulin action is due to both hepatic and peripheral insulin resistance (Hansen *et al.* 1986; Moller *et al.* 1992). In contrast to patients with GH deficiency, patients with acromegaly do not demonstrate abnormal fat distribution. It is therefore more likely that the insulin resistance in patients with acromegaly may be the result of a direct effect of excess GH exposure.

#### Lipids and lipoproteins

Growth hormone has important effects on the regulation of lipoprotein metabolism. Growth hormone deficient patients have increased levels of total cholesterol, LDL-cholesterol and apolipoprotein B (ApoB) (Cuneo *et al.* 1993; de Boer *et al.* 1994). High-density lipoprotein cholesterol levels tend to be lower, and triglyceride levels higher when compared with healthy controls (Cuneo *et al.* 1993), thus contributing to the premature atherosclerosis associated with GH-deficient patients. The lipid dysregulation in adults with GH deficiency is such that, based on data from the Framingham Study that predicts the risk of coronary heart disease from triglyceride and HDL cholesterol levels, would predict a two- to three-fold increase in coronary heart disease risk in these patients resulting from their abnormal lipid profiles alone (Abdu *et al.* 2001).

#### Body composition

The anabolic, lipolytic and antinatriuretic actions of GH have been shown in several *in vitro* and *in vivo* studies to exert an impact on body composition. The techniques used to assess body composition rely on assumptions derived from healthy subjects, e.g. constant hydration state of lean tissue, constant intracellular potassium concentration or a constant fat-free extracellular compartment. Although these assumptions may not be valid in GH-deficient adults, recent studies using imaging techniques (Bengtsson *et al.* 1993; Snel *et al.* 1995) have shown similar results to previous findings.

Reduced lean body mass and increased fat mass are important features of adult-onset GH deficiency (Binnerts *et al.* 1992; Amato *et al.* 1993; Bengtsson *et al.* 1993). Initial studies showed a mean reduction in lean body mass of 7-8%, with a similar profile reported from long-term follow-up (Gibney *et al.* 1999; Chrisoulidou *et al.* 2000). Salomon *et al.* (1989) reported a 7% higher mean fat mass in GH-deficient adults compared to with predicted values based on age, sex and height. These findings have since been confirmed by other investigators using a variety of techniques to assess body composition (Binnerts *et al.* 1992; de Boer *et al.* 1992; Beshyah *et al.* 1995a). The fat mass in GH-deficient adults are mainly distributed in the abdominal compartment, resulting in an increased waist:hip ratio (Salomon *et al.* 1989; Amato *et al.* 1993; Bengtsson *et al.* 1993).

#### Cardiovascular mortality

Excess cardiovascular mortality in hypopituitary patients with untreated GH deficiency was first reported in 1990 (Rosen and Bengtsson 1990). Rosen *et al.* (1993) later reported higher rates of hypertension, whereas others have found an increase in procoagulant factors (Johansson *et al.* 1994) in GH-deficient patients. Other markers for athero-

**Table 1** Syndrome of adult GH deficiency.

Symptoms	Increased body fat, reduced muscle bulk, muscle strength and physical fitness Impaired psychological well-being Depressed mood Emotional lability Anxiety Impaired self control Reduced physical stamina Poor motivation and energy Increased social isolation Abnormal sleep patterns
Signs	Overweight, with predominantly central (abdominal) obesity Poor muscular development Reduced exercise performance Thin, dry skin Depressed affect
Investigations	Peak GH response to hypoglycaemia < 3 µg/L Low or low normal IGF-I levels Hyperlipidaemia (high LDL cholesterol and low HDL cholesterol) Reduced lean body mass/increased fat mass Increased fasting insulin levels Reduced bone mineral density

sclerotic changes such as increased arterial intima-medial thickness and carotid arterial stiffness (Markussis *et al.* 1997), decreased flow-mediated arterial dilatation (Evans *et al.* 1999) and abnormalities in cardiac structure and function (Merola *et al.* 1993) have also been reported in these patients. Svensson *et al.* (2004) recently reported the results of a retrospective study, and found that the overall mortality and the rate of myocardial infarctions was increased in 1411 hypopituitary adults without GH replacement (mean age 56.9 years) compared to the normal Swedish population. However, they also observed an increased rate of cerebrovascular events in hypopituitary adults on long-term GH replacement therapy, thus raising the question that factors other than GH in the overall treatment may play a role in influencing the out-come in these patients (Svensson *et al.* 2004).

Variations in the replacement of other hormones such as sex steroids, glucocorticoids, and thyroid hormone, altered body composition, lipid profile and insulin sensitivity and abnormalities of cardiac structure and function, together with endothelial and dynamic functional changes may all also explain the increased cardiovascular mortality seen in patients with GH deficiency. However, as rhGH has only been available since the late 1980's, no data is yet available to ascertain the long-term effects of GH on arteriosclerosis and cardiovascular mortality.

## GROWTH HORMONE REPLACEMENT THERAPY IN GH-DEFICIENT ADULTS

### Effects of GH on insulin resistance and glucose metabolism

Previous studies have shown deleterious effects of GH replacement on insulin sensitivity in GH-deficient adults, particularly where high doses of GH were administered over a prolonged period of time. Salomon *et al.* reported an increase in both fasting glucose and insulin levels after 6 months administration of 0.2 mg/kg/day of GH replacement in GH-deficient adults (Salomon *et al.* 1989). Beshyah *et al.* showed that 6 and 18 months of GH (0.9 mg/kg/week) replacement resulted in the deterioration of the plasma insulin to glucose ratios during the OGTT with increasing duration of GH replacement (Beshyah *et al.* 1995b). Similar results were obtained by Weaver *et al.* with the reduction in insulin sensitivity after 6 months of GH (0.8 mg/kg/week) replacement in 22 GH-deficient adults using the homeostasis model of assessment, with a further reduction after 12 months (Weaver *et al.* 1995).

