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RESEARCH LETTER

Bone safety of dual-release hydrocortisone in patients with hypopituitarism

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Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis in both sexes [1, 2]. The glucocorticoid-induced decline in bone formation is associated with an increased fracture risk related both to the dose and duration of glucocorticoid treatment [3, 4].

Glucocorticoid replacement therapy is mandatory in all patients affected by adrenal insufficiency, defined as a primary or secondary impairment of adrenal gland function. Over the last few years it has become evident that patients with adrenal insufficiency, even if treated, show reduced life expectancy, poor quality of life (QoL), and increased comorbidities [5]. In fact, the absence of reliable biochemical and/or clinical markers of adequate substitution may lead clinicians to overtreat these patients in order to avoid complications such as life-threatening adrenal crises. Moreover, it is well known that the conventional glucocorticoid replacement regimens do not completely mirror the normal hormonal secretion, inducing serum cortisol peaks far beyond physiological levels. This consequent mild to moderate glucocorticoid excess may have detrimental effects at several target organ levels [6].

Negative effects on bone metabolism, including high risk of vertebral fractures, during conventional glucocorticoid replacement therapies in both primary and secondary adrenal insufficiency have been reported [7, 8], and even though data regarding central corticotropin (ACTH) deficiency are scanty so far, we have observed that a high comulative glucocorticoid replacement dose is associated with higher prevalence of vertebral morphometric fractures [9].

In this clinical setting, new drug formulations has become recently available in many countries and dual-release hydrocortisone tablets (Plenadren®, Shire), reproducing the endogenous cortisol rhythm [10], have a more favorable clinical profile [11] as far as dyslipidemia, hyperglycemia and body composition are concerned [12]. However, most of the published studies on Plenadren® were focused on primary adrenal insufficiency, whereas data concerning secondary adrenal insufficiency are scanty [1, 13].

This is the first study specifically evaluating the effects of dual-release hydrocortisone on bone in patients with secondary adrenal insufficiency.

In total 14 patients (10 females, 4 males: median age 55 years, range 31–77) were enrolled retrospectively in this longitudinal study. The inclusion criteria were: (1) age older than 18 years; (2) central hypoadrenalism treated by conventional glucocorticoid regimens for at least 12 months before the shift to Plenadren®; (3) at least 24 months of Plenadren® treatment; (4) availability of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) data before and during Plenadren®. The exclusion criteria were: (1) treatment with anti-osteoporotic drugs except for calcium and vitamin D (Table 1); (2) treatment with drugs causing osteoporosis except for those used to replace hypopituitarism.

In total 12 patients had post-surgical hypopituitarism with (n. 2) or without radiotherapy. Two patients had primary empty sella syndrome and one patient had pre-existing Cushing disease. Glucocorticoid deficiency was defined by basal serum cortisol values lower than 3 μg/dL or by low-dose (1 μg ev) ACTH-stimulated cortisol below 18 μg/dL. The main features of patients with central hypoadrenalism at baseline are reported in Table 1. All patients had growth hormone deficiency (GHD), as defined by GH peak lower than 9 μg/L for patients with a body mass index (BMI) less

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Table 1 Anthropometric and baseline clinical and biochemical features of 14 patients with secondary adrenal insufficiency enrolled in the study

Number	14
Sex (F/M)	10/4
Age (years)	55 (31–77)
BMI (Kg/m^2)	28.3 (20.0–32.4)
Treated hypothyroidism	10 (71.4%)
Treated GH deficiency	2 (14.3%)
FPG (mg/dl)	90 (57–151)
HbA1c (%)	5.9 (5.1–6.5)
Total cholesterol (mg/dL)	202 (166–253)
LDL-cholesterol (mg/dL)	102 (41–173)
HDL-cholesterol (mg/dL)	65 (36–135)
Triglycerides (mg/dL)	152 (105–214)
25OH vitamin-D (ng/mL)	42.5 (4–46)
Vitamin D treatment	13 (92.9%)
Lumbar spine BMD T-score (SD)	−1.30 (from −3.3 to +3.2)
Femoral neck BMD T-score (SD)	−1.35 (from −2.8 to +2.4)
Total hip BMD T-score (SD)	−0.30 (from −3.6 to +1.9)

Data are presented as median (range) and percentages at baseline

F Females, *M* Males, *BMI* Body Mass Index, *FPG* Fasting Plasma Glucose, *GH* Growth Hormone, *HbA1c* glycated hemoglobin, *LDL* Low-Density Lipoprotein, *HDL* High-Density Lipoprotein, *25OH vitamin-D* 25hydroxyvitamin-D, *BMD* Bone Mineral Density, *SD* Standard Deviation

than 29 kg/m^2 and lower than 4.0 µg/L for those with a BMI greater than 30 kg/m^2 during stimulating test with arginine (30 g) plus GH-releasing hormone (1 µg/kg). Two of GHD patients were under treatment with recombinant GH (rGH) during the study period. In total 10 patients had central hypothyroidism, as defined by serum free-thyroxine (fT4) values below the reference laboratorary range, and all of them were treated with L-thyroxine.

