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Long-term follow-up of bone mineral density in Addison's disease

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Summary

BACKGROUND AND AIMS There is conflicting evidence regarding the long-term effects of long-term glucocorticoid replacement therapy (GRT) on bone mineral density (BMD) in patients with chronic adrenal insufficiency. Our aim was to evaluate bone turnover and changes in BMD in patients on GRT.

PATIENTS AND METHODS We have studied 25 subjects (six men, 19 women; aged 62·4 ± 11·3 years, duration of disease 21·7 ± 11·7 years, fasting cortisol 63 ± 36 nmol/l) on GRT (hydrocortisone 30 mg/day or prednisone 7·5 mg/day). BMD was assessed at the lumbar spine (LS; L2–L4), proximal femur (PF) and ultra distal radius (UR) by dual energy X-ray absorptiometry (DXA). The rates of bone loss were calculated using previous DXA measurements at the LS (48 and 60 months earlier). Serum calcium, phosphate alkaline phosphatase (ALP), bone ALP, serum osteocalcin (BGP), intact parathyroid hormone (PTH) and 25(OH) vitamin D were also measured.

RESULTS BMD [Z-score; 95% confidence interval (95% CI)] was normal at the LS: (–1·15–+0·07); PF: (–0·90–+0·22) and UDR (–0·77–+0·36). No significant differences were found according to the type of replacement therapy or sex. No significant bone loss (g/cm^2; 95% CI) was detected at the LS: (–0·021–+0·023). Fifty-six per cent of patients met osteoporotic criteria; a greater proportion of patients treated with prednisone had osteoporosis compared with those an hydrocortisone. All bone markers were in their normal ranges.

CONCLUSIONS Patients on long-term therapy do not show accelerated bone loss at the lumbar spine. Nevertheless, a considerable proportion of patients, mainly those treated with prednisone, showed densitometric osteoporosis.

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Patients with adrenal insufficiency require lifelong glucocorticoid replacement therapy (GRT) and it has been proposed that glucocorticoid therapy should be assessed in these patients and over replacement avoided, to reduce the long-term risk of steroid-induced osteoporosis (Peacey *et al.*, 1997).

However, there is conflicting evidence regarding the long-term effects of GRT on bone mass in patients with Addison's disease, which has been reported to be reduced only in postmenopausal women (Devogelaer *et al.*, 1987; Florkowski *et al.*, 1994), only in men (Zelissen *et al.*, 1994) and, on the contrary, also to be normal in both sexes (Valero *et al.*, 1994; Braatvedt *et al.*, 1999). Potential explanations for these contradictory data include the type of GRT, the duration of the disease, the proportion of hypogonadal patients, methodology and criteria used for bone loss measurements and the small numbers of patients included. The majority of these studies have focussed on patients with long-term GRT but there are few data which prospectively assess the changes in bone mineral density (BMD). On the other hand, there is still no agreement regarding the recommended glucocorticoid for maintenance in these patients, hydrocortisone, cortisone acetate and prednisone being used currently (Orth, 1994).

The aim of this study was to assess long-term changes in BMD and bone turnover markers in patients with Addison's disease treated with hydrocortisone or prednisone replacement who were regularly followed-up in our outpatient clinic.

Patients and methods

We have studied 25 patients (six males, 19 females) with Addison's disease from our outpatient clinic who gave informed consent. Mean age was 62·4 ± 11·3 years, mean body mass index (BMI) 27·1 ± 11·7 kg/m^2 and the mean duration of GRT 21·7 ± 11·7 years (range 6–49 years). A total of 84·2% (16/19) of the women were postmenopausal (i.e. menopausal amenorrhoea > 1 year). Patients were independent for activities of daily living, undertook moderate exercise and had an adequate calcium and vitamin D intake as evaluated with a questionnaire. There were no major medical illnesses apart from Addison's disease and all were Caucasian. None of the patients were treated with other therapy known to affect bone metabolism, including sex-hormone

replacement therapy in women. Men did not report symptoms of hypogonadism and therefore biochemical evaluation of this potential deficit was not performed. Patients with autoimmune adrenal insufficiency were tested periodically and those with other autoimmune diseases as type 1 diabetes mellitus or Hashimoto's thyroiditis were included if they were well controlled.