Using the hyperinsulinaemic euglycaemic clamp, Fowelin *et al.* demonstrated that fasting glucose and insulin levels were elevated after 6-week GH replacement, but returned to baseline at 26 weeks (Fowelin *et al.* 1993). These changes suggest short-term reductions in insulin-mediated glucose utilisation induced by GH therapy, with the reversal of these changes over time, perhaps secondary to altered body composition. Using the iv glucose tolerance test, O'Neal *et al.* demonstrated a marked reduction in insulin sensitivity after 7 days of GH (0.7 mg/kg/week) replacement, associated with increased FFA levels in a group of GH-deficient adults (O'Neal *et al.* 1994). After 3 months of GH treatment, fasting insulin and C-peptide levels remained elevated but all other variables had returned to baseline. Rosenfalck *et al.*, using the iv glucose tolerance test and the minimal model, reported similar findings after 4 months of GH (6 mg/m<sup>2</sup>) therapy of reduced insulin sensitivity despite favourable changes in body composition, and an inadequate enhancement of insulin secretion (Rosenfalck *et al.* 1999). Using a lower GH dose (mean 0.53 mg/day) for 30 months, Rosenfalck *et al.* further reported a reduction in insulin sensitivity in these patients despite an increase in lean body mass and a reduction of fat mass (Rosenfalck *et al.* 2000). In another study employing the hyper-insulinaemic euglycaemic clamp technique with serial muscle biopsies to measure total glycolysis and glu-

cose storage rates, Christopher *et al.* noted a persistent worsening in insulin sensitivity in GH-deficient adults treated with GH (0.7 mg/kg/week) for 6 and 24 months (Christopher *et al.* 1998). Compared to matched controls, total glycolysis, glucose storage rates, and glycogen synthase activity were reduced, whereas intramuscular glucose and glycogen concentrations were increased and decreased respectively, both prior to and after GH therapy (Christopher *et al.* 1998). These metabolic muscle abnormalities of insulin action persisted in the GH-treated patients, despite reductions in abdominal fat (Christopher *et al.* 1998). This contrast with the data by Hwu *et al.*, where insulin sensitivity was noted to return to baseline levels after 12 months of GH (0.8 mg/kg/week) replacement (Hwu *et al.* 1997). However, their subjects were younger (mean age of 29.5 years), leaner (BMI: 22.8 kg/m<sup>2</sup>), and were not insulin resistant prior to the commencement of GH replacement (Hwu *et al.* 1997). In line with the results reported by Hwu *et al.*, Jorgensen *et al.* also noted the normalisation in insulin sensitivity in a small group of GH-deficient subjects after 5 years of GH replacement (Jorgensen *et al.* 1994). One explanation for this is that the GH deficiency of their subjects were also of childhood onset, similar to Hwu *et al.* (1997), suggesting that childhood onset disease responds differently to GH replacement compared to their adult onset counterparts (Attanasio *et al.* 1997). Other longer-term studies, however, show no changes in insulin sensitivity with GH replacement. Gibney *et al.* (1999) and Chrisoulidou *et al.* (2000) failed to show any difference after 10 and 7 years respectively in fasting glucose and insulin levels in GH-deficient adults receiving GH replacement.

Growth hormone replacement has been shown to enhance lipid oxidation in GH-deficient adults (Salomon *et al.* 1997). Suppression of FFA during hyperinsulinaemic clamps in GH-deficient adults is also less than that of the matched healthy control subjects, even after the reduction in abdominal fat mass post-GH therapy (Christopher *et al.* 1998). Thus, free fatty acid together with the defective glucose phosphorylation and muscular glycogen synthase activity in GH-treated GH-deficient adults probably plays a prominent role in the persistence of insulin resistance in GH-treated subjects, although the exact site of the defect(s) in insulin action is still unknown (Christopher *et al.* 1998).

Thus, GH-deficient adults are predisposed to insulin resistance, and most long-term studies using various doses of GH replacement have demonstrated the diabetogenic effects of GH replacement, despite its favourable effects on body composition. The exact mechanism is unclear, but may be related to the chronic induction of GH in altering FFA metabolism, thus implying that the GH doses used in many studies may have been still too high. Despite the persistence of hyperinsulinaemia with modest worsening in insulin sensitivity in some patients, no study has demonstrated any adverse long-term sequelae on glucose tolerance, although the net impact of continuing insulin resistance and hyperinsulinaemia is a theoretical risk for future cardiovascular events.

### Effects of GH on body composition

Many studies have been performed examining the effects of GH replacement on body composition in GH-deficient adults. Although these studies differ considerably in terms of age, the presence or absence of multiple pituitary hormone deficiency, whether GH deficiency was childhood or adult onset, and the various methods employed, the results are remarkably consistent. Using various methods to assess body composition, studies have shown that mean lean body mass increases between 2 to 5.5 kg following GH replacement in both childhood and adult onset GH-deficient adults compared to untreated controls (Binnerts *et al.* 1992; Amato *et al.* 1993; Bengtsson *et al.* 1993). More recent studies employing lower GH doses have revealed similar results (Rosenfalck *et al.* 2000), with skeletal muscle increasing in a parallel manner. Significant increases in thigh muscle cross-sectional area (Jorgensen *et al.* 1994) have been ob-



served, with these changes being sustained up to 10 years following the commencement of GH replacement (Gibney *et al.* 1999; Chrisoulidou *et al.* 2000).

Growth hormone replacement results in a reduction of mean fat mass between 4 to 6 kg in both childhood-onset and adult-onset GH-deficient adults compared to untreated controls (Binnerts *et al.* 1992; Amato *et al.* 1993; Bengtsson *et al.* 1993), with important changes occurring in the abdominal region (Salomon *et al.* 1989). Studies using computed tomography (Bengtsson *et al.* 1993) and magnetic resonance imaging (Snel *et al.* 1995) have shown that the reduction in abdominal fat mass is mainly due to a reduction in visceral fat mass, but these changes were not sustained in long-term follow-up studies (Gibney *et al.* 1999; Chrisoulidou *et al.* 2000) possibly because of the confounding factor of ageing. However, these studies did reveal that GH replacement prevented the increase in waist:hip ratio associated with ageing, suggesting that GH replacement does induce beneficial effects on the distribution of body fat, despite ageing. These findings are of great significance given the well-known association between visceral obesity and coronary heart disease, and the predisposition of GH-deficient adults with premature mortality from cardiovascular disease (Rosen and Bengtsson 1990).