Before the study entry, all patients had been treated with either cortisone acetate (4 cases) or hydrocortisone (10 cases) at the median doses of 28 mg and 20 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 24-h urinary cortisol. Patients were shifted to Plenadren® due to persistent asthenia and/or low adherence to multiple corticosteroid daily doses. The dose of dual-release hydrocortisone was the same as that of hydrocortisone or equivalent received during the conventional therapeutic regimens; more in detail 15 mg, 20 mg, 25 mg, and 30 mg were given in three, five, two, and four patients, respectively and the dose was administered once daily in the morning. All patients were instructed to add a rescue dose of hydrocortisone during an intercurrent illness or stress (5 or 10 mg dose according to severity of stress and symptoms).

The main end-point of this 24-month study was the evaluation of dual-release hydrocortisone effects on BMD at lumbar spine, femoral neck and total hip. As secondary end-points, we evaluated the effects of dual-release hydrocortisone on fasting plasma glucose (FPG), serum glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, triglycerides (TG).

The protocol was approved by local Ethical Committee. According to the Ethical Committee, a written consent was not needed due to the observational and retrospective nature of the study.

BMD was measured at baseline and after 24 months of dual-release hydrocortisone treatment by DXA at lumbar spine, femoral neck, and total hip (Hologic Inc., QDR-4500W Waltham, MA). In aged 50 years or older patients (9 cases) BMD was expressed as T-score, comparing the results with those obtained in a sex-matched Caucasian population at peak of bone mass. A T-score less than or equal to −2.5 SD at the hip or spine was defined as osteoporosis, whereas osteopenia was defined as a T-score between −1 and −2.5 SD. In younger than 50 years patients (5 cases), the results were expressed as Z-score, comparing the results with those obtained in an age and sex-matched Caucasian population. A Z-score of −2.0 SD or lower was used to define a BMD "below the expected range for age" [14]. The coefficients of variation in the DXA measurements for BMD, bone mineral content (BMC) and area were 0.614%, 2.981% and 2.89%, respectively.

Serum 25hydroxyvitamin-D (25OH vitamin-D), FPG, serum HbA1c, LDL-cholesterol, HDL-cholesterol and TG were measured at baseline and after 3, 12, and 24 months of dual-release hydrocortisone treatment, using standard commercial assays.

Data are presented as median and range, unless otherwise stated. Wilcoxon sign rank and Friedman tests were used to evaluate changes in BMD and biochemical parameters during 24-month treatment with dual-release hydrocortisone. Mann Whitney test was performed to compare quantitative data between males and females. McNemar test was used to evaluate changes in prevalence of pathological BMD after 24 months of treatment with dual-release hydrocortisone. Spearman rank order correlation was performed to identify the determinants of BMD changes. A p-value < 0.05 was considered statistically significant.

Our 14 patients had a median duration of treated hypopituitarism of 10 years (range 3–28) and the median daily dose of dual-release hydrocortisone was 20 mg (range 15–30 mg/day).

At baseline, 10 out of 14 patients (71.4%) had pathological BMD values at either skeletal site. Specifically, in 50 years or older patients, osteopenia and osteoporosis were found in 6 (66.6%) and three (33.3%) patients. In younger

patients (5 cases), the prevalence of BMD "below the expected range for age" at either skeletal site was 20%.

After 24 months of treatment with dual-release hydrocortisone, a significant increase in BMD values at lumbar spine and femoral neck was observed, without statistically significant change in total hip BMD (Fig. 1). Two patients with baseline pathological BMD (one with low BMD for age and one with osteopenia) normalized BMD values after 24 months of treatment (McNemar test, $p = 0.50$). The median changes in BMD were +10.0, +11.5 and +3.1% at lumbar spine, femoral neck and total hip, respectively. No significant sex differences in BMD changes at lumbar spine ($p = 0.63$), femoral neck ($p = 0.94$) and total hip ($p = 0.38$) as well as no significant correlations between age of patients and BMD changes at either skeletal site were observed (data not shown). The large majority of patients was on vitamin D treatment and serum 25OH vitamin-D did not change during the treatment (from 42.5 ng/mL, range: 4–46 to 42.0 ng/mL, range: 27.7–44, $p = $ NS).

