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Original Article

Quantitative Ultrasound of Bone and Markers of Bone Turnover in Cushing's Syndrome

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Abstract. Quantitative ultrasound (QUS) of bone is a valuable tool in the assessment of postmenopausal osteoporosis. QUS and new markers of bone turnover have been poorly assessed in Cushing's syndrome, however. Twenty-five patients with Cushing's syndrome (20 women, 3 men; mean age ± SEM: 38 ± 2 years) were studied and compared with 35 age- and sex-matched control patients (mean age ± SEM: 38 ± 2 years). The following variables were measured in both groups: QUS parameters at the heel (BUA; SOS; Stiffness Index, SI); bone mineral density (BMD) at both the lumbar spine (LS) and femoral neck (FN) by dual-energy X-ray absorptiometry; and serum markers of bone turnover (osteocalcin, procollagen type I N- and C-terminal propeptides (PINP and PICP), bone alkaline phosphatase (BAP), procollagen type I C-terminal telopeptide (ICTP) and urinary type I collagen C-telopepetide breakdown products (CTX)). Both BUA and SI were decreased in patients with Cushing's syndrome ($p<0.01$) but not SOS ($p=0.08$). BMD was also strongly decreased in Cushing's syndrome, at both the LS and FN ($p<0.005$). The two markers of bone turnover statistically significantly different between the two groups were osteocalcin (mean ± SEM: 3.5 ± 0.7 ng/ml (Cushing's syndrome) vs 6.4 ± 0.5 ng/ml (controls, $p<0.01$)) and CTX (mean ± SEM: 148.7 ± 17.1 μg/mmol Cr (Cushing's syndrome) vs 220.8 ± 22.9 μg/mmol Cr (controls), $p<0.05$). The areas under the receiver operating characteristic curve (AUC) were 0.72 (BUA), 0.73 (SI), 0.90 (BMD_{LS}), 0.81 (BMD_{FN}), 0.83 (osteocalcin) and 0.64 (CTX) respectively. AUC was significantly higher for BMD_{LS} than for both BUA and SI ($p<0.05$). Conversely AUC was not statistically significantly different for BMD_{FN} as compared with either BUA or SI. AUC was also higher for osteocalcin than for other markers of bone turnover. In conclusion, QUS of bone seems to be a relevant tool for assessing bone involvement in Cushing's syndrome. QUS does have a lower sensitivity compared with DXA, however, and the relevance of QUS cannot be ascertained until some longitudinal data are forthcoming. Except for CTX, the other new markers of bone turnover assessed in this study (PINP, PICP, BAP and ICTP) do not seem of interest in Cushing's syndrome.

Keywords: Bone densitometry; Cushing's syndrome; Markers of bone turnover; Ultrasound

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Introduction

Osteoporosis due to an excess of endogenous corticosteroids was described for the first time in 1932 by Harvey Cushing. Osteoporosis due to glucocorticoid excess is the primary cause of secondary osteoporosis and accounts for about 25% of cases of osteoporosis. Corticosteroid-induced osteoporosis (CIOP) is usually the result of pharmacologic use of steroid to suppress chronic inflammatory states but can also be due to endogenous hypercortisolism. The occurrence of low bone mass in Cushing's syndrome (CS) has been well demonstrated using bone densitometry by dual-energy

X-ray absorptiometry (DXA) and findings suggest that bone mineral density (BMD) is decreased by 15–20% in active CS, particularly for sites rich in trabecular bone such as the lumbar spine [1–4].

Quantitative ultrasound (QUS) measurement of bone is a new peripheral technique that has demonstrated to predict fracture risk, especially in elderly women [5,6]. Compared with bone densitometry QUS devices have several advantages. They do not use ionizing radiation, they are cheap and some of them are portable. QUS has been poorly investigated in metabolic bone diseases, however (except for osteoporosis), though some data suggest that QUS measurements could be useful in mild primary hyperparathyroidism [7]. In a recently published study we also showed that QUS parameters were decreased to the same extent as BMD in patients with CIOP due to exogenous glucocorticoid excess [8]. Also Daens et al. [9] showed that the Stiffness Index (SI) was decreased by 12.7% (against 11% for BMD at the lumbar spine) in a group of patients receiving pharmacologic doses of steroids for more than 1 year. Nevertheless, to our knowledge QUS parameters of bone have not been assessed in endogenous corticosteroid excess.

