Adult growth hormone replacement: current understanding

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Initial studies of growth hormone (GH) replacement in adults used weight- and surface area-based dosing regimes extrapolated from paediatric practice. Much of the beneficial effects were pharmacological rather than physiological. Furthermore, weight-based dosing regimens resulted in lower overall doses in females who require approximately threefold greater GH secretion in health to maintain a similar insulin-like growth factor-I level to males. This inequality of dosing explains studies reporting that males respond more efficaciously to GH replacement. Recent studies individualising GH doses to normalize serum insulin-like growth factor-I level have shown a similar spectra of beneficial effects to earlier weight-based studies; however, the degree of these effects on biological sequelea was reduced. Using this individualised dosing regimen, both genders responded equally to GH replacement for most biological end-points. The effect of GH replacement on bone mineral content is complex, and is dependent on the onset of GH deficiency, age of the patient and dosing regimen. GH is increasingly recognized as being intricately involved in regulation of surrogate markers of vascular risk and endothelial dysfunction, replacement of which normalises these indices. Definitive data on the effect of GH on mortality is awaited. Studies of 5–10 years duration suggest that beneficial effects of GH are maintained long-term. A depot preparation of GH is currently under investigation and, if proven to be efficacious and safe, might be a more acceptable therapy to a proportion of patients.

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Abbreviations

AO	adult-onset
BMC	bone mineral content
BMD	bone mineral density
CO	childhood-onset
FM	fat mass
GH	growth hormone
GHD	growth hormone deficiency
HDL	high-density lipoprotein
IGFBP-3	insulin-like growth factor binding protein-3
IGF-I	insulin-like growth factor-I
LBM	lean body mass
LDL	low-density lipoprotein
LVEF	left ventricular ejection fraction
TC	total cholesterol
WHR	waist-hip ratio

Introduction

The increased availability of growth hormone (GH) in the mid-1980s resulting from advances in recombinant DNA technology presented the opportunity for GH replacement in adults with severe GH deficiency (GHD). The initial randomized double-blind placebo-controlled studies published in 1989 showed that GH replacement in hypopituitary adults had beneficial effects on body composition, muscle strength, exercise capacity and serum lipids, and increased both glomerular filtration and metabolic rate [1,2]. A deleterious effect on fasting glucose and insulin was noted.

The adult GHD syndrome is characterised by abnormal body composition (increased fat mass [FM] and reduced lean body mass [LBM]), reduced exercise tolerance and muscle strength, osteopenia, an adverse lipid profile, elevated pro-coagulant factors, impaired cardiac indices and reduced psychological well-being [3,4]. Support for the role of GH in physiological and metabolic homeostasis of the adult is derived from studies reporting beneficial effects of GH replacement on the above biological sequelea [3,4].

Although clinical practice has moved away from the use of weight-based dosing regimens towards individualisation of GH doses, as undertaken with other hormone replacements, the majority of the literature continues to be based on weight-based dosing regimens. The impact of individualised dosing on biological end-points therefore remains unclear. Differences both in baseline abnormalities and response to replacement amongst subgroups of hypopituitary patients have recently become apparent and shed some light on contradictory outcomes of studies. The impact of GH on vascular disease and bone remain important issues, and insights into which patients will benefit from GH replacement continue to evolve. Finally, for GH to be a viable long-term treatment option, the beneficial effects must be maintained and free from serious side-effects.

Growth hormone replacement dose

Although the abnormalities described in GH-deficient hypopituitary adults are not contested, it is difficult to determine the proportion relating directly to GHD from that caused by non-physiological replacement of additional anterior pituitary hormones and the sedentary life-style

associated with hypopituitarism. At present, opinion leans towards GHD being responsible for the majority of the observed abnormalities; support for this view-point comes from studies showing that GH replacement reverses these abnormalities almost entirely. This finding must be taken in context with the observation that the vast majority of GH replacement studies used GH doses now considered to be supra-physiological. In paediatric practice, supra-physiological GH doses augment growth velocity in GH insufficient and normal children. In GH-deficient adults, GH replacement dose-dependently increases serum insulin-like growth factor-I (IGF-I), fasting insulin and LBM, decreases FM and impairs insulin sensitivity [5,6]. It is therefore unclear in studies using weight-based dosing regimens (which frequently result in supraphysiological IGF-I levels) whether the observed benefits are pharmacological or physiological.

Recently, studies individualising GH replacement by slowly titrating the GH dose to normalize serum IGF-I have been reported. The methodology of these studies reflects management of patients in clinical practice and provides a more realistic assessment of the degree of abnormality relating directly to GHD in hypopituitary patients. Using individualised GH dosing regimens, improvements in body composition have been inconsistent [7,8,9••,10,11•,12–16]. Serum lipids generally showed a reduction of 0.2–0.4 mmol/L in total cholesterol [7,9••,10] and 0.3–0.5 mmol/L in low-density lipoprotein (LDL) cholesterol [7,9••,10], although not in all studies [11•]. No change [9••,10,11•] or a transient increase [7] in high-density lipoprotein (HDL) cholesterol, as well as both decreases [10] and more frequently no change in triglyceride levels [7,9••,11•], has been reported. Increased lipoprotein(a) levels have been observed [9••]. No change occurs in the renin-angiotensin system [17]. Systolic and diastolic blood pressure are reduced and heart rate increased [14]. Fasting glucose levels are unaffected [11•] or elevated [7]; fasting insulin increases [13]; and glycosylated haemoglobin levels have been reported to both increase [7,11•] and be unaffected [12]. Bone mineral density (BMD) increases of approximately 3.5% at the lumbar spine and increases at the ultradistal radius [11•] following 18 months GH therapy [18] have been observed, but no change in BMD has been observed as frequently [11•,18]. Improvements in quality of life in selected cohorts have consistently been shown [8,11•,12,15].

