Corticosteroid therapy and bone mass — comparison of rheumatoid arthritis and systemic lupus erythematosus

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This study was designed to evaluate the effects of low-dose corticosteroid (CS) therapy for rheumatoid arthritis (RA) and of high-dose CS therapy for systemic lupus erythematosus (SLE) on metacarpal bone mass in young (premenopausal) subjects. Ninety-eight patients with RA, 63 patients with SLE and 85 healthy controls of comparable age, race, sex and nutritional status were studied. Metacarpal bone mass was measured by radiogrammetry using a digitiser. In the RA patients, mean bone mass of CS-treated subjects (27%) was 52,31 g/cm^2, while that of untreated subjects was 56,69 g/cm^2 ($P < 0,02$). In the SLE group, mean bone mass of CS-treated subjects (76%) was 61,47 g/cm^2 and that of untreated subjects 62,36 g/cm^2 ($P > 0,1$). Although patients with SLE required larger cumulative doses of CS for longer periods, their bone mass was higher than that of the RA subjects ($P < 0,01$). None of the patients had femoral neck or vertebral crush fractures. In RA, bone loss was probably a feature of severe disease rather than of CS therapy.

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There is controversy concerning the mechanism whereby corticosteroid (CS)-related bone loss is mediated.[1] One of the major defects in the design of previous studies has been that many of the subjects were postmenopausal at the time of evaluation. Numerous techniques have been devised for normalisation of the menopausal period, but it is impossible to separate the effects of age and the menopause from those of CS therapy.[2,3] It is not known whether it is the total daily dose, total duration or cumulative dose of CS that is important.[4] Recently, Sambrook *et al.*,[5] using dual-photon absorptiometry (DPA) measurement at the spine and hip, showed that low-dose CS therapy does not increase trabecular bone loss in rheumatoid arthritis (RA).

Suda *et al.*[6] studied the effects of hydrocortisone on osteoclasts generated in cat bone marrow cultures, and found that osteoclast numbers and size were reduced. These findings are compatible with the suggestion that CS may act directly on osteoclasts, which, *in vivo,* may result in decreased resorption of bone and indirectly in decreased bone formation as well. However, it is not clear to what extent these findings can be extrapolated to man. Rickers *et al.*[7] concluded that high-dose prednisone therapy has an effect on cortical and trabecular bone.

It has been suggested that the place of CS therapy in RA needs to be re-evaluated, favouring earlier use of such therapy in combination with disease modifying agents.[8-10] Comparisons of bone loss between polymyalgia rheumatica (PMR) and RA[11] are invalidated by the age of subjects who suffer from PMR. There are also very few reports of bone mass measurement in systemic lupus erythematosus (SLE), where young females often need high-dose CS therapy.[12]

Against this background, a study was designed to compare bone mass at various sites in young, ambulant patients with RA and SLE.

Patients and methods

Sixty-three ambulant young patients (under 50 years of age) with SLE and 98 with RA were studied between April 1985 and September 1986. They were all regularly attending an outpatient lupus clinic or an arthritis clinic at Groote Schuur Hospital. Age under 50 years, independent ambulation and disease classification according to the American Rheumatism Association (ARA) revised criteria[13,14] were the main basis for selection. Pregnant women were excluded. A protocol was designed to record age, race, sex, age at onset of disease, duration of disease and criteria for diagnosis of SLE[13] or RA.[14] Age at onset was taken as the age at which the first acceptable symptoms of the disease occurred.[15] A complete physical examination was carried out by one of us (A. A. K.). Laxity of tendons was not specifically evaluated. The Keitel function test (KFT),[16] a useful global measure of disability in polyarthritis, was performed in both groups (by A. A. K.), its components being scored as previously described.[17] Patients were categorised for disability using the ARA functional classification.[18] Nutritional status was assessed using body diameters[19] and skinfold thicknesses.[20] Patients with RA were additionally evaluated for disease activity using standard criteria.[17] The records were examined to determine which patients had taken CS in the course of their disease. In all patients standardised radiographs were taken of both hands, the left hip and the lumbar spine centred at L3. Detailed dietary, smoking and alcohol consumption histories were also obtained, but the results will be confined to an analysis of the relationship between bone mass and CS therapy.

