GH replacement in adults: interactions with other pituitary hormone deficiencies and replacement therapies

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Abstract

Severe GH deficiency (GHD) in adults has been described as a clinical entity. However, some of the features associated with GHD could be due to unphysiological and inadequate replacement of other pituitary hormone deficiencies. This may be true for glucocorticoid replacement that lacks a biomarker making dose titration and monitoring difficult. Moreover, oral estrogen replacement therapy decreases IGF1 levels compared with the transdermal route, which attenuates the responsiveness to GH replacement therapy in women. In addition, in untreated female hypogonadism, oral estrogen may augment the features associated with GHD in adult women. Important interactions between the hormones used for replacing pituitary hormone deficiency occur. Introducing GH replacement may unmask both an incipient adrenal insufficiency and central hypothyroidism. Therefore, awareness and proper monitoring of these hormonal interactions are important in order to reach an optimal replacement therapy. This review will focus on the complex hormonal interactions between GH and other pituitary hormones in GHD and in GH replacement.

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Introduction

Hypopituitarism acquired in adult life is often a result of pituitary or peripituitary tumors and their treatment (1–3), most frequently represented by a nonfunctioning pituitary adenoma (4, 5). In a large study (6), the prevalence of hypopituitarism from pituitary tumors was 28/100 000 with nontumor origin of hypopituitarism representing ∼30% of the cases.

The history of hormonal replacement of hypopituitarism started during the 19th century, as desiccated thyroid hormone became available in 1891. During the third decade of the 20th century, the discovery and purification of sexual steroids emerged (7); in the mid-20th century, the first reports of glucocorticoid (GC) replacement were published; and the first placebo-controlled trials of growth hormone (GH) replacement therapy in adults were published in 1989 (8, 9) after recombinant human GH became available (1).

With the availability of recombinant human GH treatment, the use in severe GH deficiency (GHD) in childhood was possible and enhanced the interest of possible consequences of GHD in adults. The

first data of excess mortality in adult hypopituitary patients receiving conventional replacement therapy with unreplaced GHD were reported in 1990 (10). Further data have confirmed that hypopituitary patients have excess cardiovascular and cerebrovascular mortality (5, 10–12), which has been designated to untreated GHD or the treatment modalities of the underlying pituitary disease, such as cranial irradiation (5).

Mortality data from long-term GH replacement therapy from controlled trials are as yet unavailable; a positive outcome of GH replacement is indicated by a study (13) in which the morbidity in myocardial infarction, cerebrovascular disease, and malignancies was increased in untreated GHD patients, but was similar or lower than that of the normal population in patients receiving GH replacement. Although these data support the impact of GH on outcome in hypopituitary patients, further supportive data are needed before the impact of GH replacement on morbidity and mortality remains to be proven.

The clinical efforts made to define and replace GHD in adults have put focus on hypopituitarism in general. The impact of other replacement therapies with GC, thyroxine (T_4), and sex steroids on the clinical features of hypopituitarism and their interactions with GHD and GH replacement has, therefore, been studied. These therapies do not completely mirror

endogenous hormonal production and their monitoring is also made difficult by the lack of good biomarkers of their action. This review will focus on the impact of GC, thyroid hormone, and sex steroid hormone deficiency and their treatments on clinical features associated with adult GHD.

Adult GHD

The clinical features associated with adult GHD are abdominal obesity, decreased lean body mass (LBM), reduced muscle strength and exercise capacity, increased serum concentration of low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP), reduced bone mineral density (BMD), dry skin, and impaired psychological well being (1, 14, 15).

The efficacy of GH treatment was initially evaluated in short-term-controlled studies with improvement in body composition, lipids, and quality of life (QoL) (16). These results are also found in long-term studies (17–20) with a reduction in total body fat and a progressive improvement of total- and LDL-C. After an initial deterioration, HbA1c decreases progressively (17). In addition, muscle mass and LBM increase and muscle strength improves, at least during the first 5 years of treatment (18, 20). Improvement in QoL occurs, predominantly, during the first year of GH treatment, but a successive improvement is observed (19, 21) and after 8 years of GH treatment, the GHD patients have attained the same QoL score as the normal population (19). All these data support the importance of GHD *per se* for the phenotype described above of the adult GHD patient. However, it should be remembered that most patients being replaced with GH in the GHD trials have had multiple pituitary hormone deficiencies (MPHD) and, therefore, the impact of those on the baseline status cannot be excluded.

