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Impact of hydrocortisone replacement on bone mineral density and bone turnover markers in patients with primary adrenal insufficiency

Meriem Yazidi [1], Cyrine Danguir [1], Dhouha Maamer [2], Ibtissem Oueslati [1], Karima Khiari [3], Mohamed Elleuch [4], Moncef Feki [2], Melika Chihaoui [1]

[1]Department of Endocrinology, University of Tunis El Manar, Faculty of Medicine of Tunis, La Rabta Hospital, 1007 Tunis, Tunisia; [2]Department of Biochemistry, University of Tunis El Manar, Faculty of Medicine of Tunis, La Rabta Hospital, Tunis, Tunisia; [3]Department of Endocrinology, University of Tunis El Manar, Faculty of Medicine of Tunis, Charles Nicolle Hospital, Tunis, Tunisia; [4]Department of Rheumatology, University of Tunis El Manar, Faculty of Medicine of Tunis, La Rabta Hospital, Tunis, Tunisia
E-mail: meriemyazidi@gmail.com

Objective. The study was aimed to assess the effect of hydrocortisone (HC) replacement therapy on bone mineral density (BMD) and bone turnover markers in patients with primary adrenal insufficiency (PAI).

Methods. A cross-sectional study was conducted in 37 PAI patients treated with HC. BMD and selected bone turnover markers (β-crosslaps and osteocalcin) were measured. A stepwise binary logistic regression model was applied to determine the independent variables associated with low BMD.

Results. Osteoporosis was noted in 14.3% and osteopenia in 34.3% of cases. These patients were older (p=0.01) and received higher daily HC dose compared to patients with normal BMD (p=0.01). BMD values in the lumbar spine and the femoral neck were negatively correlated with daily HC dose (r=–0.36, p=0.03 and r=–0.34, p=0.05, respectively). Plasma osteocalcin was negatively correlated with disease duration (r=–0.38, p=0.02) and cumulative HC dose (r=–0.43, p<0.01). In multivariate analysis, a daily HC dose ≥12 mg/m2/day was independently associated with a higher risk of osteopenia/osteoporosis [OR (95% CI), 9.0 (1.1–74.6); p=0.04].

Conclusions. Impaired bone mineralization in patients with PAI is correlated with HC dose. A daily HC dose ≥12 mg/m^2/day was associated with an increased risk of osteopenia and osteoporosis in these patients.

Key words: primary adrenal insufficiency, bone mineral density, bone turnover markers, hydrocortisone, osteoporosis

Detrimental effects of glucocorticoids at pharmacological doses on bone metabolism have been well demonstrated (Weinstein 2011). In primary adrenal insufficiency (PAI), glucocorticoids are prescribed at much lower doses for the purpose of replacement. Despite the substitutional nature of the corticosteroid therapy, patients with PAI seem to be overexposed to the deleterious effects of glucocorticoids on bone (Bentivegna et al. 2018).

There are conflicting data regarding the factors associated with the impaired bone mineralization in these patients. Glucocorticoid dose seems to be the main factor associated with the risk of osteoporosis (Zelissen et al. 1994; Chikada et al. 2004; Lovas et al. 2009; Koetz et al. 2012; Schulz et al. 2016). The current trend is for a downwards revision of the prescribed doses (Bornstein et al. 2016). Inconsistent correlations have been found between detrimental effects on

Corresponding author: Meriem Yazidi, Department of Endocrinology, University of Tunis El Manar, Faculty of Medicine of Tunis, La Rabta Hospital, 1007 Tunis, Tunisia; phone: +21698266061; e-mail: meriemyazidi@gmail.com.

bone and age, gender, disease duration, type of glucocorticoids, and hormones such as adrenocorticotropin (ACTH) and dehydroepiandrosterone sulfate (DHEA-S).

Most studies have been limited by the heterogeneity of the population studied and the methods used to assess the impact on bone, which were often limited to a bone mineral density measurement (BMD). The present study is aimed to assess the influence of hydrocortisone (HC) replacement therapy on BMD and selected bone turnover markers in patients with PAI.