Radiographs of both hands were taken at a tube distance of 100 cm. The exposure and development times were standardised for the purpose of this study.[21] The right 2nd metacarpal index,[22] whole-bone ash,[23] 6 metacarpal hand score (6MHS) and 6 metacarpal percent cortical area (6M%CA)[24] were calculated by a computer-assisted technique.[21] Radiogrammetry was used because single-photon absorptiometry and DPA were not available at the research centre.

Measurements of medullary width (MW) and total width (TW) at the midshaft of 6 metacarpals were made by a single observer (A. A. K.), using a Houston Hipad Digitizer interfaced with an IBM personal computer.[21] The combined cortical thickness (CCT) was calculated as the difference between TW and MW. Calculations of metacarpal bone mass were automatically generated by the computer within seconds. The validity of this method has been reported previously. The intra-observer differences were not significant.[21] The Vernier caliper was not used. The right wrist was graded according to the Larsen index,[25] and the right carpal length was measured for calculation of the carpometacarpal ratio (CMR).[26]

The left hip radiographs were taken in 15° of internal rotation as suggested by Singh.[27] This was graded by a single observer (A. A. K.) according to the Singh index of trabecular osteoporosis (OP).[27,28] The cortical thickness 1 cm proximal to the lesser trochanter was measured as recommended by Fredensborg and Nilsson.[29] The 3rd lumbar vertebra was graded for OP according to the method of Saville.[30]

Eighty-five marginally matched healthy volunteers were used as controls for this study. The same selection criteria were applied with respect to age and pregnancy, and the same radiographs were taken. No volunteer with a medical disease of any kind requiring regular treatment was accepted. Dietary, smoking and alcohol consumption histories were obtained, and nutritional status was recorded.

Six groups were defined for comparison of the effects of CS therapy on bone mass, as follows: (*i*) all RA v. all SLE v. controls; (*ii*) RA-CS v. SLE-CS; (*iii*) RA-CS v. controls; (*iv*) SLE-CS v. controls; (*v*) RA-CS v. RA-no CS; and (*vi*) SLE-CS v. SLE-no CS. The groups were compared for differences in MW, TW, CCT, 6MHS and right 2nd metacarpal cortical area percent (CA%).

Statistical methods

The mainframe computer at the Institute for Biostatistics of the Medical Research Council was used for all the statistical calculations. The SAS package[31,32] and BMDP statistics software[33] were used for all conventional analyses. Multivariate discriminant and regression analyses were used to compare the treated and untreated groups. Spearman correlation coefficients were used in the construction of the correlation matrix. Linear trends were evaluated using the concept of generalised additive models[34] as well as the principle of least squares.[31,32] Appropriate corrections in the probability were made for multiple comparisons.[35]

Results

A total of 246 individuals were studied. Table I shows that the three groups were marginally matched for race, sex and nutritional status. Coloured women predominated. Patients with SLE were younger (mean age 32 years) than the healthy controls (mean age 34 years) ($P > 0,05$), while patients with RA were slightly older (mean age 38 years) ($P < 0,05$).

Table I. Race and sex distribution of the subjects under study

	Controls	RA	SLE
Total No.	85	98	63
White male	3	5	–
White female	25	16	5
Coloured male	19	16	3
Coloured female	37	48	48
Indian male	–	–	1
Indian female	1	2	2
Black male	–	3	–
Black female	–	10	4
Lean body weight*(dm²)	69,59	70,0	68,78
Lean body mass† (g/ml)	1,097	1,098	1,098

* Nutritional status using body diameters.
† Nutritional status using skinfold thickness.

