CLINICAL STUDY

Glucocorticoid replacement therapy and vertebral fractures in hypopituitary adult males with GH deficiency

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Abstract

Objective: GH deficiency (GHD) and glucocorticoid excess are associated with increased risk of fragility fractures. We aimed to evaluate whether the prevalence of vertebral fractures may be influenced by glucocorticoid over-replacement in hypopituitary males with GHD.

Design: Cross-sectional study.

Methods: Fifty-one adult hypopituitary patients (all males; mean age 55 years, range: 23–81) with severe adult-onset GHD (replaced in 21 patients and untreated in 30 patients) and glucocorticoid deficiency on replacement treatment were studied for vertebral fractures using a radiological and morphometric approach.

Results: Vertebral fractures were observed in 31 patients (60.8%) in correlation with untreated GHD, urinary cortisol values, and cortisone doses. Patients were stratified according to treatment of GHD, and current and cumulative cortisone doses. In untreated GHD, vertebral fractures occurred more frequently in patients who had received higher (greater than median) cumulative and current doses of cortisone compared with patients who had received lower (less than median) drug doses (95.2 vs 50.0%, $P=0.009$ and 90.5 vs 55.6%, $P=0.04$ respectively). In untreated GHD, fractured patients had significantly higher urinary cortisol values compared with patients without vertebral fractures (84 $\mu\text{g}/24\text{ h}$, range: 24–135 vs 49 $\mu\text{g}/24\text{ h}$, range: 30–96; $P=0.04$). In treated GHD patients, by contrast, the prevalence of vertebral fractures was not influenced by cumulative and current cortisone doses and urinary cortisol values.

Conclusions: Glucocorticoid over-replacement may increase the prevalence of vertebral fractures in patients with untreated GHD. However, treatment of GHD seems to protect the skeleton from the deleterious effects of glucocorticoid overtreatment in hypopituitary patients.

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Introduction

Glucocorticoids are known to have potentially negative effects on bone metabolism, and glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis (1). The central mechanism of glucocorticoid action on the skeleton is the inhibition of osteoblast differentiation and function (2). It is clinically relevant that bone metabolism may be altered in terms of decreased bone turnover even in patients receiving glucocorticoids at standard replacement doses for adrenal deficiency, specifically when high doses are used (3). However, the effects of glucocorticoid over-replacement therapy on bone mineral density (BMD) seemed to be variable, and only data on clinical fractures are available (4–7).

GH and insulin-like growth factor 1 (IGF1) are anabolic hormones for bone with stimulating effects

on bone modeling and remodeling, and with positive effects on longitudinal growth (8). Their main effect is stimulation of osteoblastogenesis and differentiated function of mature osteoblasts (9, 10). GH deficiency (GHD) in adult patients causes marked decrease of bone turnover with reduction of bone mass and increased risk of fragility fractures (11).

Most adult GHD patients have other pituitary deficiencies, such as gonadotropin, corticotropin, and thyrotropin deficiencies, the effects of which on bone metabolism and fractures of hypopituitary patients have not been completely clarified (8, 12–16). Moreover, it is unknown whether replacement therapies of other pituitary deficiencies may influence the skeletal abnormalities occurring in GHD, although an impact on quality of life and metabolic disorders was demonstrated (17–20). It is worth noting that hormones used to replace hypopituitarism (i.e. thyroxine (T_4),

sex hormones, and glucocorticoids) may have direct effects on bone which may be clinically relevant in patients receiving relatively high doses of these drugs. Indeed, an overtreatment of hypopituitarism may occur in some patients, since replacement therapies do not completely mirror the endogenous hormonal production and their monitoring is also made difficult by the lack of good biomarkers of their action (20).