Therefore, using a low-dose individualised GH dosing regimen results in smaller changes in body composition and metabolic indices compared with earlier studies using supra-physiological weight-based GH doses extrapolated from the paediatric practice.

Effect of gender and age of onset

Differences are recognized both in abnormalities before initiation of GH replacement and in response to treatment between males and females. IGF-I levels are lower in GH-deficient females and males [8,9••,19–23]. In comparison with males, female patients with GHD have equivalent body mass index, higher FM and leptin levels, and lower LBM [10,19,20,24]; similar bone mineral content (BMC), BMD and markers of bone turnover [23,25]; a more adverse lipid profile characterised by higher total cholesterol (TC), LDL cholesterol and HDL cholesterol [7,10,23]; and a similar degree of impairment of quality of life [21].

The dichotomy in response to GH replacement between genders is dependent on whether GH is administered on a weight- or surface area-based dosing regimen or, alternatively, individually titrated to normalize the serum IGF-I level. Earlier weight-based dosing regimens led to a greater increase in IGF-I in males than in females [6,23,25,26]. Males also demonstrate greater increases in LBM [5,19,26], decreases in FM [5,19,23], more favourable changes in the lipid profile [19,23] and higher increments in markers of bone turnover and improvements in BMD [23,25,26]. With individualisation of the GH dose by titration according to serum IGF-I, females require a higher GH dose to normalize their serum IGF-I than do males [7,8,9••,10,22]. However, males and females demonstrate similar changes in body composition, leptin and quality of life [8,15,24]. Improvements in the lipid profile are found to occur primarily in females [10] in whom greater abnormalities are found at baseline.

In summary, the use of a weight-based dosing regimen leads to greater GH doses administered to males, who physiologically [27] and during replacement require less GH to maintain a normal serum IGF-I than do females. It is therefore not unexpected that greater GH-associated changes occur in males, which probably relates to the inappropriate dosing regimen. Using a more physiological replacement regime of individually titrating the GH dose to normalize the serum IGF-I results in similar improvements in males and females, with the exception of the lipid profile.

Effect of growth hormone replacement on bone

The impact of GHD on the skeleton is dependent on the time of onset of GHD. Patients with childhood-onset (CO) GHD are osteopenic [28,29–31]; however, when GHD is acquired during adult life, the effect on BMD is less severe, with studies reporting mean BMD z-scores (measured by dual energy X-ray absorptiometry) at the lumbar spine of −0.2 to −0.8 [32–34], which fall within the normal range. A highly significant relationship between age and BMD is present in adult-onset (AO) patients. Young patients present with significant osteopenia, whereas GH-deficient adults above the age of 50 years have normal BMD [35]. Only in GH-deficient adults aged less than 30 years is there an increase in

the prevalence of lumbar spine or femoral neck z-scores below normal [35].

The effect of GH replacement on BMD of GH-deficient adults is complex. The vast majority of studies examining the effect of GH on BMD have used weight- or surface area-based dosing regimens, which frequently lead to over-replacement of GH in males and under-replacement in females. As a consequence, one might expect increased BMD in males and a lesser, or no effect, in females. The situation is complicated further by the differences in BMD at baseline outlined above, as baseline BMD affects the response to GH replacement [36]. GH replacement results in a biphasic effect on BMD in GH-deficient adults: a transient reduction in BMD occurring during the first 6–12 months therapy, returning to baseline values by 12–18 months [37,38]. Studies replacing GH in CO GHD adults have consistently shown a net increase in bone mass [31,39]. Adolescents treated with GH during childhood until reaching final height were randomized to receive GH replacement or placebo. A greater increase in total body BMC and lumbar spine BMD was observed in the patients receiving GH during the next 12 months [40], indicating the importance of GH in obtaining peak bone mass. Placebo-controlled studies of GH replacement of 6–18 months duration in cohorts exclusively, or predominantly, of AO have shown either no significant increase [26,38,41] or only a small increase in BMD [42]. Interestingly, the latter study cohort, in whom an increase in BMD was observed, was comprised exclusively of male patients [42]. In contrast to placebo-controlled studies, open treatment studies (without a placebo arm but of longer duration) frequently show increases in BMD [18,33,37]. Normal elderly provide a paradigm of relative GHD; despite significant increases in bone turnover with GH replacement in normal elderly [43–46], the majority of studies showed that GH therapy for 6–12 months did not increase BMD [43,44,47]. In two open treatment studies — the first in osteoporotic elderly females and the second in males with idiopathic osteoporosis, of two and three years duration, respectively — increases in BMD were observed [46,48]. Neither study contained a placebo arm and, in the first of these studies, patients were advised on the benefit of diet and exercise on bone mass [46]. In the second study, patients were concurrently treated with calcium and vitamin D [48].

Markers of bone formation and resorption increase with GH replacement therapy independently of whether a concomitant change in BMC or BMD is observed. Osteoprotegerin is a recently described glycoprotein of the tumour necrosis factor receptor superfamily that is secreted as a soluble protein and acts as a decoy receptor for receptor-activator-of-NF-κβ-ligand (an osteoblastic-derived promoter of osteoclast differentiation and activation). GH therapy increases serum and both trabecular and cortical bone oteoprotegerin [49,50], providing a mechanism by which GH may inhibit bone resorption and thus promote bone formation.

