ADULT GROWTH HORMONE DEFICIENCY

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ABSTRACT

Growth hormone deficiency (GHD) in adults arises as a consequence of decreased secretion of somatotropin (GH) from the anterior pituitary. The diagnosis of GHD is dependent on the demonstration of a subnormal rise in serum GH in response to one or more dynamic stimulation tests in the presence of co-existing pituitary disease or other pituitary hormone deficiencies. The syndrome of GHD is characterized by the variable presence of decreased exercise tolerance, decreased mood and decreased general well-being. These symptoms are associated with reduced bone remodelling activity, change in body fat distribution with increased central adiposity, hyperlipidaemia and increased predisposition to atherogenesis. Decreased psychological well-being and quality of life are recognised as particularly important and, from the patients' perspective, have become arguably the major indication for GH replacement therapy.

The potential mitogenic effects of IGF-I have raised concerns regarding a possible increased risk of either neoplasia or regrowth of residual pituitary and peripituitary tumours. However, extensive surveillance studies have not demonstrated an increased incidence of de novo neoplasia or tumour regrowth and follow up for over 10 years on replacement show it to be effective and safe. For extensive review of all related areas of Endocrinology, visit WWW.ENDOTEXT.ORG.

INTRODUCTION

Growth hormone deficiency (GHD) in adults arises as a consequence of decreased secretion of somatotrophin (GH) from the anterior pituitary. Until twenty years ago it was widely held that GHD had little pathophysiological consequence despite the fact that earlier anecdotal reports had suggested the presence of GH-remediable symptoms of fatigue and decreased general well-being which responded to GH replacement. In retrospect, these observations of forty years ago were delineating with considerable precision the cardinal features of the syndrome but the limitation of supplies of cadaveric GH and the focus on paediatric usage meant that further information on the adult deficiency state did not occur until 1989 when the initial trials of GH replacement therapy in adult hypopituitary patients were published. Numerous subsequent studies have provided compelling evidence for the existence of a syndrome of adult GH deficiency (1, 2, 3). This is characterised by the variable presence of decreased exercise tolerance, decreased mood and general well-being, reduced bone remodelling activity, change in body fat distribution with increased central adiposity, hyperlipidaemia and increased predisposition to atherogenesis. However, it is important to recognise that adult-onset GH deficiency is due to structural pituitary disease or cranial irradiation for other pathologies and, therefore, usually occurs in the context of additional features of hypopituitarism (4). For this reason the clinical features attributable to GH deficiency may be compounded by, or directly related to, other pituitary deficiencies. Nonetheless, the fact that GH replacement therapy may favorably alter these clinical features provides considerable surrogate evidence for GH deficiency as a causal factor.

Childhood-onset GH deficiency may occur as a consequence of structural pituitary disease (e.g. craniopharyngioma) or irradiation but, in contrast to the situation of adult-onset GH deficiency, is usually a

consequence of a partial deficiency of growth hormone releasing hormone. Interestingly, this latter phenomenon may not persist into adult life, possibly because of maturation of the hypothalamo-somatotroph axis, and it is therefore essential that dynamic tests of GH reserve be undertaken when linear growth is complete rather than assuming continuing GH deficiency. The true prevalence of adult-onset GH deficiency is difficult to estimate with certainty but a reasonable estimate may be obtained from prevalence data for pituitary macroadenoma, which approximates to 1:10000 population. Addition of cases of childhood-onset GHD persisting into adult life gives an overall prevalence of between 2 and 3 per 10000 population.

Over the past decade there has been increasing recognition that hypopituitarism is associated with premature mortality. Studies in Sweden and the UK have demonstrated a two to three fold increase in standardised mortality ratio and this is most striking in women (5, 6, 7). Specific pituitary pathologies, especially craniopharyngioma, may convey an increased mortality rate, which is likely to be independent of specific hormonal deficiencies (7). However, bearing in mind the numerical preponderance of pituitary macroadenomas as the cause of hypopituitarism, the overall findings from these studies favour an increase in morbidity and mortality from macrovascular disease and, in one of the Swedish studies, cerebrovascular disease (6). The increase in cardiovascular mortality in the initial Swedish study was paralleled by a reduction in deaths from malignant disease in males but this has not been a definite feature of subsequent observations. Much debate surrounds the mechanism for increased prevalence of vascular disease. The fact that these patients were replaced with glucocorticoids, thyroxine and in some cases gonadal steroids prompted the conclusion that untreated GH deficiency was the major causal factor. However, this interpretation makes the assumption that replacement of adrenal and thyroid deficiency was optimal and must also take account of the fact that oestrogen deficiency may not be replaced. In fact replacement, particularly with hydrocortisone, was often supraphysiological, and these doses are now significantly lower than when the original mortality data were collected.

Nonetheless, the fact that untreated GH deficiency, in the context of varying degrees of hypopituitarism, is associated with an adverse cardiovascular risk profile provides circumstantial evidence for a causative role for GH deficiency in mediating increased rates of vascular disease (8, 9, 10, 11, 12). This conclusion is further supported by a wealth of longitudinal observation documenting an improvement in central adiposity and lipoprotein profiles during GH replacement in these patients (1, 2, 3, 11, 13, 14, 15, 16). Definition of the precise relationship between GH deficiency and mortality must await long term observations of mortality rate in patients on GH replacement set against background mortality rates in the general population adjusted for national variations but a recent Dutch study provides some evidence that mortality is not increased by replacement and may play a role in normalizing it (particularly in men) (16a).

CAUSES OF GH DEFICIENCY IN ADULTS

Pituitary adenoma is statisitically the most important cause of adult-onset GHD followed by craniopharyngioma, which combined account for 65% of cases. Moderate to severe traumatic brain injury (TBI) and subarachnoid hemorrhage are increasingly recognized as a cause of hypopituitarism including growth hormone deficiency (16b,c,d,e). However the incidence is highly variable and may be transient. The spectrum of causes of GHD in adults are indicated in Table 1 using data derived from KIMS, a multinational, pharmacoepidemiological surveillance database for adult hypopituitary patients receiving GH replacement (13). KIMS currently includes approximately 15000 patients and is largely composed of adult-onset hypopituitary patients but also includes a proportion of patients with childhood-onset disease who have a higher percentage prevalence of craniopharyngioma and post-irradiation GHD; data for the first 2753 patients enrolled are shown. Assuming a correct initial diagnosis, the reversibility of isolated, idiopathic GHD of childhood is now well established with normal GH responses on dynamic testing being described in between 30 and 70% of subjects at completion of linear growth in various series. For this reason a diagnosis of childhood-onset isolated GHD should always be challenged by rigorous reinvestigation at completion of linear growth. Childhood-onset GHD due to genetic defects in GH synthesis is never reversible and that due to structural disease very rarely so. Isolated idiopathic GHD does not arise de novo in adults and this point is particularly important in the assessment of non-specific symptoms in overweight patients without additional evidence of pituitary disease; body mass index of >32 kg/m2 is associated with reduced GH reserve on dynamic testing in approximately 30% of patients but this is reversible with weight loss. However, combined

deficiency of GH and other anterior pituitary hormones, in the absence of structural disease, may be a feature of an evolving endocrinopathy due to deficiencies of the transcription factors PIT-1 or Prop-1.

The irradiation category in Table 1 refers to those instances arising as a result of primary cranial irradiation. The contribution of irradiation to the onset of GHD in patients with pituitary adenoma or craniopharyngioma has been included under the relevant pituitary adenoma category. The designation 'Other' includes various rare causes of hypopituitarism including lymphocytic hypophysitis, intracranial germ cell tumours, Langerhans` Cell Histiocytosis and granulomatous diseases. These prevalence rates derived from the KIMS database concur very closely with experience within individual large clinics.

Table 1. Cause of GH deficiency in adult patients enrolled consecutively into the KIMS database

Diagnosis	n	%
Non-functioning pituitary adenoma	844	30.7
ACTH-secreting pituitary adenoma	200	7.3
GH-secreting pituitary adenoma	55	2.0
Prolactin-secreting pituitary adenoma	305	11.1
Gonadotrophin-secreting pituitary adenoma	11	0.4
TSH-secreting pituitary adenoma	6	0.2
Pituitary tumour - secretory status unknown	40	1.5
Craniopharyngioma	357	13.0
Surgery	25	0.9
Irradiation	54	2.0
Idiopathic	353	12.8
Trauma	55	2.0
Other	448	16.3
Total	2753	

THE DIAGNOSIS OF GH DEFICIENCY

GH is secreted in a pulsatile fashion with serum measurements varying between peaks and troughs, the latter falling below the assay detection limit of conventional radioimmunoassays. For this reason, a diagnosis of GHD cannot be made by measurement of baseline serum GH concentration although a single serum GH measurement taken fortuitously at the time of a secretory peak may serve to exclude GHD. Therefore the diagnosis of GHD is dependent on the demonstration of a subnormal rise in serum GH in response to one or more dynamic stimulation tests. Options include the insulin tolerance test (ITT), glucagon test, arginine stimulation and combinations of arginine and GH releasing hormone (GHRH) or GH secretagogues. Of these possibilities, the best validated is the insulin tolerance test which has been demonstrated to distinguish reliably between GH responses in patients with structural pituitary disease and those of age matched controls across the adult age range (17). A variety of serum GH cut off points have been used to define GH deficiency. However, an international consensus (convened by the Growth Hormone Research Society) has defined severe GHD in adults as a peak response to insulin-induced hypoglycaemia of <9mU/L (<3 ng/mL) (18).