Subjects and methods

Study design. A cross-sectional two-center study was conducted at the Department of Endocrinology of the Rabta and Charles Nicolle University hospitals (Tunis, Tunisia). Eligibility criteria for the enrolling into the study included patients with confirmed PAI treated with hydrocortisone (HC), age above 18 years, and disease duration over one year. Diagnosis of PAI was confirmed by low serum cortisol and concurrent elevated ACTH levels or recent hyperpigmentation. Criteria for not inclusion included PAI secondary to bilateral adrenalectomy for Cushing's syndrome, congenital adrenal hyperplasia, condition that could influence bone metabolism (i.e., chronic inflammatory rheumatism, malabsorption syndrome disease, renal insufficiency [clearance of creatinine <80 ml/min], hyperparathyroidism, hyperthyroidism, hypogonadism, except physiological menopause), use of drugs likely to affect bone metabolism (i.e., calcium, vitamin D, calcitonin, bisphosphonates, estrogens, DHEA), and pregnancy. PAI patients receiving glucocorticoids other than HC were not included.

Thirty-seven patients with PAI were enrolled into the study. Data on socio-demographic characteristics, disease duration, treatment received, and concomitant endocrine diseases were collected from patient's medical records. Daily HC dose (in mg/m^2/day) and cumulative HC dose (daily HC dose x disease duration in years) (in mg/m^2) were calculated individually for each participant. Physical examinations (weight, height with calculation of body mass index) were also performed. The study was approved by the ethic committee of Rabta Hospital and informed consent was obtained from all participants.

Bone mineral density. BMD was measured at the lumbar spine (L1 to L4) and the femoral neck by dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, GE Healthcare, London, UK) in 35 patients. All measurements were made with the same instrument at the Rheumatology Department of the Rabta Hospital. BMD values were expressed as grams per square centimeter (g/cm^2) and the T and Z scores as the number of the standard deviations (SD). Z-scores were determined according to a Tunisian specific reference database. BMD was considered decreased if the Z-score was less than –2 SD of the mean value of age and gender matched reference population. T-scores were used to define osteoporosis and osteopenia according to WHO classification (Report WHO Study Group 1994).

Biochemical analyses. Fasting blood samples were collected on the same day as BMD measurement. Blood was immediately processed and plasma was stored at –80 °C until analyzed (within 6 months). All biochemical analyzes were performed in the same Laboratory. Plasma osteocalcin and products of degradation of C-terminal telopeptides of type-I collagen (CTx or β-crosslaps) were measured by immunoassay methods on a Cobas modular auto analyzer using the respective reagents kits (Roche Diagnostics, Rotkreuz, Switzerland). Plasma 25-hydroxyvitamin D (25-OHD), parathyroid hormone (PTH), adrenocorticotropin (ACTH), dehydroepiandrosterone sulfate (DHEA-S), thyroid-stimulating hormone (TSH) and follicle-stimulating hormone (FSH) were measured by chemiluminescence immunoassay method using a Liaison analyzer (DiaSorin Inc., Stillwater, MN) and the respective reagents kits. The inter-assay coefficients of variation were less than 12% for all the parameters assessed.

Statistical analysis. Statistical analyses were performed with the SPSS software for Windows, version 20 (SPSS Inc., Chicago, IL). Data were expressed as median with interquartile range (IQR) for quantitative variables and percentages for qualitative variables. Mann-Whitney U test was used to compare medians and Pearson's chi squared and Fisher's exact tests to compare proportions. Spearman's correlation was used to assess association between BMD and the bone turnover biochemical markers with clinical, hormonal, and therapeutic variables. Receiver operating characteristic (ROC) curves were depicted allowing determination of optimal cutoff values for daily and cumulative HC doses that discriminate osteopenia/osteoporosis from normal BMD in PAI patients. A stepwise binary logistic regression model was applied with osteopenia/osteoporosis as response variable to determine variables associated with low bone mass. Covariates were age (continuous variable), gender (female/male), smoking (never/ever), menopausal status (no/yes), disease duration (continuous variable), daily HC dose (<12/≥12 mg/m^2/

day), fludrocortisone treatment (no/yes), and plasma 25-OHD (continuous variable). A p-value<0.05 based on two-tailed calculations was considered significant.

Results

From the 37 PAI patients enrolled in the study, nine patients (24.3%) had concomitant Hashimoto's thyroiditis that was well controlled with levothyroxine. No other endocrine disease was present. Seven women were postmenopausal. All the patients were treated from diagnosis with HC, distributed in two daily doses in 91.4% of patients and in three daily doses in 8.6% of patients. Seventeen patients (45.9%) received fludrocortisone as mineralocorticoid replacement, but no one received dehydroepiandrosterone (DHEA). Patient's characteristics are shown in Table 1.