BMD sequential measurements were always performed using a dual X-ray absorptiometry (QDR 1000/w absorptiometer, Hologic Inc., Walthmam, MA, USA) of the lumbar spine (LS; L2–L4), proximal femur (PF) and ultradistal radius (UR). Results were expressed as g/cm^2 and as T- and Z-score according to a national normal population previously described (Diaz Curiel *et al.*, 1997). Lumbar BMD data were compared to previous measurements obtained 48 and 60 months before with the same densitometer. Long-term coefficient of variation for the lumbar spine BMD measurement at our centre is 1·31% (Hawkins *et al.*, 1994).

Blood sampling was done the same day bone densitometry was performed. Serum samples were obtained between 08·00 and 09·00 h after overnight fast and were immediately processed and kept frozen at –20 °C until the assay. Serum calcium (Ca, normal values 2·10–2·55 mmol/l), phosphate (P, normal values 0·70–1·48 mmol/l), creatinine (Cr, normal values 9–97 µmol/l) and alkaline phosphatase (ALP; normal values 91–258 U/l) were measured by autoanalyser (DAX 72 colourimetric method). Serum osteocalcin (BGP; Nichols Institute Diagnostics, CA, USA; normal values 2·4–10·0 µg/l), bone alkaline phosphatase (bALP; Tandem-R Ostase, Hybritech, CA, USA; normal values 0–30 µg/l), intact parathyroid hormone (IPTH; Nichols Institute Diagnostics; normal values 13–54 ng/l) and 25(OH) vitamin D (DiaSorin, MN, USA; normal values 15–50 µg/l) were assayed by standardized immunoradiometric assays (IRMAs) or radioimmunoassays (RIAs).

Statistical analyses

Results are expressed as mean ± standard deviation (SD) unless otherwise indicated. Student's *t*-test (to compare Z-scores and observed changes in BMD *vs.* expected value, i.e. 0, and to compare groups), one way ANOVA (to compare among groups), binomial test (to compare the rate of osteoporotics according to sex and type of replacement therapy) and linear regression analysis were used. *P*-values < 0·05 were considered to indicate statistical significance. All statistical analyses were done using the SPSS-PC (version 8·0) statistical software package (SPSS Inc. Chicago, IL, USA).

Results

Baseline characteristics of patients according to the type of replacement therapy are shown in Table 1, and BMD at each site of measurement is shown in Fig. 1. There were no significant differences in age, duration of disease, serum adrenocorticotropic hormone (ACTH) and cortisol levels according to the type of replacement therapy. No significant differences were found when BMD values between individuals were compared according to sex. Similarly, no significant differences were found when BMD values were compared according to sex and menopause (males, premenopausal females and menopausal females, Table 2). Patients treated with prednisone tended to show lower BMD values, but the differences were not significant (Fig. 2).

Serum bone turnover markers levels were all in the normal range: ALP: 146 ± 55 UI/l; bALP: 15·86 ± 5·08 µg/l; BGP: 6·11 ± 1·82 µg/l; as were ¡PTH and vitamin D (34·45 ± 10·51 ng/l and 33·06 ± 14·35 µg/l). No significant differences in bone markers were found among males, premenopausal and menopausal females ($P > 0·4$). The serum concentration of bALP

Table 1 Characteristics of patients according to the type of replacement therapy

	Hydrocortisone ($n = 17$)	Prednisone ($n = 8$)	*P*-value
Age (years)	63·6 ± 12·9	63·5 ± 8·3	0·986
Sex (male/female)	5/12	1/7	0·377
Duration of the disease (years)	21·9 ± 13·3	21·4 ± 8·5	0·924
Serum cortisol (nmol/l)*	63 ± 39	69 ± 16	0·659
Serum ACTH (ng/l)*	551 ± 380	462 ± 450	0·662
Mean dose (mg/day)	27·8 ± 5·1	7·5 ± 0·0	–

*Fasting values prior to first glucocorticoid dose of the day.

