Should patients with adult GH deficiency receive GH replacement?

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Preamble

This is an invited debate between the three authors, who present their opinions in two separate sections. The first section is authored by Jens O L Jørgensen and Gudmundur Johannsson both of whom recommend GH replacement (pro), whereas Ariel Barkan, who authors the second section, is against (contra).

Pro (J O L Jørgensen and G Johannsson)

‘Against stupidity, the gods themselves battle in vain.’
(From *The Maid of Orleans*, a tragedy by Friedrich Schiller)

‘My mind is made up. Don’t confuse me with the facts.’
(Uncertain origin)

Introduction

Pituitary human growth hormone (GH) was isolated 75 years ago (1), and its protein anabolic and fat catabolic effects were studied soon thereafter (2, 3, 4). Another significant leap forward was the development of a GH RIA that enabled characterization of the endogenous secretory pattern. Most of the underlying studies involved adolescent and adult subjects including patients with hypopituitarism, so the notion that GH plays a role beyond stimulation of longitudinal growth in children is that old. The supply of GH for therapeutic use was however extremely limited until the advent of biosynthetic GH in the mid-1980s, which prompted the first, randomized clinical trials of GH replacement in adult GH-deficiency (GHDA) (5, 6).

The pivotal trials and beyond

The first placebo-controlled trial was investigator-initiated and included adults with childhood-onset GHD and reported a GH-induced significant increase in muscle volume and reduction in fat volume accompanied by a significant increase in exercise capacity (5). Additional publications from the same trial revealed that GH replacement increased bone turnover (7, 8) and the extra-thyroidal conversion of T4 to T3 (9) and restored normal sweating capacity (10). The favorable changes in body composition and physical fitness prevailed during continued open GH replacement for 3 years (11, 12). The second placebo-controlled trial (6) comprised patients with adult-onset GHD and reported a significant increase in lean body mass (LBM) together with a significant reduction in fat mass. This was associated with an increase in resting energy expenditure, and data from the same study reported beneficial effects of GH replacement on exercise capacity and hyperlipidemia (13, 14, 15).

The term ‘syndrome’ was used to describe the emerging clinical picture of GHDA (16), which was substantiated by studies of the clinical features of the treatment-naïve patient (17, 18, 19). This accompanied numerous new treatment trials reporting reductions of almost 30% in visceral fat mass (20, 21, 22) and important cardiovascular effects such as reduced peripheral vascular resistance and increased cardiac output (23, 24, 25, 26, 27).

GH-untreated patients with hypopituitarism have an increased overall mortality (28, 29, 30, 31, 32). The annual incidence and prevalence of GHDA are approximately 15/million and 250/million, respectively (33). The symptoms and signs include fatigue, reduced muscle strength and

exercise capacity, visceral obesity, hyperlipidemia, and premature cardiovascular disease (28, 34). Untreated GHDA is also accompanied by reduced extracellular fluid volume (17) that reverses by replacement (35, 36, 37, 38), and impaired thermoregulation (39, 40, 41) is also present and linked to reduced sweating capacity (10).

GH antagonizes the effects of insulin on glucose metabolism, and increased insulin sensitivity with fasting hypoglycemia is a salient feature of childhood GHD (42, 43). The opposite is true for active acromegaly (44). This effect of GH is rapidly reversible (45) and operates in normal physiology when insulin activity is low (4, 46). However, the prolonged biological half-life of daily subcutaneous GH injections do not resemble the endogenous GH pattern (47) and therefore induce moderate insulin resistance (46) despite favorable changes in body composition (48).

The annual number of GHDA publications increased exponentially from 2 in 1989 to >200 in 1999 (49) including dose-finding studies in different age groups (50, 51, 52), and it was confirmed that adult patients are highly sensitive to GH (53) and that male patients are more responsive to GH as compared to females (54, 55). Collectively, this translated into guidelines for the clinical management of GHDA issued by the Growth Hormone Research Society (56) and approval of the indication by the European Union in 1994. Subsequently, meta-analyses of published data on adult GH replacement have been published on outcomes such as cardiovascular risk factors (48), physical fitness (57, 58), bone mineral density (59, 60), body composition (61), and cardiac function (62). The meta-analyses confirm and substantiate both the numerous beneficial effects of GH replacement and the mild adverse effects attributable to fluid retention and insulin resistance (48, 61) (Fig. 1).

As regards bone health, data from placebo-controlled trials for up to 1 year recorded increased bone turnover but unchanged or even reduced bone mass was observed (63), whereas a study of 18 months observed a significant increase in bone mineral density (BMD) (64). GH replacement initially increases bone remodeling and thereby reduces BMD followed by a moderate but sustained increase in BMD (59). It is uncertain if this reduces the risk of osteoporotic fractures, but observational studies suggest this to be the case (65).

It is less certain if GH replacement therapy improves the quality of life (QoL), since neither original studies nor meta-analyses provide unambiguous answers (61, 66, 67, 68). Most QoL studies depend on questionnaires, which mainly record the patient's remembrance and not day-to-day experiences in real time. Of note, the most convincing beneficial effects of adult GH replacement on QoL occurred

Figure 1

Body composition and exercise capacity in GH-deficient adults before (0) and after (12) 1-year GH replacement or placebo. An untreated group of age- and sex-matched healthy subjects (control) underwent assessment of visceral and subcutaneous fat (22). The figure is modified from the original publication (Copyright 1996, John Wiley and Sons).

in a placebo-controlled crossover study based on the response from the spouse of the patient (69). In addition, a double-blind placebo-controlled trial showed that discontinuation of long-term GH replacement reduces QoL (70). During GH replacement, both GH and insulin-like growth factor 1 (IGF-I) levels increase in the cerebrospinal fluid (71), and a placebo-controlled trial showed improved cognitive function after GH treatment (72). It is also noteworthy that the majority of the patients stay on GH replacement, which could indicate that the tools to measure quality of life and well-being do not capture the patient's self-perceived effect of treatment (73, 74).

It has been hypothesized that the phenotype of adult GHDA largely is mainly accounted for by suboptimal glucocorticoid replacement of concomitant secondary adrenal insufficiency. A contributing effect may be that GHD is associated with increased activity of the enzyme that enhances the conversion of inactive cortisone to active cortisol and this activity is suppressed by GH and IGF-I (75). However, the phenotype of hydrocortisone-replaced patients with primary adrenal insufficiency differs markedly from that of hypopituitarism and does not include either obesity or hypertension (76). Along the same line, a large observational study of adult GH

replacement therapy recorded comparable treatment response in patients with isolated GHD and patients with multiple pituitary deficits, respectively, which supports that the phenotype described in GHD hypopituitary patients relates to unreplaced GH (77).

Endogenous GH production and serum IGF-I levels decline with age (78) paralleled by the senescent changes in body composition and physical performance. Notwithstanding this, patients aged 60–80 years with documented pan hypopituitarism exhibit reduced age-corrected GH levels (79) and respond to GH replacement in much the same manner as younger patients (80, 81, 82). However, the GH dose requirement declines with age (Fig. 2).

Mortality

Increased mortality in hypopituitary patients due to cardiovascular disease is undisputed but the role of GH in this is not (28, 83). Alternative or additional causes include the underlying disease and its treatment as well as suboptimal substitution of additional pituitary deficiencies. In addition, mortality and cancer incidence are increased in acromegaly (84, 85) and epidemiological studies reveal a U-shaped association between serum IGF-I levels and all-cause mortality in the general population (86). Randomized studies of GH replacement therapy with mortality as an endpoint do not exist for good reasons, but observational studies show that mortality is reduced in GH-replaced patients as compared to GH-untreated patients (83, 87, 88, 89, 90, 91) (Fig. 2).

Conclusion

GH replacement in GHDA is by a long chalk the most well-documented therapeutic indication in pituitary endocrinology in terms of placebo-controlled trials and post-marketing surveillance studies. The healthy change in body composition in terms of reduced fat mass, in particular abdominal fat, and increased LBM is perhaps the most robust effect. A proportion of the increase in LBM is due to increased hydration, but hydration-independent measurements such as total body potassium and total body nitrogen support an increase in protein content (20).

Most studies also record improvements in bone health, physical fitness and cardiac function. An improvement in QoL is shown in many but not in all studies, but QoL is inherently difficult to measure. The level of education is similar among GH-treated adult patients as compared to the background population, but a higher proportion of the patients are unemployed, retire earlier and are less likely to live with a partner (87, 92). These socioeconomic outcomes demonstrate that hypopituitarism remains a clinical challenge, and improved and optimized treatment options are needed for these patients.

Cancer risk is not increased with long-term GH replacement (93), and mortality is reduced (87, 88) (Fig. 2). The latter observation is very reassuring even though selection bias and overall improved care in specialized centers are likely contributors. Side effects in terms of fluid retention and impaired insulin sensitivity do occur, but they are benign, dose-dependent and rapidly reversible. Still, it is important to avoid overtreatment. The daily GH dose requirement to avoid supernormal IGF-I levels and side effects is 0.1 mg or lower in male patients aged above

Figure 4. Forest plots showing the difference in SMR among hypopituitary adults without and with GH treatment

Figure 2

Meta-analysis of published studies reporting mortality (SMR) in hypopituitary adults with and without GH replacement (97) (Copyright 2018, YS Medical Media Ltd). The analysis is an extension of a previous meta-analysis (83).

70 years, which is only 10% of the dose used in the early adult trials. Careful dose titration guided by serum IGF-I concentration and clinical response is needed in order to obtain the best possible efficacy and to ensure long-term safety of treatment.

Taken together, not even the devil's advocate should be able to turn the case around and persuade any sensible jury to disregard either the negative consequences of GHD or the positive effects of GH replacement in adult hypopituitary patients.