Low bone mass in CS is explained by an uncoupling of resorption from formation. Until now the decrease in bone formation was assessed by the measurement of osteocalcin levels and, except in the study by Hermus et al. [2], the suppression of osteocalcin levels has been widely demonstrated [10–12]. Data on other markers of bone formation, such as procollagen type I C-terminal propeptide (PICP), procollagen type I N-terminal propeptide (PINP) and bone alkaline phosphatase (BAP), are more sparse and conflicting, however [11–13]. Moreover the increase in bone resorption as assessed by the measurement of serum procollagen type I C-terminal telopeptide (ICTP) and urinary type I collagen C-telopepetide breakdown products (CTX) has been well demonstrated for patients chronically receiving glucocorticoids for inflammatory states [14,15]. However, data in endogenous hypercortisolism are conflicting and scarce [2,3,12].

The aims of this study were to determine whether QUS of bone is a useful tool in active CS as compared with DXA and whether the new markers of bone turnover mentioned above (for both bone formation and resorption) are of interest in CS.

Patients and Methods

Patients

Twenty-three patients with active CS were studied (mean age ± SEM: 38 ± 2 years; median: 37 years; range: 23–59 years; Table 1). There were 20 women (2 of whom were menopausal) and 3 men. The diagnosis of CS was suspected on clinical grounds and was confirmed by standard endocrine evaluation. Eighteen patients had a cortisol-producing adenoma and 5 had pituitary-dependent CS. Selective inferior petrosal sinus samples

Table 1. Main characteristics of patients with Cushing's syndrome (CS) and controls

Variables	Values		Normal range
	CS	Controls	
Age (years)	38 ± 2	38 ± 2	
Weight (kg)	76 ± 3	67 ± 5**	
Height (cm)	163.5 ± 1.7	170 ± 2.4*	
Disease duration (years)	2.3 ± 0.4		
Plasma cortisol at 0800 hours (μg/100 ml)	18.3		9–22
Mean 24-h plasma cortisol (μg/100 ml)	17.7 ± 1.1		
UFC (μg/24 h)	392.5 ± 60.1		20–110
DHEA-S (μg/l)	4.86 ± 1.03		Women: 1.5–9 Men: 2–10
Broadband ultrasound attenuation (dB/MHz)	110 ± 3	119 ± 2*	
Speed of sound (m/s)	1472 ± 70	1552 ± 5	
Stiffness Index, SI	84 ± 4	94 ± 2**	
Lumbar spine BMD (g/cm^2)	0.91 ± 0.03	1.15 ± 0.03***	
Femoral neck BMD (g/cm^2)	0.75 ± 0.02	0.91 ± 0.02***	
Serum PICP (ng/ml)	136.1 ± 12.7	122.8 ± 6	Women: 50–170 Men: 38–202
Serum PINP (ng/ml)	51.1 ± 5.5	41.7 ± 3.6	20–80
Serum osteocalcin (ng/ml)	3.6 ± 0.7	6.4 ± 0.5***	3.5–12
Serum bone alkaline phosphatase (ng/ml)	11.3 ± 1.2	10.3 ± 0.5	<20.4
Serum ICTP (ng/ml)	3.5 ± 0.3	3.3 ± 0.4	1.8–5
Urinary CTX (μg/mmol Cr)	148.7 ± 17.1	220.8 ± 22.9*	PreM women: 70–370 PostM women:100–650 Men: 50–270

UFC, urinary free cortisol; DHEA-S, serum dehydroepiandrosterone; M, menopausal.
*p<0.05; **p<0.01; ***p<0.005.

for ACTH measurement were obtained in 5 patients to ascertain the diagnosis. The control group consisted of 35 sex- and age-matched subjects (mean age ± SEM: 38 ± 2 years; median: 37 years; range: 24–59 years; male/female ratio 5/30 = 0.16 vs 3/20 = 0.15 in patients). The control group was mainly recruited among health care staff members and more rarely among patients who attended the clinic for disorders not related to bone metabolism (i.e., low back pain or sciatica without osteoarthritis on radiographs). The protocol was approved by our local ethics committee and all subjects (patients and controls) gave informed consent.