In summary, BMD of untreated GH-deficient adults is dependent upon the timing of onset of GHD (AO versus CO), and for AO patients the age at which their deficiency occurs. BMD of CO GH-deficient adults improves with GH replacement; however, the situation in AO patients remains unclear, with conflicting data from shorter placebo-controlled studies and longer open treatment studies. Part of the difficulty in interpreting studies of AO patients lies in the adequacy of the dose in female patients and the inclusion of patients with normal BMD before replacement that are unlikely to improve further and who thus dilute any true effect of GH on BMD. The 'normal' BMD in older adults with GHD and the lack of efficacy in normal elderly suggest that the skeleton is less dependent on GH with increasing age, which is in contrast to the obvious role GH plays in obtaining peak bone mass during young adult life.

Growth hormone deficiency and the vascular system

Patients with hypopituitarism have an excess of markers of vascular risk [10,51•–53•,54,55], which culminate in an increased mortality of approximately twofold [56,57]. GHD has been proposed to be responsible, at least in part, for the excess surrogate markers and vascular mortality, although it remains unclear to what degree. The adverse vascular markers relate to the associated truncal obesity; however, this does not fully explain the observed abnormalities [55]. The importance of GH in maintenance of vascular integrity is supported by studies demonstrating improvements in surrogate markers of vascular risk with replacement. These studies show decreases in FM [26,53•], mean 24 hour blood pressure [14], TC, LDL cholesterol, triglycerides and LDL/HDL ratio [10,51•, 52•], and increases in HDL cholesterol [51•]. In contrast to these beneficial effects, GH through its peripheral anti-insulin actions inhibits glucose storage, oxidation and non-oxidative disposal without an alteration in hepatic glucose production, leading to compensatory hyperinsulinaemia [58•]. In contrast to patients receiving GH replacement, prospective evaluation of markers of vascular risk for 12 months in untreated GH-deficient adults showed increases in TC, LDL cholesterol and triglycerides, and decreases in HDL cholesterol and left ventricular ejection fraction (LVEF) [51•].

GH-deficient adults have reduced lipid peroxidation and neutrophil superoxide-generating capacity, suggesting oxidative stress is not a major aetiological feature of endothelial dysfunction in GH-deficient hypopituitary adults [53•]. Increased pro-atherogenic remnant-like particle cholesterol, both in the fasting state and post prandially [59•], correlated with interleukin-6 levels in GH-deficient adults, suggesting a mechanism by which

lipid abnormalities (associated with an inflammatory response) result in increased susceptibility to premature atherosclerosis. More direct measures of vascular integrity indicate that GH-deficient adults have increased arterial intima-medial thickness [55], reduced endothelium-derived flow-mediated dilatation [52•], reduced muscle blood flow and increased vascular resistance associated with increased sympathetic nerve activity [60]. GH replacement normalises both endothelium-derived flow-mediated dilatation and brachial artery blood flow [52•,61]. Hypopituitary adults in addition to the above effects on large and medium sized vessels show reduced capillary density, microvascular perfusion and capillary leakage [62,63]. GH replacement normalises these microvascular aberrations [62,63]. Deficiency of GH also has direct effects on cardiac function; the most frequently reported abnormalities are reduced left ventricular mass and LVEF [51•]. Increases in both left ventricular mass and LVEF occur during GH replacement [26,51•].

Long-term growth hormone replacement

There have now been several studies of 5–10 years duration examining whether the beneficial effects of GH replacement in short-term studies persist in the long-term [64,65,66•,67,68]. GH maintains the initial increase in LBM and reduction in FM [64,65,68], and prevents the age-related increase in WHR observed in untreated GH-deficient adults [68]. Increases in hand grip and knee flexor strength remain present at five years [64], although a study of 10 years failed to see an improvement in exercise tolerance [68]. Improvements occur in LDL and HDL in the absence of deterioration in glucose tolerance and hyperinsulinaemia [65,67,68]. In contrast to GH-deficient patients receiving replacement, untreated patients showed an increase in carotid intima-medial thickness when reassessed after 10 years [67]. Initial improvements in quality of life with GH therapy are maintained for at least 9–10 years [66•].

In summary, the data addressing the issue of long-term effects of GH support the beneficial effect of GH replacement on body composition, strength, surrogate markers of vascular risk and quality of life.

Treatment of specific growth hormone-deficient subgroups

Patients with type I diabetes mellitus have increased GH levels and low IGF-I. Furthermore, GH is recognized to have anti-insulin effects and has been implicated in the pathogenesis of diabetic retinopathy. GH treatment of hypopituitary patients with type I diabetes has therefore remained controversial. In these patients, Christ *et al.* [69] reported improved quality of life, decreased FM and a reduction in the incidence of hypoglycaemic attacks during six months of GH therapy, with no progression of underlying diabetic retinopathy. Insulin requirements increased 1.75-fold with no deterioration in glycaemic control [69]. Progression of retinopathy with longer-term GH replacement remains a concern.