### Effects of GH on cardiovascular risk factors

Studies with arterial ultrasonography have shown that hypopituitary GH-deficient adults have increased atheromatous plaques in carotid and femoral arteries compared with controls (Markussis *et al.* 1992). Other markers of atherosclerosis in GH-deficient patients include increased greater intima-media thickness and carotid arteries, and decreased aortic distensibility (Markussis *et al.* 1997). The effect of long-term GH replacement on intima-media thickness in hypopituitary patients has been investigated in an open study, and demonstrated potent inhibitory effects of GH replacement on intima-media thickness progression that was maintained after 2 years (Borson-Chazot *et al.* 1999), implying that GH treatment exerted vasodilatory properties on the endothelium.

Several short-term studies with GH treatment to GH-deficient adults have shown a reduction in total and LDL-cholesterol (Cuneo *et al.* 1993), and an increase in HDL-cholesterol (Russell-Jones *et al.* 1994), with unchanged triglyceride (Cuneo *et al.* 1993; Russell-Jones *et al.* 1994) levels. An 18-month placebo-controlled trial found no changes in serum lipoprotein levels (Baum *et al.* 1996), but a sustained increase in HDL-cholesterol and reduced triglyceride and LDL-cholesterol levels in two studies of 18 and 24 months of GH treatment, respectively (Beshyah *et al.* 1995b; Johannsson *et al.* 1996b). The differences in previous results might be explained by variations in the individual response, small cohorts of patients, and differences in the duration of hypopituitarism and in baseline lipoprotein levels.

Growth hormone has a complex action on lipid metabolism. Growth hormone affects both hepatic production and secretion of lipoproteins and their clearance from the circulation (Angelin and Rudling 1994), and increases the hepatic LDL receptor activity (Rudling *et al.* 1992). The increased VLDL production and turnover, together with increased LDL receptor activity will increase HDL cholesterol levels, thus explaining the favourable effects of GH treatment on HDL cholesterol despite unchanged LDL cholesterol levels (Eisenberg 1984). In contrast, the elevated triglyceride levels in GH-deficient patients might be secondary to their central adiposity (Snel *et al.* 1995) and insulin resistance (Johannsson *et al.* 1995). However, even with the reduction in central fat observed following GH treatment, triglyceride levels remain unchanged, apart from those with high baseline levels (Bengtsson 1993). The relatively unchanged triglyceride levels following GH treatment may be due to increased peripheral catabolism secondary to increased lipoprotein lipase activity in muscle (Oscarsson *et*

*al.* 1996), and the relatively unchanged S<sub>1</sub> observed after most long-term studies (Svensson *et al.* 2002; Giavoli *et al.* 2004b).

There is increasing evidence linking the association of lipoprotein (a) with coronary heart disease (Rader and Brewer 1992; Sandholzer *et al.* 1992). Apart from one study where GH treatment did not modify lipoprotein (a) levels (Russell-Jones *et al.* 1994), most studies have shown that GH treatment increased lipoprotein (a) levels (Garry *et al.* 1996; O'Halloran *et al.* 1996). The increase in lipoprotein (a) levels suggest that GH induces an increase in hepatic lipoprotein (a) secretion, as lipoprotein (a) binds to LDL receptors and GH administration induces the LDL receptor activity. The significance of the increase in lipoprotein (a) levels during GH treatment with cardiovascular disease is unclear and requires further clarification.

The effects of GH replacement on other cardiovascular surrogate markers have also been demonstrated in many, but not all studies. Adult GH-deficient patients exhibit increased fibrinogen and plasminogen-activator inhibitor type 1 activity (Johansson *et al.* 1994). Increased fibrinogen levels and plasminogen-activator inhibitor type 1 activity have been associated with increased cardiovascular morbidity and mortality (Hamsten *et al.* 1987). The effects of GH treatment on fibrinogen and plasminogen-activator inhibitor type 1 activity in GH-deficient patients are not fully elucidated, but data suggest a favourable reduction in plasminogen-activator inhibitor type 1 activity after 24 months of GH treatment (Johansson *et al.* 1996). In contrast, Hana *et al.* failed to demonstrate any changes in adiponectin levels after 12 months of GH replacement (Hana *et al.* 2004), whereas Sesmilo *et al.* reported a reduction in inflammatory cardiovascular risk markers such as C-reactive protein and interleukin-6 (Sesmilo *et al.* 2000) after 18 months of GH replacement.

Reductions in intima-medial thickness were reported after 10 years of GH replacement by Gibney *et al.* (Gibney *et al.* 1999), whereas Twickler *et al.* (Twickler *et al.* 2000) demonstrated improvements in flow-mediated dilatation after 6 months of GH replacement. Two studies of 6 months (Caidahl *et al.* 1994) and 2 years (Johannsson *et al.* 1996a) duration of GH replacement showed reduced diastolic blood pressure; however, another study failed to show any effect (Beshyah *et al.* 1994). Positive effects of GH on cardiac structure and function are more consistently reported. Amato *et al.* (1993) demonstrated increases in left ventricular mass index and left ventricular ejection fraction, while Colao *et al.* (2001) confirmed these findings in both childhood-onset and adult-onset GH deficiency; however, these parameters did not normalise.

In summary, there is sufficient evidence to indicate unequivocal improvements in most, but not all, cardiovascular risk factors following GH treatment in GH-deficient adults. Despite the lack of cardiovascular mortality data in these patients, the positive results of GH replacement studies on most surrogate markers of cardiovascular risk bodes optimism on the reduction of future cardiovascular events in these patients.