It is essential that the insulin tolerance test is carried out in dedicated units under strict supervision by experienced staff and it is contraindicated in patients with epilepsy and/or ischaemic heart disease. For those patients in whom the insulin tolerance test is contraindicated, glucagon or arginine may be used and a similar serum GH cut off is applied for the diagnosis of severe GHD (19). A particular advantage of insulin and

glucagon testing is the simultaneous assessment of the adequacy of ACTH reserve. Combinations of GHRH and either arginine (or GH secretagogues) are the most potent stimuli of GH secretion so that normative data for these tests are required in order to define GHD.

As a result of an age related increase in somatostatinergic tone, spontaneous GH secretion declines by approximately 14% per decade of adult life but this does not alter substantially the response to dynamic tests of GH reserve and the same cut-off GH concentrations can be used across the age range (20). Severe obesity may decrease the GH response to insulin hypoglycaemia to levels suggestive of GHD but this is a completely reversible phenomenon if weight loss is achieved. Failure to recognise the impact of obesity on stimulated GH secretion may result in a false positive diagnosis of GHD and it is now standard practice that the diagnosis should be made in conjunction with evidence of structural pituitary disease and/or the documentation of additional pituitary hormone deficiencies. The latter provide robust support for a diagnosis of GHD because of the increasing probability of GHD in the presence of one (c.80%) or more (c.90%) additional pituitary trophic hormone deficiencies (21). The license for GH replacement in adults stipulates that a diagnosis of GHD should be confirmed by two dynamic tests but this is not critical in a patient who has an unequivocally abnormal GH response to a single test combined with a pituitary lesion or previous history of radiotherapy and/or additional endocrine deficit.

GH secretory reserve may also be assessed by measurement of serum concentrations of the GH-dependent peptides IGF-I, IGF binding protein 3 (IGFBP3) and the acid labile subunit of the ternary complex (ALS). Of these, IGF-I is the most sensitive marker of GH action and provides a reliable test of GH reserve in childhood-onset disease. Its diagnostic value for GHD is limited by the fact that between 30 and 40% of individuals with severe GHD of adult-onset will demonstrate a serum IGF-I concentration in the low part of the normal age related reference range (17). Nonetheless, in the absence of liver dysfunction or malnutrition, which may secondarily reduce IGF-I generation, and if determined in the appropriate clinical context of pituitary disease and hypopituitarism, a decreased serum IGF-I provides strong confirmatory evidence for GHD.

CLINICAL FEATURES OF GH DEFICIENCY IN ADULTS

Adult GHD is associated with an extensive array of symptoms and physical signs which are now recognised with sufficient precision by experienced endocrinologists to justify their designation as a clinical syndrome (1, 2, 3). The cardinal manifestations are listed in Table 2. Decreased psychological well-being and quality of life are recognised as particularly important and from the patients' perspective have become arguably the major indication for GH replacement therapy. Quality of life issues have been examined using various generic measures including the Nottingham Health Profile and the Psychological General Well Being Schedule. These instruments determine various aspects of health-related and needs-based quality of life and the most prevalent findings from various studies have been deficits in the domains of mood, anxiety and social interaction. Although these findings are readily apparent in many patients with adult-onset GHD, it has proven more difficult to discern similar phenomena in patients with childhood-onset disease. This may be due to at least two factors. Firstly, standard generic quality of life instruments may be insensitive in the investigation of young people and secondly, there may be a major element of psychological adaptation or decreased expectation when the condition has commenced early in life. In an attempt to improve the reproducibility of studies of quality of life in GHD adults, questionnaires have been developed which focus on those symptoms, which are most frequently documented in hypopituitary adults during extended open interviews. One such instrument, which is now widely used for the baseline and longitudinal follow-up of patients, is the Quality of Life Assessment in Growth Hormone Deficient Adults (QoL-AGHDA). This is a needs-based instrument consisting of 25 questions with a yes/no answer format and the final score is obtained by summating all the positive responses; a higher score, to a maximum of 25, denotes poorer quality of life. The questionnaire has been shown to be reproducible in a variety of languages and satisfies Rasch analysis criteria for unidimensionality, construct validity and hierarchical ordering of items (22).

GHD is characterised by substantial changes in body composition with increments in total fat, percentage fat and particularly visceral fat mass. Methodologies employed for this purpose have included dual energy X-ray absorptiometry (11), bioelectrical impedance (1, 2, 3) or the simple measurement of the ratio of waist to hip

circumference (23) (figure 1) and there is complete concordance between all studies which have examined these aspects in hypopituitary adults. Importantly, although the prevalence of obesity is increased in hypopituitary adults, the increment in visceral fat is also evident in those patients who are non-obese (11). In parallel with changes in fat mass, lean body mass is reduced. The latter may explain the reductions in muscle strength and exercise tolerance, which have been documented in adult GHD. The degree to which lean body mass is reduced is difficult to determine because of the reduction in total body water which is also evident in the GHD state; body composition measurements, particularly bioelectrical impedance, may overestimate changes in lean body mass as a consequence of alterations in tissue hydration. Furthermore, the reduction in extracellular water, which is compounded by reduced total body sodium in GHD, may be a major factor underlying the reported reductions in exercise capacity. To this may be added the effect of reduced left ventricular function which has been described in a number of studies.

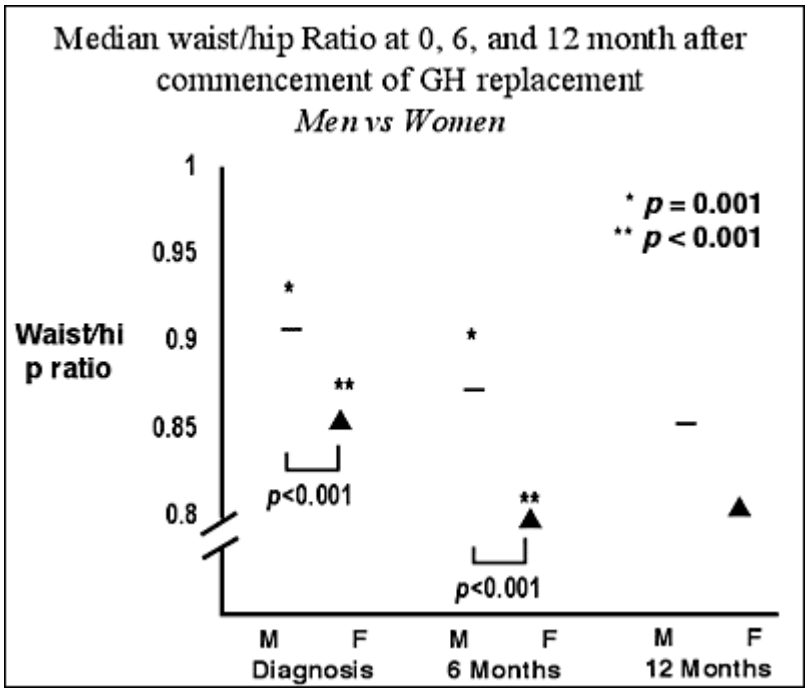

Figure 1.Data from Drake et al (ref 23)

In contrast to GHD occurring in children, adult GHD is associated with relative insulin insensitivity (8, 11) and an increased prevalence of impaired glucose tolerance and diabetes mellitus (9). The adverse changes in insulin sensitivity are predictably most obvious in obese patients but are also evident in hypopituitary patients with normal body mass index in whom the inverse relationship between insulin sensitivity and central fat mass which characterises the 'metabolic syndrome' is clearly seen (11). It is therefore likely that the changes in insulin sensitivity observed in adult GHD are due predominantly to increases in central fat mass. It has been postulated that changes in body composition and particularly fat mass might be a consequence of unphysiological glucocorticoid replacement. Against this is the fact that the doses of glucocorticoid replacement used in primary adrenal failure, which are similar to those used in hypopituitarism, are not associated with abnormalities of body composition. However, local tissue exposure to either endogenous or exogenous cortisol may be different in secondary as opposed to primary adrenal failure. The GH/IGF-I axis is now recognised to be an important modulator of the activity of the enzyme 11b hydroxysteroid dehydrogenase Type 1 (11bHSD1) (24). This isoenzyme acts as a predominant reductase, particularly in liver and adipose tissue, increasing the net conversion of inactive cortisone to cortisol. The activity of the enzyme is decreased by GH and, as a consequence GHD is associated with a shift in the equilibrium set point in favour of cortisol. It is therefore possible that the increase in central adiposity, which characterises the GHD state, could be compounded by enhanced exposure to cortisol within adipocytes; hepatic metabolism might be perturbed by a similar mechanism. These mechanisms would tend to increase serum cortisol concentrations in patients receiving hydrocortisone replacement but not in patients with intact ACTH reserve in whom negative feedback would determine maintenance of stable circulating cortisol concentrations. However, GH is a negative determinant of serum cortisol binding globulin so that comparisons between serum total cortisol concentrations between GHD and GH replete states are not valid.

Adult GHD is associated with increments in total cholesterol, LDL-cholesterol and apolipoprotein B (1, 2, 3). A modest decrement in HDL-cholesterol has also been described in some studies. These changes are evident in both sexes and are quantitatively greater in women. Despite GHD related sodium and water depletion, an increased prevalence of hypertension in adult hypopituitarism has been documented and may be related to reduced activity of nitric oxide synthase, and consequent increased peripheral vascular resistance, as a result of GHD. The changes in lipoprotein metabolism, body composition, insulin sensitivity and peripheral vascular resistance indicated above would predict increased atherogenesis in the GHD state. Indeed, several studies have reported an increase in ultrasonographically determined intima-media thickness and plaque formation in large arteries of patients with adult-onset GHD and adults with childhood-onset disease (8, 12).