The patients with SLE required CS therapy for longer periods (mean 31 months) than those with RA (mean 24 months). This is not surprising if the nature of the respective diseases is considered. Patients in the treated group received CS at some stage of their disease, and for an excess of 6 months continuously. They were not necessarily receiving CS at the time of study, and no record was kept of how long before the study CS had been discontinued. At the time of the study, 76% of the SLE group and 27% of the RA group were receiving CS therapy; 8% of the SLE group had received CS earlier on in their illness. The mean daily dose of CS in RA subjects was 12,63 mg compared with a mean daily dose of 26,5 mg in SLE. Subjects with RA consumed a mean cumulative dose of CS of 10,263 g compared with a mean cumulative dose of 21,856 g in SLE. The groups under study serve as a useful basis for comparing the effects of high-dose CS therapy (SLE) with low-dose therapy (RA) on bone mass in premenopausal subjects.

The comparison of CA% in the two groups showed that patients with SLE had a higher bone mass than patients with RA, despite the greater requirements for CS therapy. The differences found between treated and untreated subjects in either group are shown in Table II. The number of untreated SLE subjects was relatively small, as was the number of RA patients treated with CS. Although the statistical techniques were adjusted for the effect of sample size, the possibility of a type II error cannot be confidently excluded. All the subgroups had a significantly lower bone mass than normal controls ($P < 0,05$) (Fig. 1).

Duration of disease (mean ± SD) in the RA-CS group (140 ± 78 months) was significantly longer than in the RA-no CS group (88 ± 76 months) as well as in both SLE subgroups. The SLE-CS (86 ± 71 months) and SLE-no CS (53 ± 47 months) groups were not significantly different ($P > 0,05$) with respect to disease duration; the same applied to the

Table II. Bone mass in patients with RA and SLE in relation to prior use of CS*

	SLE			RA		
	CS	No CS	*P*	CS	No CS	*P*
No.	48	15		27	71	
TW (cm)	0,81	0,81	NS	0,86	0,85	NS
MW (cm)	0,31	0,29	NS	0,41	0,37	0,03
CCT (cm)	0,51	0,52	NS	0,45	0,49	0,06
CA% (g/cm²)	82,98	82,77	NS	74,07	77,56	NS
6MHS (g/cm²)	61,47	62,36	NS	52,31	56,69	0,02

*The total dose of CS used by patients with RA and SLE is compared.

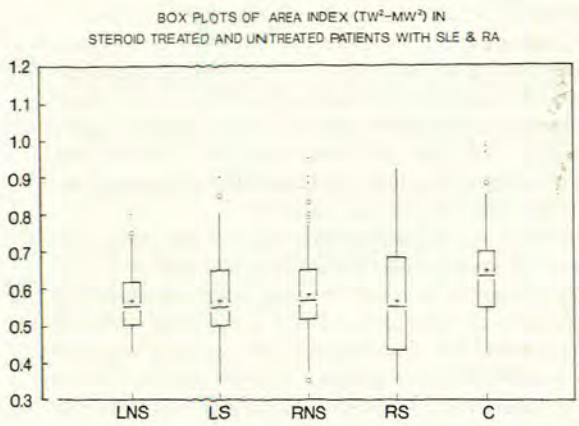

Fig. 1. Box plots of CA% in subgroups of the patients seen. The box encompasses the inter-quantal range and the cross represents the median, while the box is divided at the mean. The lines complete the 95% range and the circles represent outlies. The four patient subgroups had a significantly lower bone mass ($P < 0,05$) than the controls (C). Corticosteroid-treated (LS) and untreated (LNS) SLE patients were not significantly different ($P > 0,1$), while the RA (RS and RNS) subgroups were.

RA-no CS and the SLE-no CS groups. Multiple regression analysis showed that these differences in the RA subgroups did not explain a significant proportion of the ariation in 6MHS.