Methods

QUS. QUS measurements were performed on the nondominant heel using an Achilles machine (Lunar, Madison, WI). Two variables were measured: broadband ultrasound attenuation (BUA) and speed of sound (SOS). A third variable, i.e. the Stiffness Index (SI), which is a combination of both BUA and SOS, was also calculated. SI does not reflect the homonymous mechanical property. The in vivo short-term precision expressed as the coefficient of variation (CV) was respectively 0.23%, 2.6% and 2.6% in our center for SOS, BUA and SI [8].

BMD. Bone mineral density was measured by dual-energy X-ray absorptiometry (DXA, Sophos L-XRA, France) at the lumbar spine (BMD_{LS}) and the nondominant femoral neck (BMD_{FN}) in patients and controls. Reproducibility expressed as the CV was about 1% for the lumbar spine and 2% for the femoral neck [15].

Laboratory Investigations. The following investigations were performed in all patients: serum and 24 h urinary free cortisol (UFC) measured by radioimmunoassay (RIA; Diagnostic Products, Los Angeles, CA), serum dehydroepiandrosterone (DHEA-S) measured by RIA (Diagnostic Products, Los Angeles, CA) and serum ACTH by chemiluminescence assay (Nichols Institute Diagnostics, San Juan Capistrano, CA).

The following serum assays were undertaken in both patients and control subjects: procollagen type I C-terminal propeptide (PICP), procollagen type I N-terminal propeptide (PINP), intact osteocalcin and bone alkaline phosphatase (BAP), which reflect bone formation, and procollagen type I C-terminal telopeptide (ICTP), which reflects bone resorption. Blood samples were collected between 0730 and 0900 hours after an overnight fast. Serum samples were stored frozen at −80 °C until assay. Radioimmunologic assays were used to measure serum PICP, PINP, ICTP (Orion Diagnostica, Espoo, Finland) and osteocalcin (Cis-Bio International, Gifs/Yvette, France). Within-run and between-run total coefficients of variation (CVs) were 2.8% and 5.1% respectively for the PICP assay. Corresponding figures were 8.75% and 5.1% for the PINP assay, 4.8% and 5.7% for the ICTP assay, and 3.7% and 6.6% for the osteocalcin assay. Serum BAP was measured with a human-specific immunoradiometric assay (Hybritech, San Diego, CA). The intra- and interassay CVs were less than 7% and 9% respectively. Urinary type I collagen C-telopepetide breakdown products (CTX) were measured on a 24 h urine sample by an enzyme-linked immunosorbent assay (Osteometer, Rodovre, Denmark). The intra- and inter-assay CVs were less than 10% and 13% respectively.

Statistical Analyses

Group data are expressed as mean ± SEM unless otherwise specified. Statistical comparisons were made using Student's *t*-test for unpaired data after adjustment for weight and height and when criteria for a normal distribution were satisfied. Otherwise the nonparametric Mann–Whitney *U*-test was used. Individual values of BMD, QUS and markers of bone turnover were also expressed as the *Z*-score, that is the number of SD from the mean of sex- and age-matched controls. Receiver operating characteristic curve (ROC) analyses were generated and the areas under the curve (AUC) calculated to provide and estimate for the discriminatory capability for CS of each of the variables. AUC were compared using the method proposed by Hanley and McNeil [16]. Simple linear regression was used to determine coefficients of correlation. A p value lower than 0.05 was considered statistically significant. Statistical analyses were done using two statistical packages: Statview version 5 (SAS Institute, Cary, NC) and Medcalc version 5 (Mariakerke, Belgium).