Is it necessary to argue for adult GH replacement 25 years after its approval? No, because the facts in favor of adult GH replacement are overwhelming, and yes, because barriers to the treatment still exist, as recently documented by the European Society of Endocrinology survey (94). The reasons for continued reluctance are probably manifold, of which lack of reimbursement is a major one. Another argument against adult GH replacement may be the risk of overtreatment because acromegaly is a serious disease with excess mortality. Should this line of argumentation then also apply to replacement therapy with hydrocortisone and levothyroxine? Finally, the fact that GH is administered as a daily injection rather than an (inexpensive) tablet is undoubtedly a treatment obstacle, which may be alleviated with long-acting GH preparations (95). The above-mentioned barriers to treatment therefore prevent many adult patients with hypopituitarism and severe GHD to receive GH replacement therapy.

The indication is not to be confused with the unlicensed use of GH as an antiaging treatment. The effect of GH in this regard is unproven and probably hazardous (96).

The first anecdotal report of GH treatment of a hypopituitary adult patient in 1962 concluded that 'observations will be needed in more cases to indicate whether the favorable effect was more than coincidental' (3). Today, it is safe to reply that observations from numerous placebo-controlled trials confirm beneficial effects and justify the treatment. We rest our case.

Contra (A Barkan)

'... a beautiful hypothesis slain by an ugly fact' (Thomas Henry Huxley)

GHD leads to short stature when it is of a congenital or a prepubertal nature. Treatment with exogenous GH improves final growth and is unquestionably indicated. However, GH impoverishment of aging or the use of GH

for improvement of athletic performance is illegal, and GH administration is not approved for those indications.

In this short review, we shall concentrate on the indications for GH administration to adults with documented GHD as a consequence of hypothalamic-pituitary diseases.

The story begins with two papers from Sweden claiming GHD as a proximal cause of increased cardiovascular mortality in patients with hypopituitarism (28, 30). Subsequently, multiple studies have looked at other potential effects of GHD in adults and a new syndrome was described: adult-onset GHD (AO-GHD). It allegedly consisted of generalized weakness, fatigue, obesity, decreased muscle mass, strength and endurance, premature atherosclerosis, osteoporosis and diminished QoL. All these findings were automatically attributed to GHD since all other hormonal deficits were presumably correctly replaced, and treatment of GHD with exogenous GH was reported to have salutary effects on all of them.

In this short review, we shall critically discuss potential reasons for substituting GH in AO-GHD based on controlled studies.

Does GHD increase mortality?

In all animal models studied thus far, GHD was actually associated with the increased (by 20–70%) longevity (98). Increased cerebrovascular mortality was one of the most important arguments in favor of GH replacement in hypopituitary individuals (30) and was noticed in subsequent analyses by other groups. However, an autopsy study by Kaji *et al.* (99) in patients with hypopituitarism demonstrated an approximately two-fold increase in cerebrovascular disease (with four- to five-fold increase in cerebral hemorrhage) but paradoxically, a two- to four-fold decrease in all heart diseases and no difference in ischemic heart disease from the general population. The mechanism whereby GHD would differentially affect coronary and cerebral arteries is unknown and puzzling: it suggests that some other factor(s) might have been involved. The answer came from two large epidemiological studies involving large numbers of hypopituitary patients. In a study by Tomlinson *et al.* (29) involving 1014 hypopituitary patients from the West Midlands, increased mortality was associated with age, sex, diagnosis of craniopharyngioma, unsubstituted hypogonadism and history of cranial radiation. Jasim *et al.* (100) performed meta-analysis of 12 studies published between 1996 and 2015 that reported

on a total of 23,515 patients with hypopituitarism. Risk factors for increased mortality fully confirmed conclusions by Tomlinson *et al.* (29) but revealed some additional connections (likely due to an ~23-fold higher number of patients): younger age at diagnosis, transcranial surgery and diabetes insipidus. Remarkably, neither of these reports found any connection between increased mortality and GHD as such. Cranial radiation is a known promoter of cerebrovascular morbidity and mortality (101, 102, 103), in particular cerebral hemorrhage, fully explaining the data of Kaji *et al.* (99). The meta-analysis by Pappachan *et al.* (83) has found improvement of mortality risk with GH replacement, but the authors openly admitted that it might have been due to the potential selection bias introduced by the post-marketing surveillance of commercial databases without an untreated control group. In a study by Lindholm *et al.* (104), mortality rates in patients with normal pituitary function and hypopituitarism after surgery for nonfunctioning pituitary adenomas were not different from those in the general population and treatment with GH of GH-deficient patients did not influence survival. Van Bunderen *et al.* (90) confirmed this conclusion. Then, we should necessarily ask a question: If it is not GHD that causes increased mortality in patients with hypopituitarism, what causes it? At least two studies provided an answer: excessive replacement with glucocorticoids. The study by Hammarstrand *et al.* (105), in which one of my opponents was a co-author, found that daily hydrocortisone equivalent dose > 20 mg increased mortality rate in patients with hypopituitarism to 1.42 vs the expected 1, whereas daily doses < 20 mg maintained normal mortality rate of 0.88. In a more detailed study, Zueger *et al.* (106) had shown that patients on <20 mg hydrocortisone daily had a mortality rate of 1 vs those on no glucocorticoid replacement but did demonstrate increased mortality rates to 2.62 in those on 20–29 mg/daily and to 4.56 on >30 mg/daily. The case for glucocorticoid replacement seems to be clear. But does it mean that GHD or GH replacement does not play any role at all? That takes us into the relatively new field: metabolism of cortisol and its GH regulation. Hydrocortisone (cortisol) may exert its mineralocorticoid potential at the kidneys by inducing hypertension and hypokalemia in all of us. Luckily, kidneys express an enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11-beta HSD- 2) that converts cortisol into the biologically inactive cortisone and protects the kidneys. Renal-generated cortisone reaches abdominal fat and liver and is regenerated there into active cortisol by 11-beta-hydroxysteroid dehydrogenase type 1 (11-beta-HSD-1). GH inhibits and GHD stimulates the latter enzyme (107). Thus,

hypopituitary GHD patients may be exposed to a double hit: overdose of glucocorticoid replacement (especially in the older studies) and increased 11-beta HSD-1 induced regeneration of inactive cortisone into cortisol, resulting in a 'Cushing's-like phenotype': increased mortality, metabolic syndrome with hyperglycemia and insulin resistance, abdominal obesity, osteoporosis and neuropsychiatric abnormalities that so suspiciously overlap with the current description of AD-GHD (for detail see below). In those patients, administration of GH inhibits 11-beta-HSD-1 and mitigates at least partially the deleterious effects of glucocorticoid overdose (107).

What should any sane and non-biased physician choose: decrease the dose of glucocorticoids or add daily injections of expensive GH to mitigate the glucocorticoid-related side effects? In any other clinical situation involving other drugs, we sensibly choose the former approach. Why do some of us choose the 'bass backwards' one is a mystery.

Recently, attention was drawn to the possibility that congenital IGF-1 deficiency, whether due to GH receptor defects (Laron's syndrome) or to primary GH deficiency may confer protection from the development of malignant diseases (108). Indeed, no cases of any malignant diseases were found among homozygous patients with Laron's syndrome (prevalence 0%), whereas 18 cases were found among their 218 first-degree relatives (prevalence 8.25%) and 25 among 113 further relatives (prevalence 22.1%). Among all patients with congenital GHD (isolated GHD, multiple hormone deficiencies, GHRH receptor mutations), cancers were found in 2.3%; in their first-degree relatives of comparable mean age, it was 7.4% and in further relatives 33% (108).

What about patients treated with GH? One study (109) did find an increased risk of second neoplasm in children treated with GH but that had not been confirmed by other reports (110). Child *et al.* (111) did not find an increased incidence of cancer in adults with GHD treated with GH.

In summary, hypopituitarism is associated with increased mortality rates, the causes of which are not associated with GHD but are due to age, sex, the diagnosis of primary illness (e.g. craniopharyngioma), glucocorticoid replacement dose and therapeutic interventions (e.g. cranial radiation). There is no convincing evidence that treatment of GHD improves mortality rates and this is not surprising: no abovementioned major causes of increased mortality (craniopharyngioma, radiation therapy etc.) can even theoretically be influenced by GH replacement. On the other hand, there is no evidence that treatment of GHD induces second malignancies, which is encouraging. However, vigilant follow up of treated cases needs to be

continued: we may have not yet reached the point where such cases start showing up. In short, GH replacement in AO-GHD for the purpose of lowering mortality rate seems at the present time to be a reasonably benign but useless intervention that has neither negative nor positive influence on the mortality rate, the allegedly major consequence of hypopituitarism (28, 30).

Body composition and metabolic consequences

The most consistent effect of GH administration in patients with GHD is a decrease in fat mass (74), with a magnitude of about 2 kg after 6 months. Fat mass does not increase further over time and reverts to baseline with discontinuation of GH therapy (112). One would naturally expect it to be followed by an improvement in metabolic syndrome, hyperlipidemia and glucose handling.

In several trials (113, 114, 115), GH replacement did not improve the prevalence of metabolic syndrome but resulted in statistically significant increases in blood pressure and fasting blood glucose; ultimately, no change in metabolic syndrome was seen after 3 years of GH therapy (115).

Physiologically, GH causes insulin resistance (116) and is a 'hyperglycemic' hormone. Thus, it would be unexpected to see its administration to be accompanied by lowering plasma glucose. Indeed, all studies reported either elevation of glucose sometimes to the point of frank diabetes (117, 118) or just insulin resistance (70, 119). There are no data showing GH-induced loss of fat ameliorating insulin resistance and/or improving diabetes.