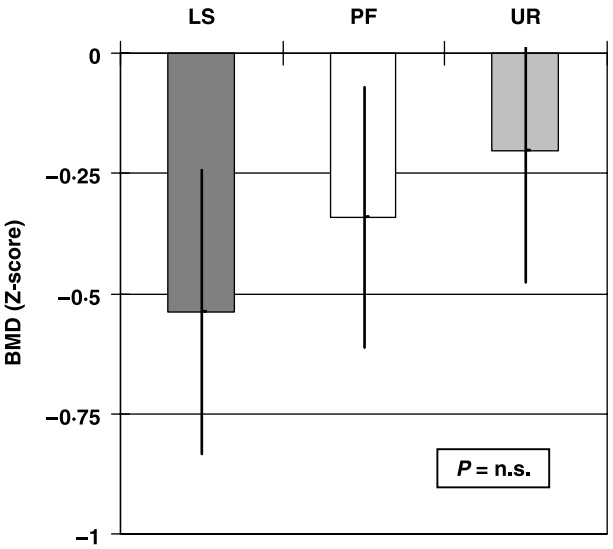

Fig. 1 Bone mineral density (Z-scores, mean ± SEM) in patients with long-term treated Addison's disease. LS, lumbar spine; PF, proximal femur; UR, ultra-distal radius. *P* = ns *vs.* 0.

Table 2 Comparisons of bone mineral density (Z-score) according to sex and menopausal status

	Males (n = 16)	Premenopausal females (n = 3)	Menopausal females (n = 6)	P-value
Lumbar spine	–0·341 ± 2·065	–0·353 ± 1·184	–0·647 ± 1·363	0·896
Proximal femur	0·220 ± 1·462	–0·623 ± 0·525	–0·498 ± 1·420	0·522
Ultradistal radius	–0·032 ± 2·279	0·370 ± 0·321	–0·375 ± 1·061	0·664

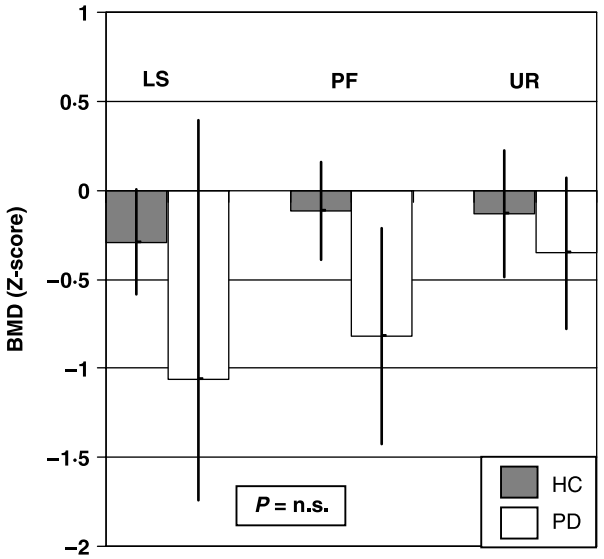

Fig. 2 Bone mineral density (Z-score, mean ± SEM) in patients with long-term treated Addison's disease according to the type of replecement therapy. HC, hydrocortisone (n = 17); PD, prednisone (n = 8). LS, lumbar spine; PF, proximal femur; UR, ultra-distal radius. P = ns.

correlated with the BMD at the lumbar spine (g/cm^2: $r = -0{\cdot}562$; Z-score: –0·543; $P < 0{\cdot}05$), but no other significant correlation between bone turnover markers and BMD was detected. Daily dose and the cumulative dose of glucocorticoids converted to milligrams of hydrocortisone equivalent (7·5 mg prednisone = 30 mg hydrocortisone) did not show any significant correlation with BMD ($P > 0{\cdot}4$). Also, duration of the disease did not correlate with BMD at any site.

The BMD at the lumbar spine had not changed significantly in comparison with measurements obtained 48 and 60 months earlier (absolute change: 0·007 ± 0·039 g/cm^2/48 months; 0·001 ± 0·011 g/cm^2/60 months).

Fifty-six per cent (14/25) of our patients had osteoporosis according to the WHO criteria (i.e. T-score < –2·5 at lumbar spine or femoral neck; WHO Study Group, 1994). The proportion of osteoporotic patients according to sex was not different from that expected (4/6 males and 10/19 females; P = 0·443); although a greater proportion of prednisone-treated patients showed osteoporosis (6/8 with prednisone *vs.* 8/17 with hydrocortisone; P = 0·046). The duration of the disease was longer in this subset of patients (20·2 ± 12·5 *vs.* 11·8 ± 8·92 years) but, again, the difference did not reach statistical significance (P = 0·083).