In a cross-sectional study, we have previously shown that untreated GHD was associated with high risk of vertebral fractures partially reverted by GH replacement (15). Since GHD causes skeletal abnormalities similar to glucocorticoid excess and glucocorticoid over-replacement was shown to produce negative skeletal effects more frequently in males than in females (4), we aimed at investigating whether glucocorticoid replacement therapy may influence the prevalence of fragility vertebral fractures in the subgroup of male patients with GHD, in relation to age, BMD, recombinant GH (rGH) treatment, and other pituitary deficiencies.

Materials and methods

We evaluated with a *post-hoc* analysis 51 adult hypopituitary patients (all males, mean age 55 years, range: 23–81) as a subgroup of patients with severe adult-onset GHD enrolled in a previously published study (15) (Table 1). Forty-seven patients became GH deficient after surgical intervention for non-functioning pituitary adenomas, whereas GHD was secondary to empty sella in four patients. At the beginning of the study, 21 patients were on replacement therapy with rGH, whereas 30 patients had never received rGH (Table 1). In the former, the median duration of the treatment was 3.0 years (range: 1–19).

All GHD males had glucocorticoid deficiency, and all of them were treated with hydrocortisone (25 cases)

or cortisone acetate (26 cases) at median daily doses of 30 and 35 mg respectively. In each patient, the glucocorticoid dose was defined on the basis of clinical judgment (i.e. control of signs and symptoms of adrenal insufficiency) and urinary cortisol values. For uniformity of data, we expressed the glucocorticoid dose in cortisone acetate equivalent, calculated by multiplying hydrocortisone doses by 1.25. Moreover, we reported the cumulative cortisone dose calculated on the basis of duration of treatment and mean dose of cortisone or equivalent. Secondary hypothyroidism was demonstrated in 39 patients (76.4%), hypogonadism in 29 patients (56.9%), and diabetes insipidus in 6 patients (11.7%). All patients were treated adequately for these pituitary deficiencies before bone analysis. Hypogonadic patients were treated with testosterone enanthate and/or propionate at doses of 200–250 mg every 2–5 weeks. The testosterone dose was adjusted on the basis of total testosterone values obtained in the last week before drug administration. The median duration of testosterone treatment was 9.5 years (range: 2–23). The patients gave informed consent to the study that was approved by local ethical committee.

BMD of the lumbar spine was measured by dual-energy X-ray absorptiometry (QDR-1000 Hologic Inc., Waltham, MA, USA), as specified previously (15). Osteopenia and osteoporosis were defined based on *T*-score -1.0 S.D. and -2.5 S.D. respectively, below the mean bone mass value of reference population (21).

A quantitative morphometric assessment of vertebral fracture in T₄–L₄ was performed using a dedicated morphometry software (Spine-X Analyzer ICAM Diagnostics, Milan, Italy), as described previously (15). The fractures were defined mild, moderate, and severe based on a height ratio decrease of 20–25%, 25–35%, and more than 35% respectively.

Blood samples were collected after an overnight fast. Serum was promptly separated and stored at -20°C until assay. Urinary cortisol was measured using RIA (Spectria, Orion Diagnostica, Finland); in our laboratory, reference range was 36–137 $\mu\text{g}/24\text{ h}$. IGF1 was measured by Immulite 2000 (DPC, Los Angeles, CA, USA). Serum total testosterone was measured by RIA; normal range for men aged 20–49 years was 2.6–15.9 ng/ml, and for men aged >50 years, it was 1.8–7.5 ng/ml. Serum free-T₄ (FT₄) concentrations were measured by double-antibody RIA (Technogenetics, Milan, Italy); normal range was 7.0–18.0 pg/ml.

Statistical analysis

All data were expressed as median and range. Unpaired data were compared using the Mann–Whitney test. Multiple comparisons were performed using Kruskal–Wallis' test with *post-hoc* Bonferroni's correction. Correlation between variables was sought using Pearson's correlation. A logistic regression model was used in the statistical analysis of risk factors for the

Table 1 Clinical and biochemical features of 51 males with severe GH deficiency (GHD) and glucocorticoid deficiency enrolled in the study.