The data on plasma lipids are also inconsistent. Sesmilo *et al.* (119) reported rapid (3 months) improvements in plasma lipids after initiation of GH replacement in AO-GHD patients, but their levels returned to baseline from month 6 to month 18 of treatment. In a meta-analysis of 37 blinded, randomized, placebo-controlled studies, GH replacement was reported to reduce LDL and total cholesterol in half the studies and had no effect in the others (48). HypoCCS data showed an increased incidence of diabetes compared to background population in the GH-treated cohorts in the United States and Sweden but not in France or Germany (117). GH treatment decreased inflammatory markers (such as C-reactive protein, interleukin-6, TNF- α), as well as carotid intima-media thickness, a predictor of coronary disease (120). But GH replacement was also reported to increase plasma concentrations of lipoprotein A, an

independent marker of cardiovascular risk (119). There are also data suggesting that the cause of abnormal body composition and metabolic abnormalities in AO-GHD patients and their improvement with GH therapy is ultimately related not to GHD or its correction but rather to overtreatment with glucocorticoids (107). Indeed, KIGS-KIMS database showed that all these parameters were proportionate to the dose of glucocorticoid replacement and that patients taking less than 20 mg of hydrocortisone daily had no manifestations of metabolic syndrome in excess of the ACTH-sufficient group (114). In addition, GHD has been shown to enhance regeneration of cortisol from cortisone by increasing 11 β -HSD type 1 activity (107). The combination of supraphysiological glucocorticoid dosages and GHD-induced increased cortisol generation from cortisone results in excessive cortisol exposure in patients with hypopituitarism treated with what was considered in the past as appropriate doses of hydrocortisone (48). Swords *et al.* (121) showed that administration of GH to glucocorticoid-treated hypopituitary adults markedly lowered their plasma cortisol milieu. If this hypothesis is true, then just a decrease of hydrocortisone replacement dose from the previously used 25–35 mg/day to the currently employed one of 10–20 mg/day may be effective in improving metabolic parameters. Indeed, Danilowicz *et al.* (122) found that just a decrease of hydrocortisone dose from the supraphysiological 35 mg per day to the currently accepted 15 mg per day for 6–12 months resulted in major body fat loss (7.1 kg of total body fat, 4.1 kg of abdominal body fat), with a trend toward increased LBM, major declines in total cholesterol and triglycerides and improvement in the QoL in those with poor values. Additionally, if the goal of GH replacement is normalization of plasma lipid profiles, the use of widely available cheap oral medications might be sufficient. Monson *et al.* (123) had shown that even older statins (pravastatin, lovastatin, simvastatin, atorvastatin and fluvastatin) were equally or even more effective than GH in normalizing plasma lipids and had no 'escape' feature (119). There are no similar studies comparing GH with rosuvastatin, the most effective preparation from that group.

One may only wonder why should we give GH (with its diabetogenic property and other negative manifestations) to hypopituitary patients with metabolic syndrome rather than lower their inappropriately high hydrocortisone doses and/or add oral, equally or more effective, and infinitely cheaper HMG CoA reductase inhibitor (statin) therapy.

Muscle mass and function

GH therapy has been associated with a measured increase in LBM, but this is not due to an increase in muscle fiber mass but rather due to accumulation of water in extracellular fluid, as GH increases sodium reabsorption and plasma renin activity (124). Open-label studies found improvements in one muscle group strength but no improvement in others (125). In a randomized, placebo-controlled crossover trial, 60 patients who had received GH therapy for more than 3 years were assigned to continue GH or placebo for 4 months. The placebo group had decreased measured thigh muscle mass (likely due to water loss) but without change in muscle strength (126). A 2-year double-blind randomized trial in GHD adolescents transitioning to adulthood did not find a statistically significant change in treadmill exercise tolerance (70). Studies in other human models fully support lack of the GH effect on physical performance. GH administration to athletes increased their fat-free mass but had no influence on their physical performance (127, 128, 129). Similarly, in GH-impooverished elderly men, administration of GH decreased their body fat content and increased muscle mass but had no effect on their functional performance (130). In a GH excess model, acromegaly, muscle mass is increased, but muscle strength and endurance are diminished (131).

Thus, there is no convincing evidence that GH improves physical performance in humans across a wide spectrum of clinical situations. The GH-induced loss of subcutaneous fat allows water-swollen muscles to stand out in sharper relief. That may explain the popularity of GH among bodybuilders.

Bone health

Patients with hypopituitarism have an increased incidence of low bone density. However, in and by itself, low bone density becomes clinically important only when it leads to bone fractures that is the real marker of any therapeutic success or failure. It is uncertain, however, whether the rate of bone fractures is due to GH deficiency or improper replacement of other pituitary hormones such as undertreatment with gonadal steroids or overtreatment with glucocorticoids and/or thyroxine (132, 133, 134). Also, the etiology of hypopituitarism seems to play a role: in AO-GHD patients with previous acromegaly, treatment with GH inexplicably increased fracture rate after more than 6 years of therapy, while in those with previous diagnoses of nonfunctioning adenoma or Cushing disease,

it remained stable (135). However, overall GH appears to increase bone density mildly to modestly and lowers fracture rate in patients without pre-existing osteoporosis and without radiological risk of fractures but was ineffective in patients with osteoporosis, that is, the group with a high risk of fractures, the very same group we worry about and treat with GH (65).

The question arises, whether standard therapy of osteoporosis with antiresorptive medications, denosumab or PTH analogs might be more effective than GH. Unfortunately, this information is by and large lacking. There are only two small studies in which alendronate was added to the GH regimen (136, 137). In both of them, alendronate significantly potentiated effects of GH, indicating that they work by separate mechanisms and that a study of alendronate alone and/or other anti-osteoporosis drugs may be justified.

Quality of Life (QoL)

QoL is a subjective and self-reported patient's view of his/her general well-being. Multiple studies have claimed low QoL in hypopituitary patients and its improvement with GH replacement. However, most of them were done in an open-label fashion and thus were subject to a placebo effect. Therefore, we have performed a search for placebo-controlled studies. The only exclusion criteria were: duration of treatment < 6 months and the number of subjects involved being less than ten. Fourteen such studies were identified (20, 21, 53, 69, 112, 127, 138, 139, 140, 141, 142, 143, 144, 145), involving a total of 908 patients and employing a total of 25 psychological tests in different combinations. In ten studies, employing one to six different tests, the results of all tests were indistinguishable between GH and placebo. In four studies, six tests showed GH being better than placebo, five tests showed GH being equal to placebo and four tests showed that placebo was more effective than GH. In total, 37 tests showed that GH was equal to placebo, 6 that GH was better than placebo and 4 that placebo was better than GH. There were occasional disagreements between the studies on the outcomes of the same test. For example, NHP energy health domain favored GH in 2 studies involving 148 and 32 subjects, but no difference was found in 2 other studies, involving 36 and 40 subjects, and there was a better effect of placebo in the largest group with 163 patients.

Overall, these results obtained in a properly performed placebo-controlled fashion demonstrate convincingly that

the administration of GH for the correction of abnormal QoL, the only approved indication for GH use by the British National Institute of Clinical Excellence (NICE) and by many medical insurance companies in the United States, differs from placebo in only one aspect: the price.

Well, that may not be exactly true: a large study involving 2737 hypopituitary patients based on Pfizer's KIMS database (146) showed that there was a linear relation between higher daily hydrocortisone dose and decline in QoL. In a population of 194 patients with primary adrenal insufficiency and 140 patients with secondary adrenal insufficiency due to hypopituitarism, Bleicken *et al.* (147) showed the deleterious effects on QoL of hydrocortisone doses greater than 30 mg per day with no difference observed between the Addisonian and hypopituitary groups. Normal QoL was observed in severely GH-deficient patients (two to four pituitary deficiencies and pathologically low IGF-1) who did not have pituitary radiation and took an average of 15 mg hydrocortisone daily (148). Swords *et al.* (121) have shown that GH administration to AO-GHD patients on hydrocortisone replacement lowers plasma cortisol milieu, a known predictor of neuropsychological distress.

Thus, again one can make a choice: to keep a hypopituitary patient with poor QoL on a high dose of hydrocortisone and add daily injections of GH to inhibit 11- β -HSD type 1 or just lower hydrocortisone to <20 mg/day. The answer appears to be certain.

The study by Miller *et al.* (149) stands apart: in a double-blinded placebo-controlled study, it has shown improved QoL in patients with GHD post-cure of acromegaly who were treated with GH. The mechanism of that is unknown, and van der Klaaw *et al.* (150) did not find any effects of GH replacement on QoL in patients with acromegaly rendered GH-deficient by surgery and radiation. The same group had previously shown that low physical and psychological QoL in patients with acromegaly depends on their osteoarthritic complaints and history of radiotherapy (150, 151, 152.).

Information for reflection

Congenital isolated GHD is the purest model to study effects of GH in adulthood. Such an opportunity was presented by the identification of a large group of GHD patients in a small Brazilian town Itabahianinya. They have a genetic form of GHD due to an inactivating mutation in the GHRH receptor. Their GH and IGF-1 levels are profoundly low, but all other hormonal systems function perfectly well.

The characteristic physical features of this isolated GHD population included short stature and truncal obesity.

Compared to age- and gender-matched controls from the same area, they have normal longevity (153), normal QoL as evaluated by commonly used questionnaires (154), no increased risk of fractures and superior muscle strength (155). They have lower areal BMD due to smaller bone mass, but when BMD is corrected for bone size, the volumetric BMD is similar to controls (156). These individuals have higher total and LDL cholesterol throughout life (157, 158), but they do not have greater carotid intima-media thickness or coronary atherosclerosis (159); their cardiovascular mortality is no different from the control population (153). Oliveira *et al.* (160) treated 20 such adults with GH for 6 months. Lipid profile and body composition improved, but carotid intimal thickness increased and carotid atherosclerotic plaques developed within 6 months of treatment, with a 52-fold higher likelihood to have a carotid atherosclerotic plaque by 12 months even after discontinuation of GH therapy. Five years after cessation of GH therapy, intima-media thickness returned to normal, but the number of atherosclerotic plaques did not change (161). Some findings in that model may not be directly applicable to AO-GHD. Nevertheless, they provide us with valuable insights on the impact of long-term isolated GHD and the potential shortcomings of GH replacement on human health.