Adult survivors of cancer rendered GH-deficient by cranial irradiation are recognized to have characteristic features of the adult GHD syndrome, including reduced stature, adverse lipid profile, osteopenia and impaired quality of life [11•,18]. GH replacement in these individuals for 12–18 months by an individualised GH dose improved quality of life and BMD at the ultradistal radius [11•]. No improvements occurred in the lipid profile or body composition in the cohort overall; however, an improvement in WHR occurred in males and a decrease in TC and triglycerides occurred in females. Failure of lumbar spine BMD to improve, which is comprised primarily of trabecular bone similar to the ultradistal radius, might be related to the high incidence of spinal irradiation (63%) in these patients [11•,18]. The exact contribution of GHD to the adverse biological sequelea in these patients is difficult to disentangle from the disease process itself and the various therapeutic interventions. The minor improvement observed in all end-points, with the exception of quality of life, during GH replacement suggests that GH is not a major aetiological factor in their pathogenesis. The dramatic improvement in quality of life with GH therapy in hypopituitary childhood cancer survivors when severely impaired remains an indication for a trial of therapy.

Safety

Cohort studies of normal subjects found the highest prevalence of prostate and breast cancer in subjects with IGF-I levels in the upper reaches of the normal range [70,71]. An increase in colonic cancers has been suggested in patients with acromegaly [72]. Although safety of GH in short-term studies is without doubt, GH does raise serum IGF-I concentration, which has both mitogenic and antiapoptotic properties, leaving the issue of long-term safety unanswered. Follow-up of 1849 patients treated with pituitary-derived GH during childhood showed an 11-fold increase in incidence of colorectal carcinoma after a mean follow-up of 16 years, and a 15-fold increase in mortality from both colorectal carcinoma and Hodgkin's disease after 21 years follow-up [73••]. Numbers in this study were small, with only six deaths from cancer in the cohort after removal of patients at high risk. Calculation of the excess risk of developing colorectal cancer and Hodgkin's disease was thus based on two patients in both cases [73••]. Reassuringly, although GH replacement increases prostate size, no change in histology or prostate-specific antigen occurs during 24–48 months GH replacement [74,75]. Three and a half years of GH replacement did not increase the recurrence rate of pituitary tumours compared with untreated GH-deficient hypopituitary patients [76], and GH therapy in high-risk children with a primary diagnosis of leukaemia or brain tumours did not increase either tumour recurrence or the incidence of secondary malignancies [77,78]. To provide

a definitive answer to whether GH replacement increases tumour incidence or mortality will require a decade of follow-up of a large number of hypopituitary patients, which is likely to be best achieved by the use of multinational surveillance programs, despite their limitations.

New therapeutic approaches

Currently licensed therapy for treatment of adult GHD entails the use of a single daily subcutaneous bolus injection administered before sleep to mimic physiological secretion. GH secretagogues hold promise of therapeutically enhancing endogenous GH secretion. Use of the GH secretagogue NN703 in GH-deficient adults showed that only 11% of patients responded with a peak GH response greater than 5 μg/L [79]. Over the seven days of the study, the GH-releasing effect of NN703 diminished, as previously observed with GH secretagogues [80]. It seems unlikely that GH secretagogues will find a role in treatment of GH-deficient adults as a result of their limited GH-releasing effect and the tolerance that occurs in these subjects.

Recently, a depot preparation incorporating GH in microspheres of biodegradable copolymer has been developed. 12 months depot GH in children, administered either monthly or twice monthly, significantly increased growth velocity, height standard deviation score and predicted adult height [81]. Side effects other than transient injection site pain and nodules were infrequent. In GH-deficient adults, depot GH at a dose of 0.25 mg/kg or 0.5 mg/kg gave GH levels in the target concentration for 10–15 days [82••]. A dose of 0.25 mg/kg maintained IGF-I within the normal range for 14–17 days in males, whereas females required a dose of 0.5 mg/kg to achieve normal IGF-I levels for approximately 14 days [82••]. Side effects included hyperinsulinaemia, erythema at the injection site, oedema, headaches and arthralgia. Depot GH provides a well-tolerated alternative to daily nocturnal injections in the treatment of both childhood and adult GHD. Further studies of efficacy are required before depot can be accepted as a therapy for adult GHD.

Conclusions

Adult GH replacement is moving away from weight-based dosing regimens extrapolated from paediatric practice towards individualization of the dose by titration against serum IGF-I. The biological response to GH reflects the degree of abnormality before treatment, which can vary according to the age of onset of GH deficiency and gender. The effect of GH on biological end-points is clearly dose-related, with individualised GH dosing leading to significantly lower GH doses and consequently less effect on GH-responsive end-points. To date, there are no randomized placebo-controlled studies of the effect of individualised GH replacement on biological end-points. Additionally, many patients have normal BMD, lipids or quality of life before treatment, which are unlikely to improve with 'physiological' replacement, but will dilute the beneficial effect seen in other patients. Studies are therefore needed in selected patient groups with specific abnormalities at baseline (e.g. osteopenia) and should be performed in a placebo-controlled design to avoid statistical errors relating to regression towards the mean. The impact of GH replacement on fracture rate and mortality are awaited and might provide the most compelling evidence for treatment. The development of a depot GH preparation could make treatment more acceptable to a greater proportion of patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann Hansen T, Skakkebaek NE, Christiansen JS: **Beneficial effects of growth hormone treatment in GH-deficient adults**. *Lancet* 1989, **1**:1221-1225.

2. Salomon F, Cuneo RC, Hesp R, Sonksen PH: **The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency**. *N Engl J Med* 1989, **321**:1797-1803.

3. de Boer H, Blok GJ, Van der Veen EA: **Clinical aspects of growth hormone deficiency in adults**. *Endocr Rev* 1995, **16**:63-86.

4. Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P *et al.*: **Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee**. *J Clin Endocrinol Metab* 1998, **83**:382-395.

