

## Spinal trabecular bone mineral content in patients with non-steroid treated rheumatoid arthritis

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**SUMMARY** Spinal trabecular bone mineral content was measured in the first, second, and third lumbar vertebrae by quantitative computed tomography in 88 patients with non-steroid treated rheumatoid arthritis. Results were compared with those obtained in 105 healthy control subjects. The mean bone mineral content in the patient group, 135.8 (SD 32.8) mg/ml  $K_2HPO_4$ , was significantly lower than that in the controls (151.9 (32.1) mg/ml,  $p < 0.01$ ). Division of patients and controls into three age groups showed that the reduction in bone mineral content was most marked in the youngest age group (21-40 years), the mean value in male patients being significantly lower than in controls (149.6 (51.3) v 171.7 (23.9) mg/ml  $K_2HPO_4$ ,  $p < 0.05$ ); in female patients in this age group the corresponding values were 160 (26.1) v 178.4 (22.0) mg/ml,  $0.05 < p < 0.1$ ). No significant difference in mean values between patients and controls was found in the other age groups. Of the 88 patients, six (7%) had abnormally low values, defined as a bone mineral content  $> 2$  SD below the normal mean. One vertebral crush fracture was found in one patient but not in any of the controls. No correlation was found between bone mineral content and body weight, duration of disease, or disability as assessed by the London and Steinbroker methods. These results demonstrate a lower spinal trabecular bone mineral content in non-steroid treated patients with rheumatoid arthritis than in age and sex matched controls, the difference being most marked in younger patients. The finding of abnormally low values in 7% of the patients indicates a slightly increased prevalence of spinal osteoporosis in these patients.

**Key word:** osteoporosis.

Generalised osteoporosis has been reported in association with rheumatoid arthritis,<sup>1-5</sup> and there is some evidence that the incidence of vertebral and femoral neck fractures may be increased in such patients.<sup>6,7</sup> At present it is unclear whether generalised osteoporosis is a direct consequence of the rheumatoid process or secondary to disease related factors such as steroid treatment<sup>3,4,8,9</sup> and inactivity.<sup>2,4,10,11</sup> The deleterious effects of steroids on bone mass, particularly in trabecular bone, are well documented,<sup>12,13</sup> but there is some disagreement over whether steroid treated patients with rheumatoid arthritis have more severe bone loss than those not receiving steroids.<sup>1,3,4,8,9,14,15</sup>

Recently, new techniques have been developed which enable accurate and reproducible measurements of bone mineral content in clinically relevant parts of the skeleton such as the vertebrae and femoral neck, where osteoporotic fracture may occur.<sup>16,17</sup> When these methods are used osteoporosis can be defined as a bone mineral content at the site of measurement  $> 2$  SD below the value for age and sex matched controls. In the present study spinal trabecular bone mineral content was measured by quantitative computed tomography in 88 patients with non-steroid treated rheumatoid arthritis to establish whether the prevalence of osteoporosis, as defined above, is increased in this disease in the absence of steroid treatment.

### **Patients and methods**

Eighty eight patients with definite or classical

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rheumatoid arthritis,<sup>18</sup> who were enrolled into a trial of second line treatment, were studied. Fifty one were female and the mean (SD) age of all patients was 51.7 (9.6) years (range 26–71). The median duration of disease was four years (range 1–25). None had received systemic steroid treatment at any time, though 14 had received intra-articular steroids. Seventy six patients had erosive disease and 77 patients were seropositive. Most patients were taking one or more of a variety of non-steroidal anti-inflammatory drugs; in addition, all were receiving second line drug treatment consisting of one of the following: penicillamine (maximum 500 mg/day) (n=31), hydroxychloroquine (400 mg/day) (n=20), and auranofin (6 mg/day) or intramuscular sodium aurothiomalate (50 mg/month) (n=37). Patients who were housebound or restricted to a wheelchair were excluded from the study as were those with a history of gastrointestinal disease or surgery, liver disease, chronic renal disease, endocrine disease, or known metabolic bone disease. Permission to carry out the study was granted by the local ethical committee. Disability was assessed by the Steinbroker<sup>19</sup> and the London<sup>20</sup> methods. The London score ranged from 0 to 3 (median 1.25). Steinbroker assessment placed 11 patients in class 1, 62 in class 2, and 15 in class 3. Control data for quantitative computed tomography were obtained from 105 healthy subjects, 57 female, aged 19–75 years (mean (SD) 45.8 (13.8)).