### BENEFITS OF GH REPLACEMENT IN ADULT GH DEFICIENCY

Adult GH deficiency is treated by replacing GH that is injected using almost painless insulin syringes or GH pen devices into the subcutaneous tissue of the abdomen or thigh muscle once a day at bedtime to mimic physiological pituitary GH secretion. The effects of GH replacement in adults with GH deficiency have been studied extensively in recent years, and these studies report remarkably consistent results (Brixen *et al.* 2000; Monson *et al.* 2000; Sesmilo *et al.* 2000; Lange *et al.* 2001; Simpson *et al.* 2002; Svensson *et al.* 2002; Hana *et al.* 2004; Maison *et al.* 2004; McCallum *et al.* 2005; Yuen *et al.* 2005). Beneficial effects on body composition have been almost universally observed, with fat mass and volume decreasing by 7% to 15%, while lean body mass and skeletal muscle volume increasing by 5% to

10% with no change in overall body weight. Growth hormone replacement also improves the impaired cardiac function and exercise performance of GH-deficient adults – effects that have been shown to persist for at least three years of GH therapy. Exercise capacity, as measured by maximal oxygen consumption, is nearly normalized with GH therapy, and consistent with this, muscle volume increases. With regard to bone, GH replacement increases markers of both bone formation and resorption, indicating a general stimulation of turnover and remodeling. Anabolic bone results are maximal among individuals with low pretreatment bone mineral density and least apparent in the elderly, in whom GH-independent mechanisms of bone loss may prevail.

The benefits of GH replacement on cardiovascular surrogate markers are, however, less clear-cut. Beneficial effects on classical lipid parameters are observed in some, but not all studies, including decreases in total cholesterol, low density lipoprotein, apolipoprotein B, and possibly triglycerides among GH-deficient patients with high baseline values. Some studies also report small increases in high density lipoprotein and lipoprotein (a), independent risk factors for coronary heart disease and myocardial infarction. The effects of GH treatment on fibrinogen and plasminogen-activator inhibitor type 1 activity in GH-deficient patients are not fully elucidated, but data suggest a favourable reduction in plasminogen-activator inhibitor type 1 activity. Other cardiovascular surrogate markers such as adiponectin do not appear to be affected, whereas reductions in C-reactive protein and interleukin-6 levels, and intima-medial thickness (Gibney *et al.* 1999) have been observed following GH therapy. However, with regard to blood pressure, two studies (Caidahl *et al.* 1994; Johannsson *et al.* 1996b) showed a reduction in diastolic blood pressure, but one study failed to demonstrate such an effect (Beshyah *et al.* 1994).

The strong consensus of published reports is that GH therapy ameliorates the psychological and social problems in GH-deficient adults. Improvements have been documented in subjective well being, mood, energy, sleep, emotional reaction, behaviour, pain perception, and overall quality of life. These endpoints are highly subjective, and proper blinding in these studies is difficult to achieve. Nevertheless, there is remarkable concordance among numerous investigations employing diverse methods of evaluation such as the Nottingham Health Profile, the Psychological and General Well-Being Schedule, the Comprehensive Psychological Rating Scale, the Symptom Checklist-90 and the General Health Questionnaire (Bengtsson *et al.* 1993; McGauley 1989), all supporting the notion that GH therapy improves the general well-being of adults with GH deficiency.

In summary, GH replacement reverses most, but not all signs and symptoms of the adult GH deficiency syndrome. Long-term follow-up data are becoming increasingly available demonstrating that the beneficial effects of GH are maintained and that GH therapy is safe; nevertheless data on long-term hard clinical endpoints such as fracture, cancer and mortality rates are still lacking at present.

## ADVERSE EFFECTS AND POTENTIAL RISKS OF GH THERAPY

Experience from several large multicentre clinical trials have shown that GH treatment is safe and well-tolerated (Chipman *et al.* 1997), and that the adverse effects of GH treatment are dose-related ranging from 0.02 to 0.1 mg/kg/week (Mardh *et al.* 1994). These side-effects were frequently observed in earlier studies employing supraphysiological doses of GH (Abs *et al.* 1999; de Boer *et al.* 1996), whereas more recent trials employing lower GH doses ranging from 0.1 to 0.8 mg/day have seen a sharp decline in the incidence of such adverse effects (Baum *et al.* 1996). Recombinant human GH is identical to the endogenous GH, thus does not elicit hypersensitivity reactions. Individuals most at risk from adverse effects are older and more obese with the largest IGF-I rise on GH replacement (Holmes and Shalet 1995). The most commonly encountered side-effects

arise from the antinatriuretic action of GH precipitating fluid retention, and manifesting as dependent oedema, paraesthesia, gynaecomastia and carpal tunnel syndrome. Arthralgias involving small or large joints are also frequently seen, but there is usually no evidence of effusion or inflammation with no detectable abnormalities on X-ray (Salomon *et al.* 1989). However, these symptoms are mild and generally resolve in the majority of patients, either spontaneously or with dose reductions (de Boer *et al.* 1996).

## FACTORS AFFECTING GH DOSING

### Physiological factors

To improve our understanding of how various factors might affect GH dosing, it is important to consider the physiological patterns of pituitary GH secretion. It has been established that GH secretion increases markedly during puberty (Martha *et al.* 1992) and pregnancy (Lonberg *et al.* 2003), but decreases gradually with aging (Zadik *et al.* 1985; Iranmanesh *et al.* 1991).

Pubertal girls secrete more GH than pubertal boys, probably because girls secrete excessive amounts of estrogen that can antagonize GH actions at the level of GH receptor expression and signalling by inhibiting Janus kinase/signal transducer and via the induction of suppressor of cytokine signaling-2, a protein inhibitor for cytokine signaling (Leung *et al.* 2004), thus leading to pituitary GH hypersecretion. After the pubertal years, GH secretion markedly diminishes at an estimated rate of 14% per decade (Shah *et al.* 1999). Nevertheless, serum GH levels are still markedly higher in premenopausal women than in men, as premenopausal women secrete 1.5 to 3-fold more GH than men (Ho *et al.* 1987; van den Berg *et al.* 1996). These differences are mainly due to higher GH secretory burst amplitudes, greater mass of GH secreted per pulse and greater GH secretory pulse amplitude probably secondary to the underlying estrogen-antagonistic effects on GH action in women (van den Berg *et al.* 1996). Thus, in GH-deficient women, higher GH doses during the initiation and maintenance phases of treatment are generally required in those with intact hypothalamic-pituitary-gonadal axis and in those on oral estrogens to achieve an equivalent clinical and biochemical response compared to men.

