Osteoporosis with Low Dose Corticosteroids: Contribution of Underlying Disease Effects and Discriminatory Ability of Ultrasound versus Bone Densitometry

PHILIP SAMBROOK, ANNA RAJ, DAVID HUNTER, VASI NAGANATHAN, REBECCA MASON, and BRUCE ROBINSON

ABSTRACT. ***Objective***. Corticosteroid use is associated with rapid bone loss, but the effect of low dose corticosteroids (CS) remains controversial and the extent to which increased fracture risk relates to quantitative effects, as reflected by change in bone mineral density (BMD), or to qualitative effects due to altered microarchitecture is unclear. Moreover the contribution of the underlying disease, for which CS are used, confounds the assessment of CS effects on bone. Our aim was to examine these effects of CS on bone.

Methods. We measured BMD, quantitative ultrasound (US), and clinical and radiological disease indices in 76 patients with rheumatoid arthritis (RA) treated with or without low dose CS. Disease effects were quantitated using the Health Assessment Questionnaire and radiological scores.

Results. BMD and US measures were significantly reduced in RA patients compared to age matched controls. Low dose CS use was associated with a further small but nonsignificant reduction in BMD, and US measures did not further discriminate CS effects on bone. Radiological score was an independent predictor of US measures, suggesting that in RA, calcaneal bone may reflect both systemic and local disease effects.

Conclusion. US did not appear to discriminate effects of low dose CS on bone better than BMD. However, underlying RA disease effects on bone are detectable by US. Quantitative US should be investigated for its utility in assessing disease activity or progress in RA. (J Rheumatol 2001; 28:1063–7)

Key Indexing Terms:

OSTEOPOROSIS	FRACTURE	RHEUMATOID ARTHRITIS
ULTRASOUND	BONE MINERAL DENSITY	CORTICOSTEROIDS

Osteoporosis is characterized not only by low bone mineral density (BMD) but also microarchitectural deterioration. Although BMD, usually assessed by dual energy x-ray absorptiometry, is currently considered the best predictor of fracture risk, quantitative ultrasound (US) appears to provide additional information regarding microarchitecture, since US waves pass through a bone at a rate dependent on its structural characteristics. Two US measures have been examined, namely broadband US attenuation (BUA), which is thought to reflect mainly bone mass and architecture, and velocity of sound (VOS), which reflects mass and elasticity of bone[1-3]. Recent studies have demonstrated US measures can discriminate between normal and osteoporotic postmenopausal women, independently of BMD[4,5].

Corticosteroids (CS) cause bone loss by a variety of mechanisms[6,7], and it has been suggested patients treated with CS may fracture at BMD thresholds different from those for other forms of osteoporosis[8,9], raising the possibility of a qualitative as well as quantitative defect of bone due to CS. However, assessment of CS effects on bone is confounded in most patients by the underlying disease for which the CS are used, since diseases like rheumatoid arthritis (RA) are associated with bone loss independently of CS use[10]. Consequently the role of low dose CS in promoting bone loss in RA remains unclear, with some studies showing bone loss increases, while others suggest improved disease control due to CS therapy may ameliorate bone loss[11-18].

We examined the effects of low dose CS on bone, both

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quantitatively and qualitatively, independently of disease effects, by measuring BMD, quantitative US, and clinical and radiological disease indices in patients with RA treated with or without low dose CS.

MATERIALS AND METHODS

Subjects were recruited consecutively from patients attending the inpatient and outpatient service of the Department of Rheumatology of the Royal North Shore Hospital. The study was approved by the hospital Human Research Ethics Committee and all patients gave informed consent. All patients satisfied the American College of Rheumatology classification criteria for RA[19].

Patients were assessed clinically for disease activity including functional class[20] and disability using the Health Assessment Questionnaire (HAQ) score[21]. Details regarding disease duration, use of disease modifying drugs, calcium intake, other medication use, and history of fractures were also recorded.