Differences between isolated GHD and multiple hormonal deficiencies

The influence of other hormonal replacement therapies than GH on the clinical features of GHD and its outcome may be judged from the studies comparing patients with isolated GHD (IGHD) and MPHD. This type of comparison was performed using the Pfizer International Metabolic Database (KIMS) with 274 patients with IGHD and 2594 patients with MPHD (22). The study was unable to detect differences in serum lipid levels, glucose metabolism, fracture rate, and QoL among the two groups of patients. As no major differences were detected between patients with IGHD and MPHD, the concept that the clinical phenotype linked to severe GHD adults is largely unaffected by other hormonal replacement therapies was strengthened. However, a large pharmaco-epidemiological study may be affected

by a selection bias of those patients included. Moreover, the criteria for GH replacement therapy are different in different countries, and finally some patients classified with severe IGHD may have other partial hormonal deficiencies, yet to be detected, that may influence the results. Therefore, it is not possible to exclude that the doses and the regime we use to replace GC, T_4, and sex steroids is influencing the outcome of patients with MPHD.

GHD testing and other pituitary hormone deficiencies

The levels of serum insulin-like growth factor 1 (IGF1) are not a sensitive test for GHD in adults unless the patient has three or more pituitary hormone deficiencies and a serum IGF1 concentration below the normal reference range (23). Otherwise, a GH stimulation test needs to be performed. The current guidelines on the diagnosis of GHD advocate that other hormonal deficiencies shall be adequately replaced before any GH testing (23).

This is based on the knowledge of other hormones that affect the tests used for GHD. Short-term deprivation of hydrocortisone (HC) therapy does not, but chronic hypocortisolism does impair GH secretion (within normal range > 15 μg/l) (24). Also, GH testing in patients suffering from acute stress or in patients receiving high doses of GC should be avoided, as there are indications that the GH response to stimulations tests such as the pyridostigmine (PD)–GHRH is reduced (25). In Cushing's syndrome, it is well known that the recovery of GH secretion occurs only after long-term correction of hypercortisolism (26).

Moreover, serum IGF1 levels are reduced in patients with central hypothyroidism (27) and GH stimulation with insulin tolerance test (ITT) (28), or GHRH (29) is blunted in hypothyroidism and restored after adequate T_4 replacement. In hyperthyroidism, IGF1 is reported to be normal or elevated (30, 31). Also, hyperthyroid patients have a normal GH response to GH-releasing peptide 6 together with a blunted GH responsiveness to GHRH (32, 33).

Hypogonadism also affects the GH secretion. Oral estrogens reduce serum IGF1 levels more than transdermal estrogens (see under heading central hypogonadism). In a study of premenauposal women studied before and after ovariectomy, the response to GHRH was reduced in hypogonadism and restored back to normal levels after transdermal estrogen replacement (34). In men with primary hypogonadism, IGF1 levels were lower than in healthy controls and were restored after testosterone replacement (35).

Furthermore, prolactin deficiency is independently associated with reduced IGF1 in GHD patients (36), and there are reports that hyperprolactinemia in nonfunctioning pituitary adenomas reduces the GH response to

GHRH but not to an ITT (37). In summary, management of other pituitary hormone deficiencies is needed in order to be able to adequately perform and interpret a diagnostic procedure for GHD.

Adrenocorticoid axis

The association between excess GC and abdominal obesity, reduced LBM and BMC, and glucose intolerance is well recognized in patients with all forms of Cushing's syndrome. In GHD and obesity, there is an increased local 11β-hydroxysteroid dehydrogenase (HSD) type 1 activity in adipose tissues (38–41) resulting in increased local cortisol exposure (38) (Fig. 1). This is reduced after GH replacement (42, 43) possibly explaining some of the metabolic features associated with hypopituitarism and severe GHD and the beneficial effects of GH therapy.

The aims of GC replacement therapy are to mimic the circadian serum steroid profile, to respond to the increased need for cortisol during physical and physiological stimulation, and to achieve normal well being, normal metabolism, and favourable long-term outcome (3), avoiding under- (44) and overreplacement (45, 46).