During pregnancy, maternal serum levels of placental GH increases from 7 weeks gestation to approximately 37 weeks when peak levels of 22 ng/ml (range: 4.64–69.22 ng/ml) are reached (Chellakooty *et al.* 2004) that gradually replaces the pulsatile pituitary GH secretion (Frankenne *et al.* 1988; Eriksson *et al.* 1989). With the onset of labour and the removal of the placenta after childbirth, a rapid fall in serum placental GH levels ensues (placental GH half-life, 15 min) (Lonberg *et al.* 2003). Wiren *et al.* reported their experience in managing GH deficiency with GH replacement therapy in 8 pregnant hypopituitary women (Wiren *et al.* 2002). They found that during pregnancy, GH therapy was safe and that GH doses had to be decreased in the second trimester of gestation and GH treatment stopped at the start of the third trimester when serum IGF-I levels started to rise (Wiren *et al.* 2002). Hence, it seems prudent that pregnant GH-deficient women on GH replacement should be monitored more frequently during and immediately after pregnancy as decrements in GH doses can be anticipated in most patients as the pregnancy progresses, whereas increments in GH doses may be necessary soon after delivery.

With decreasing GH secretion with aging (Zadik *et al.* 1985; Iranmanesh *et al.* 1991), it is not surprising to note that clinical features and therapeutic endpoints differ with patient age. For example, younger adults have fewer quality-of-life issues, but demonstrate marked decreases in bone mineral density and cardiac function. Conversely, older adults especially those over 60 years, frequently demonstrate abnormal body composition (Franco *et al.* 2006) and impaired quality of life (Burman *et al.* 1995). Furthermore, sensitivity to side-effects of exogenous GH is greater

in older patients (Holmes and Shalet 1995). Therefore, the starting dose, size of dose increments and target serum IGF-I levels should all be reduced in elderly and frail patients (Monson *et al.* 2000).

### Obesity and glucose tolerance

Obesity is characterized by marked decreases of both spontaneous and stimulated GH secretion (Veldhuis *et al.* 1991; Magiakou *et al.* 1994), yet normal or low normal serum IGF-I levels are observed (Copeland *et al.* 1990; Yamamoto and Kato 1993). In an attempt to explain the discordance between GH and IGF-I status in obesity, it has been hypothesized that the hepatic responsiveness is increased by the up-regulation of GH receptors (Bondanelli *et al.* 2001) to compensate for decreased GH levels, thus allowing for the maintenance of IGF-I secretion. We have recently shown that obese GH-deficient adults demonstrated enhanced IGF-I generation probably secondary to enhanced hepatic responsiveness to exogenous GH administration (Yuen *et al.* 2006), and that low dose GH therapy may in fact improve insulin sensitivity in these patients (Yuen *et al.* 2005). Therefore, as obesity and insulin resistance are commonly associated with the adult GH deficiency syndrome (Cuneo *et al.* 1992; Johansson *et al.* 1995), and that obesity predisposes to enhanced hepatic responsiveness to GH stimulation (Yuen *et al.* 2006), it is imperative that obese GH-deficient patients are treated with low GH doses of 0.05 mg/day to 0.1 mg/day, at least initially, to reduce the possibility of worsening glucose homeostasis and inducing unwanted side-effects.

### Concomitant medications

Women using oral estrogen as replacement therapy or for contraceptive purposes are more GH-resistant than men (Kelly *et al.* 1993; O'Sullivan and Ho 2000) because of the attenuation of GH action by estrogen (Leung *et al.* 2004; Ho *et al.* 2006). Thus, women require more GH than men in order to achieve equivalent IGF-I responses, and even that, the effects of GH on body composition in women may be blunted (Burman *et al.* 1997). Switching women to transdermal estrogen patches may allow the GH dose to be halved for equivalent IGF-I responses (Cook *et al.* 1999), presumably by lowering the estrogen exposure to the liver, the principal site of IGF-I synthesis. Given the high cost of GH, using estrogen patches instead of tablets in order to facilitate lower GH doses may be a cost-effective advantage.

Monitoring other pituitary hormone axes is also advisable after commencement of GH replacement therapy, as changes in GH dosing and other hormone replacement therapies has been reported in a clinically significant number of patients (Hubina *et al.* 2004). This is because previous studies have shown that GH replacement can lower serum free T<sub>4</sub> levels (Jorgensen *et al.* 1989a), probably due to increased deiodination of T<sub>4</sub> (Jorgensen *et al.* 1989a; Porretti *et al.* 2002), and serum cortisol levels by inhibiting the enzyme 11  $\beta$ -hydroxysteroid dehydrogenase type 1 resulting in a shift in cortisol metabolism favouring cortisone production, unmasking central hypothyroidism (Agha *et al.* 2007) and hypoadrenalism (Toogood *et al.* 2000) respectively. Thus, free T<sub>4</sub> levels should be monitored during GH treatment and doses of T<sub>4</sub> should be adjusted as necessary, whereas GH-deficient patients with low normal serum T<sub>4</sub> levels should be considered for T<sub>4</sub> replacement prior to commencement of GH therapy. Similarly, the hypothalamic-pituitary-adrenal axis should be reassessed in GH-deficient patients during GH therapy (Giavoli *et al.* 2004a). In those patients with preserved hypothalamic-pituitary-adrenal axis who have become hypoadrenal, glucocorticoid replacement should be instituted, whereas in those where glucocorticoid replacement is suboptimal, glucocorticoid doses should be increased accordingly. In contrast, patients on testosterone replacement therapy may require their GH doses to be decreased as the co-administration of testoste-

rone can potentiate GH actions, and exacerbate GH-induced adverse effects (Giannoulis *et al.* 2006).

### Compliance

Occasionally patients may find it difficult to comply with daily injections. For this reason, it may be more practical for the patient to administer his/her injections on an alternate day basis or thrice weekly. Indeed, studies have shown that daily *versus* thrice weekly rhGH injections are equally effective in GH-deficient adults in increasing serum IGF-I levels and improving lipid and bone metabolism, bone mineral density, body composition (Amato *et al.* 2000) and reversing cardiac abnormalities (Pincelli *et al.* 2003). Large pharmacodynamic and pharmacokinetic studies are presently underway examining the safety and efficacy of a once a week preparation of GH, which in the future, may benefit patients who are poorly compliant. **Table 2** summarizes the various factors that may affect dose adjustments in GH therapy in GH-deficient adults.