Patients	51
Age (years)	55 (23–81)
Duration of GHD (years)	9 (2–23)
rGH treatment (cases)	21 (41.2%)
Serum IGF1 (ng/ml)	98 (29–289)
Hypothyroidism (cases)	39 (76.4%)
Hypogonadism (cases)	29 (56.9%)
Diabetes insipidus (cases)	6 (11.7%)
Urinary cortisol values ($\mu\text{g}/24\text{ h}$)	83.0 (24.0–135.0)
Current cortisone dose (mg/day)	35.0 (12.5–75.0)
Cumulative cortisone dose (g)	91.2 (13.7–321.9)
Serum FT ₄ values (pg/ml)	11.2 (8.9–17.6)
Serum testosterone values (ng/ml)	4.1 (1.9–14.3)
Lumbar BMD <i>T</i> -score	-1.5 (-2.7 to $+1.9$)
Vertebral fractures	31 (60.8%)

rGH, recombinant GH; IGF1, insulin-like growth factor 1; FT₄, free-thyroxine; BMD, bone mineral density.

occurrence of vertebral fractures. Frequencies were compared using χ^2 test with Fisher's correction, when appropriate. Statistical significance was assumed when P values were ≤ 0.05 .

Results

In our patients, median BMD T -score was -1.5 s.d. (range from -2.7 to $+1.9$; Table 1). Fourteen patients had normal BMD, 31 (60.8%) had osteopenia, whereas osteoporosis was demonstrated in only six patients (11.8%). Vertebral fractures were observed in 31 patients (60.8%) (Table 1). Fractures were single in nine patients, whereas the remaining 22 patients showed two or more fractures. Fractures were mild in 20 patients, moderate in 9, and severe in 2 patients. Sixteen patients (51.6% of fractured patients) had one or more signs or symptoms consistent with vertebral fractures.

Univariate logistic analysis demonstrated that vertebral fractures were significantly correlated with untreated GHD, high urinary cortisol values, high current and cumulative doses of cortisone, whereas no significant correlations were demonstrated with age, BMD, serum FT_4 , total testosterone, duration of hypogonadism, and age of onset of hypogonadism (Table 2). Urinary cortisol values were significantly correlated with current ($r: 0.31$, $P=0.03$) and cumulative ($r: 0.28$, $P=0.04$) doses of cortisone.

Patients were stratified according to treatment of GHD, and current and cumulative cortisone doses defined as high or low when the values were higher or lower than the median value in the whole population

Table 2 Results of univariate logistic regression analysis with vertebral fractures as dependent variable, and age, bone mineral density (BMD), untreated GH deficiency (GHD), high current cortisone dose, high cumulative cortisone dose, high urinary cortisol values, serum free-thyroxine (FT_4) values, serum total testosterone values, age of onset and duration of hypogonadism as covariates. High cortisone doses and urinary cortisol values were defined as values higher than the medians in the whole population.

Covariates	Risk of vertebral fractures	
	Odds ratio (CI 95%)	P values
Age	1.01 (0.97–1.05)	0.53
BMD T -score	1.03 (0.64–1.60)	0.90
Untreated GHD	8.00 (2.23–28.60)	0.001
High current dose of cortisone (> 35 mg/day)	4.70 (1.37–16.50)	0.01
High cumulative dose of cortisone (> 91 g)	8.40 (2.21–31.70)	0.002
High urinary cortisol values (> 83 μ g/24 h)	5.30 (1.05–18.10)	0.04
Serum FT_4 values	0.91 (0.73–1.14)	0.44
Serum total testosterone values	0.95 (0.81–1.12)	0.54
Duration of hypogonadism	1.24 (0.88–1.50)	0.22
Age of onset of hypogonadism	0.98 (0.92–1.03)	0.38

