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Correction of cortisol overreplacement ameliorates morbidities in patients with hypopituitarism: a pilot study

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Abstract *Context* Hyporituitarism in adults is known to be associated with deleterious effects on body composition, lipid profile and quality of life (QoL). This was attributed to GH deficiency. The potential role of glucocorticoid overreplacement had never been investigated. *Objective* To investigate whether reduction in glucocorticoid replacement dose to more physiological one could ameliorate the "AO-GHD"-attributed symptomatology in patients with hypopituitarism. *Design* Eleven patients with panhypopituitarism taking 20–30 mg/day of hydrocortisone, but on no GH replacement were switched to 10–15 mg of hydrocortisone daily. Both basally and 6–12 months later, their body mass index, body composition by dual-energy X-ray absorptiometry, lipid profile, and the score of quality of life, QOL-AGHDA were measured. *Results* Within 6–12 months of lower hydrocortisone dose, subjects lost an average of 7.1 kg of total body fat and 4.1 kg of abdominal fat. No changes were seen in lean body mass, bone mineral content and HOMA-IR. Plasma total cholesterol and triglyceride concentrations decreased significantly (<0.05) and the QoL improved ($P = 0.018$). *Conclusions* Our pilot study suggests that decreasing the glucocorticoid replacement dose to ~ 15 mg/day is beneficial in terms of patients' body composition, lipid profile and quality of life.

Keywords Hypopituitarism · Cortisol replacement · Growth hormone deficiency

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Introduction

Pituitary diseases or their treatment are often followed by the development of hypopituitarism. Early studies have shown that patients with hypopituitarism, despite an apparently full replacement with glucocorticoids, thyroxine and sex steroids, still had a multitude of somatic and psychological symptoms and signs [1]. This was attributed to the unsubstituted GH deficiency (GHD) and the constellation of abnormal body composition (increased adiposity and decreased lean mass), hyperlipidemia and decreased quality of life was called an Adult-Onset GHD Syndrome (AO-GHD). Administration of GH to this population led to the amelioration of some of the AO-GHD components [2], strengthening the potential role of GHD in their pathogenesis.

Traditionally, glucocorticoid replacement consisted of daily administration of 25–35 mg of hydrocortisone or its equivalents [3, 4]. Indeed, many studies asserting the existence of AO-GHD used similar glucocorticoid replacement dosages [5–7]. However, it had been shown that the actual cortisol secretion rates in healthy humans are substantially lower than what was previously thought [8]. Thus, the replacement glucocorticoid regimens used in the past were, in fact, supraphysiological and led to a mild iatrogenic Cushing's syndrome, the clinical manifestations of which are very similar to the AO-GHD.

The purpose of this pilot study was to investigate whether reduction in glucocorticoid replacement to more physiological doses could ameliorate metabolic and psychological morbidities in patients with hypopituitarism.

Materials and methods

Subjects

This was a pilot study conducted in an open label, placebo-uncontrolled design, since the limited number of eligible participants in a single center did not allow for a double-blind, placebo-controlled design. Eleven patients with panhypopituitarism (3 men, 8 women, 50 ± 14 years old, mean ± SD) took part in the study. They were selected from the total population of hypopituitary subjects attending our endocrine clinic on the basis of receiving more than 20 mg/day of hydrocortisone. Six patients had a history of nonfunctioning pituitary tumors and 3 had a history of acromegaly. These patients underwent 1 or more pituitary surgeries and all had standard external radiotherapy 2–18 years prior to the study. One patient had a history of Sheehan's syndrome and one had pituitary cyst/abscess. All had ACTH deficiency as shown by morning plasma cortisol <5 μg/l and low ACTH concentrations and plasma cortisol response to insulin hypoglycemia or 250 μg iv Cortrosyn test to <20 μg/dl. All had TSH deficiency as evidenced by subnormal free T4 concentrations in the presence of low TSH. All had gonadotropin deficiency with low testosterone/low LH/FSH levels in men, amenorrhea with low gonadotropins in premenopausal women, and inappropriately low gonadotropins in postmenopausal women. One patient had central DI and required DDAVP. Baseline characteristics of the 11 patients are shown in Table 1.