#### MEASUREMENT OF SPINAL TRABECULAR BONE MINERAL CONTENT

Spinal trabecular bone mineral content was measured in the anterior part of the first three lumbar vertebrae by quantitative computed tomography (CT) with a Philips 350 x ray CT scanner, using a modification of the method of Cann and Genant.<sup>21</sup> Patients were positioned with the lumbar spine over a phantom containing tubes of various salt solutions and water. Scans were made through the middle of each vertebra, using a slice thickness of 6 mm, field of view of 400 mm, and tube voltage of 120 kV, and the CT number within the vertebral body of L1, L2, and L3 was compared with those of the salt solutions. In this way mineral concentrations were calculated in terms of an equivalent concentration of  $K_2HPO_4$  solution, a salt which has radiographic attenuation properties similar to those of calcium hydroxyapatite. The results were corrected for the contribution of non-mineral components to the attenuation coefficient, using calculated values of estimated soft tissue corrections based on published tissue composition data.<sup>22</sup> The lateral digital pictures of the lower dorsal vertebrae (T11 and T12) and all the lumbar vertebrae in all the patients and

controls were examined by a consultant radiologist (CE) for the presence of compression fractures.

#### STATISTICAL ANALYSIS

Correlations between continuous variables were examined by linear regression analysis, and the significance of the correlation coefficient was determined by a Student's two tailed *t* test. Relations between continuous and non-continuous data were examined by two tailed Student's *t* tests and one way analysis of variance. Differences between patients and controls were tested using an unpaired two tailed *t* test or, in the case of the 21–40 year old men, by the Wilcoxon rank sum test.

#### Results

When all the patients were considered as one group the mean (SD) spinal trabecular bone mineral content, 135.8 (32.8) mg/ml  $K_2HPO_4$ , was significantly lower than that in the controls (151.9 (32.1) mg/ml,  $p < 0.01$ ). Six patients, three women aged 50, 61, and 64 years and three men aged 39, 48, and 58 years, had abnormally low values, defined as a bone mineral content  $> 2$  SD below the mean value of age and sex matched controls. Division of female and male patients and controls into three age groups (Figs 1 and 2) showed that the reduction in bone

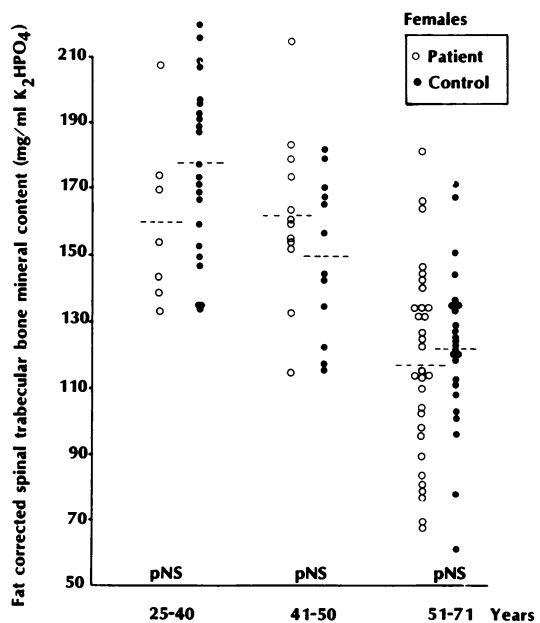


Fig. 1 Fat corrected spinal trabecular bone mineral content in female patients (○) and controls (●) with rheumatoid arthritis. The interrupted horizontal lines indicate the mean value for each group.

mineral content was significant only in the men aged 21–40 years ( $p < 0.05$ ); in women in this age group the mean (SD) value in the patients, 160 (26.1) mg/ml  $K_2HPO_4$ , was also considerably lower than that in the controls (178.4 (22.0) mg/ml), though this difference did not attain significance. Mean values were similar in patients and controls in the other age groups. The mean age and body weight were similar in the patients and controls in each age group with the exception of the mean age in the oldest age

group of men, which was significantly higher in controls than in patients (Table 1).