(Table 1) respectively. In untreated GHD, vertebral fractures occurred more frequently in patients who had received higher cumulative (Fig. 1a) and current (Fig. 1b) cortisone doses compared with patients who had received lower doses of the drug. In untreated GHD, fractured patients showed significantly higher urinary cortisol values compared with patients without vertebral fractures (84 μ g/24 h, range: 24–135 vs 49 μ g/24 h, range: 30–96; $P=0.04$). In treated GHD patients, by contrast, the prevalence of vertebral fractures was not influenced by cumulative and current cortisone doses (Fig. 1a and b). Moreover, fractured and non-fractured patients with treated GHD showed no significant difference in urinary cortisol values (71 μ g/24 h, range: 49–90 vs 75 μ g/24 h, range: 38–133; $P=0.67$).

Multivariate regression analysis demonstrated that the significant correlations between high urinary

Figure 1 Prevalence of vertebral fractures in patients with GH deficiency (GHD) and glucocorticoid deficiency under glucocorticoid replacement stratified for treatment of GHD, and cumulative (a) and current (b) cortisone doses. Cumulative and current cortisone doses were defined as high or low when the values were higher or lower than the median value in the whole population respectively.

* $P < 0.05$ high versus low cortisone doses; ** $P < 0.05$ treated versus untreated GHD.

cortisol values, high current and cumulative doses of cortisone and vertebral fractures were lost, and untreated GHD remained the most important factor predisposing to fractures in hypopituitary patients (Table 3).

Discussion

This *post hoc* analysis showed that glucocorticoid replacement therapy at high doses may favor the occurrence of vertebral fractures in patients with untreated GHD. This finding was not observed in patients with treated GHD, suggesting that rGH replacement therapy may protect bone from the negative effects of glucocorticoid over-replacement.

Some patients taking glucocorticoid replacement therapy may be over-treated (20, 22). Over the last 10 years, it has been demonstrated that daily glucocorticoid doses needed to replace adrenal insufficiency are much lower than previously thought (23, 24). The previously recommended doses of 30 mg/day of hydrocortisone or 37.5 mg/day of cortisone acetate are probably too high particularly for most patients with secondary adrenal insufficiency, in whom metabolic abnormalities were demonstrated with these glucocorticoid doses (17–19). About one half of our hypopituitary patients received high replacement doses of glucocorticoids (i.e. median dose of cortisone acetate was 35 mg) which produced high-normal urinary cortisol values in most cases. This finding confirms that urinary cortisol may be useful to monitor replacement therapy of glucocorticoid deficiency, although in most cases a correct determination of the dose required for adequate glucocorticoid replacement is often empirical and based on clinical judgment (20, 25).

Glucocorticoid excess has deleterious effects on bone impairing replication, differentiation and function of osteoblasts, and inducing apoptosis of mature osteoblasts and osteocytes (2). These effects cause suppression of bone formation that is the central feature in the pathogenesis of glucocorticoid-induced osteoporosis (1). The inhibition of bone formation with osteoporosis was

demonstrated even in patients receiving low doses of glucocorticoids as those used to replace adrenal insufficiency (3). The skeletal abnormalities were shown to be closely associated with glucocorticoid doses, suggesting that bone loss is an expression of glucocorticoid over-replacement. Previous studies investigated the effects of glucocorticoid replacement therapy on bone turnover and BMD (4–6). A few studies evaluated clinical fractures, suggesting that hydrocortisone use was not associated with an increase of fracture risk in the general population (7), as well as that GHD patients on glucocorticoid replacement did not have an increased risk of fracture (16). As a matter of fact, our study for the first time evaluated the effects of glucocorticoid replacement therapy on radiological vertebral fractures in patients with GHD. Vertebral fractures are often asymptomatic and largely under-diagnosed based upon clinical records. In fact, in the last decade the radiological and morphometric assessment of vertebral deformities has emerged as the method of choice for evaluating the true prevalence of fractures in population studies (26).