The outcome of GC replacement therapy has been considered satisfactory (47) until recently. Patients with hypopituitarism have double the standardized mortality rate (SMR) (5, 10), and young adults with hypopituitarism and concomitant adrenal insufficiency have more than sevenfold the expected mortality rate (48). Moreover, patients with Addison's disease have also been shown to have more than double the SMR (49, 50). A possible explanation for this increased mortality rate is an inappropriate GC replacement therapy; that is, both too high maintenance doses and an inadequate GC exposure in response to stress and concurrent illnesses.
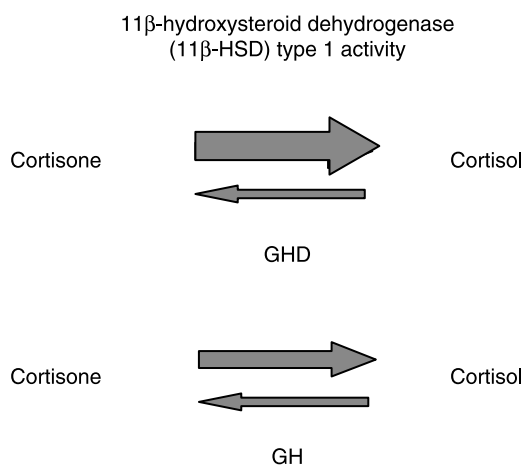
11β-hydroxysteroid dehydrogenase
(11β-HSD) type 1 activity

Figure 1 The 11β-HSD type 1 enzyme activity is enhanced in GH deficiency (GHD), thus exposing the tissues to more cortisol, whereas GH replacement inhibits the type 1 shuttle.

The daily doses of GC used for replacement therapy are being reduced during the last 10 years, as the daily cortisol production rate is substantially lower than previously thought (51, 52). The estimated daily cortisol production rate in normal subjects has been found to be between 9 and $11 \, mg/m^2$ per day (corresponding to ∼15.5–19 mg/day in an average adult subject) (52). The previously recommended dose of 30 mg/day of HC is, therefore, probably too high for most patients with adrenal insufficiency (53). This is supported by studies that have been able to reduce most patients to 20 mg HC or 25 mg cortisone acetate by individual dose titrations (54–56).

The effect of GC replacement therapy on bone metabolism and cardiovascular risk factors has been assessed (57). Zelissen *et al.* (58) found an inverse correlation between lumbar spine BMD and increasing dose of HC/kg body weight in men with Addison's disease, but not in women. Wichers *et al.* (59) conducted a randomized study in nine patients with ACTH insufficiency who were treated for three periods of 2 weeks with 15, 20, or 30 mg/day of HC. Serum levels of osteocalcin, as a marker of bone formation, reduced with increasing doses of HC, but resorption markers remained unchanged. Al-Shoumer *et al.* (60) reported that hypopituitary patients on GC replacement were more insulin resistant in the mornings when HC was administered than in the mornings when no HC was given. In contrast, Dunne *et al.* (61) found no significant difference in blood pressure and glucose metabolism over a 3-month period when reducing the daily dose of HC from 30 to 15 mg. This is in accordance with a report from McConnell *et al.* (62) who found glucose metabolism to be similar in 15 ACTH-insufficient patients who, in a randomized cross-over study, received either i.v. HC, in order to mimic the physiological serum cortisol profile, or 15 + 5 mg HC administered orally. In contrast to the above studies, 11 panhypopituitary patients with untreated GHD in an open noncontrolled study were instructed to reduce their dose from 20 to 30 mg HC/day at baseline to 10–15 mg/day (63). After 6–12 months, body weight, total and abdominal body fat mass, total cholesterol, and triglycerides had decreased and QoL score was improved.