Decreased bone mineral density is a recognised phenomenon in adult hypopituitary patients and is associated with an increased fracture risk (25, 26). Measurements of markers of bone formation and bone resorption are consistent with a low bone turnover state in GHD. Deficits in bone mineral content and density are more striking in adults with childhood-onset GHD and this is likely to be a consequence of failure to achieve genetic potential peak bone mass either because of inadequate GH replacement in childhood or its early cessation at the time of slowing of linear growth. Failure to achieve peak bone mass has important implications for the future development of osteoporosis and fracture risk. The situation in hypopituitarism is further complicated by the frequent accompaniment of gonadal steroid deficiency, frequently of unknown duration. In addition, glucocorticoid replacement for primary adrenal failure is associated with modest reductions in bone mineral density. Nonetheless, available evidence indicates that qualitatively similar changes in bone mineral density are found in adult-onset isolated GHD as in panhypopituitarism, therefore supporting a role for GHD in pathogenesis. Furthermore, these abnormalities in bone metabolism and bone density are favorably influenced by GH replacement (27, 28, 29, 30).

Table 2. Symptoms and signs of the adult growth hormone deficiency syndrome

- depressed mood
- increased anxiety
- lack of energy levels
- social isolation
- lack of positive well being
- increased body fat, particularly central adiposity
- decreased muscle mass
- decreased insulin sensitivity and increased prevalence of impaired glucose tolerance
- increased LDL cholesterol and Apo B. Decreased HDL cholesterol
- accelerated atherogenesis
- a variable decrease in cardiac muscle mass
- impaired cardiac function
- decreased total and extracellular fluid volume
- increased concentration of plasma fibrinogen and plasminogen activator inhibitor type I
- decreased bone density, associated with an increased risk of fracture

RESPONSE TO GH REPLACEMENT IN ADULT GROWTH HORMONE DEFICIENCY

QUALITY OF LIFE AND PSYCHOLOGICAL WELL-BEING

Potentially, the greatest immediate indication for growth hormone supplementation is in patients who are assessed as having impaired quality of life (QoL). The early high dose placebo controlled trials suggested that around 50% of these patients demonstrated a significant improvement and a desire to continue with replacement longer term (3). The greatest benefit was shown in patients who had severe GHD and greater

distress, in terms of energy and vitality, prior to commencing growth hormone. More recent experience using lower doses with fewer side effects, indicate clear improvement with wish to continue of >90% in patients selected on the basis of a perceived QoL deficit (23, 31). A six month course of optimally-titrated GH replacement is usually needed before the benefits can be assessed clearly, although many patients show a substantial improvement in QoL within three months. For reasons that are unclear, a small proportion of patients (<20%) may not demonstrate significant subjective benefit in QoL until 9 to 12 months after commencing treatment (22). It is important to recognise that the time taken to achieve a maintenance dose of GH may extend to 12 weeks in some patients and is longer on average in women (23); this should be recognised in therapeutic trials of GH replacement with a finite time frame. It is clear that the time taken to derive subjective benefit from GH replacement in many patients provides strong evidence against a pure placebo effect in this respect. Furthermore, the duration of benefit in QoL, which has been observed for periods of up to 10 years, is similarly indicative of a therapeutic rather than a placebo phenomenon (16). Patients QoL improves most rapidly in the first 12 months of treatment, but even after this there is continued improvement towards the country specific population mean, with particular improvement in problems socializing, tenseness and self-confidence, which normalize to the background population (32). This improvement is seen in patients with all aetiologies of growth hormone deficiency including previous acromegaly (32a, 32b) and traumatic brain injury 32c and has also been shown to produce an improvement in cognition in the latter (32c). However, not all aspects of quality of life normalize and this is particularly true in patients under 60yrs of age. This may simply reflect coming to terms with a chronic disease, but hypopituitary patients are deficient in other hormones such as dehydroepiandrosterone (DHEA) and testosterone in females, even if ACTH replete. Replacement of these has been shown to have a positive benefit in terms of quality of life in addition to GH (33, 34, 35).

The reasons for the differences in QoL outcome between the early studies and current clinical practice has been the subject of much debate and at least two factors are likely to be particularly relevant. Firstly, the initial randomised control trials utilised GH doses based on body weight or surface area and did not take account of the substantial variation in individual responsiveness to GH occurring as a result of gender and other factors. This strategy resulted in excessive GH doses in men and obese subjects and relative undertreatment of women. The adverse symptoms associated with excess GH doses included arthralgia and myalgia, due to GH-induced antinatriuresis, and it is probable that these factors may have obscured potential subjective benefit. In addition, it is probable that the strict entry criteria inherent in any placebo-controlled study designed to prove concept may have inadvertently eliminated those patients who were most likely to demonstrate benefit in QoL. This latter phenomenon is readily evident when baseline indices of quality of life in patients enrolled into randomised control trials are compared with those of patients commencing GH replacement selectively in the clinical practice setting (23, 31, 37, 38).

The mechanism for the beneficial effect of GH on well-being and QoL remains speculative. GH has been shown to cross the blood brain barrier and to exert physiological effects in the central nervous system as evidenced by the generation of neurotransmitters. However, the effects of GH in restoring normal hydration and increasing exercise capacity are additional potential contributors to the positive effects on well-being.

BODY COMPOSITION: FAT MASS, FAT DISTRIBUTION AND LEAN BODY MASS

Growth hormone replacement produces a significant redistribution of body mass, decreasing body fat, and particularly central fat, and increasing lean body mass (1, 2, 3, 4, 38a). Body fluid balance is also restored. The beneficial effects of GH on total body fat and its distribution have been examined by means of dual energy X-ray absorptiometry, computerised tomography, bioelectrical impedance and ratio of waist to hip circumference (figure 1) and qualitatively similar results obtained with excellent concordance between virtually all reported studies. The restoration of normal total body water may result in an artefactual increment in determinations of lean body mass particularly when the latter is measured by bioelectrical impedance. The abnormal fat distribution in GHD is characterised by an increase in the ratio of waist to hip circumference and during long term follow up, serial measurement of waist circumference provides a simple, rapid and reproducible means of monitoring improvement in body fat distribution.

Reductions in body fat are attributed to the lipolytic effect of GH but additional indirect hormonal effects may be important. The conversion of thyroxine to triiodothyronine was shown to be enhanced by GH in early studies of GH replacement although this is a dose related phenomenon and is less evident with the lower doses in current use. However, the enzyme which interconverts cortisol and cortisone thus controlling glucocorticoid clearance in vivo,11bHSD1, shows increased activity in the GH deficient state and is normalised by low dose GH replacement; the consequent increase in cortisol metabolism may result in reduced tissue specific exposure to glucocorticoid in adipocytes and hepatocytes (24). The latter effect provides an additional explanation for decreased total and central fat mass during GH replacement.

EXERCISE CAPACITY AND PERFORMANCE

Increased exercise capacity, as measured by maximal oxygen uptake, power output and isometric muscle strength, has been observed during GH replacement in GHD adults. The impact of these changes for individual patients is variable and dependent on age and previous exercise requirements. It is intuitively probable that the improvements depend at least in part on improvements in lean body mass. However, restoration of normal circulating volume may also play a positive role. In addition, improvement in psychological well-being might be expected to enhance physical activity whilst the latter may have a reciprocal beneficial effect on well-being.

CARBOHYDRATE METABOLISM AND INSULIN SENSITIVITY

Untreated GHD of adult onset is associated with reduced insulin sensitivity, which is, at least in part, related to increased central adiposity (9, 11). The latter improves within the first 3 months of GH replacement but this does not result in an immediate improvement in insulin sensitivity (11). In fact, because of the antagonistic effects of GH on the actions of insulin mediated by hepatic effects, and the increase in circulating free fatty acids, there is on average a further decline in insulin sensitivity, which subsequently returns to baseline over the first year of GH replacement therapy (9). The decline in insulin sensitivity during GH therapy is associated with a slight elevation of fasting plasma glucose and a parallel increase in glycated haemoglobin, both within the normal reference range (figure 2). Importantly, the increment in glycated haemoglobin is not evident in patients with prior abnormality of glucose tolerance but is significantly correlated with baseline body mass index, the latter emphasising the importance of additional dietary and lifestyle advice in these patients. Reference to the KIMS database indicates that there is an increased baseline prevalence of impaired glucose tolerance and diabetes mellitus prior to commencing GH replacement but subsequently the incidence of new cases of diabetes is not increased provided body mass index is accounted for. As yet, the long-term effects of GH replacement on insulin sensitivity are unclear but are likely to vary depending on age and duration of pituitary disease.