Summary and conclusions

1. GH cannot lower cerebrovascular morbidity and mortality in patients with AO-GHD, because neither is due to GHD but due to complications of radiotherapy in patients with pituitary tumors.
2. GH administration to patients with AO-GHD may be modestly capable of improving lipid profile and increasing bone density. However, there are other medications specifically designed for both of those problems that are infinitely cheaper, potentially more effective and definitely more convenient (a tablet vs an injection). Their use vs GH administration needs to be addressed in approved protocols.
3. GH administration to AO-GHD increases muscle mass at the expense of water accumulation but does not improve muscle strength and endurance.
4. Many patients are still treated with supraphysiological doses of glucocorticoids that have been shown to negatively affect metabolic processes, bone integrity with subsequent development of fractures and neuropsychiatric status (subjective perception of QoL). Lowering the daily dose of glucocorticoids improved

the severity of what are believed to be manifestations of AO-GHD. In patients with no ACTH deficiency or on a lower dose of glucocorticoid replacement and without a history of radiotherapy the QoL is normal. GH by definition cannot correct impaired QoL due to physical impairments such as arthropathy, limitations and stress of a 'chronic illness' or the circumstances of life.

In short, the beautiful hypothesis of GH replacement being a panacea for all real and imagined ills of AO-GHD seems to be slain by a whole slew of ugly facts.

Declaration of interest

J O L J has received lecture fees from Novo Nordisk, Pfizer and Sandoz. A B has nothing to disclose. G J has received lecture fees from Novartis, Novo Nordisk, Pfizer, Sandoz, Merck Serono, and Otsuka as well as consultancy fees from Astra Zeneca and Shire.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- Beck JC, McGarry EE, Dyrenfurth I & Venning EH. Metabolic effects of human and monkey growth hormone in man. *Science* 1957 **125** 884–885. (<https://doi.org/10.1126/science.125.3253.884>)
- Raben MS. Growth hormone. *New England Journal of Medicine* 1962 **266** 31–35. (<https://doi.org/10.1056/NEJM196201042660109>)
- Raben MS. Growth hormone. *New England Journal of Medicine* 1962 **266** 82–86. (<https://doi.org/10.1056/NEJM196201112660207>)
- Rabinowitz D & Zierler KL. A metabolic regulating device based on the actions of human growth hormone and of insulin, singly and together, on the human forearm. *Nature* 1963 **199** 913–915. (<https://doi.org/10.1038/199913a0>)
- Jørgensen JO, Pedersen SA, Thuesen L, Jørgensen J, Ingemann-Hansen T, Skakkebaek NE & Christiansen JS. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet* 1989 **1** 1221–1225. ([https://doi.org/10.1016/s0140-6736\(89\)92328-3](https://doi.org/10.1016/s0140-6736(89)92328-3))
- 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. *New England Journal of Medicine* 1989 **321** 1797–1803. (<https://doi.org/10.1056/NEJM198912283212605>)
- Jørgensen JS, Pedersen SA, Jørgensen JO, Riis BJ, Christiansen C, Christiansen JS & Skakkebaek NE. Effects of growth hormone (GH) on plasma bone Gla protein in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* 1990 **70** 916–919. (<https://doi.org/10.1210/jcem-70-4-916>)
- Schlemmer A, Johansen JS, Pedersen SA, Jørgensen JO, Hassager C & Christiansen C. The effect of growth hormone (GH) therapy on urinary pyridinoline cross-links in GH-deficient adults. *Clinical Endocrinology* 1991 **35** 471–476. (<https://doi.org/10.1111/j.1365-2265.1991.tb00930.x>)
- Jørgensen JO, Pedersen SA, Laurberg P, Weeke J, Skakkebaek NE & Christiansen JS. Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine-substituted central hypothyroidism. *Journal of Clinical Endocrinology and Metabolism* 1989 **69** 1127–1132. (<https://doi.org/10.1210/jcem-69-6-1127>)
- Pedersen SA, Welling K, Michaelsen KF, Jørgensen JO, Christiansen JS & Skakkebaek NE. Reduced sweating in adults with growth hormone deficiency. *Lancet* 1989 **2** 681–682. ([https://doi.org/10.1016/s0140-6736\(89\)90930-6](https://doi.org/10.1016/s0140-6736(89)90930-6))
- Jørgensen JO, Pedersen SA, Thuesen L, Jørgensen J, Møller J, Müller J, Skakkebaek NE & Christiansen JS. Long-term growth hormone treatment in growth hormone deficient adults. *Acta Endocrinologica* 1991 **125** 449–453. (<https://doi.org/10.1530/acta.0.1250449>)
- Jørgensen JO, Thuesen L, Müller J, Ovesen P, Skakkebaek NE & Christiansen JS. Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. *European Journal of Endocrinology* 1994 **130** 224–228. (<https://doi.org/10.1530/eje.0.1300224>)
- Cuneo RC, Salomon F, Wiles CM, Hesp R & Sonksen PH. Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. *Journal of Applied Physiology* 1991 **70** 695–700. (<https://doi.org/10.1152/jappl.1991.70.2.695>)
- Cuneo RC, Salomon F, Wiles CM, Hesp R & Sonksen PH. Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. *Journal of Applied Physiology* 1991 **70** 688–694. (<https://doi.org/10.1152/jappl.1991.70.2.688>)
- Cuneo RC, Salomon F, Watts GF, Hesp R & Sonksen PH. Growth hormone treatment improves serum lipids and lipoproteins in adults with growth hormone deficiency. *Metabolism: Clinical and Experimental* 1993 **42** 1519–1523. ([https://doi.org/10.1016/0026-0495\(93\)90145-e](https://doi.org/10.1016/0026-0495(93)90145-e))
- Cuneo RC, Salomon F, McGauley GA & Sonksen PH. The growth hormone deficiency syndrome in adults. *Clinical Endocrinology* 1992 **37** 387–397. (<https://doi.org/10.1111/j.1365-2265.1992.tb02347.x>)
- Rosen T, Bosaeus I, Tolli J, Lindstedt G & Bengtsson BA. Increased body fat mass and decreased extracellular fluid volume in adults with growth hormone deficiency. *Clinical Endocrinology* 1993 **38** 63–71. (<https://doi.org/10.1111/j.1365-2265.1993.tb00974.x>)
- Rosen T, Eden S, Larson G, Wilhelmsen L & Bengtsson BA. Cardiovascular risk factors in adult patients with growth hormone deficiency. *Acta Endocrinologica* 1993 **129** 195–200. (<https://doi.org/10.1530/acta.0.1290195>)
- Rosen T, Hansson T, Granhed H, Szucs J & Bengtsson BA. Reduced bone mineral content in adult patients with growth hormone deficiency. *Acta Endocrinologica* 1993 **129** 201–206. (<https://doi.org/10.1530/acta.0.1290201>)
- Bengtsson BA, Eden S, Lonn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tolli J, Sjöström L & Isaksson OG. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *Journal of Clinical Endocrinology and Metabolism* 1993 **76** 309–317. (<https://doi.org/10.1210/jcem.76.2.8432773>)
- Whitehead HM, Boreham G, McIlraith EM, Sheridan B, Kennedy L, Atkinson AB & Hadden DR. Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. *Clinical Endocrinology* 1992 **36** 45–52. (<https://doi.org/10.1111/j.1365-2265.1992.tb02901.x>)
- Jørgensen JO, Vahl N, Hansen TB, Thuesen L, Hagen C & Christiansen JS. Growth hormone versus placebo treatment for one year in growth hormone deficient adults: increase in exercise capacity and normalization of body composition. *Clinical Endocrinology* 1996 **45** 681–688. (<https://doi.org/10.1046/j.1365-2265.1996.8720883.x>)
- Böger RH, Skamira C, Bode-Böger SM, Brabant G, von zur Mühlen A & Frolich JC. Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. A double-blind, placebo-controlled study. *Journal of Clinical Investigation* 1996 **98** 2706–2713. (<https://doi.org/10.1172/JCI119095>)
- Beshyah SA, Shahi M, Skinner E, Sharp P, Foale R & Johnston DG. Cardiovascular effects of growth hormone replacement therapy in