The metabolic effects of different doses of GC for replacement therapy were studied in a large study of more than 2000 patients (4). A significant GC dose–response relationship was demonstrated with waist circumference, serum triglyceride concentration, total- and LDL-C levels, and body mass index (BMI; Fig. 2A–D). Of interest was that patients receiving HC equivalent doses of < 20 mg/day had a similar metabolic profile to those with an intact hypothalamus–pituitary–adrenal axis. This study is, therefore, the first to demonstrate that a mean HC equivalent replacement dose ≥ 20 mg augments the metabolic perturbations associated with hypopituitarism and untreated GHD.
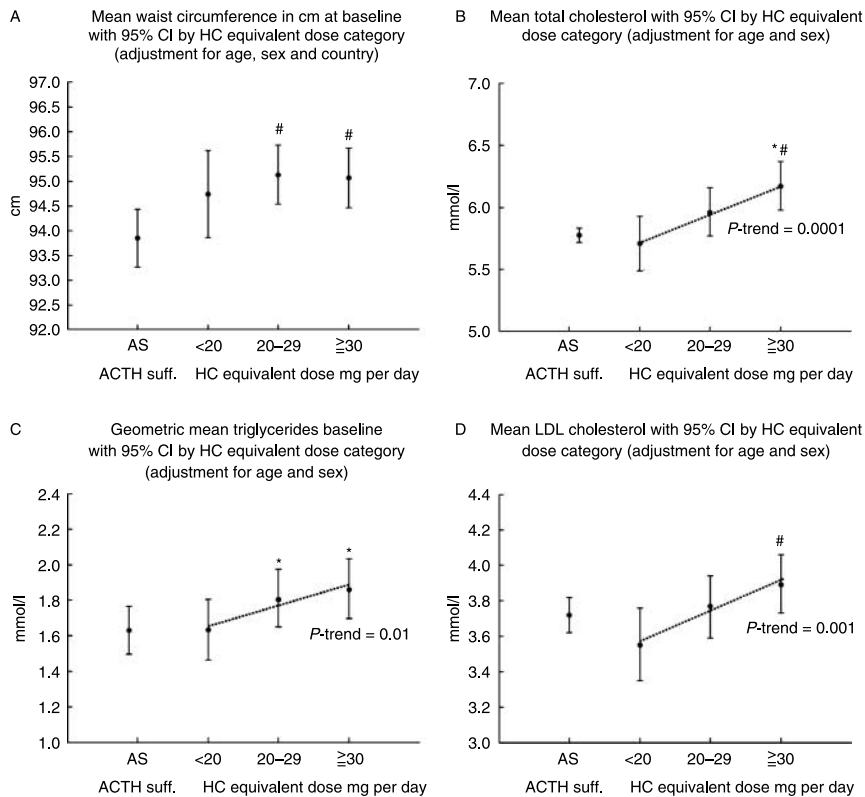
Figure 2 Hydrocortisone (HC) equivalent dose categories in ACTH-deficient and ACTH-sufficient patients with GHD before GH replacement. The broken line represents a dose–response analysis within the glucocorticoid-treated groups. (A) Waist, [#]$P<0.001$ versus AS; (B) total cholesterol, [*]$P<0.0001$ versus AS, [#]$P<0.0001$ vs <20 mg/day; (C) triglycerides logarithmic transformed, [*]$P<0.001$ versus AS; (D) LDL cholesterol, [#]$P<0.05$ vs <20 mg/day. Published in *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3954–3961. Reproduced with permission of The Endocrine Society (4).

These metabolic associations with GC doses remained after 1 year of GH treatment.

However, it is of some surprise in this large cohort of subjects that the relationship between these factors and the dose of GC was not stronger, indicating that other endocrine insufficiencies may have strong modulating effects and attenuate some of the differences between the ACTH-deficient and the sufficient patients. It is also possible that increased tissue exposure of cortisol, as a result of increased 11β-HSD type 1 activity occurring in both ACTH-deficient and replete GHD subjects, may exert a major influence over and above that resulting from different exogenous GC dose. The most common daily dose of HC in the study was 30 mg. The study, therefore, clearly indicates that lower doses are advocated for the use of replacement therapy in patients with secondary adrenal insufficiency.

Recent studies have demonstrated that well being and QoL are compromised in patients with both primary and secondary AI (64–66). Of interest is that the pattern of deficit according to the questionnaires used is similar among patients with primary adrenal insufficiency and those with hypopituitarism, indicating that a common denominator for this might be the quality of the GC replacement. In a recent study using a subcutaneous infusion pump to re-establish the physiological circadian rhythm of cortisol, patients were able to reduce their total daily doses while experiencing improved levels of subjective health and well being (67). It is, therefore, likely that the pattern of HC delivery and the total plasma cortisol exposure profile are of importance for patient outcome in both primary and secondary adrenal insufficiency.

Central hypothyroidism

It is possible that untreated mild CH or poorly replaced CH can have clinical features that are associated with severe GHD.