5. Kehely A, Bates PC, Frewer P, Birkett M, Blum WF, Mamessier P, Ezzat S, Ho KK, Lombardi G, Luger A *et al.*: **Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms**. *J Clin Endocrinol Metab* 2002, **87**:1974-1979.

6. Yuen K, Ong K, Husbands S, Chatelain P, Fryklund L, Gluckman P, Ranke M, Cook D, Rosenfeld R, Wass J, Dunger D: **The effects of short-term administration of two low doses versus the standard GH replacement dose on insulin sensitivity and fasting glucose levels in young healthy adults**. *J Clin Endocrinol Metab* 2002, **87**:1989-1995.

7. 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 therapy: a two year study**. *Clin Endocrinol (Oxf)* 2000, **53**:453-459.

8. Drake WM, Coyte D, Camacho Hubner C, Jivanji NM, Kaltsas G, Wood DF, Trainer PJ, Grossman AB, Besser GM, Monson JP: **Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults**. *J Clin Endocrinol Metab* 1998, **83**:3913-3919.

9. •• Ekman B, Lindstrom T, Nystrom F, Olsson AG, Toss G, Arnqvist HJ: **A dose titration model for recombinant GH substitution aiming at normal plasma concentrations of IGF-I in hypopituitary adults**. *Eur J Endocrinol* 2002, **147**:49-57.
This study describes methodology for dose-titration and individualisation of GH doses in GH treatment of hypopituitary adults.

10. Murray RD, Wieringa GE, Lissett CA, Darzy KH, Smethurst LE, Shalet SM: **Low-dose GH replacement improves the adverse lipid profile associated with the adult GH deficiency syndrome**. *Clin Endocrinol (Oxf)* 2002, **56**:525-532.

11. • Murray RD, Darzy KH, Gleeson HK, Shalet SM: **GH-deficient survivors of childhood cancer: GH replacement during adult life**. *J Clin Endocrinol Metab* 2002, **87**:129-135.

This study describes the effect of individualised GH replacement therapy in GH-deficient survivors of childhood cancer.

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

13. Randeva HS, Murray RD, Lewandowski KC, O'Callaghan CJ, Horn R, O'Hare P, Brabant G, Hillhouse EW, Shalet SM: **Differential effects of GH replacement on the components of the leptin system in GH-deficient individuals**. *J Clin Endocrinol Metab* 2002, **87**:798-804.

14. Ahmad AM, Hopkins MT, Weston PJ, Fraser WD, Vora JP: **Effects of GH replacement on 24-h ambulatory blood pressure and its circadian rhythm in adult GH deficiency**. *Clin Endocrinol (Oxf)* 2002, **56**:431-437.

15. Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP: **Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement**. *Clin Endocrinol (Oxf)* 2001, **54**:709-717.

16. Ahmad AM, Guzder R, Wallace AM, Thomas J, Fraser WD, Vora JP: **Circadian and ultradian rhythm and leptin pulsatility in adult GH deficiency: effects of GH replacement**. *J Clin Endocrinol Metab* 2001, **86**:3499-3506.

17. Ekman B, Ohman PK, Arnqvist HJ, Lindstrom T, Nystrom FH: **Individualized growth hormone substitution with normalized IGF-I levels does not stimulate the renin-angiotensin-aldosterone system**. *Clin Endocrinol (Oxf)* 2002, **57**:473-479.

18. Murray RD, Adams JE, Smethurst LE, Shalet SM: **Spinal irradiation impairs the osteo-anabolic effects of low-dose growth hormone replacement in adults with childhood-onset GH deficiency**. *Clin Endocrinol (Oxf)* 2002, **56**:169-174.

19. Attanasio AF, Bates PC, Ho KK, Webb SM, Ross RJ, Strasburger CJ, Bouillon R, Crowe B, Selander K, Valle D, Lamberts SW: **Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status–3-year results from the HypoCCS Database**. *J Clin Endocrinol Metab* 2002, **87**:1600-1606.

20. Attanasio AF, Lamberts SW, Matranga AM, Birkett MA, Bates PC, Valk NK, Hilsted J, Bengtsson BA, Strasburger CJ: **Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult Growth Hormone Deficiency Study Group**. *J Clin Endocrinol Metab* 1997, **82**:82-88.

21. Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Smethurst LE, Shalet SM: **Influences on quality of life in GH deficient adults and their effect on response to treatment**. *Clin Endocrinol (Oxf)* 1999, **51**:565-573.

22. Murray RD, Howell SJ, Lissett CA, Shalet SM: **Pre-treatment IGF-I level is the major determinant of GH dosage in adult GH deficiency**. *Clin Endocrinol (Oxf)* 2000, **52**:537-542.

23. Burman P, Johansson AG, Siegbahn A, Vessby B, Karlsson FA: **Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women**. *J Clin Endocrinol Metab* 1997, **82**:550-555.

24. White HD, Ahmad AM, Guzder R, Wallace AM, Fraser WD, Vora JP: **Gender variation in leptin circadian rhythm and pulsatility in adult growth hormone deficiency: effects of growth hormone replacement**. *Clin Endocrinol (Oxf)* 2003, **58**:482-488.

25. Johansson AG, Engstrom BE, Ljunghall S, Karlsson FA, Burman P: **Gender differences in the effects of long term growth hormone (GH) treatment on bone in adults with GH deficiency**. *J Clin Endocrinol Metab* 1999, **84**:2002-2007.