Discussion

This study has shown that axial and appendicular BMDs in patients on long-term GRT are not significantly different from those in normal population, and that the long-term follow-up of these patients does not show any accelerated bone loss. Also, no significant differences have been detected between both sexes, or according to sex and menopausal status. Nevertheless, the present study has two main limitations: the first is related to the small number of patients which enhances the possibility of missing a significant effect of glucocorticoids on bone mass; the second is the lack of a control group to compare the values of bone markers which may underestimate the suppression of bone formation related to glucocorticoids, in particular in postmenopausal women who would be expected to show higher levels.

In addition to the effects on PTH and vitamin D, glucocorticoids reduce bone formation and increase bone resorption. The reduction in bone formation has been related to a direct inhibitory effect on osteoblasts; inhibition of production of IGF-I and testosterone; and to an increase in osteoblast and osteocyte apoptosis (Canalis & Avioli, 1992; Manolagas & Weinstein, 1999). Glucocorticoids also increase bone resorption by a direct effect, by reduced secretion of androgens and oestrogens and by increased secretion of parathyroid hormone (Manolagas & Weinstein, 1999) but do not affect the bone-resorbing activity of mature osteoclasts, because these cells do not have functional glucocorticoid receptors.

Previous studies in patients with treated Addison's disease have yielded conflicting results (Devogelaer *et al.*, 1987; Florkowski *et al.*, 1994; Valero *et al.*, 1994; Zelissen *et al.*, 1994). BMD at the radius measured with single photon absorptiometry has been reported to be low in postmenopausal women with Addison's disease, but unrelated to the duration of the disease as shown by Devogelaer *et al.* (1987). These authors have suggested

that the observed reduction in adrenal androgens in postmenopausal women could be the main determinant of the low bone mass, although 25% of their reported males were also osteoporotic.

On the other hand, in those studies which have reported DXA measurements, BMD has been shown to be normal for most patients, although the finding of osteopenia was more usual in those patients with higher daily doses of glucocorticoids and/or longer duration of the disease (Florkowski *et al.*, 1994; Valero *et al.*, 1994; Zelissen *et al.*, 1994; Braatvedt *et al.*, 1999). According to these findings, in this study, a normal bone mass is observed in patients with treated Addison's disease as a group, without significant differences between the sexes. These data, taken together with the lack of a significant bone loss during the 60 months of follow-up with the same high-precision densitometer, and with the normal values of the bone turnover markers, suggest that hydrocortisone and prednisone replacement therapy at the doses for Addison's patients used in our study is not associated with either trabecular bone loss or osteopenia.

Nevertheless, a great proportion of patients fulfilled densitometric criteria for postmenopausal osteoporosis, similar to that recently described by others (Hereux *et al.*, 2000). The finding of densitometric osteoporosis was not related with sex, current or accumulated dose of glucocorticoids, or with duration of the disease. However, osteoporosis was present in a greater proportion of prednisone-treated patients. It is still controversial whether there is any safe dose of glucocorticoids which may be not associated with an accelerated bone loss. Our data suggest potential bone detrimental attributes for prednisone; nevertheless, this result must be viewed with some caution and**,** although the low number of patients may underestimate the effects of therapy, the lack of significant differences between the BMD of patients treated with hydrocortisone and those treated with prednisone should be taken into account.

One surprising result is the lack of significant changes in BMD during the 60 months of follow-up. Our population is comprised mainly of females with established menopause (> 10 years), well after the rapid bone loss associated to menopause. Moreover, the deficits in calcium and vitamin D ingestion detected in the initial evaluation of our cohort (Valero *et al.*, 1994) were corrected, which may have influenced the evolution of the bone density.

In conclusion, our study confirms that patients with Addison's disease taking long-term GRT do not show, as a group, significant osteopenia or accelerated bone loss at the level of the lumbar spine. Nevertheless, a considerable proportion of patients, mainly those treated with prednisone, showed densitometric osteoporosis.

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