Four patients (11.4%) had decreased BMD at the lumbar spine. No patient had decreased BMD at the femoral neck. Five patients (14.3%) had osteoporosis and 12 patients (34.3%) had osteopenia. By the means of ROC curves, optimal cutoff values for daily and cumulative HC doses that discriminate osteopenia/osteoporosis from normal BMD were set at 12 mg/m²/day and 80 mg/m², respectively (Figure 1).

Patients with osteopenia/osteoporosis were older receiving higher daily HC doses than normal BMD patients (Table 2). BMD at the lumbar spine negatively correlated with daily HC dose and BMD at the femoral neck negatively correlated with cumulative HC dose. Plasma osteocalcin negatively correlated with disease duration and cumulative HC dose (Figure 2). Neither BMD nor bone turnover markers (i.e., β-crosslaps, osteocalcin) correlated with age or any of the studied hormonal parameters (i.e., 25-OHD, PTH, ACTH, DHEA-S, TSH, FSH). In multivariate analysis, daily HC dose ≥12 mg/m²/day was the single independent factor associated with osteopenia/osteoporosis in PAI patients [multi-adjusted OR (95% CI) =9.0 (1.10–74.6); p=0.04] (Table 3).

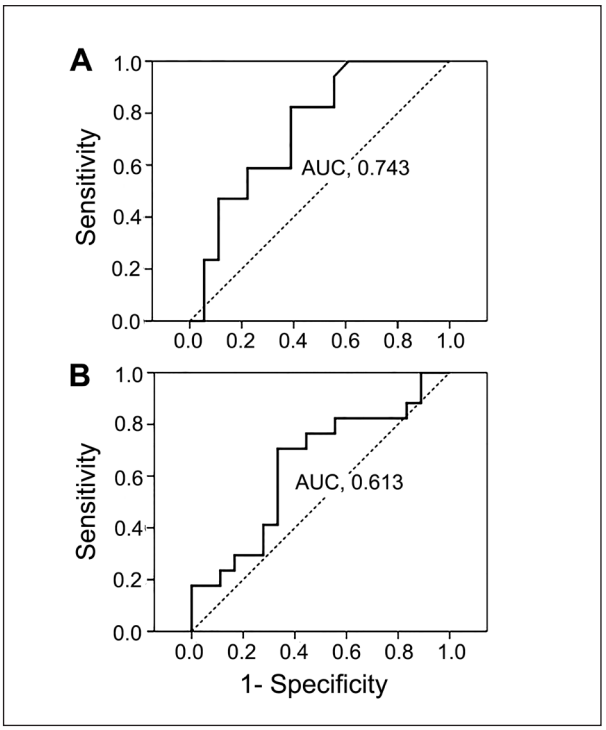


Figure 1. Receiver operating characteristic (ROC) curves for daily **(A)** and cumulative **(B)** hydrocortisone (HC) doses discriminating osteopenia/osteoporosis in primary adrenal insufficiency (PAI) patients.

Table 1
Characteristics of study participants (n=37).

Variable	Median (Interquartile range)
Age (years)	45 (37–55)
Sex-ratio (males/females)	0.48
Disease duration (years)	6.0 (4.0–10.0)
Daily hydrocortisone dose (mg/m²/day)	12.9 (10.9–5.6)
Cumulative hydrocortisone dose (mg/m²)	81.0 (45.2–130)
Body mass index (kg/m²)	25.5 (22.2–29.7)
Bone mineral density*	
BMD at the spine (g/cm²)	1.13 (1.03–1.21)
BMD at the femoral neck (g/cm2)	0.99 (0.93–1.10)
Z-score at the spine (SD)	–0.40 (–1.10–0.40)
Z-score at the femoral neck (SD)	0.00 (–0.60–0.70)
T-score at the spine (SD)	–0.50 (–1.70–0.00)
T-score at the femoral neck (SD)	–0.20 (–0.90–0.20)
Markers of bone turnover (reference range)	
Osteocalcin (17–40 ng/ml)	19 (16–27)
β-crosslaps (10–60 ng/dl)	45 (35–71)
Regulating hormones (reference range)	
25-hydroxyvitamin D (20–60 ng/ml)	9.72 (7.44–14.9)
Parathyroid hormone (15–50 pg/ml)	44.8 (32.9–63.5)
Adrenocorticotropin (10–50 pg/ml)	34.9 (21.5–249)
DHEAS (30–300 μg/dl)	49.0 (10.0–239)
TSH (0.35–4.95 mIU/L)	1.82 (1.02–2.75)
FSH (1.5–25 mIU/mL)	9.24 (6.33–22.2)

Abbreviations: BMD – bone mineral density; DHEAS – dehydroepiandrosterone sulfate; FSH – follicle-stimulating hormone; TSH – thyroid-stimulating hormone. *BMD was measured in 35 patients.