A correlation matrix (Spearman) showed that in the RA group only, the 6 metacarpal index just reached significance when compared with the cumulative dose of CS therapy ($P = 0,05$; $r = -0,2$). No correlation was found with daily dose or duration of therapy. The Larsen index at the right wrist also correlated significantly with the total dose of CS ($P < 0,02$; $r = 0,25$), suggesting that in RA the patients with more severe disease required such therapy (not shown). In SLE, the daily dose of CS correlated with 2nd metacarpal CCT ($r = -0,25$; $P = 0,06$), but not with CA% ($P > 0,1$). In the patients with RA, there was a significant negative correlation of daily dose with metacarpal length ($P < 0,05$). However, the correlation with TW, MW, CCT and 6MHS was not statistically significant ($P > 0,05$; $r < 0,2$). Medullary width was the only variable that reached a significant correlation with daily dose, duration and total CS dose ($0,05 < P < 0,1$) in RA, but not in SLE. There was no significant trend of bone mass with respect to increasing cumulative dose of CS in SLE ($P > 0,5$; $r = 0,03$) or RA ($P > 0,5$; $r = -0,05$).

Table III shows a comparison of the functional status in the two groups of patients. It is clear that the ARA functional classification does not differentiate the groups adequately; however, the KFT was significantly different ($P < 0,01$). Although the KFT correlated significantly with 6MHS and CA% in the RA group, there was no significant correlation between these variables in the SLE group. The hand function index (HFI) did not correlate significantly with bone mass in RA or SLE subjects.

Table III. Functional assessment in RA and SLE

	RA	SLE
ARA functional class		
1	22	45
2	76	18
UK functional class		
1	16	38
2	34	13
3	48	12
HFI (mean ± SD)	27,21 ± 10,17	12,89 ± 9,27
Shoulder (mean ± SD)	2,13 ± 2,97	0,04 ± 0,2
Lower limb (mean ± SD)	8,7 ± 7,43	1,72 ± 3,49
KFT* (mean ± SD)	38,04 ± 16,44	14,65 ± 10,65

* The KFT was divided according to areas of the body representing the hands and wrists (HFI), shoulders and lower limbs.

Stepwise discriminant analysis of the RA subgroups showed that the Larsen index at the right wrist was the best predictor of CS usage, with a sensitivity of 85% and specificity of only 42%. When the Larsen index was included together with 6MHS, the sensitivity was 80% and specificity 36%. In the patients with SLE, none of the radiological measures of bone and cartilage loss was able to predict the group using CS therapy.

Femoral cortical thickness was not significantly different between CS-treated and untreated subjects with RA or SLE ($P > 0,1$). The Singh index at the left femur was in the osteopenic range in 1 SLE patient taking CS therapy. The same patient had an osteopenic spine. There were no significant differences in trabecular pattern at the femur and 3rd lumbar vertebra in CS-treated and untreated patients with RA or SLE.

Discussion

The effect of corticosteroid therapy on bone is controversial.[1] Most studies are flawed by the overlap with postmenopausal osteoporosis, making it difficult to remove the confounding effect of this important variable. Studies of premenopausal subjects are generally flawed by statistical errors related to small sample size.[30] Some reports suggest that the effect of CS is confined to trabecular bone, sparing the cortical bone of the metacarpals and femoral neck.[6,7] It is not at all clear why this selective attack on trabecular bone should occur, since osteoblasts and osteoclasts from these areas have similar *in vitro* responses to biochemical stimuli. One possible explanation for these apparent differences could be the relative insensitivity of the Vernier caliper technique of radiogrammetry,[36] as well as single-photon absorptiometry (SPA).[37] Studies with SPA measurement of bone mass have shown differences between CS-treated and untreated subjects, offering the diephysial mass/metaphysial mass (trabecular/cortical) ratio as a measure of this effect of CS therapy.[37] However, Rickers *et al.*[7] have shown that the effects of CS on cortical and trabecular bone are similar.