**Table 2** Factors that modify GH dosing.

Increase GH dose	Decrease GH dose
• Young patients	• Elderly patients
• Titration of dose	• Titration of dose
• Low serum IGF-I levels	• High serum IGF-I levels
• Addition of oral estrogen	• Pregnancy
• Change from transdermal to oral estrogen	• Discontinuation of oral estrogen
• To induce lipolysis	• Change from oral to transdermal estrogen
• To improve quality of life	• Worsening glucose tolerance
	• To improve quality of life
	• Side-effects

### DOSING STRATEGIES

Increasing attention has been devoted to devising optimal treatment strategies that maximize the clinical benefit of GH treatment, while minimizing the risks that may result from prolonged excessive GH exposure. Following previous experience in the paediatric setting, GH replacement therapy in adult hypopituitarism was calculated in earlier trials based on body weight and/or surface area (Bengtsson *et al.* 1993; Jorgensen *et al.* 1989b; Salomon *et al.* 1989). With increasing clinical experience, it soon became apparent that such a dosing strategy was too simplistic as the GH doses required for normal linear growth exceeded those required for adult replacement.

Problems with side effects due to excessive doses have since led to recommendations for steady dose reductions. The strategy put forward by the recently published guidelines from the American Endocrine Society involve dosing GH independent of body weight, starting with a low dose that is unlikely to cause adverse effects, then gradually increasing this to the minimal dose that normalizes serum IGF-I levels without causing unacceptable side effects (Molitch *et al.* 2006) (**Table 3**). Further to these published guidelines (Molitch *et al.* 2006), we also suggest that low GH doses (0.1 to 0.2 mg/day) should be administered to GH-deficient patients with diabetes, obese GH-deficient patients, and those with a previous history of gestational and family history of diabetes, while in female pregnant patients, to consider lowering or even stopping GH therapy altogether, as guided by serum IGF-I levels. Subcutaneous injections should be administered in the evening to mimic physiological GH secretion (Ho *et al.* 1987). The high degree of inter-individual variability in both subcutaneous GH absorption and GH sensitivity make this individualized titration method superior to standard weight-based dosing strategies. Once maintenance doses are achieved, fasting glucose, IGF-I, T<sub>4</sub>, cortisol, testosterone and lipid levels, and overall clinical status including assessment of quality of life should be monitored at 6 to 12-monthly intervals. If the initial bone DXA scan is abnormal, repeat bone DXA scans are recom-

**Table 3** Recommendations for adult GH replacement therapy by the American Endocrine Society, 2006 (Molitch *et al.* 2006).

Starting dose	Age < 30 yr: 400-500 µg/day (may be higher for patients transitioning from paediatric treatment); age 30-60 yr: 300 µg/day and age > 60 yr: 100-200 µg/day.
Dose titration	At 1-2 month intervals, increase dose in steps of 100-200 µg/day based on clinical response, serum IGF-I levels, side effects, and individual considerations such as glucose intolerance. Larger time intervals and smaller dose increments may be required in older patients.
Goal	Aim for serum IGF-I levels at the upper half of the range appropriate for age and gender, unless side effects are significant.
Monitoring	At 6-monthly intervals once maintenance doses are achieved. Monitoring should include clinical evaluation, assessment of side-effects, quality of life and serum IGF-I levels. The lipid profile and a fasting glucose should be assessed annually. If the initial bones DXA scan is abnormal, repeat evaluations at 1- to 2-yr intervals. Hypopituitary patients on thyroid and glucocorticoid hormone replacement may need dose adjustments after starting GH replacement.
Special situations	Important to retest patients transitioning from pediatric to adult care, especially those who had isolated GH deficiency, and consideration should be given to minimize lengthy interruptions in their GH therapy.
Length of GH therapy	The length of GH therapy is unclear. If benefits are being achieved, treatment should continue, but if there are no apparent or objective benefits of treatment after at least 1 yr, discontinuing GH therapy may be appropriate.

mended at 1- to 2-yearly intervals to assess the need for additional treatment modalities for bone protection.

The length of GH administration remains unclear. If the patient reports significant benefits after at least 9 months of therapy, then GH treatment should be continued indefinitely; however if there are no apparent or objective benefits of treatment or if the cost of treatment to the patient is an issue, then it may be more appropriate to stop treatment.

### ONE UNIT'S 5-YEAR EXPERIENCE OF GH DOSING IN GH-DEFICIENT ADULTS

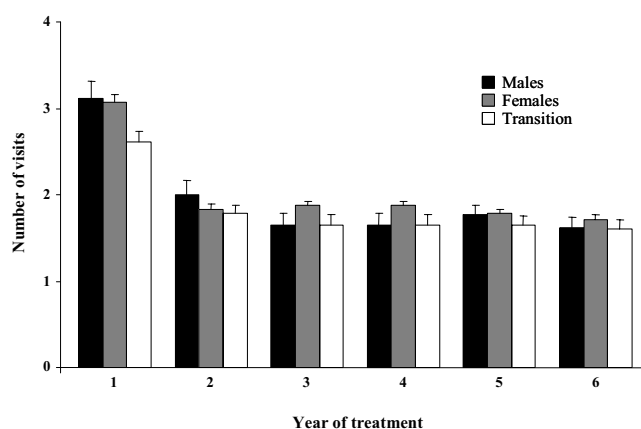
With a variety of clinical considerations in mind, we elected to review our GH treatment practices at the Oregon Health and Science University adult endocrine clinic in Portland, Oregon, USA over a 5-year period from January 2001 to December 2005. While this review is not intended to imply that our experience is the only way to prescribe this drug, given the large number of patients we care for, we propose that this experience most likely represents the clinical situations encountered by many endocrinologists treating adults with GH deficiency in the USA and UK.