Velocity of sound (VOS) and broadband attenuation (BUA) were measured in the nondominant heel using a McCue CUBA II (McCue, Hampshire, UK). No patient had severe ankle deformity. The precision of quantitative ultrasound (US) measurements in 11 CS treated RA patients assessed by duplicate measurements was 2.4% for BUA and 0.15% for VOS. Radiographs of the same foot scanned by QUS were obtained and a modified Larsen score determined[22]. BMD of the lumbar spine and hip were measured using a Hologic 4500W (Hologic Inc., Waltham, MA, USA). The precision of these measures determined in our laboratory from duplicate measurements of BMD in 30 CS treated subjects participating in a clinical trial was 1% for the lumbar spine and 2% for the femoral neck. Lateral radiographs of the thoracolumbar spine were also obtained to detect prevalent vertebral fractures. Vertebral fractures were assessed semiquantitatively and defined as present when there was a 20% reduction of anterior, middle, or posterior vertebral height.

BMD, BUA, and VOS were expressed as Z scores (comparison to aged and sex matched normals, respectively). Regression equations for Z scores were determined from measurements in healthy subjects. These control subjects comprised 454 female and 56 male subjects aged 18–80 years, recruited for studies of the discriminant ability of US measures for prediction of BMD and genetic studies of BMD. Subjects with diseases or drugs that could affect bone metabolism were excluded. The method of recruitment of these controls and their health status assessment has been described[23].

Statistical analysis. Unpaired t tests were used to compare CS treated and nonsteroid treated patients. Multiple regression analysis was used to determine the significant predictors of BMD and QUS. A backwards stepwise approach was used, where all independent variables were included in the model, and at each step a partial F ratio of 3.996 was used to remove variables. Variables included in the initial model were body weight, disease duration, Larsen score, and HAQ. CS dose was also included as a forced variable in multivariate analyses. Although the HAQ and Larsen variables were graded at each joint using a categorical grading system, when summed each variable was continuous and Kolmogorov–Smirnov tests confirmed they were normally distributed. Analyses were performed using Statview 5.0 (SAS Institute).

RESULTS

The characteristics of the patients with RA are shown in Table 1. A total of 76 patients were assessed, of whom 40 were receiving corticosteroids (mean daily prednisone dose 6.8 mg, mean duration 5.7 yrs). Patients categorized as "no steroids" had never received oral CS; however, previous intraarticular steroid use was not an exclusion criterion. The CS and nonsteroid treated groups were well matched for age, sex, and weight. Of the various clinical measures of RA, only the HAQ score was significantly different between the 2 groups, reflecting the generally more active disease of the CS treated group.

Table 1. Patient characteristics (mean ± SE).

	Corticosteroid Treated, n = 40	Nonsteroid Treated, n = 36
Sex (F/M)	35/5	32/4
Age (yrs)	60.9 ± 2.0	58.9 ± 2.2
Weight (kg)	66.3 ± 2.2	65.4 ± 2.5
Corticosteroid daily dose (mg)	6.8 ± 0.4	—
Disease duration (yrs)	13.6 ± 1.8	11.7 ± 1.4
HAQ	1.24 ± 0.11	0.77 ± 0.13*
Functional class	1.95 ± 0.14	1.97 ± 0.10
No. of DMARD	1.5	1.2
Larsen score	7.2 ± 1.2	6.9 ± 1.2

*p < 0.006. DMARD: disease modifying antirheumatic drugs.

BMD and US values, VOS, and BUA, expressed as Z scores, are shown in Table 2. BMD and US measures were all significantly reduced in patients with RA compared to healthy controls ($p < 0.001$, data not shown). BMD values were about 0.3 to 0.4 standard deviations (SD) lower in CS treated patients than nonsteroid treated patients, but these differences were not statistically significantly different. US values were also marginally lower in CS treated patients than nonsteroid treated patients, but less so than for BMD (about 0.1 to 0.2 SD). However, overall reductions in US measures in both RA groups were greater than for BMD at either site (about 1 to 1.2 SD below compared to age matched healthy subjects).

Vertebral fractures were present in 7 CS and 4 nonsteroid treated patients. BMD and US values were generally significantly lower in fracture than nonfracture subjects for all patients combined and in CS treated patients only (Table 3).