Table 2
Clinical and biochemical characteristics of patients according to osteopenia or osteoporosis (n=35)

Variable	T score <–1 DS (n=17)	T score ≥–1 DS (n=18)	p-value
Age, median (IQR), years	54.0 (42.5–58.5)	39.5 (35.5–47.0)	0.01
Females, n (%)	9 (52.9)	15 (83.3)	0.06
Postmenopausal women, n (%)	5 (29.4)	2 (11.1)	0.22
Smokers, n (%)	3 (17.6)	2 (11.1)	0.65
Disease duration, median (IQR), years	7.01 (5.0–10)	5.53 (3.02–10.7)	0.38
BMI, median (IQR), kg/m^2	25.2 (22.2–27.9)	27.9 (22.5–30.4)	0.26
Daily HC dose, median (IQR), mg/m^2/day	14.2 (12.4–17.2)	11.7 (10.5–13.7)	0.01
Daily HC dose ≥ 12 mg/m^2/day, n (%)	14 (82.4)	8 (44.4)	0.02
Cumulative HC dose, median (IQR), mg/m^2	98.5 (61.9–158)	58.7 (41.3–121)	0.16
Cumulative HC dose≥ 80 mg/m^2, n (%)	12 (70.6)	6 (33.3)	0.03
Treatment with fludrocortisone, n (%)	8 (47.1)	7 (38.9)	0.62
Osteocalcin, median (IQR), µg/l	19.1 (15.5–34.6)	20.1 (16.8–28.3)	0.90
β-crosslaps, median (IQR), µg/l	0.53 (0.37–0.79)	0.43 (0.30–0.65)	0.21
25-OHD, median (IQR), ng/ml	8.38 (7.40–11.6)	11.2 (8.00–16.3)	0.36
PTH, median (IQR), pg/ml	37.9 (32.9–60.2)	46.8 (28.1–60.4)	0.75
DHEA-S, median (IQR), µg/dl	21.0 (10.0–205)	49.5 (10.0–287)	0.55
ACTH, median (IQR), pg/ml	34.9 (25.9–188)	31.8 (19.0–465)	0.88
TSH, median (IQR), mUI/L	1.63 (1.12–3.18)	1.74 (0.91–2.56)	0.46
FSH, median (IQR), mUI/mL	12.3 (6.81–34.0)	9.62 (5.81–14.4)	0.47

Abbreviations: ACTH – adrenocorticotropin; BMT – body mass index; β-crosslaps – products of degradation of C-terminal telopeptides of type-I collagen; DHEA-S – dehydroepiandrosterone sulfate; FSH – follicle-stimulating hormone; 25-OHD – 25-hydroxyvitamin D; HC – hydrocortisone; IQR – interquartile range; PTH – parathyroid hormone; TSH – thyroid-stimulating hormone.

Table 3
Multivariate analysis results.

Variable	p-value	Adjusted OR	[CI 95%]
Age	0.47	0.95	[0.82–1.09]
Females	0.08	10.75	[0.72–159.02]
Postmenopausal women	0.36	5.72	[0.13–240.52]
Smokers	0.66	0.52	[0.02–9.91]
Disease duration	0.80	0.98	[0.84–1.14]
25-hydroxyvitamin D	0.81	1.02	[0.85–1.23]
Daily HC dose ≥12 mg/m^2/day	0.04	9.00	[1.08–74.60]
Treatment with fludrocortisone	0.83	1.22	[0.19–7.80]

Abbreviations: CI – confidence interval; HC – hydrocortisone; OR – odds ratio.

Discussion

This study showed decreased BMD (Z-score <–2 SD) in 11% of PAI patients at the lumbar spine. Osteopenia and osteoporosis (T-score <–1 SD) were diagnosed in near half of the patients. The study confirmed the role of an advanced age in bone loss, but revealed that daily HC dose is the main contributor to osteopenia/osteoporosis in PAI patients.