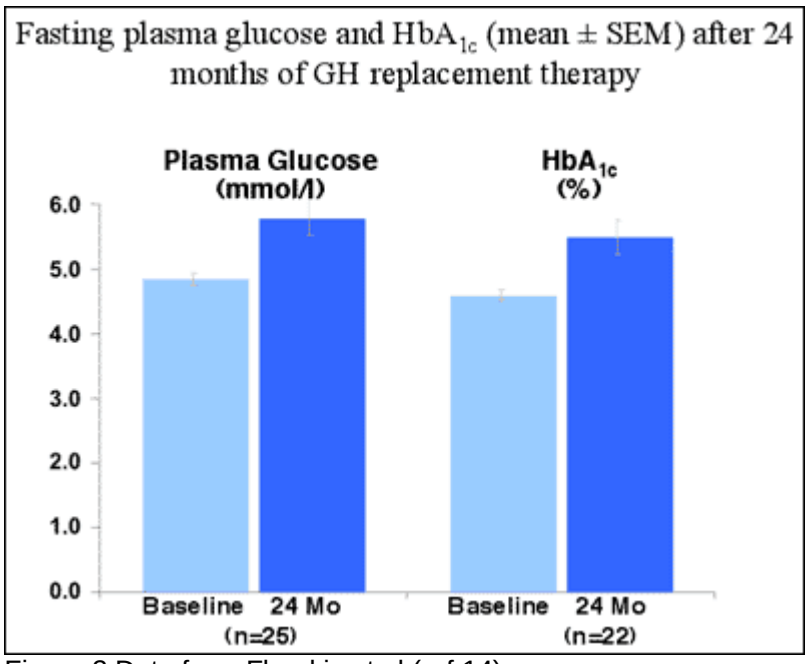

Figure 2.Data from Florakis et al (ref 14)

SERUM LIPOPROTEIN PROFILES

The effect of GH replacement on lipoprotein profiles has been examined in various studies using differing dose regimens. Regardless of whether the GH dose has been based on body weight or titrated against serum IGF-I the universal finding has been a reduction of serum total cholesterol. accounted for virtually entirely by a reduction in LDL-cholesterol (14). The extent of this reduction is greatest in those patients with higher baseline serum cholesterol (figure 3) and the median change in an unselected hypopituitary population is between 0.3 and 0.4 mmol/L (14, 15). Importantly, the improvement in LDL-cholesterol is additive to the effects of HMG CoA reductase inhibitors if the patient is receiving concurrent therapy (figure 4) and possibly even synergistic (39). The degree of reduction of serum LDL-cholesterol during GH replacement would predict an overall reduction in cardiovascular events in the region of 20%. In addition, some studies have documented an increase in serum HDL-cholesterol but serum triglyceride levels remain unchanged. Serum lipoprotein(a) has been shown to increase in some studies in patients who demonstrated favorable changes in LDL-cholesterol (11, 40) but the data remain somewhat contradictory by virtue of Lp(a) assay differences; the overall significance in terms of cardiovascular risk is unclear.

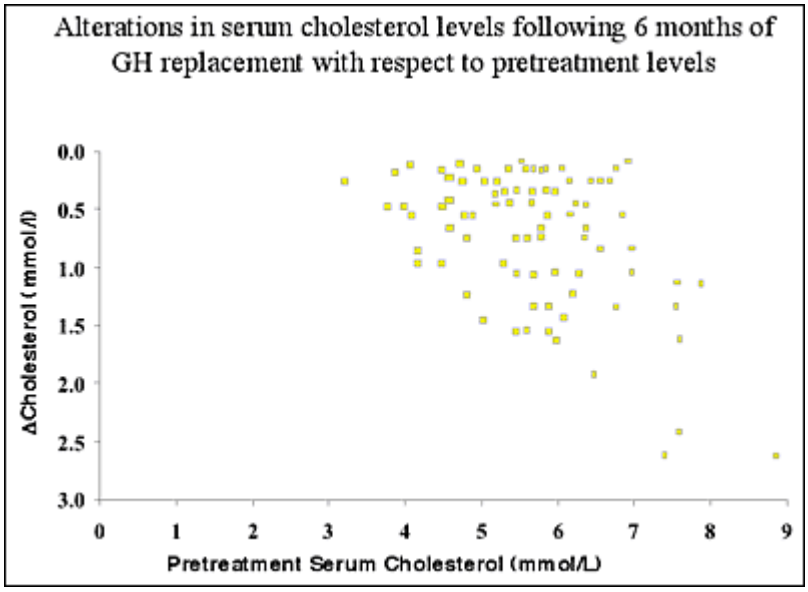

Figure 3.Data from Florakis et al (ref 14)

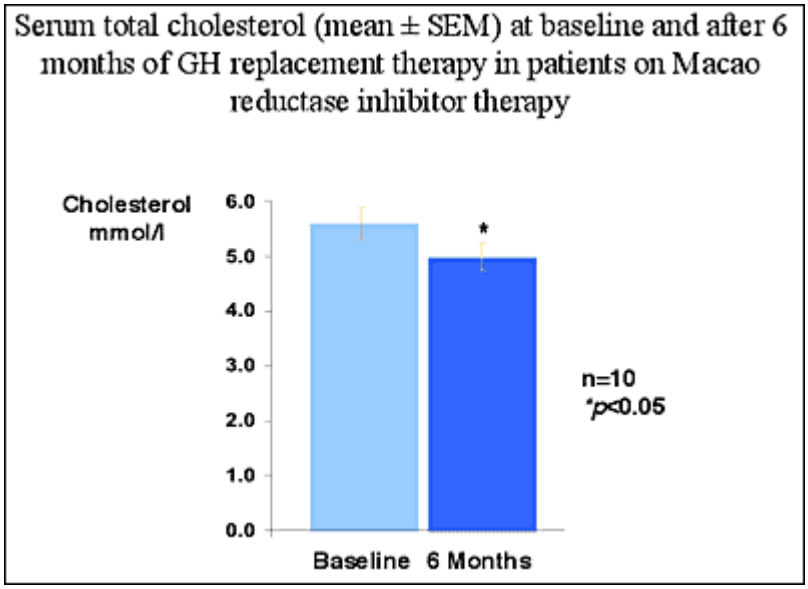

Figure 4.Data from Florakis et al (ref 14)

CARDIAC AND PERIPHERAL VASCULAR EFFECTS

The GH/IGF-I axis is a recognised modulator of cardiac function and a positive inotropic effect of GH/IGF-I occurs early in the natural history of acromegaly. In contrast, GHD is associated with a reduction in left ventricular wall mass and cardiac output which is most evident in childhood-onset disease. The variable discordance between childhood-onset and adult-onset GHD in this regard is likely to be due to additional factors impacting on cardiac morphology in adult-onset, including an increased prevalence of hypertension. GH replacement results in increased left ventricular wall mass, fractional shortening, stroke volume and favorable changes in the echocardiographically determined e/a ratio reflecting improved diastolic function (3). In some studies in adult-onset patients, left ventricular hypertrophy has been documented during GH replacement, confirming further the heterogeneity in response to GH replacement. Importantly, GH replacement does not increase blood pressure; in fact, a modest reduction may be seen in patients with pre-existing hypertension reflecting increased generation of nitric oxide as a result of activation of nitric oxide synthase.

INDICES OF BONE REMODELLING AND BONE MINERAL DENSITY

GHD is associated with reduced activity of bone formation and resorption. GH replacement reverses this situation rapidly resulting in increases in markers of bone formation (e.g. osteocalcin and bone specific alkaline phosphatase) and bone resorption (e.g. urine deoxypyridinoline) (30). This increase in bone metabolism eventually results in an increase in bone mineral density (BMD) but this is not evident for approximately 18 months of treatment and is preceded by a reduction attributable to an increase in the bone remodelling space (28). The fact that BMD increases under the influence of GH replacement at physiological doses provides important surrogate evidence for an aetiological role for GHD in mediating the reduced BMD observed in hypopituitarism. The improvement is quantitatively more obvious in men than women despite the achievement of similar serum IGF-I SD scores and therefore constitutes a genuine difference in gender susceptibility (figure 5). Although the improvement in BMD would predict a reduction in fracture rates confirmation of this necessitates long term follow up. Evidence is now emerging supporting a lower fracture risk with growth hormone replacement. A prospective cohort study has shown that GH deficient patients

treated with GH before the onset of osteoporosis have a lower fracture risk than those untreated, over a mean follow up of 4.6 years (SD 3.8). (40.1)

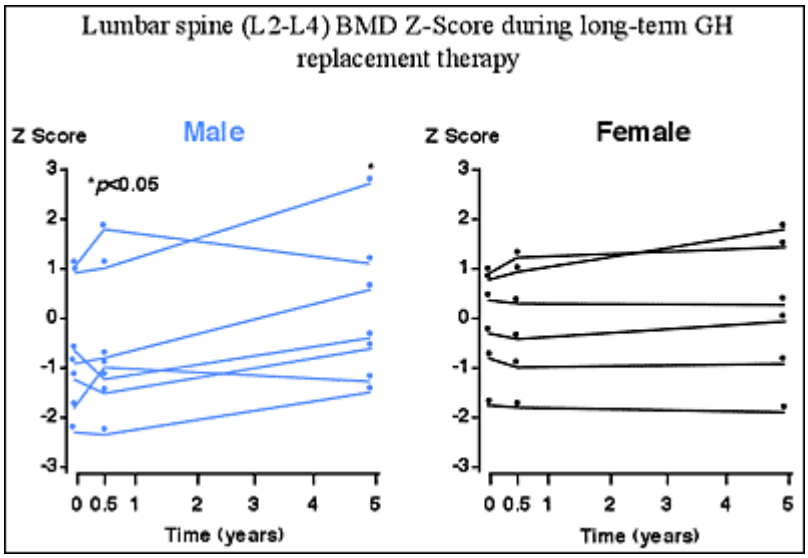

Figure 5.Data from Drake et al (ref 30)

INTERACTIONS WITH OTHER PITUITARY AND ADRENAL HORMONES

GH is known to inhibit 11BHSD-1, therefore favoring metabolism to inactive cortisone over active cortisol. Hence patients who are partially ACTH deficient or on suboptimal replacement should be carefully monitored as initiation of GH may lead to partial cortisol deficiency (41).