During the 24-month treatment, a significant decrease in FPG was observed (from 90 mg/dL, range: 57–151 to 79 mg/dL, range: 59–135; $p = 0.02$), without significant changes in serum HbA1c ($p = 0.28$), total cholesterol ($p = 0.51$), LDL-cholesterol ($p = 0.26$), HDL-cholesterol ($p = 0.76$) and TG ($p = 0.22$).

Aim of our study was to investigate for the first time the impact of dual-release hydrocortisone on bone in hypopituitary patients with secondary adrenal insufficiency.

For many years long-term replacement therapy in these patients was thought to have no negative impact due to its substitutive nature, but in the last few years many data on the deleterious effects of conventional treatment with glucocorticoid drugs (hydrocortisone, cortisone acetate, and prednisone) on both skeletal health and cardiovascular risk markers have been published [8, 15].

At the enrollment, the majority of our patients showed BMD in the osteoporotic or osteopenic range, consistently with previous findings suggesting that even glucocorticoid replacement treatment may compromise skeletal health. Plenadren® better mimics the normal ultradian rhythm of cortisol secretion and reduces cortisol peaks and exposure in the late part of the day compared to conventional treatment. Theoretically, this more physiological treatment should therefore minimize the side effects of long-term replacement therapy. Our data show a significant increase in BMD values both at hip and spine after 24 months of replacement therapy with dual-release hydrocortisone and interestingly, the mean change was comparable to that already observed in kidney transplant patients after withdrawal of glucocorticoid therapy [16, 17]. We can hypothesize that Plenadren®, better reproducing the physiological cortisol secretion, may reverse the suppression of bone turnover induced by the conventional therapy, with an increased

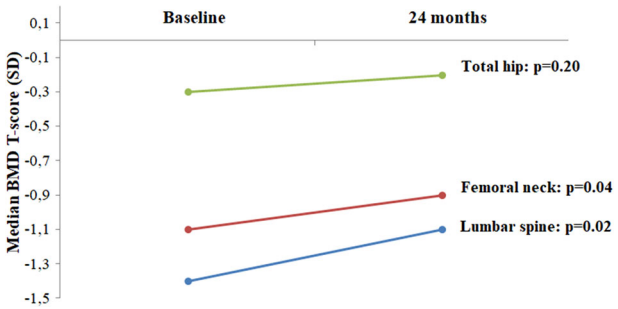

Fig. 1 Outcome of bone mineral density (BMD) T-score at lumbar spine, femoral neck and total hip during 24-month treatment with dual-release hydrocortisone. Data are presented as median and the comparisons are performed by non-parametric Wilcoxon's test

bone formation. This may be particularly true in a population with mainly untreated GHD [18, 19], in which we have already shown that skeletal health may be more profoundly affected particularly by fracturative events [20, 21].

Previous studies reported an improvement in several cardiometabolic parameters including waist circumference, BMI, HbA1c, total, and LDL-colesterol in patients with primary [12, 22] and secondary [22] adrenal insufficiency treated with dual-release hydrocortisone. Consistently, we observed a significant reduction in blood glucose (altough not in HbA1c and other metabolic parameters) in our patients.

Main limitations of our study are the small number of patients enrolled, which is consistent with the rarity of the disease, the retrospective nature of the study and the uncontrolled selection of patients who were shifted from conventional treatments to dual-release hydrocortisone. In particular, the low number of patients treated with rhGH did not allow to investigate the relative impact of treated and untreated GH deficiency on skeletal end-points during exposure to variable doses of corticosteroids [9]. Patients' selection (i.e., the switch to Plenadren® was based on clinical judgment) can be a bias for the interpretation of the results. However, the study design reflected the clinical practice and the results of this study may provide useful information concerning the skeletal impact of Plenadren® in the real-life. Moreover, since the patients were not blinded to the treatment, we did not perform analyses on subjective parameters, such as the items of QoL questionnaires. Nevertheless, these data represent the first attempt ever to evaluate the impact of new regimens of glucocorticoid therapy on bone. Finally, no data on bone biochemical markers and on fractures were available with concomitant lack of information on both the possible mechanism of the bone benefits of Plenadren® and on its clinical impact.

In conclusion, our data support the bone safety of Plenadren® in hypopituitarism, with a potential advantage on BMD of this more physiological substitution. If this effect

will be confirmed in larger controlled studies collecting also fracture data it may represent an added value of this treatment and osteoporosis/osteopenia could be included among the criteria for posing the indication to the shift from conventional treatment to Plenadren® substitution in patients with hypopituitarism.

Compliance with ethical standards

Conflict of interest A.G. is a consultant for Shire. The remaining authors declare that they have no conflict of interest.

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