26. Ezzat S, Fear S, Gaillard RC, Gayle C, Landy H, Marcovitz S, Mattioni T, Nussey S, Rees A, Svanberg E: **Gender-specific responses of lean body composition and non-gender-specific cardiac function improvement after GH replacement in GH-deficient adults**. *J Clin Endocrinol Metab* 2002, **87**:2725-2733.

27. Iranmanesh A, Lizarralde G, Veldhuis JD: **Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men**. *J Clin Endocrinol Metab* 1991, **73**:1081-1088.

28. Attanasio AF, Howell S, Bates PC, Frewer P, Chipman J, Blum WF, Shalet SM: **Body composition, IGF-I and IGFBP-3 concentrations as outcome measures in severely GH-deficient (GHD) patients after childhood GH treatment: a comparison with adult onset GHD patients**. *J Clin Endocrinol Metab* 2002, **87**:3368-3372.

29. de Boer H, Blok GJ, van Lingen A, Teule GJ, Lips P, van der Veen EA: **Consequences of childhood-onset growth hormone deficiency for adult bone mass**. *J Bone Miner Res* 1994, **9**:1319-1326.

30. Kaufman JM, Taelman P, Vermeulen A, Vandeweghe M: **Bone mineral status in growth hormone-deficient males with isolated and multiple pituitary deficiencies of childhood onset**. *J Clin Endocrinol Metab* 1992, **74**:118-123.

31. O'Halloran DJ, Tsatsoulis A, Whitehouse RW, Holmes SJ, Adams JE, Shalet SM: **Increased bone density after recombinant human growth hormone (GH) therapy in adults with isolated GH deficiency**. *J Clin Endocrinol Metab* 1993, **76**:1344-1348.

32. Holmes SJ, Economou G, Whitehouse RW, Adams JE, Shalet SM: **Reduced bone mineral density in patients with adult onset growth hormone deficiency**. *J Clin Endocrinol Metab* 1994, **78**:669-674.

33. Janssen YJ, Hamdy NA, Frolich M, Roelfsema F: **Skeletal effects of two years of treatment with low physiological doses of recombinant human growth hormone (GH) in patients with adult-onset GH deficiency**. *J Clin Endocrinol Metab* 1998, **83**:2143-2148.

34. Abrahamsen B, Hangaard J, Horn HC, Hansen TB, Gregersen G, Hansen-Nord M, Vahl N, Junker P, Andersen M, Hagen C: **Evaluation of the optimum dose of growth hormone (GH) for restoring bone mass in adult-onset GH deficiency: results from two 12-month randomized studies**. *Clin Endocrinol (Oxf)* 2002, **57**:273-281.

35. Murray RD, Columb B, Adams JE, Shalet SM: **The osteopenia of adult GH deficiency is age-dependent [abstract]**. *British Endocrine Societies Annual Meeting, Belfast, 2001*:P107.

36. Johannsson G, Rosen T, Bosaeus I, Sjostrom L, Bengtsson BA: **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**:2865-2873.

37. Kann P, Piepkorn B, Schehler B, Andreas J, Lotz J, Prellwitz W, Beyer J: **Effect of long-term treatment with GH on bone metabolism, bone mineral density and bone elasticity in GH-deficient adults**. *Clin Endocrinol (Oxf)* 1998, **48**:561-568.

38. Sneppen SB, Hoeck HC, Kollerup G, Sorensen OH, Laurberg P, Feldt-Rasmussen U: **Bone mineral content and bone metabolism during physiological GH treatment in GH-deficient adults — an 18-month randomised, placebo-controlled, double blinded trial**. *Eur J Endocrinol* 2002, **146**:187-195.

39. Vandeweghe M, Taelman P, Kaufman JM: **Short and long-term effects of growth hormone treatment on bone turnover and bone mineral content in adult growth hormone-deficient males**. *Clin Endocrinol (Oxf)* 1993, **39**:409-415.

40. Drake WM, Carroll PV, Maher KT, Metcalfe KA, Camacho-Hubner C, Shaw NJ, Dunger DB, Cheetham TD, Savage MO, Monson JP: **The effect of cessation of growth hormone (GH) therapy on bone mineral accretion in GH-deficient adolescents at the completion of linear growth**. *J Clin Endocrinol Metab* 2003, **88**:1658-1663.

41. Cuneo RC, Judd S, Wallace JD, Perry Keene D, Burger H, Lim Tio S, Strauss B, Stockigt J, Topliss D, Alford F *et al.*: **The Australian multicenter trial of growth hormone (GH) treatment in GH-deficient adults**. *J Clin Endocrinol Metab* 1998, **83**:107-116.

42. Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenhein DS, Schoenfeld DA, Michel TH, Wittink H, Klibanski A: **Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. a randomized, placebo-controlled trial**. *Ann Intern Med* 1996, **125**:883-890.

43. Marcus R: **Recombinant human growth hormone as potential therapy for osteoporosis**. *Baillieres Clin Endocrinol Metab* 1998, **12**:251-260.

44. Saaf M, Hilding A, Thoren M, Troell S, Hall K: **Growth hormone treatment of osteoporotic postmenopausal women — a one-year placebo-controlled study**. *Eur J Endocrinol* 1999, **140**:390-399.

45. Brill KT, Weltman AL, Gentili A, Patrie JT, Fryburg DA, Hanks JB, Urban RJ, Veldhuis JD: **Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men**. *J Clin Endocrinol Metab* 2002, **87**:5649-5657.