Results

The main characteristics of patients with CS and control subjetcts are represented in Table 1.

QUS measurements were decreased in patients with CS as compared with controls for both BUA ($p<0.01$) and SI ($p<0.005$) but not for SOS ($p=0.08$). The mean decreases were 7.6% for BUA, 5.2% for SOS and 10.6% for SI. The mean (± SEM) *Z*-scores were −0.86 ± 0.31 for BUA, −0.29 ± 0.27 for SOS and −0.70 ± 0.31 for SI (Table 2).

Table 2. *Z*−scores and areas under the ROC curves (AUC) for QUS measurements, BMD (at both the lumbar spine, femoral neck) and markers of bone turnover in 23 patients with Cushing's syndrome.

Variables	*Z*−scores	AUC
Broadband ultrasound attenuation (dB/MHz)	−0.86±0.31	0.72
Speed of sound (m/s)	−0.29±0.27	0.62
Stiffness index, SI	−0.70±0.31	0.73
Lumbar spine BMD (g/cm^2)	−1.54±0.17	0.90
Femoral neck BMD (g/cm^2)	−1.10±0.17	0.81
Serum PICP (ng/ml)	0.37±0.36	0.56
Serum PINP (ng/ml)	0.47±0.28	0.63
Serum osteocalcin (ng/ml)	−0.99±0.27	0.83
Serum bone alkaline phosphatase (ng/ml)	0.34±0.4	0.5
Serum ICTP (ng/ml)	0.10±0.13	0.62
Urinary CTX (μg/mmol Cr)	−0.53±0.13	0.64

BMD was also decreased in patients with CS, at both the lumbar spine and femoral neck ($p<0.005$). The mean decreases were 20.9% for BMD_{LS} and 17.6% for BMD_{FN}. The mean *Z*-scores ($\pm$ SEM) were -1.54 ± 0.17 for BMD_{LS} and -1.10 ± 0.17 for BMD_{FN} (Table 2).

In the group of patients with CS there was no significant corelation between QUS measurements and BMD. Indeed at the lumbar spine *r* values were 0.08, 0.16 and 0.14 for BUA, SOS and SI respectively. At the femoral neck *r* values were also not significant: 0.05, 0.02 and 0.06. Conversely we found significant correlations between QUS and BMD in controls at both the lumbar spine (*r* ranging from 0.48 to 0.59) and the femoral neck (*r* ranging from 0.41 from 0.48).

AUC was statistically higher for BMD_{LS} than for QUS measurements ($p<0.05$; Fig. 1). Conversely AUC for BMD_{FN} was not statistically significantly different from AUC for either BUA or SI.

Both serum osteocalcin and urinary CTX levels were decreased in patients with CS compared with control subjects ($p<0.005$ and $p<0.05$ respectively). Conversely serum levels of PICP, PINP, BAP and ICTP were not statistically significantly different between the two groups ($p=0.44$, $p=0.17$, $p=0.97$ and $p=0.13$ respectively). The mean *Z*-scores ($\pm$ SEM) were -0.99 ± 0.27 for osteocalcin, -0.53 ± 0.13 for CTX, 0.37 ± 0.36 for PICP, 0.47 ± 0.28 for PINP, 0.34 ± 0.4 for BAP and 0.10 ± 0.13 for ICTP (Table 2). AUC was statistically higher for osteocalcin than for other markers of bone turnover ($p<0.05$) for each comparison (Fig. 2).

There was no relationship between disease duration and BMD, QUS measurements or the level of markers of bone turnover. A negative correlation was found between plasma cortisol (at 0800 hours or the mean over 24 h) and BMD at both the lumbar spine ($r = -0.54$, $p<0.05$ and $r = -0.48$, $p<0.05$ respectively) and femoral neck ($r = -0.59$, $p<0.01$ and $r = -0.46$, $p<0.05$ respectively). Conversely plama cortisol (at 0800 hours or mean 24 h) did not correlate with QUS measurements or the level of markers of bone turnover. No correlation was found between UFC and either BMD or QUS measurements of bone. In the same manner UFC did not correlate with markers of bone turnover. Also DHEA-S did not correlate with BMD, QUS measurements of bone or markers of bone turnover.

