Prolonged low-dose corticosteroid therapy and osteoporosis in rheumatoid arthritis

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SUMMARY Thirty-one patients with rheumatoid arthritis maintained on prednisolone 5 mg daily for an average period of 9.4 years were assessed radiologically to determine the degree of osteoporosis in their spine and peripheral skeleton. They were compared with a control group of 32 rheumatoid patients who had never received corticosteroids. The steroid-treated patients had more severe osteoporosis than the controls, though the difference was not statistically significant. In the female patients the spine appeared to be more sensitive than the peripheral skeleton to the osteoporotic effect of corticosteroids.

Osteoporosis is a recognised complication of rheumatoid arthritis (RA), with juxta-articular involvement occurring in the early stages of the disease. A more generalised form may follow affecting the axial as well as the appendicular skeleton.¹⁻³ The pathophysiology of osteoporosis is still unknown, though many aetiological factors have been implicated.⁴ In patients with RA such factors may include immobilisation, poor nutrition, chronic inflammation, and corticosteroid therapy.⁵ The part played by low-dose corticosteroids is not entirely clear, and various studies have produced conflicting results.^{1 6-12} A major difficulty has been the lack of accurate and sensitive tests to assess the degree of osteoporosis. Newer techniques, such as the estimation of total body calcium as measured by neutron activation analysis, can provide an objective assessment of osteoporosis. This method, however, cannot give a differential assessment of the various parts of the skeleton. Although radiological methods may have their drawbacks,¹³ they do allow a differential study of the skeleton to be made.

The object of the present study was to investigate the effect of oral prednisolone 5 mg daily on the axial and appendicular skeleton of patients with RA.

Patients and methods

Thirty-two consecutive outpatients with RA receiving prednisolone 5 mg daily were studied. A further 31 rheumatoid outpatients who had never had corticosteroids and matched with the first group for age,

sex, disease severity, and duration were also studied. None of the patients had clinical evidence or a past history of any disorder likely to affect their skeleton. Such disorders included Paget's disease, osteomalacia, hepatic or renal disease, hyperparathyroidism, thyrotoxicosis, and diabetes. The age, sex, duration, and severity of their disease, drug therapy, duration of prednisolone therapy, and number of postmenopausal years in the female patients were recorded.

The arthritis was graded according to the Steinbrocker's functional index¹⁴ as mild (classes 1 and 2) or severe (classes 3 and 4). Such classification was carried out by the same observer (VH) on all patients. The following biochemical indices were measured: serum calcium, phosphate, alkaline phosphatase (AP), and albumin. Serum alanine transferase (AST) and gamma-glutamyl transferase (γ GT) were also measured if the AP was raised. Radiographs were taken with a standard technique by a single x-ray machine at the same time of day. The following views were obtained: anteroposterior view of the right femur, posteroanterior view of the hands, and lateral view of the lumbar spine centred on L3. The cortical thickness of the femur and right middle metacarpal were measured with a ruler and a magnifying glass as described by Barnett and Nordin¹⁵ (the sum of the thickness of the 'medial' and 'lateral' cortices of the shaft divided by the diameter and multiplied by 100). The points of measurement were the mid point of the metacarpal and 14 cm from the lesser trochanter along the femur. Only the homogeneous and compact bone was measured. Vertebral body density was graded by the method of Saville³ as follows: Grade 1: minimal loss of bone

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Table 1 Clinical details of patients studied

	Steroids	No steroids
Number of patients	32	31
Female Patients	19	19
Average age	59.4 years	58.5 years
Average disease duration	14.0 years	12.9 years
Severe disease	9	8
Postmenopausal female patients	16	17
Average number of years after menopause	13.8 years	14.0 years
Duration of steroid therapy	9.4 years	—
Duration of steroid therapy in males	10.6 years	—
Duration of steroid therapy in females	8.6 years	—

Table 2 Metacarpal (MC) and femoral cortex scores

	Steroid group		Nonsteroid group	
	MC	Femur	MC	Femur
All patients*	31.6	50.9	34.6	51.9
Female patients*	29.1	49.1	31.7	51.7
Postmenopausal female patients*	24.6	47.0	29.0	50.3
Male patients†	37.1	54.2	39.2	52.2

* $p > 0.5$. † $0.1 < p < 0.5$.

density; end plates begin to stand out giving a stencil-like effect. Grade 2: vertical striations more obvious; end plates thinner. Grade 3: more severe loss of bone density than grade 2; end plates less visible. Grade 4: ghost-like vertebral bone; density no greater than soft tissue; no trabecular pattern. Grades 1 and 2 were classified as mild and grades 3 and 4 as severe osteoporosis.

Spinal radiographs were examined by 2 observers independently, each completing his assessment within a relatively short period of time. On completion results were compared, and if there was a difference of more than one grade a second assessment was

made. All the films were studied without knowledge of the patients' clinical details or therapy. Cortical thickness and spinal porosity were assessed independently.