46. Sugimoto T, Kaji H, Nakaoka D, Yamauchi M, Yano S, Sugishita T, Baylink DJ, Mohan S, Chihara K: **Effect of low-dose of recombinant human growth hormone on bone metabolism in elderly women with osteoporosis**. *Eur J Endocrinol* 2002, **147**:339-348.

47. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE: **Effects of human growth hormone in men over 60 years old**. *N Engl J Med* 1990, **323**:1-6.

48. Gillberg P, Mallmin H, Petren-Mallmin M, Ljunghall S, Nilsson AG: **Two years of treatment with recombinant human growth hormone increases bone mineral density in men with idiopathic osteoporosis**. *J Clin Endocrinol Metab* 2002, **87**:4900-4906.

49. Ueland T, Bollerslev J, Flyvbjerg A, Hansen TB, Vahl N, Mosekilde L: **Effects of 12 months of GH treatment on cortical and trabecular bone content of IGFs and OPG in adults with acquired GH deficiency: a double-blind, randomized, placebo-controlled study**. *J Clin Endocrinol Metab* 2002, **87**:2760-2763.

50. Lanzi R, Losa M, Villa I, Gatti E, Sirtori M, Dal Fiume C, Rubinacci A: **GH replacement therapy increases plasma osteoprotegerin levels in GH-deficient adults**. *Eur J Endocrinol* 2003, **148**:185-191.

51. • Colao A, di Somma C, Pivonello R, Cuocolo A, Spinelli L, Bonaduce D, Salvatore M, Lombardi G: **The cardiovascular risk of adult GH deficiency (GHD) improved after GH replacement and worsened in untreated GHD: a 12-month prospective study**. *J Clin Endocrinol Metab* 2002, **87**:1088-1093.

A 12-month prospective study of the effect of untreated and treated GHD on surrogate markers of cardiovascular risk and cardiac function.

52. • Smith JC, Evans LM, Wilkinson I, Goodfellow J, Cockcroft JR, Scanlon MF, Davies JS: **Effects of GH replacement on endothelial function and large-artery stiffness in GH-deficient adults: a randomized, double-blind, placebo-controlled study**. *Clin Endocrinol (Oxf)* 2002, **56**:493-501.

Placebo-controlled study of the effect of GH replacement on vascular function.

53. • Smith JC, Lang D, McEneny J, Evans LM, Scanlon MF, Young I, Davies J: **Effects of GH on lipid peroxidation and neutrophil superoxide anion-generating capacity in hypopituitary adults with GH deficiency**. *Clin Endocrinol (Oxf)* 2002, **56**:449-455.

Study demonstrating that GH-deficient adults, despite increases in the prevalence of vascular disease, do not have increased oxidative stress.

54. Gleeson HK, Souza AH, Gill MS, Wieringa GE, De ABES, Barretto-Filho JA, Shalet SM, Aguiar-Oliveira MH, Clayton PE: **Lipid profiles in untreated severe congenital isolated growth hormone deficiency through the lifespan**. *Clin Endocrinol (Oxf)* 2002, **57**:89-95.

55. Leonsson M, Hulthe J, Oscarsson J, Johannsson G, Wendelhag I, Wikstrand J, Bengtsson BA: **Intima-media thickness in cardiovascularly asymptomatic hypopituitary adults with growth hormone deficiency: relation to body mass index, gender, and other cardiovascular risk factors**. *Clin Endocrinol (Oxf)* 2002, **57**:751-759.

56. Rosen T, Bengtsson BA: **Premature mortality due to cardiovascular disease in hypopituitarism**. *Lancet* 1990, **336**:285-288.

57. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewart PM: **Association between premature mortality and hypopituitarism. West Midlands prospective hypopituitary study group**. *Lancet* 2001, **357**:425-431.

58. • Bramnert M, Segerlantz M, Laurila E, Daugaard JR, Manhem P, Groop L: **Growth hormone replacement therapy induces insulin resistance by activating the glucose-fatty acid cycle**. *J Clin Endocrinol Metab* 2003, **88**:1455-1463.

This study examines the effect of GH replacement on glucose, lipid and protein metabolism, and discusses the relationship between GH-induced metabolic changes.

59. • Twickler TB, Dallinga-Thie GM, Visseren FL, de Vries WR, Erkelens DW, Koppeschaar HP: **Induction of postprandial inflammatory response in adult onset growth hormone deficiency is related to plasma remnant-like particle-cholesterol concentration**. *J Clin Endocrinol Metab* 2003, **88**:1228-1233.

GH-deficient adults are shown to have increased remnant-like particle cholesterol that correlates with inflammatory markers, suggesting a possible mechanism for the reported premature vascular disease.

60. Scott EM, Greenwood JP, Stoker JB, Mary DA, Gilbey SG: **Sympathetic nerve hyperactivity is associated with increased peripheral vascular resistance in hypopituitary patients with growth hormone deficiency**. *Clin Endocrinol (Oxf)* 2002, **56**:759-763.

61. Smith JC, Lane HA, Lewis J, Dann S, Goodfellow J, Collins P, Evans LM, Scanlon MF, Davies JS: **Endothelial function and coagulant factors in growth hormone-treated hypopituitary adults receiving desmopressin**. *J Clin Endocrinol Metab* 2003, **88**:2152-2156.

62. Hana V, Prazny M, Marek J, Skrha J, Justova V: **Reduced microvascular perfusion and reactivity in adult GH deficient patients is restored by GH replacement**. *Eur J Endocrinol* 2002, **147**:333-337.