GH deficiency was documented in all subjects by plasma IGF-1 concentrations that were below age/gender adjusted normal limits (34.0 ± 6.8 ng/ml, range non-detectable to 59 ng/ml). Three patients also underwent insulin hypoglycemia, and their maximal plasma GH concentrations were below 3 μg/l.

Patients with history of acromegaly had GH deficiency documented by low IGF1 for at least a year prior to the study.

Prior to the study, all patients received replacement therapy with L-thyroxine 0.075–0.15 mg/day, testosterone enanthate in men 250 mg IM every 2 weeks or estrogen/progesterone in premenopausal women (started after the documentation of low IGF-1 levels), and DDAVP as needed in 1 subject. Glucocorticoid replacement was given as hydrocortisone 15–20 mg in the morning, 5–10 mg in the afternoon. The total daily dose was 20–30 mg/day. They never received GH replacement therapy.

Protocol

The study was approved by the Institutional Review Board and conducted after written consent by the subjects was obtained.

At baseline, patients' weight and height were recorded, morning (fasting) level of serum lipids, plasma glucose and insulin were measured, and a 24 h urine collection for free cortisol (on the customary hydrocortisone replacement) was submitted.

Dual-energy X-ray absorptiometry was conducted to calculate total regional fat mass, lean body mass and bone mineral content. A Spanish version of QoL-AGHDA questionnaire [9] was utilized to assess the subjects' quality of life. Control values for QoL-AGHDA were obtained in 23 healthy Argentinian subjects (10 men, 13 women, 23–64 years of age). The mean ± 2 SD in this group was 5.5 ± 3.4.

Table 1 Baseline characteristics of the 11 patients

Patients	Sex	Age	Etiology of hypopituitarism	Number of deficits	Change in hydrocortisone dose (mg)
1	F	42	Sheehan syndrome	5	30–15
2	F	41	Surgery and radiotherapy for nonfunctioning adenoma	4	20–15
3	M	77	Surgery for nonfunctioning adenoma	4	30–10
4	M	45	Surgeries (3) and radiotherapy for nonfunctioning adenoma	4	30–15
5	F	41	Surgeries (2) and radiotherapy for acromegaly	4	30–10
6	F	67	Surgeries (3) and radiotherapy for nonfunctioning adenoma	4	30–15
7	F	65	Surgeries (2) for pituitary cyst and abscess	4	20–10
8	F	54	Surgeries (2) and radiotherapy for acromegaly	4	30–15
9	F	38	Surgeries (2) and radiotherapy for nonfunctioning adenoma	5	30–15
10	F	43	Surgeries (3) and radiotherapy for nonfunctioning adenoma	4	20–15
11	F	33	Surgeries (2) and radiotherapy for acromegaly	4	20–10

The subjects were then instructed to decrease their hydrocortisone replacement dose to 10–15 mg/day (5–10 mg in the morning and 5 mg in the afternoon).They were told that this adjustment was done based on contemporary data regarding cortisol requirements and asked to contact the investigators in case of worsened health. The possibility of potential beneficial effects upon body composition and QoL was not discussed. The subjects were seen in the clinic at 3-month intervals. Eight subjects were followed for a year, and three were followed for 6 months. At the end of the protocol the studies conducted at baseline were repeated (DEXA scan was not done in one subject).

Assays

Urinary free cortisol was measured by RIA (Immunotech, Beckman, USA). Insulin was measured by chemiluminescent assay (Immulite, DPC, Diagnostic Product Corporation, USA). Plasma glucose and serum lipids were measured according to standard methods (Biosystems, Spain). Serum low-density lipoprotein (LDL) cholesterol was calculated. HOMA-IR was calculated as [insulin mIU/ml $\times$ glucose (mg/dl)]/22.5 $\times$ 18.

Statistical analysis

Data were analyzed by paired Student's *t*-test. *P* values < 0.05 were regarded as statistically significant. Data are shown as mean $\pm$ standard error of the mean, M $\pm$ SE.