In CH, the bioactivity of TSH (68) is reduced because of inadequate hypothalamic stimulation that causes the pituitary to secrete abnormally glycosylated TSH. TSH in this form has a longer half-life than normal TSH (69), which explains the normal and sometimes slightly elevated levels of TSH seen in CH (70). Using reduced levels of TSH for the diagnosis of CH is, therefore, not useful.

In CH, reduced serum T_4 level is the single best criterion for diagnosis. In mild CH, thyroid hormone levels may, however, be within the lower normal range (71–74). In addition, diagnosing partial CH may be blurred by the 25% intra-individual variation of free T_4 (FT_4) (71), which also suggests that CH cases are found when thyroid hormone levels are in the lower parts of the reference range. Therefore, a decrease of $FT_4 > 20\%$ in a patient with pituitary disease is indicative of CH (75).

The diagnosis of CH is, therefore, in many cases not straightforward. Patients with nonthyroidal illness (NTI) may have values that overlap with those of CH. Therefore, analyses should be repeated and evaluated in the light of the clinical situation. A clue to distinguishing these two conditions is the evaluation of triiodothyronine (T_3) (76, 77).

GH replacement increases conversion of T_4 to T_3 and decreases that of T_4 to reversed T_3 (9, 78, 79). Therefore, careful monitoring of thyroid function is mandatory during GH treatment (78), as it may indicate changes in the T_4 dose needed. Patients with untreated GHD may have higher FT_4 levels than on GH replacement; GH therapy may, therefore, unmask undiagnosed CH (74, 79, 80). This effect is also seen in children with MHPD, but not in children with IGHD (81). The same mechanism may induce high FT_4 in a previously well-replaced patient when GH treatment is started (80). Also to be considered is that both transdermal and oral estrogens increase thyroxin-binding globulin and patients may need higher L-T_4 replacement doses when these therapies are combined (75).

In addition, the thyroid hormonal system in hypopituitary patients is influenced by GC replacement (82). GCs seem to reduce the conversion of T_4 to T_3, which may have an impact in patients on overly high dose of HC. Also, induction of GC replacement may unmask an undiagnosed CH. Moreover, it is a well-known clinical concept that evaluation of the adrenal axis is mandatory before initiating T_4 replacement, as it otherwise may trigger an adrenal crisis in patients with untreated adrenal insufficiency by accelerating the metabolism of cortisol (83) and increasing the metabolic rate.

Because of the uncertainty of using basal thyroid hormone levels in the evaluation of CH, other tests have been developed. Patients with CH have a blunted nocturnal surge (84, 85) in TSH circadian secretion (86–88). However, this may be found in NTI (89), in post-operative patients (90, 91), during starvation (92), and in severe primary hypothyroidism (93). The TRH stimulation test is used in the diagnosis of CH (94, 95), but its value has been questioned (96, 97). In addition, in some early studies, bovine TSH stimulation was considered for the diagnosis of CH (98, 99), but its use was terminated due to commonly occurring allergic reactions (100). Recently, the use of recombinant human TSH (rhTSH) as a diagnostic tool in CH has been studied. Patients with newly diagnosed CH and no previous T_4 treatment exhibited a less pronounced increase in thyroid hormone levels after administration of 0.9 mg rhTSH than controls (Fig. 3). The usefulness of rhTSH for the diagnosis of CH remains to be proven.

Monitoring serum TSH level for judging an appropriate T_4 replacement level in CH is not useful, making T_4 replacement more arbitrary and increasing the risks of both under- and overreplacement. This could result in consequences similar to those described for both subclinical hypo- and hyperthyroidism (101–107).
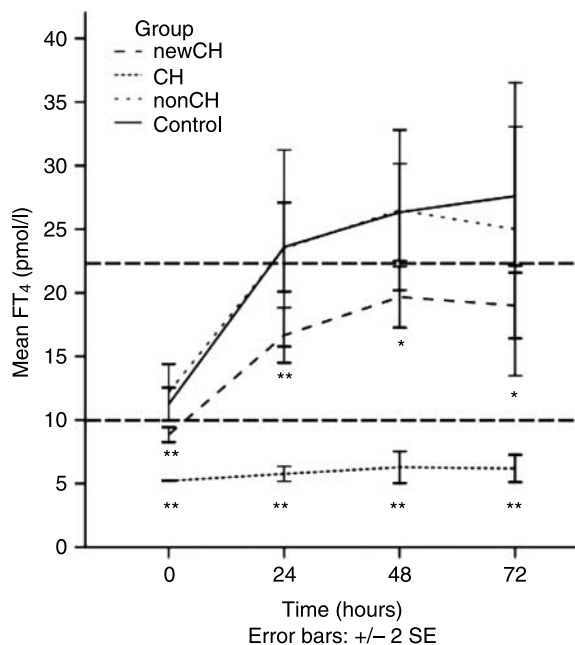