63. Oomen PH, Beentjes JA, Bosma E, Smit AJ, Reitsma WD, Dullaart RP: **Reduced capillary permeability and capillary density in the skin of GH-deficient adults: improvement after 12 months GH replacement**. *Clin Endocrinol (Oxf)* 2002, **56**:519-524.

64. Svensson J, Stibrant Sunnerhagen K, Johannsson G: **Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength**. *J Clin Endocrinol Metab* 2003, **88**:2061-2069.

65. Svensson J, Fowelin J, Landin K, Bengtsson BA, Johansson JO: **Effects of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults**. *J Clin Endocrinol Metab* 2002, **87**:2121-2127.

66. • Gilchrist FJ, Murray RD, Shalet SM: **The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults**. *Clin Endocrinol (Oxf)* 2002, **57**:363-370.

Improvement in quality of life is considered an important end-point in GH replacement, and this study shows these improvements to be maintained long-term.

67. Gibney J, Wallace JD, Spinks T, Schnorr L, Ranicar A, Cuneo RC, Lockhart S, Burnand KG, Salomon F, Sonksen PH, Russell-Jones D: **The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients**. *J Clin Endocrinol Metab* 1999, **84**:2596-2602.

68. Chrisoulidou A, Beshyah SA, Rutherford O, Spinks TJ, Mayet J, Kyd P, Anyaoku V, Haida A, Ariff B, Murphy M *et al.*: **Effects of 7 years of growth hormone replacement therapy in hypopituitary adults**. *J Clin Endocrinol Metab* 2000, **85**:3762-3769.

69. Christ ER, Simpson HL, Breen L, Sonksen PH, Russell-Jones DL, Kohner EM: **The effect of growth hormone (GH) replacement therapy in adult patients with type 1 diabetes mellitus and GH deficiency**. *Clin Endocrinol (Oxf)* 2003, **58**:309-315.

70. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M: **Circulating concentrations of insulin-like growth factor-I and risk of breast cancer**. *Lancet* 1998, **351**:1393-1396.

71. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M: **Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study**. *Science* 1998, **279**:563-566.

72. Jenkins PJ, Fairclough PD, Richards T, Lowe DG, Monson J, Grossman A, Wass JA, Besser M: **Acromegaly, colonic polyps and carcinoma**. *Clin Endocrinol (Oxf)* 1997, **47**:17-22.

73. •• Swerdlow AJ, Higgins CD, Adlard P, Preece MA: **Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study**. *Lancet* 2002, **360**:273-277.
Although limited by small numbers, this study shows that childhood pituitary-derived GH therapy may increase future cancer incidence.

74. le Roux CW, Jenkins PJ, Chew SL, Camacho-Hubner C, Grossman AB, Besser GM, Monson JP: **Growth hormone replacement does not increase serum prostate-specific antigen in hypopituitary men over 50 years**. *Eur J Endocrinol* 2002, **147**:59-63.

75. Colao A, Di Somma C, Spiezia S, Filippella M, Pivonello R, Lombardi G: **Effect of growth hormone (GH) and/or testosterone replacement on the prostate in GH-deficient adult patients**. *J Clin Endocrinol Metab* 2003, **88**:88-94.

76. Hatrick AG, Boghalo P, Bingham JB, Ayres AB, Sonksen PH, Russell-Jones DL: **Does GH replacement therapy in adult GH-deficient patients result in recurrence or increase in size of pituitary tumours?** *Eur J Endocrinol* 2002, **146**:807-811.

77. Swerdlow AJ, Reddingius RE, Higgins CD, Spoudeas HA, Phipps K, Qiao Z, Ryder WDJ, Brada M, Hayward RD, Brook CGD *et al.*: **Growth hormone treatment of children with brain tumours and risk of tumor recurrence**. *J Clin Endocrinol Metab* 2000, **85**:4444-4449.

78. Leung W, Rose SR, Zhou Y, Hancock ML, Burstein S, Schriock EA, Lustig R, Danish RK, Evans WE, Hudson MM, Pui CH: **Outcomes of growth hormone replacement therapy in survivors of childhood acute lymphoblastic leukemia**. *J Clin Oncol* 2002, **20**:2959-2964.

79. Svensson J, Monson JP, Vetter T, Hansen TK, Savine R, Kann P, Bex M, Reincke M, Hagen C, Beckers A *et al.*: **Oral administration of the growth hormone secretagogue NN703 in adult patients with growth hormone deficiency**. *Clin Endocrinol (Oxf)* 2003, **58**:572-580.

80. Rahim A, O'Neill PA, Shalet SM: **Growth hormone status during long-term hexarelin therapy**. *J Clin Endocrinol Metab* 1998, **83**:1644-1649.

81. Reiter EO, Attie KM, Moshang T Jr, Silverman BL, Kemp SF, Neuwirth RB, Ford KM, Saenger P: **A multicenter study of the efficacy and safety of sustained release GH in the treatment of naive pediatric patients with GH deficiency**. *J Clin Endocrinol Metab* 2001, **86**:4700-4706.

82. •• Cook DM, Biller BM, Vance ML, Hoffman AR, Phillips LS, Ford KM, Benziger DP, Illeperuma A, Blethen SL, Attie KM *et al.*: **The pharmacokinetic and pharmacodynamic characteristics of a long-acting growth hormone (GH) preparation (nutropin depot) in GH-deficient adults**. *J Clin Endocrinol Metab* 2002, **87**:4508-4514.
This is the first study of the use of GH depot in adult hypopituitary patients.