Results

The baseline and final (6 or 12 months) data are summarized in Table 2.

At baseline, 8 of 10 subjects had UFC above the upper limit of the normal range (90 μg/24 h). In 5 subjects UFC was elevated 1.5–2.5-fold above the upper normal limit (141–259 μg/24 h). The decrease in cortisol replacement dose led to the normalization of UFC in all subjects, with the values ranging between 20% and 75% of the upper limit of the normal range.

A decrease in the hydrocortisone replacement was not accompanied by any symptoms or signs of adrenocortical failure. No subject reported fatigue, weakness, tiredness, low energy, or orthostatic lightheadedness. The blood pressure remained normal in 9/11. Two persisted with mild hypertension (baseline systolic BP 120 $\pm$ 14.8 mmHg and diastolic BP 72.7 $\pm$ 6.5; final systolic BP 113.6 $\pm$ 11.2 and diastolic BP 70.9 $\pm$ 11.4).

Within 6–12 months of initiation of lower hydrocortisone replacement dose, 10/11 subjects lost 1–9 kg of weight (Fig. 1). This was accompanied by the loss of an average of 7.1 kg of total body fat and of 4.1 kg of abdominal fat (Fig. 1) in the 10 patients with complete sets of DEXA studies. The amount of lean body mass remained stable. No changes were observed in bone mineral content either in the hip or in the lumbar spine.

No changes were seen in plasma glucose and insulin concentrations and, consequently, in HOMA-IR.

Plasma total cholesterol and triglyceride concentrations decreased on the average by 27 mg/dl and 100 mg/dl

Table 2 The baseline and final (6 or 12 months) data of the studied patients

	Baseline	Final	*P*
UFC, μg/24 h (n = 10)	126 ± 19.8	46 ± 6.8	0.004
BMI, kg/m^2	31.5 ± 1.1	29.4 ± 1	<0.001
Weight, kg (n = 11)	82.7 ± 3.6	77.6 ± 4	<0.001
Total body fat, kg (n = 10)	36.8 ± 2.4	29.7 ± 2.4	<0.01
Abdominal fat, kg (n = 10)	20.7 ± 1.5	16.6 ± 1.5	<0.01
Bone mineral content (g/cm^2) (n = 10)	1.141 ± 0.027	1.143 ± 0.031	0.8
Hip (n = 10)	1.038 ± 0.119	1.035 ± 0.120	0.9
Spine (n = 10)	0.898 ± 0.151	1.014 ± 0.116	0.3
Lean body mass, kg (n = 10)	41.3 ± 1.5	42.4 ± 2	0.09
Fasting Insulin, mIU/ml (n = 11)	11.1 ± 3	11 ± 2.9	0.9
Fasting Glucose, mg/dl (n = 11)	76 ± 3.4	77.6 ± 3.5	0.7
HOMA index (n = 11)	2.2 ± 0.7	2.2 ± 0.7	1
Cholesterol mg/dl (n = 11)	237.1 ± 15.7	210.8 ± 15.8	0.002
LDL cholesterol mg/dl (n = 11)	150.9 ± 16.9	138 ± 15.2	0.1
HDL cholesterol mg/dl (n = 11)	52.6 ± 3.8	42.5 ± 4.7	0.08
Triglycerides mg/dl (n = 11)	215.4 ± 31.2	151.5 ± 35.8	0.009
AGHDA Score (n = 11)	10.2 ± 1.3	8 ± 1.2	0.018