Our study confirms that RA is a cause of significant osteopenia. This was probably a reflection of the disease process rather than the effect of therapy.[4] The fact that our patients with SLE had a higher bone mass than the RA group supports the suggestion that CS therapy was coincidental in the bone loss of the RA group, even though there are several other differences in the effects of the two diseases. There is further evidence that the bone loss of RA is more likely to be a feature of disease than of therapy.[5,38,39] We have shown that 6MHS correlates significantly with other markers of disease activity in RA.[17] This supports the suggestion that the disease-modifying effects of low-dose CS therapy in RA need careful evaluation.[8-10]

Stepwise discriminant analysis supports the concept that CS therapy in RA is generally confined to patients with more severe disease. The Larsen index[24] is an established measure of severity of RA and shows significant correlation with a reduced CMR.[25] Resorptive changes may indicate severity or longer duration.[40] We found that osteopenia was a surrogate measure of severity rather than an effect of CS therapy in RA. Our analysis did not address other possible variables that may have explained this difference in bone mass between treated and untreated RA subjects. However, owing to small sample size, the statistical properties of the Spearman correlation coefficients, and the technique applied in calculating trends, it is necessary to be cautious about inferences. Another possible explanation for the difference between the SLE and the RA groups could be that patients with SLE are somehow protected against the development of CS-induced OP. In that regard, patients with SLE have been shown to have lower circulating levels of tumour necrosis factor (TNF).[41]

Our patients with SLE required higher doses of oral CS therapy for longer periods than those with RA, yet the metacarpal bone mass was greater. Although the patients with SLE had less severe arthritis of the hands than those with RA, the HFI[18] was a poor predictor of both metacarpal bone mass and CS therapy in both groups. The mean age of the two groups was consistent with the age at peak bone mass. Age differences were, therefore, unlikely to be responsible for the differences in bone mass between the RA and the SLE subjects. The fact that the SLE group had a higher bone mass than the RA group is important, since it may suggest that CS-mediated bone loss is reversible. This is contrary to the findings of others.[42,43] Perhaps this controversy is due to the fact that our patients were premenopausal. It is also possible that the absence of local chemical substances such as TNF[41] in SLE result in less bone resorption in that group.

Kennedy *et al.*[38] found that CS therapy in RA significantly reduced bone mass only in patients over 45 years of age. In males, this loss did not become statistically significant until after the age of 55 years. Mueller,[44] comparing RA patients and asthma patients taking CS therapy, found that only patients with RA showed a loss of bone mass with such treatment. Hahn and Hahn[45] concluded that CS-related

osteoporosis is more common in children and in women over the age of 50 years. Reid *et al.*[4] found that in RA patients using CS therapy total body calcium was closely correlated with mean daily dose, but not with duration of treatment or mean cumulative dose.

Schorn[46] reported that area index was reduced in RA patients irrespective of CS therapy, but comparisons were not made between CS-treated and untreated patients. Wordsworth *et al.*[47] found that spinal OP tended to increase with age and CS therapy (less than 10 mg daily), often leading to pathological fractures. Saville and Kharmosh[39] showed that this was a feature of age rather than of CS therapy. Hajiroussou *et al.*[48] in a study of prolonged low-dose CS therapy in RA, found no significant differences when compared with matched RA patients not given CS therapy. They concluded that the risk of developing OP should perhaps not be considered a definite contraindication to the use of low-dose CS therapy in RA. None of the patients in our study had a history of pathological fractures of the wrist, hip or vertebra, and there was no radiographic evidence of such changes.