One patient, a man aged 40 years, had a compression fracture of T12. Spinal bone mineral content in this patient was within normal limits (148 mg/ml  $K_2HPO_4$ ). No compression fractures were seen in the control group. Linear regression analysis in the patient group showed no significant correlations between bone mineral content and body height, weight, disease duration, or London score. No significant differences were found in bone mineral content between patients with erosive or non-erosive disease, seropositive or seronegative disease, or between those who had or had not received intra-articular steroids. One way analysis of variance showed no correlation between spinal bone mineral content and either the type of second line treatment or the Steinbrocker assessment.

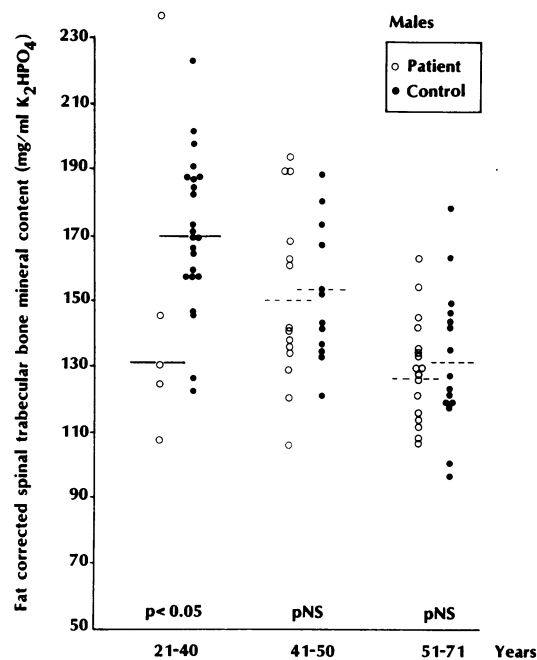


Fig. 2 Fat corrected spinal trabecular bone mineral content in male patients (○) and controls (●) with rheumatoid arthritis. The interrupted horizontal lines indicate the mean value for each group; in the 21–40 year age group median values are shown by a continuous horizontal line.

## Discussion

In this study a significantly lower spinal trabecular bone mineral content was found in a large group of non-steroid treated patients with rheumatoid arthritis than in the age and sex matched controls. In addition, there was a significantly increased prevalence of spinal osteoporosis, defined as a bone mineral content  $>2$  SD below the normal mean in these patients. The significant reduction in bone mineral content in the whole group of patients was largely due to the low values obtained in the youngest age group of both sexes, particularly men, although in three of the four other subgroups, the mean value in patients was lower than that in controls. As the number of male patients aged 21–40 years was small the results obtained on comparison with controls have to be interpreted with some caution, particularly as the significance level achieved ( $p < 0.05$ ) was low. The lower values obtained for bone mineral content in younger patients than in controls are consistent, however, with our previous findings.<sup>23</sup> These showed that in a

Table 1 Age and body weight in the three groups of patients and controls

	21–40 Years		41–50 Years		51–71 Years	
	Patients	Controls	Patients	Controls	Patients	Controls
Age (years)						
Men	36.4 (5.9) <sup>†</sup>	32.6 (3.6)	46.2 (3.0)	43.3 (2.2)	56.8 (3.7)	63.0 (5.9) <sup>*</sup>
Women	34.7 (4.5)	32.2 (4.4)	46.7 (2.0)	45.5 (2.4)	59.3 (6.1)	60.5 (6.1)
Body weight (kg)						
Men	73.0 (9.3)	74.0 (10.1)	77.3 (8.9)	77.6 (12.4)	76.2 (7.2)	75.2 (10.2)
Women	56.9 (7.9)	57.0 (6.9)	62.8 (12.7)	60.9 (9.8)	60.7 (7.7)	63.9 (12.1)

<sup>\*</sup> $p < 0.01$ .