GH also interacts with the TSH axis. Patients without defined TSH deficiency demonstrate a reduction in serum thyroxine (T4) after initiation of GH replacement, although maintain stable serum liothyronine (T3). Patients on thyroxine replacement frequently require an increase in their dose (42) The mechanism remains unclear, but it has been postulated that GH may enhance peripheral conversion of T4 to T3 but also have a central inhibitory effect on TSH release at least in children.

Women require a higher GH dose than men to achieve a similar increment in IGF-I. GH sensitivity is blunted in females on oral oestrogen (30, 43). Transdermal oestrogen reduces IGF-I generation to a lesser extent than oral oestrogen and the effect of oestrogen is thought to be mainly due to first pass metabolism inhibiting hepatic synthesis of IGF-I (44, 45). Testosterone stimulates GH secretion centrally. It also amplifies GH stimulation of IGF-I (46).

In additional to gonadal steroids, DHEA replacement has been shown to have an impact on IGF-I generation and psychological well-being (33, 34). DHEA improves psychological wellbeing independently of an effect on IGF-I (34). DHEA has been shown to potentiate IGF-I generation (47, 48) such that females on DHEA replacement require a lower GH dose to achieve the same IGF-I (47) (Figure 6). The mechanism is unknown, but DHEA is metabolised to testosterone and it is postulated that increased serum testosterone may be responsible, hence explaining the lack of a DHEA effect in men who are either eugonadal or are on testosterone replacement.

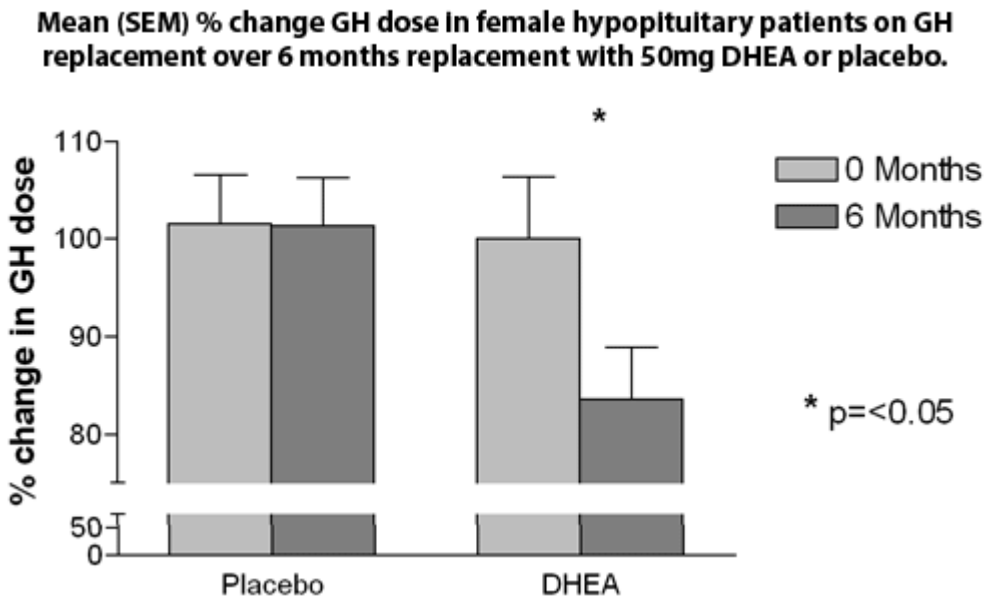

Figure 6.Data from Brooke et al (Ref 47).

SELECTING PATIENTS FOR GROWTH HORMONE REPLACEMENT

The diagnosis of GHD in adults is usually straightforward and consensus guidelines have been established with generalised acceptance. Nonetheless there is continuing debate regarding the selection of patients for GH replacement. Practice varies between countries and is undoubtedly influenced by availability of funding for treatment (38). In UK clinical practice, patients are selected for treatment on the basis of perceived need according to one or more of a number of specific criteria outlined below.

- defined severe GHD with the insulin tolerance test (ITT), glucagon, arginine, or alternative tests such as arginine plus growth hormone releasing hormone (GHRH).
- Peak GH response <9mU/l (<3ng/mL) to ITT. The appropriate threshold for the diagnosis of severe GHD using the other provocative tests needs to be cross-validated against the "gold standard" - the ITT definition.
- Patient already receiving full supplementation of other deficient hormones as required.
- Reduced QoL (including a subjective reduction in exercise tolerance or stamina) is the major indication for offering GH replacement. The selection of whom to treat is based on the patient's own perception of QOL reinforced by the objective assessment utilising a disease-specific questionnaire ("adult growth hormone deficiency assessment" - AGHDA) or alternative validated questionnaire.
- GH replacement should also be considered in patients in whom an adverse cardiovascular risk profile and/or osteopenia have been demonstrated.

ESTABLISHING THE MAINTENANCE GH DOSE

The doses used in published studies vary widely and much of the published data in this area is derived from dosing schedules established on body weight or surface area criteria which were in effect an extrapolation of earlier paediatric practice. Ongoing assessment in the routine clinical setting has indicated that patients can now be managed on much lower doses (23, 31, 49). Using a widely accepted clinical strategy, patients are commenced on 0.3 mg somatotrophin subcutaneously once a day initially. The dose is reviewed every two weeks according to clinical response, serum IGF-I and any side effects and the dose is increased if necessary

at 4 weekly intervals until the maintenance level is achieved (23). This results in a median dose requirement of 0.4 mg daily with a greater sensitivity to a given dose in male patients so that median dose requirement is lower in men. A sustained release once weekly growth hormone preparation is currently undergoing clinical trials and may be an alternative in the future (49a. Serum IGF-I may be in the lower part of the age related reference range in approximately 40% of patients with adult-onset hypopituitarism before any GH treatment across the total age range and this becomes more likely with advancing age. An empirical strategy is to use the minimum dose of growth hormone, which places the serum IGF-1 level between the median value and the upper limit of the age matched normal range for the individual patient. This approach minimises the risk of overtreatment and the potential sequelae, which may ensue. Serum IGF binding protein-3 and acid-labile subunit lack sensitivity for the titration of GH replacement and are not recommended for this purpose. IGF-I, however, is regulated by several other factors than growth hormone and changes in body composition can be seen with the addition of growth hormone even without any alteration in the IGF-I. For this reason other biomarkers of growth hormone action are being sought (49b).

ADVERSE EFFECTS

The main adverse effects directly attributable to GH replacement result from the correction of the sodium and water depletion present in GHD patients. They manifest as arthralgia, myalgia, oedema and carpal tunnel syndrome and are usually rapidly reversible with GH dose reduction. They were predominantly a feature of early experience when GH dose was determined by body weight rather than being based on a titration regimen commencing with a low starting dose as described above. Such adverse effects were predictably more frequent in male patients reflecting their greater sensitivity to GH. Benign intracranial hypertension is a recognised complication of GH replacement in paediatric practice but is much less likely in adult patients especially when low doses are used. However, persistent severe headache should prompt examination and investigation to exclude raised intracranial pressure. The potential mitogenic effects of IGF-I have raised concerns regarding a possible increased risk of either neoplasia or regrowth of residual pituitary and peripituitary tumours. Extensive surveillance studies based on large multinational databases, including several thousand patients on GH replacement followed longitudinally, have not demonstrated an increased incidence of de novo neoplasia and prospective magnetic resonance imaging studies have not indicated an increased risk of pituitary or parasellar tumour regrowth (50, 51). In the childhood cancer survivor study (51a) there was no increased risk of recurrence over 5years follow up in those who received growth hormone and on 15 year follow up of patients with previous cranial irradiation who receive growth hormone replacement there is no increased risk of malignancy (51b). In addition, there has been no correlation between the serum IGF-I within the normal reference range and risk of further malignancy (51c).

GH REPLACEMENT IN ELDERLY HYPOPITUITARY PATIENTS

Published work indicates that the baseline characteristics and response to GH replacement in hypopituitary patients aged over 65 years are qualitatively similar to those in younger patients (52, 53, 53a). Importantly, GH deficiency in the elderly is distinguishable on dynamic tests from the well-recognised physiological reduction in spontaneous GH secretion with advancing age (20). It is therefore appropriate to consider older hypopituitary patients for GH replacement and to apply similar criteria to those outlined above.

TRANSITION BETWEEN PAEDIATRIC AND ADULT CARE FOR CHILDHOOD ONSET GHD

Confirmation of persisting GHD at the time of completion of linear growth is important, particularly for patients with isolated GHD. In the presence of a structural lesion in childhood, a low IGF-I (in the absence of poorly controlled diabetes, liver disease or oral oestrogen) is enough to confirm GHD, without a provococation test

(53b). Subsequently, decisions must be taken regarding recommencement of GH or longitudinal clinical observation off treatment. Arguments supporting continuation of GH therapy include the observation of increased accumulation of fat mass off treatment (54, 55) and continued acquisition of bone mass in young adults continuing GH in contrast to static bone mass in those discontinuing treatment at the time of completion of linear growth (56). There is no detriment seen in QoL in those patients who withdraw from GH at the completion of linear growth. There is an apparent improvement in insulin sensitivity but, as is the case during normal puberty, this may not be beneficial in the context of continuing somatic development. Given that the major indication for adult GH replacement is the impairment of QOL, then there is no clear consensus as to which patients should continue therapy seamlessly, virtually without interruption, and in which patients it may be reasonable to undertake a period of careful clinical assessment. A consensus meeting convened by The European Society for Paediatric Endocrinology suggested offering continuation of therapy (after retesting) and monitoring those who decline continuation of treatment. If therapy is continued the optimum dosing strategy has not been clearly defined although a titration approach as outlined above would seem empirically appropriate (57). The current Endocrine Society Clinical practice guidelines recommend growth hormone therapy to be continued after adult height to allow full skeletal and muscle maturation, which is often delayed in this population (53b).