Statistical analysis of the results was carried out by the χ^2 test.

Results

Details of the patients are shown in Table 1. The duration of corticosteroid therapy ranged from 3 to 23 years with a mean of 9.4 years. The biochemical indices of all the patients were normal except for a minimally elevated AP in 5 patients, in 4 of whom the γ GT was also raised. Both enzyme abnormalities were considered to be of liver origin as may sometimes be seen in patients with RA.¹⁶ Table 2 shows the average metacarpal and femoral scores. Patients in the steroid group generally had lower scores, indicating a thinner cortex. However, the difference between the 2 groups was not statistically significant ($p > 0.5$). When the postmenopausal female patients of the 2 groups were compared, the difference was slightly greater but still failed to reach statistical significance ($0.1 < p < 0.5$).

The grades of spinal density for all the patients in the 2 groups are shown in Table 3. Severe osteoporosis (grades 3 and 4) was commoner among patients of the steroid group as compared with the control group. This difference, however, was not statistically significant ($0.1 < p < 0.5$). When the female patients of the 2 groups were compared, the difference was greater, but once again it failed to reach statistical significance ($0.05 < p < 0.1$). Similar results were found among the postmenopausal female patients. For male patients the effect of steroid therapy on spinal porosity was even less apparent.

Discussion

The part played by low-dose corticosteroid therapy in

Table 3 Spinal density

	Steroid group			Nonsteroid group		
	Normal	Mild osteoporosis	Severe osteoporosis	Normal	Mild osteoporosis	Severe osteoporosis
All patients*	0	16	16*	2	19	10*
Female patients†	0	6	13†	1	11	7†
Post menopausal female patients†	0	5	11†	0	10	7†
Male patients	0	10	3	1	8	3

* $0.1 < p < 0.5$. † $0.05 < p < 0.1$.

the aetiology of osteoporosis in patients with RA remains to some extent ill defined. Some studies have shown no increased risk of osteoporosis in corticosteroid-treated patients compared with control groups.^{1 8 10 11} Others have suggested that low-dose corticosteroids play a significant role in the osteoporosis of RA.^{6 7 9 12 17} The average daily dose in these studies was equal to or less than 10 mg prednisolone or its equivalent. In the radiological studies generalised osteoporosis was assessed by the cortical thickness of one or more of the following bones: metacarpal, radius, femur, and clavicle. There have only been 2 reports^{1 6} in which the spinal density of patients with RA on long-term corticosteroid therapy was assessed radiologically and compared with that in a group of patients who had never been on such therapy. McConkey *et al.*¹ failed to show any effect on the spinal density due to corticosteroids, while Saville and Kharmosh⁶ found that patients with RA over the age of 50 had significantly more spinal osteoporosis if treated with corticosteroids. However, disease severity or duration was not taken into account in the latter study, and McConkey did not group his patients according to their age and sex. Other methods used for the assessment of osteoporosis included photon absorptiometry¹⁷ and neutron activation analysis, which estimates total body calcium.^{11 12} Although these methods are considered to be more sensitive, they cannot demonstrate differential loss of bone density.

Riggs *et al.*¹⁸ reported that the central and peripheral skeletons may develop different degrees of osteoporosis, and Howland *et al.*¹⁹ described more severe osteoporosis in the axial than in the appendicular skeleton of patients with Cushing's disease. In view of these observations it would seem important to examine both the peripheral and central skeleton independently for the assessment of osteoporosis in patients with RA who have been on long-term low-dose corticosteroid therapy.

We assessed osteoporosis of the peripheral skeleton by measuring the metacarpal and femoral cortex, while osteoporosis of the central skeleton was assessed by examining the third lumbar and adjacent vertebrae. Our results suggest that there is a tendency to more severe osteoporosis in the corticosteroid-treated patients both in the spine and in the periphery. The difference, however, from the control group was not statistically significant. We also noted that in female patients the central skeleton appeared to be more sensitive than the peripheral skeleton to the effect of corticosteroids. This finding would support Howland's observation on the distribution of osteoporosis in patients with Cushing's disease.¹⁹

Thus it would seem that long-term corticosteroid therapy with doses no greater than 5 mg prednisolone

daily does increase the degree of osteoporosis in patients with RA. It would also seem that female patients receiving such therapy run a greater risk of developing spinal osteoporosis. Despite these observations the difference between the corticosteroid and non-corticosteroid groups does not reach statistical significance and it could be argued that the osteoporotic effect of low doses of these compounds is unimportant. Therefore the risk of developing osteoporosis should perhaps not be considered a definite contraindication to the use of low-dose corticosteroids in patients with RA.

Newer techniques such as computed tomography²⁰ and dual photon absorptiometry²¹ may in the future give a clearer idea of the exact role of these compounds in the pathogenesis of osteoporosis.

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