Figure 3 The figure shows the high-dose rhTSH response (0.9 mg i.m.) in six patients with previous treated central hypothyroidism (CH), six newly diagnosed CH (newCH), six patients with hypopituitarism without CH (nonCH), and six healthy controls in FT_4. *$P < 0.05$, **$P < 0.01$ newCH- or CH group versus controls. Values are mean. Error bars = s.e.m. The horizontal broken lines represent normal range. Published in *European Journal of Endocrinology* 2008 **159** 153–160. Reproduced with permission of the European Society of Endocrinology.

In children with documented mild CH and short stature, increasing serum FT_4 from the lower third to near the upper third of the normal reference interval during 6 months significantly increases growth velocity (108). Thus, minor thyroid dysfunction may have detrimental effects on patient outcome.

Recommendations for adequate T_4 replacement in adult patients with CH are based on a few reports (75, 77, 109–111) that direct dosing by weight, TSH and FT_4 levels. In 1999, Ferretti *et al.* (77) describe a mean dose of T_4 of 1.5 ± 0.3 µg/kg body weight that is modified according to age, targeting normal free T_3 without signs of overreplacement. Alexopoulou *et al.* (75) used a mean dose of 1.6 ± 0.5 µg/kg body weight/day resulting in suppressed TSH in 75% of patients, and Shimon *et al.* (110) observed a suppression of TSH below 0.1 mU/l predicting euthyroidism in 92% of cases, rather than 34% when TSH was > 1 mU/l. Finally, Carrozza *et al.* (109) recommended FT_4 to be in the mid-normal or in the upper part of the reference range, which was supported in another study (111). In this study, it was observed that CH patients on empirical T_4 doses (1 ± 0.05 µg/kg per day) had worse outcome in terms of BMI, total-, LDL-, and HDL-cholesterol than patients on a body weight-guided dosing (1.6 µg/kg per day) (111).

The above dose titration studies, therefore, suggest that FT_4 should be in the upper range of normal, TSH levels should be below 0.1 mIU/l using modern sensitive assays, and the dose of L-T_4 should be targeted at ∼1.6 µg/kg per day meaning 112 µg per day for a 70 kg person. To what extent these recommendations are being used is not known and, most importantly, the outcome of various dose exposure of L-T_4 in hypopituitary patients remains to be determined. This is an important piece of information in the light of the impact subclinical hypo- and hyperthyroidism have on outcome (101, 105, 107).

Central hypogonadism

There are some well-recognized interactions between the GH–IGF1 axis and sex steroids. These interactions seem to play a role in the treatment of hypopituitarism. Whether current therapy of sex steroid replacement therapy affects the clinical consequences of hypopituitarism and affects the phenotype of severe GHD is less well known, except for the impact of oral route of estrogen replacement on metabolism on hypopituitary women. Moreover, there are also indications that untreated hypogonadism in women may explain to some extent their increased cardiovascular mortality (5).

There is a first pass hepatic effect of oral estradiol that results in lowering of serum IGF1 in both healthy and GHD women (112). Serum IGF1 in the GH-deficient state is lowered further by oral estrogen, but unaffected by transdermal therapy (113). This observation may explain why some investigators have observed IGF1 levels to be lower in hypopituitary women than men, despite having a similar degree of impaired GH responses to insulin-induced hypoglycemia (114). Women with hypopituitarism may be more susceptible to the hepatic effects of oral estrogen administration because of the loss of feedback GH response. The level and degree of IGF1 suppression are greater in GH-deficient women than post-menopausal (GH-sufficient hypogonadal) women in response to oral estrogen treatment (115). Cook *et al.* observed that GH requirements in men were not different from those in women not taking estrogens, but that women taking oral estrogens required at least a twofold greater dosage of GH (116).