- hypopituitary adults. *European Journal of Endocrinology* 1994 **130** 451–458. (<https://doi.org/10.1530/eje.0.1300451>)
- 25 Thuesen L, Christiansen JS, Sørensen KE, Jørgensen JO, Orskov H & Henningsen P. Increased myocardial contractility following growth hormone administration in normal man. An echocardiographic study. *Danish Medical Bulletin* 1988 **35** 193–196.
 - 26 Thuesen L, Jørgensen JO, Müller JR, Kristensen BO, Skakkebaek NE, Vahl N & Christiansen JS. Short and long-term cardiovascular effects of growth hormone therapy in growth hormone deficient adults. *Clinical Endocrinology* 1994 **41** 615–620. (<https://doi.org/10.1111/j.1365-2265.1994.tb01827.x>)
 - 27 Cuneo RC, Salomon F, Wilmschurst P, Byrne C, Wiles CM, Hesp R & Sonksen PH. Cardiovascular effects of growth hormone treatment in growth-hormone-deficient adults: stimulation of the renin-aldosterone system. *Clinical Science* 1991 **81** 587–592. (<https://doi.org/10.1042/cs0810587>)
 - 28 Rosen T & Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990 **336** 285–288. ([https://doi.org/10.1016/0140-6736\(90\)91812-o](https://doi.org/10.1016/0140-6736(90)91812-o))
 - 29 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. ([https://doi.org/10.1016/s0140-6736\(00\)04006-x](https://doi.org/10.1016/s0140-6736(00)04006-x))
 - 30 Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH & Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clinical Endocrinology* 1997 **46** 75–81. (<https://doi.org/10.1046/j.1365-2265.1997.d01-1749.x>)
 - 31 Bates AS, Van't Hoff W, Jones PJ & Clayton RN. The effect of hypopituitarism on life expectancy. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 1169–1172. (<https://doi.org/10.1210/jcem.81.3.8772595>)
 - 32 Svensson J, Bengtsson BA, Rosen T, Oden A & Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3306–3312. (<https://doi.org/10.1210/jc.2003-031601>)
 - 33 Stochholm K, Gravholt CH, Laursen T, Jørgensen JO, Laurberg P, Andersen M, Kristensen LØ, Feldt-Rasmussen U, Christiansen JS, Frydenberg M, *et al.* Incidence of GH deficiency – a nationwide study. *European Journal of Endocrinology* 2006 **155** 61–71. (<https://doi.org/10.1530/eje.1.02191>)
 - 34 Markkuss V, Beshyah SA, Fisher C, Sharp P, Nicolaides AN & Johnston DG. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet* 1992 **340** 1188–1192. ([https://doi.org/10.1016/0140-6736\(92\)92892-j](https://doi.org/10.1016/0140-6736(92)92892-j))
 - 35 Møller J, Frandsen E, Fisker S, Jørgensen JO & Christiansen JS. Decreased plasma and extracellular volume in growth hormone deficient adults and the acute and prolonged effects of GH administration: a controlled experimental study. *Clinical Endocrinology* 1996 **44** 533–539. (<https://doi.org/10.1046/j.1365-2265.1996.728550.x>)
 - 36 Møller J, Jørgensen JO, Frandsen E, Laursen T & Christiansen JS. Body fluids, circadian blood pressure and plasma renin during growth hormone administration: a placebo-controlled study with two growth hormone doses in healthy adults. *Scandinavian Journal of Clinical and Laboratory Investigation* 1995 **55** 663–669. (<https://doi.org/10.3109/00365519509075396>)
 - 37 Kamenicky P, Mazziotti G, Lombes M, Giustina A & Chanson P. Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. *Endocrine Reviews* 2014 **35** 234–281. (<https://doi.org/10.1210/er.2013-1071>)
 - 38 de Boer H, Blok GJ & Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. *Endocrine Reviews* 1995 **16** 63–86. (<https://doi.org/10.1210/edrv-16-1-63>)
 - 39 Juul A & Skakkebaek NE. Growth hormone deficiency and hyperthermia. *Lancet* 1991 **338** 887. ([https://doi.org/10.1016/0140-6736\(91\)91543-4](https://doi.org/10.1016/0140-6736(91)91543-4))
 - 40 Juul A, Behrenscheer A, Tims T, Nielsen B, Halkjaer-Kristensen J & Skakkebaek NE. Impaired thermoregulation in adults with growth hormone deficiency during heat exposure and exercise. *Clinical Endocrinology* 1993 **38** 237–244. (<https://doi.org/10.1111/j.1365-2265.1993.tb01001.x>)
 - 41 Juul A, Hjortskov N, Jepsen LT, Nielsen B, Halkjaer-Kristensen J, Vahl N, Jørgensen JO, Christiansen JS & Skakkebaek NE. Growth hormone deficiency and hyperthermia during exercise: a controlled study of sixteen GH-deficient patients. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 3335–3340. (<https://doi.org/10.1210/jcem.80.11.7593447>)
 - 42 Jørgensen JO, Flyvbjerg A, Lauritzen T, Alberti KG, Orskov H & Christiansen JS. Dose-response studies with biosynthetic human growth hormone (GH) in GH-deficient patients. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 36–40. (<https://doi.org/10.1210/jcem-67-1-36>)
 - 43 Jørgensen JO, Møller J, Alberti KG, Schmitz O, Christiansen JS, Orskov H & Møller N. Marked effects of sustained low growth hormone (GH) levels on day-to-day fuel metabolism: studies in GH-deficient patients and healthy untreated subjects. *Journal of Clinical Endocrinology and Metabolism* 1993 **77** 1589–1596. (<https://doi.org/10.1210/jcem.77.6.8263146>)
 - 44 Møller N, Schmitz O, Jørgensen JO, Astrup J, Bak JF, Christensen SE, Alberti KG & Weeke J. Basal- and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. *Journal of Clinical Endocrinology and Metabolism* 1992 **74** 1012–1019. (<https://doi.org/10.1210/jcem.74.5.1569148>)
 - 45 Krusenstjerna-Hafstrom T, Clasen BF, Møller N, Jessen N, Pedersen SB, Christiansen JS & Jørgensen JO. Growth hormone (GH)-induced insulin resistance is rapidly reversible: an experimental study in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 2548–2557. (<https://doi.org/10.1210/jc.2011-0273>)
 - 46 Møller N & Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocrine Reviews* 2009 **30** 152–177. (<https://doi.org/10.1210/er.2008-0027>)
 - 47 Jørgensen JO. Human growth hormone replacement therapy: pharmacological and clinical aspects. *Endocrine Reviews* 1991 **12** 189–207. (<https://doi.org/10.1210/edrv-12-3-189>)
 - 48 Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P *et al.* Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2192–2199. (<https://doi.org/10.1210/jc.2003-030840>)
 - 49 Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmensen 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. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 382–395. (<https://doi.org/10.1210/jcem.83.2.4594>)
 - 50 Møller J, Jørgensen JO, Lauersen T, Frystyk J, Naeraa RW, Orskov H & Christiansen JS. Growth hormone dose regimens in adult GH deficiency: effects on biochemical growth markers and metabolic parameters. *Clinical Endocrinology* 1993 **39** 403–408. (<https://doi.org/10.1111/j.1365-2265.1993.tb02386.x>)
 - 51 de Boer H, Blok GJ, Popp-Snijders C, Stuurman L, Baxter RC & van der Veen E. Monitoring of growth hormone replacement therapy in adults, based on measurement of serum markers. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 1371–1377. (<https://doi.org/10.1210/jcem.81.4.8636336>)
 - 52 Johannsson G, Rosen T & Bengtsson BA. Individualized dose titration of growth hormone (GH) during GH replacement in hypopituitary

- adults. *Clinical Endocrinology* 1997 **47** 571–581. (<https://doi.org/10.1046/j.1365-2265.1997.3271123.x>)
- 53 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. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 107–116. (<https://doi.org/10.1210/jcem.83.1.4482>)
 - 54 Johannsson G, Bjarnason R, Brannert M, Carlsson LM, Degerblad M, Manhem P, Rosen T, Thoren M & Bengtsson BA. The individual responsiveness to growth hormone (GH) treatment in GH-deficient adults is dependent on the level of GH-binding protein, body mass index, age, and gender. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 1575–1581. (<https://doi.org/10.1210/jcem.81.4.8636370>)
 - 55 Burman P, Johannsson AG, Siegbahn A, Vessby B & Karlsson FA. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 550–555. (<https://doi.org/10.1210/jcem.82.2.3776>)
 - 56 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on adult growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 379–381. (<https://doi.org/10.1210/jcem.83.2.4611>)
 - 57 Rubeck KZ, Bertelsen S, Vestergaard P & Jørgensen JO. Impact of GH substitution on exercise capacity and muscle strength in GH-deficient adults: a meta-analysis of blinded, placebo-controlled trials. *Clinical Endocrinology* 2009 **71** 860–866. (<https://doi.org/10.1111/j.1365-2265.2009.03592.x>)
 - 58 Widdowson WM & Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4413–4417. (<https://doi.org/10.1210/jc.2008-1239>)
 - 59 Barake M, Klibanski A & Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 852–860. (<https://doi.org/10.1210/jc.2013-3921>)
 - 60 Xue P, Wang Y, Yang J & Li Y. Effects of growth hormone replacement therapy on bone mineral density in growth hormone deficient adults: a meta-analysis. *International Journal of Endocrinology* 2013 **2013** 216107. (<https://doi.org/10.1155/2013/216107>)
 - 61 Hazem A, Elamin MB, Bancos I, Malaga G, Prutsky G, Domecq JP, Elraiyah TA, Abu Elnour NO, Prevost Y, Almandoz JP, *et al.* Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis. *European Journal of Endocrinology* 2012 **166** 13–20. (<https://doi.org/10.1530/EJE-11-0558>)
 - 62 Maison P & Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* 2003 **108** 2648–2652. (<https://doi.org/10.1161/01.CIR.0000100720.01867.1D>)
 - 63 Hansen TB, Brixen K, Vahl N, Jørgensen JO, Christiansen JS, Mosekilde L & Hagen C. Effects of 12 months of growth hormone (GH) treatment on calciotropic hormones, calcium homeostasis, and bone metabolism in adults with acquired GH deficiency: a double blind, randomized, placebo-controlled study. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 3352–3359. (<https://doi.org/10.1210/jcem.81.9.8784096>)
 - 64 Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenheim 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. *Annals of Internal Medicine* 1996 **125** 883–890. (<https://doi.org/10.7326/0003-4819-125-11-19961210-00003>)
 - 65 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 and Endocrinology* 2015 **3** 331–338. ([https://doi.org/10.1016/S2213-8587\(15\)00098-4](https://doi.org/10.1016/S2213-8587(15)00098-4))
 - 66 Deijen JB, Arwert LI, Witlox J & Drent ML. Differential effect sizes of growth hormone replacement on quality of life, well-being and health status in growth hormone deficient patients: a meta-analysis. *Health and Quality of Life Outcomes* 2005 **3** 63. (<https://doi.org/10.1186/1477-7525-3-63>)
 - 67 Arwert LI, Deijen JB, Witlox J & Drent ML. The influence of growth hormone (GH) substitution on patient-reported outcomes and cognitive functions in GH-deficient patients: a meta-analysis. *Growth Hormone and IGF Research* 2005 **15** 47–54. (<https://doi.org/10.1016/j.ghir.2004.11.004>)
 - 68 Falletti MG, Maruff P, Burman P & Harris A. The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: a meta-analysis of the current literature. *Psychoneuroendocrinology* 2006 **31** 681–691. (<https://doi.org/10.1016/j.psyneuen.2006.01.005>)
 - 69 Burman P, Broman JE, Hetta J, Wiklund I, Erfurth EM, Hagg E & Karlsson FA. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 3585–3590. (<https://doi.org/10.1210/jcem.80.12.8530603>)
 - 70 Filipsson Nystrom H, Barbosa EJ, Nilsson AG, Norrman LL, Ragnarsson O & Johannsson G. Discontinuing long-term GH replacement therapy: a randomized, placebo-controlled crossover trial in adult GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 3185–3195. (<https://doi.org/10.1210/jc.2012-2006>)
 - 71 Johannsson JO, Larson G, Andersson M, Elmgren A, Hynsjö L, Lindahl A, Lundberg PA, Isaksson OG, Lindstedt S & Bengtsson BA. Treatment of growth hormone-deficient adults with recombinant human growth hormone increases the concentration of growth hormone in the cerebrospinal fluid and affects neurotransmitters. *Neuroendocrinology* 1995 **61** 57–66. (<https://doi.org/10.1159/000126813>)
 - 72 Arwert LI, Veltman DJ, Deijen JB, van Dam PS & Drent ML. Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study. *Neuroendocrinology* 2006 **83** 12–19. (<https://doi.org/10.1159/000093337>)
 - 73 Holdaway IM, Hunt P, Manning P, Cutfield W, Gamble G, Ninow N, Staples-Moon D, Moodie P & Metcalfe S. Three-year experience with access to nationally funded growth hormone (GH) replacement for GH-deficient adults. *Clinical Endocrinology* 2015 **83** 85–90. (<https://doi.org/10.1111/cen.12691>)
 - 74 Elbornsson M, Götherström G, Bosæus I, Bengtsson BÅ, Johannsson G & Svensson J. Fifteen years of GH replacement improves body composition and cardiovascular risk factors. *European Journal of Endocrinology* 2013 **168** 745–753. (<https://doi.org/10.1530/EJE-12-1083>)
 - 75 Moore JS, Monson JP, Kaltsas G, Putignano P, Wood PJ, Sheppard MC, Besser GM, Taylor NF & Stewart PM. Modulation of 11beta-hydroxysteroid dehydrogenase isozymes by growth hormone and insulin-like growth factor: in vivo and in vitro studies. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 4172–4177. (<https://doi.org/10.1210/jcem.84.11.6108>)
 - 76 Dalin E, Nordling Eriksson G, Dahlqvist P, Hallgren Å, Wahlberg J, Ekwall O, Söderberg S, Rönnelid J, Olcén P, Winqvist O, *et al.* Clinical and immunological characteristics of autoimmune Addison disease: a Nationwide Swedish Multicenter Study. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 379–389. (<https://doi.org/10.1210/jc.2016-2522>)
 - 77 Abs R, Mattsson AF, Bengtsson BA, Feldt-Rasmussen U, Góth MI, Koltowska-Häggström M, Monson JP, Verhelst J, Wilton P & KIMS Study Group. Isolated growth hormone (GH) deficiency in adult patients: baseline clinical characteristics and responses to GH