Simple univariate analyses revealed weak negative correlations between BMD/US measures and HAQ ($r = –0.35$, $p < 0.01$ for femoral neck; $r = –0.28$, $p < 0.05$ for both BUA and VOS), RA duration ($r = –0.34$, $p < 0.01$ for lumbar BMD, $r = –0.44$, $p < 0.001$ for femoral neck BMD and VOS; $r = –0.37$, $p < 0.01$ for BUA), and CS dose ($r = –0.44$, $p < 0.01$ for femoral neck BMD). The relative effects of disease

Table 2. BMD and ultrasound values expressed as Z scores in patients compared to healthy controls (mean ± SE).

	Corticosteroid Users, n = 40	Steroid-free Controls, n = 36
Lumbar BMD	–0.75 ± 0.20	–0.42 ± 0.28
Femoral neck BMD	–0.83 ± 0.16	–0.45 ± 0.22
BUA	–1.18 ± 0.22	–0.97 ± 0.19
VOS	–1.217 ± 0.25	–1.20 ± 0.23

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Table 3. Difference in bone measures between RA patients with and without vertebral fracture.

	Fracture Group, n = 11	Non-Fracture Group, n = 65	p
Lumbar BMD	0.83 ± 0.16	0.93 ± 0.17	0.09
Femoral BMD	0.62 ± 0.18	0.82 ± 0.14	0.005
BUA	44 ± 15	74 ± 20	0.0001
VOS	1560 ± 51	1616 ± 50	0.001
n (corticosteroid pts only)	7	33	
Lumbar BMD	0.78 ± 0.16	0.90 ± 0.14	0.06
Femoral BMD	0.51 ± 0.12	0.68 ± 0.12	0.002
BUA	42 ± 14	74 ± 20	0.004
VOS	1552 ± 58	1618 ± 50	0.007

BUA: broadband ultrasound attenuation. VOS: velocity of sound.

and CS therapy were subsequently assessed by stepwise multiple regression analysis. Since age was a significant predictor at all sites, the regression coefficients of predictor variables shown in Table 4 were determined after age adjustment of BMD and US values (i.e., using Z scores as the dependent variable). Weight was a significant predictor variable for femoral neck BMD but not lumbar spine BMD, VOS, or BUA. CS dose was a weak significant predictor variable only for femoral neck BMD, but not for lumbar BMD or for either US measure. Radiological disease (Larsen score) was a significant predictor at 3 measurement sites, lumbar and femoral neck BMD and BUA, but not calcaneal VOS. For VOS, significant predictor variables were disease duration and HAQ score.

DISCUSSION

Osteoporosis is a common clinical problem in patients with RA. However, dissecting out the relative contributions of the underlying inflammatory process, associated reduced mobility, and corticosteroids in the etiology of bone loss in RA has proved difficult. Moreover, whether low dose CS promote osteoporosis in RA remains controversial, with some studies suggesting a possible protective effect by disease suppression[17]. We have attempted to control for these disease related factors in this study by using well validated objective measures of physical and functional disability (HAQ) and radiological damage (Larsen score). Except in the regression analyses at the femoral neck site, we were unable to detect a statistically significant difference between nonsteroid and CS treated patients. This is likely to be due to insufficient power to detect small differences. However, study power needs to be related to clinical significance. Because the differences we observed between corticosteroid and nonsteroid treated patients were small, we would have needed a sample size of 480, 4366, and 5722, respectively, to demonstrate a statistically significant (but questionable clinically significant) difference for lumbar BMD, BUA, and VOS.

Since quantitative US measures are thought to reflect not only bone mass but also bone architecture, the ability of US to discriminate the effects of CS on bone, independently of BMD, is of interest. Our study found no better discrimination of CS effects on bone by US than BMD, but suggested US may be a better discriminator of the underlying disease effects of RA on bone than BMD. Importantly, worsening disease activity assessed by HAQ score was significantly associated with reduced VOS values, and radiological damage, assessed by Larsen score, was associated with reductions in BUA.

It might be argued that US, as a peripheral measurement

Table 4. Univariate and multivariate associations between age adjusted densitometric and ultrasound values and predictor variables.