We retrospectively reviewed the medical charts of 102 GH-deficient adults treated with GH replacement therapy [53 women (mean age ± SD: 49.0 ± 1.4 yr; age range: 32-72 yr) and 25 men (mean age ± SD: 53.8 ± 2.6 yr; age range: 36-77 yr) with adult-onset GH deficiency and 24 'transition' patients with childhood-onset GH deficiency (mean age ± SD: 22.0 ± 0.5 yr; age range: 17-25 yr)] at our institution. All of the patients were Caucasian Americans. One patient developed GH deficiency at age 23 as a result of a prolactin-secreting pituitary tumor. This patient deserves special comment because she became pregnant whilst on GH therapy, and required dose reductions in the second trimester and discontinuation of GH therapy in the third trimester.

All patients had to have received GH treatment for the first 5 years of GH therapy to be included in this analysis. Patients who were GH-deficient during childhood were retested to confirm GH deficiency. Our criteria for defining adult GH deficiency included low serum IGF-I levels, inadequate response to either insulin (peak <5.0 µg/L) or argi-

nine plus growth hormone-releasing hormone (<4.6 µg/L), and plausible causes for hypopituitarism (e.g., tumor, surgery, irradiation, history of head trauma) (Billir *et al.* 2002).

Treatment objectives that have guided GH dose changes in our patients have focused on serum IGF-I levels, body composition, bone mineral density, and quality of life. We did not utilize a target serum IGF-I concentration, but rather attempted to maintain serum IGF-I levels in the normal range appropriate for age and sex. If serum IGF-I levels exceeded the normal range, the GH dose was reduced by approximately 20%. Visceral adipose tissue was measured by waist circumference measurements and dual X-ray absorptiometry (DXA), while bone mineral density was quantitated by DXA scans. We attempted to improve quality of life, but did not assess this with formal questionnaires. Lastly, we reduced the GH dose by 20% if side-effects occurred, such as muscle and joint pain or carpal tunnel syndrome, and advised our patients that side-effects may be transient after starting or raising the dose of GH, and may persist up to 10 to 14 days. If the side-effects persisted more than 21 days, the dose was subsequently lowered by a further 20%.



**Fig. 6** Mean (± SEM) frequency of clinic visits by year for adult male and female patients and transition patients. Data for year 1 excludes the initial visit, when GH treatment was begun.

The number of scheduled clinic visits for adult male and female patients and transition patients are shown in **Fig. 6**. The number of visits in the first year represents those occurring after the initial visit (when GH treatment had begun). Therefore, the total mean number of visits during the first year is approximately 4, and for each subsequent year, approximately 2. We also decided to examine the number of visits required for dose titration before maintenance doses were achieved. On this basis, we performed an analysis to identify the time required for serum IGF-I levels to peak in a subset of 13 patients receiving a low GH dose of 0.2 mg/day for the first 10 weeks (**Fig. 7**). Data from one patient in this subset are displayed in **Fig. 8**. This patient's serum IGF-I and IGFBP-3 levels were concordant over the 10-week period. The peak for both IGF-I and IGFBP-3 levels occurred at 6 weeks, and declined at 8-10 weeks. We do not believe that adherence was an issue for the decline in serum IGF-I and IGFBP-3 levels. Rather, we suspect that an increase in metabolic activity caused by an increase in GH effects led to a more rapid disposal of GH and possibly IGF-I. We did not consider IGF-I levels to be a critical factor when initiating or escalating the GH dose in this initial titration period; instead we focused on patient tolerance and safety. For this reason, we tend to maintain the GH dose at a given level for at least 1 month before escalating to a higher dose.

Other practical issues associated with patient care were also considered: the physician's and the patient's schedule, and reimbursement factors. When these factors are considered, the actual visit interval during the first year is generally 3 months and, in subsequent years, 6 months.

Starting GH doses, along with peak and maintenance

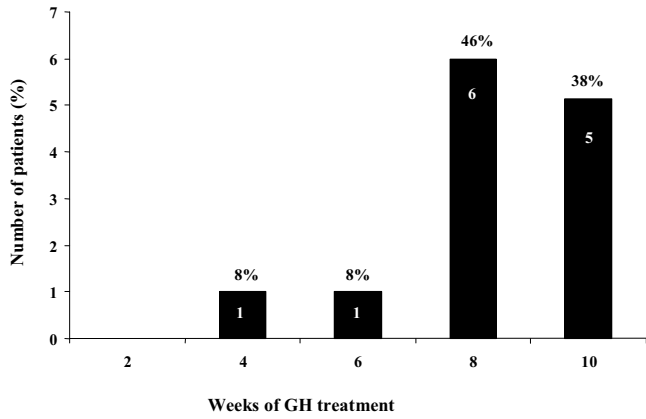


Fig. 7 Time required to achieve peak GH effect, as measured by peak serum IGF-I levels, in 13 receiving GH 0.2 mg/day for 10 weeks.

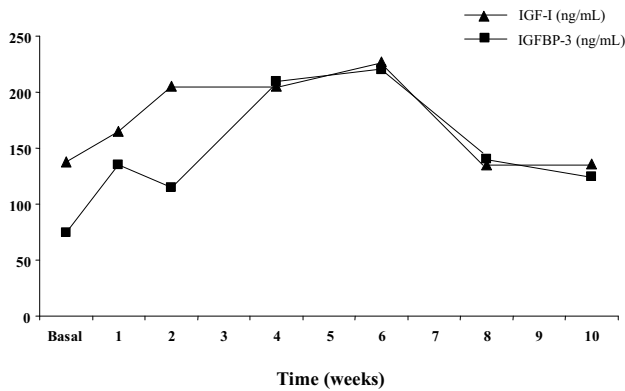


Fig. 8 Serum IGF-I and IGFBP3 levels in a patient receiving GH 0.2 mg/day for 10 weeks.

Table 4 Mean ( $\pm$  SE) doses of GH (mg/day) used in patients with GH deficiency at the Oregon Health and Science University.