Discussion

Our study shows that QUS measurements are decreased in patients with CS for both BUA and SI ($p<0.01$ and $p<0.05$, respectively) but not for SOS ($p=0.08$). The mean decreases compared with results observed in controls were 7.6% for BUA, 5.2% for SOS and 10.6% for SI. To our knowledge this the first study to have assessed the usefulness of QUS measurements in CS. It is in agreement with one previous study in which we assessed the usefulness of QUS measurements of bone in a sample of patients who received corticosteroids for more than 1 year [8]. Indeed, in this study we found that BUA was reduced by 6.3%, SOS by 1.6% and SI by

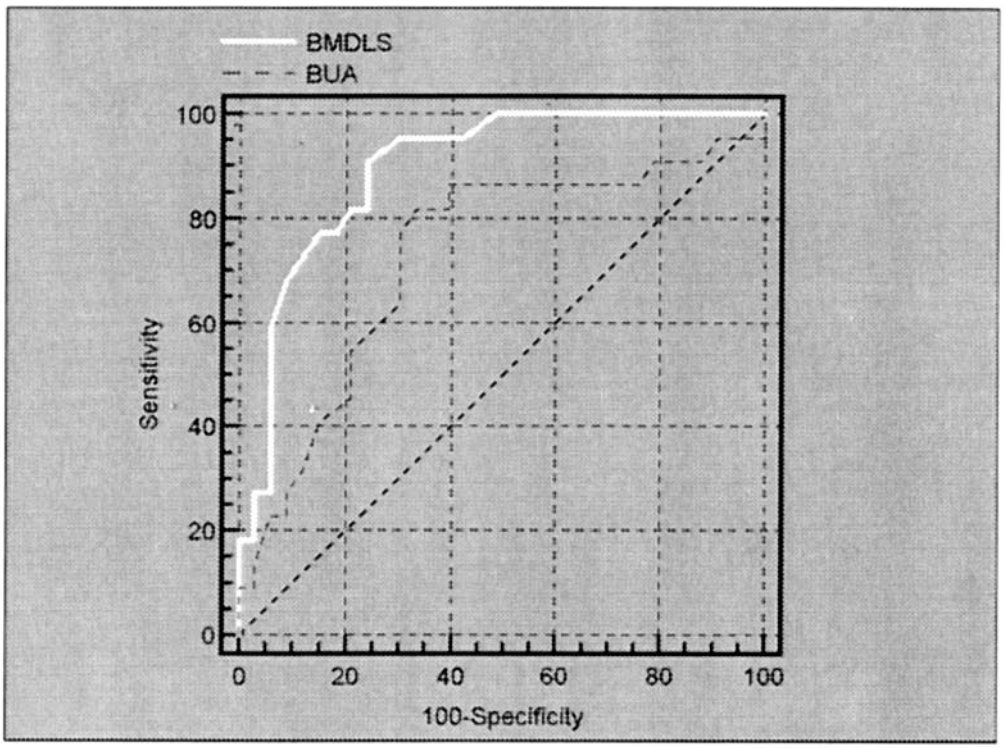

Fig. 1. ROC curves for bone mineral density at the lumbar spine (BMDLS) and broadband ultrasound attenuation (BUA).