- replacement in comparison with hypopituitary patients. A sub-analysis of the KIMS database. *Growth Hormone and IGF Research* 2005 **15** 349–359. (<https://doi.org/10.1016/j.ghir.2005.06.018>)
- 78 Veldhuis JD, Roelfsema F, Keenan DM & Pincus S. Gender, age, body mass index, and IGF-I individually and jointly determine distinct GH dynamics: analyses in one hundred healthy adults. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 115–121. (<https://doi.org/10.1210/jc.2010-1669>)
 - 79 Toogood AA, O'Neill PA & Shalet SM. Beyond the somatopause: growth hormone deficiency in adults over the age of 60 years. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 460–465. (<https://doi.org/10.1210/jcem.81.2.8636250>)
 - 80 Toogood AA & Shalet SM. Growth hormone replacement therapy in the elderly with hypothalamic-pituitary disease: a dose-finding study. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 131–136. (<https://doi.org/10.1210/jcem.84.1.5408>)
 - 81 Fernholm R, Brannert M, Hagg E, Hilding A, Baylink DJ, Mohan S & Thoren M. Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 4104–4112. (<https://doi.org/10.1210/jcem.85.11.6949>)
 - 82 Franco C, Johannsson G, Bengtsson BA & Svensson J. Baseline characteristics and effects of growth hormone therapy over two years in younger and elderly adults with adult onset GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 4408–4414. (<https://doi.org/10.1210/jc.2006-0887>)
 - 83 Pappachan JM, Raskauskiene D, Kutty VR & Clayton RN. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 1405–1411. (<https://doi.org/10.1210/jc.2014-3787>)
 - 84 Dal J, Leisner MZ, Hermansen K, Farkas DK, Bengtson M, Kistorp C, Nielsen EH, Andersen M, Feldt-Rasmussen U, Dekkers OM, et al. Cancer incidence in patients with acromegaly: a cohort study and meta-analysis of the literature. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 2182–2188. (<https://doi.org/10.1210/jc.2017-02457>)
 - 85 Holdaway IM, Bolland MJ & Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *European Journal of Endocrinology* 2008 **159** 89–95. (<https://doi.org/10.1530/EJE-08-0267>)
 - 86 Burgers AM, Biermasz NR, Schoones JW, Pereira AM, Renehan AG, Zwahlen M, Egger M & Dekkers OM. Meta-analysis and dose-response metaregression: circulating insulin-like growth factor I (IGF-I) and mortality. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 2912–2920. (<https://doi.org/10.1210/jc.2011-1377>)
 - 87 Stochholm K, Berglund A, Juul S, Gravholt CH & Christiansen JS. Socioeconomic factors do not but GH treatment does affect mortality in adult-onset growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 4141–4148. (<https://doi.org/10.1210/jc.2014-1814>)
 - 88 Olsson DS, Trimpou P, Hallen T, Bryngelsson IL, Andersson E, Skoglund T, Bengtsson BÅ, Johannsson G & Nilsson AG. Life expectancy in patients with pituitary adenoma receiving growth hormone replacement. *European Journal of Endocrinology* 2017 **176** 67–75. (<https://doi.org/10.1530/EJE-16-0450>)
 - 89 Berglund A, Gravholt CH, Olsen MS, Christiansen JS & Stochholm K. Growth hormone replacement does not increase mortality in patients with childhood-onset growth hormone deficiency. *Clinical Endocrinology* 2015 **83** 677–683. (<https://doi.org/10.1111/cen.12848>)
 - 90 van Bunderen CC, van Nieuwpoort IC, Arwert LI, Heymans MW, Franken AA, Koppeschaar HP, van der Lely AJ & Drent ML. 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. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 3151–3159. (<https://doi.org/10.1210/jc.2011-1215>)
 - 91 Gaillard RC, Mattsson AF, Akerblad AC, Bengtsson BÅ, Cara J, Feldt-Rasmussen U, Koltowska-Haggstrom M, Monson JP, Saller B, Wilton P, et al. Overall and cause-specific mortality in GH-deficient adults on GH replacement. *European Journal of Endocrinology* 2012 **166** 1069–1077. (<https://doi.org/10.1530/EJE-11-1028>)
 - 92 Holmer H, Svensson J, Rylander L, Johannsson G, Rosen T, Bengtsson BÅ, Thoren M, Hoybye C, Degerblad M, Brannert M, et al. Psychosocial health and levels of employment in 851 hypopituitary Swedish patients on long-term GH therapy. *Psychoneuroendocrinology* 2013 **38** 842–852. (<https://doi.org/10.1016/j.psyneuen.2012.09.008>)
 - 93 Stochholm K & Johannsson G. Reviewing the safety of GH replacement therapy in adults. *Growth Hormone and IGF Research* 2015 **25** 149–157. (<https://doi.org/10.1016/j.ghir.2015.06.006>)
 - 94 Martel-Duguech LM, Jorgensen JOL, Korbonits M, Johannsson G, Webb SM, Amadidou F, Mintziori G, Arosio M, Giavoli C, Badiu C, et al. ESE audit on management of adult growth hormone deficiency in clinical practice. *European Journal of Endocrinology* 2021 **184** 323–334. (<https://doi.org/10.1530/EJE-20-1180>)
 - 95 Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BMK, Boguszewski MCS, Casanueva FF, Chanson P, Chatelain P, Choong CS, Clemmons DR, et al. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. *European Journal of Endocrinology* 2016 **174** C1–C8. (<https://doi.org/10.1530/EJE-16-0111>)
 - 96 Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM & Hoffman AR. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Annals of Internal Medicine* 2007 **146** 104–115. (<https://doi.org/10.7326/0003-4819-146-2-200701160-00005>)
 - 97 Jørgensen JO, Hermansen K, Stochholm K & Juul A. Adult growth hormone deficiency: from transition to senescence. *Pediatric Endocrinology Reviews* 2018 **16** (Supplement 1) 70–79. (<https://doi.org/10.17458/per.vol16.2018.jhs.adultghdeficiency>)
 - 98 Bartke A. Minireview: Role of the growth hormone/insulin-like growth factor system in mammalian aging. *Endocrinology* 2005 **146** 3718–3723. (<https://doi.org/10.1210/en.2005-0411>)
 - 99 Kaji H & Chihara K. Direct causes of death in Japanese patients with hypopituitarism as analyzed from a nation-wide autopsy database. *European Journal of Endocrinology* 2004 **150** 149–152 doi:10.1530/eje.0.1500149
 - 100 Jasim S, Alahdab F, Ahmed AT, Tamhane S, Prokop LJ, Nippoldt TB & Murad MH. Mortality in adults with hypopituitarism: a systematic review and meta-analysis. *Endocrine* 2017 **56** 33–42. (<https://doi.org/10.1007/s12020-016-1159-3>)
 - 101 O'Connor MM & Mayberg MR. Effects of radiation on cerebral vasculature: a review. *Neurosurgery* 2000 **46** 138–149; discussion 150. (<https://doi.org/10.1093/neurosurgery/46.1.138>)
 - 102 Rim CH, Yang DS, Park YJ, Yoon WS, Lee JA & Kim CY. Radiotherapy for pituitary adenomas: long-term outcome and complications. *Radiation Oncology Journal* 2011 **29** 156–163. (<https://doi.org/10.3857/roj.2011.29.3.156>)
 - 103 van Varsseveld NC, van Bunderen CC, Ubachs DHH, Franken AA, Koppeschaar HP, van der Lely AJ & Drent ML. Cerebrovascular events, secondary intracranial tumors, and mortality after radiotherapy for nonfunctioning pituitary adenomas: a subanalysis from the Dutch National Registry of growth hormone treatment in adults. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 1104–1112. (<https://doi.org/10.1210/jc.2014-3697>)
 - 104 Lindholm J, Nielsen EH, Bjerre P, Christiansen JS, Hagen C, Juul S, Jørgensen J, Kruse A, Laurberg P & Stochholm K. Hypopituitarism and mortality in pituitary adenoma. *Clinical Endocrinology* 2006 **65** 51–58. (<https://doi.org/10.1111/j.1365-2265.2006.02545.x>)
 - 105 Hammarstrand C, Ragnarsson O, Hallén T, Andersson E, Skoglund T, Nilsson AG, Johannsson G & Olsson DS. Higher glucocorticoid replacement doses are associated with increased mortality in patients with pituitary adenoma. *European Journal of Endocrinology* 2017 **177** 251–256. (<https://doi.org/10.1530/EJE-17-0340>)