Wolthers *et al.* compared changes in IGF1, fat oxidation, and protein metabolism in hypopituitary women on GH treatment during oral and transdermal administration (113). GH treatment significantly increased IGF1 levels in a stepwise, dose-dependent manner; however, mean IGF1 levels were significantly lower during oral estrogen at each GH dose.

Gender-related changes in body composition in response to GH replacement treatment in hypopituitary adults have been consistently observed from investigators regardless of the body composition techniques used. Johannsson *et al.* (117) observed that the increases in fat-free mass and total body water were more marked in men than women, as was the reduction in total body fat. In a placebo-controlled 9-month trial, Burman *et al.* (118) observed that GH treatment induced a greater reduction in the proportion of total body fat and in abdominal fat mass in men than women, as estimated by dual-energy X-ray absorptiometry. A large prospective study reported a progressive separation in fat mass, body nitrogen, and body potassium (indirect measures of body protein and cell mass respectively) between men and women treated for up to 5 years with GH indicating a degree of GH resistance in women (119, 120).

In addition, oral estrogen induced protein synthesis and secretion from the liver with increased levels of systemic inflammatory markers such as CRP (112). This together with the observation that oral estrogen, and not transdermal, attenuates the protein anabolic and lipid utilization effects of GH (112) might explain in part the reduced efficacy of GH treatment in hypopituitary women. It may also explain some previous observations that women seem to have a larger cardiovascular burden in the untreated GHD state than men (121) with more adverse lipid profile and more marked abdominal obesity in particular (122).

The data obtained from the KIMS database seem to support this hypothesis (123). The majority of women of fertile years with hypopituitarism within KIMS takes oral estrogen replacement therapy. The waist-to-hip ratio was greater in women taking oral estrogens, again suggesting that oral estrogens reduce the action of GH on fat mass. In addition, women using the oral contraceptive had lower serum IGF1 levels and required twice the GH dose compared with patients receiving transdermal estradiol (123). Estrogen replacement by the oral route, therefore, aggravates existing metabolic and body compositional abnormalities of the GH-deficient state and results in a relative resistance to GH replacement therapy, at least in terms of the effects on serum IGF1.

Whether the regime of testosterone replacement affects the clinical feature of hypopituitarism in men is less studied. Untreated hypogonadism has, however, many similarities to adult GHD such as low BMD, LBM, and increased body fat mass (124). In hypophysectomized, castrated, male rats, testosterone administration does not increase serum levels of IGF1 or IGF1 gene expression in the liver (125). However, combined GH and testosterone treatment augments the serum IGF1 increase and the increase in extracellular water in response to GH alone, suggesting that testosterone enhances the effect of GH (126). This may to some degree explain some of the sexual dimorphism in response to GH.

Summary

Replacement therapy of MPHD in hypopituitarism is complex. Many of the hormones do not have reliable biomarkers to monitor adequacy other than the

hormone itself. Therefore, monitoring is based on dose traditions together with clinical evaluation of the individual patients and together with targeting the serum levels of the hormone being replaced within the normal range. Adequacy of replacement is, therefore, not easy to evaluate in an individual patient. GH replacement has on the other hand a unique position as a biomarker of its action; serum IGF1 allows for a more precise dose titration and treatment monitoring.

In this review, we have reviewed data suggesting that other replacement therapies and their regime clearly affect the clinical features associated with severe GHD in adults. Moreover, it is likely that this influences the outcome of adult patients with hypopituitarism. This seems to be most obvious for GC replacement therapy and the route of estrogen replacement in hypopituitary women. On the other hand, the few data available indicate that the severity of the clinical feature of IGHD and patients with MPHD do not differ suggesting the importance of untreated GHD only. There are also some important interactions between hormones that need to be considered when replacing hypopituitary patients. Some of those are well known such as the unmasking of adrenal insufficiency when commencing T_4 treatment, and others are less well known such as the unmasking of adrenal insufficiency and central hypothyroidism when initiating GH replacement therapy.

The post-marketing surveillance database of adult GH replacement therapy has become a useful tool to unravel more unsolved questions in the hypopituitary patients such as the adequacy of current GC, T_4, and sex steroid replacement therapy.

Declaration of interest

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