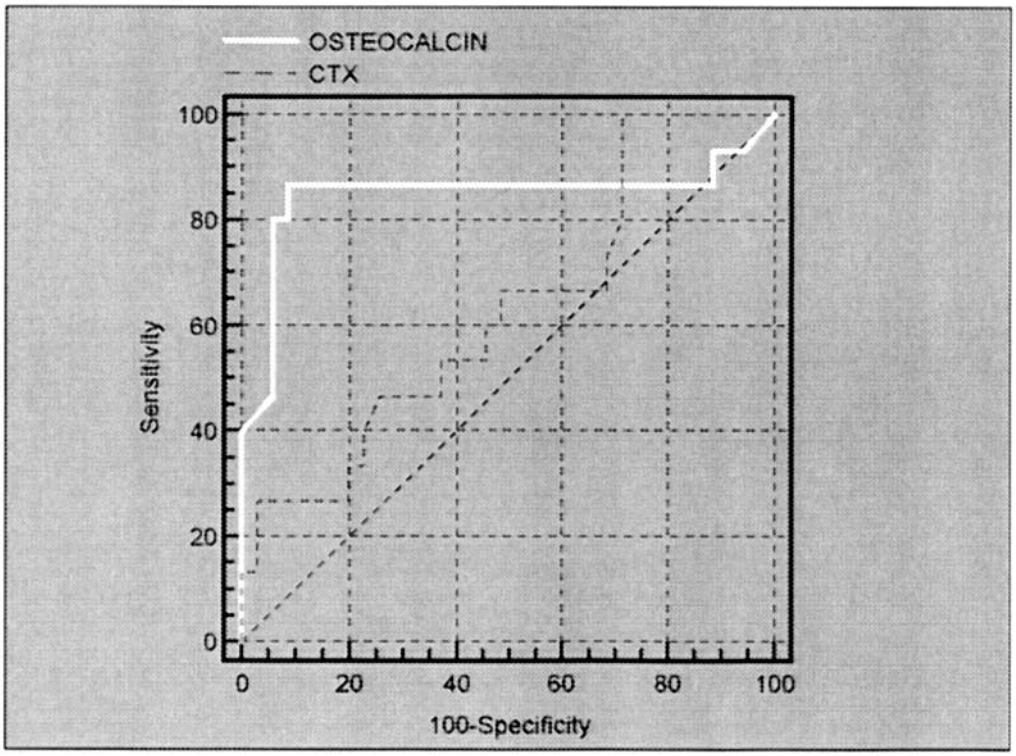

Fig. 2. ROC curves for osteocalcin and urinary CTX.

15.8% compared with values obtained in control subjects. In the same manner Daens et al. [9] showed that QUS measurements were decreased in patients with CIOP (−5.8% for BUA, −1.3% for SOS and −12.7% for SI). However, in these two previous studies the decrease in QUS measurements in CIOP was similar to that of BMD_{LS}. For instance Blanckaert et al. [8] found that BMD_{LS} was decreased by 11.5% and Daens et al. [9] found it was decreased by 11% in patients treated with corticosteroids compared with controls. Conversely in the present study we found that the decrease in BMD_{LS} was about 2 times greater compared with SI. Finally the decrease in BMD_{FN} in patients with corticosteroid excess in the present study was comparable to that reported by Blanckaert et al. (17.6% vs 16.7% respectively) [8]. The reason why we found a discrepancy between QUS measurements and BMD in endogenous glucocorticoid excess as compared with exogenous glucocorticoid excess is not known. However, the mean age of the patients in the study of Blanckaert et al. [8] and in the present study was not the same (61 years vs 38 years). Secondly the mechanisms leading to bone loss are probably different in endogenous glucocorticoid excess compared with exogenous glucocorticoid excess. Indeed glucocorticoids are given to patients suffering from inflammatory disorders and the disease being treated may increase bone turnover and cause bone loss (even in patients who do not receive corticosteroids). This finding has been particularly well demonstrated for patients with rheumatoid arthritis [15]. It is therefore possible that age and inflammatory disease modify the relationship between BMD and QUS measurements in patients with CIOP. The absence of significant correlation between QUS measurements and BMD in CS suggests that these two methods do not reflect the same feature of bone and could explain our findings, i.e., the fact that BMD was decreased more than the QUS measurements in patients with CS. Finally it is possible that the relationship between BMD and QUS is not the same in CS and CIOP. Indeed in our previous study on QUS measurements in CIOP we found significant correlations between QUS and BMD for BUA (r = 0.41 for lumbar spine; r = 0.49 for femoral neck) whereas such a relationship was not found in CS.