- 106 Zueger T, Kirchner P, Herren C, Fischli S, Zwahlen M, Christ E & Stettler C. Glucocorticoid replacement and mortality in patients with nonfunctioning pituitary adenoma. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E1938–E1942. (<https://doi.org/10.1210/jc.2012-2432>)
- 107 Stewart PM, Toogood AA & Tomlinson JW. Growth hormone, insulin-like growth factor-I and the cortisol-cortisone shuttle. *Hormone Research* 2001 **56** (Supplement 1) 1–6. (<https://doi.org/10.1159/000048126>)
- 108 Werner H, Lapkina-Gendler L, Achlaug L, Nagaraj K, Somri L, Yaron-Saminsky D, Pasmanik-Chor M, Sarfstein R, Laron Z & Yakar S. Genome-wide profiling of Laron syndrome patients identifies novel cancer protection pathways. *Cells* 2019 **8** 596. (<https://doi.org/10.3390/cells8060596>)
- 109 Ergun-Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W, Yasui Y, Robison LL & Sklar CA. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3494–3498. (<https://doi.org/10.1210/jc.2006-0656>)
- 110 Wilson P, Matisson AF & Darendeliler F. Growth hormone treatment in children is not associated with an increase in the incidence of cancer: experience from KIGS (Pfizer International Growth Database). *Journal of Pediatrics* 2010 **157** 265–270. (<https://doi.org/10.1016/j.jpeds.2010.02.028>)
- 111 Child CJ, Zimmermann AG, Woodmansee WW, Green DM, Li JJ, Jung H, Erfurth EM, Robison LL & HypoCCS International Advisory Board. Assessment of primary cancers in GH-treated adult hypopituitary patients: an analysis from the Hypopituitary Control and Complications Study. *European Journal of Endocrinology* 2011 **165** 217–223. (<https://doi.org/10.1530/EJE-11-0286>)
- 112 Hoffman AR, Kuntze JE, Baptista J, Baum HB, Baumann GP, Biller BM, Clark RV, Cook D, Inzucchi SE, Kleinberg D, et al. Growth hormone (GH) replacement therapy in adult-onset GH deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2048–2056. (<https://doi.org/10.1210/jc.2003-030346>)
- 113 van der Klaauw AA, Biermasz NR, Feskens EJM, Bos MB, Smit JW, Roelfsema F, Corssmit EP, Pijl H, Romijn JA & Pereira AM. The prevalence of the metabolic syndrome is increased in patients with GH deficiency, irrespective of long-term substitution with recombinant human GH. *European Journal of Endocrinology* 2007 **156** 455–462. (<https://doi.org/10.1530/EJE-06-0699>)
- 114 Filipsson H, Monson JP, Koltowska-Häggström M, Mattsson A & Johannsson G. The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3954–3961. (<https://doi.org/10.1210/jc.2006-0524>)
- 115 Attanasio AF, Mo D, Erfurth EM, Tan M, Ho KY, Kleinberg D, Zimmermann AG, Chanson P & International Hypopituitary Control Complications Study Advisory Board. Prevalence of metabolic syndrome in adult hypopituitary growth hormone (GH)-deficient patients before and after GH replacement. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 74–81. (<https://doi.org/10.1210/jc.2009-1326>)
- 116 Surya S, Horowitz JF, Goldenberg N, Sakharova A, Harber M, Cornford AS, Symons K & Barkan AL. The pattern of growth hormone delivery to peripheral tissues determines insulin-like growth factor-1 and lipolytic responses in obese subjects. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 2828–2834. (<https://doi.org/10.1210/jc.2009-0638>)
- 117 Attanasio AF, Jung H, Mo D, Chanson P, Bouillon R, Ho KK, Lamberts SW, Clemmons DR & HypoCCS International Advisory Board. Prevalence and incidence of diabetes mellitus in adult patients on growth hormone replacement for growth hormone deficiency: a surveillance database analysis. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 2255–2261. (<https://doi.org/10.1210/jc.2011-0448>)
- 118 Woodmansee WW, Hartman ML, Lamberts SWJ, Zagar AJ, Clemmons DR & International HypoCCS Advisory Board. Occurrence of impaired fasting glucose in GH-deficient adults receiving GH replacement compared with untreated subjects. *Clinical Endocrinology* 2010 **72** 59–69. (<https://doi.org/10.1111/j.1365-2265.2009.03612.x>)
- 119 Sesmilo G, Biller BM, Llevadot J, Hayden D, Hanson G, Rifai N & Klibanski A. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. *Annals of Internal Medicine* 2000 **133** 111–122. (<https://doi.org/10.7326/0003-4819-133-2-200007180-00010>)
- 120 Gazzaruso C, Gola M, Karamouzian I, Giubbini R & Giustina A. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH: an update. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 18–29. (<https://doi.org/10.1210/jc.2013-2394>)
- 121 Swords FM, Carroll PV, Kisalu J, Wood PJ, Taylor NF & Monson JP. The effects of growth hormone deficiency and replacement on glucocorticoid exposure in hypopituitary patients on cortisone acetate and hydrocortisone replacement. *Clinical Endocrinology* 2003 **59** 613–620. (<https://doi.org/10.1046/j.1365-2265.2003.01894.x>)
- 122 Danilowicz K, Bruno OD, Manavela M, Gomez RM & Barkan A. Correction of cortisol overreplacement ameliorates morbidities in patients with hypopituitarism: a pilot study. *Pituitary* 2008 **11** 279–285. (<https://doi.org/10.1007/s11102-008-0126-2>)
- 123 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. *Clinical Endocrinology* 2007 **67** 623–628. (<https://doi.org/10.1111/j.1365-2265.2007.02935.x>)
- 124 Ehrnborg C, Ellegård L, Bosaeus I, Bengtsson BA & Rosén T. Supraphysiological growth hormone: less fat, more extracellular fluid but uncertain effects on muscles in healthy, active young adults. *Clinical Endocrinology* 2005 **62** 449–457. (<https://doi.org/10.1111/j.1365-2265.2005.02240.x>)
- 125 Christ ER, Cummings MH, Westwood NB, Sawyer BM, Pearson TC, Sönksen PH & Russell-Jones DL. The importance of growth hormone in the regulation of erythropoiesis, red cell mass, and plasma volume in adults with growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 2985–2990. (<https://doi.org/10.1210/jcem.82.9.4199>)
- 126 Woodhouse LJ, Mukherjee A, Shalet SM & Ezzat S. The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. *Endocrine Reviews* 2006 **27** 287–317. (<https://doi.org/10.1210/er.2004-0022>)
- 127 Mauras N, Pescovitz OH, Allada V, Messig M, Wajnrajch MP, Lippe B et al. Limited efficacy of growth hormone (GH) during transition of GH-deficient patients from adolescence to adulthood: a phase III multicenter, double-blind, randomized two-year trial. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 3946–3955. (<https://doi.org/10.1210/jc.2005-0208:15855257>)
- 128,128. Deyssig R, Frisch H, Blum WF & Waldhör T. Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. *Acta Endocrinologica* 1993 **128** 313–318. (<https://doi.org/10.1530/acta.0.1280313>)
- 129 Frisch H. Growth hormone and body composition in athletes. *Journal of Endocrinological Investigation* 1999 **22** (Supplement) 106–109.
- 130 Papadakis MA, Grady D, Black D, Tierney MJ, Gooding GA, Schambelan M & Grunfeld C. Growth hormone replacement in healthy older men improves body composition but not functional ability. *Annals of Internal Medicine* 1996 **124** 708–716. (<https://doi.org/10.7326/0003-4819-124-8-199604150-00002>)
- 131 Lopes AJ, Ferreira AS, Walchan EM, Soares MS, Bunn PS & Guimarães FS. Explanatory models of muscle performance in acromegaly patients evaluated by knee isokinetic dynamometry:

- implications for rehabilitation. *Human Movement Science* 2016 **49** 160–169. (<https://doi.org/10.1016/j.humov.2016.07.005>)
- 132 Bouillon R, Koledova E, Bezlepikina O, Nijs J, Shavrikhova E, Nagaeva E, Chikulaeva O, Peterkova V, Dedov I, Bakulin A, *et al.* Bone status and fracture prevalence in Russian adults with childhood-onset growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 4993–4998. (<https://doi.org/10.1210/jc.2004-0054>)
 - 133 Mazzioti G, Mormando M, Cristiano A, Bianchi A, Porcelli T, Giampietro A, Maffezzoni F, Serra V, De Marinis L & Giustina A. Association between l-thyroxine treatment, GH deficiency, and radiological vertebral fractures in patients with adult-onset hypopituitarism. *European Journal of Endocrinology* 2014 **170** 893–899. (<https://doi.org/10.1530/EJE-14-0097>)
 - 134 Mazzioti G, Porcelli T, Bianchi A, Cimino V, Patelli I, Mejia C, Fusco A, Giampietro A, De Marinis L & Giustina A. Glucocorticoid replacement therapy and vertebral fractures in hypopituitary adult males with GH deficiency. *European Journal of Endocrinology* 2010 **163** 15–20. (<https://doi.org/10.1530/EJE-10-0125>)
 - 135 van Varsseveld NC, van Bunderen CC, Franken AA, Koppeschaar HP, van der Lely AJ & Drent ML. Fractures in pituitary adenoma patients from the Dutch National Registry of growth hormone treatment in adults. *Pituitary* 2016 **19** 381–390. (<https://doi.org/10.1007/s11102-016-0716-3>)
 - 136 Biermasz NR, Hamdy NAT, Pereira AM, Romijn JA & Roelfsema F. Long-term skeletal effects of recombinant human growth hormone (rhGH) alone and rhGH combined with alendronate in GH-deficient adults: a seven-year follow-up study. *Clinical Endocrinology* 2004 **60** 568–575. (<https://doi.org/10.1111/j.1365-2265.2004.02021.x>)
 - 137 Biermasz NR, Hamdy NA, Janssen YJ & Roelfsema F. Additional beneficial effects of alendronate in growth hormone (GH)-deficient adults with osteoporosis receiving long-term recombinant human GH replacement therapy: a randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 3079–3085. (<https://doi.org/10.1210/jcem.86.7.7669>)
 - 138 Underwood LE, Attie KM, Baptista J & Genentech Collaborative Study Group. Growth hormone (GH) dose-response in young adults with childhood-onset GH deficiency: a two-year, multicenter, multiple-dose, placebo-controlled study. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5273–5280. (<https://doi.org/10.1210/jc.2003-030204>)
 - 139 Beshyah SA, Freemantle C, Shahi M, Anyaoku V, Merson S, Lynch S, Skinner E, Sharp P, Foale R & Johnston DG. Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults. *Clinical Endocrinology* 1995 **42** 73–84. (<https://doi.org/10.1111/j.1365-2265.1995.tb02601.x>)
 - 140 Wallymahmed ME, Foy P, Shaw D, Hutcheon R, Edwards RH & MacFarlane IA. Quality of life, body composition and muscle strength in adult growth hormone deficiency: the influence of growth hormone replacement therapy for up to 3 years. *Clinical Endocrinology* 1997 **47** 439–446. (<https://doi.org/10.1046/j.1365-2265.1997.2801076.x>)
 - 141 Verhelst J, Abs R, Vandeweghe M, Mockel J, Legros JJ, Copinschi G, Mahler C, Velkeniers B, Vanhaelst L, Van Aelst A, *et al.* Two years of replacement therapy in adults with growth hormone deficiency. *Clinical Endocrinology* 1997 **47** 485–494. (<https://doi.org/10.1046/j.1365-2265.1997.3041112.x>)
 - 142 Baum HB, Katznelson L, Sherman JC, Biller BM, Hayden DL, Schoenfeld DA, Cannistraro KE & Klibanski A. Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 3184–3189. (<https://doi.org/10.1210/jcem.83.9.5112>)
 - 143 Bollerslev J, Hallén J, Fougner KJ, Jørgensen AP, Kristo C, Fagertun H, Gudmundsen O, Burman P & Schreiner T. Low-dose GH improves exercise capacity in adults with GH deficiency: effects of a 22-month placebo-controlled, crossover trial. *European Journal of Endocrinology* 2005 **153** 379–387. (<https://doi.org/10.1530/eje.1.01971>)
 - 144 Chihara K, Kato Y, Kohno H, Takano K, Tanaka T, Teramoto A & Shimatsu A. Efficacy and safety of growth hormone (GH) in the treatment of adult Japanese patients with GH deficiency: a randomised, placebo-controlled study. *Growth Hormone and IGF Research* 2006 **16** 132–142. (<https://doi.org/10.1016/j.ghir.2006.03.012>)
 - 145 Urushihara H, Fukuhara S, Tai S, Morita S & Chihara K. Heterogeneity in responsiveness of perceived quality of life to body composition changes between adult- and childhood-onset Japanese hypopituitary adults with GH deficiency during GH replacement. *European Journal of Endocrinology* 2007 **156** 637–645. (<https://doi.org/10.1530/EJE-07-0016>)
 - 146 Ragnarsson O, Mattsson AF, Monson JP, Filipsson Nyström H, Åkerblad AC, Kołtowska-Häggström M & Johannsson G. The relationship between glucocorticoid replacement and quality of life in 2737 hypopituitary patients. *European Journal of Endocrinology* 2014 **171** 571–579. (<https://doi.org/10.1530/EJE-14-0397>)
 - 147 Bleicken B, Hahner S, Loeffler M, Ventz M, Decker O, Allolio B & Quinkler M. Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. *Clinical Endocrinology* 2010 **72** 297–304. (<https://doi.org/10.1111/j.1365-2265.2009.03596.x>)
 - 148 Ajmal A, McKean E, Sullivan S & Barkan A. Decreased quality of life (QoL) in hypopituitary patients: involvement of glucocorticoid replacement and radiation therapy. *Pituitary* 2018 **21** 624–630. (<https://doi.org/10.1007/s11102-018-0918-y>)
 - 149 Miller KK, Wexler T, Fazeli P, Gunnell L, Graham GJ, Beauregard C, Hemphill L, Nachtigall L, Loeffler J, Swearingen B, *et al.* Growth hormone deficiency after treatment of acromegaly: a randomized, placebo-controlled study of growth hormone replacement. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 567–577. (<https://doi.org/10.1210/jc.2009-1611>)
 - 150 van der Klaauw AA, Bax JJ, Roelfsema F, Stokkel MPM, Bleeker GB, Biermasz NR, Smit JWA, Romijn JA & Pereira AM. Limited effects of growth hormone replacement in patients with GH deficiency during long-term cure of acromegaly. *Pituitary* 2009 **12** 339–346. (<https://doi.org/10.1007/s11102-009-0186-y>)
 - 151,151. Wassenaar MJ, Biermasz NR, Kloppenburg M, van der Klaauw AA, Tiemensma J, Smit JW, Pereira AM, Roelfsema F, Kroon HM & Romijn JA. Clinical osteoarthritis predicts physical and psychological QoL in acromegaly patients. *Growth Hormone and IGF Research* 2010 **20** 226–233. (<https://doi.org/10.1016/j.ghir.2010.02.003>)
 - 152 van der Klaauw AA, Biermasz NR, Hoftijzer HC, Pereira AM & Romijn JA. Previous radiotherapy negatively influences quality of life during 4 years of follow-up in patients cured from acromegaly. *Clinical Endocrinology* 2008 **69** 123–128. (<https://doi.org/10.1111/j.1365-2265.2007.03169.x>)
 - 153 Aguiar-Oliveira MH, Oliveira FT, Pereira RM, Oliveira CR, Blackford A, Valença EH, Santos EG, Gois-Junior MB, Meneguz-Moreno RA, Araujo VP, *et al.* Longevity in untreated congenital growth hormone deficiency due to a homozygous mutation in the GHRH receptor gene. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 714–721. (<https://doi.org/10.1210/jc.2009-1879>)
 - 154 Barbosa JA, Salvatori R, Oliveira CR, Pereira RM, Farias CT, Britto AV, Farias NT, Blackford A & Aguiar-Oliveira MH. Quality of life in congenital, untreated, lifetime isolated growth hormone deficiency. *Psychoneuroendocrinology* 2009 **34** 894–900. (<https://doi.org/10.1016/j.psyneuen.2009.01.001>)
 - 155 Andrade-Guimarães AL, Aguiar-Oliveira MH, Salvatori R, Carvalho VO, Alvim-Pereira F, Daniel CRA, Brasileiro GAM, Santana-Ribeiro AA, Santos-Carvalho HA, Oliveira CRP, *et al.* Adult individuals with congenital, untreated, severe isolated growth hormone deficiency have satisfactory muscular function. *Endocrine* 2019 **63** 112–119. (<https://doi.org/10.1007/s12020-018-1763-5>)
 - 156 Epitácio-Pereira CC, Silva GM, Salvatori R, Santana JA, Pereira FA, Gois-Junior MB, Britto AV, Oliveira CR, Souza AH, Santos EG, *et al.*

- Isolated GH deficiency due to a GHRH receptor mutation causes hip joint problems and genu valgum, and reduces size but not density of trabecular and mixed bone. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** E1710–E1715. (<https://doi.org/10.1210/jc.2013-2349>)
- 157 Barreto-Filho JA, Alcântara MR, Salvatori R, Barreto MA, Sousa AC, Bastos V, Souza AH, Pereira RM, Clayton PE, Gill MS, *et al.* Familial isolated growth hormone deficiency is associated with increased systolic blood pressure, central obesity, and dyslipidemia. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 2018–2023. (<https://doi.org/10.1210/jcem.87.5.8474>)
- 158 Gleeson HK, Souza AH, Gill MS, Wieringa GE, Barretto ES, Barretto-Filho JA, Shalet SM, Aguiar-Oliveira MH & Clayton PE. Lipid profiles in untreated severe congenital isolated growth hormone deficiency through the lifespan. *Clinical Endocrinology* 2002 **57** 89–95. (<https://doi.org/10.1046/j.1365-2265.2002.01568.x>)
- 159 Menezes Oliveira JL, Marques-Santos C, Barreto-Filho JA, Ximenes Filho R, de Oliveira Britto AV, Oliveira Souza AH, Prado CM, Pereira Oliveira CR, Pereira RM, Ribeiro Vicente Tde A, *et al.* Lack of evidence of premature atherosclerosis in untreated severe isolated growth hormone (GH) deficiency due to a GH-releasing hormone receptor mutation. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 2093–2099. (<https://doi.org/10.1210/jc.2005-2571>)
- 160 Oliveira JL, Aguiar-Oliveira MH, D'Oliveira A, Pereira RM, Oliveira CR, Farias CT, Barreto-Filho JA, Anjos-Andrade FD, Marques-Santos C, Nascimento-Junior AC, *et al.* Congenital growth hormone (GH) deficiency and atherosclerosis: effects of GH replacement in GH-naïve adults. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 4664–4670. (<https://doi.org/10.1210/jc.2007-1636>)
- 161 Araujo VP, Aguiar-Oliveira MH, Oliveira JL, Rocha HM, Oliveira CR, Rodrigues TM, Nunes MA, Britto IM, Ximenes R, Barreto-Filho JA, *et al.* Arrest of atherosclerosis progression after interruption of GH replacement in adults with congenital isolated GH deficiency. *European Journal of Endocrinology* 2012 **166** 977–982. (<https://doi.org/10.1530/EJE-12-0062>)

Received 19 May 2021

Revised version received 15 October 2021

Accepted 28 October 2021