In a cross-sectional study, we already demonstrated that untreated GHD is associated with high risk of radiological vertebral fractures (15). In a following *post-hoc* analysis, we showed that this association was not influenced by gonadal status of patients (27). In the present study, the *post-hoc* analysis allowed to demonstrate that glucocorticoid over-replacement may further increase the prevalence of vertebral fractures in hypopituitary patients with untreated GHD. This observation is consistent with the notion that GHD and glucocorticoid excess induce similar skeletal abnormalities characterized by an inhibition of osteoblast maturation, differentiation and function (1, 8). Moreover, untreated GHD may be associated with an increased tissue exposure to cortisol due to increased activity of 11 β -hydroxysteroid dehydrogenase type 1 (28). The association between glucocorticoid over-replacement and vertebral fractures in untreated GHD patients was independent of BMD, in agreement with previous observations reporting a poor predictive value of BMD for risk of fractures in various forms of secondary osteoporosis (29–32).

In patients with treated GHD, glucocorticoid over-replacement did not influence the occurrence of vertebral fractures, the prevalence of which was lower than that found in untreated GHD. This finding would suggest that anabolic effects of GH may protect the skeleton from the deleterious effects of subtle glucocorticoid excess. Indeed, short-term rGH treatment was shown to be effective in reverting the negative effects of glucocorticoids on bone turnover (33, 34). Moreover, rGH treatment may decrease the tissue exposure to glucocorticoids inhibiting the transformation of cortisone into cortisol (35, 36).

A limitation of our study was related to the retrospective *post-hoc* design which did not allow to clarify the

Table 3 Results of multivariate logistic regression analysis using vertebral fractures as dependent variable, and untreated GH deficiency (GHD), high current cortisone dose, high cumulative cortisone dose and high urinary cortisol values as covariates. High cortisone doses and urinary cortisol values were defined as values higher than the medians in the whole population.

Covariates	Risk of vertebral fractures	
	Odds ratio (CI 95%)	P values
Untreated GHD	4.71 (1.20–19.01)	0.03
High current dose of cortisone (> 35 mg/day)	1.01 (0.18–5.80)	0.99
High cumulative dose of cortisone (> 91 g)	3.83 (0.65–22.4)	0.14
High urinary cortisol values (> 83 μ g/24 h)	1.96 (0.41–9.35)	0.39

timing of the effects of glucocorticoid replacement therapy on risk of fractures in GHD patients. Clinical studies performed in patients taking higher doses of glucocorticoids demonstrated that vertebral fractures occur early after glucocorticoid exposure (37). In our study, the close correlation between cumulative cortisone doses and vertebral fractures would suggest that risk of fractures may also be influenced by the duration of glucocorticoid replacement treatment. Another limitation of our study is the lack of biochemical data which may be important to support the hypothesis that GHD and glucocorticoid treatment may have additional negative effects on bone turnover in patients with hypopituitarism. Besides these drawbacks, our data may have interesting clinical implications. In fact, the significant correlation between glucocorticoid doses and urinary cortisol values may be suggestive for using this latter biochemical marker as a tool to monitor bone safety of glucocorticoid replacement therapy, despite the possible inter-individual variability (22, 25). The increased prevalence of vertebral fractures in patients with untreated GHD and high-normal urinary cortisol values would encourage to maintain these hormonal values in the middle or in the low-normal range to avoid glucocorticoid overtreatment even in the absence of clinically recognizable symptoms and signs of hypercortisolism. Finally, based on the lack of correlation between BMD and fractures, it appears reasonable to suggest to monitor glucocorticoid treatment by the morphometric approach in order to identify early and easily patients with unsuspected vertebral fractures. Epidemiological studies have pointed out the necessity to identify early vertebral fractures, since the presence of a single fracture even if mild and without clinical symptoms predisposes to have other more severe fractures with consequent greater clinical impact (38–40).

In conclusion, our data suggest that in untreated GHD even subtle glucocorticoid overtreatment should be avoided due to synergistic deleterious skeletal effects. Conversely, GH replacement treatment appears to minimize negative effects of glucocorticoid excess on bone health.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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