Our results are consistent with the previous reports showing BMD decrease in patients with adrenal insufficiency (Zelissen et al. 1994; Peacey et al. 1997; Chikada et al. 2004; Lovas et al. 2009; Behan et al. 2013; Chihaoui et al. 2016; Camozzi et al. 2018). Only few studies conducted on small samples have shown no decrease in BMD (Jodar et al. 2003; Arlt et al. 2006). Deleterious effects on bone have been attributed to several factors, mainly the glucocorticoids dose received and the disease duration. In the last two decades, several studies have indicated that even a slight over dose replacement of glucocorticoids had deleterious effects on bone (Valero et al. 1994; Zelissen et al. 1994; Peacey et al. 1997; Braatvedt et al. 1999; Chikada et al. 2004; Lovas et al. 2009; Behan et al. 2013; Chihaoui et al. 2016; Camozzi et al. 2018). Therefore, the recommended daily HC dose in PAI patients has been greatly reduced from an average of 30 mg to 20 mg (Bornstein et al. 2016).

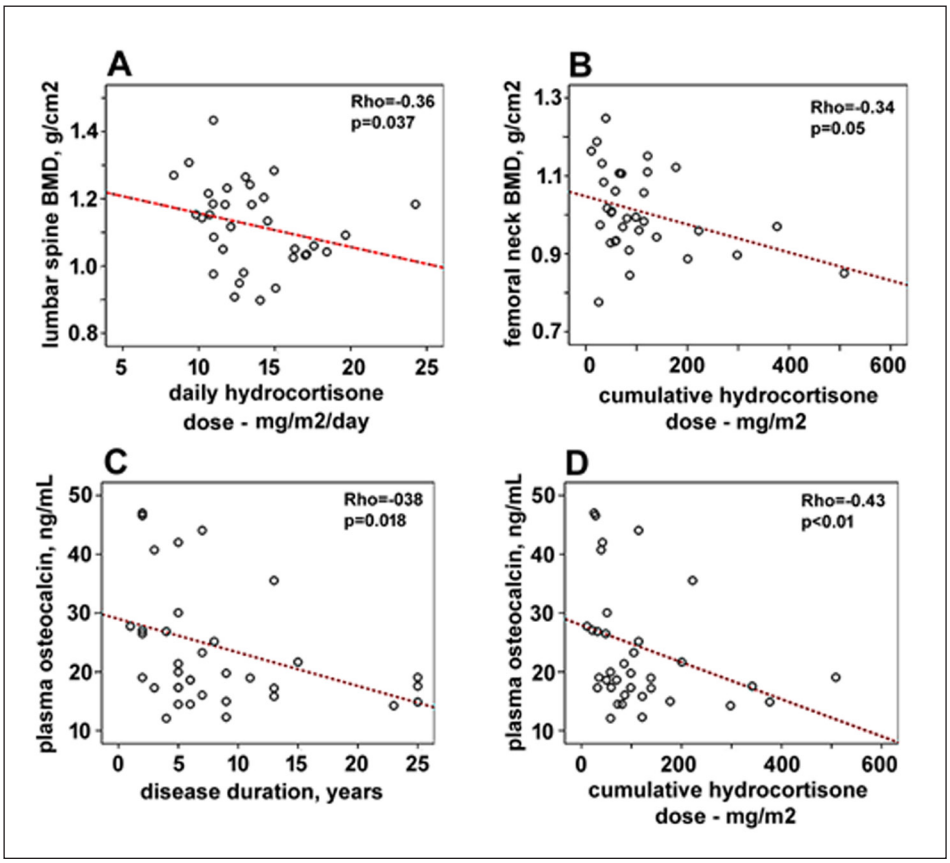


Figure 2. Correlations between the bone mineral density (BMD) at the lumbar spine and the daily hydrocortisone dose **(A)**, BMD at the femoral neck and the cumulative hydrocortisone doses **(B)**, plasma osteocalcin and the duration of the disease **(C)**, and plasma osteocalcin and the cumulative hydrocortisone dose **(D)**.

This study showed that a daily HC dose ≥12 mg/m²/day is associated with an increased risk of osteopenia/osteoporosis in PAI patients.

There are conflicting data regarding the effect of disease duration on bone loss in adrenal insufficiency patients with studies showing negative correlation (Valero et al. 1994; Braatvedt et al. 1999; Chihaoui et al. 2016; Camozzi et al. 2018). However, others have found no association with BMD (Zelissen et al. 1994; Chikada et al. 2004; Lovas et al. 2009). Correlation between BMD and disease duration could be explained by the fact that patients with longer disease duration probably received higher daily doses of glucocorticoids in the past. In the present study, the disease duration was longer in patients with osteopenia/osteoporosis. However, the difference was not significant, probably due to lack of a power. Most previous studies were limited by the heterogeneity of the population studied, especially with respect to the type of glucocorticoids received and the association with other treatments that interfere with the bone metabolism (e.g., vitamin D and DHEA).