COSTS VERSUS BENEFITS OF GH REPLACEMENT THERAPY

Population studies in Sweden have documented a significantly greater medical and social burden for patients with established hypopituitarism. This continuing cost occurs irrespective of the initial cost of treating the pituitary pathology and derives from issues including unemployment, early retirement, depressive illness and requirement for disability pension. A recent social circumstances analysis of the KIMS database has shown that approximately 11% of males and 31% of females require assistance with activities of daily living (58) (figure 7). Additional treatment cost factors, which are more difficult to quantify but which might be inferred from risk factor profiles in adult GHD populations, include increased prevalence of ischaemic heart disease and increased fracture rates. Whilst the cost of providing GH replacement to the hypopituitary population is relatively easily determined on the basis of the minimum estimate data for prevalence of GHD and the known median GH dose requirement, matching this with data for economic benefit requires a quantification of long term complications arising from surrogate markers for long term morbidity observed in GHD patients. Assessments of the effectiveness of GH replacement over time is influenced by the changing characteristics of the patients, with lower doses of GH replacement being used and a shorter period of time from diagnosis of GHD to treatment (58a). This means that accurate assessments of cost benefit using long term data has not yet been possible.

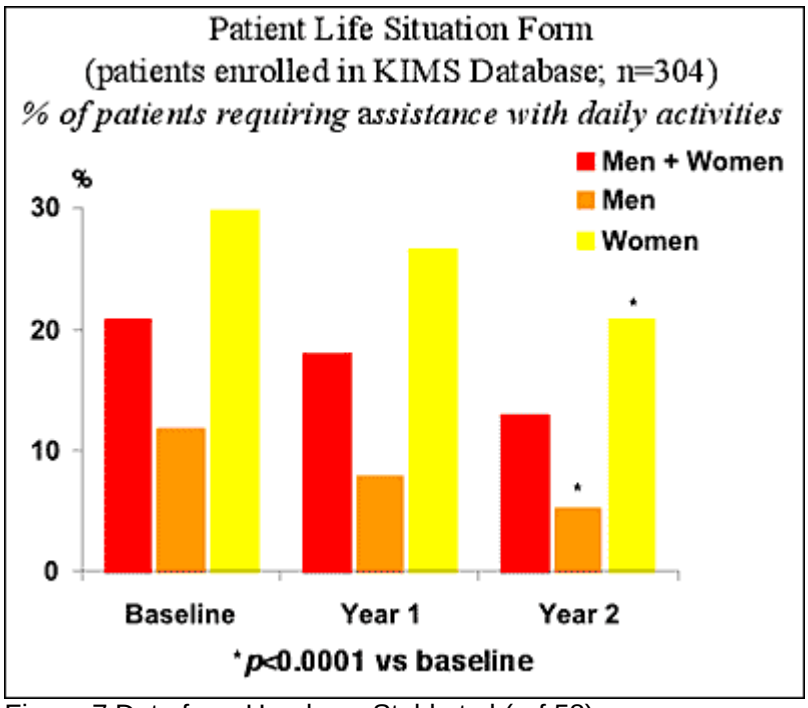

Figure 7.Data from Hernberg-Stahl et al (ref 58)

TREATMENT COSTS

Estimates of cost should recognise that a proportion of GHD adults may be ineligible for GH replacement by virtue of specific contraindications such as active malignant disease or advanced diabetic retinopathy. In addition, other patients may reject therapy on the basis of dislike of injections or absence of perceived symptoms requiring intervention. In addition the attitude of the physician will also determine the take-up of treatment. If we assume that these factors may reduce the number of patients receiving treatment to 80% of those eligible and we use a conservative estimate of prevalence of hypopituitarism of 1:10,000 then the number of patients requiring replacement is likely to be in the order of eight per 100,000 population. Using data for median GH dose requirement based on the most conservative titration dosing regimens the estimated annual cost for this population will be approximately $420,000. This estimate takes no account of the cost of treatment of childhood-onset GHD persisting into adult life. The latter could potentially triple the constituency for therapy.

ECONOMIC BENEFITS OF GH REPLACEMENT

Analysis of the economic benefit of GH replacement in adult GHD should take account of possible favorable effects on utilisation of social services in addition to the theoretical beneficial impact on rates of cardiovascular disease and fracture rates. A recent study based on patients enrolled into the KIMS database has demonstrated significant reductions in the numbers of patients requiring assistance with the activities of daily living (figure 6), a decrease in medical consultations and a decrease in hospital in-patient stays over a period of 24 months of GH replacement (figure 8).

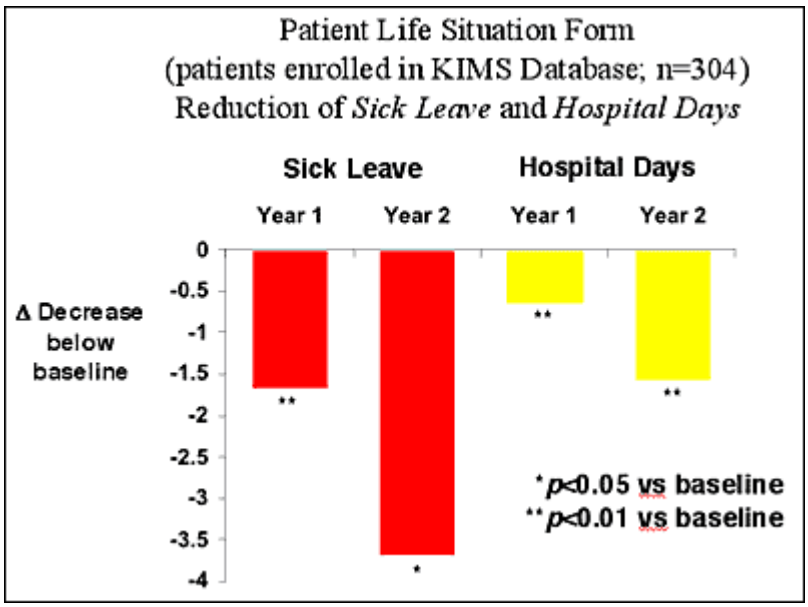

Figure 8.Data from Hernberg-Stahl et al (ref 58)

The mean decrement in serum total and LDL-cholesterol observed during GH replacement could, by analogy with other hypolipidaemic interventions, result in an approximately 20-30% reduction in cardiac ischaemic events. Clearly the long-term cost of cardiac morbidity should also be considered. The observation of substantial increments in bone mineral density during GH replacement extending over several years would also predict a reduction in fracture rates with the attendant cost of acute treatment and subsequent rehabilitation. The potential impact of GH replacement on the increased mortality rates described in hypopituitary patients can only be determined by long-term surveillance of treated patients in comparison with normal population data. The multinational databases designed to monitor safety of long-term GH replacement may provide useful information in this regard. Reassuringly, the mortality rates in the KIMS database are currently similar to the background populations (figure 9).

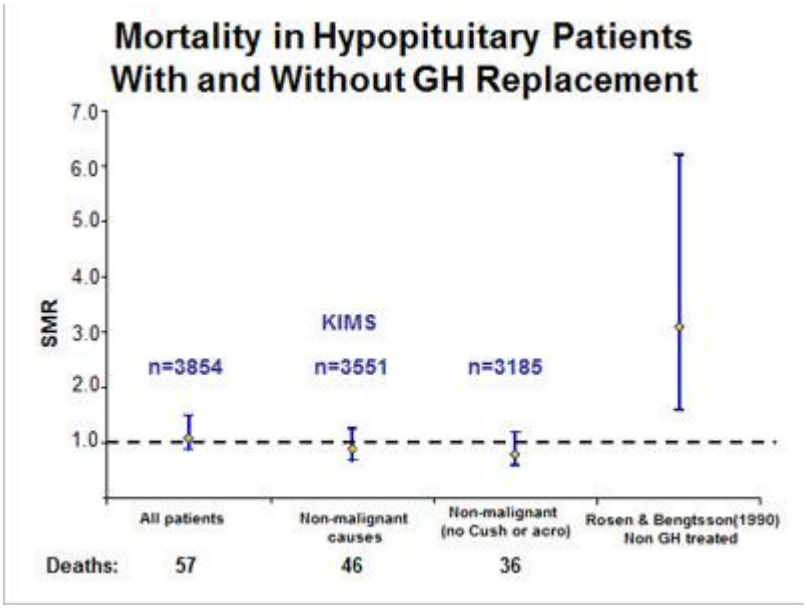

Figure 9.

References

1. Cuneo RC, Salomon F, Sönksen PH. The growth hormone deficiency syndrome in adults. Clin Endocrinol 1992, 37, 387-397.

2. De Boer H, Blok G-J, Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. Endocrine Reviews 1995, 16, 63-86.

3. Carroll PV, Christ ER et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: A Review. J Clin Endocrinol Metab 1998, 83,382-395.

4. Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumours in adults. Quarterly Journal of Medicine 1988, 262, 145-160.