Our findings regarding markers of bone turnover suggest that serum osteocalcin levels are decreased by about 44% in patients with CS compared with controls, and this finding is in keeping with several previous studies [4,10–12]. The sole exception was the study by Hermus et al. [12], who found normal values of serum osteocalcin in CS. Except for osteocalcin we did not find any abnormality in others markers of bone formation, i.e., PICP, PINP and BAP. Our findings for both PICP and PINP are in agreement with the studies by Hermus et al. [2], Piovesan et al. [10], Osella et al. [11] and Ebeling et al. [13], who did not find any difference concerning either PICP or PINP levels between CS patients and controls. The discrepancy in the present study between osteocalcin on the one hand and PICP and PINP on the other hand suggests that osteocalcin and the two peptides

cleaved during the synthesis of type I collagen reflect different osteoblastic activities. It is also important to note that these two peptides are less sensitive compared with osteocalcin. Thus in a previous study we found that in patients with primary hyperparathyroidism, a disease characterized by elevated bone turnover, osteocalcin levels were increased whereas both PICP and PINP levels were in the normal range [7]. Data on BAP are sparse and conflicting in CS. Osella et al. [11] found low levels of BAP in CS whereas Hermus et al. [2] and Ebeling et al. [13] did not find any abnormality in BAP metabolism. In the same manner Hotimsky et al. [17] found that levels of BAP were in the normal range in a small group of patients who were receiving corticosteroids for more than 6 months, whereas at the same time they found that osteocalcin was decreased by 1.2 standard deviations on average. The discrepancies between the different formation markers could be related in part to their clearance. Other studies on BAP in CS are clearly needed to address this issue.

Bone resorption as assessed by the measurement of ICTP and urinary CTX was not increased in the present study. Whereas the increase in bone resorption has been well demonstrated in patients treated by corticosteroids for inflammatory diseases [14,15], data are conflincting in CS [2,3,4,11,12]. It needs to be borne in mind that the increase in markers of bone turnover in patients with inflammatory diseases could be due to disease activity and not necessarily related to corticosteroids. Hermus et al. [2] and Osella et al. [11] found normal values of ICTP in patients with CS, in agreement with our own results. Finally ICTP should be considered as a marker of bone turnover rather than of bone resorption. To the best of our knowledge no data are available for CTX in CS. However, Sartorio et al. [12] found decreased values of ICTP in CS and ICTP has a chemical structure very similar to CTX. By contrast Di Somma et al. [3] found elevated levels of NTX and Chiodini et al. [4] found elevated levels of urinary deoxypyridinoline in patients with CS. Moreover Pearce et al. [18] demonstrated that corticosteroids given for reducing antisperm antibodies, i.e., in patients with no systemic illness, had no effect on urinary CTX. By contrast at the same time they found a 29% decrease in osteocalcin levels, suggesting that the alterations of bone metabolism encountered in their patients are very similar to that observed in CS. Finally the magnitude of the decrease in osteocalcin and CTX in the present study was not the same (44% vs 32%), suggesting an uncoupling of resorption from formation.

We did not find any correlation between UFC and markers of bone turnover nor between UFC with either BMD or QUS measurements. These findings are in agreement with previous studies on this issue [2,11]. However, we found a significant correlation between plasma cortisol (at 0800 hours or mean 24 h) and BMD at both the lumbar spine and femoral neck whereas such correlations were not found for QUS meaurements. Cortisol binding globulin (CBG) could partly explain this discrepancy. Unfortunately CBG was not measured in the present study. Finally our data also suggest that QUS and bone densitometry do not measure the same feature in CS.

In conclusion, QUS of bone seems to be a relevant tool for assessing bone involvement in CS. QUS does have a lower sensitivity compared with DXA, however, and the relevance of QUS cannot be ascertained until some longitudinal data are forthcoming. Except for CTX, the new markers of bone turnover assessed in this study (PINP, PICP, BAP and ICTP) do not seem of interest in CS.

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