All values M $\pm$ SE

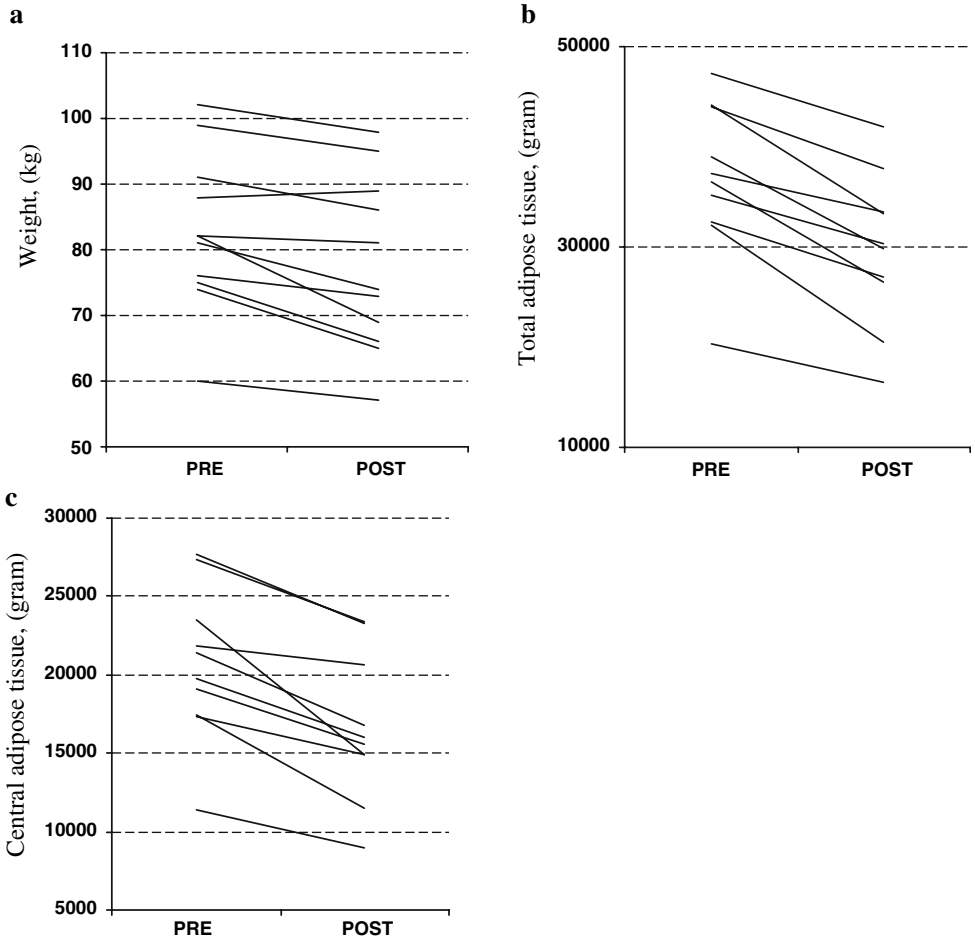

Fig. 1 Body weight, total and central adipose tissue before (pre) and after (post) decrease in hydrocortisone dose

respectively (Fig. 2) but there were no statistically significant changes in LDL cholesterol or HDL cholesterol. The Quality of Life (QoL) as measured by QoL-AGDHA improved significantly overall ($P = 0.018$) (Fig. 3). Most importantly, in the four out of six patients whose basal scores were above mean + 2 SD of the control population (the most severely affected ones) AGDHA scores decreased substantially and fell into the normal range in two of them.

Discussion

We show here that a decrease in the daily dose of hydrocortisone replacement in patients with hypopituitarism ameliorates their body composition, unfavorable lipid profile and improves their quality of life.

Patients with panhypopituitarism often exhibit unfavorable symptoms and signs despite being replaced by all other missing hormones. Since GH was the only unreplaced hormone in these patients, these abnormalities had been frequently ascribed to GH deficiency. They include abnormal body composition with increased adiposity, thin skin, osteopenia, hyperlipidemia, insulin resistance and diminished quality of life [10, 11]. Some manifestations, such as the amount of body fat [12], were clearly improved by GH administration. Despite decrease in body fat, GH-replaced hypopituitary patients exhibit only trivial and temporary improvements in plasma lipids [12] or not at all [13]. Similarly, GH treatment either does not change insulin sensitivity [14]or actually worsens it [15].Also, whereas the improvement in QoL was repeatedly asserted in many open label trials, no such finding was reported in large double-blind, placebo-controlled studies [13], even when only the patients with the most severe decrease in QoL were analyzed separately [16]. Recent studies re-examined the issue of osteopenia in hypopituitarism, and it was shown that bone density in panhypopituitary patients who were replaced with gonadal steroids but not with GH was in fact identical to the age and sex-controlled population [17]. The increase in the lean body mass after GH replacement is due mostly to water accumulation [18] and no improvement in muscle strength/endurance was seen in double-blind, placebo-controlled studies [13]. Thus, abnormal body composition, neuropsychiatric abnormalities and, perhaps, abnormal lipid profile are the most