<sup>†</sup>Values are mean (SD).

subgroup of these patients the iliac crest trabecular bone volume, assessed histomorphometrically, was reduced in younger patients with rheumatoid arthritis compared with age and sex matched controls, whereas bone volume in older patients was normal.<sup>23</sup> The results of these two studies therefore suggest that rheumatoid arthritis may be associated with premature bone loss, though the total amount of bone lost during the aging process appears to be similar to that of the normal population; longitudinal studies would be necessary to confirm this.

Previous studies of spinal bone mineral content in rheumatoid arthritis have produced conflicting results. Thus although Sambrook *et al* reported reduced bone mineral content in the lumbar spine, measured by dual photon absorptiometry, in a total of 84 steroid treated and non-steroid treated patients,<sup>24</sup> Verstraeten and Dequeker using the same method were unable to demonstrate any reduction in 104 postmenopausal patients<sup>7</sup>; indeed, non-steroid treated patients were found to have a higher spinal bone mineral content than the controls. In the only longitudinal study of spinal bone density in patients with rheumatoid arthritis Sambrook *et al* were unable to show any increase in the rate of bone loss from the spine in a small group of patients with recent onset, non-steroid treated rheumatoid arthritis.<sup>25</sup> Only a small number of patients were studied, however, and the follow up period was short.

Total body calcium, which is predominantly a measurement of peripheral cortical bone mass, has also been evaluated in a number of studies. Low total body calcium has been reported in patients with rheumatoid arthritis receiving steroids,<sup>9 26</sup> though this finding has not been invariable<sup>27</sup>; both low<sup>9 26</sup> and normal<sup>27-29</sup> total body calcium have also been reported in non-steroid treated patients. More localised measurements of radial bone mass, which includes both cortical and trabecular bone, have been made using single photon absorptiometry; most of these studies have reported reduced midshaft<sup>5 30</sup> and distal<sup>7 26</sup> radial bone mineral content in steroid treated patients<sup>7 26</sup> and in some cases, in non-steroid treated patients also.<sup>7 26 30 31</sup> In addition, an increased rate of trabecular bone loss from the distal radius was reported by Sambrook *et al*.<sup>25</sup>

In the present study only patients not receiving steroids were included so that steroid induced effects on bone mass could be excluded. In this group of patients we were unable to demonstrate any relation between spinal bone mineral content and assessments of functional disability; this may partly be due to the exclusion from our study of patients with severe disability and immobilisation. In addition, a single functional assessment carried

out at one moment in time does not take into account either the duration of the disease or its course in the past, both of which are likely to be important determinants of any effects of inactivity on bone. Attempts to correlate disease duration with bone mass have produced conflicting results<sup>1 4 10 14 31 32</sup>; in our study only a weak, non-significant, negative correlation was found ( $r = -0.111$ ,  $p$  NS).

The clinical significance of reduced bone mass associated with rheumatoid arthritis depends on the degree and site of reduction and the changes in bone structure accompanying bone loss. In the final analysis, as fracture is the most important clinical event in osteoporosis, clinical significance is best assessed in terms of the impact, if any, of bone loss on fracture rate. Two studies have indicated that there is an increased risk of osteoporotic fracture associated with rheumatoid arthritis; in one of these this was found only in steroid treated patients,<sup>7</sup> whereas in the other some increase in fracture risk was found in both steroid and non-steroid treated patients, though the risk was higher in the steroid users; disability and long duration of disease were also associated with increased fracture rate.<sup>6</sup> In the present study no significant increase in vertebral fracture rate was found in the patients compared with controls; further studies are required to establish definitely whether or not the incidence of osteoporotic fracture is increased in non-steroid treated patients with rheumatoid arthritis.

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