5. Rosén T, Bengtsson B-Å. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 1990, 336, 285-8.

6. Bülow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol 1997, 46, 75-81.

7. Tomlinson JW, Holden N, Hills RK, Clayton RN, Sheppard MC, Stewart PM. Association between premature mortality and hypopituitarism. Lancet 2001, 357, 425-31.

8. Markussis V, Beshyah SA, Fischer C, Sharp P, Nicolaides AN, Johnson DG. Detection of premature atherosclerosis by high resolution ultrasonography in symptom free hypopituitary adults. Lancet 1992, 340, 1188-92.

9. Fowelin J, Attrall S, Lager I, Bengtsson B-Å. Effects of treatment with recombinant human growth hormone on insulin sensitivity and glucose metabolism in adults with growth hormone deficiency. Metabolism 1993, 42, 1443-7.

10. Johansson J-O, Landin K, Tengboru L, Rosén T, Bengtsson B-Å. High fibrinogen and plasminogen activator inhibitor activity in growth hormone deficient adults. Arterioscler Thromb 1994, 14, 434-7.

11. Weaver JU, Monson JP, Noonan K, John WG, Edwards A, Evans KA, Cunningham JC. The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity and cardiovascular risk factors in hypopituitary adults. J Clin Endocrinol Metab 1995, 80, 153-9.

12. Capaldo B, Patti L, Oliverio U, Longobardi S, Pardo F, Vitali F, Fazio S, di Reller F, Bindi B, Lombardi G, Sacca L. Increased arterial intima-media thickness in childhood onset growth hormone deficiency. J Clin Endocrinol Metab 1997, 82, 1378-81.

13. Abs R, Bengtsson B-Å, Hernberg-Ståhl E, Monson JP, Tauber J-P, Wilton P, Wüster C on behalf of the KIMS Study Group. GH replacement in 1034 GH deficient adults: demographic and clinical characteristics, dosing and safety. Clin Endocrinol 1999, 50,703-713.

14. Florakis D, Hung V, Kaltsas G, Coyte D, Jenkins PJ, Chew SL, Grossman AB, Besser GM, Monson JP. Sustained reduction in circulating cholesterol in adult hypopituitary patients given low dose titrated growth hormone replacement: a two year study. Clin Endocrinol 2000, 53, 453-459.

15. Bengtsson B-Å, Abs R, Bennmarker H, Monson JP, Feldt-Rasmussen U, Hernberg-Ståhl E, Westberg B, Wilton P, Wüster C. The effects of treatment and the individual responsiveness to GH replacement therapy in 665 GH-deficient adults. J Clin Endocrinol Metab 1999, 84, 3929-3935.

16. Gibney J, Wallace JD, Spinks T et al. The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. J Clin Endocrinol Metab 1999, 84, 2596-2602.

16a. Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in adults. van Bunderen CC, van Nieuwpoort IC, Arwert LI, Heymans MW, Franken AA, Koppeschaar HP, van der Lely AJ, Drent ML.JCEM (2011) 96(10):3151-3159].

16b Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A. Hypothalmopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA. 2007;298:1429–1438.

16c. Klose M1, Stochholm K, Janukonyté J, Lehman Christensen L, Frystyk J, Andersen M,Laurberg P, Christiansen JS, Feldt-Rasmussen U. Prevalence of posttraumatic growth hormone deficiency is highly dependent on the diagnostic set-up: results from The Danish National Study on Posttraumatic Hypopituitarism. J Clin Endocrinol Metab. 2014;99(1):101-10.
16d. Khajeh L, Blijdorp K, Heijenbrok-Kal MH, Sneekes EM, van den Berg-Emons HJ, van der Lely AJ, Dippel DW, Neggers SJ, Ribbers GM, van Kooten F. Pituitary dysfunction after aneurysmal subarachnoid haemorrhage: course and clinical predictors-the HIPS study. J Neurol Neurosurg Psychiatry. 2014.
16e.) Gardner CJ, Mattsson AF, Daousi C, Korbonits M, Koltowska-Haggstrom M, Cuthbertson DJ.GH deficiency after traumatic brain injury: improvement in quality of life with GH therapy: analysis of the KIMS database. Eur J Endocrinol. 2015 Apr;172(4):371-81.
17. Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KY. Diagnosis of growth hormone deficiency in adults. Lancet 1994, 343 1064-8.

18. Thorner MO, Bengtsson B-Å, Ho KKY, Albertsson-Wikland KM, Christiansen JS, Faglia G, Irie M, Isaksson O, Ranke M, Rosenfeld R, Shalet S, Takano K, Van der Veen EA, Weissberger AJ. The diagnosis of growth hormone deficiency in adults: a consensus statement. J Clin Endocrinol Metab 1995, 3097-3098.

19. Rahim A, Toogood AA, Shalet SM. The assessment of growth hormone status in normal young adult males using a variety of provocative agents. Clin Endocrinol 1996, 45, 557-62.

20. Toogood AA, O'Neill PA, Shalet SM. Beyond the somatopause: growth hormone deficiency in adults over the age of 60 years. J Clin Endocrinol Metab 1996, 81, 460-465.

21. Toogood AA, Beardwell CG, Shalet SM. The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. Clin Endocrinol 1994, 41, 511-516.

22. Wirén L, Bengtsson B-Å, Johannsson G - Beneficial effects of long term GH replacement therapy on quality of life in adults with GH deficiency. Clin Endocrinol 1998, 48 613-620.

23. Drake WM, Rodriguez-Arnao J, Weaver JU, James I, Coyte D, Spector T, Besser GM, Monson JP. The influence of gender on the short and long term effects of growth hormone replacement on bone metabolism and bone mineral density in hypopituitary adults - a five year study. Clin Endocrinol 2001, 54, 525-532.

24. Gelding SV, Taylor NF, Wood PJ, Noonan K, Weaver JU, Wood DF, Monson JP. The effect of growth hormone replacement therapy on cortisol-cortisone interconversion in hypopituitary adults: evidence for growth hormone modulation of extrarenal 11*-hydroxysteroid dehydrogenase activity. Clin Endocrinol 1998, 48, 153-162.

25. Wüster C, Abs R, Bengtsson B-Å, Bennmarker H, Feldt-Rasmussen U, Hernberg-Ståhl E, Monson JP, Westberg B, Wilton P. The influence of growth hormone (GH) deficiency, GH replacement therapy and other aspects of hypopituitarism on fracture rate and bone mineral density. J Bone Min Res 2001, 16, 398-405.

26. Rosén T, Bengtsson B-Å. Increased fracture frequency in adult patients with hypopituitarism and growth hormone deficiency. Eur J Endocrinol 1997, 137, 240-245.

27. Weaver JU, Monson JP, Noonan K, Price C, Edwards A, Evans KA, James I, Cunningham J. The effects of low dose recombinant human growth hormone replacement on indices of bone remodelling and bone mineral density in hypopituitary growth hormone deficient adults. Endocrinol Metab 1996, 3, 55-61.

28. Johannsson G, Rosen T, Bosaeus I, Sjostrom L, Bengtsson B-Å. Two years of growth hormone (GH) treatment increases bone mineral content and density in hypopituitary patients with adult onset GH deficiency. J Clin Endocrinol Metab 1996, 81, 2865-7.

29. Holmes SJ, Whitehouse RW, Swindell R, Economou G, Adams JE, Shalet SM. Effect of growth hormone on bone mass in adults with adult onset growth hormone deficiency. Clin Endocrinol 1995, 42, 627-633.

30. Drake WM, Coyte D, Camacho-Hübner C, Jivanji NM, Kaltsas G, Wood DF, Trainer P, Grossman AB, Besser GM, Monson JP. Optimising growth hormone replacement therapy by dose titration in hypopituitary adults. J Clin Endocrinol Metab 1999, 83, 3913-3919.

31. Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Shalet SM. Dose titration and patient selection increases the efficacy of GH replacement in severely GHD adults. Clin Endocrinol 1999, 50, 749-757.

32. Koltowska – Häggström M, Mattsson AF, Monson JP, Kind P, Badia X, Cassanueva FF, Busschbach J, Koppeschaar HPF, Johannsson G. Does long-term GH replacement therapy in hypopituitary adults with GH deficiency normalize quality of life? EJ Endo (2006), 155, 105-119.

32a. Growth hormone deficiency after treatment of acromegaly: a randomized, placebo-controlled study of growth hormone replacement. Miller KK, Wexler T, Fazeli P, Gunnell L, Graham GJ, Beauregard C, Hemphill L, Nachtigall L, Loeffler J, Swearingen B, Biller BM, Klibanski A. J Clin Endocrinol Metab 2010: 95(2): 567-77

32b. Effect of growth hormone replacement therapy on the quality of life in women with growth hormone deficiency who have a history of acromegaly versus other disorders. Valassi E, Brick DJ, Johnson JC, Biller BM, Klibanski A, Miller KK. Endocr Pract 2012: 18(2): 209-18.

32c. Growth hormone deficient patients after traumatic brain injury – baseline characteristics and benefits after growth hormone replacement – an analysis of the German KIMS database. Kreitschmann-Andermahr I, Poll EM, Reineke A, Gilsbach JM, Brabant G, Buchfelder M, Fassbender W, Faust M, Kann PH, Wallaschofski H. Growth Horm IGF Res. 2008: 18(6): 472-8.

33. Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, Huebler D, Oettel M, Ernst M, Schulte HM, Allolio B. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med. 1999 Sep 30;341(14):1013-20.