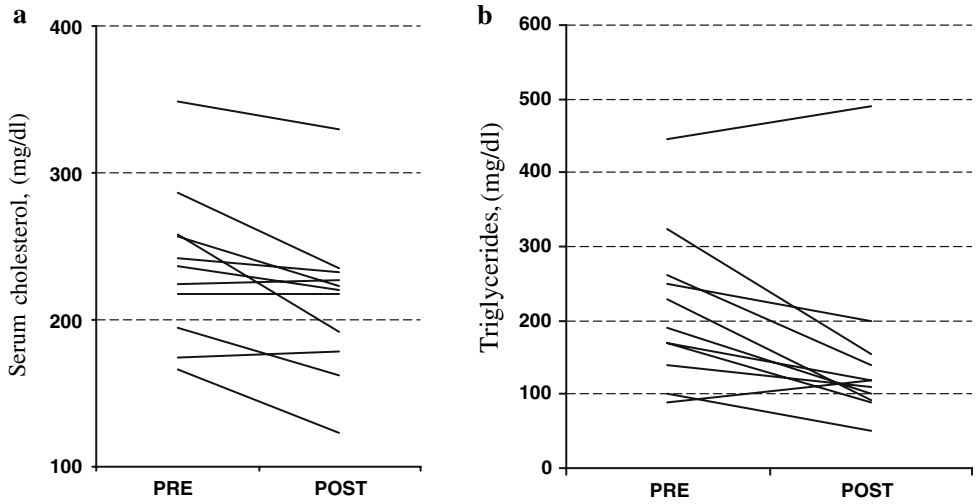

Fig. 2 Total serum cholesterol (mg/dl) and triglycerides (mg/dl) before (pre) and after (post) decrease in hydrocortisone dose

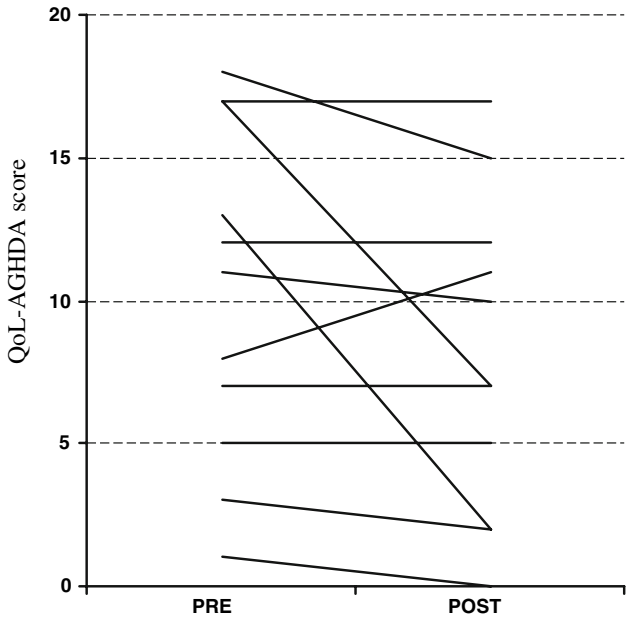

Fig. 3 QoL-AGHDA score before (pre) and after (post) decrease in hydrocortisone dose

reproducible components of panhypopituitarism that respond favorably to treatment.