	Men	Women	Transition
Starting dose	0.20 $\pm$ 0.02	0.27 $\pm$ 0.01	0.53 $\pm$ 0.04
Peak dose	0.50 $\pm$ 0.04	0.74 $\pm$ 0.04	1.53 $\pm$ 0.13
Maintenance dose	0.39 $\pm$ 0.03	0.47 $\pm$ 0.03	1.30 $\pm$ 0.12

doses, are shown in Table 4. In general, adult men received initial GH doses of 0.1-0.2 mg/day, while adult women are started at 0.2-0.3 mg/day. At each visit, the GH dose is increased by 0.1 mg (men) or 0.2 mg (women) until maintenance doses are reached. Transitioning patients received 0.8 mg/day starting dose and at each visit, this dose is escalated by 0.2 mg/day until maintenance doses are achieved. We seldom exceed 0.6 mg/day and 1.0 mg/day in adult men and women respectively, or 2.0 mg/day in transition patients. In postmenopausal women not on any oral estrogens, the GH dosing strategy is similar to that in adult men. Three target endpoints dictate the GH maintenance dose: (1) serum IGF-I levels within the normal range, (2) avoidance of side-effects, and (3) cardiovascular risk reduction, especially the reduction of visceral fat as assessed by DXA.

In each case, the GH doses employed in men were lower than those selected for women, and both were less than those required in transition patients. In many cases, GH doses were escalated over 2 years until the serum IGF-I level approached the upper cutoff level for age and gender or until side-effects precluded further increases. In most cases, the reason for reducing the GH dose was due to weight gain, the development of side-effects and elevated serum IGF-I levels.

Reasons for GH dose adjustments in male patients are shown in Fig. 9. In these patients, upward dose titration occurred primarily in the first 2 years of treatment but, in some patients, continued into the fourth year. Only rarely did a GH dose need to be reduced due to deterioration of

glucose control. In our female patients (Fig. 9), an upward dose titration dominated the first 2 years of treatment. Decreases in dose related to pain were less frequent in female than in male patients, but a deterioration in glucose control requiring dose reductions occurred more frequently in women. Changing estrogen from the oral to the transdermal route required dose reductions, and if estrogen was stopped altogether, dose reductions were necessary to avoid increasing serum IGF-I levels and causing side-effects.

In the transition group (Fig. 9), upward dose titration accounted for most of the dose changes during years 1 and 2. Weight gain required a dose reduction more often in transition patients than in the male or female adults. While the reasons for this are not entirely clear, it may be that the higher GH doses in transitioning patients may precipitate fluid retention and potentiate weight gain.

During the 10-week analysis, 2 patients discontinued GH treatment due to the development of breast and bladder cancers, 1 patient became pregnant and GH was stopped in the third trimester. Two other patients experienced worsening of their congestive heart failure, and 2 patients experi-

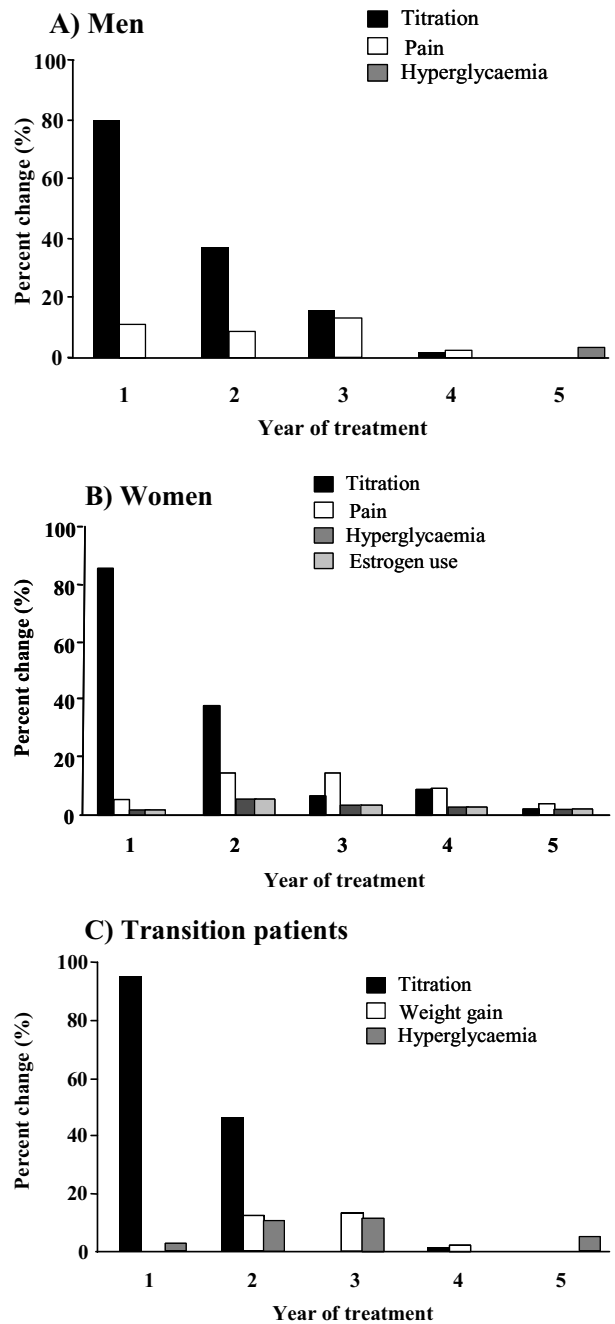


Fig. 9 Reasons for altering GH doses in A) men, B) women and C) transition patients by year of treatment.

ted heat intolerance, both suggesting excessive GH administered. In these patients, dose reductions abolished these symptoms. Rarely did an elevation of serum IGF-I levels occur during dosing unless it was associated with changes in estrogen status. Our policy is to reduce the GH dose by 50% if a woman is switched from oral estrogen to transdermal estrogen, and by 30% if the woman discontinues transdermal estrogen altogether.

## SUMMARY

Growth hormone therapy has been shown to benefit many GH-deficient adults. However, GH dosing should be individualized with close attention to avoidance of side-effects, and the induction or worsening of glucose intolerance. Past experience has taught endocrinologists that the GH doses required by adults are substantially lower than those used in the average pediatric population. Numerous factors such as side-effects, glucose intolerance, oral estrogen and oral contraceptive use, concomitant testosterone replacement therapy, pregnancy and weight changes may also dictate dose changes. Thus, the dosing regimen of GH replacement therapy in adults with GH deficiency requires not only thoughtful clinical judgment, but also careful integration of these multiple variables that demands the expertise of a trained endocrinologist.

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