34. Brooke AM, Kalingag LA, Miraki-Moud F, Camacho-Hübner C, Maher KT, Walker DM, Hinson JP, Monson JP. Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. J Clin Endocrinol Metab. 2006 Oct;91(10):3773-9.

35. Miller KK, Biller BM, Beauregard C, Lipman JG, Jones J, Schoenfeld D, Sherman JC, Swearingen B, Loeffler J, Klibanski A. Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2006 May;91(5):1683-90.

37. Baum HBA, Katznelson L, Sherman JC et al. Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult onset GH deficiency. J Clin Endocrinol Metab 1998, 83, 3184-3189.

38. Monson JP, Abs R, Bengtsson B-Å, Feldt-Rasmussen U, Wilton P. National differences in baseline characteristics and response to GH replacement in hypopituitary patients in KIMS. Endocrine Abstracts, (2001), 1, P122.

38a. Body composition and quality of life in adults treated with Growth hormone therapy: a systemic review and meta-analysis. Hazem A, Elamin MB, Bancos I, Malaga G, Prutsky G, Domecq JP, Elraiyah TA, Abu Elnour O, Prevost Y, Almoandoz JP, Zeballos-Palacios C, Velasquez ER, Erwin PJ, Natt N, Montori VM, Murad MH. Eur J Endocrinol. 2012: 166(1):13-20.

39. Monson JP, Jönsson P, Koltowska-Häggström M, Kourides I. Growth hormone (GH) replacement decreases serum total and LDL-cholesterol in hypopituitary patients on maintenance HMG CoA reductase inhibitor (statin) therapy. Clin Endocrinol (Oxf). 2007 Oct;67(4):623-8.

40. Olivecrona H, Ericsson S, Berglund L, Angelin B. Increased concentrations of serum lipoprotein(a) in response to growth hormone treatment B Med J 1993, 306, 1726-7.

40.1 Mo D, Fleseriu M, Qi R, Jia N, Child CJ, Bouillon R, Hardin DS. Fracture risk in adult patients treated with growth hormone replacement therapy for growth hormone deficiency: a prospective observational cohort study.Lancet Diabetes Endocrinol. 2015 May;3(5):331-8.
41. Toogood AA, Taylor NF, Shalet SM, Monson JP. Modulation of cortisol metabolism by low-dose growth hormone replacement in elderly hypopituitary patients. J Clin Endocrinol Metab. 2000 Apr;85(4):1727-30.

42. Agha A, Walker D, Perry L, Drake WM, Chew SL, Jenkins PJ, Grossman AB, Monson JP. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. Clin Endocrinol (Oxf). 2007 Jan;66(1):72-7.

43 Span JPT, Pieters G, Sweep C, Hermus A, Smals A. Gender difference in insulin-like growth factor - I response to Growth Hormone (GH) treatment in GH-deficient adults : Role of sex hormone replacement. Journal of Clinical Endocrinology and Metabolism 2000; 85(3):1121.

44 Christiansen J, Fisker S, Gravholt C et al. Discontinuation of estrogen replacement therapy in GH-treated hypopituitary women alters androgen status and IGF-I. European Journal of Endocrinology 2005; 152:719-726.

45 Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. Journal of Clinical Endocrinology & Metabolism 1991; 72(2):374-81.

46Meinhardt UJ, Ho KK. Modulation of growth hormone action by sex steroids. Clin Endocrinol (Oxf). 2006 Oct;65(4):413-22.

47. Brooke AM, Kalingag LA, Miraki-Moud F, Camacho-Hübner C, Maher KT, Walker DM, Hinson JP, Monson JP. Dehydroepiandrosterone (DHEA) replacement reduces growth hormone (GH) dose requirement in female hypopituitary patients on GH replacement. Clin Endocrinol (Oxf). 2006 Nov;65(5):673-80.

48. van Thiel SW, Romijn JA, Pereira AM, Roelfsema F, van Hemert A, Ballieux B, Smit JW. Effects of dehydroepiandrostenedione, superimposed on growth hormone substitution, on quality of life and insulin-like growth factor I in patients with secondary adrenal insufficiency: a randomized, placebo-controlled, cross-over trial. J Clin Endocrinol Metab. 2005 Jun;90(6):3295-303.

49. Drake WM, Howell SJ, Monson JP, Shalet SM. Optimising GH therapy in adults and children. Endocrine Reviews 2001, 22, 425-450.

49a. Effects of once-weekly sustained-release growth hormone: a double-blind, placebo-controlled study in adult growth hormone deficiency. Biller BM, Ji HJ, Ahn H, Savoy C, Siepl EC, Popvic V, Coculescu M, Roemmler J, Gavrila C, Cook DM, Strasburger C, J Clin Endocrinol Metab. 2011: 96(6): 1718-26.

49b. Idenitication of new biomarkers of low-dose growth hormone replacement therapy in GH-deficient patients. Cruz-Topete D, Jorgensen JO, Christensen B, Sackmann-Sala L, Krusenstjerna-Hafstrom T, Jara A, Okada S, Kopchick JJ. J Clin Endocrinol Metab. 2011: 96(7): 2089-97.

50. Frajese V, Drake WM, Laureiro R, Evanson J, Coyte D, Grossman AB, Besser GM, Monson JP. Hypothalamo-pituitary surveillance imaging in hypopituitary patients receiving long term growth hormone replacement therapy. J Clin Endocrinol Metab (2001), 86, 5172-5175.

51. Chung TT, Drake WM, Evanson J, Walker D, Plowman PN, Chew SL, Grossman AB, Besser GM, Monson JP. Peripituitary tumour surveillance imaging in patients receiving growth hormone replacement. Clin Endocrinol (2005), 63, 274-279.

51a. The childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, Green DM, Hammond S, Meadows AT, Mertens AC, Mulvihill JJ, Nathan PC, Neglia JP, Packer RJ, Rajaraman P, Sklar CA, Stovall M, Strong LC, Yasui Y, Zeltzer LK. J Clin Oncol 2009: 10: 27 (14): 2308-18.

51b. Long-term safety of growth hormone replacement after CNS irradiation. Mackenzie S, Craven T, Gattamaneni HR, Swindell R, Shalet SM, Brabant G. J Clin Endocrinol Metab. 2011: 96(9): 2756-61.

51c. Serum insulin-like growth factor I (IGF-I) , IGF-binding proteins 2 and 3, and the risk for development of malignancies in adults with growth hormone (GH) deficiency treated with GH: data from KIMS (Pfizer International Metabolic database). Popovic V, Mattson AF, Gaillard RC, Wilton P, Koltowska-Haggstrom M, Ranke MB. J Clin Endocrinol Metab. 2010: 95(9):4449-54.

52. Monson JP, Abs R, Bengtsson B-Å, Bennmarker H, Feldt-Rasmussen U, Hernberg-Ståhl E, Thorén M, Westberg B, Wilton P, Wüster C. Growth hormone deficiency and replacement in elderly hypopituitary adults. Clin Endocrinol 2000, 53, 281-289.

53. Fernholm R, Bramnert M, Hägg E, Hilding A, Baylink DJ, Mohan S, Thorén M. Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. J Clin Endocrinol Metab 2000, 85, 4104-4112.

53a. GH replacement therapy in elderly GH-deficient patients: a systematic review. Kokshoorn NE, Biermasz NR, Roelfsema F, Smit JW, Pereira AM, Romijn JA. Eur J Endocrinol 2011: 164(5):657-65.

53b. Evaluation and treatment of adult growth hormone deficiency deficiency: an Endocrine Society Clinical practice guideline. Molitch ME, Clemmons DR, Malzowski S, Merriam GR, Vance ML; Endocrine Society. J Clin Endocrinol Metab. 2011: 96(6):1587-609.

54. Vahl N, Juul A, Jørgensen JOL, Ørskov H, Skakkebæk N, Christiansen JS. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. J Clin Endocrinol Metab 2000, 85, 1874-1881.

55. Carroll PV, Drake WM, Maher KT, Metcalfe KA, Shaw NJ, Dunger DB, Cheetham TD, Camacho-Hübner C, Savage MO, Monson JP. Comparison of continuation or cessation of growth hormone (GH) therapy on body composition and metabolic status in adolescents with severe GH-deficiency at completion of linear growth. J Clin Endocrinol Metab (2004), 89, 3890-3895.

56. Drake WM, Carroll PV, Maher KT, Metcalfe KA, Shaw NJ, Camacho-Hübner C, Dunger DB, Cheetham TD, Savage MO, Monson JP. Cessation of growth hormone therapy at final height limits the attainment of peak bone mass in adolescent growth hormone deficient patients. J Clin Endocrinol Metab (2003), 88, 1658-1663.

57. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the growth hormone treated adolescent in the transition to adult care. Eur J Endocrinol (2005), 152, 165-170.

58. Hernberg-Ståhl E, Luger A, Abs R, Bengtsson B-Å, Feldt-Rasmussen U, Westberg B, Wilton P, Monson JP. Healthcare consumption decreases in parallel with improvements in quality of life during growth hormone (GH) replacement in hypopituitary adults with GH deficiency. J Clin Endocrinol Metab 2001, 86, 5277-5281.

58a. Variation of the baseline characteristics and treatment parameters over time: an analysis of 15 years of growth hormone replacement in adults in the German KIMS database. Kreitschmann-Andermahr I, Seigel S, Francis F, Buchfelder M, Scheider HJ, Kann PH, Wallaschofski H, Koltowska-Haggstrom M, Brabant G. Pituitary. 2012. Jul 25.