Another potential explanation for the metabolic and neuropsychiatric morbidities in panhypopituitarism is the potentially supraphysiological dose of glucocorticoids administered to these patients. Indeed, increased body adiposity, muscle weakness, thinning of the skin, hyperlipidemia, decreased insulin sensitivity and neuropsychiatric abnormalities are well-known manifestations of Cushing's syndrome. Modern, more accurate, methodologies have found that the true cortisol secretion rates in humans (5–7 mg/m^2) are less than half of the older estimates [19]. Indeed, we have found that the patients taking traditionally accepted hydrocortisone doses had UFC, a crude measure of free circulating cortisol, substantially above the normal range. The relatively modest excess in glucocorticoid replacement may have biological consequences: subjective health status in patients with hypoadrenalism is inversely proportionate to their glucocorticoid replacement dosage [20], and the "metabolic" abnormalities (BMI, waist circumference and lipids) in panhypopituitary patients have been shown to be directly proportionate to glucocorticoid replacement dosage [6]. However, neither of these studies investigated the potential influence of lowered glucocorticoid replacement dose upon psychological well-being or metabolic syndrome. Dunne et al [21] did not detect changes in body weight, glucose and insulin in patients with hypopituitarism switched from 30 mg to 15 mg of hydrocortisone per day. However, their follow-up was limited to 3 months only, whereas resolution of clinical manifestations of hypercortisolism may take significantly more time [22]. Indeed, only a 3-week long decrease in the dose of hydrocortisone in hypopituitary patients increased plasma osteocalcin, a marker of bone accretion [23].

In our pilot study we evaluated the effects of lowering the dose of hydrocortisone replacement in patients with hypopituitarism. Deficiencies of TSH, ACTH and gonadotropins were documented using standard approaches. Hartman et al. [24] have previously shown that the presence of 3 other pituitary deficiencies, especially when combined with low IGF-1 levels predicts concomitant GH deficiency with 96% certainty. This was the basis of establishing GH deficiency in 8 of the 11 patients, while the remaining 3 had, in addition, demonstrated grossly impaired GH response to insulin hypoglycemia. Patients with a history of acromegaly had been biochemically GH deficient for a long time prior to the study as evidenced by subnormal IGF-1 concentrations. Thus, the subjects involved in this study were a representative sample of patients with hypopituitarism and severe GHD.

Lowering hydrocortisone replacement dose in this group brought about many beneficial effects traditionally ascribed to GH replacement in patients with AO-GHD. The most striking finding was the amelioration of body composition with a loss of substantial amount of total and, especially, abdominal fat. This was followed by a significant decrease in total cholesterol and triglycerides, i.e. strong predictors of subsequent cardiovascular risk [25]. We found an approximate 40% decrease in plasma triglycerides, similar to what is observed in successfully treated patients with Cushing's disease [26]. Decreasing hydrocortisone dosage in our study did not improve insulin sensitivity as measured by HOMA. On the other hand, no patient in this cohort exhibited worsening of insulin sensitivity. Perhaps, the use of euglycemic hyperinsulinemic clamp technique might be more informative in future studies of that nature. Successful treatment of endogenous Cushing's syndrome reliably improves insulin sensitivity [27]. In our study, the lean body mass did not change. Patients with Cushing's syndrome do not improve their muscle function before 6 months after hormonal cure [28]. We did not assess muscle strength and endurance in our patients and this might be an important parameter to investigate in the future studies. We did not see a change in bone density. Whether longer duration of lower hydrocortisone replacement results in bone accrual needs to be verified in additional studies.

In conclusion, our pilot study suggests that decreasing the glucocorticoid replacement dose to $\sim$15 mg/day is not only safe, but beneficial in terms of patients' body composition, lipid profile and quality of life. The main shortcoming of this trial is obvious: it was conducted in an open label, placebo-uncontrolled design. However, the number of eligible patients in a single medical center is limited and most of our hypopituitary subjects were already receiving lower glucocorticoid replacement doses. Thus, the encouraging data obtained in this study justify a multicenter trial to address the issue in a double-blind, placebo-controlled design. Since these benefits occurred in the absence of concomitant GH replacement therapy, one would be tempted to speculate that the metabolic and neuropsychiatric abnormalities of panhypituitarism may be due not only to GH deficiency as such, but rather to overzealous replacement of glucocorticoids.

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