In a comprehensive essay on determining causation, Guyatt *et al.*[1] concluded that the evidence for exogenous CS as a cause of clinically important OP was weak and unproven. Their review of the literature on bone loss in RA showed that a similar statement could be made about this association in RA, at that time (1984). Byron and Mowat,[49] studying the pattern of CS prescribing in their unit, were surprised to discover that 24% were receiving CS therapy for articular disease, with a mean duration of therapy of 8,3 years. The pattern of CS prescribing at our unit has been similar[50] but the duration of CS therapy in the current study was much lower, probably owing to the selection of younger subjects. Nagant De Deuxchaisnes *et al.*[51] showed that the menopausal state had a synergistic effect on the bone-losing process accompanying low-dose CS therapy. Other workers[52-54] have added to the controversy. Our practice relating to the use of CS therapy in SLE also compares with other series.[12]

Our results do not confirm the need for a bone-sparing corticosteroid such as deflazacort in young women with rheumatic disease,[55-57] and it is not known whether these bone-sparing effects are seen at the high CS doses used in treating SLE. The relationship between CS therapy and avascular necrosis (AVN) of bone is well known. We have previously reported a prevalence of 7% in SLE,[12] comparable to that reported from other centres.[58] The role of osteoporosis in the pathogenesis of this disorder has not been critically evaluated with bone mass measurements. Early microscopic fractures due to OP could be incriminated in interfering with intramedullary haemodynamics.[59] This may also explain why AVN is sometimes seen long after CS therapy is discontinued.[12]

The results of experimental work in animals show clearly that CS have an inhibitory effect on bone development.[6] However, it is not clear to what extent these effects could be extrapolated to man. Bone biopsy and detailed calcium kinetics were not evaluated in our study. Numerous local factors have been described in the genesis of postmenopausal osteoporosis.[60,61] The inflammatory characteristics of several of these substances found also in RA, together with their negative effects on bone,[62] raise the possibility that CS could have a protective effect on bone cells. Such a theory is contrary to current medical belief, but supports an earlier suggestion by Saville and Kharmosh,[39] who described higher bone density in premenopausal RA females receiving CS therapy. Further work is required in young subjects, so that some of these important issues might be resolved. Comparison of trends in the treated and untreated groups strongly supports the suggestion that CS therapy was coincidental to the differences seen in the RA subgroups (not shown). This study did not adequately address the possible relationships between CS use and disease severity or activity, owing to difficulty in quantifying activity in SLE.[63] The predictive value of the Larsen index in the RA subjects, however, suggests that CS use is more likely in RA patients with severe disease.

Corticosteroids are important in the early management of severe rheumatic disease.[9,10] The patient is sometimes denied the potential benefit of such therapy on the basis of the potentially serious complication of OP. It is important for careful research to be directed towards a re-evaluation of the clinical relevance of bone loss in CS-treated subjects in the absence of confounding factors such as age, menopause and immobilisation. This study did not evaluate the mechanisms of CS effects on bone. Interpretation of biochemical markers of bone metabolism in rheumatic disease is confounded by the changes due to disease activity.[64] Metabolites of vitamin D cannot be measured readily and serum parathyroid hormone measurements are dependent on the reagents used.[65] Urinary excretion of calcium and inorganic phosphates may be impaired owing to lupus nephritis. However, these relationships need to be evaluated carefully in young subjects with RA and SLE. Such work might also resolve the controversy about abnormal calcium levels in RA.[65] Few similar studies in SLE have been reported.

Although disease duration and functional impairment have been shown to influence bone loss in RA,[66] neither of these variables had a significant effect in our patients. Not surprisingly, the arthritis of SLE was less disabling than that of RA. Yet, interestingly, the HFI was not a significant predictor of bone density in either disease. The KFT has been shown to be a useful marker of disease activity in RA,[17] so the relationship of bone mass to overall KFT could conceivably be a reflection of RA disease activity rather than disability.

Conclusions

There is need for a careful re-evaluation of the effects of CS on bone in young adults. Bone loss in RA and SLE is more likely to be an effect of the underlying disease than a complication of CS therapy. In young subjects bone loss may be reversible. Patients with SLE and RA provide a suitable model for studying the relationship between CS therapy, inflammation, disability and bone loss.

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