Concomitant GH and sex hormones deficiencies in secondary adrenal insufficiency may also influence the bone metabolism. In this study, to ensure the homogeneity of the population, we included only PAI patients treated with HC and excluded other conditions or treatments that could influence the bone metabolism. PAI patients receiving glucocorticoids other than HC were excluded given that pharmacokinetic profiles of other glucocorticoids (e.g., prednisolone, cortisone acetate, prednisone and dexamethasone) are different from HC (Koetz et al. 2012; Bornstein et al. 2016; Schulz et al. 2016). Most of the previous studies that investigated bone status in PAI have been limited to a measurement of BMD.

This study investigated the impact on bone health by the measurement of biochemical markers of bone turnover; β-crosslaps as a marker of bone resorption, and osteocalcin as a marker of bone formation.

These parameters are more sensitive than BMD in evaluating the bone metabolism (Civitelli et al. 2009). We found no relationship between the markers of bone turnover and BMD. Plasma osteocalcin was negatively correlated with disease duration and cumulative HC dose; however, no correlations were found with β-crosslaps. This could be because the bone formation is highly sensitive to glucocorticoids. Indeed, treatment with lower HC doses resulted in bone formation markers increase, but no change in the bone resorption markers (Peacey et al. 1997; Behan et al. 2013). Thus, a slight over dose of HC would mainly act by inhibiting the bone formation. Effect on bone resorption seems to be less important and likely observed with larger doses.

Several hormonal factors, in particular DHEA-S and vitamin D levels, are associated with adverse effects on bone (Zelissen et al. 1994; Braatvedt et al. 1999; Callies et al. 2001; Chikada et al. 2004; Gurnell et al. 2008; Lovas et al. 2009; Koetz et al. 2012). For a further elucidation of bone health in PAI, we measured several regulating hormones aiming to look for their potential interfering in bone loss. We found no correlation between plasma ACTH, DHEA-S, vitamin D, PTH, TSH, and FSH with either BMD or bone turnover markers. The impact of adrenal androgen depletion on bone health has largely been debated (Zelissen et al. 1994; Braatvedt et al. 1999; Callies et al. 2001; Gurnell et al. 2008; Lovas et al. 2009; Koetz et al. 2012; Bensing et al. 2016).

The largest DHEA trial in Addison disease showed that 12 months of DHEA replacement increases BMD in the femoral neck, but not in other skeletal sites (Gurnell et al. 2008). DHEA replacement in Addison's women resulted in a significantly lower bone resorption (collagen crosslink) and formation (bone alkaline phosphatase) markers and significantly higher BMD compared to non-DHEA-treated women (Koetz et al. 2012). However, in another trial, DHEA had no effect on the urinary cross-links excretion, but slightly increased the serum osteocalcin levels (Callies et al. 2001). Vitamin D hypovitaminosis had an impact on the bone health and was associated with bone adverse effects (Holick 2007). Plasma 25-OHD was low in most of patients enrolled in this study, which is consistent with the high incidence of vitamin D deficiency in Tunisia (Meddeb et al. 2005). However, in our series, 25-OHD levels were not associated neither with BMD nor the bone turnover markers, while hormonal measurements showed no significant associations with BMD or biochemical markers. They permitted us to exclude other bone loss causes.

Summary

The present work was addressed to study the bone loss in PAI patients by evaluating several radiological and biochemical variables of the bone status as well as several regulating factors that may interfere with PAI effect on bone. It enrolled as much homogenous sampling as possible excluding the conditions and treatments that could affect the bone health. Data arise from a multivariate analysis taking into account several potential confounders, which confers reliability to our findings. The study has also limitations. The small number of patients enrolled could prevent detecting significant associations due to a reduced power. Actually, the small sample size is related to the rarity of the disease and the severity of the eligibility criteria. Another limitation is the lack of a control group for comparison of bone turnover markers.

Conclusion

The present study revealed a high incidence of osteopenia/osteoporosis in PAI highlighting the role of HC dosage as main contributor of the bone loss. This emphasizes the necessity to prescribe the lowest acceptable glucocorticoid replacement dose in patients with PAI to avoid its adverse effects on bone. However, physicians should be aware of the fact that substantial reduction in glucocorticoids could increase the risk of an acute adrenal crisis or impairment of the patient's life quality.

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Conflicts of interest: *The authors declare no conflicts of interest.*

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