Site	Predictor Variable	Univariate* ß (p value)	Multivariate** ß (p value)
Lumbar spine	Larsen score	–0.095 (0.0001)	–0.093 (0.0001)
Femoral neck	Weight	0.030 (0.002)	0.020 (0.03)
	Larsen score	–0.084 (0.0001)	–0.065 (0.0007)
	Steroid dose	–0.082 (0.02)	–0.075 (0.02)
BUA	Larsen score	–0.086 (0.0001)	–0.073 (0.0007)
VOS	Disease duration	–0.065 (0.0001)	–0.054 (0.0007)
	HAQ	–0.736 (0.0005)	–0.586 (0.006)

*After adjustment for age; **after adjustment for age and corticosteroid dose. BUA: broadband ultrasound attenuation. VOS: velocity of sound.

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of bone, is reflecting periarticular osteoporosis, whereas BMD of the spine and hip is reflecting axial osteoporosis. Periarticular bone loss adjacent to involved joints has long been recognized in RA and appears to reflect production of cytokines by inflamed synovium in adjacent joints[24]. In addition to bone mass, BUA is thought to reflect architecture, whereas VOS reflects elasticity of bone. Our findings that radiological damage was a predictor of BUA but not VOS suggest the same inflammatory processes responsible for erosive disease may also influence architecture in the adjacent bone.

There have been a number of studies of US in RA[25-29]. England, *et al*[25] studied 69 patients with RA and observed reductions in BUA compared to controls and a relationship between these reductions and disease duration. Coombes, *et al*[26] measured BMD and US in 40 postmenopausal women with RA, all of whom had been treated with CS for 1 year. Although BMD correlated with calcaneal BUA, there was no correlation with either of these measures and age or cumulative steroid dose. Madsen, *et al*[27] measured US in 79 patients with RA, 11 of whom had not received steroids, 27 who continued, and 41 who had past exposure. BUA and VOS were significantly reduced in RA compared to controls and VOS correlated inversely with HAQ and disease duration, but the role of CS was unclear due to the large number of past users. Martin, *et al*[28] examined calcaneal US in 46 women with RA, of whom 25 were receiving low dose CS (mean prednisone dose 6.5 mg/day) therapy. US was reduced in RA patients, but there was no significant difference between the steroid and nonsteroid groups, in agreement with our study. When both groups were combined, Larsen score was negatively correlated with BUA, also consistent with our findings. Njeh, *et al*[29] measured BUA in the proximal phalanges of 51 RA patients not receiving steroids and observed a modest correlation with HAQ scores.

Two recent studies have suggested that vertebral fractures due to CS occur at a higher BMD to that observed in other forms of osteoporosis. Luengo, *et al*[8] compared fracture thresholds between 32 patients with steroid dependent asthma and vertebral fractures and 55 patients with postmenopausal osteoporosis and vertebral fractures. Calculated fracture thresholds (determined as the 90th percentile of the mean BMD) were 1.17 and 0.98 g/cm^2, respectively, suggesting that CS treated patients sustained fractures at significantly higher BMD values. Peel, *et al*[9] examined vertebral deformity prevalence in patients with RA treated with low dose CS. Vertebral fracture prevalence rates were 27.6% in RA compared to 5.8% in an age matched control population. Despite finding only a 0.8 standard deviation reduction in BMD values (which would be expected to translate into an approximate doubling of fractures), they observed an apparent 6-fold increase in the prevalence of vertebral fractures. Both studies raise the possibility of a qualitative as well as quantitative defect of bone due to corticosteroids. In contrast, our fracture prevalence rates between CS and nonsteroid users could be largely accounted for by differences in BMD.

To summarize, although CS use is associated with rapid bone loss, the extent to which increased fracture risk relates to quantitative or qualitative effects or underlying disease is unclear. We found no better discrimination of the effects of low dose corticosteroids for either BMD or US. However, disease measures, both radiological and clinical, were significantly associated with US measures, suggesting that in RA, calcaneal bone status may reflect both systemic and local disease effects. Quantitative ultrasound should be investigated for its utility for monitoring disease progress in rheumatoid arthritis.

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